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Review article

Oropharyngeal Squamous Cell Carcinoma: Prevalence and Pathogenesis

Khaled Ben Salah*

Department of Pathology, National Cancer Institute (NCI), Misrata, Libya.
***Correspondence**: k.bensalah@nci.edu.ly

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Abstract

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) increases relative to the decrease in the prevalence of squamous cell carcinoma (SCC) in other head and neck locations, given the decreased occurrence of key risk factors for head and neck squamous cell carcinoma (HNSCC) such as tobacco and alcohol usage. Human papilloma virus (HPV) infection is widely recognized as a key participant in the onset of HPV-positive (HPV+) OPSCC with a distinct epidemiological, clinical, physiological, radiological, behavioral, biological and prognostic properties from HPV-negative (HPV-) OPSCC. Currently, the oropharynx is the only anatomic subsite with a reported causative viral connection in the head and neck. These observations led to the creation of a new staging system more suitable for this distinct entity and changes in therapy paradigms.

Keywords: *Oropharyngeal Cancer, Squamous Cell Carcinoma, Prevalence, Treatment.*

Introduction

Squamous cell carcinoma of head and neck (HNSCC) is a heterogeneous group of malignancies originating from different anatomic subsites such as the oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx. They are together categorized as the 6th most prevalent malignancy across the world, with 932,000 new cases and 379,000 deaths in 2015 [1,2].

Notable epidemiological trends have been remarked in HNSCC over the past forty years, with the overall occurrence of HNSCC reducing slightly but a substantial shift seen in the relative involvement of each subsite to the overall prevalence of HNSCC [2,3]. Tumours originating from subsites, rather than the oropharynx (oral cavity, hypopharynx and larynx) have seen a drop in rates of incidence when compared with the incidence of oropharyngeal squamous cell carcinoma (OPSCC), which has progressively increased [2,4,5]. Effective public health efforts in the developed world are generally credited with reductions in tobacco and alcohol consumption at population level and simultaneous drops in tumours due to tobacco consumption as for instance non-oropharyngeal HNSCC and lung cancer [2,6,7]. However, tendencies to sexual attitudes that increase the risk of picking up sexually transmitted pathogens, like Human papilloma virus (HPV), have been connected with the increase in HPV positive (HPV+) cancers such as OPSCC and anal cancers [7,8]. Currently, HPV+ OPSCC cases are exceeding the incidence of HPV+ cervical cancer [4,9] and this is may be because at present, there is no sign of prevention of HPV+ OPSCC, since research assessing the effect of vaccines on the development of oropharyngeal squamous cell carcinoma have not been shown. Nowadays, no screening exam exists for the oropharynx, comparable to the cervical clinical examination and Pap smear, though it is supposed that OPSCC also originates from a dysplastic lesion (not established) [10-24].

Oropharyngeal squamous cell carcinoma (OPSCC)

Epidemiology and clinical presentation of HPV+ and HPV- OPSCC

Incidence of HPV+ OPSCC is significantly increased. The annual percentage rate keeps increasing, seen in, for example, the United States (5% annual percentage rate expansion in the frequency of oropharyngeal cancers) and Finland (6% increase) [21-25]. Chaturvedi et al. expected that by 2030, 50% of all cancers in the head and neck region will be linked to human papillomavirus [4,5]. The presence of a strong predilection of HPV+ HNSCC for the oropharynx has been documented by several researches [26-28]. The HPV+ OPSCC are

acknowledged as a distinct neoplastic entity, characterised by unique epidemiological, histopathological, molecular, and clinical features [2,29,30].

The representative patients with HPV+ OPSCC are middle aged (present at a younger age in comparison with their counterparts of head and neck cancer, they are more often younger than 60 years), white, have a high socioeconomic position, often lack a significant history of smoking and drinking, have a history of multiple sexual partners (more than 8–10) and most likely to have greater than four oral sex experience with different partners [31-35]. It is less likely that patients with HPV+ OPSCC will consume alcohol in comparison with HPV- OPSCC patients, or those with other types of HNSCC [30]. HPV is considered to be the most frequent infection among the infections transmitted sexually in the United States, and the main source of infection of HNSCC [36,37]. Despite the spread of HPV infection being prevalent, this high-risk virus is cleared by most people within around eighteen months [2,38], and it is thought that persistent infection is indispensable for the establishment of HPV+ cancers [2].

