75th Anniversary Commentary

HPV-Associated Head and Neck Cancer

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Abstract

Over the last two decades, it has been recognized that head and neck cancers, primarily in the oropharynx, can be a distinct entity that is causally related to human papilloma virus (HPV). Fakhry et al. (1) established in 2008 that such tumors have a strikingly better prognosis with improved responsiveness to chemotherapy as well as chemoradiotherapy and favorable survival rates. Since then, new studies have contributed to our increased understanding of this new entity, ranging from a detailed understanding of the genetic fingerprint and risk modifiers such as smoking to successful early attempts to personalize therapy with de-escalation in the definitive intent treatment setting and specific evaluation of targeted therapies in this patient population. This Commentary seeks to summarize the state of the art of our understanding of HPV-associated head and neck cancers that has emerged since the publication of seminal findings by Fakhry et al.

Head and neck squamous cell carcinoma (HNSCC) is the fifth most common non-skin cancer worldwide, with an annual incidence of 600,000 cases and about 60,000 cases annually in the United States and Europe (2). Traditionally, HNSCC has been understood as a homogeneous entity with regards to its smoking- and alcohol-related carcinogenesis, squamous cell histopathology, and biologic behavior characterized by predominant locoregional progression and recurrence after treatment. However, it is anatomically heterogeneous arising from the oral cavity, pharynx, and larynx with distinct symptomatology and surgical or radiotherapeutic approaches (3). During the past decade, infection with high-risk human papillomaviruses (HPVs), in particular HPV16, has emerged as a newly recognized risk factor for a fraction of HNSCCs, specifically HNSCCs arising in the oropharynx (tonsil, base of tongue, and soft palate) (1,4–7).

HNSCC most commonly presents as locoregionally advanced primary disease, usually with regional neck node involvement. Both the primary site and lymph nodes can be bulky and associated with symptoms of compromised speech, swallowing, and breathing as well as pain and infection. Following curative intent, stage-appropriate therapy with surgery and/or (chemo)radiation, about 40% to 50% of non-HPV-associated patients will develop disease recurrence, usually locoregionally. Systemic disease recurrence is less common, although more frequently seen when highly effective locoregional treatment approaches are applied (8,9). Once disease recurs or is metastatic outside the neck, the prognosis is universally poor, with few effective therapeutic options and a median life expectancy of only 10 months. Concomitant chemoradiotherapy or induction chemotherapy prior to radiation or surgery are commonly used with the overall body of evidence favoring the former approach. Similarly, organ preservation for laryngeal cancer should be regarded as standard of care for most patients (10). Single modality surgery and radiation are used for early-stage disease.

During the 1980s and 90s, evidence emerged that an increasing fraction (recently estimated as high as 70% in the United States) of oropharyngeal cancers was associated with high-risk human papilloma viruses, primarily HPV16 (11–13). In 2000, Gillison et al. (4) provided compelling evidence for a causal association between HPV and oropharyngeal cancer. Using polymerase chain reaction–based assays, southern blot, and in situ hybridization, they were able to detect HPV in 25% of 253 patients and described a strikingly better prognosis with improved responsiveness to chemotherapy as well as chemoradiotherapy and favorable survival rates. Since then, new studies have contributed to our increased understanding of this new entity, ranging from a detailed understanding of the genetic fingerprint and risk modifiers such as smoking to successful early attempts to personalize therapy with de-escalation in the definitive intent treatment setting and specific evaluation of targeted therapies in this patient population. This Commentary seeks to summarize the state of the art of our understanding of HPV-associated head and neck cancers that has emerged since the publication of seminal findings by Fakhry et al.
treated with two cycles of paclitaxel and carboplatin induction chemotherapy, followed by concomitant chemoradiotherapy using weekly paclitaxel. Oncogenic HPV was detected in 40% of patients. The patients with HPV-positive tumors had higher response rates and an improved two-year overall survival of 95% compared with 62% of patients with HPV-negative tumors.

**Epidemiology and Regional Differences in Incidence**

Much epidemiological work has been published in recent years. Rates of HPV-related oropharyngeal cancers have been rapidly rising in Western countries while the incidence of alcohol- and smoking-related tumors has decreased. As in other HPV-related tumors such as cervical and anal/rectal carcinomas, sexual transmission has been established and linked to the number of sexual partners as well as specific sexual practices such as oral sex.

