

# What Is the Best Treatment for Patients With Human Papillomavirus–Positive and –Negative Oropharyngeal Cancer?

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The discovery that the human papilloma virus (HPV) is associated with a high and increasing percentage of oropharyngeal squamous cell carcinomas (SCCs) is among the most significant advances in the field of head and neck oncology. HPV-positive oropharyngeal cancer (HPVOPC) has clinical, etiologic, pathologic, and molecular features that distinguish it from HPV-negative disease. Increasingly, HPVOPC is being diagnosed in clinical practice because of the easy availability of p16 immunohistochemistry, a surrogate marker of HPV. The superior prognosis of HPVOPC has led to a reexamination of treatment approaches, and clinical trials are currently investigating strategies to deintensify treatment to reduce acute and late toxicity while preserving efficacy. This is of particular interest in low-risk patients. Unfortunately, patients with HPV-negative tumors still have high rates of locoregional failure and more efficacious treatments are required. This review of oropharyngeal SCC focuses on current and investigational treatment strategies in patients with both HPV-positive and HPV-negative oropharyngeal SCC. *Cancer* 2014;120:1462–70. © 2014 American Cancer Society.

**KEYWORDS:** head and neck cancer, squamous cell carcinoma, oropharyngeal cancer, human papillomavirus.

## INTRODUCTION

Historically, squamous cell carcinomas of the head and neck (SCCHN) (oropharynx, hypopharynx, oral cavity, and larynx) were often grouped together in clinical practice and in clinical trials. This was based on multiple considerations including similar risk factors, such as tobacco and alcohol use. After recognition of the fact that oropharyngeal cancers (OPCs) may be associated with the human papillomavirus (HPV),<sup>1</sup> it has become apparent that HPV-positive OPC (HPVOPC) must be considered as an entity distinct from HPV-negative head and neck cancers. This article will briefly discuss the epidemiology, pathogenesis, and diagnosis of HPV-positive and HPV-negative SCCHN, focusing on OPCs, before reviewing the current state of knowledge regarding the optimal treatment.

### *Epidemiology of SCCHN*

Declining tobacco consumption has been associated with a decrease in the incidence of all SCCHN subsites except cancers of the base of the tongue and the tonsil, which have actually increased in incidence.<sup>2</sup> Such epidemiological evidence combined with molecular<sup>3</sup> and clinicopathologic correlative studies<sup>1</sup> indicated that HPV infection is involved in the etiology and changing epidemiology of SCC of the oropharynx. Tobacco and alcohol are not believed to be etiologic agents in HPVOPC, in contrast to HPV-negative SCCHN. The increasing incidence of HPVOPC has been linked to changes in sexual practices (eg, the number of sexual partners is associated with both oral HPV infection<sup>5</sup> and OPC).<sup>4,6</sup> HPVOPC is now the most common form of OPC in many countries.<sup>7</sup>

### *Mechanism of Carcinogenesis and HPV*

HPVs are small, nonenveloped DNA viruses that can infect keratinocytes of the skin and mucous membranes. Although HPV infection is associated with a wide spectrum of epithelial lesions, “high-risk” HPV types are associated with cancers including those of the cervix, oropharynx (predominantly HPV type 16), and anal canal. The virus contains 2 oncogenes, E6 and E7, and infection is believed to be an early step in HPV-associated carcinogenesis. The E6 and E7 proteins

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**TABLE 1.** Differences Between Patients With HPV-Positive and HPV-Negative SCCHN

Characteristic	HPV Positive	HPV Negative
Anatomic site	Tonsil and base of tongue	All sites
Demographics	Younger; higher socioeconomic status	Older; lower socioeconomic status
Risk factors	Sexual behavior	Alcohol and tobacco use
Incidence	Increasing	Decreasing
Histology	Nonkeratinized, basaloid, poorly differentiated	Keratinized
Stage at presentation	Early T classification; more advanced lymph node classification, with the lymph nodes often cystic	Variable
Molecular/pathological changes	TP53 wild-type p16 positive No EGFR overexpression	TP53 mutated High EGFR expression
Survival	Improved	Unchanged
Second primary tumors	Less common	More common

Abbreviations: EGFR, epidermal growth factor receptor; HPV, human papillomavirus; SCCHN, squamous cell carcinomas of the head and neck (oropharynx, hypopharynx, oral cavity, and larynx).

