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INVITED REVIEW

Primary Chemotherapy and Radiation as a Treatment Strategy for HPV-Positive Oropharyngeal Cancer

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Abstract The incidence of human papillomavirus-positive oropharyngeal cancer (HPV/OPSCC) is rapidly increasing, which will represent a major public health burden for decades to come. Although HPV/OPSCC is generally associated with a better prognosis than HPV-negative OPSCC, the survival rate of individuals with higher-risk clinical and pathologic features remains unchanged. Emerging evidence suggests that HPV/OPSCC is pathologically and molecularly distinct from HPV-negative OPSCC. This review focuses on summarizing treatment strategies for HPV/OPSCC by reviewing the peer-reviewed literature and noting ongoing and planned clinical trials in this disease. We also discuss the potential of designing targeted therapy based on the recent genomic findings of HPV/OPSCC.

Keywords HPV/OPSCC · Chemotherapy · Radiation

HPV-Related Head and Neck Cancer (HNC) and Related-Deaths on the Rise

The incidence of oropharyngeal squamous cell carcinoma (OPSCC), a site for head and neck cancer (HNC), is rising in developed countries including the US and Europe. In the past 2 decades, reports indicate that up to 70–80 % of OPSCC (the most common type of head and neck SCC in year 2010 [1]) in these developed countries are HPV-positive [2]. In fact, the number of HPV-positive OPSCC (hereafter named as HPV/OPSCC) is expected to continue to rise (due to oral sex, multiple sex partners, and pre-marital sex), while that of HPV-negative OPSCC has been decreasing since 1991 (which parallels the drop in smoking in the US). In fact, the total annual cases of HPV/OPSCC alone are predicted to outnumber that of all cervical cancer cases in the US by 2020 [1].

HPV/OPSCC patients are treated with standard chemo-radiation therapy or surgery with a generally high response rate [3]. However, treatment is often complicated by morbidities and the positive prognostic benefit of HPV can be mitigated by negative prognostic factors, such as smoking and lymph node metastases [4, 5]. Recurrence, metastasis, and second primary cancer still account for the majority of deaths from HPV/OPSCC. The appreciable number of deaths from recurrence or treatment failure ($\sim$15 to 18/100, even with the most aggressive current treatment [6, 7]), coupled with a dramatic surge in total number of HPV/OPSCC suggests that the total number of deaths from both HPV-positive and HPV-negative OPSCCs will be comparable. More strikingly, a recent study revealed that the highest-risk HPV/OPSCC patients had a 3-year overall survival of only 70.8 %, while the overall survival for the highest-risk HPV-negative OPSCC was 46 % [8] (original data can be found in Fig. 2 of Ref. [8]). It is therefore important to determine the most effective treatment strategy for HPV/OPSCC. Currently, there is no single standardized treatment for OPSCCs in the US. Surgery, chemotherapy, or radiation therapy, or combinations of these modalities have all been used at different

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centers in the country. To date, most clinical trials have not prospectively differentiated HPV-positive and HPV-negative OPSCCs, even though these two cancer subtypes are epidemiologically and genetically distinct [9–11]. It is anticipated that ongoing and future unbiased human clinical trials in HPV/OPSCC will help elucidate the best treatment strategie(s) for this expanding group of patients. In this article, we will focus on primary systemic and radiation therapies for these tumors and provide potential rationales for their use.

Advantages of Systemic and Radiation Therapy for OPSCC

Improvement of patient overall survival and reduction of morbidity are the key factors for determining the best treatment option for patients with cancers in the head and neck region. Generally, patients with OPSCC will require removal of the lesion and nodal metastases by surgical interventions which can be associated with postoperative complications (including bleeding, chyle leak, wound infection, etc.). Although great technological advancements in surgery, such as transoral robotic surgery may reduce morbidity [12], the overall survival rates of patients treated primarily with surgery versus systemic and/or radiation therapy are largely comparable.

Although the optimal treatment strategy for HPV/OPSCC will be determined by unbiased and well-designed clinical trials, systemic chemotherapy and radiation therapy have several practical advantages over surgery. Most importantly, adjuvant radiation (or chemoradiation) is often required following surgery, so patients treated primarily by surgical resection are still exposed to the side effects of these non-surgical approaches. In general, systemic therapy and radiation therapy are relatively more amenable to standardization across institutions and delivery on clinical protocols can be widely available in most cancer centers. Surgical approaches can be standardized to some degree where negative resection margins remain the gold standard of surgical extirpation; however, specialized surgical approaches may be limited to clinicians with certain special skill-sets and technologies, which may not be easily accessible in all centers. Because of the relative ease of standardization, results from non-surgical protocols (or clinical trials) are more readily compared.