While the United States and Europe are experiencing a substantial and increasing number of HPV-associated head and neck cancer (HNC) cases every year, the overall incidence of HPV-associated head and neck cancers remains comparatively low in many Asian countries (14–16). Within the United States, regional differences may exist, with many urban centers reporting a majority of new HNC diagnoses being HPV related, while non-urban centers still see higher proportions of HPV-negative tumors, which in part may be related to regional differences in tobacco use.

In 2008, Chaturvedi et al. described an increase in HPV-related oropharyngeal cases among younger white men based on data from nine Surveillance, Epidemiology, and End Results (SEER) program registries obtained between 1973 and 2004 (17). HPV-unrelated oropharyngeal cancers declined after 1983. Improvements in two-year survival rates were more pronounced for HPV-related cancers. Examining worldwide trends of oropharyngeal cancer, increases in the United States, Australia, Canada, Japan, and Slovakia were noted in men despite decreases in the overall incidence of oropharyngeal cancers (18). The magnitude of increase was more pronounced at younger than age 60 years. Trends in women showed both an increasing HPV-related and overall incidence of oropharyngeal cancers in a number of European countries, accompanied by an increasing lung cancer incidence likely reflecting more recent smoking patterns. An analysis of data from Australia showed significant annual increases in tonsil and base of tongue cancers in men and base of tongue cancers in women compared with other cancer sites in the oropharynx (19).

An issue of concern for many patients with HPV-related head and neck cancer is the possibility of partner infection. The prevalence of oral HPV infection in the United States between 2009 and 2010 was shown to be 6.9% and was higher in men (10.1%) (20). The incidence of infection increased with the number of sexual partners and cigarettes smoked per day. D’Souza prospectively studied 164 patients with HPV-related oropharynx cancer and 93 of their partners. Most patients were men, never smokers, and had performed oral sex. While the prevalence of oncogenic oral HPV DNA was high in male patients (61%), their female partners had similar oncogenic HPV prevalence compared with members of the general population of the same age (1.2% vs 1.3%), indicating that partners of patients with HPV-related tumors do not seem to have more frequent oral HPV infections (21). A study evaluating the history of sexual behavior between patients with oropharyngeal squamous cell cancer and other head and neck cancer sites reported that patients with oropharyngeal cancer were more likely to have over nine lifetime sex partners, to have engaged in oral/genital sex, and to have over four oral/genital sex partners (22).

Second primary cancers after index head and neck cancers have frequently been described for carcinogen-related tumors reflecting the field carcinogenesis process after prolonged smoking and alcohol exposure. Their incidence has been shown to be the lowest compared with other head and neck tumor subsites for patients with oropharyngeal squamous cell cancers (23), which may in part be responsible for the improved overall survival seen in patients with HPV-related tumors.

Another question has been whether tonsillectomy can impact the risk of oropharyngeal cancers. Tonsillectomy within one year of diagnosis of tonsil carcinoma has been shown to be associated with improved overall survival, and a remote history of tonsillectomy reduces the risk of diagnosis with tonsil carcinoma. It was not, however, associated with the overall risk of oropharyngeal carcinoma, including nontonsillar sites (24).

These epidemiologic data have had a major impact on clinical care and research for patients with HPV-associated head and neck cancer. It has become clear that biologic and prognostic differences exist with HPV-unrelated HNSCCs and that differential therapeutic approaches are required, many of which are actively being studied.

**Determination of HPV Status**

Histologically HPV-positive HNSCCs are poorly differentiated with a basaloid morphology and lack of keratinization (4). However, histologic criteria are insufficient and unreliable in making an HPV diagnosis. Immune-histochemical testing and/or HPV DNA/RNA testing are required and standard of care. A useful proxy for HPV-associated head and neck tumors is p16 immunohistochemistry (IHC) when used for oropharynx primary tumors. However, p16 IHC is not useful as an HPV surrogate for other anatomic sites, where HPV-associated tumors are rare, resulting in a high false-positive rate for calling HPV-associated tumors.

