The prevalence of HPV-positive OPC continues to increase at an epidemic rate.

Management of Oropharyngeal Cancer in the HPV Era

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Background: Historically, oropharyngeal cancer (OPC) has been attributed to risk factors such as smoking and alcohol use. The increased incidence of OPC has been driven by human papillomavirus (HPV) infection. Methods: A search of the literature involving HPV infection and OPC was performed, along with a search of ongoing clinical trials regarding HPV-positive OPC. Results: This review summarizes the differences in epidemiology and prognosis of HPV-positive OPC compared with non–HPV-related OPC. It will also discuss use of de-escalating treatment to minimize toxicity while maintaining excellent outcomes. Disease management is also addressed, including prevention and follow-up recommendations for this cohort of patients. Conclusions: HPV-positive OPC is a distinct disease, and efforts should be made to personalize its management. Preventive measures and vaccinations, along with de-escalation of treatment, may help optimize outcomes in this population.

Introduction
In 2016, an estimated 48,330 new cases of head and neck cancers will be diagnosed in the United States and 9,570 deaths are likely to be reported. Worldwide, head and neck cancers are the eighth leading cause of cancer-related deaths. Historically, head and neck cancers were largely attributed to the use of tobacco and alcohol. However, despite decreasing tobacco use, the incidence of oropharyngeal cancer (OPC) continues to rise. Today, up to 72% of persons with OPC lack the traditional risk factors of tobacco and alcohol use, with carcinogenesis driven by infection with human papillomavirus (HPV). The incidence of HPV-related OPC has increased at an epidemic rate. HPV status is now recognized as the single most prognostic factor for outcome in OPC, although it has not yet been included in staging or treatment considerations.

Patients with HPV-positive OPC are diagnosed at a younger age and have significantly better overall outcomes, making the decision to undergo de-escalation of radiotherapy (RT), chemotherapy, or surgery particularly important in this population. Alternatively, the addition or substitution of other novel therapies such as immunotherapy or targeted agents in combination with RT may be ideal in this virally driven cancer. Consideration of preventive measures, such as vaccination to decrease HPV incidence, is an important measure.

Epidemiology
HPV infection has been historically associated with some anogenital carcinomas, but it has also become...
recognized as a risk factor for head and neck cancers. The overall worldwide prevalence of HPV infection in persons with head and neck cancers is approximately 26%, with the highest percentage among those with OPC (35.6%), and OPC is most commonly attributed to the HPV-16 strain (86.7%). Other strains, such as HPV-18, -31, -33, -35, -39, -45, -51, -52, -56, -58, and -59, have also been implicated in head and neck carcinogenesis. The prevalence of HPV in head and neck cancers differs based on geographical site, with North America having a higher prevalence of HPV-associated OPC than Europe and Asia. From 1988 to 2004, the United States saw a 50% decrease in the incidence of HPV-negative head and neck cancers and a 225% increase in HPV-positive OPC. If this trend continues in the United States, the rate of HPV-positive OPC is expected to surpass cervical cancer by 2020. Patients with HPV-positive OPC are more likely to be younger (by 4–10 years), male (5:1 male to female), and white. The rising incidence of HPV-associated OPC is likely a consequence of changing sexual practices. HPV is a known sexually transmitted infection: Oral HPV prevalence appears during the ages of sexual activity initiation, with 1.5% at 12 to 15 years of age, 3.3% at 16 to 20 years, and 4.5% at 21 years or older. As part of the National Health and Nutrition Examination Survey, a study found a prevalence of oral HPV infection as high as 6.9% in participants aged 14 to 69 years. Oral HPV infection has been associated with an increasing number of lifetime oral and vaginal sex partners and, in men aged 18 to 23 years, was also associated with open-mouth kissing. In a case-control study of HPV infection and OPC, D’Souza et al showed that OPC was associated with an increasing lifetime number of oral sex partners (≥ 6 partners; odds ratio [OR] 3.4; 95% confidence interval [CI], 1.3–8.8; P = .009) and vaginal sex partners (≥ 26 partners; OR 3.1; 95% CI, 1.5–6.5; P = .002), as well as oral infection with any type of HPV (OR 12.3; 95% CI, 5.4–26.4).

After HPV is transmitted via sexual contact, the virus infects the epithelial lining of the oropharynx. The epithelial crypts that cover the base of the tongue and tonsils are more susceptible to infection because of easier access to the basal epithelial layer and they serve as a viral reservoir. In a healthy adult, 65% to 80% of oral HPV infections will clear within 12 months, but a significant decline in clearance rates is seen in immunocompromised patients.

Outcomes in Oropharyngeal Cancer in Association With Human Papillomavirus Status Retrospective Analysis

The initial retrospective data showing the prognostic value of HPV infection in OPC led multiple groups to investigate HPV status in previously completed prospective trials. HPV-positive OPC is prognostic for improved outcomes compared with HPV-negative OPC in the setting of postoperative RT, concurrent chemoradiation, RT alone, and induction chemotherapy followed by chemoradiation. Most studies show that HPV infection is independently prognostic for improved disease-free survival (DFS) and overall survival (OS), but some also show a benefit in locoregional failure (LRF) and distant metastasis (Table 1).

