Oral Oncology 108 (2020) 104736

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Perspectives

Summary from an international cancer seminar focused on human papillomavirus (HPV)-positive oropharynx cancer, convened by scientists at IARC and NCI

Aimée R. Kreimer[a,1], Anil K. Chaturvedi[a,1], Laia Alemany[b,c], Devasena Anantharaman[d], Freddie Bray[e], Mary Carrington[f,g], John Doorbar[h], Gypsyamber D'Souza[i], Carole Fakhry[i,j], Robert L. Ferris[k], Maura Gillison[l], D. Neil Hayes[m], Allan Hildesheim[a], Shao Hui Huang[n], Luiz P. Kowalski[o], Krystle A. Lang Kuhs[p], James Lewis Jr[p], Douglas R. Lowy[q,r], Hisham Mehanna[s], Andy Ness[t], Michael Pawlita[u], Maisa Pinheiro[a], John Schiller[q], Meredith S. Shiels[a], Joseph Tota[a], Lisa Mirabello[a], Saman Warnakulasuriya[v,w], Tim Waterboer[u], William Westra[x], Stephen Chanock[a,2], Paul Brennan[e,2,*]

[a] Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD, United States
[b] Catalan Institute of Oncology (ICO), IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain
[c] Epidemiology and Public Health, Centro de Investigación Biomédica en Red: Epidemiología y Salud Pública (CIBERESP), Instituto de Salud Carlos III, Madrid, Spain
[d] Rajiv Gandhi Centre for Biotechnology, Trivandrum, India
[e] International Agency for Research on Cancer, Lyon, France
[f] Basic Science Program, Frederick National Laboratory for Cancer Research, Frederick, MD, United States
[g] Ragon Institute of MGH, MIT and Harvard, Cambridge, MA, United States
[h] University of Cambridge, Cambridge, United Kingdom
[i] Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, United States
[j] Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins School of Medicine, Baltimore, MD, United States
[k] UPMC Hillman Cancer Center, Pittsburgh, PA, United States
[l] The University of Texas MD Anderson Cancer Center, Houston, TX, United States
[m] The University of Tennessee Health Science Center, Memphis, TN, United States
[n] University of Toronto, Princess Margaret Hospital, Toronto, Ontario, Canada
[o] A.C. Camargo Cancer Center, São Paulo, Brazil
[p] Vanderbilt University Medical Center, Nashville, TN, United States
[q] Laboratory of Cellular Oncology, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, MD, United States
[r] Office of the Director, National Cancer Institute, NIH, Bethesda, MD, United States
[s] Institute for Head and Neck Studies and Education, University of Birmingham, Birmingham, United Kingdom
[t] NIHR Bristol Biomedical Research Centre, University of Bristol NHS Foundation Trust and University of Bristol, Bristol, United Kingdom
[u] German Cancer Research Center (DKFZ), Heidelberg, Germany
[v] King's College London, London, United Kingdom
[w] WHO Collaborating Centre for Oral Cancer, United Kingdom
[x] Icahn School of Medicine at Mount Sinai, New York, NY, United States

* Corresponding author at: Genetic Epidemiology Group, International Agency for Research on Cancer (IARC), 150 Cours Albert Thomas, 69008 Lyon Cedex, France.

E-mail addresses: kreimera@mail.nih.gov (A.R. Kreimer), chaturva@mail.nih.gov (A.K. Chaturvedi), lalemany@iconcologia.net (L. Alemany), devasena@rgcb.res.in (D. Anantharaman), Brayf@iarc.fr (F. Bray), carringm@mail.nih.gov (M. Carrington), jd121@cam.ac.uk (J. Doorbar), Gdsouza2@jhu.edu (G. D'Souza), cfakhry@jhmi.edu (C. Fakhry), ferrrl@upmc.edu (R.L. Ferris), mgillison@mdanderson.org (M. Gillison), Neil.Hayes@uthsc.edu (D. Neil Hayes), hildesha@exchange.nih.gov (A. Hildesheim), ShaoHui.Huang@rmp.uhn.ca (S.H. Huang), lp_kowalski@uol.com.br (L.P. Kowalski), krystle.kuhs@vumc.org (K.A. Lang Kuhs), james.lewis@vanderbilt.edu (J. Lewis), lowyd@mail.nih.gov (D.R. Lowy), h.mehanna@bham.ac.uk (H. Mehanna), Andy.Ness@bristol.ac.uk (A. Ness), m.pawlita@dkfz-heidelberg.de (M. Pawlita), maisa.pinheiro@nih.gov (M. Pinheiro), schillej@dc37a.nci.nih.gov (J. Schiller), shielsms@mail.nih.gov (M.S. Shiels), joseph.tota@nih.gov (J. Tota), mirabellol@mail.nih.gov (L. Mirabello), saman.warne@kcl.ac.uk (S. Warnakulasuriya), T.Waterboer@dkfz-heidelberg.de (T. Waterboer), william.westra@mountsinai.org (W. Westra), hanocks@mail.nih.gov (S. Chanock), gep@iarc.fr (P. Brennan).

[1] Indicates co-first authors.
[2] Indicates co-last authors.

https://doi.org/10.1016/j.oraloncology.2020.104736
Received 13 March 2020; Received in revised form 14 April 2020; Accepted 20 April 2020
Available online 02 June 2020

ARTICLE INFO

Keywords:
HPV
Oropharynx cancer
Prevention
Genetics
Etiology
Screening
Therapy

ABSTRACT

Cancer of the oropharynx has attracted considerable attention in recent years given: (1) an increasing incidence in selected populations over the past three decades; (2) the discovery of human papillomavirus (HPV) infection as the driver of the increase, as opposed to the traditional risk factors such as tobacco (smoking and chewing) and alcohol; and (3) the promise of new prevention and treatment strategies. As a result of such developments, the International Agency for Research on Cancer (IARC) and the US National Cancer Institute (NCI), convened the fourth Cancer Seminar meeting in November 2018 to focus on this topic. This report summarizes the proceedings: a review of recent science on the descriptive epidemiology, etiology, biology, genetics, early detection, pathology and treatment of HPV-positive oropharyngeal cancer, and the formulation of key research questions to be addressed.

Introduction

A joint workshop led by the National Cancer Institute (NCI) and the International Agency for Research on Cancer (IARC) was held in November 2018 in Rockville, MD, USA, to discuss the state-of-the-science of HPV-positive oropharyngeal cancer epidemiology, etiology, biology, genetics, early detection, pathology and treatment. This perspective summarizes the meeting proceedings, including description of burden of disease, methods for ascertainment, HPV attributable fraction of disease, epidemiology of oral HPV and HPV-positive OPC, genetics and genomics, biology of HPV-positive OPC, prevention, and clinical -aspects.

Of note, several comprehensive reviews on HPV-positive oropharyngeal cancer have recently been published. Rather than update these reviews, we highlight important achievements and focus on key knowledge gaps and outstanding research questions.

