Introduction

There has been a remarkable shift in the epidemiology of head and neck cancer in this country over the past 30 years. While exposure to chemical mutagens such as tobacco and alcohol remains the most common risk factor for squamous cell cancers of the aerodigestive tract, a rapidly expanding subset of head and neck cancers are acquired through human papillomavirus (HPV) infection. The oropharynx is uniquely susceptible to HPV, and now up to 70% of oropharyngeal cancers in the United States are HPV-mediated oropharyngeal squamous cell carcinomas (HPV-OPSCCs).[1,2] HPV-OPSCC is fundamentally distinct (Table 1). Patients with HPV-OPSCC are frequently younger than those with tobacco-mediated oropharyngeal cancer and experience significantly better outcomes with current standard therapies. Thus, there is current impetus for treatment deintensification strategies that maintain optimal cancer outcomes, yet lessen treatment-related side effects.

Epidemiologic Trends of Head and Neck Squamous Cell Carcinoma

Squamous cell cancer of the upper aerodigestive tract accounts for more than 550,000 cancer cases, or 5% of cancer cases, worldwide each year.[3] It is endemic in countries such as India and Brazil where tobacco consumption is the cultural norm. Decreasing tobacco consumption in the United States has led to an overall decline in the incidence of head and neck cancers over the past 3 decades.[4,5] This downward trend is noted for cancers of the oral cavity, larynx, and hypopharynx, since tobacco use remains the primary risk factor for cancers in these sites. However, up to 25% of all head and neck cancers currently diagnosed in the United States are independent of tobacco use.[6] It is now well known that sexually transmitted HPV infection is the main risk factor for this subset of cancers, in which rather specific involvement of the oropharynx (tonsils and base of tongue) is expected, thus adding oropharyngeal cancer to the list of virally mediated malignancies.[7] Chaturvedi et al reviewed the Surveillance, Epidemiology, and End Results population-based data from the past 30 years and reported on the age-adjusted incidence trends of HPV-related and HPV-unrelated head and neck squamous cell carcinoma (HNSCC).[5] They noted a significant decrease in HNSCC incidence in HPV-unrelated sites (oral cavity, larynx, hypopharynx) in contrast to an impressive increase in the incidence of HNSCC in HPV-related oropharyngeal sites over the same time period.[5] Subset analyses by age group, sex, and race demonstrated that the largest increase in HPV-mediated cancers has occurred in white men in their fourth or fifth decade of life. The demographic and risk profiles of HPV-positive and HPV-negative HNSCC patients clearly differ.[8] Thus, an HPV-positive patient with HNSCC is more likely to have better dentition, less or no tobacco or alcohol use, greater marijuana use, and greater numbers of oral sex partners than an HPV-negative patient. Furthermore, these risk associations have shown a very strong dose effect, again emphasizing the distinct risk profile of HPV-positive HNSCC patients.

By the year 2020, the annual number of cases of HPV-OPSCC is projected to outnumber the cases of HPV-mediated cervical cancer in the United States.[1] The emergence of HPV-OPSCC has been deemed an epidemic of our time.

Risk Factors for HPV Infection and HPV-OPSCC

HPV infection is the most common sexually transmitted disease in the world.[9] HPV may be
transmitted by any type of sexual activity. In the United States alone, it is estimated that 20 million people are currently infected, and 6.2 million acquire a new infection each year.[10] The virus is endemic; more than 50% of persons who are sexually active will have a genital HPV infection at some time during their lives. Seven percent of the population between the ages of 14 and 69 (10% of men and 4% of women) are orally infected at any given time, but only 1% of these infections are caused by high-risk cancer-causing HPV subtypes.[11] Smoking further increases the risk of HPV infection.[11] The specific association of HPV 16 and oropharyngeal cancer was reported as early as 1998, in a study from City of Hope in which 60% to 70% of oropharyngeal cancer cases were HPV-associated.[12,13] Currently, HPV 16 accounts for 90% of high-risk oral HPV infections and confers a 15- to 230-fold increased risk of OPSCC.[8,14,15] A sentinel study by Gillison et al confirmed HPV as the actual trigger and promoter for this cancer phenotype.[16] HPV-infected persons remain oblivious to the infection, as there are no associated signs or symptoms. No current treatment exists for active HPV infection. However, a majority of those infected will clear the virus within 2 years. It is unknown why chronic infections develop in a small subset of the population that later progress to HPV-OPSCC. An effective screening test for early detection of HPV-OPSCC has not yet been defined, and no validated screening test is available. The difficulty in screening for OPSCC relates to the fact that most of these cancers originate deep in the crypts of the tonsils, which are inaccessible to simple “Pap smear equivalents” that can be readily performed in anatomic areas such as the anus or cervix.

