

# Oropharyngeal carcinoma: what the dentist should know

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## SUMMARY

HPV-related oropharyngeal carcinoma (OPC) is a clinically and molecularly distinct form of squamous cell carcinoma (SCC) which has recently shown a dramatic increase in global incidence. The aetiology, clinical presentation and overall prognosis differ from conventional tobacco and alcohol related SCC of the oral cavity. OPC is seen in a subset of younger predominantly male patients. Acquisition of high-risk HPV subtypes is related to oral sex practices with multiple partners. OPC originates deep within tonsillar crypts which hinders early clinical detection. Patients present with advanced disease and frequent cervical lymph node metastases. Despite its aggressive nature, the overall prognosis remains excellent compared with conventional oral SCC. The increased incidence of OPC is of clinical significance to the general dentist and should always be considered in the clinical differential diagnosis in a young, otherwise healthy, patient with persistent cervical lymph node enlargement. Older patients with a history of tobacco usage and alcohol consumption may also present with conventional SCC of the oropharynx. Potentially malignant disease may precede tumour development at this site in such cases. Clinical examination of the oropharynx should therefore be performed as part of routine dental consultation.

## INTRODUCTION

The oropharynx comprises the soft palate, including the uvula, base of tongue, palatine tonsillar area and the posterior pharyngeal wall (Figure 1). The true incidence of oropharyngeal cancer (OPC) is difficult to determine as data from this site is frequently intermingled with that of oral cancer due to the close anatomical relationship.<sup>1</sup> For the purpose of this article, OPC is defined as squamous cell carcinoma of the oropharynx. An increase in the incidence rates of OPC has recently been reported from several countries, irrespec-

## ACRONYM

<b>E:</b>	Early genes, as in E6, E7 etc
<b>HPV:</b>	Human Papillomavirus
<b>OPC:</b>	Oropharyngeal Carcinoma
<b>SCC:</b>	Squamous Cell Carcinoma

tive of their economic status. It is noticeable that this increase was seen in persons not associated with known risk factors such as tobacco and alcohol consumption.<sup>2</sup> It was furthermore noted that the patient profile of OPC changed from a disease of the elderly to one affecting younger people.<sup>3</sup> This has prompted several groups to suggest a different aetiological factor for OPC in this specific group.<sup>4,5</sup>

It is accepted that OPC consists of two separate diseases; one type that is associated with the classical risk factors of tobacco and alcohol usage and the other linked to human papillomavirus (HPV) infection. The emergence of HPV-associated OPC is responsible for the increase in OPC and the observed changing patient profile. Patients with HPV-associated OPC tend to be younger, more frequently male and often have no other identifiable risk factors.<sup>6</sup> It should be stressed that HPV associated OPC can, of course, also occur in patients who are tobacco and alcohol users.<sup>7</sup>

## HPV

HPV is a small DNA virus of which more than 200 subtypes have been identified. HPV infection is the most common sexually transmitted infection globally. The link between HPV and carcinogenesis was first established by Zur Hausen in 1977,<sup>8</sup> for which he subsequently received the Nobel Prize in 2008. HPVs have an affinity for epithelial tissue and are classified into high- and low-risk types based on the potential to induce an epithelial malignancy. The high-risk types include HPV-16, -18, -31, -33 and -45 with HPV-16 and -18 linked to the majority of cervical cancers.<sup>9</sup> The vast majority of HPV-associated OPC are caused by HPV-16.<sup>10</sup> Low-risk types are linked to benign lesions such as warts and papillomas.

The HPV genome has a number of genes that are important for maintaining the life cycle of the virus. The most significant as far as carcinogenesis is concerned are the early (E) genes and their coded proteins of which E6 and E7 are the most important. The E6 protein binds and degrades the p53 protein, a product from the TP53 tumour suppres-

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**Figure 1:** Anatomical area of the oropharynx.

tor gene. This gene is regarded as the guardian of the genome. It functions by controlling DNA repair during cell division by inducing programmed cell death if the repair process is unsuccessful.<sup>11</sup> The E7 protein from high-risk HPV types inactivates the retinoblastoma protein (pRb), a product of the retinoblastoma suppressor gene that prevents division of cells with damaged DNA.<sup>12</sup> Infected cells show up-regulated p16 expression due to a failure of cell cycle control through a loss of pRb. p16 is a cyclin-dependent kinase inhibitor which attempts to restore cell cycle control.<sup>13</sup> The inactivation of p53 protein and pRb of host cells infected by high-risk HPVs allows for uncontrolled cell division, even when genomic mutations are present that may eventually lead to cancer development. Low-risk HPVs also express E6 and E7 proteins that bind with p53 and pRb, however, the lower bonding affinity prevents destruction of these proteins.<sup>14,15</sup>

