Chapter 11

Human Papillomavirus in Head and Neck Cancer

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Abstract

Throughout the last three decades, there has been a notable shift in the epidemiology of head and neck cancer (HNC) worldwide. A rapidly spreading subtype of HNCs is caused by human papillomavirus (HPV) infection. HPV-related cancers are now considered to constitute 30–65% of all HNC cases and 50–80% of oropharyngeal cancers. HPV-positive oropharyngeal cancers have a unique demographic profile and tumor biology characteristics. HPV-associated patients predominantly consist of younger men with better performance status and fewer comorbid diseases. They have better dentition, higher numbers of oral sex partners, and use less amount of tobacco or alcohol, higher amount of marijuana compared with HPV-negative patients. In addition, patients with HPV-positive tumors have a 60–80% reduced mortality rates, a finding that was confirmed by multiple trials and led to several ongoing deintensification studies. This chapter describes epidemiologic features of HPV-positive HNC, risk factors for HPV infection and HPV-associated oropharyngeal cancer, HPV detection methods, mechanisms of carcinogenesis and improved treatment response, and the impact of HPV status on clinical outcome as well as deintensification approaches and potential of vaccination.

Keywords: head and neck cancer, human papillomavirus, epidemiology, carcinogenesis, treatment

1. Introduction

Head and neck cancer (HNC) involves a wide field of tumors that originate from the skull base to the clavicles including the orbits, paranasal sinuses, nasopharynx, oropharynx, hypopharynx, oral cavity, and larynx. Worldwide, the incidence of HNC accounts for more than half a million each year, 5% of all cancer cases, with being the fifth most common cancer in the world [1, 2]. The distribution of HNC varies around world, such that it is 3–4% of all cancer diagnosed in North America and the Europe, whereas HNC consists of 30% of all cancer cases in

men in India [3]. Yet, around 300,000 people die from HNC that can be seen in the global picture of the disease [4].

The well-known risk factors for HNC comprise tobacco, alcohol, poor oral health, human papillomavirus (HPV) infection (for oropharyngeal cancer), and Epstein-Barr virus (EBV) infection (for nasopharyngeal carcinoma) [5, 6]. Traditionally, HNC was related to tobacco use and alcohol exposure, and the synergistic increased risk with the combination of them [7]. HNCs are most common among 50–60 year-old individuals who are heavy smokers and alcohol users with lower socioeconomic status [8]. Additionally, the squamous cell carcinoma constitutes more than 90% of histological subtype of HNC [1].

2. Epidemiology

2.1. Changing trends in epidemiology of HPV-associated HNCs

Throughout the last three decades, there has been a notable shift in the epidemiology of HNC worldwide. The decrease in tobacco consumption has resulted in an entire reduction in the incidence of HNC during the past 30 years [9]. Since smoking maintains as the primary risk factor for the oral cavity, larynx, and hypopharynx, this declining trend is marked for these sites. However, up to 25% of all HNCs recently diagnosed are not related to tobacco use. A rapidly spreading subtype of HNCs is caused by HPV infection [10].

First suggested in 1983 by Syrjanen, HPV was reported as an initiative factor of HNC owing to its oncogenic potential, the parallel clinical characteristics in oral and genital damages, epithelia similarities, and HPV affinity for epithelial cells [11]. The evidence for a significant correlation was insufficient, until recently. In the 2000s, several reports, mainly from Sweden, established that a remarkable ratio of tonsillar cancers included HPV DNA. The increases by 2.8- and 2.9-fold were detected in the incidence of tonsillar cancer and ratio (23–68%) of HPV-positive tonsillar cancer between 1970 and 2002, in Sweden, in 2006 [12]. Immediately after this, in 2007, an arising HPV epidemic correlating with oropharyngeal SCC was reported in the United States [13]. The striking increases up to sevenfold in both HPV-positive tonsillar and base of tongue were demonstrated during the periods of 1970–2007 and 1998–2006 in 2009 and 2010 from Sweden, respectively [14, 15]. Following Dalianis group definition of "epidemic of viral-induced carcinoma," due to observation that most of the tonsillar carcinomas were HPV-associated in 2009 [14], a retrospective analysis of clinical trial material detected that HPV-related oropharyngeal cancer rate was 64% in the USA [16]. Similar retrospective analyses on oropharyngeal tumor samples revealed an increase in HPV incidence from 23, 28 to 57% from 1970s, 1980s to 1990s, respectively. Also, a constant trend in the increase was detected for recent term (68, 77, 93% incidence rates during 2000–2002, 2003–2005, 2006–2007, respectively [14]. Similarly, HPV association rate in oropharyngeal cases was increased from 16% to 73%, from 1984–1989 to 2000–2004 in the United States [17]. Furthermore, during the same periods, reports delivering similar striking rises in both oropharyngeal and HPV-positive oropharyngeal cancers have accumulated from several Western countries [3, 12–15, 17–23].

The oropharynx is distinctively sensitive to HPV, and as high as 70% of oropharyngeal cancers in the USA are HPV-related oropharyngeal squamous cell carcinomas [24]. The past 30-year Surveillance, Epidemiology, and End Results (SEER) population-based data were analyzed by Chaturvedi et al, and they evaluated the incidence trends of HPV-related and -unrelated HNC. They demonstrated a significant decline (1.85% annual reduction) in the incidence of HNC in HPV-unrelated fields (hypopharynx, oral cavity, larynx) and a remarkable rise (0.8% annual increase) in the incidence of HNC in HPV-associated oropharyngeal regions during the same period [9]. In addition, the incidence of hypopharyngeal, oral cavity, and laryngeal carcinomas notably reduced due to smoking and alcohol consumption declining in many countries [25]. On the contrary, the oropharyngeal carcinoma incidence has been reported to be increased in many countries including the UK [26], Canada [27], Australia [28], Norway [29], Denmark [30], and the Netherlands [20] over the last two decades, besides Sweden [12] and the USA [9]. HPV-related cancers are now considered to constitute 30–65% of all HNC cases and 50–80% of oropharyngeal cancers [9, 16]. HPV-positive HNC, which has distinctive epidemiologic and prognostic features [5–14] has become an expanding public health issue, is expected to be the main factor for HNC development in the forthcoming period [17].