**HPV and Virus-Mediated Oncogenesis**

HPV is a small DNA virus that is capable of infecting human keratinocytes of the skin and mucous membranes. Although there are more than 100 subtypes of HPV, HPV 16 accounts for 90% of all HPV-related head and neck cancers.[17] HPV encodes several genes that are important in tumorigenesis. Early proteins E6 and E7 are nonstructural oncoproteins (Figure 1). The E6 oncoprotein interferes with the function of tumor-suppressor protein p53 through ubiquitin-mediated p53 degradation. E7 binds to the retinoblastoma tumor-suppressor gene and inhibits its ability to repress the expressions of replication enzyme genes, thus pushing the cell cycle forward.[18] Late proteins L1 and L2 determine the virus subtype and are structural capsid proteins that encapsulate the amplified viral genomes. Virions can then be sloughed off, and the viral life cycle continues. A byproduct of HPV E7–mediated retinoblastoma inhibition is overexpression of p16 protein, a cyclin-dependent kinase inhibitor. A useful surrogate marker for HPV infection is p16 overexpression. Of all potential sites of head and neck cancer, the palatine and lingual tonsils are preferentially targeted by HPV. The highly specialized reticulated lymphoepithelium of the tonsillar crypts strongly expresses programmed death ligand 1 (PD-L1), which acts to suppress T-cell responses to HPV, thus providing an “immune-privileged” site for initial viral infection and adaptive immune resistance.[19]

**Clinical and Pathologic Presentation of HPV-OPSCC**

Up to 90% of patients with HPV-OPSCC present with an asymptomatic neck mass.[20] Some may have no evidence of a primary tumor on direct transoral examination because the tumors are typically small (early T stage) and often concealed within abundant surrounding tonsillar tissue. The neck nodes are frequently cystic, leading to nondiagnostic aspirates (Figure 2). There are opportunities for delay in diagnosis at several levels:

1. Lack of suspicion due to negative smoking history.
2. Absence of symptoms and signs in early disease.
3. Inadequate oropharyngeal examination due to lack of training or proper equipment.
4. Microscopic disease below the imaging threshold for detection.
5. Inadequacy of aspirates collected and processed from cystic nodes.
6. Random and nonsystematic oropharyngeal biopsies during surgery without the benefit of detailed imaging.

Diagnostic imaging is critical. Computed tomography (CT) and/or magnetic resonance imaging (MRI) are necessary preliminary studies. In the setting of an unknown primary, a positron emission tomography (PET)/CT scan may be helpful in localizing the primary cancer and should be performed before any surgical intervention. Ultrasound guidance may increase the diagnostic yield of fine-needle aspirates taken from abnormal neck nodes, especially if cystic.[21] Specimens should be processed for HPV markers. The feasibility of HPV detection in fine-needle aspirates from cervical lymph nodes has been confirmed using both p16 immunohistochemistry (IHC) and in situ hybridization (ISH) platforms.[22,23]
Excisional biopsy of cervical lymph nodes should be avoided if possible, particularly if performed prior to PET/CT, because inflammation from excision surgery can distort PET/CT results.[24] If the fine-needle aspirate collected from a cervical node tests positive for HPV, this should raise concern for an oropharyngeal primary tumor. Careful review of imaging should focus on any oropharyngeal soft-tissue fullness or asymmetry. In the setting of an unknown primary tumor, a palatine and/or lingual tonsillectomy for primary site detection is preferred over random biopsies. HPV-OPSCCs display poorly differentiated, nonkeratinizing, basaloid histology with permeation by lymphocytes.[25] These tumors demonstrate diffuse nuclear and cytoplasmic staining for p16.