Most HPV+ OPSCC patients present with, more likely, small primary tumors associated with advanced nodal disease [39]. These small primary oropharyngeal tumors are likely to be asymptomatic and a large proportion of patients request medical care by reason of symptoms related to nodal disease [40]. HPV+ OPSCC manifests obvious sensitivity to therapy, including first line surgery, and a considerably better prognosis and survival is seen than in those patients with HPV- OPSCC, in spite of their presentation with advanced nodal disease [29,39,41,42]. This survival improvement has led to intense enhancements in the 5-year survival rates for OPSCC, and despite the fact that overall recurrence rates are less for patients with HPV+ OPSCC (when compared with patients with HPV- OPSCC), the former presented a greater proportion of their recurrences at distant sites. These disseminated metastases are most likely to grow in unconventional locations (that is, other than in the lungs) [43-45]. Distant metastases, associated with HPV+ OPSCC, may also occur more than 24 months following initial treatment, contrary to distant metastases in patients with HPV- OPSCC, which characteristically develop within 24 months. Nevertheless, patients with HPV+ OPSCC that present metastases, again have a better treatment outcome in comparison with HPV- head and neck metastatic cancers [43,45]. Second primaries are less likely to occur in HPV+ OPSCC cases when compared with their counterparts of HPV- OPSCC [46,47].

Several explanations can be used to help clarify the reason behind the improvement in survival of HPV+ OPSCC.

They could involve causes related to the epidemiology of this disease; for instance, decreased consumption of chemical carcinogenic agents such as alcohol and tobacco, indicating the presence of an improvement in the medical status for the category of patients where HPV is regarded as a contributory cause for establishment of cancer [48]. Also, it has been proposed that the absence of mutations of p53 observed in cancers that show expression of HPV E6 such as HPV+ OPSCC could be an important cause behind the better responses to radiation treatment [48]. An additional potential interpretation is related to histopathological features that may include the more proliferative, non-keratinizing and less differentiated features of HPV+ OPSCCs that might render them more vulnerable to radiation treatment [48-53].

It is obvious that the HPV+ OPSCC has distinct molecular, epidemiological and clinical features, regarded as a reflection for unique underlying biology [54]. These observations resulted in the creation of a new staging system more appropriate to this distinct entity [55] and changes in therapy paradigms [2], [56]. HPV 16 is the main cause for more than ninety percent of HPV+ OPSCC cases, while small number of OPSCC can be ascribed to the other HPV types [57]. At present, there is no sign of prevention of HPV+ OPSCC, since research assessing the effect of vaccines on the development of oropharyngeal squamous cell carcinoma have not been shown. It has been revealed by Herrero and his group that vaccination against HR HPV reduces the incidence of oral infection in the cases that received the vaccine, with 93.3% (95% CI = 62.5% to 99.7%) as an estimation for the efficiency of the vaccination [10]. Currently, no screening exam for the oropharynx, comparable to the cervical clinical examination and Pap smear, exists though it is supposed that OPSCC also originates from a dysplastic lesion (not established).

Histopathology of OPSCC

HPV+ OPSCCs are regarded as originating from the tonsillar crypt's epithelium [27]. The tonsillar crypts likely trap infectious agents simply via lowering mechanical clearance [58]. This could explain why the oropharynx has higher levels of HPV+ cancer compared with the oral cavity (Fig. 1 A and B).