functionally inactivate the p53 and retinoblastoma (Rb) tumor suppressor proteins, respectively.<sup>8</sup> Although the majority of SCCHNs have p53 mutations, HPVOPC is generally p53 wild-type<sup>8</sup> and the inactivation of Rb in HPVOPC is associated with increased p16 expression. HPVOPC is also associated with fewer chromosomal abnormalities,<sup>9</sup> different gene expression profiles,<sup>10</sup> and lower mutation rates.<sup>11</sup> HPV-negative tumors are more likely to have an increased epidermal growth factor receptor (EGFR) gene copy number<sup>12</sup> and higher EGFR expression by immunohistochemistry (IHC),<sup>13</sup> although HPVOPC may exert some of its malignant properties via the EGFR signaling pathway.<sup>14</sup>

#### **Diagnosis of HPV-Associated SCCHN**

The optimal method of HPV detection to distinguish HPVOPC from HPV-negative SCCHN is still evolving. There are several methods for detecting HPV in SCCHN, including DNA, RNA, and protein-based tests.<sup>15</sup> Polymerase chain reaction (PCR), a highly sensitive method, can be used on fresh/frozen and formalin-fixed paraffin-embedded specimens but provides no quantitative measure of viral load, has a lower specificity, and cannot confirm whether the HPV is transcriptionally active. DNA in situ hybridization (ISH) can detect HPV within the tumor cell and evaluate whether the viral DNA has been integrated or only reflects episomal DNA. ISH enables the detection of clinically relevant HPV infections with a higher specificity but a lower sensitivity than PCR. Due to probe specificity, less-common HPV subtypes will not be detected. Reverse transcriptase-PCR amplification of viral E6/E7 mRNA is considered the “gold standard” because it detects transcriptionally active HPV but has not been found to be suitable for use in routine clinical practice. More robust reverse transcriptase-PCR techniques

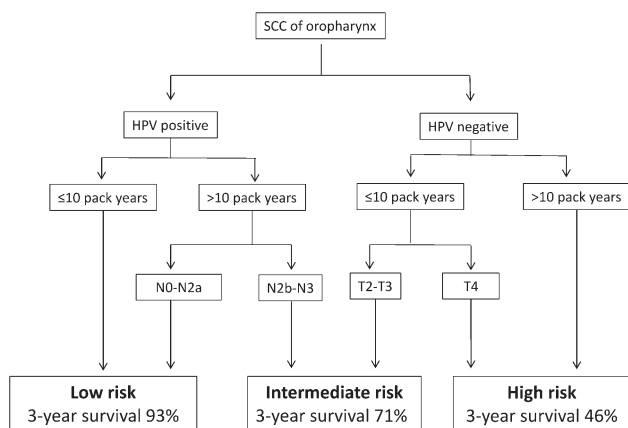
and RNA ISH tests suitable for use on formalin-fixed paraffin-embedded specimens have been developed and are promising.<sup>16</sup>

IHC staining for p16 approaches 100% sensitivity for diagnosing HPVOPC, but false-positive results can occur. Given the simplicity, robustness, and reproducibility of p16 IHC, it has become common practice to use this as a surrogate marker for HPVOPC. The interpretation of p16 IHC should be in conjunction with anatomic, histologic, and clinical considerations,<sup>17</sup> including the percentage of tumor cells staining positive,<sup>18</sup> and in clinical trials should ideally be confirmed by an appropriate HPV assay.

#### **Clinical Features and Prognosis of HPV-Associated SCCHN**

Multiple studies have highlighted the clinical differences between HPVOPC and HPV-negative OPC (Table 1). Patients with HPVOPC have tumors confined to the tonsil or base of tongue and are less likely to have a history of significant tobacco and alcohol intake. The presentation is often with a smaller primary tumor and more advanced cervical lymph node disease,<sup>19</sup> with the lymph nodes often having a cystic appearance.<sup>20</sup> Furthermore, cervical lymph nodes with HPV positivity indicate a high likelihood of the primary tumor originating from the oropharynx, which may be small, submucosal, and clinically occult.<sup>21</sup>

The prognosis of patients with HPVOPC is significantly better than that of patients with HPV-negative tumors. Initial observations in retrospective studies were subsequently confirmed in analyses of (chemo)radiation trials.<sup>22-26</sup> These studies demonstrated better locoregional control, better overall survival, and fewer deaths unrelated to head and neck cancer in HPVOPC. Furthermore, the