Currently, the highest HPV-positive HNC incidence rates have been reported in Sweden and the USA. The genital HPV infection prevalence, sexual habits, and smoking and alcohol use may affect the population-specific HPV-positive HNC incidences. The focus of HPV-related malignancies has been shifted from anogenital cancers developing predominantly in women to oropharyngeal cancers developing mainly in men due to the fact that men were reported to have >70% HPV-positive oropharyngeal cancer cases [9, 12, 15, 16, 20–22]. By 2020, the number of HPV-mediated oropharyngeal patients per year is reflected to outnumber HPV-related cervical cancer cases in the USA [17]. The HPV-mediated oropharyngeal cancer has become an epidemic of our era [31].

2.2. HPV positivity in non-oropharyngeal sites of HNC

HPV detection rates were currently reported to be between 12.6% and 90.9% in oropharyngeal carcinoma [32]. One-quarter to one-half of unknown primaries originates from oropharyngeal region [33, 34] and the HPV presence in cervical lymph node metastases is a strong marker of oropharyngeal subsite for unknown primary regions [33, 35]. Although the association between oropharyngeal carcinoma (predominantly soft palate, the tonsils, base of tongue) and HPV is well known, the role of HPV in other head and neck subsites etiology is not well established. The presence of HPV DNA was not demonstrated in laryngeal, nasopharyngeal, hypopharyngeal, and oral cavity cancers in older studies, whereas recently published studies using more advanced methodologies and analyzed HPV gene expression products (e.g., p16) reported that HPV existed in non-oropharyngeal sites in small proportions which explains the increased incidence of oropharyngeal carcinoma compared with other HNCs [1, 36–38].

The prevalence of HPV-mediated HNCs was found as 25.9% in a systematic review of 60 published studies using PCR-based methods while it was higher in oropharyngeal carcinoma (35.6%) than both oral (23.5%) and laryngeal (24.0%) carcinoma. HPV-16 and the second most common high-risk type HPV-18 were detected in 86.7% and only 2.8% of the HPV-positive

oropharyngeal carcinoma [39]. In addition, in a meta-analysis of 39 publications with 3649 HNC patients which investigated HPV in European population, the prevalence of HPV was found to be 40.0%, while it was most dominant in tonsillar cancer (66.4%) and lowest in pharyngeal (15.3%) and tongue (25.7%) cancers [36].

Unlike oropharyngeal cancers, HPV etiologic role in other HNC sites remains unclear. Concerning other head and neck subsites, HPV may play a role in the supraglottic larynx cancer [40], which might constitute the high-risk HPV infection rate established in laryngeal cancer, since its marginal field is adjacent with the oropharynx [28, 29, 41, 42]. Overall, contemporary studies using gold standard methods (type-specific HPV E6/E7 mRNA) from the United States detected the presence of HPV in less than 5% of non-oropharyngeal HNCs [17, 43]. Nevertheless, the estimate for the HPV infection-mediated non-oropharyngeal HNCs varies widely in the literature. While the estimated prevalence of HPV is 24% in the larynx, 31% in the nasopharynx, oral cavity 6–20%, and 21% in the sinonasal tract [44, 45], the studies mainly from the USA based on *in situ* hybridization (ISH) assays and E6/E7 mRNA detection suggest that the HPV association was found in 3% of oral cavity, 7% of larynx, and 0% of hypopharynx cancers [43]. Many factors including the border of anatomic classification of head and neck subsites and HPV detection methods contribute to this instability. The identification of certain markers of HPV-induced carcinogenesis and the correct rule out of the oropharynx as tumor origin site are substantial forthcoming issues in HPV-related non-oropharyngeal HNC estimation [43]. In addition, another topic which remains to be clarified is whether HPV tumor status in non-oropharyngeal sites may be implicated as a strong independent prognostic indicator such as in oropharyngeal cancers [16, 46–48].

2.3. The characteristics of HPV-positive HNC cancer patients

The demographic and risk features of HPV-positive and HPV-negative HNC patients differ remarkably. First, HPV(+) patients are younger than HPV(−) ones [49]. The HPV-related cancers develop in those aged 40–55 [50] who are 4–10 years younger than HPV-negative patients [16, 51]. This age difference might explain the increase in oropharyngeal cancer incidence in younger individuals in developed countries [17, 52]. Given that HPV-associated patients are younger at diagnosis, they have better performance status [16, 47, 50] with fewer comorbid diseases [16, 51, 53].

Second, although HNC is generally more common in men than women, a notably larger rate of HPV-positive oropharyngeal cancer is diagnosed in men than HPV-negative ones [17]. This is convenient with the data that oral HPV16 infection is five times more common in men compared with women in the USA [54].

Third, HPV-HNC has been found to develop more frequently in white than black patients. HPV-positivity rate is 29–34% in whites compared to only 0–4% in blacks [55, 56], while HPV-positive versus -negative rumors occurring in whites are 92–97% and 75–78%, respectively [16, 46, 55]. Thus, in contrast to blacks, the incidence of oropharyngeal cancer has increased in whites which is probably caused by higher HPV-HNC rates in whites compared with blacks in the USA [57]. Furthermore, the socioeconomic status differs in HPV-positive patients from

HPV-negative ones. HPV-positive patients have higher income and are more educated with higher rates of being married [51, 54].

The HPV-positive HNC patients have better dentition, higher numbers of oral sex partners, and use less amount of tobacco or alcohol, higher amount of marijuana compared with HPV-negative patients. In addition, these risk factors have a powerful dose effect, revealing the distinguishing risk profile for HPV-positive patients [17]. Furthermore, these patients without environmental risk factors have persistent infection with high-risk HPVs [17].

3. Risk factors for HPV infection and HPV(+) oropharyngeal cancers

HPV-16 which is detected in about 90% of the HPV(+) oropharyngeal cancers is the most common among several high-risk HPV types. Currently, HPV-16 is the only HPV type which is accepted as cancer inducing in the HNC [58, 59]. In addition, there are other high-risk HPV types with a less significant function and different manner than HPV-16 [37]. Among these, HPV-58, HPV-35, HPV-33, and HPV- 45 were detected in 10–15% of HPV(+) oropharyngeal cancer [38, 60, 61]. At present, HPV 16 constitutes 15- to 230-fold increased risk for oropharyngeal cancer [50, 62]. HPV has been confirmed to induce and promote the development of oropharyngeal cancer [63].

