Review

HPV in oropharyngeal cancer: the basics to know in clinical practice

HPV nel carcinoma dell'orofaringe: le nozioni base da conoscere nella pratica clinica

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SUMMARY

The incidence of oropharyngeal squamous cell carcinoma (OPSCC) is rising in contrast to the decreasing incidence of carcinomas in other subsites of the head and neck, in spite of the reduced prevalence of smoking. Human papilloma virus (HPV) infection, and in particular type 16 (HPV-16), is now recognized as a significant player in the onset of HPV positive OPSCC, with different epidemiological, clinical, anatomical, radiological, behavioural, biological and prognostic characteristics from HPV negative OPSCC. Indeed, the only subsite in the head and neck with a demonstrated aetiological viral link is, at present, the oropharynx. These observations lead to questions regarding management choices for patients based on tumour HPV status with important consequences on treatment, and on the role of vaccines and targeted therapy over the upcoming years.

KEY WORDS: Human Papillomavirus • Head and Neck cancer • Oropharyngeal cancer • Squamous Cell Carcinoma • Prognosis • Treatment • Prevention • Vaccination • Clinical Trial

RIASSUNTO

L'incidenza del carcinoma spinocellulare dell'orofaringe (OPSCC) è in aumento in contrasto con la diminuzione dell'incidenza di carcinomi in altre sedi del distretto cervico-facciale, nonostante la ridotta prevalenza del fumo. L'infezione da Papilloma Virus Umano (HPV), in particolare di tipo 16 (HPV 16), è ora riconosciuto come un importante fattore nell'insorgenza di HPV OPSCC positivo, con diverse caratteristiche radiologiche, epidemiologiche, cliniche, anatomiche, biologiche e prognostiche rispetto all'HPV OPSCC negativo. In effetti l'unica sede del distretto cervico-facciale con un collegamento virale eziologico dimostrato è, attualmente, l'orofaringe. Queste osservazioni portano a domande riguardanti le scelte di gestione per i pazienti in base allo stato del tumore HPV con importanti conseguenze sul trattamento e sul ruolo dei vaccini e terapia mirata per i prossimi anni.

PAROLE CHIAVE: *Papilloma Virus Umano • Tumori del distretto cervico-facciale • Tumori dell'orofaringe • Carcinoma spinocellulare • Prognosi • Trattamento • Prevenzione • Vaccinazione • Studi clinici*

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Introduction

Head and neck cancer, which includes tumours that arise from the oral cavity, oropharynx, larynx, hypopharynx and sinonasal tract, represents a serious health care problem in many parts of the world, and ranks as the sixth most common cancer worldwide [1]. These tumours are linked by common characteristics including a male predominant appearance in the 5-6th decade of life, a strong aetiological link with prior tobacco, alcohol use or betel nut chewing [2], and a histopathological resemblance [3]. About 90% of head and neck cancers are squamous cell carcinomas (HNSCC).

The estimated annual burden of HNSCC is approximately 650,555 incident cases and approximately 300,000 resultant deaths [4 5]. It is considered the sixth leading cause of cancer mortality and oropharyngeal squamous cell carcinoma (OPSCC) accounts for approximately 50,000 incident cases, which is low in comparison with other head and neck squamous cell carcinoma (HNSCC) [5 6].

Multiple studies have demonstrated that the incidence of HNSCC has remained stable or even declined in the late 1980s, due to the gradual decrease in smoking and alcohol which are the primary risk factors for these cancers [2]. Despite this, the incidence of oropharyngeal squamous cell carcinoma with different characteristics, particularly

in the base of the tongue and tonsil subsites, has increased by 2-3% annually during 1973-2001, and then by 5.22% annually from 2000 to 2004 in the USA [7]. Similar trends have been noted in other countries. In particular, one study suggests that the annual number of HPV-associated oropharyngeal cancers in the United States will overtake the incidence of invasive cervical cancer cases in the United States by 2020 [8]. There is also a discrepancy in incidence of OPSCC between developed and developing countries of oropharyngeal cancer [9].

The developing world has a relatively low proportion of OPSCC (1-10% of HNSCCs), which appears to remain stable (or even to decrease) over time, while the incidence of HNSCC has steadily increased in most countries [4 10].