**HPV Testing**

A reliable surrogate marker for HPV infection in patients with OPSCC is p16 IHC, given its high sensitivity (p16 IHC is falsely negative in only 4% of cases).[26] Strong nuclear and cytoplasmic expression is highly predictive of HPV-OPSCC. In cases with intermediate levels of p16 expression, ISH or reverse transcription-polymerase chain reaction (RT-PCR) should be performed.[26] PCR-based assays cannot differentiate integrated DNA from episomal viral DNA (passenger virus), which significantly lowers the specificity of the test. DNA ISH can detect integrated viral DNA, which increases its specificity in the clinical setting, although its sensitivity is lower than that of PCR.[27] The ISH test is easily performed in the surgical pathology laboratory. Lewis et al found that 98.5% of nonkeratinizing OPSCCs were positive for HPV by ISH, compared with only 13.6% of keratinizing OPSCCs.[26] The development of RNA ISH probes to E6/E7 microRNA permits direct visualization of viral transcripts in routinely processed tissues and has created the opportunity for accurate HPV detection in the clinical care setting.[28] RNA ISH may soon become a favored test for HPV confirmation of p16-positive tumor samples, especially since p16 may also be overexpressed through non–virally mediated mechanisms. This overexpression may lead to a false-positive result (p16-positive, HPV-negative) that could result in nonoptimal patient counseling and management decisions. It is expected that RNA ISH to E6/E7 will become the favored method for HPV-OPSCC testing in the future.

Cancer Care Ontario has recommended the following testing procedures in patients with HNSCC:[29]:
1. Tumors of all adult OPSCC patients should be routinely tested for HPV.
2. Metastatic cervical nodal tissue of patients with an unknown head and neck primary tumor should be routinely tested for HPV.
3. HPV status in OPSCC should initially be determined using p16 IHC, because of the high sensitivity of this test.

**Impact of HPV on Prognosis**

Multiple studies have confirmed the favorable impact of HPV positivity in patients with OPSCC.[30-33] Of interest, a favorable prognosis is seen even in recurrent or metastatic HPV-OPSCC, which necessitates intensive intervention in this setting as well. Ang et al published the largest retrospective analysis of the impact of HPV on outcomes in OPSCC within the Radiation Therapy Oncology Group (RTOG) 0129 study, which employed cisplatin with either standard or accelerated fractionation radiation.[34] HPV testing was performed using ISH. The 3-year rates of overall survival (OS) were 82.4% (95% confidence interval [CI], 77.2–87.6) in the HPV-positive OPSCC subgroup and 57.1% (95% CI, 48.1–66.1) in the HPV-negative OPSCC subgroup, while the 3-year rates of progression-free survival were 73.7% (95% CI, 67.7–79.8) and 43.4% (95% CI, 34.4–52.4), respectively. Patients with HPV-OPSCC had a 58% lower risk of death (hazard ratio [HR], 0.42 [95% CI, 0.27–0.66]; P < .001) and a 51% lower risk of progression (HR, 0.49 [95% CI, 0.33–0.74]; P < .001). Patients were further divided into risk-of-death categories (low, moderate, and high) based on their HPV status, tumor burden, and tobacco use (Figure 3). Three-year survival was 93%, 70.8%, and 46.2% in the low-, moderate-, and high-risk groups, respectively. Tobacco use had a negative impact on prognosis, independent of HPV status. This study, while retrospective, clearly confirmed a better prognosis for HPV-positive patients with OPSCC.

In a retrospective analysis of the TAX 324 trial, HPV testing was performed using E6/E7 PCR methods. This study examined triple-agent vs double-agent induction chemotherapy. Eighty-two percent of HPV-positive patients were alive at 5 years compared with 35% of HPV-negative patients (P < .0001).[35] The improved survival was attributed to significantly better locoregional control in the patients with HPV-OPSCC but was also due to fewer disease-unrelated deaths in this predominantly younger and healthier subgroup of OPSCC patients.