Radiation Alone: In a phase 3 trial conducted by the Radiation Therapy Oncology Group (RTOG), patients with head and neck squamous cell carcinoma (SCC) were randomized to 4 different fractionation regimens: standard fractionation (70 Gy), concomitant boost (72 Gy), split-regimen hyperfractionation (67.2 Gy), or hyperfractionation (81.6 Gy). From this trial, Gillison et al reviewed 190 evaluable patients by p16 expression, of which 75 (39.5%) were p16 positive. Positive p16 expression predicted improvements in rates of 5-year LRF (28.9% vs 54.9%; P < .001), DFS (43.6% vs 19.0%), and OS (49.0% vs 19.6%), but p16 expression showed no difference in distant metastasis (11.0% vs 13.0%; P = .71) or second primary tumors (13.8% vs 11.4%; P = .4).

Lassen et al evaluated the relationship of p16 status from 2 previous phase 3 trials (Danish Head and Neck Cancer Group [DAHANCA] 5 and 7). DAHANCA 5 enrolled 414 patients who were randomized to conventionally fractionated RT (5 fractions/week) with or without the hypoxic radiosensitizer nimorazole. Because this trial showed improved outcomes with the addition of nimorazole, the agent was added to both arms of DAHANCA 7, which randomized 786 patients to conventional RT (5 fractions/week) vs accelerated RT (6 fractions/week) to a dose of 66 to 68 Gy. The retrospective analysis of the 2 trials consisted of 336 patients with OPC evaluable by p16 assays, of which 120 (36%) were positive for p16. In this study, p16-positive tumors were smaller in size (P < .0002), more likely to have nodal spread (P < .02), and had an improved rate of 5-year locoregional tumor control (72% vs 38%; P < .001). On multivariate analysis, the presence of p16-positive OPC independently predicted a benefit in LRF (hazard ratio [HR] 0.29; 95% CI, 0.19–0.44), tumor site failure (HR 0.24; 95% CI, 0.14–0.42), disease-specific death (HR 0.28; 95% CI, 0.17–0.41), and OS (HR 0.31; 95% CI, 0.23–0.41; P < .0001). In a larger subset that included data from all 794 patients with head and neck SCC analyzed from the DAHANCA 6 and 7 trials, accelerated fractionation was observed to have an LRF benefit in both the p16-positive and p16-negative groups, along with a disease-specific survival benefit in p16-positive tumors.

Concurrent Chemotherapy: In a phase 3 trial, the RTOG randomized patients with stage III/IV head and neck SCC to standard fractionation RT
with 3 cycles of cisplatin or accelerated RT with 2 cycles of cisplatin.\textsuperscript{10} No difference was seen in outcomes between the 2 arms; therefore, the arms were pooled in this retrospective analysis. Of the 721 patients enrolled, 323 had evaluable OPC specimens: 206 (63.8\%) were positive for HPV infection (via in situ hybridization).\textsuperscript{10} HPV-positive tumors had improved rates of 3-year LRF (13.6\% vs 35.1\%; \(P < .001\)), DFS (73.7\% vs 43.4\%; \(P < .001\)), and OS (82.4\% vs 57.1\%; \(P < .001\)).\textsuperscript{10} HPV status was not associated with distant metastasis at 3 years (8.7\% vs 14.6\%; \(P = .23\)).\textsuperscript{10} In 214 study participants (66\%), this study also showed that elevated p16 expression (via immunohistochemistry) was more prognostic for both DFS and OS than HPV status.\textsuperscript{10} The authors suggest that HPV-16 in situ hybridization has a high sensitivity rate for HPV-16, but non–HPV-16 may have been misclassified as being negative for HPV, thus accounting for HPV-16-negative study participants with elevated p16 expression.\textsuperscript{10} This study was one of the first to use recursive partitioning analysis to stratify study participants with OPC into risk groups based on stage, smoking status, and p16 status.\textsuperscript{10}

In another phase 3 trial conducted by the RTOG, patients with stage III/IV head and neck SCC were randomized to accelerated RT (mainly 70 Gy in 6 weeks or 72 Gy in 6 weeks via concomitant boost) and concurrent cisplatin (100 mg/m\textsuperscript{2} on days 1 and 22) with or without cetuximab (400 mg/m\textsuperscript{2} loading dose the week before RT, then 250 mg/m\textsuperscript{2} per week during RT).\textsuperscript{29} No difference was seen in outcome between the 2 arms. Of the 891 study participants analyzed, Table 1.—Retrospective Analysis of Select Cooperative Trials of OPC

