

Primary Care Updates in Human Papillomavirus-Associated Oropharyngeal Cancers

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ABSTRACT

Human papillomavirus-associated oropharyngeal cancers (HPV-OPCs) are a major health problem globally. Trends indicate increasing incidence of HPV-OPCs. Vaccination allows opportunities to prevent HPV-OPC and other HPV-associated cancers. However, US vaccination rates are very low. Those diagnosed and treated for HPV-OPC have long-term effects impacting the rest of their lives. This article will focus on HPV-OPC trends and major staging classification changes, reviews treatment modalities and survivorship issues, and will discuss primary prevention to impact the incidence of HPV-OPCs.

Keywords: HPV, human papillomavirus, oropharyngeal cancers, survivorship, vaccination

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INCIDENCE

In 2018, the American Cancer Society estimates 51,540 new oral cavity and pharynx cancers, with an estimated 10,030 deaths in the US.¹ This estimate includes the increasing incidence of human papillomavirus-associated oropharyngeal cancers (HPV-OPCs), especially among young white men.

The most common sexually transmitted infection is HPV.² HPV infection causes cancers of the cervix, anus, and oropharynx.² HPV-associated cancers have significantly increased over the last 2 decades.³

Squamous cell carcinoma is the most common histology in oropharyngeal cancers, regardless of HPV status. HPV-OPC occurs most often in young (45 to 65 years) healthier persons, with little or no tobacco exposure and limited alcohol exposure.⁴ HPV-OPCs impact males 3:1 to females.⁵ For unknown reasons, it tends to occur in white patients more than blacks and is higher in non-Hispanics compared with Hispanics.⁶

PATHOPHYSIOLOGY

Asymptomatic HPV infections are common and may clear without chronic infection. There are over 150

HPV viruses, with 13 high-risk strains associated with oncogenesis.² HPV-16 infection is most likely to progress to cancer.² HPV-16 infection has a propensity to infect the oral cavity epithelial surface and causes 90% of HPV-OPC squamous cell carcinomas. However, HPV-18, -31, -33, and -35 are also high-risk types in head and neck cancer (HNC).⁷

From exposure, new HPV-OPCs may present 10 to 30 years later.⁵ Therefore, the exposure may not have occurred from a current sexual partner. It does not indicate promiscuous sexual behavior or infidelity. It is associated with an increased number of sexual partners.⁵ HPV infection can spread through sexual contact occurring through mucosa-to-mucosa contact (vaginal, anal, penile, and oral). Oral sex and deep kissing have been linked to oropharyngeal infection.⁸ Having 1 HPV-associated cancer indicates an increased risk of HPV-OPC. High-risk types can lead to chronic infection, abnormal cell development, and progression to cancer. High-risk HPV makes 2 proteins, E6 and E7, that inactivate tumor-suppressor proteins p53 and retinoblastoma protein, normally controlling cell proliferation. This uncontrolled cell growth leads to cancer.⁹

SCREENING

There is no known screening test for oropharyngeal cancers or identifying oral HPV infections. Specifically, there is no established serum, saliva, or cytology test, but it remains a research topic.⁵ HPV-OPCs typically begin in the base of the tongue or tonsil and, therefore, are not visible. The oropharynx includes the base of the tongue, pharyngeal tonsils, tonsillar pillars, glossotonsillar sulci, anterior soft palate, uvula, and pharyngeal walls. It often presents with a neck mass (Figure).

HPV-OPC CHARACTERISTICS

At diagnosis, HPV-OPCs tend to be locoregional, where metastasis outside the head and neck is uncommon. Patients usually have small primary masses but large bulky neck nodes. HPV-positive patients often have fewer medical comorbidities because they are usually younger and non-smokers. Second primary cancers are less likely in HPV-positive patients because of lower tobacco/alcohol risks associated with other cancers.³

DISTINGUISHING HNC TYPE

A new understanding of oropharyngeal biology changes our approach to treatments. There are 2 distinct diseases: tobacco/alcohol-associated HNC and HPV-OPC. Since the early 1990s, tobacco/alcohol-associated HNC (HPV-negative) incidence has decreased, attributed to the declining use of tobacco. Concurrently, HPV infections have increased HPV-OPCs (HPV-positive). The RTOG 9003 study showed, regardless of HPV-status (N=165),

smoking was associated with decreased overall survival (OS) and progression-free survival.¹⁰ The lowest risk and best prognosis were noted in HPV-positive patients with no smoking history (93% 3-year OS); those HPV-positive with >10-year smoking history were deemed an intermediate risk (70.8% 3-year OS); and those HPV-negative with >10-year smoking history were considered highest risk (46.2% 3-year OS).¹⁰

HPV-OPCs are highly treatment responsive and very radiation sensitive. HPV-OPCs have a better prognosis than HPV-negative HNC, but this depends on early diagnosis and location.¹¹ Cure rates of 80% to 90% are noted in HPV-positive versus 50% to 60% in HPV-negative patients.¹¹ Early detection and prevention are very important. The initial work-up of a HNC would include the necessary components listed in Table 1, but may also include some of the additional evaluations 'as indicated.'

STAGING

TNM staging considers primary tumor size and site (T), lymph node involvement (N), and metastasis (M). TNM stage determines treatment recommendations. In 2016, (implementation 1/2018) the American Joint Committee on Cancer (AJCC) 8th Edition Cancer Staging Manual created a separate staging algorithm for HR-HPV-OPC (high-risk HPV), distinguishing it from tobacco/alcohol-associated OPCs. There are separate chapters for HR-HPV-OPC and non-HPV-OPC. Pertinent to HR-HPV-OPC, the 8th edition has 2 separate staging systems: cTNM for clinically staged and pTNM

Table 1. Oropharyngeal Cancer Work-up (Varies Depending on Head and Neck Sub-type)

Necessary components	Additional 'as indicated' components
History, physical, complete head and neck exam	Mirror and fiber optic exam
Dental evaluation	Panorex
CT and/or MRI of primary site and CT neck, with contrast	CT chest with or without contrast FDG-PET for Stage III–IV disease
Pre-anesthesia studies	Endoscopy with anesthesia
Multidisciplinary consultation as clinically indicated	Nutrition, speech, swallowing evaluations/therapy, and audiogram
Primary-site biopsy or fine-needle aspiration with HPV testing.	

Abbreviations: CT, computerized tomography; MRI, magnetic resonance imaging; FDG-PET, fluorodeoxyglucose-positron emission tomography.

Data from the National Comprehensive Cancer Network.¹²

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