The Eastern Cooperative Oncology Group (ECOG) 2399 trial was a phase II prospective study of...
patients with stage III and IV, M0, oropharynx and larynx cancer that examined paclitaxel/carboplatin induction chemotherapy followed by concurrent chemotherapy with paclitaxel and standard fractionation radiation therapy.[30] Tumors were tested for HPV by p16 IHC. Patients with HPV-positive OPSCC had a 61% lower risk of death (HR, 0.39 [95% CI, 0.15–1.05]; \(P = .06\)) and a 62% lower risk of progression (HR, 0.38 [95% CI, 0.12–1.15]; \(P = .09\)) than patients with HPV-negative OPSCC, after adjustments for age, tumor stage, and ECOG performance status.

In a prospective analysis, Rischin et al reported results of a randomized phase III study of radiation therapy with cisplatin, with or without tirapazamine, in 206 patients with OPSCC.[31] Two-year OS was significantly better in patients with p16-positive vs p16-negative tumors (91% vs 74%; HR, 0.36; \(P = .004\)).

Surgical series likewise support the favorable impact of p16 positivity in OPSCC. Rich et al reported on 84 patients with stage III or IV oropharyngeal cancers treated with transoral laser microsurgery (TLM) ± adjuvant therapy.[32] Patients with p16-positive tumors had significantly higher 5-year OS and disease-specific survival (DSS) rates than those with p16-negative tumors: 90% (95% CI, 79–96) vs 25% (95% CI, 1–66) (\(P < .0001\)), and 94% (95% CI, 82–98) vs 50% (95% CI, 1–91) (\(P = .0078\)), respectively.

Collectively, these multiple studies performed retrospectively and prospectively have confirmed the superior prognosis of HPV-positive vs HPV-negative OPSCC. The excellent prognosis in HPV-positive patients may have considerable treatment implications in the future.

Treatment Options

Treatment of HNSCC is aimed at reducing the risk of locoregional and distant failure and may employ surgery, radiation therapy, and/or chemotherapy. In patients with HPV-OPSCC, triple-modality therapy should be avoided to minimize toxicity; single-modality therapy should be provided if possible. Of interest, prognosis of HPV-OPSCC seems to be generally favorable, independent of treatment modality.[35]

Early-stage OPSCC, defined as T1-2N0, is associated with an excellent prognosis; therefore, single-modality treatment with either surgery or radiation alone is considered optimal.[33] Although no studies have yet specifically addressed this issue, patients with HPV-positive, stage III, T1-2N1 OPSCC may also qualify for single-modality treatment. This group of HPV-positive patients is of particular interest in the current clinical trials aimed specifically at OPSCC.

The majority of patients with HPV-OPSCC present with nodal metastasis, and therefore advanced stage III or IV disease. As a result, combination therapies are indicated. Given the favorable prognosis for patients with HPV-OPSCC, ongoing clinical trials are examining the efficacy of risk-stratified treatment de-escalation strategies (Table 2). Until evidence supports such an approach, current national guidelines caution against any such treatment modifications outside the context of institutional review board–approved protocols.[33] The current standard of care for HNSCC is driven by site and TNM stage, and for now remains independent of HPV status.

Radiation therapy

Early studies attempted to establish the optimal fractionation of radiation delivered as treatment for HNSCC. Neither RTOG 9003[36] nor RTOG 0129[37] identified a survival advantage for altered fractionation over standard once-daily fractionation. In general, radiotherapy alone should be reserved for patients with early-stage (stage I/II) HNSCC tumors. Radiation monotherapy may eventually prove sufficient for a broader group of patients with HPV-OPSCC, although this remains to be determined (see Table 2).

Chemoradiation therapy

The efficacy of chemoradiotherapy in advanced head and neck cancers has been well established, irrespective of HPV status.[38] Chemotherapy can be given either as induction therapy or concurrently with radiotherapy, and both options offer improved survival over radiation alone in advanced-stage disease. The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) showed an absolute survival benefit of 6.5% at 5 years associated with concurrent or induction administration of chemotherapy with radiation therapy.[38,39] Concurrent chemoradiotherapy proved superior to induction chemotherapy followed by radiation in the setting of initial definitive treatment for patients with advanced OPSCC.[36] Chemotherapy is also given concurrently with radiation in the adjuvant high-risk setting (ie, positive/close surgical margins, significant extracapsular nodal extension).[40-42] In the European Organisation for Research and Treatment of
Cancer (EORTC) 22931 and RTOG 9501 studies, the combined treatment arm was notable for improved locoregional control and disease-free survival.[43] High-dose cisplatin has been widely accepted as the standard concurrent agent in patients with HNSCC, although comparative studies with other agents have not been completed. In the Intergroup study for patients with locally advanced (M0) head and neck cancer, the treatment group with the best survival rate received radiation plus concurrent cisplatin.[44] Although the survival benefit of cetuximab delivered concurrently with radiotherapy was established by Bonner et al, who demonstrated a 10% survival advantage at 3 years with this regimen in stage III/IV HNSCC,[45] no completed trials to date have directly compared cetuximab with cisplatin.