Burden of HPV positive oropharyngeal cancer worldwide

Oropharyngeal cancer (OPC) includes lesions arising from these anatomic sites and subsites: the base of tongue/lingual tonsil (ICD-10 codes C01.9 and C2.4), palatine tonsil (C9.0, C09.1, C09.8, C09.9), oropharynx (C10.0 to C10.9, excluding C10.1, C110.4-7), pharyngeal tonsils (C11.1), soft palate (C05.1), uvula (C05.2), pharynx not otherwise specified (C14.0), and Waldeyer ring (C14.2) [1] Approximately 100,000 new cases of oropharyngeal cancer occur annually worldwide; regional differences in incidence can vary between 5/100,000 and 10/100,000 (for all ages) [2]. Despite notable declines in tobacco use, oropharyngeal cancer incidence has increased over recent decades in several high-income countries (e.g., Australia, Canada, Denmark, Japan, Netherlands, Norway, Sweden, Taiwan, USA, and the UK), initially among men < 60 years [1,3,4]. In many countries, molecular epidemiologic studies have established HPV infection as the cause of rising incidence [5–7]. It is hypothesized that oral HPV exposure increased as a result of changes in sexual behavior in birth cohorts from the 1930s to 1950s and decreases in tonsillectomy rates (which results in more tissue available for infection by the virus) account for the observed rise in HPV positive oropharyngeal cancer incidence in men since the 1990s [1,8,9].

In the USA, studies have documented changes in the oropharyngeal cancer incidence trajectory over the past decade, moderation of the original increases among mid-life individuals (ages 45–60 years), sustained increases among older ages (ages 65+ years), and the emergence of a modest rise in incidence in women [9,10]. It remains to be seen whether these emerging oropharyngeal cancer incidence trends will continue to persist in the USA and/or begin to manifest in other parts of the world (Table 1).

Methods for assessment of HPV presence in oropharyngeal cancer

Current methods for testing oropharyngeal cancer tumor tissues include HPV DNA detection, quantitative type-specific PCR, HPV DNA sequencing, detection of HPV E6/E7 mRNA, in-situ hybridization, and immunohistochemistry [11–15]. In studies that have compared HPV detection methods in oropharyngeal cancers show that the proportion that are positive for HPV is overestimated by HPV DNA genotyping alone but the combination of more rigorous markers tend to produce lower estimates for attributable fractions [11,12,16].

HPV attributable fraction in oropharyngeal cancer

Current estimates vary greatly. Between 5% and 80% of oropharyngeal cancers are attributable to HPV, with substantial geographic variability [17]. Regions with high HPV attributable fractions include northern Europe and the USA [11,16], which reflects the relative burden of tobacco-/alcohol-attributable oropharyngeal cancer as well as prevalent sexual practices. Worldwide, HPV16 causes the majority (> 90%) of HPV positive oropharyngeal cancer, followed by HPV33, HPV35 and HPV18 [11,18]. In contrast to cervical cancer, HPV33 is the second most frequent HPV type in oropharyngeal cancer and HPV18 is far less frequent. Robust data on HPV attributable fractions and trends over time are not available for many countries.

Epidemiology of oral HPV infection and HPV positive oropharyngeal cancer

To date, most published studies on the epidemiology of oral HPV infection suggest that oral HPV infection, the underlying cause of HPV positive oropharyngeal cancer, is rare in the general population—1% prevalence for HPV16 and < 5% prevalence for all other oncogenic HPV types, which most likely reflects the presence of subclinical or asymptomatic infections [19,20]. While oral HPV prevalence tends to be significantly higher among HIV populations, these increases do not translate to a substantially higher burden of oropharyngeal cancer in this population (i.e.: standardized incidence ratio < 3.0) [21].

Oral HPV is primarily transmitted through oral sex with an infected partner; consequently, infection prevalence is strongly associated with the number of lifetime as well as recent oral sexual partners [19]. Oral HPV prevalence displays a bi-modal age-pattern, with an initial peak at ages 25–30 years and a second peak at ages 55–60 years. It is unknown if this second peak reflects recent acquisition, reactivation of latent (immune controlled) infections due to age-related immune-senescence, or birth-cohort effects. Both oral HPV prevalence and HPV positive oropharyngeal cancer are more common in men [5,19,22]. The reasons for the male predominance is unknown. Current hypotheses include a heightened immune-susceptibility in males, e.g. because of less frequent seroconversion after genital infection, as well as greater transmission of HPV through the performance of oral sex on females [19,22]. The rates of incidence and persistence, and the predictors of HPV oral infection remain poorly characterized, mainly due to a paucity of studies of the natural history of oral HPV infection [23].

Smoking and alcohol, the traditional risk factors for oropharyngeal cancer, appear to be independently associated with risk of HPV positive oropharyngeal cancer. However, the interaction of these risk factors

with HPV remains unclear [24–30]. Little is known regarding the association of other established (tobacco/betel-quid chewing) or emerging factors (oral hygiene, oral microbiome) with risk of HPV positive oropharyngeal cancer.

Key outstanding research questions pertaining to the epidemiology of oral HPV/HPV positive oropharyngeal cancer include the confirmation and elucidation of the observed bimodal age-prevalence of oral HPV infection; male predominance; characterization of the natural history of oral HPV, with an emphasis on the steps between initial infection and the later development of cancer; and investigation of the role of established and emerging risk factors for HPV positive oropharyngeal cancer (Table 1).

Genetics and genomics

Recent genomic studies of HPV positive oropharyngeal cancer have focused on the tumor, host, and variation within the oncogenic virus. The Cancer Genome Atlas (TCGA) study of head and neck cancers included only 33 oropharyngeal cancer cases, the majority of which were HPV positive [31]. A subsequent comprehensive analysis of a larger dataset of HPV positive tumors demonstrated multiple genomic features that distinguish these tumors from HPV negative cancers [32]. These include unique mutation signatures, recurrent somatic mutations profiles, candidate driver genes, regions of subchromosomal gains and losses and gene expression profiles [31,32]. Patterns of chromosomal loss and gain for HPV positive tumors are consistent with other

Table 1
State-of-the-science and outstanding research questions on HPV positive oropharynx cancer.

