REVIEW

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The role of HPV infection in oropharyngeal cancer

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Abstract

Background: Human papilloma virus (HPV)-positive oropharyngeal squamous cell carcinoma (OPSCC) has been recognized as a distinct disease entity associated with oral HPV infection with high-risk serotypes, mainly among white man at younger age. Lifetime number of oral sex partners of HPV-positive OPSCC patients is the strongest risk factor associated. HPV type 16 is now established as oncogenic and it is the main cause (over the 80%) of this type of OPSCC, followed by HPV 18 (3%). Nowadays, it is reported a dramatic rising of HPV-positive OPSCC, mainly in developed countries, including Australia, Canada, Denmark, Netherlands, Norway, Sweden, Poland, Slovakia, Switzerland, Estonia, France, Japan, United States (US) and United Kingdom. At present, the yearly number of new incidence OPSCC cases given to HPV worldwide has been estimated of 29 000 by the *International Agency for Research on Cancer* (IARC). If incidence trends continue, the annual number of HPV-positive oropharyngeal cancers is expected to overcome the annual number of cervical cancers by the year 2020, in the US. *Aim*: The aim of this paper is to review the recent data about several topics including risk factors of HPV-positive OPSCCs, guidelines in diagnostic evaluation, treatment, prognosis and prevention strategies, through prophylactic HPV vaccine on both sexes. Nowadays, HPV detection is a clinical standard of care for oropharyngeal malignancy by reporting tumors as HPV positive or p16 positive.

Keywords: HPV type 16 infection, oropharyngeal squamous cell carcinoma, p16 immunohistochemistry, HPV vaccine.

Introduction

The campaign against tobacco and alcohol abuse has determined the decrease or stabilization of laryngeal, hypopharyngeal and oral squamous cell cancers in the developed countries, last decade. In contrast, it has been mentioned the upsurge of oropharyngeal squamous cell carcinoma (OPSCC). The major etiological role of human papilloma virus (HPV) in OPSCC has been proved since 2011. The epidemic rising of OPSCC is being attributed to a significant increase in HPV infection, as long as HPV determines the most common sexually transmitted infection worldwide. This latest public issue is a matter of concern for all the international community. Based on *European Cancer Observatory* (EUCAN) 2012, the highest incidence of OPSCC together with oral squamous cell carcinoma (OSCC) among Eastern European countries were reported in Hungary, Slovakia and Romania, for Western European countries were detected in France, Germany and Belgium, and for Northern European countries were observed in Denmark, Lithuania and United Kingdom [1, 2]. More than 70% of OPSCC cases and over 50% of tonsillar cancers in the United States (US) have been associated with high-risk HPV serotypes [3]. There are over 200 HPV serotypes, but the most common in OPSCC (80–95%) and also in anogenital cancers (52–58%) is the high-risk HPV subtype 16. Other HPV types rarely found in OPSCC are HPV 18, 31, 33, and 35 [4].

OPSCCs are different from OSCCs and are named as HPV-positive or HPV-negative tumors, based on the *World Health Organization* (WHO) *2017 New Classification of Head and Neck Tumors* [5]. The typical locations of HPV-positive OPSCC are base of the tongue and palatine tonsils. HPV-positive OPSCCs have a lower risk of death than HPV-negative cases. The incidence of other secondary tumors or distant metastases is reported to be lower at the onset, but they are supposed to develop later, on the following five years and this implies the responsibility for a long-term medical surveillance [6].

The authors want to highlight that HPV detection is a clinical standard of care for oropharyngeal malignancy and review the recent data about HPV-positive OPSCCs epidemiology and oncogenesis, guidelines for diagnostic evaluation, current treatment strategies, prognosis and prevention strategies, including routine prophylactic HPV vaccine.

Epidemiology of HPV-positive OPSCC

The incidence of HPV-positive OPSCC is three-fold higher for males than for females. Patients tend to be Caucasians, about 40–55 years. They have less exposure to tobacco and alcohol, higher socio-economic status and education and have an overexposure to unprotected sex. Among risk factors are mentioned oral sex with multiple partners from an earlier age, history of previous sexually transmitted infection or HPV-associated genital cancer, marijuana usage, persistent immunosuppression [*e.g.*, human immunodeficiency virus (HIV) positive] and maybe French kiss [7]. HPV-positive OPSCC is supposed to be a sexually acquired disease, through direct oro-genital contact. *Via* mucosal wounds or abrasions, HPV infects the basal epithelial cells. Regularly, local infection is cleared in 90% of individuals during the first two years, through a specific T-cell mediated immunity and will not lead to a malignant process. Persistence of HPV infection, especially in case of association of multiple high-risk HPV types, increases the risk of developing cancer after decades. A recent study observed HPV 16 E6 seropositivity before development of OPSCC by around 10 years, point out that seroreactivity may establish individuals at higher risk than general population [8], but there are a few case-control studies about the evidence of HPV infection prior to development of OPSCC.