TO PUT THAT INTO CONTEXT

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WHAT DON’T WE KNOW?
HPV-related oropharynx cancer (HPVOPC) has become a well-recognized entity and a growing health problem. While we have knowledge of the demographics of HPVOPC (especially its relationship to sexual behavior), its clinical presentation, and differences in prognosis compared with other oropharynx cancers, we know little of the real biology of the cancer. Almost all data on HPVOPC derive from clinical experience and retrospective analysis, and there are still huge gaps in our knowledge. Why is HPVOPC highly responsive? What is the immunology of this cancer, and can immunotherapy be refined enough to cure the cancer without drugs or radiotherapy? HPVOPC also presents a number of conundrums. For example, although p16 is far more prevalent in HPV-positive OPC than in HPV-negative cancers, p16 is not sufficient to identify HPV-positive OPC. Tests for p16 will be falsely positive in 6% of cases. Also, while the disease is highly responsive, it also appears to be highly aggressive, with a high rate of metastases that are not amenable to treatment with surgery or chemoradiotherapy (CRT).

WHAT ISSUES MOST NEED TO BE ADDRESSED?
Radiotherapy dose de-escalation is critical. The major short- and long-term morbidity for patients is related to radiation dose and extent. The vast majority of HPVOPC patients will live 30 to 50 years and therefore are especially at risk for long-term consequences of radiotherapy. Thus, every effort should be made to leverage surgery and chemotherapy to reduce radiotherapy dose and field size. Encouraging clinical trials that examine de-escalating radiotherapy is the most important priority for our patients today.

In the HPVOPC subgroup of RTOG 0129, progression-free survival (PFS) at 3 years was only 70%, and at 8 years it was 64%. This is not high, given the curability of this disease. In TAX 324, the 5-year PFS in HPVOPC patients with advanced disease was 78%. Our experience is that there is an increasing rate of late metastases in patients treated with CRT only. We need to be able to determine who is at risk and needs systemic therapy.

Unfortunately, there is a clear risk of added acute and late toxicities with concurrent chemoradiation regimens for locoregionally advanced head and neck cancers, especially in the setting of cisplatin therapy. Some patients, specifically the elderly, do poorly after chemoradiotherapy.[46] RTOG trials defined severe late toxicity as chronic grade 3/4 pharyngeal or laryngeal toxicity, feeding tube dependence for 2 or more years after registration, and/or potential treatment-related deaths (eg, caused by pneumonia) within 3 years, which occurred in 43%, 20%, and 10% of patients,
respectively.[47] In the GORTEC trial, which compared chemoradiation to radiation alone for advanced-stage OPSCC, concurrent chemoradiation proved superior in both locoregional control and OS but at the cost of a higher rate of mucositis, an increased need for feeding tubes, and a higher rate of late complications.[48] The treatment-related mortality rate for chemoradiation therapy for head and neck cancers in randomized clinical trials is reported to be approximately 3% to 4%.[47]

Toxicity may prove to be less problematic with modern intensity-modulated radiation therapy, and it may perhaps be further ameliorated by the frequent substitution of cetuximab for cisplatin. Cetuximab, a chimeric antibody directed against the epidermal growth factor receptor, is the only biologic agent currently approved by the US Food and Drug Administration for the treatment of HNSCC. With the exception of acneiform rash and infusion reactions, the addition of cetuximab to radiation therapy is not associated with an increased risk of grade 3/4 toxic side effects.