Area	State-of-the-science	Key research areas/questions
Burden	– OPC incidence rates of 5–10/100,000 – HPV established as the cause of rising incidence in men (age 50 to 60) in developed countries – Geographic variability in contemporary HPV attributable proportions (5%-80%), with higher proportions (> 70%) in North America, northern Europe, and other countries – Emerging data on plateauing of rising incidence in young men in high income countries with now rising incidence in older ages, early signs of rising incidence in women, and rising incidence in additional countries .	– Is the rising incidence a phenomenon restricted to men (aged 50 to 60) in high income countries? – Have incidence rates in high income countries peaked? – Is HPV positive OPC increasing in low/middle income countries?
Epidemiology	– Oral HPV infection is primarily sexually transmitted – Prevalence follows a bimodal pattern with peaks at ages 25–30 and 55–60 years – Oral HPV prevalence and HPV positive OPC are more common in men – Presence of antibodies to HPV16E6 associated with a > 100-fold increased risk of OPC – Association of traditional risk factors (tobacco and alcohol) and emerging OPC risk factors remains poorly quantified, as does interaction of HPV with these risk factors	– Identification of the reasons for the bimodal age-prevalence pattern as well as the male predominance of oral HPV infection/-associated OPC – Estimation of the main effects and interactions of established and emerging factors (oral health/microbiome) towards risk of HPV positive OPC – Characterization of the natural history of oral HPV infection – Absolute risk of future OPC development for oral HPV DNA detection by age
Genetics and genomics	– HPV positive OPC characterized by different somatic mutational profiles compared to HPV negative OPC – Risk of HPV positive OPC associated with the HLA haplotype *DRB1*1301 – DQA1*0103 – DQB1*0603*	– Characterization of somatic changes in HPV positive OPC in large, representative studies – Further elucidation of the associations of host genetic polymorphisms with HPV positive OPC risk – Investigation of the role of viral genomics in risk of HPV positive OPC across geographic and ancestral backgrounds
Biology	– HPV16 causes over 90% of HPV positive OPC – HPV positive OPC arise from the specialized crypt epithelium in the lingual and palatine tonsils – High PD-L1 expression in the crypt epithelium provides immunological refuge for the infection/tumor Natural history of oral HPV infection, encompassing establishment of infection and progression to cancer, remains poorly characterized	– Characterization of the natural history of HPV induced carcinogenesis in the oropharynx, including estimation of latency and identification of precancerous states – Discovering the reasons for the unique susceptibility of the tonsil crypt epithelium to HPV16-carcinogenesis – Development of model systems to study HPV induced carcinogenesis in the oropharynx – Elucidation of the postulated immune-evasion processes in the crypt epithelium and development of therapeutic strategies targeting them
Prevention	– Prophylactic HPV vaccination has high efficacy against oral HPV infection prevalence – Markers of HPV exposure, such as systemic HPV16 E6 antibodies and oral HPV16 DNA, are strongly associated with risk of HPV positive OPC – Secondary prevention and early detection through screening is not currently feasible due to lack of an identifiable HPV induced precancerous lesion, screening modalities, and risk-mitigation strategies	– Understanding the relevance of the second age-peak in oral HPV prevalence for risk of HPV positive OPC – Estimation of the effectiveness of an extended upper age-limit for catch-up HPV vaccination – Discovery of HPV induced precancer in the oropharynx and the identification and validation of screening methods and treatment strategies for secondary prevention and early detection
Clinical care	– HPV positive OPC patients have higher survival than HPV negative OPC patients – HPV testing through p16 immunohistochemistry is currently recommended for all newly-diagnosed OPC patients and patients with unknown head and neck primaries – Revised cTNM and pTNM staging of HPV positive OPC in the AJCC 8th edition – Numerous investigations underway to determine optimal treatment de-escalation for HPV positive OPC patients	– Identification of markers to improve the accuracy of tumor HPV determination beyond p16 immunohistochemistry – Identification and incorporation of additional prognostic factors for improved staging of HPV positive OPC – Development and validation of prediction models to identify patients who could benefit from de-intensified treatments – Identification of optimal treatment protocols for HPV positive OPC patients that preserve disease control and reduce short-and-long-term treatment-related toxicities – Follow up biomarkers to detect recurrences in HPV driven OPC

OPC, oropharynx cancer.

squamous cell carcinomas [31,33–35]. When compared to HPV negative oral cancers, HPV positive cancers have significantly more frequent gains in 3q and losses of 11q, 13q, 14q, 16p and 16q [32]. By contrast, common amplifications of chromosome 7p and deletions of 9p containing the EGFR and CDKN2A genes, respectively, are rare in HPV positive oropharyngeal cancer when compared to other squamous carcinomas. The initial reports of a differential dependence on driver gene alterations extends to frequent amplifications of the transcription factor E2F1 and deletions or inactivating mutations of TRAF3. However, E2F1 is one of many genes whose expression is significantly altered by amplification in this chromosomal region. Notably, TRAF3 and E2F1 alterations frequently found in HPV positive oropharyngeal cancer are rare in cervical cancer. Emerging data also suggest a role for viral integration and structural alterations of the viral genome [36]. While these observations provide an initial assessment of the landscape of somatic events, ongoing larger studies will develop a more comprehensive genomic profile of HPV positive oropharyngeal cancer.

Germline genetic factors also play an important role in susceptibility to HPV positive oropharyngeal cancer and could also explain differences in response to treatment and survival. The human leukocyte antigen (HLA) region (6p21.3) influences susceptibility to HPV positive oropharyngeal cancer [37]. Specifically, a four-fold protective effect was observed with the HLA haplotype *DRB1*1301 - DQA1*0103 - DQB1*0603* for HPV positive but not HPV negative oropharyngeal cancer [37]. This haplotype has also been reported to be strongly protective against cervical cancer, which suggests specificity for HPV positive cancers. These observations imply a role for major histocompatibility class 2 genes in the recognition and elimination of HPV infection.

Analysis of the HPV genome is a rapidly evolving field that has provided insights into the molecular epidemiology and basic biology of HPV induced cervical cancer [38–40]. Recent studies show that HPV16 variants strongly influence risk of different histologic subtypes of cervical cancer and conservation of E7 oncogene is essential for carcinogenesis [38–40]. HPV genomics also influences risk of cervical cancer in distinct race/ethnic groups [39,41] and worldwide HPV type distribution [42,43]. Future studies of HPV genomics and oropharyngeal cancer are needed to address the unique susceptibility of the oropharynx to HPV16 induced carcinogenicity as well as explain the differences in HPV attributable fractions due to geographic or ancestral backgrounds.

Biology of HPV positive oropharyngeal cancer

HPV positive oropharyngeal cancer primarily arises from the specialized reticulated crypt epithelium in the lingual and palatine tonsils [44,45]. The stratified squamous surface epithelium of the tonsils invaginates into multiple crypts and transitions into the reticulated crypt epithelium. Little is known regarding the HPV induced carcinogenic process in the crypt epithelium, but it is anticipated that crypt epithelium facilitates virus infection by virtue of its reticulated structure, and that epithelial cells at this site support deregulated viral gene expression because they are controlled by different regulatory pathways than those that normally regulate the epithelial basal layer [46].

The unique architecture of the tonsillar crypts explains several clinical and histopathologic features of HPV positive oropharyngeal cancer [44,45]. HPV positive oropharyngeal cancer often retains the appearance of the reticulated epithelium lining the tonsillar crypts (i.e. permeating lymphocytes, basaloid cells), and thus might best be regarded as highly differentiated tumors rather than poorly differentiated when the crypt epithelium is used as a reference point of tumor differentiation. Although HPV positive oropharyngeal cancers are routinely characterized as non-keratinizing morphology, this reflects the histology of the normal tonsillar crypt [44,45]. Importantly, the tonsillar crypt epithelium is characterized as a discontinuous basement membrane [44,45]. This compromised barrier to tumor invasion may provide ready access of even small tumors to the underlying lymphatics. Indeed, HPV positive oropharyngeal cancers are characterized in TNM staging by lower T-category and greater nodal involvement when compared to HPV negative oropharyngeal cancer [47]. Such access of oropharyngeal tumor cells to regional lymph nodes is exemplified by the greater nodal involvement of squamous cell carcinoma originating in the oropharynx vs. the oral cavity. Although the occurrence of a virally-induced cancer in an immune-rich environment appears paradoxical, the crypt epithelium has high PD-L1 expression, which provides a mechanism for immune-evasion of the infection/tumor [44,45].

