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Commentary

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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 an inverse relationship of HPV detection with alcohol and smoking exposure. Importantly, HPV-related patients appeared to have improved disease-specific survival. As these observations were confirmed and expanded in subsequent years, interest in a prospective evaluation of the association of tumor HPV status with therapeutic response and survival increased.

On that background, the 2008 paper by Fakhry et al. (1) reporting improved survival of patients with HPV-positive head and neck cancer in the Eastern Cooperative Oncology Group (ECOG) 2399 protocol was a landmark publication. Ninety-six patients with oropharyngeal or laryngeal cancer were prospectively

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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 comparably 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 pretest 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.

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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 extracapsular 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 afatinib, 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 (→common 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 *E2F1* 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-kB) 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).

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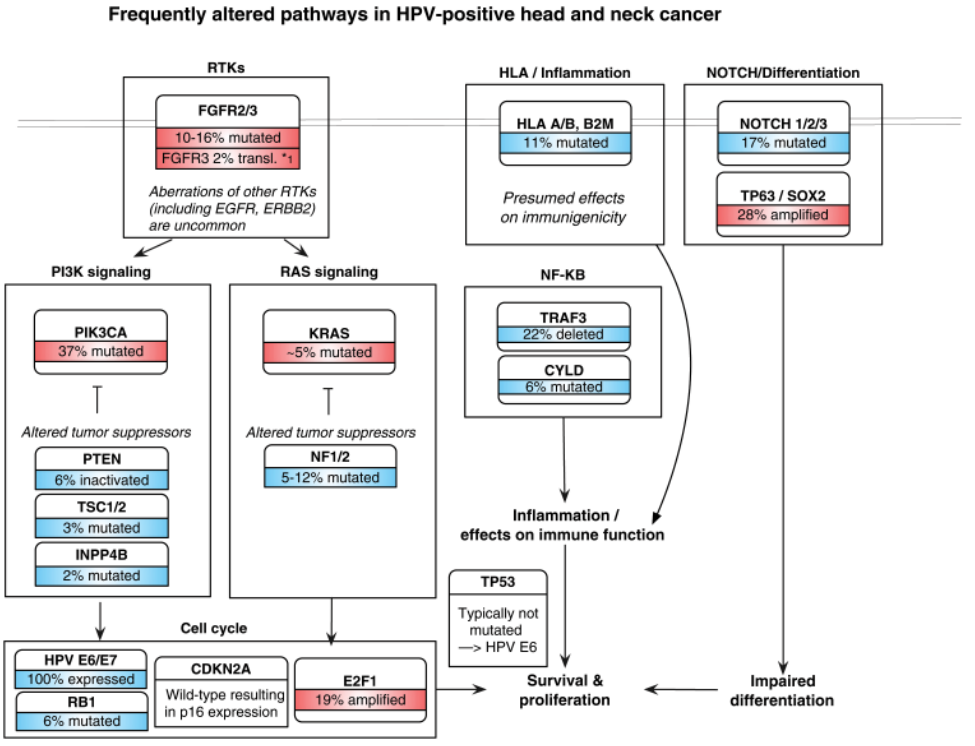

Figure 1. Overview of key genetic aberrations in major signaling pathways in human papillomavirus (HPV)–positive head and neck cancers. **Red** indicates activating changes in presumed oncogenes, while **blue** indicates inactivating changes in presumed tumor suppressor genes. Alteration percentages are based on the The Cancer Genome Atlas head and neck cancer (HNC) report (42) and a second cohort (47,53). While CDKN2A is usually wild-type in HPV-positive HNC and used as a surrogate diagnostic marker (= p16 IHC), normal p16 expression also occurs in 5% to 8% of HPV-negative tumors and contributes to false-positive HPV testing results. HPV = human papillomavirus.

HPV Viral Integration

HPV-associated tumors are characterized by the integration of viral DNA; eg, 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, eg, 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