**Figure 1.** Risk classification of oropharyngeal SCC by HPV status according to Ang et al.<sup>25</sup> SCC indicates squamous cell carcinoma.

improved prognosis is independent of treatment modality.<sup>22,24</sup>

The analysis by Ang et al<sup>25</sup> is noteworthy because it also reported the impact of smoking on outcome in patients with American Joint Committee on Cancer (5th edition) stage III or stage IV HPVOPC. The overall survival of patients with HPVOPC was significantly better than that of patients with HPV-negative tumors, with a reported 3-year survival rate of 82.4% compared with 57.1%. The 3-year progression-free survival rate was also found to be significantly better in patients with HPVOPC (73.7% vs 43.4%). A recursive partitioning analysis stratified patients into low-risk, intermediate-risk, and high-risk groups according to survival, with 3-year survival rates of 93%, 70.8%, and 46.2%, respectively (Fig. 1), based on HPV status, tumor stage, and smoking history. The impact of smoking status on overall survival and disease-specific outcomes in patients with HPVOPC has been confirmed in other studies.<sup>27,28</sup>

Locoregional failure remains the major site of disease recurrence in patients with HPV-negative tumors, with 15% to 35% of patients with locally advanced disease developing a locoregional recurrence within 3 years. Locoregional failure is less common among patients with HPVOPC (6%-13%).<sup>25,26</sup> The majority of studies report similar rates of distant metastases between patients with HPV-positive and HPV-negative oropharyngeal SCC.<sup>25,26,29</sup> Some studies have suggested that HPVOPC may have a different pattern of spread, with metastases more often involving multiple organs and developing later than in HPV-negative tumors.<sup>29</sup> Recursive partitioning analysis of 505 patients with OPC classified patients

according to their risk of distant metastases. Patients with HPVOPC with T4 or N3 disease had a high risk of distant metastasis, with 24% developing distant metastases at 3 years (compared with an 18% risk of locoregional failure). Furthermore, it was reported in that same study that patients with N2c disease, irrespective of smoking status, may have a lower distant control rate with radiotherapy alone compared with chemoradiotherapy, but this needs to be interpreted cautiously in view of the small number of patients in the study who received radiotherapy alone. To the best of our knowledge there are no validated biological/molecular markers to identify the minority of patients with HPVOPC who have a poor prognosis. One recent publication identified low tumor-infiltrating lymphocytes as a marker for poor prognosis among patients with HPVOPC,<sup>30</sup> with outcomes similar to patients with HPV-negative OPC. Further studies are required to ascertain markers that will identify poor-prognosis patients with HPVOPC.

Among HPV-negative patients, the risk of distant metastases was found to be high among those with T3-T4 or N3 disease, with a rate of 28% at 3 years (compared with a 38% risk of locoregional failure).<sup>31</sup>

### Management of OPC According to Stage and HPV Status

Management decisions regarding OPC must take into account not only disease control and survival outcomes, but also toxicities and long-term functional outcomes. The use of multidisciplinary teams is essential<sup>32</sup> and the value of each of the main treatment modalities (ie, surgery, radiotherapy, and chemotherapy/biological agents) must be evaluated for each individual case.

### Early-stage disease

Early-stage disease comprises tumors of stage I (T1 measuring  $\leq 2$  cm, without lymph node involvement) and stage II (T2 measuring  $> 2$  cm and  $\leq 4$  cm, without lymph node involvement). Historically, OPCs were frequently treated with open surgery with or without postoperative radiotherapy, but because of the significant morbidity, particularly the effects on speech and swallowing, upfront radiotherapy has been widely used for organ preservation. Despite there being to our knowledge no randomized trials published to date comparing surgery and radiotherapy, retrospective data and a meta-analysis of nonrandomized studies have suggested that upfront radiotherapy is associated with comparable locoregional control and survival but with lower rates of severe complications.<sup>33,34</sup>

Currently, radiotherapy is most likely the most commonly used single modality in patients with early-stage OPC. HPVOPCs are considered to be more radiosensitive than HPV-negative tumors<sup>35</sup> and are associated with significantly better outcomes.<sup>22</sup> When single-modality radiotherapy is recommended, the use of altered fractionation improves outcomes compared with conventional fractionation,<sup>36</sup> independent of HPV status.<sup>37</sup>