p16 IHC measures the protein product of the tumor suppressor gene CDKN2A, which is lost in the vast majority of HPV-negative tumors but is universally wild-type and expressed in HPV-associated tumors (25). p16 is a repressor of the D cyclins acting via phosphorylation of the retinoblastoma tumor suppressor protein (RB1). p16 plays a key role in the regulation of the cell cycle. In the setting of HPV-associated tumors, E7 viral oncoproteins degrade RB1 and enhanced p16 expression (26). In addition to E7 in HPV-associated HNSCCs, RB1 loss can also occur in HPV-negative tumors, eg, via mutation resulting similarly in p16 expression. Hence p16 expression is not specific for HPV-associated cancers, and p16 expression occurs in 5% to 8% of HPV-negative HNSCCs (27). Accordingly, in cases where the pre-test probability is high for HPV, such as tumors of the oropharynx in Western countries, the true-positive rate for p16 as an indication of HPV is high and use of p16 IHC performs well. Application of p16 IHC to large phase II and III studies has shown p16 to be an outstanding prognostic biomarker (6,28,29). However, when the pretest probability is low, such as in the oral cavity tumors, the true-positive rate of p16 IHC falls to 41.3%, rendering p16 IHC an ineffective HPV surrogate diagnostic (30,31).

To better address the issue of HPV testing inaccuracies including limitations of anatomic allocation (eg, oropharyngeal vs oral tongue tumors), some larger centers have implemented algorithm HPV testing using both p16 and confirmatory molecular testing, eg, by HPV-E6/ E7 PCR or RNA-ISH, both of which are formalin-fixed, paraffin-embedded (FFPE) tissue compliant (32). HPV testing algorithms hold potential to improve the accuracy of treatment allocation for HPV-specific therapies such as de-escalation in the near future, albeit validation in clinical trials is pending.
Clinical Implications of HPV-Positive HNSCCs

With the profound epidemiologic shift from carcinogen-induced to HPV-related HNSCCs in Western countries has come the recognition that the baseline patient characteristics allow for the characterization of two distinct clinical cohorts. HPV-positive HNSCC patients typically present at a younger age, with varying degrees of tobacco exposure; their primary tumors are frequently small and can be hard to detect while lymph nodal disease is frequently advanced (33). Lower rates of smoking are seen. However, many patients with HPV-associated oropharyngeal carcinoma in recent series are also current or former smokers (60%-70%), with true nonsmokers constituting only a minority (6,34,35). Also, the male-to-female predominance of approximately 3:1 remains similar to the pattern seen in non-HPV-related head and neck cancers but is poorly understood as risk factors for HPV transmission should apply equally to both sexes. Finally, while TNM staging would characterize many of these HPV+ tumors as locoregionally advanced, their prognosis is strikingly better and much more in line with earlier-stage HPV-negative tumors. While the majority of patients have stage IV disease because of the advanced N-stage, the clinical outcomes are excellent, with 80% or higher three-year survival (4,36–38). Some of the traditional prognostic factors such as extra-capsular spread and perineural invasion may hold less importance in this disease, and T and N stage as well as smoking history are the most important prognostic factors (6,35). Improved outcomes are seen across treatment modalities, including chemotherapy, radiation, chemoradiation, and potentially even surgery, and apply to both the curative intent as well as metastatic disease setting.

HPV status, although clearly prognostic, has yet to be incorporated into the staging classification (4). In an analysis from the Princess Margaret Hospital, current TNM staging failed to reflect survival prognosis for HPV-associated oropharyngeal cancers. Recursive partitioning analysis based TNM stage grouping including smoking history yielded more accurate reflection of survival. The authors argued for revising the American Joint Committee on Cancer/Union for International Cancer Control TNM stage for HPV-associated oropharyngeal SCC (36). Going forward, it will be imperative to incorporate nonanatomic determinants of survival, specifically HPV and smoking status, in the staging of HNSCCs similar to other nonanatomic factors that have been integrated to the staging of melanoma, esophageal cancer, and thyroid cancer.

Although outcomes are clearly improved compared with HPV-negative tumors, the implications for patient selection for therapy by HPV status have not yet been firmly established (37). Chemotherapy agents with activity in non-HPV head and neck cancer are usually also active in HPV-related disease, although detailed studies based on HPV status are pending. An interesting example was the recent LUX-1 study where methotrexate second-line therapy showed a response rate of 13.5% in HPV-associated tumors compared with 1.5% in HPV-negative HNSCCs. Secondly atafinib, an epidermal growth factor receptor (EGFR)/human epidermal growth factor receptor 2 inhibitor showed a 0% response rate in p16+ tumors and an 11.1% response rate in p16- tumors (39). Furthermore, other studies suggest that the EGFR antibody cetuximab also shows a low or absent single-agent response rate when used in HPV-positive patients (40,41). At a molecular level, HPV-associated tumors have generally shown low levels of EGFR protein expression and absence of EGFR gene amplification (42,43).