Key research questions pertaining to the biology and carcinogenesis of HPV positive oropharyngeal cancer include identification of reasons for the unique susceptibility of the crypt epithelium to HPV16-mediated carcinogenesis, development of model systems to study the carcinogenic processes in the oropharynx, elucidation of the postulated immune-evasion processes and identification of targeted therapeutic strategies.

Prevention of HPV positive oropharyngeal cancer

Although the current prophylactic HPV vaccines are not licensed for the prevention of oral HPV infections or oral cancers, vaccination likely confers strong (> 90%) protection against oral HPV infection prevalence, as evidenced in a post-hoc analysis of a randomized clinical trial of the bivalent HPV vaccine and in a US-representative surveillance study [48–50]. The World Heath Organization focuses their HPV recommendation on females given the overwhelming burden of HPV-associated cervical cancer; of the 630,000 new HPV-related cancers annually, > 85% are cancers of the cervix [51]. However, some countries with adequate cervical cancer screening programs now have similar burden of HPV disease in females and males. Consequently, gender neutral vaccination is recommended for adolescents/young adults. In the United States, for example, children aged nine to 26 years are recommended to receive the HPV vaccine, with an option for shared clinical decision making to the age of 45.[52] Importantly, while HPV vaccines have demonstrated oral HPV vaccine efficacy when administered to young adults, it is unknown whether HPV infections detected at older ages are incident or re-ermegent latent infections for which the vaccine would not protect; age at causal infection acquisition has not been modeled. Consequently, the effectiveness of an extended age catch-up vaccination program for the prevention of HPV positive oropharyngeal cancer is unclear, even if high vaccine efficacy is demonstrated at older ages.

Screening for secondary prevention and early-detection is being considered as a prevention strategy for HPV positive oropharyngeal cancer among older vaccine-ineligible individuals [53,54]. Current research efforts are focused on addressing the fundamental principles of screening and include [8,53]: 1) who to screen (identification of biomarkers and risk-stratification tools); 2) what to screen for (identification of an HPV induced precancer/early-cancer in the oropharynx); 3) how to screen (identification of screening modalities); and 4) how to manage screen-positive individuals (identification of appropriate treatments for precancer/early-stage cancer).

Recent studies have made considerable progress on the identification of biomarkers, such as systemic HPV antibodies or oral HPV DNA [55,56]. Antibodies against the oncoprotein E6 are considered markers of HPV positive oropharyngeal cancer. Antibodies are strongly associated with HPV induced tumors at or prior to cancer-diagnosis (> 100-fold risk). Seropositivity is rare (< 1% prevalence) in cancer-free individuals [55–58]. Specifically, HPV16 E6 antibody seropositivity has been reproducibly demonstrated to have high sensitivity (> 90%) and specificity (> 99%) for the diagnosis of concurrent HPV16-positive oropharyngeal cancer (tumor-HPV positivity by the gold-standard of E6*I mRNA-positivity) [59]. E6-seropositivity precedes cancer diagnosis by 5–15 years, underscoring its potential utility as a screening biomarker. HPV DNA detection in oral rinse samples among patients

with HPV-driven tumors (i.e., biomarker sensitivity) ranged from 30 to 77%; the range restricting to HPV type 16 was 45 to 82% [60–63]. A recent study demonstrated oral HPV DNA detection was 81% sensitive and 100% specific for the diagnosis of recurrent HPV 16-positive oropharyngeal cancer [64].

Despite the promising estimates for sensitivity and specificity, the current value these markers have for population-wide oropharyngeal cancer screening remains low because positive predictive value (PPV) is predicated on the prevalence of the disease. The estimated PPV for 10-year oropharyngeal cancer risk by either marker is low (< 10%) and the number needed to be screened for the identification of one HPV positive oropharyngeal cancer is approximately 13,000 [65]. In addition to the low PPV, there are additional limitations that make screening for HPV positive oropharyngeal cancer unfeasible. First, an HPV-induced precancer or early-stage cancer akin to carcinoma *in-situ* has yet to be described. Second, currently available imaging modalities, such as ultrasound and MRI, remain unproven for the identification of early-stage cancer. Third, there are no risk-mitigation strategies for the prevention of cancer through treatment of precancer/early cancer or reduction in morbidity/mortality through the treatment of early-cancer [8,54,66].

Collectively, these considerations argue against screening for HPV positive oropharyngeal cancer in clinical settings at this time. Yet, several risk-stratification tools, such as E6-seropositivity, are under active investigation and could enable cost-efficient design of studies to address the current challenges of identification of early stage HPV induced cancer, viable screening modalities, and risk-mitigation strategies.

Clinical aspects of HPV positive oropharyngeal cancer

HPV positive oropharyngeal cancer patients experience a 50% to 80% reduction in five-year risk of progression and death when compared to HPV negative oropharyngeal cancer patients (45% and 50%, respectively) [67–69]. The improved prognosis, coupled with the rapidly rising HPV positive incidence, has prompted the introduction of routine HPV testing of tumor samples, novel clinical and pathologic staging systems, and clinical trials of modified therapies for this patient population [70,71].

The College of American Pathologists and the American Society of Clinical Oncology recommend routine HPV testing of tumors from all newly-diagnosed oropharyngeal cancer patients and patients with unknown head and neck primaries to guide patient counseling and clinical trial design [70,71]. The recommended method for determination of tumor HPV status (primary tumor tissue) is p16 immunohistochemistry staining, though it has relatively low (85%) specificity. Oncogenic HPV testing through DNA or RNA in-situ hybridization may be recommended by clinicians, pathologists, or researchers.[70,71] Further, tumor HPV status is now included in the 8th edition of the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) staging manual [70,71].

The emergence of HPV-positive oropharyngeal cancer has led to the introduction of revised staging-systems [72,73]. Specifically, the AJCC/UICC 7th edition of TNM staging (TNM-7) for HPV positive oropharyngeal cancer was neither predictive of a patient's survival experience nor discriminatory of survival across stages I-IV. This was mainly due to lack of prognostication among TNM-7 N1-N2b subset which subsequently has been re-termed as cN1 in the 8th edition TNM (TNM-8) [72–75]. Thus, the AJCC recently introduced novel clinical and pathologic TNM classification in the 8th edition [72–74]. For HPV positive patients (determined by p16 immunohistochemistry staining), the clinical staging (cTNM) comprises stage I (T1-T2 and N0-N1); stage II (T3, N2); stage III (T4, N3), and stage IV (M1 disease). Importantly, this 8th TNM edition is predicted to reclassify nearly 50% M0 patients with stage IV disease by the 7th edition (TNM-7) as stage I disease [72–74]. The novel pathology TNM staging (pTNM) comprises stage I (pT1-T2, ≤ 4 nodes); stage II (pT1-T2, 5 + nodes); and stage III (pT3-T4, 5 + nodes) [72–74]. Recent validation analyses of the novel staging systems show improved discrimination of survival across stages for HPV-positive patients [76]. There is, however, controversy pertaining to prognostic differences in cTNM vs. pTNM as well as the lack of consideration in pTNM for laterality of nodes, radiographic extranodal extension and other patient factors [77].