The developed world features a relatively high and variable proportion of OPSCCs (15-30% of HNSCC). For example, a central belt of European countries has the highest OPSCC proportions in the developed world (up to 30% of HNSCCs) with the remainder of Europe being characterised by slightly lower OPSCC proportions, while the overall HNSCCs incidence has remained stable or has even shown a declining trend over the same period [4 11 12]. These demographic data prompted researchers to search for further risk factors contributing to the incidence of OPSCC.

The impact of HPV as a risk factor for OPSCC

Most studies have demonstrated that features tobacco and alcohol consumption are major, common risk factors for HNSCC, but over the last 10-15 years HPV infection has been increasingly recognised as a major aetiological factor for a subset of HNSCCs [7-10], including mostly OPSCC. HPV infection in the aetiology of OPSCC was first shown by Gillison et al. [13]; numerous case series studies conducted in the late 1990s and 2000s evaluated the prevalence HPV infection in oropharyngeal cancer using molecular techniques such as PCR and in situ hybridisation [8 14 15]. Indeed, over the last five years it has become increasingly clear that HPV plays a pathogenic role in this subset of head and neck cancers, with distinct epidemiologic, clinical and molecular characteristics. These findings have created new opportunities for improved therapy and primary prevention for these HNSCCs [16].

At present, it should be clear that the only subsite in the head and neck with a demonstrated role for HPV infection in the aetiology of cancer is the oropharynx, as noted in the most important report by Gillison et al. [13] and confirmed by Stransky et al. in 2011 [13 17].

From a biological point of view, HPV is a DNA oncovirus and is epitheliotropic. There are over 120 different HPV subtypes, including the low-risk types such as HPV 6 and HPV 11, responsible for benign proliferation of epithelium, and the high-risk oncogenic types HPV 16 and HPV 18 which are both well-established initiators of over 90% of cervical cancers, 70% of anogenital cancers, 5% of non-oropharyngeal SCC [17] and 20-72% of OPSCC [2 4 12 17]. The oncogenic nature of high risk HPVs is due to the immortalising and transforming properties of HPV oncoproteins E6 and E7, which target the p53 and pRB tumour suppressor pathways, respectively, rendering infected cells susceptible to mutations and cancer formation [18 19]. Since the majority of HPV-HNSCCs are OPSCC, we will mainly discuss OPSCC.

Classification of oropharyngeal cancer according to HPV

According to the National Comprehensive Cancer Network (NCCN) [20] guidelines, 'HPV testing is recommended for all oropharyngeal tumours'. In addition, according to the US National Cancer Institute (NCI) [21] and Cancer Therapy Evaluation Programme (CTEP) [22], HPV status must be included as a stratification factor for trials including oropharynx cancer patients. Much evidence suggests that HPV-positive and HPV-negative OPSCCs represent distinct subgroups of OPSCC, each with unique epidemiological and biological profiles [4 5 17 21 23-27].

Differences between HPV positive and HPV negative OPSCCs

Epidemiological factors

HPV-positive patients tend to be younger with a median age of diagnosis of 54 years, less exposure to tobacco and alcohol [28-30], and higher socioeconomic status and education [31]. HPV positivity is less frequent in blacks than in Caucasians (4% of HNSCC in blacks *vs.* 34% in whites) [32], with a three fold higher incidence in males than females [28 33 34].

As in cervical cancer, oral HPV infection appears to be a sexually-acquired disease. Although the natural history of oral HPV infection is not well defined, D'Souza and colleagues recently showed in a case-control study that a high (≥ 26) number of lifetime vaginal-sex partners and 6 or more lifetime oral-sex partners were associated with an increased risk of OPSCC [odd ratio (OR) 3.1 and 3.4, respectively] [35]. An increased risk of HPV-associated OPSCC in female patients with a history of HPV-associated anogenital cancers and their male partners is also consistent with HPV transmission to the oropharyngeal cavity [36 37]. The recent increased incidence of this disease may thus reflect societal changes in sexual behaviour that have occurred over time in the developed world [38 39].