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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] NCT01084083	Eastern Cooperative Oncology Group (ECOG-ACRIN)	PII, NR, AL	Induction chemotherapy	LR: Cetuximab + RT (54Gy) HR: Cetuximab + RT (69Gy)	1. Induction based risk stratification 2. Lower RT dose 3. Substitution of cisplatin with cetuximab (CRT)
RAVD Chicago Trial [75] NCT01133678	University of Chicago	PII, NR, AL	Induction chemotherapy	LR: Volume de-escalated CRT (PTV2 omission) HR: CRT	1. Induction based risk stratification 2. RAVD (Response adjusted volume de-escalation = PTV2 omission)
UNC 1120 [74] NCT01530997	University of North Carolina	PII, NR, AL	–	a) CRT with 60Gy, and lower dose cisplatin b) selective/ confirmatory surgery	1. Lower RT dose 2. Lower Cisplatin dose (CRT)
Ongoing Trials					
RTOG 1016 NCT01302834	Radiation Therapy Oncology Group (NRG)	III, R	–	Cetuximab-RT *randomized vs.* Cisplatin-RT	Substitution of cisplatin with cetuximab (CRT)
ECOG 3311 NCT01898494	Eastern Cooperative Oncology Group (ECOG-ACRIN)	II, NR, AL	TORS	LR: observation IR: lower dose RT HR: CRT	1. Surgery based risk stratification 2. Surgery single modality 3. Lower RT dose (CRT)
Quaterback NCT01706939	Mount Sinai Hospital	III, R, AL	Induction chemotherapy	LR: lower RT dose CRT, *randomized vs.* CRT HR: CRT	1. Lower RT dose (CRT) 2. Use of cetuximab acceptable instead of platinum
NRG-HN002 NCT02254278	NRG Oncology	II, R	–	UNC 1120 regimen (CRT with 60Gy, and lower dose cisplatin) *randomized vs.* IMRT alone	1. Omission of chemotherapy (CRT) 2. Lower RT dose (CRT) 3. Lower cisplatin dose (CRT)
NCT01088802	Johns Hopkins University	II	–	Lower IMRT doses to both PTV1 and PTV2	Lower RT dose (CRT)
NCT01891695	University of Virginia	II, AL	–	Lower nodal dose in clinical N0 patients	1. Nodal stage based risk stratification 2. Lower nodal dose
OPTIMA NCT01847326	University of Chicago	II, NR, AL	Induction chemotherapy	LR: 50Gy RT alone IR: 45Gy CRT HR: CRT	1. Induction based risk stratification 2. Lower Radiation dose 3. RAVD (Response adjusted volume de-escalation = PTV2 omission 4. 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.

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 pathologic staging is derived, conferring accurate staging that more

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precisely can modulate adjuvant treatment. Current prospective trials are underway to determine the role of surgery in de-escalation, including a larger phase II trial (ECOG 3311 [NCT01898494]) evaluating whether surgery alone would be indicated for early-stage, low-volume disease or if lower doses of radiation suffice for intermediate-risk tumors.

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

Experimental Therapies

Experimental therapies include vaccines, targeted therapy, and immunotherapy. Therapeutic vaccination strategies are novel investigations with limited data. Preventive HPV Food and Drug Administration–approved vaccines are recommended by the Centers for Disease Control and Prevention for women and men and will likely drastically affect the incidence of HPV-associated HNSCC in the future.

Two potential targets in HPV-associated oropharyngeal SCC are *PIK3CA* and *FGFR2/3* (42,47,68–70). In fact, the PI3K pathway appears to be the most commonly altered pathway in HPV-associated oropharyngeal SCC, and development of PI3K inhibitors such as alpelisib is ongoing. FGFR aberrations occur somewhat preferentially in HPV+ HNSCC, in approximately 10% of tumors (47). Some of these (eg, FGFR3/TACC3 translocations) appear to appear to have driver character and are potentially targetable.

One of the most promising therapies in oncology is immunomodulation of the PD-1/PD-L1 immune checkpoint. There are preclinical and clinical data that provide rationale to block the PD1/PD-L1 pathway, and this may apply in particular to the 'inflamed' variant of HPV-associated HNSCC with high levels of tumor-infiltrating lymphocytes and expression of immune checkpoints (62). In a HNSCC cohort of 192 patients in the Keynote 12 trial, treatment with the monoclonal anti-PD1 antibody pembrolizumab yielded a 23.7%% response rate, including durable and complete responses, with activity in both HPV-associated and HPV-negative tumors (71). Importantly, the impact on overall survival appeared to be pronounced in this early series of heavily pretreated patients, with an overall survival of 10 months. Activity with the anti-PD-L1 antibody durvalumab has also been reported for HNSCC (72), and development of the anti-PD-1 antibody nivolumab is ongoing, including HPV+ HNSCC.

Studies such as ECOG 1308 have been able to leverage the dramatically improved outcomes for HPV-associated HNSCC patients via de-escalating therapy and using induction chemotherapy as a differentiating factor. This may eventually lead to less toxicity, which is important in the younger HPV population with presumed long life expectancy (38). In addition, molecular monitoring and surveillance using somatic mutations and/or HPV genes from saliva and plasma will facilitate precision care for patients with HPV-associated HNSCC (73).

Conclusion and Outlook

Since the original publication by Gillison et al. (4) first describing the link of HNC and HPV and the follow-up publication by Fakhry et al. firmly establishing striking prognostic implications of HPV status, it has become clear that HPV status is a strikingly robust and strong prognostic biomarker for HNSCC. Since then, our understanding of the underlying biology and many clinical implications has increased exponentially, and we are now on the verge of modifying treatment approaches studied initially in HPV-negative tumors and providing less toxic therapy to many patients with HPV-positive tumors, as well as potentially appropriate targeted/palliative treatment approaches including immunotherapies, HPV vaccines, and other new approaches.

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