When looking at anti-EGFR therapy combined with chemotherapy, the data are less clear, with one study using the anti-EGFR antibody panitumumab indicating a lack of benefit in p16+ HNSCCs, while the EXTREME study using cetuximab showed marked benefit in a similar population, albeit using differing p16 methodologies (44,45).

Finally, the addition of cetuximab to radiotherapy resulted in marked benefit in p16-positive and HPV ISH-positive HNSCCs, suggesting a possible synergistic interaction of EGFR blockade with radiation for such tumors (46). The RTOG 1016 trial (NCT01302834) evaluating cetuximab-radiation vs cisplatin radiation may eventually help clarify the data regarding cetuximab use in combination with radiation.

Overall, these data demonstrate that it is essential for all future trials to collect accurate HPV status in order to better understand treatment implication by HPV status as HPV-associated and HPV-negative HNSCCs are distinct biologic entities.

HPV HNSCC Genetic Fingerprint

An overview of the common genetic aberrations in key signaling pathways is provided in Figure 1.

Mutations

The mutation rate in HPV-positive and -negative tumors are quantitatively similar (42,47). However, the specific mutational signatures are distinct, with an APOBEC mutation pattern in HPV-positive tumors (cytosine to thymidine C>T mutations [TpC]) vs a smoking mutational pattern in HPV-negative tumors (C→thymidine transversions) (42).

In HPV-associated tumors (as well as other viral tumors), increased cytosine deaminase mutagenesis appears to relate to overexpressed APOBEC enzymes (48,49). This may also have implications for the high frequency of canonical, helical domain PIK3CA mutations (E542K/E545K) while in HPV-negative tumors PIK3CA mutations are more evenly distributed throughout the entire gene (50). Driver mutations in KRAS (G12C and G12V), which are otherwise uncommon in squamous histology, occur at low frequency (1%-5%) in HPV-associated HNSCCs (47,51).

Structural Alterations

Copy number aberrations in HPV-positive and HPV-negative tumors are in part concordant (eg, amplifications of 1q, 3q, 5p, 8q, and deletions of 3p, 5q, 11q) (42,47,52,53). However, a number of changes are HPV specific; eg, 20% of HPV-associated tumors show EZF1 amplification (20q1), which is essential for cell cycle initiation and proliferation.

Another prominent difference between HPV-associated and HPV-negative HNSCCs is chromosome 7, where HPV-associated tumors universally lack EGFR amplification, which is present in approximately 15% of HPV-negative tumors (54). TRAF3 is a ubiquitin ligase and regulator for nuclear factor-κB-inducing kinase (NF-κB) signaling (55). A second HPV-specific deletion occurs at chromosome 11q, a region with several prominent tumor suppressor genes including ATM.

In terms of amplifications, a prominent difference between HPV-negative and -positive tumors occurs on chromosome 7, where HPV+ tumors lack EGFR amplification, which is common in HPV-negative tumors (54), albeit therapeutic implications for EGFR amplification remain unclear for HNSCC.

With respect to deletions, TRAF3 is exclusively lost in approximately 20% of HPV-associated tumors, a gene involved in antiviral immunity. A second HPV-specific deletion occurs for the tumor suppressor ATM (11q) (55-58).
HPV Viral Integration

HPV-associated tumors are characterized by the integration of viral DNA; e.g., high expression of HPV E6 and E7 RNA quantification often results from integration into the genome while the remainder appears to have episomal HPV (59). The viral integration site may not be fully random and usually occurs in or near genes, including HNSCC-relevant tumor suppressors such as RAD51 and ETS2 (59–61).

HPV Expression Subtypes

In the genetically annotated cohort of HPV-associated HNSCCs (43), two types of HPV-associated tumors were identified based on expression profiling: 1) the inflamed mesenchymal HPV-intrinsic subtype (IMS) showed high levels of tumor-infiltrating lymphocytes (TILs) and prominent immune escape, while 2) the classical intrinsic subtype (CL) of HPV-associated tumors was immunologically inert. Inflamed tumors showed a trend towards improved survival with curative intent therapy but most importantly may have implications for the emerging role of immunotherapies, e.g., with PD-1 inhibition (62).