Probably, in addition to focal genomic instability that is HPV induced, other cofactors, such as immunodepression [*e.g.*, acquired immunodeficiency virus (AIDS)], genetic susceptibility and nutritional factors could promote the onset of OPSCC. It is clear that tobacco and alcohol interactions have less importance to HPV-positive OPSCC than for HPV-negative OPSCC [9].

Oncogenetic mechanism of HPV infection

Any type of HPV can cause growth of abnormal cells and can lead to the condition of benign and premalignant lesions, but the high-risk types are identified three-fold more numerous in different cervical cancers, anogenital cancers and OPSCCs [10]. The majority of HPV-associated cancers enclose HPV deoxyribonucleic acid (DNA) integrated into the host cell genome and express two viral genes, *E6* and *E7*. These genes encode oncoproteins that harm tumor suppressors but also impede the anti-viral, anti-proliferative, anti-angiogenic and immunostimulatory effects of type I interferon (IFN). The biology of HPV-positive OPSCC is typified by p53 and retinoblastoma protein (pRb) down-regulation and compensatory up-regulation of p16 protein. In contrast, tobacco-related OPSCC is characterized by low-expression of p16, up-regulation of pRb and various *p53* mutations. It has been observed an inverse relation between HPV presence and *p53* mutations, which could explain the appreciable sensitivity of these tumors to radiation [11].

Clinical presentation and paraclinical diagnosis

Many people with early-stage HPV-positive tumors are asymptomatic and do not seek testing. The lesion can be revealed by neck swelling as unique sign. HPV-negative tumors are more likely to determine sore throat or dysphagia at early onset. Initial assessment of patients by anamnesis and medical history is followed by a complete ear, nose and throat (ENT) clinical examination, including palpation of cervical lymph nodes.

Early oropharyngeal malignancy can appear as firm erythroplakia or exophytic/fungating mass or persistent ulcer. Certainly, there are no evidences for any specific precursor lesions of HPV-associated OPSCC. After clinical exam, patients are assessed by endoscopy, imaging tests and biopsy. HPV-positive carcinomas specifically have occult primary lesions or well-defined borders small primary tumors (T1–T2) or/and large cystic nodal metastases [12].

Direct laryngoscopy using white light and narrow-band imaging (NBI) endoscopy with narrow-bandwidth filters can detect superficial premalignant lesions, early oropharyngeal cancers or recurrences. NBI endoscopy is useful to assessment of squamous cell carcinoma of unknown primary (SCCUP) origin [13]. Fiberoptic pan-endoscopy can reveal a second respiratory and upper digestive tract cancer. Cross-sectional imaging is required in all cases. Magnetic resonance imaging (MRI) is recommended for primary site and computed tomography (CT) scan for neck and chest. Positron emission tomography (PET) combined with CT is recommended for assessment of response after chemoradiotherapy and for recurrence. Histological study and p16 immunochemistry are mandatory to complete the diagnosis and staging. Oropharyngeal carcinoma histopathology reports should be prepared according to *Guidelines*. HPV testing for oropharyngeal cancer should be executed within a diagnostic service, where the laboratory practice and reporting standards are quality guaranteed [14].

HPV testing

Direct HPV testing for DNA or E6/E7 messenger ribonucleic acid (mRNA) are *in situ hybridization (ISH)* and *polymerase chain reaction (PCR)*. Indirect HPV testing is *immunohistochemistry (IHC)* with identification of the tumor suppressor *p16 protein* expression.

Based on the systematic review and on expert panel consensus, high-risk HPV verification is recommended for all new OPSCC sufferers either from the primary tumor or from cervical nodal metastases, using p16 IHC, but it is not commonly recommended for other head and neck carcinomas. p16 overexpression is an settled, robust surrogate biomarker for HPV-mediated carcinogenesis, but only for oropharyngeal location, with 96.8% sensitivity and 83.8% specificity. It is also a major positive prognostic marker of OPSCC. Pathologists are to communicate tumors as HPV positive or p16 positive [15].