With the identification of HPV as a powerful and independent risk factor for HNC, data are accumulating concerning the oral HPV infection epidemiology. The prevalence of oral HPV infection has been estimated as 7% in population-based studies in the United States and significantly correlated with male gender, older age, current smoking, and various sexual habits (e.g., the number of oral sexual partners during lifetime) [54]. HPV infection which may be contaminated by any type of sexual contact has become the most frequent disease that transmits sexually in the world [64]. The estimated number of individuals who are currently infected and expected to be infected each year is 20 million and 6.2 million in the United States alone [65]. Even though the orally infected rate among the population aged between 14 and 69 (10% of men, 4% of women) is 7%, the cancer-causing HPV subtypes consist of only 1% of these infections [54].

HPV-infected persons are unaware of the infection, since there are no correlated signs or symptoms. No effective treatment has been developed for active HPV infection, currently. Fortunately, the virus will be cleared in most of the infected persons within 2 years. It remains unknown how to identify those in whom the infection will become chronic and progress to HPV-HNC in time. Since the most of carcinogenesis occurs deep in the crypts of the tonsils where simple "Pap smear equivalents" are inaccessible in contrast to anus or cervix, an efficient screening test for early detection of HPV-related oropharyngeal cancer does not exist, yet [31].

Marijuana smoking has been shown to be an independent risk factor for HPV-mediated HNC, while the duration, intensity, and total years of marijuana use increase the risk. Marijuana use is suggested to cause oropharyngeal cancer development since the cannabinoids bind to the

CB2 receptor of immune modulatory cells found in the tonsillar tissue which results in reduced immune response, lower resistance to viral infections, and antitumor functions [66].

It has been shown that HPV is less frequent in ex-, current-smokers, and tobacco chewers than nonsmokers and nonchewers [67]. Interestingly, in contrast to HPV(−) HNC, HPV(+) HNC decreases with increasing lifetime tobacco consumption [50]. On the one hand, rates of past and current tobacco use in HPV-oropharyngeal squamous cell carcinoma (OSCC) are reported to be 65% as opposed to 74% in HPV-negative OSCCs [6]. On the other hand, oral HPV infection presence is separately correlated with current smoking, but not lifetime smoking history [54]. Similarly, heavy alcohol consumption is less common in HPV(+) HNC patients compared with HPV-negative HNC ones [50]. Although heavy alcohol use (>21 drinks per week) is related to increased incidence of both HPV(+) and HPV(−) HNC, it is not correlated with oral HPV infection with the adjustment for sexual habits [54]. The complex role of alcohol remains to be identified.

Other significant factors in the increasing incidence of HPV infection and HPV(+) HNC are the changes in sexual behaviors, early sex debut, and number of oral-vaginal partners [68]. In addition, oral-oral contact and HPV transmission at birth may also lead to oral HPV infection [69, 70]. HPV transmits mainly through sexual contact directly with vaginal or anal intercourse, oral sex, or any mucosal contact. Also, oral HPV infection is more correlated with a genital HPV infection status, compared with oral sex activity in young males, suggesting autoinoculation as a potential HPV transmission route [71]. The first sexual encounter at younger ages, increasing number of sexual partners as well as more oral sex are reported by Americans [72, 73]. Additionally, the lifetime prevalence of oral sex was reported to be increased from 50% in 1970 to 90% in 2006 in a French study [73]. Furthermore, HPV exposure increases the HNC development risk, and HPV-16 seropositivity leads to cancer development 9 years earlier [74].

4. Diagnosis and histopathology

4.1. Clinical and pathologic presentation

An asymptomatic neck mass is the presentation of the disease in up to 90% of HPV(+) oropharyngeal cancer patients [75]. The neck nodes are generally in cystic structure which results in nondiagnostic aspiration materials. The diagnosis may be delayed due to no suspicious history because of being a nonsmoker, insufficient examination, and non-diagnostic aspirates of cystic lymph nodes. Ultrasound-guided fine-needle aspirates taken from cystic neck nodes may increase the chance of early diagnosis [76]. The utility of HPV detection in theses aspirates using p16 immunohistochemistry (IHC) and ISH has been shown [77]. In cases of unknown primary, a palatine and/or lingual tonsillectomy is superior to random biopsies.

HPV(+) oropharyngeal carcinoma exhibits a nonkeratinizing, basaloid, well-differentiated histology with diffuse nuclear and cytoplasmic p16 staining [66]. The HPV-positive tumor pathologic properties differ from HPV-negative ones showing lobular growth, having infiltrating lymphocytes, but not surface dysplasia or keratinization [66]. In addition, HPV-

positive tumors present frequently with smaller primary tumors but advanced nodal metastasis [46, 50]. Despite being not pathognomonic, major histopathological features of HPV-mediated tumors are the presence of classic koilocytes, perinuclear cytoplasmic halos, nuclear dysplasia with the addition of presence of dyskeratosis, atypical immature metaplasia, macrocytes, and binucleation as minor properties [78].

4.2. HPV detection tests/methods

The detection of cyclin-dependent kinase inhibitor 2A (p16Ink4A or p16) by IHC is recognized as a standard test for HPV positivity in a tumor in many clinics and during clinical trial enrollment. The HPV-16 E7 protein downregulates Rb and frees E2F, its regulatory partner which upregulates p16. IHC detection of p16 is a fast, cheap, and easily available method and is the standard method for HPV status assessment in clinics [79].With a false-negative rate of 4%, p16 IHC is a reliable marker in HPV infection, given that strong nuclear and cytoplasmic staining is extremely predictive for HPV(+) HNC [80]. By contrast, in cases with intermediate p16 expression levels, ISH or reverse transcription-polymerase chain reaction (RT-PCR) is required [80]. The inability of PCR-based assays to distinguish integrated DNA from episomal viral DNA decreases the test specificity remarkably in contrast to ISH in which sensitivity is lower compared to PCR [81]. Furthermore, the RNA ISH E6/E7 microRNA probes enable the direct scanning of viral transcripts which means accurate HPV detection [82]. It may be used as a HPV confirmation test in p16-positive samples, due to the fact that p16 is also overexpressed in non-virally induced situations. Given the different survival rates of the p16(+)/HPV(−) subgroups, considering personalized approaches, these patients should be evaluated as a distinct subcategory that is why using both ISH and p16 is recommended for HPV assessment [83]. In a recent study, which used both three methods, the sensitivity of p16 was detected as 100%, whereas its specificity was 74% in oral cancer and 93% in oropharyngeal cancer [84]. Cancer Care Ontario recommends routine HPV test in oropharyngeal cancer, in metastatic cervical nodes from an unknown head and neck primary and the use of p16 IHC as an initial test for its high sensitivity in patients with HNC [31].

