The Epidemic of HPV-Associated Oropharyngeal Cancer Is Here: Is It Time to Change Our Treatment Paradigms?

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Abstract

Although relatively uncommon, oropharyngeal cancers are increasing in incidence despite declining prevalence of smoking and in direct opposition to a decreasing incidence of all other head and neck cancers. An epidemic of human papillomavirus (HPV)–associated oropharyngeal cancers seems to account for these incidence trends. Important demographic, behavioral, and prognostic characteristics define this unique population. Changes in prevention, diagnosis, evaluation, staging, and treatment are needed. This article summarizes the epidemiology and clinical behavior of HPV-associated oropharyngeal cancer and discusses evolving/potential paradigms of treatment. However, data are currently insufficient to change treatment paradigms for HPV-associated oropharyngeal cancer outside of a closely monitored clinical trial. (JNCCN 2011;9:665–673)

The Epidemic of HPV-Associated Oropharyngeal Cancer

Significant site admixture occurs in the annual United States “Cancer Statistics” overview in which all sub-sites of pharyngeal cancer are listed as the single site “pharynx” (including not only oropharyngeal cancers but also hypopharyngeal and nasopharyngeal cancers), and base of tongue (lingual tonsil or oropharyngeal tongue) cancers are often listed collectively with oral (mobile or oral cavity) tongue cancers as the generic site “tongue.” Regardless of these site admixtures and without consideration of a growing and aging United States population, the number of both pharyngeal and tongue cancers is increasing (approximately 13,000 and 11,000, respectively, in 2010). As early as 2005, a conflict in the trends in age-adjusted incidence rates was noted, with increasing or stagnate rates for tongue and oropharyngeal cancer but significantly decreasing rates for laryngeal, hypopharyngeal, and oral cavity cancer (Figure 1). More careful site stratification has made it apparent that age-adjusted incidence of oropharyngeal cancer is rising dramatically (estimated at 5% annual increase) in the United States, whereas oral cavity cancer incidence is falling (approximately −2% annually). Furthermore, the increase in oropharyngeal cancer incidence seems to be seen primarily in middle-aged (40–59 years) white men. Notably, these trends among white men have completely eliminated the dramatic racial disparity that existed in oral cavity/pharyngeal cancer incidence.

As a result of the Surgeon General’s warning and the mounting evidence showing the association between tobacco and cancer, per capita tobacco consumption and cigarette smoking prevalence rates declined consistently since the mid-1960s (Figure 2). In 1965, more than half of men and one-third of women in the United States were actively smoking, and currently fewer than a quarter of men and fewer than one-fifth of women smoke. As might be expected for diseases with a long initiation associated with chronic tobacco exposure, the primary public health goal of reducing lung cancer (and laryngeal, oral cavity,
and hypopharyngeal cancer) incidence did not begin until the late 1980s. However, during this same period, oropharyngeal cancer incidence initially plateaued and subsequently rose dramatically (Figure 1). These complex trends in oropharyngeal cancer incidence are consistent with the decline of one carcinogenic exposure (smoking) but, during the same period, the emergence of a second unrelated etiologic exposure.

Several lines of evidence have established the carcinogenic potential of human papillomavirus (HPV), and since the early 1990s HPV DNA has been consistently identified in many head and neck cancers. A systematic review and meta-analysis have confirmed that the oropharynx is the principal site of head and neck cancers and that HPV type 16 accounts for more than 90% of positive cases. Cohorts consisting of patients chiefly from the 1990s had reported HPV prevalence rates of approximately 50%, whereas more recent reports ranged from 70% to 80%.

Numerous case series have also established that HPV-positive oropharyngeal cancers have unique demographic, behavioral, and clinical characteristics. Patients with HPV-positive oropharyngeal cancer are often middle-aged white men, of higher socioeconomic status, and nonsmokers and non-drinkers. However, sexual behaviors do seem to be associated with this disease, and patients with HPV-positive oropharyngeal cancer as a group have a higher number of sexual partners, particularly oral sexual partners. HPV-positive oropharyngeal cancers tend to occur in either the tonsils or base of tongue rather than other oropharyngeal subsites, and they often have nonkeratinizing histologies, including basaloid, lymphoepithelial, or poorly differentiated carcinomas. Finally, these patients usually present for medical care because of nodal metastases and, after initial evaluation, are found to have small primaries with multiple positive nodes.