An important point to mention is that there is no clear case-control study addressing the evidence for HPV prior to development of OPSCC (i.e. temporal association), with the exception of a Scandinavian study by Mork et al.

which showed that the presence of HPV 16 L1 antibodies in pre-diagnostic serum samples was associated with a 14.4-fold increased risk of oropharyngeal cancer. Importantly, the presence of HPV 16 antibodies preceded oropharyngeal cancers by more than 10 years, underscoring a temporal association. These data confirmed that oral HPV infection increases the risk of developing OPSSC [40].
Lastly, it is possible that in addition HPV infection, other risk factors or cofactors such as genetic susceptibility or nutritional factors or tobacco and alcohol interaction have an important role in cancer onset. There is an objective need for more analytic epidemiological studies in males and females diagnosed with HPV positive oropharyngeal cancer younger than 50 years of age [40].

Anatomical sites

Several studies have noted an increased incidence of HPV-associated oropharyngeal cancers, especially tonsillar and tongue cancer. For example, in the USA they have risen by 3.9% and 2.1% among men and women, respectively, in the age group from 20 to 44 years, between 1973 and 2004 [2 41]. Similar patterns have been noted in Sweden for tonsillar cancer which rose 2.9-fold between 1970 and 2001, increasing by 2.6% per year in men and 1.1% in women [11 42].
The preference of HPV for the oropharynx is unexplained, but may be related to the unique presence of transitional mucosa in the oropharynx, predominantly found in the tonsillar tissue and which shows histological similarities to the cervical mucosa [2 11]. Another possibility lies within the genetic features of HPV 16, which accounts for more than 90-95% of all HPV associated oropharyngeal cancers, as it may facilitate survival in the tonsillar crypt epithelium [43 44]. It is also possible that the invagination of the mucosal surface of the tonsil may favour virus capture and maintenance by promoting its access to basal cells (the only dividing cells in the epithelium) [45]. If this is true, tonsillar tissue could be a reservoir for HPV in the upper aerodigestive tract. This view is partly supported by the fact that when oral samples are collected by oral rinse, the detection rate of HPV is much higher than with swabs. Finally, the persistence of HPV in tonsillar tissue might be of importance in the immune response to HPV [46].

Biological profiles

Recent global genomic screening studies searching for a biological distinction among HPV-positive and negative OPSCC have shown that HPV-induced carcinogenesis has a clear impact on the acquisition and maintenance of specific chromosomal gains and losses within tumour cells, in which OPSCCs with transcriptionally active HPV-DNA are characterised by occasional chromosomal loss/allelic imbalance [47]. Conversely, those lacking HPV-DNA are characterised by gross deletions that involve entire or large parts of chromosomal arms [32 48].
Furthermore, ploidy studies have confirmed that HPV-positive tonsillar cancers feature a lower number of chromosomal alterations compared to their HPV-negative counterparts [49 50].
The biology of HPV-positive oropharyngeal cancer is typified by p53 degradation, retinoblastoma protein (RB) down-regulation and p16 up-regulation. By contrast, tobacco-related oropharyngeal cancer is characterised by p53 mutations, down-regulation of p16 and RB up-regulation [45].
Interestingly, recent studies observed an inverse correlation between the presence of HPV and p53 mutations [17].

Clinical stage at presentation

Multiple studies have shown that HPV-positive tumours are more likely to present with early T stage (T1-T2) [51] and higher N stage (usually cystic and multilevel) [52], and have distinct histological features, such as moderate/poor tumour differentiation and non-keratinising or basaloid pathology [14 19 51]. The incidence of distant metastases was seen to be lower in patients with HPV positive tumours. Furthermore, metastases developed later and with a very different pattern from patients with HPV-negative tumours. HPV-positive oropharyngeal cancer had a 28% reduction in the risk of death and a 49% reduction in the risk of disease recurrence [53]. Secondary primary tumour (SPT) in patients with HPV-positive cancer is very rare, and has improved better survival rate compared to patients with HPV negative tumours [45].

Radiological imaging

Recent studies have shown radiological difference between HPV-positive and HPV-negative oropharyngeal cancer. Specifically, HPV-positive carcinomas often had small or even occult primary lesions with well-defined borders and cystic nodal metastases, whereas HPV-negative primaries more often had poorly defined borders and invasion of adjacent muscle [52 54].