Antibodies against HPV in the serum can be used to measure the cumulative exposure to HPV infection [85]. HPV16 E6 or E7 antibodies were detected in 65% of HPV(+) oropharyngeal cancer patients which indicates that they are useful tools as HPV markers in the unavailability of appropriate cytologic or histologic materials [67]. The detection of HPV antibodies in saliva instead of serum may lead to common false negative results, since antibodies in oral sampling are fewer compared with those in serum [85].

Currently, several methods including The Roche linear array HPV genotyping test, the Hybrid Capture 2, and a PCR bead-based multiplex method present for HPV typing [86–88]. Nevertheless, since E6 and E7 mRNA by RT-PCR demonstrate functional HPV expression, it is widely accepted as the gold standard [89]. The correlation between the steps of HPV infection to cell, detection targets, and methods is shown in **Table 1**.

Step	HPV infection	Detection target	Suitable methods
1	HPV endocytosis HPV episome HPV DNA integration	DNA detection	PCR ISH
2	E6 mRNA E7 mRNA	RNA detection	PCR ISH
3	Protein E6 Protein E7	Oncoprotein detection	Monoclonal antibodies
4	Rb:E2F P16	P16 overexpression detection	Monoclonal antibodies

Table 1. Correlation between the steps of HPV infection to cell, detection targets and methods.

5. Carcinogenesis

Currently, HPVs consist of over 81 different subtypes of HPVs classified on the basis of their L1 protein, separated based on cutaneous and mucosal site tropism, and divided in low-, and high-risk viruses according to correlation with cancers [90]. The high-risk HPV types may be classified as follows: highest risk types (HPV 16, 18, 31, 45), other high-risk types (HPV 33, 35, 39, 51, 52, 56, 58, 59), and probably high-risk types (HPV 26, 53, 66, 68, 73, 82). Oncogenic HPV types 16, 18, 31, 33, and 35 are related to HPV(+) HNC, while HPV-16 is most frequently found in oropharyngeal cancer [91, 92]. Majority of the cases of HPV(+) HNC arise from the oropharyngeal region due to epithelial injury predisposition of its location and lack of protective keratin layer that leads to easy virus exposure of the basal cells [93].

HPVs are circular, non-enveloped, epitheliotrophic, double-stranded DNA viruses belonging to family *Papovaviridae* with an approximately 8000 base pair-sized viral genome carrying early open-reading frame (ORF), late ORF, and noncoding control region between these two regions with histones within a 52–55-nm virion [94]. HPV genome encodes two structural capsid proteins (L1 and L2), two regulatory proteins (E1, E2), three oncoproteins (E5, E6, E7) [94]. The early region encodes the regulatory proteins, E1-E2, E4-E7, which are responsible for gene regulation, replication, and pathogenesis, while the late region encodes the two structural proteins, L1, L2, which form the viral capsid and have no known role in carcinogenesis but are substantial immune response targets to HPV infection. The E4 protein is thought to ease viral particle release into the surroundings and be responsible for G2 arrest in HPV-infected cells [95, 96].

The best-known relation between high-risk HPVs and cancer is established for the uterine cervix. However, HPV is also correlated with vaginal, vulvar, anal, and penile cancers, and especially since 2007, it has also been demonstrated to be a risk factor for oropharyngeal cancer [15, 95, 96]. HPV-16 and HPV-18 remain the main mediating factors in most HPV-related cancers. For instance, they are associated with 70% of cases with cervical cancer [94]. Approx-

imately 50% of penile cancers include HPV DNA, predominantly HPV-16 [93], while HPV-16 accounts for more than 90% of HPV(+) oropharyngeal cancers [74].

The palatine and lingual tonsils are predominant targets of HPV among all other potential sites of HNC. The basal cells are infected by HPV in the stratified squamous epithelium. The reticulated lymphoepithelium of tonsillar crypts expresses programmed death ligand 1 (PD-L1), which suppresses response of T-cells against HPV, and leads to an "immune-privileged" region for viral infection initiation and adaptation to immune resistance [97]. Virus enters through microinjuries in the epithelium, although the receptor and mechanism of this entry remain unknown. Prior to virus entry to the cell by endocytosis, heparin sulfate is considered to mediate the virus particle attachment to the cell [98]. HPV infection of epithelial cells causes different types of viral protein expression and production of 20 to 100 and thousands of viral DNA per cell in the basal layer and superficial layers, respectively [98]. While majority of other virus infections result in the production of progeny from the same target cell, the HPV-infected cells undergo mitosis and continue differentiation [99]. Thus, basal cells are not the only proliferating cells in the infected epithelium since infected suprabasal cells have active cell cycle and differentiation [100].

The three HPV oncoproteins E5, E6, and E7 promote uncontrolled cellular proliferation to lead viral amplification, initiate, and contribute to progression of cancer through the same mechanism and induce genomic instability [101–103]. As in cervical cancer, E6 and E7 oncoproteins are mainly responsible for the malignant transformation and progression in HNCs [101, 102]. Since silencing the E6 and E7 oncogene expression in HPV16(+) human oropharyngeal squamous cell lines led to p53 and Rb tumor suppressor activation and apoptosis induction, these two oncoproteins are thought to be required for maintaining malignant processes [104].

High-risk HPV E7 oncoproteins play a critical role in initiating DNA synthesis by binding and inactivating the Rb and its related pocket proteins p107 and p130 which are tumor suppressor genes by targeting them for degradation [98]. Rb, the most well-known pocket protein family member functions to prevent excessive cell growth by inhibiting cell cycle progression [105]. The Rb inactivation by E7 causes E2F transcription factor overexpression with the cell cycle gene upregulation, leading to the cell transition from G1 to S phase [106]. The inactivation of pRb increases levels of p16/CDKN2A which is an inhibitor of cdk4/cyclin D and cdk6/cyclin D and promotes aberrant cell proliferation [107]. Thus, increased levels of p16/CDKN2A expression correspond as a diagnostic biomarker for transcriptionally active HPV infection and virus-mediated deregulation of cell cycle [108]. E7 oncoproteins also have ability to affect gene transcription by influencing histone acetylation in regulatory regions via either histone acetyl transferases or histone deacetylases [109].