<table>
<thead>
<tr>
<th>Study</th>
<th>RCT Phase</th>
<th>Location</th>
<th>No. of Patients (Oropharynx)</th>
<th>Method of HPV Detection</th>
<th>HPV+ OPC, %</th>
<th>Treatment, Type (%)\textsuperscript{b}</th>
<th>Systemic Therapy</th>
<th>RT Dose, Gy</th>
<th>Follow-Up, mo</th>
<th>OS Rate</th>
<th>5-y DFS</th>
<th>5-y HR (95% CI)</th>
<th>5-y HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ang\textsuperscript{10}</td>
<td>3</td>
<td>United States</td>
<td>323</td>
<td>ISH p16</td>
<td>63.8</td>
<td>Concurrent: Cisplatin (d1 and 22)</td>
<td>57.6</td>
<td>3-y: 82.4% vs 57.1% P &lt; .001</td>
<td>0.42 (0.27–0.66) P &lt; .001</td>
<td>3-y: 73.7% vs 43.4% P &lt; .001</td>
<td>0.49 (0.33–0.74) P &lt; .001</td>
<td>3-y: 13.6% vs 35.1% P &lt; .001</td>
<td></td>
</tr>
<tr>
<td>Ang\textsuperscript{29}</td>
<td>3</td>
<td>United States</td>
<td>321</td>
<td>p16</td>
<td>73.2</td>
<td>Concurrent: Cisplatin (d1 and 22) + cetuximab (loading dose followed by wkly dose)</td>
<td>28.8</td>
<td>3-y: 85.6% vs 60.1% P &lt; .001</td>
<td>0.32 (0.20–0.51) P &lt; .001</td>
<td>3-y: 72.8% vs 49.2% P &lt; .001</td>
<td>0.49 (0.33–0.71) P &lt; .001</td>
<td>3-y: 17.3% vs 32.5% P &lt; .001</td>
<td></td>
</tr>
<tr>
<td>Fakhry\textsuperscript{32}</td>
<td>2</td>
<td>United States</td>
<td>62</td>
<td>ISH p16</td>
<td>61.0</td>
<td>Induction chemotherapy + chemoRT</td>
<td>39.1</td>
<td>—</td>
<td>0.39 (0.15–1.05) P = .06</td>
<td>—</td>
<td>0.38 (0.12–1.15) P = .09</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Gillison\textsuperscript{31}</td>
<td>3</td>
<td>United States</td>
<td>190</td>
<td>p16</td>
<td>39.5</td>
<td>None</td>
<td>70 (SFX)</td>
<td>111.6</td>
<td>5-y: 49% vs 19.6% P = .02</td>
<td>0.61 (0.42–0.89) P = .02</td>
<td>5-y: 43.6% vs 19%</td>
<td>0.65 (0.46–0.93) P = .02</td>
<td>5-y: 28.9 vs 54.9% P &lt; .001</td>
</tr>
<tr>
<td>Lassen\textsuperscript{14}</td>
<td>3</td>
<td>Denmark</td>
<td>336</td>
<td>p16</td>
<td>36.0</td>
<td>RT (SFX) (65) RT (AFX) (35)</td>
<td>30.4</td>
<td>—</td>
<td>0.31 (0.23–0.41) P &lt; .0001</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>5-y: 28% vs 62% P &lt; .001</td>
</tr>
</tbody>
</table>

\textsuperscript{continued on next page}
Table 1. — Retrospective Analysis of Select Cooperative Trials of OPC, continued

<table>
<thead>
<tr>
<th>Study</th>
<th>RCT Phase</th>
<th>Location</th>
<th>No. of Patients (Oropharynx)</th>
<th>Method of HPV Detection</th>
<th>HPV-OPC, %</th>
<th>Treatment, Type (%)a</th>
<th>Systemic Therapy</th>
<th>RT Dose, Gy</th>
<th>Follow-Up, mo</th>
<th>OS Rate</th>
<th>HPV-HR (95% CI)</th>
<th>5-y DFS</th>
<th>HPV-HR</th>
<th>LRF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lohaus34a</td>
<td>—</td>
<td>Germany</td>
<td>126</td>
<td>PCR</td>
<td>48.0</td>
<td>Surgery + PORT + cisplatin</td>
<td>Concurrent cisplatin</td>
<td>64 (SFX)</td>
<td>47.0</td>
<td>—</td>
<td>0.36 (0.17–0.73)</td>
<td>&lt; .01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Posner35</td>
<td>3</td>
<td>United States</td>
<td>111</td>
<td>PCR</td>
<td>50.5</td>
<td>Induction TPF + chemoRT (49)</td>
<td>Induction PF + chemoRT (51)</td>
<td>70–74 (SFX)</td>
<td>83.0</td>
<td>0.2 (0.1–0.38)</td>
<td>&lt; .0001</td>
<td>0.5 (0.78–0.87)</td>
<td>&lt; .0001</td>
<td>5-y: 13% vs 42%</td>
</tr>
<tr>
<td>Rischin30</td>
<td>3</td>
<td>United States Canada, New Zealand, Australia</td>
<td>185</td>
<td>PCR, p16</td>
<td>57.0</td>
<td>Concurrent standard cisplatin + RT</td>
<td>Concurrent lower-dose cisplatin + tirapazamine + RT</td>
<td>70 (SFX)</td>
<td>29.0</td>
<td>0.43 (0.02–0.93)</td>
<td>&lt; .001</td>
<td>0.39 (0.20–0.74)</td>
<td>&lt; .0003</td>
<td>—</td>
</tr>
</tbody>
</table>

aMulticentered retrospective trial.
bPercentage in each subgroup.

AUX-C = accelerated fractionation with concomitant boost, AUX-S = accelerated fractionation with split radiotherapy, AUX = accelerated fractionation, AUC = area under the curve, CI = confidence interval, DFS = disease-free survival, HPV = human papillomavirus, HR = hazard ratio, HFX = hyperfractionation, ISH = in situ hybridization, LRF = locoregional failure, OPC = oropharyngeal cancer, OS = overall survival, PCR = polymerase chain reaction, PF = cisplatin/fluorouracil, PORT = postoperative radiotherapy, RCT = randomized controlled trial, RT = radiotherapy, SFX = standard fractionation, TPF = docetaxel/cisplatin/fluorouracil.