HPV-associated oropharyngeal cancers chiefly from single-institution case series have distinctive demographic, behavioral, and clinical characteristics. Population level trends in oropharyngeal cancer mirror these characteristics and support HPV as the cause of the national increase in oropharyngeal cancer incidence. First, the increasing incidence appears greatest among the middle-aged white male population. Although many behavioral researchers have suggested that oral sex prevalence has risen over the past 3 decades, reliable data on these national trends are lacking. However, smoking prevalence has

![Figure 1](image-url)  
**Figure 1**  Age-adjusted SEER incidence rates for laryngeal cancers, floor of mouth/gingival/other mouth cancer, tongue cancers, and oropharyngeal cancers in the United States.
clearly dropped over this period and, as expected, tobacco-associated malignancies have subsequently declined in incidence, with a notable exception being oropharyngeal cancer. More specifically, the increasing incidence seems to be restricted to the oropharyngeal subsites that tend to be HPV-positive (tonsils and base of tongue). National trends also show a rising proportion of higher-grade tumors for cancers of the tongue and tonsil but not of other sites. Additionally, in recent years a greater proportion of patients with oropharyngeal cancer have been presenting with regional rather than localized disease. Most importantly, several groups have shown a dramatic increase in HPV-positive oropharyngeal cancer over time among archived tumor specimens within population-based registries. Taken together, the findings within case series and these national epidemiologic trends support the assertion that the United States is experiencing an epidemic of HPV-associated oropharyngeal cancers, in direct opposition to a declining incidence of tobacco-associated cancers. Additionally, no clinically applicable equivalent to the routine cervical Pap test is available for detecting oropharyngeal premalignancy or in early cancer screening.

Clinical Behavior of HPV-Associated Oropharyngeal Cancer

National trends also show a dramatic improvement in 5-year relative survival rates for patients with tonsil and tongue cancer, in direct contrast to the relatively stagnate survival for those with laryngeal and oral cavity cancer. Some oncologists believe that the greater use of multimodality chemoradiation in the treatment of oropharyngeal cancer can account for the observed dramatically improved survival; however, treatment of laryngeal cancer has undergone a similar evolution without improvements in survival rates. More likely, the dramatic changes in oropharyngeal cancer survival are from the shift in disease origin and a corresponding responsiveness to treatment. Interestingly, disparities in survival for African Americans, not explained by disparities in classic prognostic confounders, may be ascribed to a difference in oropharyngeal cancer origin (chiefly tobacco-related among African Americans and HPV-associated among white Americans).

Although early series exploring the prevalence of HPV-positivity among head and neck cancers suf-
ferred from site admixture (oropharynx mixed with nonoropharyngeal sites), stage/treatment heterogeneity, and other retrospective confounding factors, these studies were relatively consistent in finding an improved survival for HPV-positive patients.\(^{35}\) In 2008, Fakhry et al.\(^{36}\) reported the first multicenter clinical trial in which tumors were prospectively tested for HPV (ECOG 2399 phase II trial), which showed that 61\% of 62 oropharyngeal cancers were HPV-positive, and immunohistochemistry for p16 overexpression was used to confirm the association. Patients with HPV-positive oropharyngeal cancers had significantly better overall and progression-free survival in univariate analyses, but only a borderline effect remained after multivariate analyses. Recently, the results of a Radiation Therapy Oncology Group phase III trial (RTOG 0129) were reported for the subgroup of patients with oropharyngeal cancer (N = 433), among whom HPV and p16 status could be determined retrospectively in 323 patients.\(^{37}\) Of these patients, 64\% were HPV-positive, 66\% were p16 positive, and these 2 markers were highly correlated. Patients with HPV-positive tumors had significantly better overall and progression-free survival than those with HPV-negative tumors, and these results remained highly significant after multivariable adjustment. The difference in outcome was more striking when analyzed using p16 status.