Prognosis

Several studies have shown that patients with HPV-positive oropharyngeal cancer, identified through PCR, in situ hybridisation or p16 immunohistochemistry on tumour tissues, have a significantly improved overall and disease-free survival compared to patients with HPV-negative oropharyngeal cancer patients [29 53 55-61] (Table I). This holds true even after adjustment for differences in favourable prognostic factors associated with HPV positive patients (younger age, better performance status, fewer comorbidities, less smoking). Ang et al. reported that these prognostic factors explained only 10% of the observed survival differences between two subgroups [29]. However, other studies reported that survival rates improved among non-smoker HPV positive patients com-

Table I. Selected studies reporting the association of HPV infection with oropharyngeal cancer prognosis.

Study	Author, year	# of cases	HPV detection	Follow-up	OS positive vs. negative tumours
ECOG[58] 2399	Fakhry, 2008	96	HPV 16 DNA ISH	2	2-yr survival (95% *vs.* 62%)
RTOG[29] 0129	Ang, 2010	323	HPV 16 DNA ISH	4.8	3-yr survival (82.4%, *vs.* 57.1%)
TROG[59] 02.02	Rischin, 2010	185	p16 IHC	5	2-yr survival (91% *vs.* 74%)
DHANCA[60] 6,7	Lassen, 2011	794	p16 IHC	5	(62% *vs.* 47%)[c], (52% *vs.* 48%)[*]
TAX[61]) 324	Posner, 2011	111	HPV 16 DNA PCR	5	5 yr survival (82%-35%)

ISH: in situ hybridisation; IHC: immunohistochemistry; PCR: polymerase chain reaction; OS: overall survival; [*] accelerated radiotherapy; [c] conventional radiotherapy.

pared to smokers patients even in recurrent tumours, underscoring once again the benefits acquired from smoking cessation[62,63].

Why does HPV positive orophrangeal cancer have a better prognosis?

1. HPV-positive tumours may harbour fewer or different genetic alterations, which can be associated with better response to therapy[17,64].
2. HPV-positive tumours have higher radiosensitivity, probably due to intact apoptotic response to radiation[58,65].
3. The absence of field cancerisation in HPV-positive tumours[53].
4. Immunologic response may be play a role in the improved response to radio- and chemotherapy in HPV-positive tumours (due to the stimulation of immune response directed to viral specific tumour antigens[66].
5. Younger age, good performance status, fewer comorbidities of HPV-positive oropharyngeal cancer patients may also contribute to improved survival[67].

The impact of HPV on clinical management

The standard treatment for OPSCCs at present is mainly dependent on the stage of the disease and patient and clinician preferences. Single-modality treatment, in the form of surgery or radiotherapy, is usually recommended for early (T1-T2, N0) disease. For advanced stage disease, standard treatments include chemoradiotherapy with or without neck dissection, or surgical resection with reconstruction and postoperative chemoradiotherapy, as required. These current standard methods of treatment appear to apply to both HPV positive and negative subgroups[68,69].

1) Non-surgical treatment options for OPSCCs

The emergence of HPV-OPSCCs in younger patients with better prognosis and survival rates in comparison to non-HPV OPSCCs have prompted clinicians to address changes in the non-surgical management according to HPV status[2].

Multiple studies[29,58-61,68-70] tackling this issue have concluded that (Tables I, II):

1. Overall survival rates increase with HPV positive status, low EGFR and high p16[72].
2. Patients with HPV negative disease have a poorer prognosis, and therefore usually require more intensive treatment. Studies (TAX 324[61], TROG 02.02[59]) have suggested that for patients with HPV DNA-negative tumours, treatment intensification improves outcomes compared to standard treatment, but overall outcome is still poor.
3. Smoking cessation and strategies to target EGFR and Bcl-xL[70] are important adjuncts in the treatment of oropharyngeal cancer.
4. Achievement of acceptable cure rates with minimal long-term morbidity with HPV positive oropharyngeal cancer is possible.