Clinical Research

De-escalation

The majority of patients with oropharyngeal HPV-associated HNSCC presents with advanced-stage disease and undergoes multimodality treatment, including chemoradiotherapy or surgery followed by adjuvant radiotherapy +/- chemotherapy (NCCN). Regardless of the modality, treatment is associated with morbidity and occasional mortality (63,64). Given the much improved prognosis for HPV-associated oropharyngeal cancer, head and neck oncologists are actively exploring ways to limit toxicity related to treatment by reducing the number of treatment modalities and/or reducing intensity/dose of a given modality without compromising efficacy (65). Many studies are underway to define de-escalation more precisely.

One strategy of de-escalation is to utilize targeted therapy instead of chemotherapy to minimize toxicity while maintaining efficacy compared with cytotoxic chemotherapy. The efficacy and safety of cetuximab, an EGFR inhibitor, with radiotherapy vs radiotherapy alone was demonstrated in a general population of HNSCC patients in a randomized controlled trial (64). Five-year overall survival was improved without adverse toxicity compared with the radiation-alone control arm. In contrast, the RTOG 0522 trial demonstrated that the addition of cetuximab to cisplatin and radiotherapy did not improve outcome (66). A large phase III trial evaluating the role of cetuximab with radiotherapy- vs cisplatin-based chemoradiotherapy in p16-positive oropharyngeal cancer patients has been enrolled by the RTOG, with outcome data pending at this time (RTOG 1016 [NCT01302834]).

Induction chemotherapy has been evaluated in assessing the tumor response and, accordingly, adjusting the radiation dose. Early results reported from the ECOG 1308 trial suggest the feasibility of radiation dose escalation to 54 Gy after complete response with induction chemotherapy with paclitaxel, cisplatin, and cetuximab (38).

Another area of interest is possible omission of chemotherapy in HPV-positive patients. O’Sullivan et al., in a study of 505 patients who were treated with radiotherapy or chemoradiotherapy, demonstrated that patients at low risk for distant metastatic disease (T1-3, N0-2a) with HPV-positive oropharyngeal...
SCC may be treated with radiotherapy alone and encouraged a prospective clinical trial (35).

De-intensification of radiation has included reducing the overall dose of radiation to less than 60 Gy volume of radiation and altered fractionation with the goal of improving the quality of life by limiting radiation dose to the pharyngeal constrictors. More definitive data on this approach are awaited.

Trans-oral surgery may offer a platform for treatment de-intensification for HPV-associated oropharyngeal SCC. Contrary to the poor functional outcomes and morbidity that were associated with trans-mandibular approaches to the oropharynx, trans-oral surgery offers good survival, functional, and quality-of-life outcomes (67). An added benefit to surgery is that pathological staging is derived, conferring accurate staging that more

Table 1. Selection of completed and ongoing de-escalation trials in p16+/HPV-positive oropharyngeal cancers, illustrating the major approaches to de-escalation such as adjustments to the radiation dose, the radiation field, concurrent chemotherapy regimen, use of induction chemotherapy, and use of transoral robotic surgery (TORS)*