321 (36%) had OPC assayable by p16 assays, and, of these, 235 (73.2%) were p16 positive. Study patients with p16-positive OPC had improved rates of 3-year LRF (17.3% vs 32.5%; P < .001), DFS (72.8% vs 49.2%; P < .001), and OS (85.6% vs 60.1%; P < .001). This was one of the first studies to show a significant association between p16 and distant metastasis rate (3 years: 6.5% vs 17.0%; P = .005). The Trans Tasman Radiation Oncology Group conducted a phase 3 trial that randomized patients with stage III/IV head and neck SCC to standard RT (70 Gy in 35 fractions in 7 weeks) concurrently with either standard bolus cisplatin (100 mg/m² on day 1 of weeks 1, 4, and 7) or decreased dosage of cisplatin (75 mg/m² on day 1 of weeks 1, 4, and 7) in addition to tirapazamine (290 mg/m² on day 1 of weeks 1, 4, and 7 and 160 mg/m² 3 times a week for weeks 2 and 3). A total of 465 study patients with OPC received treatment, and 185 (40%) specimens were evaluable and received at least 60 Gy of radiation; of these, 106 (57%) were positive for p16 expression (via immunohistochemistry). Overall, 2-year DFS (87% vs 72%; P = .003) and OS (91% vs 74%; P = .004) benefits were seen in p16-positive study patients. When the 2 arms were individually compared, the OS benefit of p16-positive tumors was significant in the cisplatin-alone arm (89% vs 68%; P = .021) but no longer significant in the group receiving tirapazamine (94% vs 80%; P = .36). A trend for improved locoregional control was seen in the tirapazamine arm among study participants negative for p16 (HR 0.33; 95% CI, 0.90–1.24; P = .13).

Induction Chemotherapy: The Eastern Cooperative Oncology Group (ECOG) conducted a phase 2 trial to determine outcomes with induction chemoradiotherapy in patients with resectable stage III/IV SCC of the larynx and oropharynx. Of the 111 patients enrolled, Fakhry et al was able to evaluate 96 patients, 62 (64.5%) of whom had OPC. Study patients underwent 2 cycles of induction chemotherapy (carboplatin/paclitaxel) followed by concurrent RT (70 Gy in 35 fractions in 7 weeks) and weekly paclitaxel. HPV status, defined by in situ hybridization and p16 status, was...
positive in 38 (61%) of the study patients with OPC. Patients positive for HPV infection had a higher response rate to induction chemotherapy (82% vs 55%; \( P = .01 \)) and rate of 2-year OS (95% vs 62%; \( P = .005 \)).

Posner et al conducted a phase 3 trial that randomized patients with stage III/IV head and neck SCC to 2 arms of induction chemotherapy docetaxel 75 mg/m²/cisplatin 100 mg/m²/fluorouracil 1000 mg/m² for 4 days vs cisplatin 100 mg/m²/fluorouracil 1000 mg/m² for 5 days every 3 weeks for 3 cycles, followed by concurrent RT (70–74 Gy in 7–7.5 weeks) and weekly carboplatin (area under the curve = 1.5). Of the 264 study patients with OPC, 111 of those specimens were evaluable; of those, 56 (50%) were positive for HPV-16 on reverse transcriptase–polymerase chain reaction. Study patients positive for HPV infection had improved rates of 5-year LRF (13% vs 42%; \( P = .0006 \)), DFS (78% vs 28%; \( P < .001 \)), and OS (82% vs 35%; \( P < .001 \)). Although study patients with HPV-positive OPC had a lower rate of distant metastasis (5% vs 11%), this result was not significant.

Meta-Analysis
Two meta-analyses examined the relationship between HPV and head and neck SCC outcomes. Ragin et al evaluated 23 studies and showed that HPV-positive head and neck SCC was associated with an improved outcome when compared with HPV-negative head and neck SCC with regard to DFS (HR 0.62; 95% CI, 0.5–0.8) and OS (HR 0.85; 95% CI, 0.7–1.0). A more recent meta-analysis that included 42 studies found a more pronounced DFS (HR 0.41; 95% CI, 0.27–0.64) and OS (HR 0.43; 95% CI, 0.35–0.52) benefit in patients with HPV-positive head and neck SCC. In this meta-analysis, little difference was seen when comparing the survival rates of the studies that adjusted for risk factors (age, sex, smoking, alcohol, stage) to those that did not, suggesting that the benefit seen in patients positive for HPV infection may be largely attributable to the HPV infection itself.

Current De-Escalation Trials for Human Papillomavirus–Positive Oropharyngeal Cancer Substituting Cisplatin With Cetuximab
The addition of cisplatin to RT has been shown to improve rates of survival in head and neck cancers by 5% to 8% but at the cost of significant adverse events, including ototoxicity (23%–50%), peripheral neuropathy (30%–86%), nephrotoxicity (20%–41%), and myelosuppression (<5%). These toxicities have led to the investigation of alternative systemic agents, such as cetuximab, which is a monoclonal antibody that targets epidermal growth factor receptor. A phase 3 study of locally advanced head and neck cancers found that adding cetuximab to RT prolonged rates of locoregional control, DFS, and OS. With the exception of acneiform rash and infusion reactions, cetuximab was well tolerated with little additional toxicity. This study did not evaluate outcome in terms of HPV status but did show an enhanced benefit in younger age (<65 years) and those with OPC, a finding that suggests an agent could be used to effectively treat patients with HPV-positive OPC. A retrospective analysis of this trial showed a benefit with cetuximab in both p16-positive and p16-negative study patients with respect to rates of locoregional control, DFS, and OS. Previous studies have shown that epidermal growth factor receptor has a higher expression in those who smoke and is inversely related to HPV status, which may explain the limited efficacy of cetuximab in HPV-positive cervical cancers. In a trial conducted by the RTOG, the addition of cetuximab to chemoradiotherapy showed no benefit in the setting of HPV-positive OPC.