All these data suggest that HPV status can be used in the clinical decision-making processes to select patients for less aggressive non-surgical treatment. Thus, assessing HPV presence is of utmost importance. This is especially true considering long-term outcomes of HPV-positive younger patients, since they are at risk of a lifetime compromised quality of life as a result of chronic toxicities due to chemoradiotherapy. p16 immunohistochemistry (IHC) is a current marker to detect HPV presence. However, it can be associated with a high rate of false positive/false negative responses, prompting the need for new surrogate markers for oral HPV infection. These concerns were also reported by Rietbergen et al.[71] and Bussu et al.[72]. Thus, in clinical practice it is not recommended to rely on p16 IHC alone to screen for HPV positivity.

Currently, there are on-going oncological trials that attempt to answer some questions regarding deintensification of treatment (Table III):

1. Can we use neoadjuvant chemotherapy followed by reduced radiotherapy dose in HPV positive patients?
2. What is the intensity of adjuvant therapy required in p16-positive oropharynx cancer patients?
3. Can cetuximab provide selective radiosensitisation compared with cisplatin?
4. Should the volume treated be reduced by not administering prophylactic radiotherapy to areas at risk of microscopic disease?
5. Is it possible to reduce the dose of radiation therapy when given with standard doses of chemotherapy?
6. What is the exact role of immune activation in HPV positive patients?

Table II. Retrospective analyses of HPV status and/or p16 immunohistochemical staining status as a surrogate biomarker of HPV infection and survival outcome in Phase III outcome.

Study	Treatment Regiment	Total N (n included)	Progression-Free Survival	Overall Survival	Conclusion
RTOG 0129 Ang et al. 2010 [29]	Standard-fractionated radiation + cisplatin *vs.* hyperfractionated radiation + cisplatin	743 (323)	HPV+/p16 HPV-/p16 3-yr 73.7% 3 yr 43% 3-yr 74.4% 3 yr 38%	HPV+/p16HPV-/p16 3-yr 82.4% 3 yr 57.1% 3-yr 83.6% 3-yr 51.3%	No survival differences seen between the 2 treatment arms. Secondary analysis confirmed significantly improved survival in patients with HPV-positive tumours vs. HPV-negative disease.
DAHANCA 5 Lassen et al. 2009 [70 71]	Radiation	195 (156)	5-yr p16+ (70%)	5-yr p16+ (62%)	Improved loco-regional control when nimorazole was added to radiotherapy was restricted to p16-negative patients. Improved survival in p16-positive patients treated with radiotherapy alone.
	Radiation+nimorazole	219 (175)	5-yr p16- (40%)	5-yr p16- (26%)	
DAHANCA 6&7 Lassen et al. 2011 [60]	5 Fractions w/radiation	726 (385)	5-yr p16+ (78%)	5-yr p16+ (62%)	Accelerated radiotherapy significantly improves outcome in HNSCC compared to conventional fractionation. The observed benefit was independent of tumour p16 status, and the use of a moderately accelerated radiotherapy regimen seemed advantageous for HPV/p16 positive HNSCC.
	6 Fractions w/radiation	750 (409)	5-yr p16- (64%)	5-yr p16 -(47%)	
TROG 02.02 Rischin et al. 2010 [59]	Radiation+cisplatin vs. radiation+cisplatin+tirapazamine	861 (185)	2-yr p16+ (87%)	2-yr p16+ (91%)	While there was no difference in the p16-positive group, there was a trend for improved loco-regional control with tirapazamine in p16 negative patients. The study clearly demonstrated that HPV associated oropharyngeal cancer treated with a standard regimen of concurrent cisplatin and radiation has a better outcome compared with HPV-negative OPSCC.
			2-yr p16- (72%)	2-yr p16- (74%)	

Table III. On-going clinical trials (ClinicalTrials.gov).

Study ID	NCI Trial ID	Trial Type	Total (N)	Treatment arm	Primary Endpoint
E1308	NCT01084083	Phase II	160	Sequential therapy: cisplatin/paclitaxel/cetuximab Complete response: IM RT (27 fractions) Non complete response: IM RT (33 fractions) 1cetuximab	2-yr PFS
J0988	NCT01088802	Phase I/II	60	IMRT (lower dose) + cisplatin	Toxicity/LRC
National Cancer Institute (NCI)	NCT01585428	Phase II	-	Fluderabine/cyclophosphamide/ Young TIL /Aldesleukin	Tumour response / duration
RTOG 1016	NCT01302834	Phase III	706	IMRT hyperfractionation+cisplatin *vs.* IMRT hyperfractionation +cetuximab	5-yr OS
University of Michigan Cancer Center	NCT01663259	-	-	Standard dose radiotherapy+cetuximab for stage III/IV OPSCC	Rate of recurrence
ECOG1308	NCT01084083	Phase II	83	Induction chemotherapy followed by cetuximab With low dose *vs.* standard dose IMRT	2-yr PFS
Mount Sinai School of Medicine	NCT01358097	Observational	-	Biomarkers of immune function as predictors of HNSCC in response to therapy	-