To date, the precise role of chemotherapy for patients with advanced-stage HPV-OPSCC has not been defined. This issue is especially important in this younger patient subgroup with a generally favorable prognosis because the toxicity of concurrent chemotheraphy may not be justifiably offset by any meaningful clinical benefit. The benefit of chemotherapy in addition to radiation therapy, both in the upfront and adjuvant settings, needs to be carefully calibrated through future clinical trials aimed at this patient subpopulation.

### Surgical treatment

Technologic advances, including transoral robotic surgery (TORS) and transoral laser microsurgery (TLM), have pushed surgery back into the discussion for frontline treatment of HNSCC. Small primary tumors—as are common in HPV-OPSCC—with resectable nodal disease lend themselves to surgical resection. Transoral surgery (TOS) has changed the way these small tumors can be treated.

Traditional surgical treatment involved large operations that required mandibulotomies and free flap reconstructions. TOS allows for less invasive surgical approaches, shorter hospital stays, avoidance of tracheotomy and gastrostomy tubes, less pain, faster recovery with fewer complications, and less cost compared with traditional surgical techniques.[49] In addition, the functional deficits are manifest upfront with minimal long-term sequelae. A direct comparison with nonsurgical treatment of HNSCC is lacking; however, a review of early data from TORS resections showed an 80% to 90% 2-year OS.[50] Oncologic results following TLM are equally impressive: Local control rates reached 85% in earlier studies,[51] and more recent studies reported a 5-year OS of 78% and a local control rate of 97%.[52]

As surgeons gain more experience with new technologic approaches, some are now operating on more locally advanced tumors. Weinstein et al achieved excellent outcomes with TORS in stage III/IV oropharyngeal carcinomas: the 2-year DSS was 90%.[53] In a group of 47 patients, 38% avoided chemotherapy and 11% avoided both chemotherapy and radiation therapy; only one patient required a long-term gastrostomy tube. The same group of investigators further validated the TORS technique in HPV-positive patients and demonstrated outcomes comparable to those achieved in HPV-negative patients.[54]

Haughey et al reported similar results with the TLM technique.[52] In their study, 90% of patients demonstrated p16 positivity and 34% of patients presented with advanced T-stage disease. Despite these findings, local, locoregional, and distant disease control each exceeded 90%. Forty-eight percent of patients avoided primary tumor bed radiation therapy, 84% avoided chemotherapy, and 26% of patients received no adjuvant therapy at all. Furthermore, most patients (87%) had excellent swallowing scores. Severe long-term swallowing difficulty occurs mainly in patients with large T4 tumors, especially those that involve the base of the tongue. These data regarding functional outcomes after surgery are promising.

Haughey et al also found that outcomes sequentially worsen with each additional adjuvant modality after surgery.[52] TOS should be reserved for the anatomicly amenable patient in whom a safe operation may be performed and unnecessary adjuvant therapy can be avoided, with predicted favorable postoperative functioning.

Management of at-risk or involved neck nodes is a common concern in patients with HPV-OPSCC. The best approach to lymphadenopathy is often multidisciplinary; it may include surgical resection or radiation to the involved neck compartments.[33] A neck dissection may be either staged or performed at the same time as TOS. In early tumors with no clinically apparent lymph node involvement, selective neck dissection should be performed. With clinically involved nodes, an ipsilateral, modified radical neck dissection is usually sufficient in most oropharyngeal tumors, whereas bilateral neck dissection is advised in larger base-of-tongue primary tumors that approach or cross midline. The extent of node dissection is often adjusted based on nodal location and volume,
but levels II–IV should be included in the lymphadenectomy because level IV node involvement is common, especially in base-of-tongue tumors, and predicts a worse prognosis.[55]

Extracapsular spread from nodal disease is traditionally a prognostic indicator in head and neck cancer that is used to determine whether chemotherapy should be used in addition to adjuvant radiation. A recent finding that patients with p16-positive OPSCC have no difference in 5-year DSS despite extracapsular spread has significant implications for therapy.[56] In patients with p16-positive OPSCC who have nodal extracapsular spread, the addition of chemotherapy to radiation therapy seems to offer no survival advantage.[57] The ADEPT trial is a randomized phase III study actively investigating the role, if any, of nodal extracapsular spread in HPV-OPSCC (see Table 2).