Current treatment guidelines are similar for HPV positive and HPV negative oropharyngeal cancer patients [78,79]. However, in view of the typical HPV positive oropharyngeal cancer patient profile (i.e. good performance status, fewer co-morbidities) and high survival, the field is investigating treatment de-intensification strategies to reduce treatment toxicities, while preserving disease control [80–85]. These strategies include use of immunotherapy (nivolumab, pembrolizumab, or durvalumab for cisplatin-ineligible/resistant patients), reduction in radiation dose (surgery + radiotherapy or induction chemotherapy + radiotherapy), and surgery-alone for very-low-risk patients [80–84,86–88].

Key research questions pertaining to clinical aspects of HPV positive oropharyngeal cancer include further development of risk stratification tools, increased precision of diagnostic modalities, improvements in the accuracy of tumor HPV determination beyond p16 immunohistochemistry, improvements in staging scheme to incorporate additional prognostic variables, such as extracapsular spread of disease, and importantly, the identification of patients most likely to benefit from treatment de-escalation.

Conclusion

Research over the past 20 years has established HPV positive oropharyngeal cancer as an important disease entity in many countries, with unique epidemiologic, molecular, pathologic, and clinical characteristics. Yet, as outlined in this meeting report, many key questions remain. Ongoing multidisciplinary collaborations across laboratory scientists, geneticists, epidemiologists, and clinicians hold promise for improved characterization of the burden, etiology, and natural history of HPV positive oropharyngeal cancer, and ultimately, the identification of effective prevention (beyond the current vaccination schedules which will only have an impact after several decades) and treatment strategies for this disease in the near future.

Funding

The meeting was funded jointly by the International Agency for Research on Cancer (IARC) and the Division of Cancer Epidemiology and Genetics (DCEG) of the US National Cancer Institute Intramural Research Program (no grant number applicable).

Declaration of Interests

The authors have declared no conflicts of interest.

Acknowledgements

The authors thank Ms. Betty Yu for her assistance organizing the meeting and Dr. Mónica S. Sierra for her assistance in finalizing manuscript. Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

References

[1] Chaturvedi AK, Anderson WF, Lortet-Tieulent J, Curado MP, Ferlay J, Franceschi S, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. J Clin Oncol 2013;31:4550–9. https://doi.org/10.1200/JCO.2013.50.3870.

[2] Shield KD, Ferlay J, Jemal A, Sankaranarayanan R, Chaturvedi AK, Bray F, et al. The global incidence of lip, oral cavity, and pharyngeal cancers by subsite in 2012. CA Cancer J Clin 2017;67:51–64. https://doi.org/10.3322/caac.21384.

[3] Hwang TZ, Hsiao JR, Tsai CR, Chang JS. Incidence trends of human papillomavirus-