E7-mediated proliferation results in the activation of p53-dependent growth inhibition and apoptosis. To counteract this, HPV E6 causes p53 degradation which leads to apoptosis inhibition and uncontrolled cellular growth as a consequence [101]. E6 transcript produces a 19-kDa protein that binds with a ubiquitin protein ligase (E6AP) that will result in p53 tumor suppressor protein ubiquitination (posttranslational modification) and proteosomal degradation [101]. The p53 regulates the cell cycle by controlling the transition from G1 to the S phase at checkpoint by inducing cyclin inhibitor (p16, p21, and p27) expression [110]. Hence, E6

oncoprotein deregulates cell cycle checkpoints both at G1/S and G2/M in the case of cellular stress such as DNA damage which results in genomic instability. Moreover, E6 protein has the ability to downregulate p53 function either by direct binding or by interacting with the histone acetyltransferases (ADA3) and histone acetyltransferase binding proteins (p300 and CREB) [111, 112]. In addition, it can associate with *ras* and E7 for *in vitro* cell transformation [113]. Furthermore, E6 oncoprotein can activate cellular telomerase by upregulating human telomerase hTERT which leads to cellular immortalization [114]. E6 targets not only p53, but also Bak and Myc proteins which regulate apoptosis [115].

Additionally, the E5 protein works together with E6 and E7 to induce proliferation in infected cells and is considered to have a more minor role in host cell transformation. It also blocks apoptosis in the late process of HPV-induced carcinogenesis [103].

Several studies report that both E6 and E7 bind multiple complementary cooperators that perform oncogenic impacts other than p53 and pRb degradation. Despite the robust growth inducing functions of these HPV oncoproteins, extra oncogenic events are required for malignant development. Although high-risk E6 and E7 cause genomic instability [116], the mutation rate in HPV(+) tumors seem to be lower than in HPV(−) ones [59, 117]. E6 and E7 oncoproteins may lead to chromosomal segregation errors and aneuploidy development during mitosis [118]. Due to the E7 induction of CDK2 activation, multiple immature centrioles are formed which results in several centrosome synthesis rounds [119]. Eventually, E6 and E7 cause these cells with aberrant mitoses to proliferate by inhibiting G2-M checkpoint control and apoptosis [120].

It has been demonstrated that HPV-mediated carcinogenesis causes significantly fewer genomic changes than HPV-independent ones. Particularly, HPV(+) HNC is associated with less mutated p53, higher EGFR expression, and more chromosomal aberrations (3p, 9p, and 17p) [63, 121–123]. It has been confirmed by whole-exome sequencing of HNC that HPV(+) HNC has a distinct genetic entity from HPV(−) HNC which has more mutations compared with HPV(+) ones, independent of smoking [59, 117]. While HPV(+) tumors have no p53 mutation, p53 mutation rate was 78% in HPV(−) cancers [59]. These data indicate that HPV-mediated oncogenesis is correlated with cellular dysregulation to a lesser degree which may be the underlying explanation of better treatment response. HPV(+) tumor differs from HPV(−) HNC not only biologically, but also clinically. They tend to present at earlier T stage with extensive nodal involvement. Despite the fact that distant metastasis may constitute a major problem in HPV(+) tumors, their prognosis is better, especially in locally advanced diseases [124].

6. Mechanisms of improved response to treatment

The prognostic advantage of HPV positivity may be explained to some extent by the patient population features affected with younger age, higher performance status, fewer comorbid diseases, and less tobacco and alcohol exposure. However, after adjustment to these conditions in multivariate analyses, the improved survival of HPV(+) patients still maintains [16, 46].

Actually, these factors only account for approximately 9% of the survival difference between patients with HPV(+) and HPV(−) tumors, which means that the survival difference seems to be largely resulted by HPV status [16, 125]. It is clear that the higher response rate of HPV(+) tumor to therapy is caused by a basic biological difference between HPV(+) and HPV(−) HNCs. It is accepted that intrinsic factors of each individual tumor (e.g., mutations, HPV status) may modulate the microenvironment of tumors [126]. These alterations have the ability to influence immune response, stromal structure, and tumor vasculature [126]. Not only experimental studies but also several clinical studies have demonstrated that patients with HPV/p16(+) tumors had a much better prognosis compared with HPV/p16(−) ones [16].

It has been suggested that the immune system plays a significant role in rejection process of HPV(+) tumors because of viral protein expressions that reveal T-cell responses performing a long-term immunosurveillance. Accumulating evidence over the years appears to reinforce this hypothesis. Spanos et al. [127] showed superior tumor control in HPV(+) cell lines implanted into immunocompetent mice compared with immunocompromised mice [127]. HPV-specific circulating HPV16 E7-specific CD8+ T cells and IFNγ-producing T cells have been defined in patients with HPV(+) HNC [128]. A greater alteration from naive to effector and memory T cells has been shown in patients with HPV(+) compared with both healthy donors and patients with HPV(−) tumors which indicates higher tumor response in HPV(+) patients [129]. In addition, it has been reported that the programmed death-1 (PD-1) positive T-cell presence was associated with improved survival in HPV(+) HNC patients [130]. Moreover, circulating anti-HPV16 antibodies which are suggested to associate with clinical outcome have been detected in HPV(+) HNC patients [92]. Furthermore, radiation may induce expression loss of CD47 which is an important transmembrane cell surface marker in self-identification in HPV(+) cell lines that explains the interaction between the immune system and radiotherapy [131].

Even though radiosensitivity is mainly based on the cell ability to detect DNA damage and repair it, tumor oxygenation status may also be a factor for radiotherapy response [132]. In this context, in the Danish Head and Neck Cancer Group (DAHANCA)-5 study, the ratio of patients with high plasma osteopontin (a marker of hypoxia) levels was greater in HPV(−) tumors than in HPV(+) ones, indicating more hypoxia in HPV(−) group [133]. On the contrary, neither IHC staining for carbonic anhydrase IX (upregulated in hypoxic conditions) nor pO2 level of tumor was found to associate with HPV status of tumor in another study [134].