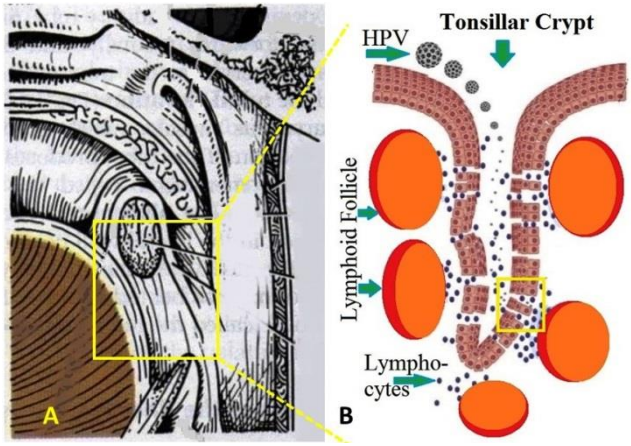

Figure 1 A and B. *Tumor progression in HPV+ OPSCC. A. The presence of a strong predilection of HPV+ HNSCC for the oropharynx, comprising lingual tonsils, the palatine tonsils and base of the tongue. B. In tonsillar crypt, HPV obtains entrance to keratinocytes in the basal layer passing through breaches in the reticulated epithelium. Adapted from Faraji, F., et al [2].*

Areas of transition between tumor and normal epithelium are regarded as less frequent than in HPV- OPSCCs [27]. The latter occasionally may show histological progression from dysplasia into an invasive growth via carcinoma in situ [27]. However, molecular investigations of HPV+ OPSCC suggest progressive genetic alterations of the infected tonsillar epithelium, which influence aberrant basal cell differentiation, dysplasia, carcinoma in situ and, eventually, invasive carcinoma (Figure 2 A, B, C, D and E) [2].
The invasive component of HPV+ OPSCCs is in the form of sheets, lobules or ribbons of malignant keratinocytes [27]. Central necrosis or cystic degeneration and tumor infiltrating lymphocytes (TILS) can be seen [27]. In contrast to OSCC, desmoplasia is often inconspicuous [27]. Cytologically, the HPV+ OPSCC tumor cells often show a basaloid phenotype with a high nuclear-to-cytoplasmic ratio; there are syncytial appearances, whereas intercellular bridges and keratin pearls / keratinisation of single cells are often lacking [27]. It is controversial whether this morphology simply reflects the origin from the tonsillar crypts or in HPV related phenomenon [27].

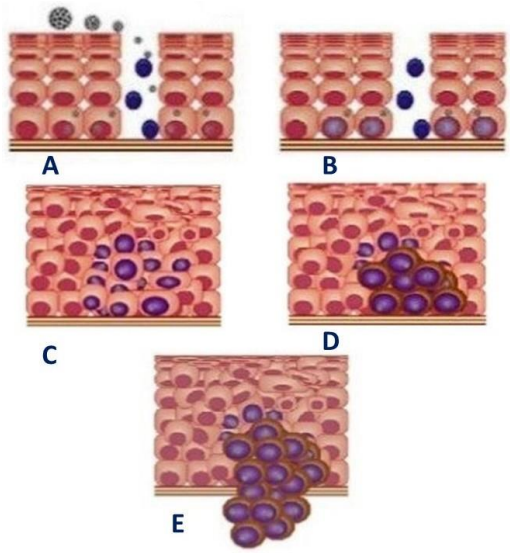

Figure 2. *Peculiar differentiation of basal cells of the tonsillar epithelium as a result of: A. infection of tonsillar Crypt followed by B. Aberrant basal stem cell differentiation. C. dysplasia. D. carcinoma in situ. E. invasive carcinoma. Adapted from Faraji, F., et al [2].*

As in other forms of squamous cancers, the earliest sign of invasion in HPV+ OPSCC is expected to be a breach in the continuity of the basal lamina followed by irregular extensions of the transformed epithelial cells into the subepithelial stroma. This qualifies as micro-invasion. Eventually, frank invasion is established and accompanied by desmoplasia,

angiogenesis and inflammatory/immune reaction. Nevertheless, and in contrast with OSCC, the distinction between dysplasia, carcinoma in-situ and micro-invasion is more difficult in HPV+ SCC. Possibly, reflects the poorly defined junction between the reticulated epithelium and the underlying lymphoid tissue, attributable in turn to the incomplete basal lamina and the abundant sub-/-intra-epithelial lymphocytes; the aforementioned inconspicuous desmoplasia adds to the difficulties [27]. Immunohistochemical staining for cytokeratins would allow the difficulties to be overcome, but its routine application is unrealistic. The difficulties may also account for the notion of occult, tonsillar carcinomas, metastasis to cervical lymph nodes being often the first clinical manifestation [27].