Even though HPV/OPSCC patients have reduced risk of death from cancer when compared with HPV-negative OPSCC patients [3, 13], there are several factors that should be considered when selecting treatment:

(1) It is known that the positive prognostic benefit of HPV in OPSCC patients is often mitigated by the negative prognostic effects of smoking and there exist subgroups of patients with poorer prognosis as shown by a recent study conducted in HPV/OPSCC patients [8], who may need more aggressive therapy.
(2) Even with the general good prognosis of HPV/OPSCC, current therapies are associated with excess morbidities. Long-term morbidities, such as swallowing dysfunction, reduced saliva production, and dysgeusia should be taken into consideration as emerging data suggest that HPV/OPSCC patients are younger [7, 14].
(3) The rates of death from second primary tumors in HPV/OPSCC and HPV-negative OPSCC were found to be similar [8], accounting for $\sim$10 % of all deaths. Therefore, treatment optimization aiming at reducing deaths from second primary tumors, even in HPV/OPSCC patients (as well as HPV-negative OPSCC) is a clinically important problem.
(4) Thus far, no study has been devoted to determine the specific factors contributing to disease recurrence or the development of micro-metastases in HPV/OPSCC, which accounts for many deaths in HPV/OPSCC. It is unclear if tumors that are more likely to recur or metastasize in HPV/OPSCC will be genetically distinct, which may allow for the development of specific targeting strategies for these patients.

Recent Clinical Trials in HPV/OPSCC

Clinicians are just beginning to determine if HPV-positive and HPV-negative HNC require distinct treatment approaches [7], which is challenging in the absence of evidence-based preclinical and clinical studies on treatment optimization. Here, we attempt to summarize results from recent representative retrospective studies and prospective clinical trials in head and neck cancer, with a focus on HPV/OPSCC.

Cumulative data from many retrospective studies consistently indicate that patients with HPV/OPSCC have a better prognosis than individuals with HPV-negative OPSCC [3, 15, 16]. A Danish clinical trial showed that radiation alone was able to achieve good disease control in p16-positive patients (where p16 serves as a surrogate marker for HPV infection). The locoregional tumor control rate was 58 % in p16-positive patients versus 28 % in p16-negative patients, and the 5-year overall survival rates were 62 and 26 %, respectively [17]. In a clinical study of 465 OPSCC patients, Rischin et al. [18] showed that p16-positive OPSCC patients had a better response when treated with cisplatin followed by radiotherapy than p16-negative OPSCC patients.

Fakhry et al. [13] reported the first prospective multicenter trial, thus far, to evaluate the association of HPV infection and treatment outcome in 96 HNC patients (the study included 62 OPSCC and 34 laryngeal cancer patients, treated with induction carboplatin and paclitaxel, followed by radiation therapy with concurrent paclitaxel). In this study, HPV positivity was confirmed in ~60 % (38/62, by DNA in situ hybridization) of OPSCC. Analysis of the OPSCC patients alone in this prospective study confirmed the findings from previous retrospective studies that HPV/OPSCC patients demonstrated increased overall and progression-free survival compared with patients with HPV-negative OPSCC [1]. In this study, smoking status in the 62 OPSCC patients was not associated with patient survival in contrast to the recent findings in a large scale retrospective study by Ang et al. [8]. Prospective evaluation of smoking in HPV/OPSCC is required to determine how it influences response to therapy.

A large-scale retrospective study with verified HPV status in 323 OPSCC patients (HPV DNA positivity was detected in 63.8 % by DNA in situ hybridization) was conducted and the results of accelerated-fractionation radiotherapy + cisplatin versus standard-fractionation radiotherapy + cisplatin were compared [8]. The results suggested that both treatment strategies are comparable in terms of overall patient survival, achieving a 3-year overall survival rate of ~60 to 70 % [8]. However, in-depth analysis revealed, for the first time, that further stratification among the HPV/OPSCC patients can segregate the patients into low, intermediate, and high-risk groups (regarding risk of death). The study reported that tobacco smoking independently associated with worse overall survival and progression-free survival in HPV/OPSCC patients and smoking significantly contributed to a higher risk of death in this group of patients (increased death risk of 1 % by each additional pack-year of tobacco smoking, where a pack year is defined as the equivalent of smoking one pack of cigarettes per day for 1 year). Together with HPV status, smoking, and nodal and primary tumor staging, the study further showed that among HPV/OPSCC, the highest-risk HPV/OPSCC patients had a 3-year overall survival of only 70.8 % (vs. 93.0 % for the lowest-risk HPV/OPSCC patients) [8]. While the results from this large scale retrospective study need to be confirmed prospectively, these findings suggest that treatment of HPV/OPSCC patients may be stratified (by smoking, nodal and primary tumor staging) and individuals in the high-risk group can be offered enrollment in trials for more intensive and effective investigational therapies, while patients in the low-risk category may be offered less intensive treatments "without compromising their survival" [8]. Although the results of this retrospective study require prospective validation, these findings may serve as a guideline for treatment stratification among HPV/OPSCC patients.

