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The Current State of Biological and Clinical Implications of Human Papillomavirus-Related Oropharyngeal Cancer

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In the effort to control human papillomavirus-related oropharyngeal cancer, the head and neck oncology community has devoted much effort to understanding its disease biology and clinical behavior, and refining strategies to address early diagnosis and optimal management for the affected population. This review identifies articles published up to March 2017 on tumor biology and clinical implications of human papillomavirus-related oropharyngeal cancer, and summarizes the findings in some key areas. These include potential screening strategies, possible anatomical features responsible for early lymph node involvement and its implication for staging, biological mechanisms to explain superior outcomes compared to traditional nonviral-related mucosal cancers, re-appreciation of traditional prognostic factors (eg, hypoxia, extranodal extension, and smoking), and current efforts to optimize management for this patient population. The review reflects the global effort to mitigate the influence of this burgeoning disease.
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Introduction

The rapid emergence of human papillomavirus-related (HPV+) oropharyngeal cancer (OPC) has changed the head and neck cancer (HNC) landscape significantly in many Western countries,[1-5] and the current trend appears to show no sign of slowing down in high HPV prevalence jurisdictions.[6,7] Although HPV+ OPC mostly occurs in a relatively young population (median age: 55-60 years), a rising trend is also observed in elderly patients.[8,9] In fact, HPV+ OPC now comprises most of the head and neck squamous cell carcinoma referral in North America.

Although arising in the same anatomical location as smoking-related or HPV-negative (HPV–) OPC, HPV+ OPC is now recognized as a distinct disease entity, with very different molecular profile,[10-13] clinical-radiological presentation,[14,15] and treatment response and outcomes.[16,17] In essence, tumor HPV status has emerged as a "diagnostic" biomarker to identify a new disease rather than a "prognostic" biomarker within a "homogeneous" disease entity. The eighth edition TNM staging includes a new TNM classification for HPV+ OPC. The 2017 World Health Organization/International Agency for Research on Cancer Classification of Head and Neck Tumors (fourth edition) has also introduced "*SCC, HPV-positive*" for HPV+ OPC recognizing its distinction as a new disease.[18] Clinical trials are now addressing HPV+ and HPV– diseases separately.

In response to the "quandary" of the rising tide of HPV+ OPC, significant progress has been made in understanding tumor biology and clinical behavior, and in developing preventative strategies. For example, HPV+ OPC tumors often lack p53 mutations; they also involve cervical lymph nodes earlier and are frequently accompanied by a cystic nodal architecture. They also may exhibit a more prolonged nodal regression after (chemo-)radiation[19] with paradoxically superior outcomes. Current research directions have shifted from observational studies describing unique clinical behavior to understanding biological mechanisms and refining management strategies accordingly. This review aims to summarize current understanding of HPV+ tumor biology to uncover its clinical implication on the natural course of the disease, risk

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stratification and prognostication, investigational treatment approaches, and potential screening and preventative strategies.

The Quest for HPV-Induced Precursor Lesions in Oropharynx

HPV-related precancerous lesions have been identified in cervical, anal, penile, vaginal, and vulvar regions. Recognizing these characteristics has enabled implementation of cancer screening in these disease sites. However, whether similar precancerous lesion exist in the oropharynx remains debatable. A multi-institutional study of tonsil tissue from 4095 healthy individuals in the United Kingdom (UK) did not find any precursor lesion.[20] Fakhry et al evaluated the feasibility of conducting a "Pap smear equivalent" cytology test (collected by bilateral tonsil "brushing") from patients presenting with oropharyngeal abnormalities and human immunodeficiency virus-infected individuals. Among those with oropharyngeal abnormalities, both oral HPV16 infection and the presence of cytologic abnormalities were strongly associated with the presence of invasive OPC. In contrast, cytologic abnormalities were rare and were not associated with oral HPV16 infection among human immunodeficiency virus-infected individuals. The absence of detectable precancerous lesions among individuals without clinical disease probably reflects the difficulty in accessing deep tonsillar crypts.[21] The French "Split" trial also showed that tonsil "brushing" appeared to be less reliable in detecting HPV[22] compared to an oral rinse method,[23] and furthermore, neither are OPC-specific. Thus, the lack of an identifiable HPV-induced precursor lesion in the oropharyngeal mucosa together with the unavailability of a reliable noninvasive measure to detect abnormal cytology poses a challenge for screening and early diagnosis.[24]