Most recently, the results of a Trans-Tasman Radiation Oncology Group phase III trial (TROG 02.02) were reported for the subgroup of patients with oropharyngeal cancer (N = 465), among whom HPV and p16 status could be determined retrospectively in 206 patients.\(^{38}\) Of these patients, 57\% were p16-positive, and 86\% of p16-positive tumors were HPV-positive. Patients with p16-positive tumors had significantly better overall and failure-free survival than those with p16-negative tumors, and these results remained significant after multivariable adjustment. Two additional phase III head and neck cancer trials have presented data stratified by HPV-status, with both supporting the findings of improved survival for patients with HPV-positive cancers; however, only limited subgroup analyses restricted to patients with oropharyngeal cancer were reported.\(^{22,39}\)

Now that HPV is accepted as an important prognostic factor in oropharyngeal cancer, a clear algorithm of what constitutes an HPV-positive tumor is needed. Although research studies have used numerous methods to define HPV-positivity, clinical pathology laboratories will need an accepted common methodology for clinical application, a process currently in evolution but likely to include more than a single assay.\(^{35,40}\) Because the overexpression of p16 is highly correlated with HPV-positivity, many laboratories find that testing for p16 using immunohistochemistry is a simple and cost-effective first step to exclude the HPV-negative cases from further testing.\(^{38,40}\) Subsequent HPV in situ hybridization testing will confirm HPV-positivity in most p16-positive cases.\(^{40}\) However, a relatively small subset of p16-positive but HPV in situ–negative tumors remains a group with unclear status, for which more intensive testing will ultimately require standardization.\(^{38,40,41}\)

Among patients with head and neck cancer, smokers have a much worse prognosis than never-smokers.\(^{42,43}\) Although many HPV-positive tumors have an HPV-driven phenotype with excellent prognosis, emerging data suggest that other molecular alterations (derived chiefly from tobacco exposures) contribute to cancer phenotype and prognosis even among HPV-positive tumors. Smokers tend to have oropharyngeal cancers with mutated p53 and epidermal growth factor receptor (EGFR) overexpression, and lower HPV titer and p16 expression.\(^{44}\) Although patients with HPV-negative oropharyngeal cancer consistently have the worst prognosis, patients with HPV-positive oropharyngeal cancer who have the highest HPV16 titer or p16 expression and those who have wild-type p53 or low EGFR expression have a better prognosis than those with low HPV16 titer or p16 expression or with mutant p53 or high EGFR expression.\(^{43–46}\) These retrospective data suggest that identification of other complementary markers can further refine prognostic classification and hopefully predict tumor response to various therapy modalities.

An HPV-driven phenotype would seem more likely to occur in nonsmokers, and wild-type p53, low EGFR, high p16, and high HPV titer in oropharyngeal cancers may be associated with a lack of smoking exposure.\(^{44}\) An attempt to further stratify oropharyngeal cancer prognosis beyond HPV status was conducted using recursive partitioning analysis of phase III trial data.\(^{37}\) Although molecular data such as p53 mutation status and EGFR expression were not available, prospectively obtained smoking data were recorded. Prognostic factors were identified and incorporated into a prognostic model to stratify patient outcomes.
into low-, intermediate-, and high-risk groups (Figure 3). As expected, the high-risk group consisted principally of smokers with HPV-negative tumors (only 11% were nonsmokers with large primaries). However, this analysis was able to identify a low-risk group with a 3-year overall survival rate of more than 90%, consisting of HPV-positive patients with no or limited smoking history (only 23% were smokers with limited nodal stage: N0, N1, and N2a). Contemporary studies have found very limited stratification of HPV-associated oropharyngeal cancer outcomes attributable to the TNM staging system, partly because very few HPV-positive cancers present without adenopathy.\textsuperscript{25,37,38,43–46} However, the studies outlined earlier suggest the existence of a HPV-driven oropharyngeal cancer group with extremely good prognosis independent of stage and within the larger sample of HPV-positive cancers.\textsuperscript{37,43–46} This prognostic stratification seems to be consistent and powerful, and thus may lead to modification of the current TNM staging system through the incorporation of HPV status, and possibly smoking status.

**Figure 3** Classification of patients with oropharyngeal cancer from RTOG 0129 into risk-of-death categories through recursive partitioning analysis and Kaplan-Meier estimates of overall survival according to those categories. From Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. N Engl J Med 2010;363:33; with permission.
Current Standards, Future Opportunities

Although the head and neck cancer specialty is rethinking and debating the paradigm of oropharyngeal cancer management, the goals are clear: individualize care, reduce toxicity, and maximize survival. To advance these goals, customizing care is critical and will require stratification of patients beyond the current TNM staging system and a more sophisticated understanding of the predictive effect of HPV status. To reiterate, HPV-positive oropharyngeal tumors occurring in nonsmokers seem to have a cancer phenotype that is driven by the HPV oncoproteins E6 and E7 and their effects on tumor suppressor/apoptosis/ cell cycle pathways, whereas HPV-positive oropharyngeal cancers occurring in smokers often also have the classic tobacco-associated somatic alterations and a cancer phenotype of mixed origin. It is postulated that HPV-positive cancers in nonsmokers have intact apoptotic mechanisms and thus in theory are more responsive to cytotoxic therapies, whereas HPV-negative and HPV-positive cancers occurring in smokers have somatic alterations in these mechanisms that are associated with resistance to cytotoxic treatments and thus recurrence.