Several ongoing phase 3 trials are investigating outcomes in patients with stage III/IV HPV-positive OPC and are comparing standard concurrent cisplatin with cetuximab (NCT01855451, NCT01302834, NCT01874171). Table 2 details several ongoing trials (as of publication) studying the effect of de-escalation in the setting of HPV-positive OPC (NCT01302834, NCT01874171, NCT01855451, NCT01530997, NCT01088802, NCT01891695, NCT02254278, NCT01706939, NCT01084083, NCT01898494, NCT02215265, NCT01687413). One study, RTOG 1016, enrolled patients with p16-positive stage III/IV OPC-SCC (excluding T1–2 N1 or M1 disease) treated with accelerated intensity-modulated radiotherapy (IMRT; 70 Gy in 35 fractions in 6 weeks) and then randomized them to 2 cycles of bolus cisplatin (100 mg/m² on days 1 and 22) or weekly cetuximab (400 mg/m² loading dose then 250 mg/m² weekly; NCT01302834). This was a noninferiority trial with a primary end point of OS and the goal of determining whether substituting cetuximab for cisplatin allows for a decrease in morbidity without sacrificing survival. This is similar to the trial being performed in the United Kingdom, which has enrolled patients with stage III/IV p16-positive OPC-SCC treated with accelerated IMRT and then randomized to either 3 cycles of bolus cisplatin vs weekly cetuximab (NCT01874171). Higher-risk patients, defined as having M1 disease or a smoking history longer than 10 pack-years or those with greater than N2a staging, were excluded from this study. The primary end point is severe acute and late toxicity (grades 3–5), with secondary end points of survival and disease control. A similar trial located in Australia will study patients with standard fractionated RT (70 Gy in 35 fractions in 7 weeks) who are randomized to either weekly cisplatin (40 mg/m²) or weekly cetuximab, with the primary end point of toxicity and secondary end points of survival and locoregional control (NCT01855451).
Table 2. — Ongoing De-Escalation Trials for HPV-Positive OPC-SCC

<table>
<thead>
<tr>
<th>Trial (NCT No.)</th>
<th>Phase</th>
<th>No. of Study Patients</th>
<th>Outcome Measure</th>
<th>Study Aim</th>
<th>Study Design</th>
<th>Deintensification</th>
<th>Medication</th>
<th>Radiation Dose/Fraction</th>
<th>Inclusion Criteria</th>
<th>Method of HPV Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Substitution of Cisplatin With Cetuximab</strong></td>
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<tr>
<td>De-ESCALaTE: Cet vs Cis Toxicity (NCT01874171)</td>
<td>3</td>
<td>304</td>
<td>Cost</td>
<td>LRC</td>
<td>QOL</td>
<td>OS</td>
<td>Toxicity (≥ grade 3)</td>
<td>Compare toxicity and outcomes between cisplatin and cetuximab with accelerated RT</td>
<td>RT + cetuximab RT + cisplatin</td>
<td>Cisplatin (3 wk for 3 cycles) Cetuximab (loading dose before RT, then wkly with RT)</td>
</tr>
<tr>
<td>RTOG1016 (NCT01302834)</td>
<td>3</td>
<td>706</td>
<td>DFS</td>
<td>Distant metastasis</td>
<td>LRC</td>
<td>OS</td>
<td>Toxicity</td>
<td>Compare toxicity and outcomes between cisplatin and cetuximab with accelerated RT</td>
<td>RT + cetuximab RT + cisplatin</td>
<td>Cisplatin (3 wk for 2 cycles) Cetuximab (loading dose before RT, then wkly with RT)</td>
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<td>TROG 12.01/ACTRN1261300-0279729 (NCT01855451)</td>
<td>3</td>
<td>200</td>
<td>DFS</td>
<td>Distant metastasis</td>
<td>LRF</td>
<td>QOL</td>
<td>OS</td>
<td>Toxicity</td>
<td>Compare toxicity and outcomes between cisplatin and cetuximab with conventional RT</td>
<td>RT + cetuximab RT + cisplatin</td>
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<td><strong>Deintensification of Chemoradiotherapy</strong></td>
<td></td>
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<tr>
<td>LCCC1120 (NCT01530997)</td>
<td>2</td>
<td>43</td>
<td>Complete pathological response rate</td>
<td>DSS</td>
<td>LRC</td>
<td>OS</td>
<td>QOL</td>
<td>Determine response and toxicity with de-escalated RT</td>
<td>RT + cisplatin</td>
<td>RT dose Intravenous cisplatin (wkly)</td>
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<tr>
<td>J0988 (NCT01088802)</td>
<td>2</td>
<td>60</td>
<td>Adverse events Late toxicity (≥ grade 3)</td>
<td>QOL</td>
<td>Determine response and toxicity with de-escalated RT</td>
<td>RT (de-escalated) + cisplatin</td>
<td>RT dose Cisplatin (wk 1–3 and 5–7)</td>
<td>63 and 75 Gy in 35 fractions in 7 wk</td>
<td>T1-3 Any resectable node</td>
<td>HPV DNA p16 HPV DNA + p16</td>
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<tr>
<td>NRG−HN002 (NCT02254278)</td>
<td>2</td>
<td>296</td>
<td>Distant metastasis HPV biomarkers</td>
<td>LRC</td>
<td>OS</td>
<td>PFS</td>
<td>Toxicity</td>
<td>Determine if cisplatin is needed in lowered RT dose</td>
<td>SFX RT + cisplatin AFX RT</td>
<td>RT dose ± cisplatin Intra-venous cisplatin (wkly) None</td>
</tr>
<tr>
<td>UVA-16766 (NCT01891695)</td>
<td>1</td>
<td>45</td>
<td>NO nodal control rate</td>
<td>PFS</td>
<td>Toxicity</td>
<td>Determine response and toxicity with de-escalated elective nodal RT</td>
<td>RT Elective nodal RT</td>
<td>Unspecified</td>
<td>39.6 Gy</td>
<td>Stages I–IVb</td>
</tr>
</tbody>
</table>

continued on next page
**Table 2. — Ongoing De-Escalation Trials for HPV-Positive OPC-SCC, continued**