related head and neck cancer in Taiwan, 1995–2009. Int J Can 2015;137:395–408. https://doi.org/10.1002/ijc.29330.
[4] Mork J, Moller B, Dahl T, Bray F. Time trends in pharyngeal cancer incidence in Norway 1981–2005: a subsite analysis based on a reabstraction and recoding of registered cases. Can Causes Control 2010;21:1397–405. https://doi.org/10.1007/s10552-010-9567-9.
[5] Chaturvedi AK, Engels EA, Pfeiffer RM, Hernandez BY, Xiao W, Kim E, et al. Human papillomavirus and rising oropharyngeal cancer incidence in the United States. J Clin Oncol 2011;29:4294–301. https://doi.org/10.1200/JCO.2011.36.4596.
[6] Hammarstedt L, Lindquist D, Dahlstrand H, Romanitan M, Dahlgren LO, Joneberg J, et al. Human papillomavirus as a risk factor for the increase in incidence of tonsillar cancer. Int J Can 2006;119:2620–3. https://doi.org/10.1002/ijc.22177.
[7] Hocking JS, Stein A, Conway EL, Regan D, Grulich A, Law M, et al. Head and neck cancer in Australia between 1982 and 2005 show increasing incidence of potentially HPV-associated oropharyngeal cancers. Br J Can. 2011;104:886–91. https://doi.org/10.1038/sj.bjc.6606091.
[8] Gillison ML, Chaturvedi AK, Anderson WF, Fakhry C. Epidemiology of human papillomavirus-positive head and neck squamous cell carcinoma. J Clin Oncol 2015;33:3235–42. https://doi.org/10.1200/JCO.2015.61.6995.
[9] Zumsteg ZS, Cook-Wiens G, Yoshida E, Shiao SL, Lee NY, Mita A, et al. Incidence of oropharyngeal cancer among elderly patients in the United States. JAMA Oncol 2016;2:1617–23. https://doi.org/10.1001/jamaoncol.2016.1804.
[10] Tota JE, Best AF, Zumsteg ZS, Gillison ML, Rosenberg PS, Chaturvedi AK. Evolution of the oropharynx cancer epidemic in the United States: moderation of increasing incidence in younger individuals and shift in the burden to older individuals. J Clin Oncol 2019;37:1538–46. https://doi.org/10.1200/JCO.19.00370.
[11] Castellsague X, Alemany L, Quer M, Halec G, Quiros B, Tous S, et al. HPV involvement in head and neck cancers: comprehensive assessment of biomarkers in 3680 patients. J Natl Cancer Inst 2016;108:djv403. https://doi.org/10.1093/jnci/djv403.
[12] Holzinger D, Schmitt M, Dyckhoff G, Benner A, Pawlita M, Bosch FX. Viral RNA patterns and high viral load reliably define oropharynx carcinomas with active HPV16 involvement. Can Res 2012;72:4993–5003. https://doi.org/10.1158/0008-5472.CAN-11-3934.
[13] Boscolo-Rizzo P, Pawlita M, Holzinger D. From HPV-positive towards HPV-driven oropharyngeal squamous cell carcinomas. Can Treat Rev 2016;42:24–9. https://doi.org/10.1016/j.ctrv.2015.10.009.
[14] Mena M, Taberna M, Tous S, Marquez S, Clavero O, Quiros B, et al. Double positivity for HPV-DNA/p16(ink4a) is the biomarker with strongest diagnostic accuracy and prognostic value for human papillomavirus related oropharyngeal cancer patients. Oral Oncol 2018;78:137–44. https://doi.org/10.1016/j.oraloncology.2018.01.010.
[15] Smeets SJ, Hesselink AT, Speel EJ, Haesevoets A, Snijders PJ, Pawlita M, et al. A novel algorithm for reliable detection of human papillomavirus in paraffin embedded head and neck cancer specimen. Int J Can 2007;121:2465–72. https://doi.org/10.1002/ijc.22980.
[16] Ndiaye C, Mena M, Alemany L, Arbyn M, Castellsague X, Laporte L, et al. HPV DNA, E6/E7 mRNA, and p16INK4a detection in head and neck cancers: a systematic review and meta-analysis. Lancet Oncol 2014;15:1319–31. https://doi.org/10.1016/S1470-2045(14)70471-1.
[17] de Martel C, Plummer M, Vignat J, Franceschi S. Worldwide burden of cancer attributable to HPV by site, country and HPV type. Int J Can 2017;141:664–70. https://doi.org/10.1002/ijc.30716.
[18] Saraiya M, Unger ER, Thompson TD, Lynch CF, Hernandez BY, Lyu CW, et al. US assessment of HPV types in cancers: implications for current and 9-valent HPV vaccines. J Natl Can Inst 2015;107:djv086. https://doi.org/10.1093/jnci/djv086.
[19] Gillison ML, Broutian T, Pickard RK, Tong ZY, Xiao W, Kahle L, et al. Prevalence of oral HPV infection in the United States, 2009–2010. JAMA 2012;307:693–703. https://doi.org/10.1001/jama.2012.101.
[20] Wood ZC, Bain CJ, Smith DD, Whiteman DC, Antonsson A. Oral human papillomavirus infection incidence and clearance: a systematic review of the literature. J Gen Virol 2017;98:519–26. https://doi.org/10.1099/jgv.0.000727.
[21] Chaturvedi AK, Madeleine MM, Biggar RJ, Engels EA. Risk of human papillomavirus-associated cancers among persons with AIDS. J Natl Cancer Inst 2009;101:1120–30. https://doi.org/10.1093/jnci/djp205.
[22] Chaturvedi AK, Graubard BI, Broutian T, Pickard RK, Tong ZY, Xiao W, et al. NHANES 2009-2012 Findings: Association of Sexual Behaviors with Higher Prevalence of Oral Oncogenic Human Papillomavirus Infections in U.S. Men. Cancer Res. 2015;75:2468-77. https://doi.org/10.1158/0008-5472.CAN-14-2843.
[23] Kreimer AR, Pierce Campbell CM, Lin HY, Fulp W, Papenfuss MR, Abrahamsen M, et al. Incidence and clearance of oral human papillomavirus infection in men: the HIM cohort study. Lancet 2013. https://doi.org/10.1016/S0140-6736(13)60809-0.
[24] Anantharaman D, Muller DC, Lagiou P, Ahrens W, Holcatova I, Merletti F, et al. Combined effects of smoking and HPV16 in oropharyngeal cancer. Int J Epidemiol 2016;45:752–61. https://doi.org/10.1093/ije/dyw069.
[25] Applebaum KM, Furniss CS, Zeka A, Posner MR, Smith JF, Bryan J, et al. Lack of association of alcohol and tobacco with HPV16-associated head and neck cancer. J Natl Cancer Inst 2007;99:1801–10. https://doi.org/10.1093/jnci/djm233.
[26] Chaturvedi AK, D'Souza G, Gillison ML, Katki HA. Burden of HPV-positive oropharynx cancers among ever and never smokers in the U.S. population. Oral Oncol 2016;60:61–7. https://doi.org/10.1016/j.oraloncology.2016.06.006.
[27] Gillison ML, D'Souza G, Westra W, Sugar E, Xiao W, Begum S, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. J Natl Cancer Inst 2008;100:407–20. https://doi.org/10.1093/jnci/djn025.