## HPV-ASSOCIATED OPC

A retrospective study on the incidence and involvement of HPV in tonsillar carcinoma in Sweden showed an increase of 2.8% from 1970 to 2002, while the HPV-positive tumours gradually increased from 23% in the 1970s to 68% in the 2000s.<sup>16</sup> Similar results were reported from a retrospective US study on OPC that found the proportion of HPV-positive OPC changed from 35% in the period 1956 to 1969 compared with 72% between 2007 and 2009.<sup>17</sup>

A population-based study in the US has determined the oral prevalence of HPV to be 6.9% with a prevalence of 3.7% for high-risk types while the prevalence for HPV-16 was only 1%.<sup>18</sup> The oral HPV prevalence is furthermore three to four times higher in patients with HIV/AIDS.<sup>19</sup> Oral HPV infection is more common in women with cervical HPV infection but there is no evidence to support auto-inoculation between different anatomical sites.<sup>20</sup> Oral HPV infection is sexually transmitted and linked to the lifetime and recent number of oral and vaginal sex partners.<sup>18</sup> There also appears to be a bimodal age pattern of oral HPV prevalence with peaks at 30-34 years and 60-64 years of age.<sup>18</sup>

The majority of HPV associated OPCs develop in the lingual and palatine tonsillar area, especially from crypt lining epithelium. It is still uncertain why the tonsillar crypt lining epithelium is targeted by HPVs. These tumours have a prominently endophytic growth pattern and are furthermore characterised by presentation at an advanced clinical stage. Cervical lymph node metastases are typical at the time of presentation de-

spite the small size of the primary tumour. The nodal metastases are often cystic in nature due to central necrosis resulting from rapid tumour growth. The presence of neck metastases is frequently the only sign at presentation and it may be difficult to find the primary tumour in an oropharyngeal site. Tobacco associated tonsillar tumours on the other hand typically arise from the surface epithelium and exhibit a more exophytic growth pattern.<sup>21</sup> The presence of HPV in a subset of OPCs should not be extrapolated to the oral cavity. There is good evidence that HPV is of limited importance in oral carcinogenesis.<sup>22,23</sup>

HPV-associated OPC typically presents with a lobular growth pattern on histological evaluation while the tumour cells have a basaloid appearance with very little or no keratin formation. Dysplasia is seldom detected within the overlying epithelium. These histological features, when present, are highly suggestive of an HPV-related aetiology, however, they are not pathognomonic of HPV involvement and may be encountered in tobacco-associated OPC.

The gold standard to determine HPV involvement remains the demonstration of HPV DNA integration into the host genome through *in situ* hybridisation. This technique is time consuming, expensive and is not available in all diagnostic histopathology laboratories. Immunohistochemical (IHC) demonstration of p16 protein, upregulated due to pRb loss, is often used as a surrogate marker for HPV positivity. This technique is sensitive but not very specific and will only be positive in about 80% of HPV associated OPC.<sup>24</sup> The p16 gene is frequently mutated in tobacco-associated carcinogenesis resulting in negative p16 IHC findings in these tumours.

HPV positive OPC patients have a significantly better outcome compared with HPV negative OPC patients. A meta-analysis demonstrated a 28% reduced risk of death and a 49% reduction in tumour recurrence in HPV positive OPC patients compared with HPV negative patients.<sup>25</sup> The precise mechanism of this favourable prognosis of HPV positive patients is unclear but it is postulated to be linked to the absence of field carcinogenesis and the relatively low rate of genetic mutations compared with HPV negative OPC patients.<sup>26</sup> The interaction between smoking and HPV status has also been investigated. The overall survival of HPV positive OPC patients who are non-smokers is excellent compared with HPV negative smokers (95% vs. 63%). The survival of HPV positive smokers is similar to HPV negative non-smokers (71% - 80%).<sup>27</sup>

Early detection of HPV-associated OPC appears to be problematic. The absence of dysplasia in the overlying epithelium as well as the difficulty in clinically assessing the deep tonsillar crypt epithelium is responsible for the absence of detectable pre-cancerous lesions in patients at risk. There is thus limited success for prevention through primary screening.<sup>28</sup> This highlights the potential use of HPV vaccines as a primary prevention mechanism. The US Centre for Disease Control and Prevention has recently recommended the use of routine vaccination of boys and men aged 9-21 years.<sup>29</sup>

## CONCLUSION

HPV-associated OPC differs from HPV-negative OPC and is on the increase. Unfortunately, there is currently no efficient strategy for the early detection of these premalignant lesions which could lead to the prevention of the tumours. Patients presenting with a neck mass without any detectable intraoral tumour or predisposing factors should be carefully examined for the presence of a small primary tumour. HPV-negative OPC, by contrast, is frequently associated with mucosal changes which precede the development of cancer which implies that clinical examination of the oropharynx should be included as part of the routine soft tissue examination performed in dental practice.

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