| Trial name                  | Sponsor                        | Trial details | Pre-radiation treatment | RT-based treatment            | De-escalation element/s                                      |
|-----------------------------|--------------------------------|---------------|-------------------------|-------------------------------|-------------------------------------------------------------|
| **Completed Trials**        |                                |               |                         |                               |                                                             |
| ECOG 1308 [38]              | Eastern Cooperative Oncology Group (ECOG-ACRIN) | PII, NR, AL   | Induction chemotherapy   | LR: Cetuximab + RT (54Gy)    | 1. Induction based risk stratification                        |
| NCT01084083                 |                                |               |                         | HR: Cetuximab + RT (69Gy)    | 2. Lower RT dose                                             |
|                             |                                |               |                         |                               | 3. Substitution of cisplatin with cetuximab (CRT)            |
| RAVD Chicago Trial [75]     | University of Chicago          | PII, NR, AL   | Induction chemotherapy   | LR: Volume de-escalated CRT (PTV2 omission) HR: CRT          | 1. Induction based risk stratification                        |
| NCT01133678                 |                                |               |                         |                               | 2. RAVD (Response adjusted volume de-escalation = PTV2 omission) |
| UNC 1120 [74]               | University of North Carolina   | PII, NR, AL   | –                       | a) CRT with 60Gy, and lower dose cisplatin b) selective/confirmatory surgery | 1. Lower RT dose                                             |
| NCT01530997                 |                                |               |                         |                               | 2. Lower Cisplatin dose (CRT)                                |
|                             |                                |               |                         |                               |                                                             |
| **Ongoing Trials**          |                                |               |                         |                               |                                                             |
| RTOG 1016                   | Radiation Therapy Oncology Group (NRG) | III, R        |                         | Cetuximab-R T randomized vs. Cisplatin-R T | Substitution of cisplatin with cetuximab (CRT) |
| NCT01302894                 |                                |               |                         |                               |                                                             |
| ECOG 3311                   | Eastern Cooperative Oncology Group (ECOG-ACRIN) | II, NR, AL    | TORS                    | LR: observation IR: lower dose RT HR: CRT                    | 1. Surgery based risk stratification                        |
| NCT01898494                 |                                |               |                         |                               | 2. Surgery single modality                                    |
| Quaterback                  | Mount Sinai Hospital           | III, R, AL    | Induction chemotherapy   | LR: lower RT dose CRT, randomized vs. CRT HR: CRT            | 3. Lower RT dose (CRT)                                       |
| NCT01706939                 |                                |               |                         |                               | 4. Use of cetuximab acceptable instead of platinum           |
| NRG-HN002                   | NRG Oncology                   | II, R         | –                       | UNC 1120 regimen (CRT with 60Gy, and lower dose cisplatin) randomized vs. IMRT alone | 1. Omission of chemotherapy (CRT)                           |
| NCT02254278                 |                                |               |                         |                               | 2. Lower RT dose (CRT)                                       |
| NCT01088802                 | Johns Hopkins University       | II            | –                       | Lower IMRT doses to both PTV1 and PTV2                       | 3. Lower cisplatin dose (CRT)                                |
| NCT01891695                 | University of Virginia         | II, AL        | –                       | Lower nodal dose in clinical N0 patients                      | 4. Use of cetuximab acceptable instead of platinum           |
| OPTIMA                      | University of Chicago          | II, NR, AL    | Induction chemotherapy   | LR: 50Gy RT alone IR: 45Gy CRT HR: CRT                       | 1. Nodal stage based risk stratification                     |
| NCT01847326                 |                                |               |                         |                               | 2. Lower nodal dose                                          |
|                             |                                |               |                         |                               | 3. Induction based risk stratification                        |
|                             |                                |               |                         |                               | 4. Lower Radiation dose                                       |
|                             |                                |               |                         |                               | 5. RAVD (Response adjusted volume de-escalation = PTV2 omission) |
|                             |                                |               |                         |                               | 6. Omission of chemotherapy (CRT)                            |

*II/III = Phase of Trial; AL = Treatment algorithm allocating HPV-associated cancer patients to different risk categories and associated treatment modalities; CRT = Chemoradiotherapy; HR = High risk (definitions vary by protocol); for trials employing induction LR/IR/HR assessment is usually based on response to induction chemotherapy; IR = Intermediate risk; LR = Low Risk; NR = Non-randomized; OP = Oropha; pts = patients; R = Randomized; RT = Radiation; TORS = transoral robotic surgery.
Experimentally, HPV can modulate and even induce certain types of tumors. This has opened up new possibilities for treatment, as current strategies are often limited and have side effects. HPV-positive tumors, in particular, benefit from targeted therapies that specifically target the virus.

For an overview of recently completed as well as ongoing de-escalation trials, please refer to Table 1.