Current standards of care include radiation alone or surgery alone for stage I/II oropharyngeal cancer (and selected patients with low-volume stage III). Available options established through prospective trials for more locally advanced cancers are radiation with concurrent cisplatin or cetuximab, induction chemotherapy followed by radiation with or without concurrent systemic therapy, and surgery with postoperative radiation with or without concurrent cisplatin. However, these treatment options induce severe acute toxicities, swallowing dysfunctions, and long-term morbidities, which have not been fully documented and are particularly concerning in younger patients with highly curable HPV-associated oropharyngeal cancers.

Based on emerging data, head and neck oncologists are beginning to address whether and to what extent therapy for HPV-associated oropharyngeal carcinoma can be deintensified. Because of the risk of compromising tumor control, treatment deintensification should be conducted in closely monitored clinical trials. Achieving reduced toxicity will either require reducing the extent and impact of current therapies or adopting novel therapies with inherently less toxicity. Because cancer cure remains paramount, it is the group with the best prognosis in whom less aggressive therapy with equivalent cure rates might best be feasible.

The development and introduction of high-precision intensity-modulated radiation therapy (IMRT) allows delivery of tumoricidal doses while limiting normal tissue toxicity. Whether intensity-modulated proton therapy can further improve functional outcomes of radiotherapy must be addressed. In a retrospective series of 299 consecutive patients with oropharyngeal cancer treated with radiation alone at a single-institution, the 5-year estimated locoregional control rate was 85%. This result was confirmed by a recent phase II multi-institutional prospective trial (RTOG 0022), which showed that radiation alone yielded an estimated locoregional control rate of 91% in 69 patients with T1–2, N0–1 (including some radiologically N2B) oropharyngeal carcinoma. Despite requiring bilateral irradiation, the use of IMRT was associated with low long-term toxicity. These results with radiation alone seem to warrant evaluation of whether some patients with HPV-associated oropharyngeal carcinoma traditionally treated with concurrent chemoradiotherapy (low-volume stage III) can be well managed with radiation alone and thus be spared the added acute and late toxicity of chemotheraphy. Similarly, surgery alone may be an option for patients with stage I, II, and low-volume stage III disease in whom final pathologic assessment/staging may not yield adverse features requiring adjuvant postoperative radiotherapy or concurrent chemotherapy.

Two additional strategies to deintensify therapy are combining standard radiation dose with less-toxic targeted agents and combining an effective systemic therapy or promising new combinations with lower radiation dose. For example, both cisplatin and cetuximab are now considered acceptable concurrent agents to radiotherapy for locally advanced oropharyngeal cancer. Available efficacy data are more extensive for cisplatin and radiation, but these same studies suggest that concurrent cetuximab overall seems to be less toxic than cisplatin. In a secondary analysis of a phase III trial of radiation alone versus radiation with concurrent cetuximab, the latter was associated with improved survival principally in subgroups likely to have HPV-positive tumors. Further refinements in radiation field and dose, broadening the role of radiation alone, administering less-toxic
concurrent agents, or using novel combinations with lower-dose radiation are all intriguing options to deintensify treatment of HPV-associated oropharyngeal cancer. However, ad hoc application of these treatment approaches is strongly discouraged, and clinical trials with these designs will have to proceed in an incremental and measured way, because reasonable salvage options after radiation are limited.\(^6\)