Recently, there has been renewed interest in the surgical treatment of OPC with the advent of robotic surgery. Preliminary results of transoral robotic surgery (TORS), a minimally invasive technique, have been associated with encouraging oncologic, functional, and quality-of-life outcomes, particularly in patients with early T classification HPVOPC.<sup>38</sup> Comparative trials with robust functional and quality-of-life outcomes will be required to determine whether TORS offers advantages over a primary radiation approach. A current phase 2 trial (ORATOR [Radiotherapy vs Trans-Oral Robotic Surgery] [NCT01590355]) is being conducted comparing primary radiotherapy with TORS in patients with early-stage oropharyngeal SCC. In trials investigating TORS in patients with more advanced disease, patient selection will be critical to avoid potentially overtreating some patients with trimodality therapy when chemoradiation is a standard treatment option. A randomized, 4-arm, phase 2 Eastern Cooperative Oncology Group trial (NCT01898494) compares transoral surgery with transoral surgery with the addition of either low-dose or standard-dose postoperative radiotherapy or postoperative chemoradiotherapy.

Patients with early primary tumors (T1 and/or T2) with N1 disease (ie, a single involved lymph node measuring  $\leq 3$  cm), despite being classified as having stage III disease according to the 7<sup>th</sup> edition of the TNM staging system, are considered to have a relatively good prognosis<sup>39</sup> and are often treated with a single modality. In light of the good prognosis of HPVOPC, it is reasonable to treat patients with T1-2N1 HPVOPC with radiotherapy alone. Conversely, one could argue that patients with T2N1 HPV-negative tumors should be treated with concurrent chemoradiation, given the poorer prognosis and their inclusion in some previous chemoradiation trials.

#### Locoregionally advanced disease

Locoregionally advanced OPC comprises patients with T3 (tumors measuring  $> 4$  cm) or T4 tumors (ie, tumor invading adjacent tissues) or patients with lymph node involvement, particularly N2 or N3. The optimal treatment of patients with locally advanced disease involves

any given combination and sequence of surgery, radiotherapy, and chemotherapy.

Combination chemotherapy and radiotherapy. Multiple studies have reported that the addition of chemotherapy to radiotherapy improves locoregional control and overall survival in patients with locoregionally advanced SCCHN.<sup>40</sup> A widely accepted standard of care is high-dose cisplatin administered concurrently with radiotherapy, although other options include concurrent carboplatin and infusional 5-fluorouracil,<sup>41</sup> concurrent cetuximab,<sup>42</sup> and induction chemotherapy.<sup>43,44</sup> We will discuss the possible implications of the tumor's HPV status on decision-making.

Concurrent chemoradiotherapy. Given the significant acute and long-term toxicities of concurrent chemoradiotherapy, with up to 18% to 29% of survivors requiring gastrostomy tubes<sup>45,46</sup> and late unexplained mortality,<sup>47</sup> and the good prognosis of HPVOPC, clinical trials currently are investigating deintensification treatment strategies. However, it should be noted that the majority of these toxicity data precede the availability of intensity-modulated radiotherapy. It is likely that late toxicity will be less with modern radiotherapy treatment planning,<sup>48</sup> but nevertheless it remains important to define the optimal treatment strategy that maintains efficacy and minimizes toxicity.

These trials will need to establish the noninferiority of the deintensified regimens as well as the anticipated improvement in acute and long-term morbidity. Given the good prognosis, the expected low rate of disease events, and the potential for late-occurring metastases, these trials will require larger numbers of patients followed for long periods. Different approaches have been suggested, including lower doses of radiotherapy (Treatment De-Intensification for Squamous Cell Carcinoma of the Oropharynx [NCT01088802]), conventional rather than altered fractionation radiotherapy when given with concurrent chemotherapy, and the use of less toxic concurrent systemic regimens such as weekly cisplatin<sup>49</sup> or cetuximab. Many of the trials have included all HPV-positive patients, but it is questionable whether patients outside the low-risk group (however defined) should be considered suitable for deintensification trials. Using the Radiation Therapy Oncology Group criteria, the HPV-positive, intermediate-risk group had a 3-year survival rate of 70% compared with 90% for the low-risk group,<sup>25</sup> and in the study from the Princess Margaret Hospital, high-risk patients (defined as those with T4 and/or N3 disease)

had locoregional and distant control rates of approximately 80% compared with low-risk patients, among whom these rates approached 95%.<sup>31</sup>