OS: overall survival, LRC: loco-regional control; DFS: disease-free survival; IMRT: intensity modulated radiation therapy; PFS: progression-free survival; TIL: tumour infiltrating lymphocytes.

2) Surgical treatment options for OPSCCs

All treatment modalities for OPSCC have similar oncological outcomes [73], but functional outcomes have significant and critical considerations when managing younger HPV positive patients with an longer expected lifetime. While nonsurgical deintensification trials are

showing great promise [29 58-61 70-72], minimally-invasive approaches, especially transoral robotic surgery (TORS), have gained more favour by achieving the satisfactory oncological outcomes without compromising functional outcome [73 74]. Indeed, three-dimensional visualisation allows the ability to manipulate [75] and perform reconstruction of the oropharynx without the need for mandibulotomy and/or pharyngotomy, thus reducing the morbidity of extensive surgery [76]. It also facilitates safer exposure and resection of the primary tumour, thereby providing complete pathologic evaluation and impacting the use of clinically-established adjuvant therapies [77]. These include use of concurrent chemotherapy [78] and effective lower doses of radiotherapy, which contribute to a decrease of swallowing dysfunction [79]. The postoperative target volume for radiation is typically smaller, and with modern techniques such as intensity modulated radiotherapy (IMRT) this procedure can significantly reduce the dose delivered to uninvolved normal structures. In patients requiring postoperative concurrent chemoradiation, this offers the potential to reduce the risk of late complications [80].

The incorporation of TORS, not only to improve oncologic results but also to decrease the long-term toxicity risks caused by non-surgical strategies, is crucial for HPV positive patients since they typically present at a younger age. To date, there are few surgical trials investigating the role of TORS in HPV positive patients. For instance, Cohen et al. [81] found no differences in oncological outcomes, overall survival or loco-regional control between HPV-positive and negative groups patients who underwent TORS surgery stratified by HPV status. Nonetheless, TORS surgery was suitable for both subgroups. The Mount Sinai group reported no differences in overall survival or loco-regional control in patients stratified by smoking status, with the assumption that patients without a smoking history are predominantly HPV positive [82].

The failure to show statistically significant differences in HPV-positive and HPV-negative tumours in TORS surgical trials for early T stage differences is unclear. It is possible that these studies were small and thus lack the statistical power to show survival differences, or that the survival advantage in HPV-positive tumours does not apply to early T-stage tumours that are surgically resected. Lastly, one may argue that HPV-negative tumours are less radio-responsive, and surgical resection provides better prognosis in the cohort being studied [83].

New multi-institutional studies are needed to confirm the exact impact of TORS on the quality of life and survival outcomes of HPV negative and positive OPSCC patients.

Future directions in HPV-positive OPSCCs

HPV-induced carcinogenesis has been extensively studied in the most widely accepted HPV-related malignancy, namely cervical cancer. HPV-associated cancers continuously express the HPV E6 and E7 viral oncogenes even during advanced stages, and repression of viral oncogene expression can prevent growth or survival of cervical cancer cells [84]. These findings raise the possibility that even late-stage HPV-associated cancers can be treated through HPV-targeted approaches with drugs that interfere with the expression or function of the viral oncoproteins or with therapeutic vaccines that elicit a cytolytic immune response in cells expressing these oncoproteins.

Vaccination

The world has greatly benefited from vaccine programmes in controlling the morbidity and mortality of infectious diseases. Hepatitis B virus (HBV) vaccine, developed for the prevention of hepatitis B virus infection, is considered the first vaccine against a major human cancer, hepatocellular carcinoma [85]. Recently, a prophylactic HPV vaccine has been included in national immunisation programmes of most developed countries with the hope of also being included in developing countries within the next few years, with the goal of preventing cervical and other non-cervical HPV related cancers [86].