In two prospective trials investigating the impact of hypoxic modification (using nimorazole or tirapazamine) in HNC, the use of hypoxic cell radiosensitizer provided a trend toward better locoregional control in HPV(−) tumors but had no significant benefit in HPV(+) tumors [53, 135]. Surprisingly, HPV/p16-positive tumors appeared to be insensible to hypoxic modifier and revealed no benefit from nimorazole after which was suggested that HPV/p16(+) HNCs are less hypoxic than HPV(−) ones, and this might contribute to the better prognosis [135]. However, in studies evaluating the hypoxia with imaging markers including (18)F-fluoroazomycin arabinoside positron emission tomography/computed tomography (FAZA PET/CT)), dynamic contrast enhanced-MRI (DCE-MRI), and proton magnetic resonance spectroscopy ((1)H-MRS), no correlation between HPV positivity and intratumoral hypoxia was

detected [136, 137]. Additionally, recent *in vitro* evidence comparing radiation response of HPV/p16(+) and (−) cell lines under hypoxia showed no difference regarding gene regulation patterns, while oxygen enhancement ratio (OER) of HPV/p16(+) cells was found similar to HPV/p16(−) ones [138].

Finally, it has been hypothesized that viral oncoproteins play a substantial role in improved treatment sensitivity. It has been shown that low levels of residual wild-type p53 in HPV(+) cells may be activated by radiation, resulting in increased cell death [139]. Recently, Rieckman et al. [140] demonstrated decreased survival fraction, increased double strand breaks levels, and extensive G2 arrest pointing to compromised DNA repair capacity in HPV/p16(+) cell lines compared with HPV(−) cell lines after irradiation [140].

7. Clinical considerations

7.1. Impact of HPV on prognosis (clinical studies)

The changing epidemiology of HPV-positive oropharyngeal cancer formed a new patient population in the clinic that consists of individuals at younger ages without a heavy alcohol or smoking history and with more advanced neck diseases [141]. The natural history of HPV-positive HNC began to be written with many retrospective studies published in the late 1990s to early 2000s. In a study of 42 patients, HPV(+) tonsil cancer revealed higher survival rates compared with HPV(−) ones [142]. In addition, in a German study including 208 HNC sample patients with HPV(+) samples had better survival despite more adverse pathological results [143]. Furthermore, in a Swedish study with 60 patients, HPV(+) oropharyngeal cancer patients were found to have higher 5-year OS rates (53.5% vs. 31.5%) and reduced recurrence risk irrespective of gender, age, or disease stage [144]. Gillison et al. retrospectively analyzed 252 HNC patients in 2000, and patients with HPV(+) HNC from all sites had a 40% reduction in death risk ($p = 0.07$) and a 59% reduction in disease-related death risk ($p = 0.02$) after adjustment for age, nodal status, and alcohol consumption [63]. Finally, a meta-analysis of 37 studies analyzing HPV and HNC reported that HPV(+) oropharyngeal cancer patients had a 28% reduced death risk and a 49% lower disease-failure risk compared with HPV(−) ones in 2007 [145].

In the Danish DAHANCA-5 phase III clinical trial, samples from 156 patients of whom 74 were oropharyngeal cancer patients were collected prospectively. Of oropharyngeal cancer samples, 24 were p16(+) and had a locoregional control benefit (OR, 5.1) compared with those with p16(−) samples [146]. In a phase II prospective trial of 42 oropharyngeal cancer patients of whom pretreatment biopsy HPV-positivity rate was 67%, HPV titer was correlated with improved induction chemotherapy response ($p = 0.001$), chemoradiation response ($p = 0.005$), overall survival ($p = 0.007$), and disease-specific survival (DSS) ($p = 0.008$) [147]. Similarly, in the Trans-Tasman Radiation Oncology Group (TROG), 20.02 trial which retrospectively reviewed for HPV and p16 status, a higher 2-year overall survival rate (91% vs. 74%; HR, 0.36; $p = 0.004$) and failure-free survival (87% vs. 72%; HR, 0.39; $p = 0.003$) were detected in 57% of 185 oropharyngeal cancer patients with p16 positivity compared with HPV(−) patients [53].

Several studies have demonstrated the favorable effect of HPV positivity in oropharyngeal cancer patients [46, 53, 148]. First, in 2008, the Eastern Cooperative Oncology Group (ECOG) 2399 trial which was a phase II prospective study including stages III and IV, M0, oropharynx and larynx cancer patients treated with paclitaxel/carboplatin induction chemotherapy followed by concurrent paclitaxel and radiotherapy showed that patients with HPV(+) oropharyngeal cancer (HPV detection method was p16 IHC) had a 61% lower death risk (HR, 0.39; $p = 0.06$) and a 62% lower progression risk (HR, 0.38; $p = 0.09$) than patients with HPV(−) ones, after adjustments for age, ECOG performance status, and disease stage [46]. Following this, Ang et al. [16] reported the largest retrospective examination of Radiation Therapy Oncology Group (RTOG) 0129 study about HPV effect on survival in oropharyngeal cancer where HPV positivity was tested by ISH. The 3-year overall survival rates were 82.4% and 57.1% in the HPV(+) and HPV(−) subgroups, respectively, while the 3-year progression-free survival rates were similarly better in HPV(+) subgroup compared with HPV(−) ones (73.7% vs. 43.4%). In addition, HPV(+) patients had a 58% lower death risk (HR, 0.42; $p < 0.001$) and a 51% lower progression risk (HR, 0.49; $p < 0.001$). Furthermore, patients were classified into risk-of-death categories (low, moderate, high) based on a recursive partitioning analysis according to HPV status, tumor burden, and tobacco use. The low-risk group included patients with HPV(+) cancer with the exception of smokers with advanced nodal metastasis, while smoker patients with HPV(+) tumors and advanced nodal metastasis or nonsmoker patients HPV(−) tumors of stage T2 or T3 were considered to be at intermediate risk. On the contrary, nonsmoker patients with HPV(−) T4 tumors or smoker patients with HPV(−) tumors consisted of high-risk group while 3-year survival rates of low-, moderate-, and high-risk patients were 93%, 70.8%, and 46.2%, respectively. Importantly, smoking had a negative factor on prognosis, regardless of HPV status [16]. Similarly, in the retrospective analysis of TAX 324 trial, which investigated triple-agent versus double-agent induction chemotherapy confirmed the better prognosis of HPV(+) patients, 5-year overall survival rates were significantly higher in HPV(+) group compared with HPV(−) (82% vs. 35%, $p < 0.0001$). The HPV status was tested using E6/E7 PCR methods in this study [47].