For many years, the unrecognized emergence of HPVOPC with its associated better prognosis masked the lack of progress in the treatment of patients with locoregionally advanced HPV-negative SCCHN. Results remain poor in the treatment of HPV-negative head and neck cancer, with locoregional failure still representing the major site of failure in patients treated with chemoradiation. Treatment strategies targeting hypoxia have been extensively studied in unselected patients with SCCHN. To the best of our knowledge, no trial to date has definitively established that a regimen targeting hypoxia has improved outcomes compared with standard chemoradiation. A trial of nimorazole reported improvements in locoregional control and disease-specific survival compared with radiation alone. Furthermore, analyses of the nimorazole and tirapazamine trials have suggested that any benefit observed with hypoxic modification is restricted to the HPV-negative population.<sup>26,50</sup> The European Organization for Research and Treatment of Cancer is testing the addition of nimorazole to chemoradiation in patients with HPV-negative head and neck cancer (NCT01880359). New hypoxic cytotoxins (eg, TH-302 and SN30000) could also be tested in this setting in the future.<sup>51,52</sup>

Concurrent cetuximab and radiotherapy. The pivotal trial by Bonner et al demonstrated a significant benefit for concurrent cetuximab and radiotherapy compared with radiotherapy alone.<sup>53</sup> Unfortunately, this trial has not published the results for HPV status to date, although the clinical profile of those patients who appeared to benefit the most from cetuximab is suggestive of HPV-associated disease: younger patients, males, oropharyngeal primary tumor site, smaller primary tumors, and more extensive lymph node involvement.<sup>42</sup> However, this is only speculative and should not affect clinical decisions without more concrete evidence, especially in light of the uncertainty in the metastatic setting about the relative efficacy of EGFR-targeting agents in HPV-positive and HPV-negative groups.

Lapatinib, a dual tyrosine kinase inhibitor of EGFR and human epidermal growth factor receptor 2 (HER2), has been tested in a phase 3 postoperative trial (NCT00424255) and in a small randomized phase 2 trial in combination with chemoradiation. In the latter trial, a substudy suggested a possible benefit from the addition of lapatinib (concurrent plus maintenance) in the p16-

negative patient population.<sup>54</sup> Further trials in the HPV-negative population are planned.

Induction chemotherapy. The role of induction chemotherapy in patients with locally advanced OPC remains uncertain.<sup>24</sup> Trials of induction chemotherapy, including recently reported trials with the combination of docetaxel, cisplatin, and 5-fluorouracil, have often demonstrated a decrease in distant metastases compared with concurrent chemoradiation, without improvements in progression-free or overall survival.<sup>40,55</sup> HPVOPC is associated with a higher rate of response to induction chemotherapy<sup>23</sup> and a role for induction chemotherapy could be explored in the higher-risk HPV-positive patients, in whom distant disease may be the most common site of failure.<sup>31</sup> For the majority of patients with HPVOPC who have an excellent prognosis, the adoption of induction chemotherapy, with its associated toxicity, is difficult to justify.

### **Metastatic Disease**

The median survival of patients with incurable recurrent/metastatic SCCHN is approximately 5 months to 8 months.<sup>56</sup> Recent studies have suggested that survival may be longer in patients with HPVOPC compared with patients with HPV-negative tumors, although the differences were not found to be statistically significant.<sup>57,58</sup> To the best of our knowledge, the EXTREME trial (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer) was the first trial to demonstrate a significant improvement in survival in this population with the addition of cetuximab to 5-fluorouracil and platinum-based chemotherapy, with the median survival improving from 7.4 months to 10.1 months.<sup>44</sup> The SPECTRUM trial (Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer), using another EGFR-targeting antibody (panitumumab), demonstrated a similar, but not statistically significant, trend in favor of adding panitumumab to chemotherapy.<sup>59</sup> The question of whether there is differential activity of EGFR inhibitors in HPV-positive and HPV-negative tumors remains controversial. A preplanned analysis of the SPECTRUM trial revealed that HPV-negative patients had an improvement in overall survival with the addition of panitumumab, yet there was no benefit noted among the HPV-positive patients.<sup>59</sup> Similarly, in the phase 2 BIBW 2992 trial, HPV-positive patients were found to have a lower response rate to EGFR inhibition compared with HPV-negative patients.<sup>60</sup> However, others have shown no association