<table>
<thead>
<tr>
<th>Trial (NCT No.)</th>
<th>Phase</th>
<th>No. of Study Patients</th>
<th>Outcome Measure</th>
<th>Study Aim</th>
<th>Study Design</th>
<th>Deintensification</th>
<th>Medication</th>
<th>Radiation Dose/Fraction</th>
<th>Inclusion Criteria</th>
<th>Method of HPV Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG1308 (NCT01084083)</td>
<td>2</td>
<td>83</td>
<td>2-y PFS Biomarkers OS QOL Toxicity</td>
<td>Determine if response to induction chemotherapy allows for safe RT de-escalation</td>
<td>2 cohorts stratified by response to induction chemotherapy: Induction chemotherapy then concurrent cetuximab with response-dependent RT dose (CR) low-dose RT or (PR/stable) standard-dose RT</td>
<td>RT dose</td>
<td>Induction: 3 cycles of paclitaxel (d 1, 8, 15), cisplatin (d 1), cetuximab (loading dose then wkly) Concurrent: Cetuximab (wkly)</td>
<td>CR: 54 Gy/27 fractions PR/stable: 66 Gy/33 fractions</td>
<td>Stages III–IVb, resectable</td>
<td>HPV DNA p16 HPV DNA + p16</td>
</tr>
<tr>
<td>Quarterback Trial (NCT01706939)</td>
<td>3</td>
<td>365</td>
<td>Biomarkers LRC OS PFS Toxicity</td>
<td>Determine if response to induction chemotherapy allows for safe RT de-escalation</td>
<td>2 arms for CR/PR: Induction chemotherapy then carboplatin with either low-dose RT or standard-dose RT</td>
<td>RT dose</td>
<td>Induction: TPF for 3 cycles Concurrent: Carboplatin (wkly)</td>
<td>56 Gy/28 fractions 70 Gy/35 fractions</td>
<td>Stages III–IV, M0, without active smoking history (&lt; 20 py in last 20 y or smoked within last 2 y</td>
<td>HPV DNA p16</td>
</tr>
<tr>
<td>ADEPT (NCT01687413)</td>
<td>3</td>
<td>496</td>
<td>CSS DFS Distant metastasis LRC Toxicity</td>
<td>Determine if cisplatin added to low-dose RT has benefit in ECE-</td>
<td>TORS followed by RT TORS followed by RT + cisplatin</td>
<td>Cisplatin</td>
<td>Cisplatin (wkly)</td>
<td>60 Gy/30 fractions in 6 wk</td>
<td>T1–4a, SM+: with ECE-</td>
<td>p16</td>
</tr>
<tr>
<td>ECOG3311 (NCT01898494)</td>
<td>2</td>
<td>377</td>
<td>OS PFS QOL Surgical bleeding SM+ rate Toxicity</td>
<td>De-escalation of adjuvant treatment based on histopathological assessment</td>
<td>3 cohorts stratified by risk: Surgery followed by: Low risk: Observation Intermediate risk: (A) Low-dose RT (B) Standard RT High risk: Standard RT + cisplatin</td>
<td>RT dose</td>
<td>Low/intermediate: None High: Cisplatin (wkly)</td>
<td>None (A) Low-dose RT (B) Standard RT (C) Standard RT + cisplatin</td>
<td>Stages III–IVa</td>
<td>p16</td>
</tr>
<tr>
<td>PATHOS (NCT02215265)</td>
<td>2/3</td>
<td>242</td>
<td>DFS OS QOL Swallowing function Toxicity</td>
<td>De-escalation of adjuvant treatment based on histopathological assessment</td>
<td>3 cohorts stratified by risk: Surgery followed by: Low risk: Observation Intermediate risk: (A) Low-dose RT (B) Standard RT High risk: (A) Standard RT (B) Standard RT + cisplatin</td>
<td>RT dose and cisplatin</td>
<td>Low/intermediate: None High: Cisplatin (wkly)</td>
<td>None (A) Low-dose RT (B) Standard RT (C) Standard RT + cisplatin</td>
<td>Stages T1–3, N0–2b Exclude current smokers (&lt; 2 y of diagnosis) with N2b disease</td>
<td>p16</td>
</tr>
</tbody>
</table>

AFX = accelerated fractionation, CSS = cancer-specific survival, CR = complete response, DSS = disease-specific survival, ECE = extracapsular extension, HFX = hyperfractionation, HPV = human papillomavirus, LRC = locoregional control, LRF = locoregional failure, OPC = oropharyngeal cancer, OS = overall survival, PFS = progression-free survival, PR = partial response, py = pack year, QOL = quality of life, RT = radiotherapy, SCC = squamous cell carcinoma, SFX = standard fractionation, SM = surgical margins, TOR = transoral robotic-assisted surgery, TPF = docetaxel/cisplatin/fluorouracil.
Deintensification of Chemoradiotherapy