Advances in transoral surgery and the development of robotic systems are also being advocated as treatment deintensification. Although these approaches are certainly less morbid than traditional transcervical resections, most patients with oropharyngeal cancer have nodal metastases, and therefore most patients who undergo surgery will still require postoperative radiotherapy.\(^5\) Although definitive transoral resection seems to be a reasonable option for patients presenting with small primaries without nodal metastases, and has a lower long-term toxicity profile than definitive radiotherapy, these patients (stage I and II) are rare, particularly for HPV-positive oropharyngeal cancer. Only a well-organized, multi-institutional clinical trial with a stringent quality assurance program and long-term collection of functional outcomes can properly determine the role of transoral resection in the treatment of HPV-associated oropharyngeal carcinoma. Although the dose is lower than with definitive radiotherapy for patients requiring postoperative radiotherapy, the long-term toxicity profile and acute complications associated with transoral resection and postoperative radiotherapy have not been formally compared with radiotherapy. Other issues for study will be the added costs and longer treatment times for patients treated with surgery and postoperative radiotherapy, and the potential cost savings and lower toxicity for surgical patients avoiding chemotherapy or radiotherapy. Although the advantages of a clinical trial comparing transoral surgery in combination with postoperative radiotherapy with definitive radiotherapy alone are clear, patient acceptance of this type of randomization and the complexity of a trial such as this likely preclude a phase III design.

Ideally, scientific questions to be addressed will vary among the different risk categories of patients with head and neck cancer. The HPV-associated oropharyngeal carcinoma is a prime example of such a dilemma. Ideally, scientific questions to be addressed differ among the 3 risk categories of oropharyngeal carcinomas presented previously. However, the power limitations of dividing an already relatively rare disease into several groups with distinct features make the feasibility of launching multiple clinical trials, even in the intergroup setting, questionable. Other challenges include lack of funding, particularly to support functional assessment and translational studies, and physician and patient biases preventing enrollment into randomized comparative trials. Consequently, the field will partly rely on prospective data with inferred comparative survival, toxicity, and costs from parallel phase II and other designs, such as prospective registries.

Clinical trials have been proposed and some are ongoing to address potential modifications of treatment for HPV-positive oropharyngeal cancer. The ECOG is conducting an active phase II trial (E1308) for HPV-associated oropharyngeal carcinoma. This trial was designed to study the use of induction paclitaxel, cisplatin, and cetuximab followed by 54 Gy of radiation in 27 fractions, with concurrent cetuximab for patients who had a clinical and radiographic complete response at the primary, and 69.3 Gy of radiation in 33 fractions of radiotherapy with concurrent cetuximab for those who had a less than complete response at the primary. The sample size is 75 patients and may ultimately support a more definitive trial of induction chemotherapy with lower-dose radiotherapy. The Radiation Therapy Oncology Group is currently developing a phase III clinical trial (RTOG 1016) to formally compare 70 Gy of radiation in 35 fractions over 6 weeks with concurrent cisplatin, with the same radiation regimen with concurrent cetuximab. The study is designed to accrue 706 patients with p16-positive oropharyngeal cancer and is intended to show that cetuximab concurrent with radiation is not inferior to treatment with cisplatin concurrent with radiation in this patient population, but that the overall side effect profile of cetuximab may be more favorable. Additionally, this trial will prospectively collect smoking data to confirm the strong stratification of HPV-associated oropharyngeal cancer outcomes that smoking provides. At the University of Maryland, the response to and safety of the MAGE-A3/HPV16 vaccine for recurrent, progressive, or metastatic oropharyngeal cancer is being explored. In the United Kingdom, a phase I trial of recombinant listeria HPV16 vaccine (REALISTIC trial) as an adjuvant to standard definitive therapy is
being conducted at 3 centers (Liverpool, Royal Marsden, and Cardiff).

Conclusions
The increasing incidence of oropharyngeal cancer in the United States represents the emergence of a distinct entity of HPV-associated cancers. These cancers tend to occur in middle-aged white men of medium to high socioeconomic status, are associated with oral sexual behaviors, and are very responsive to currently available, yet rather toxic, therapies. Several problems exist, including a need for prevention efforts to be expanded beyond tobacco/alcohol control, a need for oropharyngeal premalignancy and early cancer screening, a consistent approach to HPV testing, and a revision in the current oropharyngeal cancer staging system. Most importantly, because the prognosis of a subset of these HPV-positive oropharyngeal cancers is excellent, many of these patients are probably overtreated with the current aggressive multidisciplinary approach. Consequently, a careful, measured, and scientific approach is needed to modify the current treatment paradigms. Current trials will begin to address the choice of agents concurrent to radiotherapy, the concepts of induction chemotherapy combined with reduced radiation dose, the potential of therapeutic vaccines, and the role of transoral/robotic surgery. No justification exists to modify treatment of HPV-associated oropharyngeal cancer outside of a closely monitored protocol study setting.

References
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