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# Oral Cancer and HPV Connection: A Review

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HPV is the leading cause of oropharyngeal cancers and a few oral cavity cancers with increasing mortality across the globe. The risk factors for oral cancer are well known. Factors like tobacco chewing, smoking, alcohol consumption and actinic radiation have been extensively studied and clinically validated. However, Recently HPV has been shown to be a significant risk factor for oral and oropharyngeal cancers. The HPV family contains around 200 strains but it is important to note that only nine out of them are high risk and associated with cancers. Amongst them HPV16 is most strongly related with oral cancer. HPV associated cancers are different from cancers originating from other etiologies and thus, require a novel multidisciplinary treatment approach. The article is a review of Molecular Biology, Risk Factors, Clinical aspects, Diagnosis, and Treatment of HPV associated Oral cancer.

**KEYWORDS:** Human Papilloma Virus, HPV16, Oral cancer, Oropharyngeal Cancer

## INTRODUCTION

Cancer is an unrestricted growth of cells, which march into other tissues and cause destruction. Every hour, a person dies of oral cancer in the United States<sup>1</sup> and approximately 14 deaths per hour are reported in India.<sup>2</sup>

Various risk factors for oral cancer are well known. Factors like tobacco chewing, smoking, alcohol consumption and actinic radiation have been extensively studied and clinically validated. However, with growing awareness, these traditional factors are declining. Sadly, this does not taper off the incidence of oral cancer, which has led to emergence of new risk factors, one of them being Human Papilloma Virus.<sup>3</sup>

In addition to its role in carcinogenesis in cervical cancer, HPV has been shown to be a significant risk factor for oral and oropharyngeal cancers.

## KNOW THE MOLECULAR BIOLOGY

The human papilloma virus (HPV) belongs to the family of double-stranded DNA viruses. It infects the epithelial cells of skin and mucosa. The HPV family contains around 200 strains but it is important to note that only nine out of them are high risk and associated with cancers. Amongst them HPV16 is the most strongly related. A recent

NHANES study suggests, roughly 2.1 million Americans on a given day have an oral HPV16 infection.<sup>4</sup>

HPV being epitheliotropic in nature infects basal layer of the squamous epithelium. It integrates with the DNA of the host cell, thereby dysregulating the expression of oncoproteins E6 and E7. This results in the functional inactivation of human tumor-suppressor proteins p16, p53 and pRb, which culminates to cell immortalization. However, it has been documented that the development of cancer in HPV infected cell may take over 10 years and essentially requires multiple additive crucial epigenetic alterations.<sup>5</sup>

## HPV AND ORAL CANCER

HPV is the leading cause of oropharyngeal cancers and a few of oral cavity cancers, particularly occurring at the base of tongue and the tonsillar region. Albeit it affects both males and females but middle-aged males (30-55 yrs) are 4 times more susceptible. In contrast with HPV negative oral cancers, HPV positive cancers occurs in healthy, non-smokers and non-drinkers.

## Risk Factors

Increased number of sexual partners predisposes

to the risk of being infected with HPV.

HIV infected patients and those with immunosuppressant drug therapy are more vulnerable for HPV infection.

### Clinical aspects

Besides the conventional signs and symptoms of oral cancer, HPV associated cancers differ in the following facets:

- Some authors have demonstrated a high prevalence of HPV in erosive and atrophic lesions.
- HPV associated cancers are more likely to present with an early stage (T1/T2) tumor, which can be comparatively smaller.
- There is a more advanced nodal involvement (N2/N3) and the appearance of affected lymph nodes is often cystic.
- These are more aggressive in nature.
- HPV associated cancers are less likely to have a second malignancy.

### DIAGNOSIS

OSCC cannot be diagnosed radiographically, so histopathological methods and serological tests are used. Histologically, its presence denotes a subset of basaloid squamous carcinoma with a more indolent behavior.

There are various serological tests for detection of HPV, but they differ in their analytical sensitivity. Immunohistochemistry for p16 (a tumor suppressor protein overexpressed in HPV associated cancers) is said to be highly sensitive for HPV and can be used routinely as a surrogate for HPV status. Confirmation is done using standard methods based on PCR assays, in-situ Hybridization, and Southern Blot Hybridization for detection of HPV DNA.<sup>6</sup>

### STAGING

The emerging evidences suggest that the contemporary TNM staging for oral cancer designed empirically for non-HPV associated oral cancer seems unsuited for HPV-related OSCC. The basis of which is suggested to be the improved prognosis of HPV associated OSCC, despite presenting at advanced stages.

Provisionally, an alternative staging system for HPV-related OSCC has been developed by the

International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S).<sup>7</sup>

### TREATMENT

Treatment of oral cancers require a multidisciplinary approach. The therapeutic treatment modalities are generally surgery and radiation with or without concomitant chemotherapy.

Although, the treatment for HPV associated oral cancers is currently the same as for those with HPV negative cancers, literature suggests that there is an increased sensitivity of HPV positive oral cancers to chemo-radiotherapy as compared to their negative counterparts. HPV positive oral cancers thus have a better prognosis and survival rate as compared to HPV negative ones.<sup>8</sup>

We can conclude that knowledge of HPV status of an oral cancer patient is vital and imperative as it can both guide and predict the outcome of therapy.

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