Clinical and pathological TNM categories for HPV-positive OPSCC

Since 2017, *American Joint Committee on Cancer (AJCC) Cancer Staging* has drawn attention to some important changes [16]. There are two different staging systems for p16-positive and for p16-negative OPSCCs. The prediction of survival is done in accordance with the presence/absence of HPV. There is *no Tis stage*

(carcinoma in situ) for p16-positive OPSCCs because of the typical non-aggressive pattern, but also the lack of a distinct basement membrane of Waldeyer's ring epithelium. On stage T4 there are no "a" and "b" categories, according to the superposition of the overall survival curves. All patients with distant metastases are included in stage IV group, which is not subdivided and this is quite different to stage IV of HPV-negative OPSCCs. Clinical involvement of lymph nodes less 6 cm in size, whether one or multiple, as long as they are ipsilateral are included in the same *N1* category. The contralateral or bilateral lymph nodes are classified as *N2*. The lymph nodes larger than 6 cm are the *N3* category, associated with the worst survival.

Differential diagnosis considerations in HPV-positive OPSCC

Leukoplakia

Leukoplakia appears like a white patch that does not rub off, in contrast to fungal infection. It is quite common in the oral cavity and can range from lichen planus to early invasive carcinoma but keratinization is not a feature of HPV-positive OPSCC.

Parapharyngeal tumors

Parapharyngeal tumors can appear as well-defined, exophytic, protruding masses in the oropharyngeal wall, behind tonsil and posterior pillar that are displaced toward the midline. In contrast, HPV-positive carcinomas specifically have occult primary lesions or small primary tumors. Bimanual examination of neck reveals the lower part of parapharyngeal tumor in retromandibular and submandibular regions, in continuity with the bulging mass from oropharynx [17]. CT and/or MRI imaging are useful evidences for diagnosis.

Cystic metastatic cervical nodes

Cystic metastatic cervical nodes have been strongly associated with HPV-positive OPSCC but can cause wrong diagnosis of *branchial cleft cysts*. Fine-needle aspiration (FNA) with cytology and IHC testing for p16 is highly recommended *versus* open biopsy. Finding HPV in a cervical metastatic carcinoma of unknown primary (CUP) origin is a powerful indicator of OPSCC. Base of tongue mucosectomy and bilateral tonsilectomy with histopathological (HP) and immunohistochemical studies should also be performed.

Chronic hypertrophic tonsillitis

Chronic hypertrophic tonsillitis and other particular pathological entities have to be differentiated from OPSCC. The asymmetrical pattern and many vascular anomalies are suggestive for neoplastic angiogenesis and can be one of the distinctive clinical features for early diagnosis that has to be confirmed by HP findings [18].

Anatomopathology of HPV-positive OPSCC

HPV-positive OPSCC usually arises from reticulated epithelium layer of the tonsillar crypts. The deep mucosal invaginations favor virus capture into crypts and promote its access to basal epithelial cells.

Typical microscopic features associated with HPV infection are *basaloid and non-keratinizing appearances*. If p16 or direct HPV testing is not available, but OPSCC shows these typical microscopic features, *WHO* recommends the terminology of "*squamous cell carcinoma, HPV not tested, morphology highly suggestive of HPV association*".

In contrast to head and neck squamous cell carcinoma (HNSCC), the non-keratinizing status has no negative prognostic value for HPV-positive OPSCC. That is the reason why, the 2017 *WHO Classification* discourages histological grading of HPV-positive OPSCC. Critical prognostic factors are metastatic lymph nodes and safe postoperative margins. Other factors, like depth of tumor invasion, perineural and extracapsular nodal extension (ENE) should be evaluated as potentially important negative prognostic circumstance in subjects with HPV-associated OPSCC who undergo primary surgery [19].

Current treatment strategies in HPV-positive OPSCC

Current recommendations in the US and the European Union are applied to both HPV-positive and HPV-negative OPSCC, according to the stage. Primary surgery (transoral or open resection of the tumor with or without neck dissection) or definitive radiotherapy is recommended at early stages (T1–2, N0–1). It is very encouraging that the results are good for all patients with HPV-positive tumors, regardless of the type of *unimodal* treatment they have received, with similar local disease control and over 85% survival rates. On the other hand, local advanced p16-positive OPSCCs have better survival and response to *multimodal* treatment (chemoradiation) than HPV-negative tumors. A *multidisciplinary* medical board is highly desirable and includes a dietetician and a speech-language/swallowing therapist, to provide a wide range of recommendations for various clinical circumstances and patient's preferences [20].