Since recognition of the prognostic significance of HPV in OPSCC, ongoing and planned clinical trials are designed to test HPV-selective treatments (Table 1). These trials are not only limited to interventional therapies, comparing different treatment arms, but are also focused on the effects of HPV vaccines in targeting HPV-infected tumor cells, as well as on biomarker investigations. In addition, it is also anticipated that various technological advancements in treatment modalities contribute to improved survival.

One ongoing Phase III study is comparing the clinical outcome of 2 combination treatment arms with agents currently used in HNC treatment. This trial is designed to determine if radiation therapy combined with cisplatin versus cetuximab is more efficacious for HPV/OPSCC patients (defined by p16 positivity) (ClinicalTrials.gov Identifier: NCT01302834; RTOG-1016; a phase III trial of radiotherapy plus cetuximab versus chemoradiotherapy in HPV-Associated oropharynx cancer) (Table 1). Results from this clinical trial will help determine if the only currently FDA-approved molecular targeting agent for HNC, cetuximab, is more effective than cisplatin in combination with radiation treatment for HPV/OPSCC. Results from a recent study comparing radiotherapy alone versus radiotherapy plus cetuximab suggested OPSCC patients (although HPV status was not determined) experienced increased benefit from radiation + cetuximab combination (vs. radiotherapy alone), implicating the potential benefits of the addition of cetuximab in HPV/OPSCC [19].

A recently completed ECOG trial, (E1308; Clinicaltrial.gov Identifier: NCT01084083, closed on 19th Oct, 2011) (A phase II trial of induction chemotherapy followed by Cetuximab (Erbitux) with low dose vs. standard dose IMRT in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx) was conducted to determine the efficacy of cetuximab followed by cetuximab and two different doses of IMRT (intensity-modulated radiation therapy) in treating patients with HPV-associated stage III or stage IV cancer of the oropharynx that can be removed by surgery. Results are pending.

It is anticipated that there will be more new investigational agents evaluated in HPV/OPSCC as the biology of this cancer type is more completely elucidated. One such trial is an ongoing Phase I trial of vorinostat (also called SAHA, a Histone deacetylase (HDAC) inhibitor) in the treatment of advanced oropharyngeal carcinoma of the head and neck (ClinicalTrial.gov Identifier, NCT01064921), which is evaluating the safety (as well as dose escalation) of vorinostat when given together with cisplatin and radiation therapy in treating patients with stage III or stage IVa OPSCC, which is either unresectable or borderline resectable.