**TABLE 2. Registered Phase 3 and Randomized Phase 2 Clinical Trials in HPV-Positive or HPV-Negative Oropharyngeal Cancer**

Trial	Phase	HPV Status	Major Inclusion Criteria <sup>a</sup>	Treatment	RT Schedule <sup>b</sup>
EORTC-1219 (NCT01880359) <sup>c</sup>	3	Negative	Oropharynx/larynx/hypopharynx primary tumor, stage III or IV (M0)	Accelerated RT plus cisplatin vs accelerated RT plus cisplatin plus nimorazole	70Gy/35/6
RTOG-1016 (NCT01302834)	3	Positive	T1-2,N2a-N3 or T3-4,any N	Accelerated IMRT plus high-dose cisplatin vs accelerated IMRT plus cetuximab	70Gy/35/6
TROG 12.01 (NCT01855451)	3	Positive	Stage III (excluding T1-2N1) or IV (excluding T4, N3 or M1) if ≤10 pack-y smoking history. If > 10 pack-y smoking history, only N0-N2a	RT plus weekly cetuximab vs RT plus weekly cisplatin	70Gy/35/5
The Quarterback Trial (NCT01706939)	3	Positive	Oropharynx/unknown primary/nasopharynx, stage III or IV disease (M0), active smokers or >20 pack-y excluded	Three cycles of induction TPF: Responders randomized to RT (70Gy) plus weekly carboplatin vs RT (56Gy) plus weekly carboplatin plus cetuximab	70Gy/35/5 vs 56Gy/28/5
De-ESCALaTE (NCT01874171)	3	Positive	Stage III-IVa (T3N0-T4N0, and T1N1-T4N3) ≥N2b disease and smoking history > 10 pack-y excluded	RT plus high-dose cisplatin vs RT plus cetuximab	70Gy/35/5
ADEPT (NCT01687413)	3	Positive	Transoral resection (R0 margin) T1-4a, pN-positive with extracapsular spread	IMRT vs IMRT plus cisplatin	60Gy/30/5
E3311 (NCT01898494)	2	Positive	Resectable stage III-IVb oropharyngeal SCC	Transoral resection and subsequent treatment by risk stratification: <i>Low risk</i> <sup>d</sup> - observation only; <i>High risk</i> <sup>e</sup> - postoperative IMRT (66Gy) with wky cisplatin; <i>Intermediate risk</i> <sup>f</sup> - randomized to IMRT (50Gy) vs IMRT (60Gy)	66Gy/33/5, 50Gy/25/5 vs 60Gy/30/5
RTOG 1221 (NCT01953952)	2	Negative	Transoral resectable stage III-IV (T1-2, N1-2b; T3,N1-2b if primary tumor > 1cm from midline)	ChemoRT (weekly cisplatin) vs transoral endoscopic surgery and risk-based adjuvant treatment: <i>Low risk</i> <sup>g</sup> - no adjuvant treatment; <i>Intermediate risk</i> <sup>h</sup> - IMRT (60Gy); <i>High risk</i> <sup>i</sup> - adjuvant chemoRT (wky cisplatin plus 60Gy; 6-Gy boost if positive resection margins and/or ECE)	
TRYHARD RTOG 3501 (NCT01711658)	2	Negative	Stage III-IV (T2N2-3 or T3-4,any N) oropharynx/larynx/hypopharynx	RT plus cisplatin (d 8 and 29) plus placebo vs RT plus cisplatin (d 8 and 29) plus lapatinib (concurrent plus 12 mo of adjuvant)	70Gy/35/5

Abbreviations: ChemoRT, chemoradiotherapy; ECE, extracapsular extension; EORTC, European Organization for Research and Treatment of Cancer; Gy, grays; HPV, human papillomavirus; IMRT, intensity-modulated radiotherapy; LVI, lymphovascular invasion; PNI, perineural invasion; RT, radiotherapy, technique not specified; RTOG, Radiation Therapy Oncology Group; SCC, squamous cell carcinoma; TPF, docetaxel, cisplatin, and 5-fluorouracil; TROG, Trans Tasman Radiation Oncology Group.

<sup>a</sup>All require oropharyngeal SCC unless otherwise specified.

<sup>b</sup>RT schedule shown as the total RT dose in gray/number of fractions/fractions per week.

<sup>c</sup>Not yet recruiting.

<sup>d</sup>Low risk includes T1-2N0-1, negative margins.