**References**

1. Fakhry C, Westra WH, Li S, 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(4):261–269.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65(1):5–29.
3. Brockstein BE, Vokes EE. Head and neck cancer in 2010: Maximizing survival and minimizing toxicity. *Nat Rev Clin Oncol* 2011;8(2):72–74.
4. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. *J Natl Cancer Inst* 2000;92(9):709–720.
5. Chung CH, Gillison ML. Human papillomavirus in head and neck cancer: its role in pathogenesis and clinical implications. *Clin Cancer Res* 2008;14(22):6758–6762.
6. Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363(1):24–35.
7. Marur S, D’Souza G, Westra WH, et al. HPV-associated head and neck cancer: a virus-related cancer epidemic. *Lancet Oncol* 2010;11(9):761–789.
8. Brockstein B, Haraf DJ, Rademaker AW, et al. Patterns of failure, prognostic factors and survival in locoregionally advanced head and neck cancer treated with concomitant chemoradiotherapy: a 9-year, 337-patient, multistitutional experience. *Ann Oncol* 2004;15(8):1179–1186.
9. Salama JK, Stenson KM, Kistner EO, et al. Induction chemotherapy and concurrent chemoradiotherapy for locoregionally advanced head and neck cancer: a multi-institutional phase II trial investigating three radiotherapy dose levels. *Ann Oncol* 2008;19(10):1787–1794.
10. Forastiere AA, Zhang Q, Webber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. *J Clin Oncol* 2013;31(1):845–852.
11. Snijders PJ, Cromme FV, van den Brule AJ, et al. Prevalence and expression of human papillomavirus in tonsillar carcinomas, including a possible viral etiology. *Int J Cancer*. 1992;51(2):485–490.
12. Haraf DJ, Nodaenski E, Brachman D, et al. Human papillomavirus and p53 in head and neck cancer: clinical correlates and survival. *Clin Cancer Res* 2006;12(24):765–762.
13. Wilczynski SP, Lin BT, Xie Y, et al. Detection of human papillomavirus DNA and oncoprotein overexpression are associated with distinct morphological patterns of tonsillar squamous cell carcinoma. *Am J Pathol* 1998;152(1):145–156.
14. Ahlgren PN, D’Souza G, Li S, et al. Prevalence of human papillomavirus in head and neck cancers in European populations: a meta-analysis. *BMC Cancer*. 2014;14:968.
15. Jiron J, Sethi S, Ali-Fehmi R, et al. Racial disparities in Human Papillomavirus (HPV) associated head and neck cancer. *Am J Otolaryngol*. 2014;35(2):147–153.
16. Loges E, Li S, Westra WH, et al. Human papillomavirus (HPV) 16 and the prognosis of head and neck cancer in a geographical region with a low prevalence of HPV infection. *Cancer Causes Control*. 2014;25(4):461–471.
17. Chaturvedi AK, Engels EA, Anderson WF, et al. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. *J Clin Oncol* 2008;26(4):612–619.
18. Chaturvedi AK, Anderson WF, Lortet-Tieulent J, et al. Worldwide trends in incidence rates for oral cavity and oropharyngeal cancers. *J Clin Oncol* 2013;31(9):5550–5559.
19. Hocking JS, Stein A, Conway EL, et al. Head and neck cancer in Australia between 1982 and 2005 show increasing incidence of potentially HPV-associated oropharyngeal cancers. *Br J Cancer*. 2011;104(5):886–891.
20. Gillison ML, Broutian T, Pickard BK, et al. Prevalence of oral HPV infection in the United States, 2009–2010. *JAMA*. 2012;307(7):693–703.
21. D’Souza G, Gross ND, Pai SI, et al. Oral human papillomavirus (HPV) infection in HPV-positive patients with oropharyngeal cancer and their partners. *J Clin Oncol*. 2014;32(23):2466–2474.
22. Dabestani KR, Li G, Tortorella-Luna G, et al. Differences in history of sexual behavior between patients with oropharyngeal squamous cell carcinoma and patients with squamous cell carcinoma at other head and neck sites. *Head Neck*. 2011;33(6):847–855.
23. Morris LG, Sikora AG, Patel SG, et al. Second primary cancers after an index head and neck cancer: subsite-specific trends in the era of human papillomavirus-associated oropharyngeal cancer. *J Clin Oncol*. 2011;29(6):739–746.
24. Fakhry C, Andersen KK, Christensen J, et al. The Impact of Tonsillectomy upon the Risk of Oropharyngeal Carcinoma Diagnosis and Prognosis in the Danish Cancer Registry. *Cancer Prev Res (Phila)*. 2015;8(7):583–589.
25. Schlachet NF, Brandwein-Gensler M, Nuovo GJ, et al. A comparison of clinically utilized human papillomavirus detection methods in head and neck cancer. *Mod Pathol*. 2011;24(10):1295–1305.
26. Boyer SN, Wazer DE, Band V. E7 protein of human papilloma virus-16 induces degradation of retinoblastoma protein through the ubiquitin-proteasome pathway. *Cancer Res*. 1996;56(20):4620–4624.
27. Liang C, Marris CJ, McClean MD, et al. Biomarkers of HPV in head and neck squamous cell carcinoma. *Cancer Res* 2012;72(19):5004–5013.
28. Nguyen-Tan PF, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent immunotherapies, HPV vaccines, and other new approaches.
cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol. 2014;32(34):3858–3866.