Two FDA-approved HPV prophylactic vaccines are currently available [87]. The quadrivalent vaccine was initially approved in the US in 2006, and is composed of four HPV type-specific virus-like particles (VLPs) from the major capsid protein L1 of HPV types 6, 11, 16 and 18, combined with aluminium phosphate adjuvant. These are the most common HPV types found in 70% of cervical cancers and 90% of non-cervical cancers [87 88]. The bivalent HPV vaccine, approved in 2009, is composed of two HPV types, 16 and 18, which cause 70% of cervical cancers [86]. The efficacy of the quadrivalent vaccine was 100% in preventing HPV 16 and 18 related cervical intraepithelial neoplasia (CIN) grades 2/3 and vulvar and vaginal intraepithelial neoplasia (VIN) 2/3, and 98.9% in preventing HPV 6, 11, 16 and 18 related genital warts [89]. The bivalent vaccine is 98.1% efficacious in HPV 16 and 18 related CIN 2/3 prevention [90].

The Advisory Committee on Immunization Practices (ACIP) and the Centers for Disease Control and Prevention (CDC) recommends [88 90 91]:

- routine vaccination of girls aged 11 or 12 years that can be started at 9 years of age;
- catch-up vaccination for females aged 13-26 years;
- routine vaccination of boys aged 11 or 12 years;
- routine vaccination recommended for both men who have sex with men (MSM) and immunocompromised individuals aged 22 through 26 years;
- men aged 13 to 21 years who were not previously vaccinated;
- men aged 22 to 26 years may also receive the vaccine;
- can be given to lactating women, patients with minor

acute illnesses and women with equivocal or abnormal Pap test.

HPV vaccine should be delivered through a series of 3 intramuscular injections over a 6-month period of time, at 0, 2 and 6 months for the quadrivalent vaccine and 0, 1 and 6 months for the bivalent one [89], inducing strong immune memory with persistent antibody up to 6.4 years (bivalent) and up to 9.5 years (HPV 16 VLP used in quadrivalent) thus entailing long-term duration of protection against infections caused by pathogenic HPVs and their disease sequelae [92].

The entrance of males into vaccination programmes is primarily due to the estimation of 7,500 cases of HPV-related cancer, primarily head and neck and anal cancer, which occur in men each year in the United States alone [93]. Furthermore, the rates of anal cancer in homosexual males are extremely high, and thus vaccination may contribute in immunisation with subsequent reduction of HPV sexual transmission.

In the future, the currently available vaccines may also show promising results on preventing HPV-associated OPSCC caused by HPV 16, and longitudinal studies comparing the incidence of disease before and after the introduction of the vaccine may clarify this issue.

Unfortunately, the prophylactic vaccine is not effective on established infections and cancer lesions, so the study of a therapeutic HPV vaccine to treat HPV-associated cancer remains an area of crucial importance [94].

Different immunotherapeutic vaccines targeting E7 and/or E6 have been developed over the last decade including peptide/protein, dendritic cell (DC), plasmid DNA and viral vector-based therapies, but with limited success in preclinical and clinical phase studies [95 96]. A recent Italian study developed a promising therapeutic vaccine based on an integrase defective lentiviral vector (IDLV) to deliver a mutated non-oncogenic form of the HPV 16 E7 protein, considered as a tumour specific antigen for immunotherapy of HPV-associated cervical cancer, fused to calreticulin (CRT), a protein that is able to activate natural killer T cells (NKTs). A single intramuscular injection prevented tumour growth in 90% of early stage tumour-bearing mice, without adjuvants and/or drug treatments. These promising results may suggest that a safe anticancer immunotherapeutic vaccine may be available in the future for human use [94].

Targeted therapies

Evaluation of epithelial growth factor receptor (EGFR)-targeted therapies in HNSCC patients have been based on the observation that EGFR is highly expressed in HNSCC, and its over-expression has been associated with reduced survival in several studies [97]. For clinical use, EGFR can be targeted either by antibodies recognising the ligand-binding domain of EGFR or by EGRF tyrosine kinase inhibitors (TKIs). Cetuximab is a humanised mouse anti-EGFR IgG1 monoclonal antibody, offering improved loco-regional control and overall survival in locally-advanced HNSCC in combination with radiotherapy [98].