In summary, HPV-oropharyngeal tumors frequently lend themselves to minimally invasive surgical treatment. Surgery is likely to play a larger role in HPV-OPSCC, since the surgeons’ experience in treating these tumors is growing and preliminary reports have been favorable. The traditional approach of postoperative chemoradiation therapy for nodal extracapsular extension within lymph nodes in patients with HPV-OPSCC is being challenged.

Posttreatment Expectations and Prognosis

Disease progression within 3 years of treatment occurs in 10% to 25% of patients with HPV-OPSCC.[58] The majority of recurrences are locoregional and occur in the first year after completion of treatment. In general, patients with HPV-OPSCC have decreased rates of locoregional failure but similar rates of distant metastasis compared with patients who have non–HPV-OPSCC.[59] The lung is the most common site of distant relapse in both groups. In disease relapse, p16 status continues to be a favorable prognosticator. Timely detection and salvage intervention for relapsed disease are beneficial.

There is currently no recommendation for any change in the posttreatment surveillance algorithm based on p16 status. During surveillance, second primary tumors are quite rare in patients with HPV-OPSCC compared with those who have tobacco-mediated oropharyngeal cancers.[59,60] This is thought to result from the intact genetic constitution of HPV-mediated tumors in contrast to tobacco-mediated tumors.

Future Directions

Although there are currently no recommended treatment modifications for HPV-OPSCC, several current trials are evaluating this precise issue. The concept of deintensification developed after demonstration of the excellent prognosis of HPV-positive tumors, many of which are likely being overtreated (see Figure 3).[34] In addition, a shift in patient demographics toward younger patients who survive longer after treatment has led to consideration of the long-term complications of chemoradiation therapy.

Such complications drive several ongoing trials directed specifically at HPV-OPSCC (see Table 2). These trials address deintensification through various strategies: (1) radiation alone in risk-stratified OPSCC, (2) decreased dose of radiation, (3) substitution of cetuximab for cisplatin, and (4) surgical resection followed by a reduction/elimination of chemotherapy or radiation therapy. The results of these studies will likely be critical in defining optimal treatment strategies.

In summary, a multidisciplinary approach is required for the optimal treatment of patients with HPV-positive OPSCC. As of now, there are no treatment guidelines directed specifically at this population (Table 3). Ideally, all patients should be directed toward clinical trials in order to answer important questions regarding prognosis and treatment. Furthermore, all patients should be stratified according to surgical resectability. There is an emerging trend toward minimally invasive surgical resection that may prove to decrease overall treatment-related morbidity. Both ECOG 3311 and ADEPT are national surgical trials that are actively investigating risk-adjusted adjuvant therapies in the HPV-OPSCC patient population. These trials will clarify pertinent risk factors in HPV-OPSCC and will refine treatment strategies accordingly, such that excellent oncologic and functional outcomes can be simultaneously realized.

Conclusion

The incidence of HPV-OPSCC is growing rapidly in the United States. Affected patients have unique risk profiles and presentations. HPV imparts a favorable prognosis for those with oropharyngeal cancer. Treatment modifications to optimize both oncologic and functional outcomes are currently being investigated, with results of ongoing trials expected to define optimal therapeutic strategies in
the years ahead.

Financial Disclosure: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

Figure 1. Human papillomavirus (HPV) is a sexually transmitted virus a...

Figure 2. Imaging Studies of HPV-Positive OPSCC

Figure 3. Risk Stratification for Oropharyngeal Squamous Cell Carcinom...

Table 1. Comparison of HPV-Negative and HPV-Positive Head and Neck Cancers

Table 2. Notable Ongoing Deintensification Trials in HPV-OPSCC
Table 3. Summary: Management and Treatment Options in HPV-OPSCC

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<td>Recommendations</td>
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<td>US-guided needle biopsy yields in cervical nodes</td>
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<td>If palpation of the neck is normal, it may point to</td>
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<td>oropharynx as potential site of primary tumor</td>
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<td>PET/CT may be helpful in determining the primary site; if found</td>
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<td>should be done before biopsy</td>
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<td>AUA and stage-dependent treatment</td>
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<td>No modifications based on HPV status at this time</td>
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<td>Determination of treatment is under active study</td>
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<td>Refer patient to a clinical trial if possible</td>
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Table 3. Summary: Management and Treatment Options in HPV-OPSCC

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