Several trials are also attempting to deintensify the radiation dose in the setting of HPV-positive OPC-SCC by maintaining weekly cisplatin and de-escalating the dose to the primary tumor (LCCC1120, J0988) or elective nodes (J0988, UVA-16766). A phase 2 trial enrolled patients with HPV-positive OPC-SCC (excluding T4, N3, M1 disease) who had a smoking history of no more than 10 pack-years or those who used to smoke but stopped more than 5 years ago, and then treated them with weekly cisplatin (30 mg/m²) and concurrent IMRT (60 Gy in 30 fractions; NCT01530997). The primary end point was complete pathological response rate based on required biopsy of the primary site and dissection of pretreatment regions of lymph-node involvement 4 to 14 weeks following chemoradiation. The 43 patients enrolled had an 86% (37 of 43) pathological response rate and all 6 non-pathological-response rate cases had microscopic residual disease (1 primary site and 5 nodal sites). At a median follow-up of 15 months, all study patients were alive and had no evidence of disease. This trial is similar to an Australian study, in which the researchers are de-escalating study patients to 63 Gy in 35 fractions with concurrent weekly cisplatin; severe late toxicity (grade ≥ 3) is the primary end point (NCT01088802). Another study is also looking at de-escalating elective nodal volumes from 50.0 to 39.6 Gy in stage I/IVb HPV-positive OPC-SCC (NCT01891695). In that study, nodal control is being evaluated as the primary end point.

Favorable risk is being investigated in a phase 2 randomized trial using a de-escalation rate of radiation from 70 to 60 Gy (NCT02254278). In this study, participants with stage III/IV HPV-positive OPC-SCC (T12N12b or T3N02b) and a smoking history of no longer than 10 pack-years will be randomized to either accelerated-fractionation RT alone (60 Gy in 30 fractions in 5 weeks) or standard-fractionation RT (60 Gy in 30 fractions in 6 weeks) with concurrent weekly cisplatin (40 mg/m²). The primary objective is to select the arm with a 2-year DFS rate of at least 85% without unacceptable swallowing toxicity at 1 year.

Induction Chemotherapy Followed by Lower-Dose Radiation

A phase 2 trial conducted by the ECOG has enrolled patients with resectable stage III/IVb HPV-positive OPC initially treated with 3 cycles of induction paclitaxel (90 mg/m² on days 1, 8, and 15), cisplatin (75 mg/m² on day 1), and cetuximab (loading dose 400 mg/m²; weekly dose 250 mg/m²) followed by clinical/radiological evaluation (NCT01084083). Patients with a clinical complete response (CR) to induction chemotherapy underwent de-escalated RT (54 Gy in 27 fractions) and concurrent weekly cetuximab, whereas patients with a clinical partial response (PR) or stable disease received standard RT to 70 Gy with cetuximab. Preliminary data show CRs in 62 of the 80 study patients (78%) and PRs/stable disease in 15 (18%) of study patients after induction chemotherapy and then subsequently treated with de-escalated and standard RT, respectively. The de-escalated RT group had a similar rate of 1-year DFS compared with the standard RT group (91% vs 87%), and the rate was even higher in study patients with a smoking history shorter than 10 pack-years (97%). Patients with high-risk features, including T4 disease, N2c disease, and a longer smoking history (>10 pack-years), had suboptimal DFS rates between 84% and 88%. Because this trial altered many variables from standard chemoradiotherapy, it is difficult to determine which variable could be adjusted to improve outcomes in patients with HPV-positive disease and high-risk features.

Following the study data from Posner et al., a follow-up phase 3 trial was initiated and enrolled patients with stages III/IV HPV-positive OPC-SCC who were treated with 3 cycles of induction docetaxel/cisplatin/fluorouracil followed by clinical/radiological evaluation (NCT01706939). Patients with a PR or CR to induction chemotherapy will undergo a 2:1 randomization of reduced-dose RT (56 Gy/28 fractions) vs standard-dose RT (70 Gy/35 fractions) with concurrent weekly carboplatin. Patients with M1 disease and active smokers (> 20 pack-years during the last 20 years or smoking < 2 years ago) were excluded from the study. The primary end point will be the difference in DFS rate with reduced-dose RT.

Ufront Surgery

Minimally invasive surgery, such as transoral robotic-assisted surgery, was approved in 2009 by the US Food and Drug Administration for the treatment of patients with T1- to T2-staged OPC. However, up to 80% of patients may also receive adjuvant RT. As of publication, multiple trials are in progress that will employ upfront surgery for OPC and randomize adjuvant treatment strategies based on histopathological features (NCT01898494, NCT01687413, NCT02215265).

A phase 2 trial conducted by the ECOG is stratifying patients with stage III/IVa HPV-positive OPC based on pathological findings after surgery (NCT01898494). The study participants will undergo upfront transoral robotic-assisted surgery and neck dissection and are to be stratified into 3 risk groups: low, intermediate, and high. The low-risk group (those with T12N01 disease with negative margins) will receive no further treatment. Those defined as having intermediate risk (< 1 mm positive extracapsular extension [ECE], 2–4 positive lymph nodes, perineural/lymphovascular invasion) will be randomized to either low-dose IMRT (50 Gy/25 fractions) or standard-dose IMRT (60 Gy/30 fractions). Those in the high-risk group (positive margins, ECE > 1 mm or ≤ 5 positive lymph...
nodes) will receive IMRT (66 Gy/33 fractions) with weekly cisplatin (40 mg/m²). In addition to evaluating the DFS rate, they will investigate surgical effectiveness (margin status) and complication rates such as bleeding.