Table 1 HPV/HNC clinical trials according to www.clinicaltrials.gov

Type	ClinicalTrials.gov Identifier	Phase	Trial Title	Agent(s)
Vaccine containing	NCT01462838	Phase I/II	Phase I/IIa study of immunization with a p16INK4a peptide combined with MONTANIDE ISA-51 VG in patients with advanced HPV-associated cancers	A vaccine with P16_37-63 with the vaccine adjuvant Montanide® ISA-51 VG
	NCT00704041	Phase I	A Phase 1 open label, dose escalation study to evaluate the effect of four doses of MAGE-A3/ HPV 16 Trojan peptides 0001 and 0002 administered subcutaneously	A vaccine against MAGE-A3 and HPV-16
	NCT00257738	Phase I	A Phase 1 open label, dose escalation study to evaluate the effect of four doses of MAGE-A3/ HPV 16 Trojan peptides 0001 and 0002 administered subcutaneously in combination with montanide and GM-CSF on immunological response, safety, tolerability, and preliminary efficacy in patients with squamous cell carcinoma of the head and neck	A vaccine against MAGE-A3 and HPV-16
	NCT01493154	Phase I	A Phase I clinical trial assessing the safety and feasibility of administration of pNGVL4a-CRT/ E7(Detox) DNA vaccine using the intramuscular TriGridTM delivery system in combination with cyclophosphamide in HPV-16 associated head and neck cancer	pNGVL4a-CRT/E7 (detox) DNA vaccine in combination with cyclophosphamide
Drug/radiation intervention	NCT01358097	Phase I	Biomarkers of immune function as predictors of head and neck squamous cell carcinoma (HNSCC) in response to therapy	Radiation, chemotherapy, robotic surgery
	NCT01384799	Phase I	A phase I dose escalation study to investigate the safety and pharmacokinetics of intravenous CUDC-101 with concurrent cisplatin and radiation therapy in subjects with locally advanced human papillomavirus negative head and neck cancer	CUDC-101, cisplatin, radiation
	NCT01221753	Phase II	A Phase II study of Docetaxel/Cisplatin/5-Fluorouracil (TPF) induction chemotherapy followed by concurrent chemoradiotherapy using a modified radiation dose in patients with newly diagnosed HPV positive, locally advanced squamous cell carcinoma of the oropharynx	Docetaxel, cisplatin, 5-FU, carboplatin, cetuximab, radiation (intensity modulated radiation therapy)
	NCT01084083	Phase II	A phase II trial of induction chemotherapy followed by cetuximab (Erbitux) with low dose versus standard dose IMRT in patients with HPV-associated resectable squamous cell carcinoma of the oropharynx	Cetuximab, radiation (intensity modulated radiation therapy)
	NCT01302834	Phase III	Phase III trial of radiotherapy plus cetuximab versus chemoradiotherapy in HPV-associated oropharynx cancer	Cetuximab, cisplatin, radiation
	NCT01268579	Phase 0	A pilot study to assess the pharmacodynamic effects of ribavirin in patients with tonsil and/or base of tongue squamous cell carcinoma	Ribavirin

Lack of Preclinical Therapeutic Studies in HPV/ OPSCC Models

The identification of effective therapeutic agents for evaluation in preclinical models of HPV/OPSCC should guide therapy design for clinical translation. However, there is a lack of drug screening efforts to identify the best therapy or combination therapies in the few HPV/OPSCC cell models that have been identified thus far. In the NCI-60 panel for drug screening (a collection of 60 human cancer cell lines), HNC cell lines are not included. To date, the major hurdle for HPV/OPSCC screening is the paucity of relevant HPV/ OPSCC cell line models to be used for larger scale drug screening. Currently, there are only 5 HPV/HNC cell lines reported (UD-SCC-2 from hypopharynx, UPCI:SCC90 from the base of tongue, UM-SCC47 from lateral tongue,

93-VU-147T from the floor of the mouth and UM-SCC-104 from recurrent oral cavity [20]; and only one of these was derived from the oropharynx (UPCI:SCC90). Therefore, the development of additional HPV/OPSCC cell models will be of paramount importance to enhance the drug development process for HPV/OPSCC.

Thus far, there are only several preclinical therapeutic studies using HPV/OPSCC cell line models to examine the efficacy of therapy. Using shRNA targeting of HPV-16 E6 and E7 in HPV/OPSCC cells, Rampias et al. [21] showed that these HPV oncoproteins can be efficiently inhibited with marked induction of apoptosis in these cells by restoring p53 and pRb tumor suppressor pathways, suggesting that specific targeting of E6 and E7 oncoproteins can be an effective approach. An interesting study by Gupta et al. [22] showed that HPV/OPSCC cells are sensitive to radiation and the addition of nelfinavir (NFV), which inhibits AKT, can further enhance radiosensitivity in vitro, suggesting the potential benefits of AKT targeting in HPV/OPSCC. The effect of an antiviral drug, cidofovir (an antiviral drug used to treat HPV-induced laryngeal papillomatosis and other viral infection) has also been examined in HPV/OPSCC cells (UPCI:SCC90), however, its effect on the restoration of p53 activity in vitro was modest [23].

Preclinical studies have also been performed by engineering HPV oncoproteins into HPV-negative HNC cells. Harris et al. [24] engineered FaDu cells to stably express the HPV-16 E6 oncoprotein and showed that these cells can be targeted by radioimmunotherapy with an E6-specific antibody. Using a similar approach, Pang et al. [25] reported that by engineering HPV-16 E6 oncoprotein into HPV-negative OPSCC cell lines (UM-SCC4 and WSU-HN6), the cancer cells became more sensitive to irradiation. This finding supports the notion that the HPV proteins enhance radiosensitivity of cancer cells to radiation, which is consistent with findings in HPV/OPSCC patients.