Jordaan RC, Lingen MW, Perez-Ordonez B, et al. Validation of methods for oropharyngeal cancer HPV status determination in US cooperative group trials. Am J Surg Pathol. 2012;36(7):945–954.

Lingen MW, Xiao W, Schmitt A, et al. Low etiologic fraction for high-risk human papillomavirus in oral cavity squamous cell carcinomas. Oral Oncol. 2013;49(1):49–58.

Chung CH, Zhang Q, Kong CS, et al. p16 protein expression and human papillomavirus status as prognostic biomarkers of nonoropharyngeal head and neck squamous cell carcinoma. J Clin Oncol. 2014;32(35):3930–3938.

Westra WH. Detection of human papillomavirus (HPV) in clinical samples: evolving methods and strategies for the accurate determination of HPV status of head and neck carcinomas. Oral Oncol. 2014;50(9):771–779.

Hawkins LS, D’Souza G, Westra W, 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(4):407–420.

O’Sullivan B, Huang SH, Siu LL, et al. Deintensification candidate subgroups in human papillomavirus-related oropharyngeal cancer according to minimal risk of distant metastasis. J Clin Oncol. 2013;31(5):543–550.

Huang SH, Xu W, Waldron J, 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(9):836–845.

Das LG, Karrison TG, Witt ME, et al. Comparison of outcomes of locoregionally advanced oropharyngeal and non-oropharyngeal squamous cell carcinoma over two decades. Ann Oncol. 2015;26(1):198–205.

Cmelak A, Li S, Marur S, et al. E1308: Reduced-dose IMRT in human papillomavirus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC). J Clin Oncol. 2014;32(5s):abstr LBA6006.

Machiels JP, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as first-line treatment for recurrent/metastatic squamous cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. Lancet Oncol. 2015;16(5):583–594.

Vokes EJ, Cohen E, Melotek JM, et al. Radiation plus cetuximab versus methotrexate as first-line treatment for low-risk HPV-associated oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC). J Clin Oncol. 2015;7(293):293ra104.

Seiwert T, Burtsev B, Weiss J, et al. Inflamed-phenotype gene expression signatures to predict benefit from the anti-PD-1 antibody pembrolizumab in PD-L1+ head and neck cancers. J Clin Oncol. 2015;33(suppl):abstr 6017.

Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation with cetuximab-included radiotherapy and survival. Lancet Oncol. 2010;11(1):21–28.

Mirghani H, Menon F, Blanchard P, et al. Treatment de-escalation in HPV-positive oropharyngeal carcinoma: ongoing trials, critical issues and perspectives. Int J Cancer. 2015;136(3):e130384.

Ang KK, Zhang Q, Rosenthal DI, et al. Randomized phase III trial of concurrent accelerated radiation plus cetuximab with or without cetuximab for stage III to IV head and neck carcinoma: RT02-522. J Clin Oncol. 2014;32(7):2940–2950.

de Almeida JR, Li R, Magnuson JS, et al. Oncologic Outcomes After Transoral Robotic Surgery. A Multi-institutional Study JAMA Otolaryng Head Neck Surg. 2015;1–9.

Agrawal N, Frederick MJ, Pickering CR, et al. Exome sequencing of head and neck squamous-cell carcinomas in head and neck squamous cell carcinomas. Nature. 2013;517(7536):576–582.

Gillison ML, D’Souza G, Westra WH. Detection of human papillomavirus in clinical samples: evolving methods and strategies for the accurate determination of HPV status of head and neck carcinomas. J Natl Cancer Inst. 2013;105(7):491–504.

Huang SH, Xu W, Waldron J, 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(9):836–845.

Das LG, Karrison TG, Witt ME, et al. Comparison of outcomes of locoregionally advanced oropharyngeal and non-oropharyngeal squamous cell carcinoma over two decades. Ann Oncol. 2015;26(1):198–205.

Cmelak A, Li S, Marur S, et al. E1308: Reduced-dose IMRT in human papillomavirus (HPV)-associated resectable oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC). J Clin Oncol. 2014;32(5s):abstr LBA6006.

Machiels JP, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as first-line treatment for low-risk HPV-associated oropharyngeal squamous carcinomas (OPSCC) after clinical complete response (cCR) to induction chemotherapy (IC). J Clin Oncol. 2015;7(293):293ra104.