The popular belief that HPV+ OPSCCs are poorly or undifferentiated, seems inappropriate in view of their origin from the crypt epithelium. In this vein, they can be regarded as highly differentiated tumours instead [27]. Accordingly, the degree of keratinization which is one of the histopathologic features traditionally considered to influence prognosis of conventional OSCC [59] is of little or no use in OPSCC. Nevertheless, the presence of anaplasia and multiple tumour-cell nuclei in non-keratinizing p16+/small-cell HPV+ OPSCC, has been regarded as influencing prognosis [27,60].

Persistent, integrated HPV infection is essential for the cellular transformation [15]. The particular structure of tonsillar epithelium allows HPV to escape immunological surveillance and effects persistent infection in turn. This is coordinated by E6, and E7 [2]. In addition, the replicating HPV affects the differentiation of keratinocytes in the crypt epithelium [15]. The entrance of the virus into keratinocytes likely depends on receptors present on the surface of the latter; α6β4 integrins may act as such receptors [15]. Recent investigations on the interaction between HPV and receptors on the surface of basal and supra-basal keratinocytes also suggest that the binding process involves a single or group of receptors; the initial process is centred on single receptor, whereas its completion depends on different receptors. Accordingly, entrance of HPV to keratinocyte may start with α6β4 integrin and completed by surface heparin sulphate proteoglycans (HSPGs), such as syndecan-1 [15]. The virus preferentially enters basal keratinocytes; this is supported by investigations on HPV-associated carcinomas of the cervix [58].

The pathology of nodal metastases in HPV+ OPSCC, is characterised by cystic degeneration of the tumour deposit. It is a common finding and its recognition via the MRI pre-operative of a neck swelling is an indicator of an occult HPV+ OPSCC [27].

Prognostic features

Being the oropharyngeal carcinoma infected with HPV is a good prognostic feature. The improved prognosis associated with positive HPV status steadily trumps conventional prognostic features based on morphology of the tumour, including tumour grade and histologic subtype [27]. Further, the presence of anaplasia, as well as cell multinucleation in the tumour, are predictors for poor outcomes in patients diagnosed with non-keratinising p16 positive OPSCC [27]. However, the HPV positivity is superseded if the tumour presents the phenotype of the small cell variant, which is an unfavourable prognostic feature [27].

Conclusion

Compared with other head and neck cancers worldwide, especially in Western countries, cases of oropharynx squamous cell carcinomas have progressively increased over the last 20 years. HPV is considered to be the most frequent infection among the infections transmitted sexually in the United States, and the main source of infection of HNSCC. Despite the spread of HPV infection being prevalent, this high-risk virus is cleared by most people within around eighteen months and it is thought that persistent infection is indispensable for the establishment of HPV+ cancers. It is obvious that the HPV+ OPSCC has distinct molecular, epidemiological and clinical features, regarded as a reflection for unique underlying biology. These observations resulted in the creation of a new staging system more appropriate to this distinct entity and changes in therapy paradigms. HPV 16 is the main cause for more than ninety percent of HPV+ OPSCC cases. In comparison to cervical cancer, HPV+ OPSCC pathologically originates from the tonsillar crypts, characterized by its potency to metastasize and this is attributable to the breached basement membrane of the crypt epithelium or may be due to the intraepithelial vessels that are present in this category of cancer. Yet, we must always stress that prevention is the best cure against cancer, especially in those malignancies where the main pathogenic agent is known.

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