The retrospective subanalysis of 190 patients with oropharyngeal cancer in the RTOG 9003 study, a 4-arm, phase III trial which compared different RT protocols, p16 positivity was found to correlate with T1 stage, better performance status, absence of anemia, and less tobacco consumption. Independently from assigned treatment, the p16(+) oropharyngeal cancer group had better 5-year overall and progression-free survival, lower 5-year locoregional failure but similar 5-year distant metastasis rates compared with p16(−) ones [149]. Additionally, a recently published retrospective analysis of RTOG 0129 and RTOG 0522 revealed that HPV(+)oropharyngeal cancer patients had better overall survival even after disease progression compared with HPV(−) group. Moreover, salvage surgery was detected to provide significantly improved prognosis [150]. Another recent retrospective subanalysis of the phase III trial, IMCL-9815 Bonner trial [53, 54], which evaluated the impact of the role of cetuximab addition to radiotherapy in patients with locally advanced HNC, based on HPV status determined by p16 IHC, p16 positivity was confirmed as a powerful prognostic determinant for oropharyngeal cancer patients [151].

Likewise, surgical reports further confirmed the favorable effect of p16 positivity in oropharyngeal cancer. Rich et al. [148] reported that in a cohort of 84 stage III or IV oropharyngeal cancers, patients who received transoral laser microsurgery (TLM) ± adjuvant therapy, p16 positivity was significantly associated with higher 5-year overall survival (90% vs. 25%, $p < 0.0001$) and disease-specific survival (DSS) rates (94% vs. 50%, $p = 0.0078$) [148]. Furthermore, two recent meta-analysis of clinical trial data of oropharyngeal cancer patients demonstrated hazard ratios for better overall survival of 0.49 and 0.47 correlated with HPV positivity [125, 152]. Overall, patients with HPV(+) tumors have a 60–80% reduced mortality rates, a finding that was confirmed by multiple trials.

The HPV(+) tumors had some unique features. The TAX324 trial analysis showed that HPV(+) patients had T1 or T2 tumors more commonly (49% vs. 20%) and better ECOG performance status (ECOG 0: 77% vs.49%) [47] which was in parallel with the results TROG 02.02 and ECOG 2399 trials [46, 53]. In addition, it has been shown that cystic lymph node metastases were associated with HPV(+) tonsil cancer in a surgical series of neck dissection [153]. Furthermore, Princess Margaret Hospital data of N2-3 HNC patients ($n = 493$) detected that HPV(+) lymph nodes ($n = 257$) were larger (2.9 vs. 2.5 cm), more commonly in cystic structure (38% vs. 6%), regressed more frequently after treatment (36% vs. 41%), and more likely to be eliminated after 36 weeks (90% vs. 0%) compared with HPV(−) ones [154].

7.2. The role of HPV in recurrent/metastatic HNC

The characteristics of metastatic disease in HPV(+) patients differ from HPV(−) ones in terms of sites and time, since metastases is more likely to develop at sites other than lungs and may occur after 2 years following the initial treatment. Locally advanced diseases (T4 and N3-N2C) are the risk factors for metastasis development in HPV(+) disease [16]. Princess Margaret Hospital reviewed the distant metastasis rates in 457 HPV(+) and 167 HPV(−) oropharyngeal cancer cases and found that metastasis rates were similar at 3 years. HPV(+) tumors were more likely to develop metastases after a long interval, such that metastases occurred within 2 years in 24 of 25 HPV(−) cases, while metastasis development were detected 3 years post treatment in 13% of HPV(+) cases. In addition, dissemination pattern was more common in HPV(+) patients (33% vs. 0%). Nevertheless, post-metastases 2-year survival was significantly better in HPV(+) group compared with HPV(−) group (11% vs. 4%, $p = 0.02$) [155]. These findings were confirmed by additional recent retrospective reports showing similar unique metastatic spread patterns [53, 156–158].

Recently, the impact of HPV in recurrent-metastatic HNC was evaluated in large trials. In the phase III EXTREME randomized trial which assessed the benefit of cetuximab addition to platinum + 5-fluorouracil (5-FU) in patients with recurrent-metastatic HNC as first-line therapy, paired tissue samples were analyzed for p16 expression by IHC using a 70% expression cutoff value and HPV via oligonucleotide hybridization test [159]. The p16 and HPV positivity was correlated with higher survival rates compared with p16 and HPV negativity in both cetuximab and control groups [159]. Since the predictive analyses indicated that cetuximab addition to chemotherapy improved survival rates independently from p16 or HPV status, these biomarkers did not have any significance in treatment efficacy prediction. By

contrast, in the phase III SPECTRUM randomized trial which assessed the benefit of panitumumab addition to chemotherapy instead of cetuximab in recurrent-metastatic HNC, a nonsignificant difference between HPV(+) and HPV(−) groups was demonstrated. Furthermore, the benefit of panitumumab was not detected in p16(+) group in contrast to p16(−) group [159].

The pooled analysis of patients with recurrent-metastatic HNC from E1395, a phase III trial comparing platinum + 5-fluorouracil with cisplatin + paclitaxel and E3301, a phase II trial evaluating irinotecan + docetaxel demonstrated that patients with HPV(+)/p16(+) disease had better overall survival than HPV(−)/p16(−) ones [160]. Taken together, these three studies indicate the positive impact of HPV positivity on improved survival. The efficiency of anti-EGFR antibodies on survival of HPV(+) and HPV(−) patients remains to be clarified. Hence, further studies including only oropharyngeal cancer patients are required in recurrent-metastatic setting since the impact of HPV positivity at other sides of HNC is not fully known.