[28] Herrero R, Castellsague X, Pawlita M, Lissowska J, Kee F, Balaram P, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. J Natl Cancer Inst 2003;95:1772–83. https://doi.org/10.1093/jnci/djg107.
[29] Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM, et al. Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection. J Natl Cancer Inst 1998;90:1626–36. https://doi.org/10.1093/jnci/90.21.1626.
[30] Smith EM, Ritchie JM, Summersgill KF, Hoffman HT, Wang DH, Haugen TH, et al. Human papillomavirus in oral exfoliated cells and risk of head and neck cancer. J Natl Cancer Inst 2004;96:449–55. https://doi.org/10.1093/jnci/djh074.
[31] Network Cancer Genome Atlas. Comprehensive genomic characterization of head and neck squamous cell carcinomas. Nature 2015;517:576–82. https://doi.org/10.1038/nature14129.
[32] Gillison ML, Akagi K, Xiao W, Jiang B, Pickard RKL, Li J, et al. Human papillomavirus and the landscape of secondary genetic alterations in oral cancers. Genome Res 2019;29:1–17. https://doi.org/10.1101/gr.241141.118.
[33] Cancer Genome Atlas Research Network. Comprehensive genomic characterization of squamous cell lung cancers. Nature 2012;489:519–25. https://doi.org/10.1038/nature11404.
[34] Cancer Genome Atlas Research Network, Albert Einstein College of Medicine, Analytical Biological Services, Barretos Cancer Hospital, Baylor College of Medicine, Beckman Research Institute of City of Hope, et al. Integrated genomic and molecular characterization of cervical cancer. Nature. 2017;543:378-84. https://doi.org/10.1038/nature21386.
[35] Cancer Genome Atlas Research Network, Analysis Working Group: Asan University, B. C. Cancer Agency, Brigham and Women's Hospital, Broad Institute, Brown University, et al. Integrated genomic characterization of oesophageal carcinoma. Nature. 2017;541:169-75. https://doi.org/10.1038/nature20805.
[36] Parfenov M, Pedamallu CS, Gehlenborg N, Freeman SS, Danilova L, Bristow CA, et al. Characterization of HPV and host genome interactions in primary head and neck cancers. Proc Natl Acad Sci USA 2014;111:15544–9. https://doi.org/10.1073/pnas.1416074111.
[37] Lesseur C, Diergaarde B, Olshan AF, Wunsch-Filho V, Ness AR, Liu G, et al. Genome-wide association analyses identify new susceptibility loci for oral cavity and pharyngeal cancer. Nat Genet 2016;48:1544–50. https://doi.org/10.1038/ng.3685.
[38] Mirabello L, Clarke MA, Nelson CW, Dean M, Wentzensen N, Yeager M, et al. The Intersection of HPV Epidemiology, Genomics and Mechanistic Studies of HPV-Mediated Carcinogenesis. Viruses. 2018;10. https://doi.org/10.3390/v10020080.
[39] Mirabello L, Yeager M, Cullen M, Boland JF, Chen Z, Wentzensen N, et al. HPV16 Sublineage Associations With Histology-Specific Cancer Risk Using HPV Whole-Genome Sequences in 3200. Women. J Natl Cancer Inst 2016;108. https://doi.org/10.1093/jnci/djw100.
[40] Mirabello L, Yeager M, Yu K, Clifford GM, Xiao Y, Zhu B, et al. HPV16 E7 genetic conservation is critical to carcinogenesis. Cell 2017;170(1164–74):e6https://doi.org/10.1016/j.cell.2017.08.001.
[41] Xi LF, Koutsky LA, Hildesheim A, Galloway DA, Wheeler CM, Winer RL, et al. Risk for high-grade cervical intraepithelial neoplasia associated with variants of human papillomavirus types 16 and 18. Can Epidemiol Biomarkers Prev. 2007;16:4–10. https://doi.org/10.1158/1055-9965.Epi-06-0670.
[42] Nicolas-Parraga S, Alemany L, de Sanjose S, Bosch FX, Bravo IG. Differential HPV16 variant distribution in squamous cell carcinoma, adenocarcinoma and adenosquamous cell carcinoma. Int J Can 2017;140:2092–100. https://doi.org/10.1002/ijc.30636.
[43] Chen Z, Ho WCS, Boon SS, Law PTY, Chan MCW, DeSalle R, et al. J Virol 2017;91. https://doi.org/10.1128/jvi.01285-17.
[44] Lyford-Pike S, Peng S, Young GD, Taube JM, Westra WH, Akpeng B, et al. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Can Res 2013;73:1733–41. https://doi.org/10.1158/0008-5472.CAN-12-2384.
[45] Pai SI, Westra WH. Molecular pathology of head and neck cancer: implications for diagnosis, prognosis, and treatment. Annu Rev Pathol 2009;4:49–70. https://doi.org/10.1146/annurev.pathol.4.110807.092158.
[46] Egawa N, Egawa K, Griffin H, Doorbar J. Human papillomaviruses; epithelial tropisms, and the development of neoplasia. Viruses 2015;7:3863–90. https://doi.org/10.3390/v7072802.
[47] Huang SH, Xu W, Waldron J, Siu L, Shen X, Tong L, et al. Refining American Joint Committee on Cancer/Union for International Cancer Control TNM stage and prognostic groups for human papillomavirus-related oropharyngeal carcinomas. J Clin Oncol 2015;33:836–45. https://doi.org/10.1200/jco.2014.58.6412.
[48] Chaturvedi AK, Graubard BI, Broutian T, Pickard RKL, Tong ZY, Xiao W, et al. Effect of Prophylactic Human Papillomavirus (HPV) Vaccination on Oral HPV Infections Among Young Adults in the United States. J Clin Oncol 2017;36:262–7. https://doi.org/10.1200/JCO.2017.75.0141.
[49] Herrero R, Quint W, Hildesheim A, Gonzalez P, Struijk L, Katki HA, et al. Reduced prevalence of oral human papillomavirus (HPV) 4 years after bivalent HPV vaccination in a randomized clinical trial in Costa Rica. PLoS ONE 2013;8:e68329https://doi.org/10.1371/journal.pone.0068329.
[50] Schlecht NF, Masika M, Diaz A, Nucci-Sack A, Salandy A, Pickering S, et al. Risk of Oral Human Papillomavirus Infection Among Sexually Active Female Adolescents Receiving the Quadrivalent Vaccine. JAMA Network Open. 2019;2:e1914031-e. https://doi.org/10.1001/jamanetworkopen.2019.14031.
[51] World Health Organization. Global Cancer Observatory. International Agency for Research on Cancer. Cervix uteri fact sheet. 2018.
[52] Petrosky E, Bocchini Jr. JA, Hariri S, Chesson H, Curtis CR, Saraiya M, et al. Use of 9-valent human papillomavirus (HPV) vaccine: updated HPV vaccination recommendations of the advisory committee on immunization practices. MMWR