<sup>e</sup>High risk includes > 1mm ECE or >5 metastatic lymph nodes, or positive resection margins.

<sup>f</sup>Intermediate risk includes close/<3-mm resection margin, <1mm ECE, 2-4 metastatic lymph nodes.

<sup>g</sup>Low risk: T1-2, N0, negative resection margins, no LVI/PNI.

<sup>h</sup>Intermediate risk: close resection margins, LVI or PNI. ≥ 1 involved lymph node.

<sup>i</sup>High risk: ≥5 involved lymph nodes, ECE, positive resection margins.

between HPV status and response to EGFR inhibitors,<sup>61</sup> including preliminary results from the EXTREME trial.<sup>62</sup>

### **New Biology, New Treatments**

Cetuximab, an anti-EGFR antibody, is currently the only approved targeted therapy for patients with SCCHN, although research has revealed other potential molecular targets in SCCHN, including other EGFRs (eg, HER2, HER3) and the phosphoinositide 3-kinase pathway (PI3K).

Targeting other EGFRs has produced some early promising results with afatinib (irreversible tyrosine kinase inhibitor of EGFR and HER2),<sup>63</sup> lapatinib (dual EGFR and HER2 inhibitor),<sup>54</sup> and dacomitinib (pan-EGFR inhibitor),<sup>64</sup> all of which demonstrate some clinical activity. However, as previously mentioned, the interaction between EGFR pathway inhibition and HPV status is currently unclear.

Alterations in the PI3K pathway (PI3K/AKT/mammalian target of rapamycin [mTOR]) are common in patients with head and neck cancers<sup>65</sup> and may confer resistance to EGFR inhibitors,<sup>66</sup> and mutations may be more common in patients with HPV-positive tumors.<sup>67</sup> PI3K inhibition is another promising target in SCCHN and phase 1 and 2 trials are currently underway.

Another approach generating excitement in the field of oncology is immunotherapy, specifically the inhibition of programmed cell death-1 (PD-1) or its associated ligand (PD-L1).<sup>68</sup> A current phase Ib trial includes patients with SCCHN as a specific cohort (NCT01848834). One recent study has suggested a role for PD-1–PD-L1 interaction in the initial HPV infection and subsequent immune resistance of HPV-associated tonsillar cancer,<sup>69</sup> providing a rationale for such antibodies in the HPV-positive cohort.

### **Management Guidelines**

Because p16 and/or HPV provides important prognostic information, it is therefore reasonable to include p16 in the routine workup of a patient with OPSCC. However, pending the results of ongoing trials, current recommendations are to treat patients according to their stage of disease at presentation, irrespective of HPV status. Patients with OPC should be encouraged to enroll on clinical trials specifically targeting HPV-positive and HPV-negative cohorts (Table 2).

### **Follow-Up and Second Malignancies**

The goals of follow-up among patients with SCCHN include assessment for cancer recurrence, long-term

toxicities, and second primary tumors. Patients with primary SCCHN have a significant risk of developing second malignancies, either synchronous or metachronous, most commonly of the upper aerodigestive system and lung. The rate of second primary tumors is in the order of 3% to 5% in patients with early-stage tumors<sup>70</sup> and is believed to be associated with smoking-related “field cancerization”. Available data suggest that patients with HPV-associated tumors, particularly nonsmokers, are significantly less likely to present with second malignancies, although there may be a small increase in cases of cervical cancer.<sup>71,72</sup> To our knowledge, the optimal screening for second primary tumors is not known, although one may consider low-dose computed tomography scans of the chest in patients with a significant history of smoking.<sup>74</sup>

### **Prevention of HPV-Associated OPC**

HPVOPC is now the most common HPV-associated malignancy in the United States. The Advisory Committee on Immunization Practices recommends the routine vaccination of all females aged 11 years to 12 years; the vaccination of unvaccinated women between the ages of 13 years and 26 years; and, since 2011, the routine vaccination of boys. Given the sexually transmitted nature of HPV infection, it is hoped that vaccination will decrease the rate of all HPV-associated cancers, including cervical cancer, OPC, and anogenital cancers.

### **Conclusions**

The recent developments separating OPC into distinct prognostic groups according to HPV status has been one of the most significant advances in head and neck cancer. Current studies will further delineate the optimal treatment for these patients and will hopefully result in better outcomes for patients with both HPV-positive and HPV-negative tumors.

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