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Perspective

HPV-mediated oropharyngeal carcinogenesis: An overview

Oropharyngeal squamous cell carcinoma (OPSCC) has been shown to exhibit a strong association with human papillomavirus (HPV)[1]. The association has so far been inferred to be of a causal nature. Studies have found significant differences between HPV-associated OPSCC and OPSCC due to other causes including tobacco and alcohol[2]. Thus, studies have focussed on delineating the clinicopathological characteristics of OPSCC with and without the HPV association. The presence of HPV is confirmed by the identification of the viral genetic materials in the clinical samples by PCR. Given the cost of PCR, several researchers have assessed the use of p16, a more economical surrogate marker for HPV. In this context, immunohistochemistry (IHC) is typically employed to assess the expression of p16[3]. The use of IHC allows for inclusion of a larger sample size. One such study with a considerable sample size assessed the IHC expression of p16INK4a in OPSCC cases from a tertiary cancer centre in South India[4]. Only a minor proportion (12 cases) of the total sample (143 cases) were p16 positive. There was no significant difference in the histological type (keratinizing/non-keratinizing) of the OPSCC nor the overall survival time. Thus, the authors concluded that there was no difference in the clinicopathological characteristics based on the presence or absence of p16 expression (for HPV). Despite the lack of statistical significance, the p16-positive cases did have predilections, such as the site of occurrence (base of the tongue) and early presentation at a younger age group. Furthermore, although not significant, the keratinizing type was relatively more common among the HPV (p16 expressing) OPSCC.

Similar studies have been published over the past few decades using several diagnostic modalities and targets[5,6]. The major limitation observed in such studies was the presence of confounding factors. Most studies included OPSCC cases with a known risk factor (*eg.* tobacco/alcohol); thus, it was not possible to assess HPV as an independent risk factor. Furthermore, such studies often did not distinguish the OPSCC based on anatomic locations. This lack of subdivision based on the location was a major limitation as not all oropharyngeal cancers have a strong association with HPV. Unlike pharyngeal OSCC, cancer of the oral cavity has a tentative association with HPV[5,6]. There is contradicting evidence that has prevented the confirmation of the nature of this association between HPV and oral cancer. Thus, combining cancer under a broad term such as 'oropharyngeal' could be misleading. In such cases, it is vital to perform a subgroup analysis based on the anatomical location.

Another major factor to consider is that not all in HPV-mediated carcinogenesis would have a p16 overexpression. The pRb destabilization by the viral E-7 oncoprotein results in the bypass of the Rb-dependent cell cycle arrest represented as p16 overexpression. It is possible that instead of E7-mediated pathway, the carcinogenesis is through the viral E-6 oncoprotein, in which cases, p53 is suppressed, inducing FoxM1B and dysregulating the cell cycle[3]. For comprehensive evidence of an HPV-mediated oral/pharyngeal carcinogenesis, the following guidelines could be helpful: (*i*) either include cases only from the oral cavity or pharyngeal location or perform subgroup analysis based on anatomical locations; (*ii*) identify the presence of the virus by detecting its genetic material from the cancerous tissue using PCR; (*iii*) the sample collected for assessing the HPV presence must be an incisional/excisional biopsy specimen of cancer. It cannot be the salivary sample or a cytology specimen; and (*iv*) once the presence of the virus is confirmed, assess if the cancer is associated with HPV through immunohistochemical staining for p16 and p53. A p16 overexpression and/or p53 suppression would indicate a potential HPV-mediated carcinogenesis.

***Conflicts of Interest*:** None.

Shankargouda Patil†
College of Dental Medicine, Roseman University of Health Sciences, South Jordan, UT 84095, USA
dr.ravipatil@gmail.com

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