7.3. Prognostic factors

Combined with being a nonsmoker, HPV DNA/RNA presence and p16 overexpression are strong prognostic markers [16]. Smoking, the most important risk factor for HNC overall, affects negative survival and response to treatment [161]. In addition, tobacco exposure has been shown to be a significant independent factor for prognosis in patients with HPV(+) oropharyngeal cancer, as it predicted progression and death risk in a dose-dependent pattern. Independently from HPV status and other factors, each pack-year of smoking increases the progression and death risk and the risk of second primary cancers of by 1% and 1.5%, respectively. Furthermore, the risk of death doubles if patients do not quit smoking during radiotherapy [161]. Based on the data of RTOG 0129 trial, a risk stratification for oropharyngeal cancer patients was developed using HPV status, history of smoking (>10 pack-years), and disease stage [16].

Other factors which are correlated with poor prognosis are local extension, disease stage at presentation, cervical node involvement, and rich vascular and lymphatic network [162]. Tumor thickness greater than 5 mm is significantly correlated with occult lymph node metastasis which is suggested to be a stronger determiner of prognosis than TNM staging by some authors. It has been shown that tumor differentiation, angiogenesis, extracapsular extension, and perineural invasion had significant role in prognosis determination [162]. Regarding treatment associated factors, cervical node dissection and disease free margins are important [162], since local relapse rates are 64–84% in patients with positive surgical margins [163].

Concerning the molecular markers, aberrations in chromosomes 3, 9, 11, 13, and 17 and tumor suppressor genes (p53 and pRb) are significant for prognosis [162]. In addition, cytokeratin 8/18 has been shown to be an independent factor correlated with poor prognosis [162, 163]. Furthermore, the absent/low expression of MHC class I, CD44, or CD98 has strong prognostic value for HPV(+) oropharyngeal cancer patients such that MHC class I staining absence defines 3-year disease-free and overall survival with 95–100% probability [164–166]. Moreover, higher

CD8+ tumor infiltrating lymphocyte (TIL) counts is also a prognostic marker for patients with HPV(+) oropharyngeal cancer [167].

HPV16 E6 and E7 in serum were demonstrated to be the most predictive factor in determining the HNC prognosis among the several biomarkers. E6/E7 seropositivity was associated with improved survival, whereas their seronegativity was correlated with poor prognosis irrespective of the DNA or p16 status [168]. Another suggested prognostic factor for survival is pretreatment tumor HPV copy number; higher tumor HPV copy number was correlated with better induction chemotherapy (p = 0.001) and chemoradiotherapy (p = 0.005) response, disease-specific (p = 0.004) and overall survival and (p = 0.008) after adjustment for other significant factors [147]. Similarly, higher viral load was shown to be correlated with improved recurrence-free (p = 0.0037) and overall (p = 0.028) survival in tonsil cancer patients [169]. Furthermore, the presence of both HPV16 and p16 indicated significantly improved prognosis compared with either p16 or HPV16 alone [170].

7.4. Deintensification of treatment in HPV(+) oropharyngeal cancer

Three principal routes have been drawn in treatment deintensification: (1) EGFR inhibitor use (mostly Cetuximab) instead of cisplatin, concurrently with radiotherapy; (2) radiotherapy dose reduction with concurrent chemotherapy (based on induction chemotherapy response); and (3) minimally invasive transoral surgery use followed by reduced adjuvant treatment according to the histopathological properties of the excised tumor.

Since responses to treatment alter even between HPV(+) oropharyngeal cancer patients, defining appropriate patient subgroup is essential. It must be emphasized that all patients with HPV(+) oropharyngeal cancer are not suitable candidates for deintensification approaches. The clinical trial cohorts' analysis indicates some evidence. Some of them suggest that lifetime tobacco use history of >10 pack-years in HPV(+) patients with advanced regional nodal metastasis (N2b, N3) as well as smoking during radiotherapy decreases survival time (3-year overall survival rate of 70.8%) [16, 161]. The Italian study which reported that intermediate-risk patients are not convenient for deintensification trials confirmed these findings [171]. Furthermore, O'Sullivan et al. [27] demonstrated that the 3-year distant control rates of HPV(+) oropharyngeal cancer with advanced T stage (T4) or nodal (N3) was 72% and 78%, respectively [124]. Hence, late recurrences and relapses as distant metastasis are not rare in HPV(+) oropharyngeal cancer. These data indicate the presence of a limit of the biologic advantage provided by HPV positivity and may be helpful in determining patient subgroup that requires chemotherapy use in order to treat early micrometastasis. Both amount of smoking and locoregionally advanced disease have implications in designing deintensification trials for HPV(+) oropharyngeal cancer patients.

Many clinical trials have been planned to evaluate the efficiency of treatment deintensification in HNC patients and recently they have been reviewed by Masterson et al. [152] in detail. Enrolling patients into these trials to define optimum treatment of HPV(+) oropharyngeal cancer is encouraged. Nevertheless, besides as a clinical trial, there is not sufficient data for the treatment reduction or modification according to HPV positivity until we receive the results from these deintensification studies.

7.5. Prevention-vaccination

There are two prophylactic HPV vaccines available commercially; Gardasil® (Merck & Co., Whitehouse Station, NJ, USA) and Cervarix® (GlaxoSmithKline Biologicals, Rixensart, Belgium). The virus-like proteins (VLPs) are used to create HPV major capsid protein L1 neutralizing antibodies. Gardasil is a quadrivalent L1 VLP recombinant vaccine protecting against HPV6, -11, -16, and -18, while Gardasil 9 provides protection against five additional HPV genotypes 16, 18, 31, 33, 45, 52, and 58. In contrast, Cervarix is a bivalent L1 VLP recombinant vaccine against HPV-16 and -18. Both HPV vaccines are highly effective in anogenital HPV infection prevention and consequent anal and cervical cancer development.

Despite the fact that the prophylactic value of vaccination for oropharyngeal cancer has not been proven in randomized trials yet, both the Cervarix and Gardasil vaccines are expected to prevent oropharyngeal HPV16 and -18 infections and consequent oropharyngeal cancer, since HPV16 is the most common type detected in oropharyngeal cancer [172]. The vaccination efficiency was estimated as 93.3% in 7466 women who were aged 18–25 years and randomized to HPV16/18 (Cervarix) vaccine versus hepatitis A vaccine as control for oral HPV 16/18 prevalence evaluation 4 years after vaccination [173]. In addition, cross-sectional study of US population as part of the National Health and Nutrition Examination Survey (NHANES) oral HPV infection prevalence was reduced significantly in 290 vaccinated women compared with 1985 unvaccinated women (0% vs. 0.5%) [54].

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