HPV Vaccines

HPV is known to be etiologically associated with several human cancers, including cancers of the cervix, anus, penis, vulva, vagina as well as head and neck. HPV vaccines are expected to protect against most HPV-induced cancers. Currently, there are 2 HPV vaccines for clinical use: the Gardasil® vaccine (also called HPV4), a quadrivalent vaccine, which protects against four HPV types: 6, 11, 16, and 18; and the Cervarix® vaccine (also called HPV2), a bivalent vaccine that targets two HPV types: 16 and 18. In October, 2009, the FDA approved HPV vaccination of girls and women, aiming to reduce cervical cancer incidences. The vaccines are known to protect the vaccinated individuals against persistent cervical HPV infection for up to 5–8 years, and effectively prevents precancerous to cancerous change of cervical cells due to HPV infection [26, 27]. An HPV vaccine was recently approved (the Gardasil® vaccine) for use in boys and men due to convincing epidemiologically link to HPV-related cancers in males (including HPV/OPSCC, anal and penile cancers.). In October 2011, the Advisory Committee on Immunization Practices (ACIP) announced its recommendation for "routine vaccination of males aged 11 or 12 years and the vaccination can be started beginning at age 9". Males aged 13 through 26 may be vaccinated [28]. Although the effects of HPV vaccination on HPV/OPSCC incidence will only be revealed with time, several ongoing clinical trials have been designed to look at the therapeutic benefits of HPV vaccine in HPV/OPSCC, either alone or in combination with anti-cancer drugs (such as cyclophosphamide) or with vaccines (e.g. p16INK4a peptides) (Table 1). These trials aim at evaluating the immunological boosting effects of vaccine-based treatment strategies in addition to safety evaluations. A Phase I clinical trial was recently completed to determine the antitumor effects of HPV vaccines in various solid tumors (HNC, cervical cancer, anal cancer, esophageal cancer, penile cancer and vulvar cancer) (NCT00019110), the results of which are still pending. Another clinical trial is exploring the use of a MAGE-A3/HPV16 vaccine for OPSCC patients with local or distant metastases following primary therapy, for whom surgery is not an option (ClinicalTrial.gov Identifier: CT00704041). In this trial, patients are screened for HPV positivity and MAGE-A3 positivity (MAGE-A3 is a tumor-specific antigenic peptide recognized by T cells [29] with the expectation that vaccination may enhance T cell function) [29, 30]. In the United Kingdom, there is an ongoing phase I trial of recombinant listeria HPV-16 vaccine (REALISTIC trial; a phase I, dose escalation trial of recombinant *Listeria Monocytogenes* (L_m)-based vaccine encoding human papillomavirus serotype 16 target antigens (ADXS11-001) in patients with HPV-16 positive oropharyngeal carcinoma). The study is assessing the safety of this vaccine in patients treated for HPV-16/OPSCC (http://www.liv.ac.uk/cancerstudies/research/head-neck/realistic.htm). It is anticipated that the results from these trials may help determine the role of HPV vaccines as treatment for HPV/OPSCC.

Potential Targeted Therapy Based on Genomic Findings of HPV/OPSCC

Characterization of the human cancer genome is revealing new and unexpected genetic alterations in many tumor lineages that impact our understanding of human cancer biology and may inform cancer treatment strategies [31, 32]. Elucidation of the critical gain-of-function alterations

can lead to the development of more effective molecular targeting strategies for cancers shown to be driven, at least in part, by the presence of key oncogene mutations [33–37]. Previously, our incomplete understanding of the molecular mechanisms of HPV/HNCs (including HPV/OPSCC) has limited the rationale design of targeted therapy against genomic aberrations in these cancers. However, 2 recent comprehensive genomic studies (by whole exome sequencing efforts) of HNC reveal that somatic mutations (mutations derived from tumor tissues) can potentially be harnessed for therapy [38, 39]. In both studies, mutational profiles were reported for several HPV/OPSCC tumors, which contained significantly fewer mutations compared to HPV-negative HNC. It is likely that more in-depth analysis of the mutational profiles of HPV/OPSCC, followed by larger validation studies, may reveal novel targets for therapeutic intervention in these cancers. Identification of "driver" mutations in HPV/OPSCC will facilitate the rational design of treatment strategies based on the genomic alterations of patient tumors.

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