Morb Mortal Wkly Rep. 2015;64.
[53] Kreimer AR. Prospects for prevention of HPV-driven oropharynx cancer. Oral Oncol. 2013;50:555–9. https://doi.org/10.1016/j.oraloncology.2013.06.007.
[54] Kreimer AR, Shiels MS, Fakhry C, Johansson M, Pawlita M, Brennan P, et al. Screening for human papillomavirus-driven oropharyngeal cancer: Considerations for feasibility and strategies for research. Cancer 2018;124:1859–66. https://doi.org/10.1002/cncr.31256.
[55] Kreimer AR, Johansson M, Waterboer T, Kaaks R, Chang-Claude J, Drogen D, et al. Evaluation of human papillomavirus antibodies and risk of subsequent head and neck cancer. J Clin Oncol 2013;31:2708–15. https://doi.org/10.1200/JCO.2012.47.2738.
[56] Kreimer AR, Johansson M, Yanik EL, Katki HA, Check DP, Lang Kuhs KA, et al. Kinetics of the human papillomavirus Type 16 E6 antibody response prior to oropharyngeal. Cancer J Natl Cancer Inst 2017;109. https://doi.org/10.1093/jnci/djx005.
[57] Lang Kuhs KA, Anantharaman D, Waterboer T, Johansson M, Brennan P, Michel A, et al. Human papillomavirus 16 E6 antibodies in individuals without diagnosed cancer: a pooled analysis. Can Epidemiol Biomarkers Prev 2015;24:683–9. https://doi.org/10.1158/1055-9965.EPI-14-1217.
[58] Kreimer AR, Ferreiro-Iglesias A, Nygard M, Bender N, Schroeder L, Hildesheim A, et al. Timing of HPV16-E6 antibody seroconversion before OPSCC: findings from the HPVC3 consortium. Ann Oncol 2019;30:1335–43. https://doi.org/10.1093/annonc/mdz138.
[59] Lang Kuhs KA, Kreimer AR, Trivedi S, Holzinger D, Pawlita M, Pfeiffer RM, et al. Human papillomavirus 16 E6 antibodies are sensitive for human papillomavirus-driven oropharyngeal cancer and are associated with recurrence. Cancer 2017;123:4382–90. https://doi.org/10.1002/cncr.30966.
[60] D'Souza G, Gross ND, Pai SI, Haddad R, Anderson KS, Rajan S, et al. Oral human papillomavirus (HPV) infection in HPV-positive patients with oropharyngeal cancer and their partners. J Clin Oncol 2014;32:2408–15. https://doi.org/10.1200/JCO.2014.55.1341.
[61] Agrawal Y, Koch WM, Xiao W, Westra WH, Trivett AL, Symer DE, et al. Oral human papillomavirus infection before and after treatment for human papillomavirus 16-positive and human papillomavirus 16-negative head and neck squamous cell carcinoma. Clin Can Res 2008;14:7143–50. https://doi.org/10.1158/1078-0432.CCR-08-0498.
[62] Rettig EM, Wentz A, Posner MR, Gross ND, Haddad RI, Gillison ML, et al. Prognostic implication of persistent human papillomavirus type 16 DNA detection in oral rinses for human papillomavirus-related oropharyngeal carcinoma. JAMA Oncology 2015;1:907–15. https://doi.org/10.1001/jamaoncol.2015.2524.
[63] Martin-Gomez L, Fulp WJ, Schell MJ, Sirak B, Abrahamsen M, Isaacs-Soriano KA, et al. Oral gargle-tumor biopsy human papillomavirus (HPV) agreement and associated factors among oropharyngeal squamous cell carcinoma (OPSCC) cases. Oral Oncol 2019;92:85–91. https://doi.org/10.1016/j.oraloncology.2019.03.019.
[64] Fakhry C, Blackford AL, Neuner G, Xiao W, Jiang B, Agrawal A, et al. Association of oral human papillomavirus DNA persistence with cancer progression after primary treatment for oral cavity and oropharyngeal squamous cell carcinoma. JAMA Oncol. 2019;1:985–92. https://doi.org/10.1001/jamaoncol.2019.0439.
[65] Tota JE, Gillison ML, Katki HA, Kahle L, Pickard RK, Xiao W, et al. Development and validation of an individualized risk prediction model for oropharynx cancer in the US population. Cancer 2019;125:4407–16. https://doi.org/10.1002/cncr.32412.
[66] Kreimer AR, Chaturvedi AK. HPV-associated Oropharyngeal Cancers-Are They Preventable? Cancer Prev Res (Phila). 2011;4:1346–9. https://doi.org/10.1158/1940-6207.CAPR-11-0379.
[67] Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tan PF, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med. 2010;363:24–35. https://doi.org/10.1056/NEJMoa0912217.
[68] Fakhry C, Westra WH, Li S, Cmelak A, Ridge JA, Pinto H, et al. Improved survival of patients with human papillomavirus-positive head and neck squamous cell carcinoma in a prospective clinical trial. J Natl Cancer Inst. 2008;100:261–9. https://doi.org/10.1093/jnci/djn011.
[69] Sedghizadeh PP, Billington WD, Paxton D, Ebeed R, Mahabady S, Clark GT, et al. Is p16-positive oropharyngeal squamous cell carcinoma associated with favorable prognosis? A systematic review and meta-analysis. Oral Oncol 2016;54:15–27. https://doi.org/10.1016/j.oraloncology.2016.01.002.
[70] Fakhry C, Lacchetti C, Rooper LM, Jordan RC, Rischin D, Sturgis EM, et al. Human papillomavirus testing in head and neck carcinomas: ASCO clinical practice guideline endorsement of the college of american pathologists guideline. J Clin Oncol 2018;36:3152–61. https://doi.org/10.1200/JCO.18.00684.
[71] Lewis Jr. JS, Beadle B, Bishop JA, Chernock RD, Colasacco C, Lacchetti C, et al. Human papillomavirus testing in head and neck carcinomas: guideline from the college of american pathologists. Arch Pathol Lab Med 2018;142:559–97. https://doi.org/10.5858/arpa.2017-0286-CP.
[72] Lydiatt W, O'Sullivan B, Patel S. Major changes in head and neck staging for 2018. Am Soc Clin Oncol Educ Book. 2018;38:505–14. https://doi.org/10.1200/EDBK_199697.
[73] Huang SH, O'Sullivan B. Overview of the 8th Edition TNM Classification for Head and Neck Cancer. Curr Treat Options Oncol. 2017;18:40. https://doi.org/10.1007/s11864-017-0484-y.
[74] O'Sullivan B, Huang SH, Su J, Garden AS, Sturgis EM, Dahlstrom K, et al. Development and validation of a staging system for HPV-related oropharyngeal cancer by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S): a multicentre cohort study. Lancet Oncol. 2016;17:440–51. https://doi.org/10.1016/S1470-2045(15)00560-4.
[75] Husain ZA, Chen T, Corso CD, Wang Z, Park H, Judson B, et al. A Comparison of prognostic ability of staging systems for human papillomavirus-related oropharyngeal squamous cell carcinoma. JAMA Oncol. 2017;3:358–65. https://doi.org/10.1001/jamaoncol.2016.4581.
[76] Zhan KY, Eskander A, Kang SY, Old MO, Ozer E, Agrawal AA, et al. Appraisal of the AJCC 8th edition pathologic staging modifications for HPV-positive oropharyngeal cancer, a study of the National Cancer Data Base. Oral Oncol. 2017;73:152-9. https://doi.org/10.1016/j.oraloncology.2017.08.020.
[77] Fakhry C, Zevallos JP, Eisele DW. Imbalance Between Clinical and Pathologic Staging in the Updated American Joint Commission on Cancer Staging System for Human Papillomavirus-Positive Oropharyngeal Cancer. J Clin Oncol 2018;36:217–9. https://doi.org/10.1200/JCO.2017.75.2063.
[78] Colevas AD, Yom SS, Pfister DG, Spencer S, Adelstein D, Adkins D, et al. Guidelines Insights: Head and Neck Cancers, Version 1.2018. J Natl Compr Canc Netw. 2018;16:479–90. https://doi.org/10.6004/jnccn.2018.0026.
[79] Adelstein DJ, Ismaila N, Ku JA, Burtness B, Swiecicki PL, Mell L, et al. Role of Treatment Deintensification in the Management of p16 + Oropharyngeal Cancer: ASCO Provisional Clinical Opinion. J Clin Oncol. 2019;37:1578–89. https://doi.org/10.1200/JCO.19.00441.
[80] Mesia R, Taberna M. HPV-related oropharyngeal carcinoma de-escalation protocols. Lancet Oncol. 2017;18:704–5. https://doi.org/10.1016/S1470-2045(17)30250-4.
[81] Taberna M, Mena M, Pavon MA, Alemany L, Gillison ML, Mesia R. Human papillomavirus-related oropharyngeal cancer. Ann Oncol. 2017;28:2386–98. https://doi.org/10.1093/annonc/mdx304.
[82] Bhatia A, Burtness B. Human Papillomavirus-Associated Oropharyngeal Cancer: Defining Risk Groups and Clinical Trials. J Clin Oncol. 2015;33:3243–50. https://doi.org/10.1200/JCO.2015.61.2358.
[83] Mehanna H. Update on De-intensification and Intensification Studies in HPV. Recent Results Cancer Res. 2017;206:251–6. https://doi.org/10.1007/978-3-319-43580-0_20.
[84] Oosthuizen JC, Doody J. De-intensified treatment in human papillomavirus-positive oropharyngeal cancer. Lancet 2019;393:5–7. https://doi.org/10.1016/S0140-6736(18)32930-1.
[85] Masterson L, Moualed D, Liu ZW, Howard JE, Dwivedi RC, Tysome JR, et al. De-escalation treatment protocols for human papillomavirus-associated oropharyngeal squamous cell carcinoma: a systematic review and meta-analysis of current clinical trials. Eur J Cancer. 2014;50:2636–48. https://doi.org/10.1016/j.ejca.2014.07.001.
[86] Howard J, Dwivedi RC, Masterson L, Kothari P, Quon H, Holsinger FC. De-intensified adjuvant (chemo)radiotherapy versus standard adjuvant chemoradiotherapy post transoral minimally invasive surgery for resectable HPV-positive oropharyngeal carcinoma. Cochrane Database Syst Rev. 2018;12:CD012939. https://doi.org/10.1002/14651858.CD012939.pub2.
[87] Gillison ML, Trotti AM, Harris J, Eisbruch A, Harari PM, Adelstein DJ, et al. Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial. Lancet 2019;393:40–50. https://doi.org/10.1016/S0140-6736(18)32779-X.
[88] Mehanna H, Robinson M, Hartley A, Kong A, Foran B, Fulton-Lieuw T, et al. Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial. Lancet 2019;393:51–60. https://doi.org/10.1016/S0140-6736(18)32752-1.