Earlier Nodal Involvement and Its Implication in Diagnosis and Staging

The HPV carcinogenesis process occurs at the basal cell layer of the oropharyngeal mucosa. This anatomical location is clinically relevant. Electron microscopy studies of this epithelial layer have revealed that the basement membrane of the tonsillar crypt is discontinuous and rich in intraepithelial capillaries,[25] which might facilitate tumor cell foci accessing underlying lymphatics resulting in lymph node involvement earlier in the course of tumor progression. Thus, it could partially explain the clinical observation that most (>90%) HPV+ OPCs have clinical nodal involvement, even when primary tumors are small (T1-T2).[26]

The disproportionally earlier nodal involvement relative to the size of the primary tumor presents a diagnostic dilemma. Reports have shown that about two-thirds of HPV+ OPC patients present with an asymptomatic neck mass as the first sign requiring medical attention, and often results in misdiagnosis as a benign condition in generally healthy individuals who otherwise have a relative lack of risk factors.[15,27] Cervical nodal metastasis presenting without an obvious primary (termed "unknown primary") most often originates from an HPV+ OPC.[28,29]

The earlier nodal involvement in HPV+ OPC has also changed the prognostic value of the traditional N-category within the TNM classification that has relied on size, number, and side of neck affected.[30] The multi-institutional study of 1907 HPV-positive OPC by *the International Collaboration on Oropharyngeal cancer Network* (ICON-S) demonstrated that, while prognosis worsens in line with higher T category, the seventh edition N classification was inadequate in depicting prognosis. In fact, there is minimal separation in overall survival (OS) among N1, N2a, and N2b subsets, and the ICON-S study consequently reclassified them into a single category as "N1," while bilateral or contralateral neck nodes are now termed "N2."[26] The ICON-S N classification has now been adopted in the eighth edition TNM for HPV+ OPC. It is the first time in the head and neck cancer TNM classification that T4 or N3 M0 disease is not classified as stage IV in this unique disease setting.[31]

It is interesting that although nodal involvement is often evident earlier in HPV+ OPC, the topographic distribution of involved lymph nodes is not different between HPV+ and HPV– OPC.[14,32,33] This strongly suggests that the lymphatic drainage pathways are similar for both diseases. Therefore, there is no indication to modify treatment of candidate lymph node regions with either surgery or radiotherapy based on tumor HPV status.

Potential Role of HPV16 E6 Serology for Screening and Surveillance

Recently, HPV E6 serum antibody has shown a promising role in early detection of HPV+ OPC. The E6 antibody is rarely detected in healthy individuals[34] but is very high in patients with HPV+ OPC (>90% of patients with HPV+ OPC, 0% of partners, and 7.4% of healthy volunteers),[35] and it is much lower in non-OPC (oral cavity, larynx) and genital HPV+ cancers (eg, cervix, vagina, vulva, and penis), excepting anal cancer.[36] These differences in host-immune response might reflect variations in the tumor microenvironment across anatomical locations. In addition, serum HPV16 E6 antibody was detectable in >90% of patients with HPV+ OPC 2-10 years before their cancer diagnosis.[36] For this reason, it is alluring to consider the use of this biomarker to design a screening algorithm for HPV+ OPC and anal cancers.[37] However, the choice of study endpoint and monitoring method in seropositive patients presents a dilemma as there is no visible precancerous lesion to screen, even though severe dysplasia can exist. Bilateral tonsillectomy is not an ideal detection procedure for E6 seropositive patients as it is invasive and would be unable to address the risk of tumor in the base of tongue (BOT) which accounts for nearly 50% of HPV+ OPC [14]. One possible solution is the use of ultrasound to identify