Other humanised anti-EGFR antibodies such a panitumumab or zalutumumab are currently being evaluated in phase II/III clinical trials and may evolve as alternatives to cetuximab [99]. Additional prospective clinical trials are on-going to assess the value of cetuximab in management of HPV-positive OPSCCs.

Conclusions

To date, the available data corroborate some well-established concepts: oropharynx tumours have been steadily increasing over the last 20 years compared to other cancers of the head and neck worldwide, particularly in Western countries. SEER data suggest that about 18% of all head and neck carcinomas in the USA were located in the oropharynx in 1973, compared to 31% of such squamous cell tumours in 2004. Similarly, in Sweden, the proportion of oropharyngeal cancers HPV positive has steadily increased, from 23% in the 1970s to 57% in the 1990s, and as high as 93% in 2007. These data indicate that HPV is now the primary cause of tonsillar cancer in North America and Europe.

The biology of HPV-positive oropharyngeal cancer is characterised by p53 degradation, retinoblastoma RB pathway inactivation and p16 up-regulation. In contrast, tobacco-related oropharyngeal cancer is characterised by p53 mutation and down-regulation of CDKN2A (encoding p16ink4A). HPV-positive oropharyngeal cancer seems to be more responsive to chemotherapy and radiation than HPV-negative disease.

The choice of the best viral detection method in tumours is a matter of controversy, and both in-situ hybridisation and PCR are commonly used; p16 IHC is also being used to detect HPV infection, but with unreliable results [71 72]. Thus, there is clearly a need for new surrogate markers for HPV infection to give patients the best treatment strategies.

The presence of HPV 16 can also be thought of as a prognostic marker for enhanced overall and disease-free survival, but its use as a predictive marker has not yet been proven. Many questions about the natural history of oral HPV infection are still under investigation.

Regarding disease management, based on the present information, we can consider HPV-positive oropharyngeal cancer as a distinct subset of HNSCC with a more favourable outcome. Patients with HPV-positive oropharyngeal cancer are typically young and in good health. In future clinical trials, cancer centres should stratify head and neck patients by HPV status. Regardless of treatment modality, an opportunity now exists to investigate less intense treatment strategies that do not compromise survival

outcomes, but lower the risk of fatal side effects. Thus, providing a high level quality of life with the fewest treatment complications are important considerations. Potential long-term side effects of concurrent chemoradiation include dysphagia, xerostomia, feeding-tube dependency from fibrosis and scarring of the pharyngeal muscles, chronic aspiration and chronic fatigue.

However, we must always emphasise that the best cure against cancer is prevention, especially in those malignancies in which the main pathogenic agent is known. Finally, the authors wish to suggest reader to consult two very recent and excellent reviews: "New insights into human papillomavirus-associated head and neck squamous cell carcinoma" [100] and "Human papilloma virus (HPV) in head and neck region: review of literature [101].

List of Abbreviations:

CTEP: Cancer therapy evaluation programme.
DHANCA: Danish Head And Neck Cancer Group.
DNA: Deoxynucleic acid
E6: Early oncoprotein6
E7: Early oncoprotein7
ECOG: Eastern Cooperative Oncology Group
FDA: Food and Drug Administration
EGFR: Epithelia Growth Factor Receptor
HNSCC: Head and Neck Squamous Cell Carcinoma
HPV: Human Papilloma Virus
ISH: in situ hybridization
NCCN: National Comprehensive Cancer Network
PCR: Polymerase Chain Reaction
pRb: retinoblastoma tumour suppressor
OPSCC: OroPharyngeal Squamous Cell Carcinoma
RTOG: Radiation Therapy Oncology Group
TKI: Tyrosine Kinase Inhibitors
TLM: Transoral Laser Microsurgery
TROG: Trans-Tasman Radiation Oncology Group
TORS: Trans Oral Robotic Surgery
USA: United States of America
BCL-XL: B-cell lymphoma-extra large
SEER: Surveillance, Epidemiology and End Results Program

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