De-escalation of current therapy options in HPV-positive OPSCC

De-intensification of treatment protocols for HPV-positive OPSCC

De-intensification of treatment protocols for HPV-positive OPSCC has been included in ongoing clinical trials. There are mentioned less invasive surgical procedures, such as organ preservation by transoral robotic surgery (TORS) or transoral laser microsurgery (TLM). Reduction of radiation therapy (RT) dose or replacing chemoradiation with definitive radiotherapy and using targeted molecular agents or immunotherapy/checkpoint inhibitors instead of chemotherapy are also less-toxic procedures that can be adequate in selected patients, for better quality of life.

Minimally invasive surgery

Minimally invasive surgery, such as TORS, is approved for all types of OPSCC at early stages and offers advantages over open surgery for decreasing the morbidity. The goal of oncological TLM is complete tumor resection with maximal normal tissue preservation. A good selection of

cases to achieve adequate tumor-free margins is an important issue. Margin assessment has to be done in real time, using frozen sections. A wide or clear margin is over 5 mm. A close margin of 1–2 mm is considered inadequate at the level of base of tongue. In contrast to TLM, TORS involves *en bloc* elimination of the tumor in preponderance of cases. As a result, surgical margins can be more handily interpreted [21].

Immunotherapy with immunomodulators

There are some ongoing studies about immunotherapy with immunomodulators. Toll-like receptors, cytokines [interleukin (IL)-2, IL-12, granulocyte-macrophage colony-stimulating factor (GM-CSF) and IFN-α], T-cell therapy, vaccines against tumor cells, bacterial vectors (*Listeria monocytogenes*) and live viral vectors have proven to be effective. Recently, an Italian study mentioned a therapeutic vaccine for activation of natural killer T (NKT) cells that is made from an integrase-defective lentiviral vector (IDLV) that delivers a mutated non-oncogenic form of the HPV 16 E7 protein fused to calreticulin (CRT). It is suggested that a safe *anticancer immunotherapeutic vaccine* for human use will be available in the near future [22]. Other studies have shown an immune resistance mechanism, which is mediated through programmed cell death protein-1 (PD-1) and ligand of this (PD-L1). Usage of anti-PD-L1 and anti-PD-1 antibodies in patients with advanced cancer may become a new safe approach to HPV-positive OPSCCs [23].

Prevention of OPSCC using HPV vaccine

Strategies against HPV infection, such as health education (*e.g.*, condoms usage) and vaccination on both sexes, can prevent further occurrence of HPV-positive cervical cancers and OPSCCs. The vaccination campaign against HPV has started since 2006 in Australia and after that, in many other American and European countries. After the first six years of vaccination in US, the prevalence of HPV infection among females aged 14 to 24 has significantly decreased [24, 25]. The *Immunization Schedule* has been approved by the *Advisory Committee on Immunization Practices*, *American Academy of Pediatrics* and *American College of Obstetricians and Gynecologists* since January 2018. *Routine vaccination* with *Gardasil 9* is recommended for all adolescents (girls and boys) aged 11 to 12 (it can start at age 9) or aged 18 if they have not previously received vaccination and for the immunocompromised individuals aged 22 to 26, as well. *Catch-up vaccination* is recommended for females and males aged 13 to 26 if they were not previously and/or adequately vaccinated. Such a mass campaign against HPV, may well lead to the significant decrease (with over 90%) in the OPSCC's prevalence worldwide, after the year 2060.

Conclusions

The role of high-risk HPV infection, especially serotype 16, in oncogenesis is well demonstrated. Overexpression of p16 is a settled, robust surrogate biomarker for HPV-mediated carcinogenesis, but only for oropharyngeal location. High-risk HPV testing is suggested for all new OPSCC patients, either from the primary tumor or from cervical nodal metastases, applying p16 IHC, but it is not routinely recommended for other head and neck carcinomas. Strategies against HPV infection, such as health education and routine vaccination on both sexes' adolescents and young adults (aged 9–26 years old) can prevent further occurrence of HPV-positive cervical cancers and OPSCCs also. The vaccine cannot help to clear an infection but can prevent people from getting a new HPV serotype.

Conflict of interests

The authors declare no conflict of interests.

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