A UK phase 2/3 trial is randomizing intermediate-risk patients (T3 or T1–2 with additional risk factors, N2a or N2b, close margins [1–5 mm], or perineural/lymphovascular invasion) to postoperative low- (50 Gy/25 fractions) or standard-dose RT (60 Gy/30 fractions; NCT02215265). High-risk patients (positive margins [< 1 mm]) will be randomized to IMRT (60 Gy/30 fractions) with or without weekly cisplatin (40 mg/m²). The exclusion criteria for this study are those with T4, N2c–3, or M1 disease and those with N2b disease who currently smoke. The primary end point will be the effect of RT de-escalation on swallowing function and toxicity.

Among patients with HPV-positive OPC who choose to undergo surgery, retrospective data suggest no advantage to adjuvant concurrent chemotherapy in those with extracapsular extension. An ongoing phase 3 trial is investigating the optimal adjuvant treatment in persons who are ECE positive (NCT01687413). In this study, those with p16-positive OPC-SCC who underwent transoral robotic-assisted surgery with negative margins and who were positive for ECE will be randomized to IMRT (60 Gy/30 fractions in 6 weeks) with or without weekly cisplatin (40 mg/m²). DFS will be the primary end point.

**Future Therapeutic Approaches**

Evidence suggests that improved outcomes in patients with HPV-positive OPC can be attributed to the T-cell–mediated immune response. The presence of infiltrating T cells may also be prognostic for improved outcomes (margin status) and complication rates such as bleeding.

Programmed death ligand 1 (PDL-1) is a checkpoint inhibitor that binds to T cells and can cause decreased T-cell function. Anti-PDL-1 can induce an immunogenic response in various cancers by improving T-cell activity and function. PDL-1 expression is common in HPV-positive OPC, with expression levels higher than HPV-negative OPC (49%–70% vs 29%–34%). Preliminary analysis in a phase 1b multicohort study involving pembrolizumab showed that 99 study patients with recurrent/metastatic head and neck cancers had a response rate of 18.2%, regardless of HPV status (NCT01848834). Future studies may focus on the effectiveness of anti-PDL-1 in patients with HPV-positive OPC, especially in the upfront adjuvant setting.

**Management of Human Papillomavirus—Positive Oropharyngeal Cancer Prevention**

HPV-associated OPC has a different set of risk factors than conventional head and neck cancers. It is important to educate patients on the risk factors associated with this disease and recommend safe sexual practices, as well as help them to understand how to minimize their exposure to tobacco and alcohol products. HPV-induced malignancies have been studied in other disease sites for decades. Preventive measures, such as HPV vaccines, can reduce the risk of HPV infection and theoretically decrease the incidence of HPV-associated OPC.

The most common vaccines for HPV are bivalent (HPV-16, -18), tetravalent (HPV-6, -11, -16, -18), and 9-valent (HPV-6, -11, -16, -18, -31, -33, -45, -52, -58). Initially, recommendations for HPV vaccines were advocated for adolescent females for the prevention of cervical cancer; however, the US Food and Drug Administration has approved HPV vaccines for use in both sexes to prevent the spread of infection and subsequent malignancy. The Advisory Committee on Immunization Practices recommends HPV vaccination be initiated at the age of 11 or 12 years, but the vaccine can be started as early as 9 years of age and as late as 26 years of age. Healthy males are recommended
to undergo vaccination up to 21 years of age, whereas females and high-risk males (those who are immunocompromised, men who have sex with men) are recommended up to 26 years of age. Contraindications to the vaccine include pregnancy and immediate hypersensitivity reaction.

A randomized controlled trial in Costa Rica showed that the bivalent vaccination of women had a significantly decreased prevalence of oral HPV infection and a vaccine effectiveness rate of 93.3%. Because oral HPV infection can increase the risk of OPC by 1200%, HPV vaccination may aid in the prevention of oropharyngeal malignancy in addition to anogenital malignancies. Overall, HPV vaccination is a relatively safe preventive measure and should be considered in all adolescents.

Follow-Up

Guidelines from the National Comprehensive Cancer Center do not differentiate between HPV-related and unrelated head and neck cancers. They recommend that a history should be taken and a physical examination should be performed every 1 to 3 months for year 1, 2 to 6 months for year 2, 4 to 8 months for years 3 to 5, and then annually thereafter. Imaging is recommended within 6 months and chest imaging is recommended if clinically indicated in patients with a history of smoking. However, patients with HPV-positive OPC typically present at a younger age, have fewer smoking-related comorbidities, have improved outcomes, and experience significantly less rates of toxicity.

A retrospective study evaluated severe (grade ≥ 3) toxicity and LRF rates in patients with HPV-positive OPC to help determine the optimal clinical follow-up. Of the 232 study patients with HPV-positive OPC, 21 (9%) had severe late toxicity and a 3-year locoregional control rate of 94%. The study showed that 64% of events (toxicity or failure) occurred within the first 6 months of follow-up, with an incidence event rate lower than 2% on subsequent follow-up. The authors recommend reducing follow-up in patients with HPV-positive OPC to every 3 months for the first 6 months, then every 6 months for the first 2 years, and then annually thereafter.

Conclusions

The incidence rate of oropharyngeal cancer (OPC) associated with human papillomavirus (HPV) infection is growing at an epidemic rate. HPV-driven oncogenesis makes persons with HPV-associated OPC biologically distinct from persons with OPC not associated with HPV infection, and efforts are being made to personalize the management of this type of OPC. Preventive measures, such as education about sexual practices and other risk factors, along with HPV vaccinations, should be considered. Because this population has an excellent response to treatment, clinical trials are available to de-escalate treatment to minimize toxicity without sacrificing disease control or survival rates. New therapeutic approaches are also being explored, such as immunomodulators, which may improve outcomes in this patient population.

References


