

Oropharyngeal Cancer

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Abstract: Carcinoma of the oropharynx is of squamous histology in over 90% of cases. Oropharyngeal squamous cell carcinoma (OSCC) displays significant heterogeneity in terms of etiology, biology, and clinical behavior. It has now become clear that a subset is initiated by infection with high-risk human papillomavirus (HPV) types, especially type 16. This review summarizes the epidemiology, clinical presentation, molecular pathogenesis, diagnosis, and therapy of OSCC, focusing on the HPV-associated cases; it also details the need for a better understanding of the molecular pathogenesis of the different types of OSCC in order to improve treatment.

The oropharynx is composed of the tonsils, base of tongue, soft palate, and oropharyngeal wall. Tumors arising in these areas are squamous cell carcinomas in over 90% of cases and display significant heterogeneity in terms of etiology, biology, and clinical behavior. Mounting epidemiologic, molecular, and clinical evidence suggests that high-risk human papillomaviruses (HPVs; especially type 16) account for disease pathogenesis in many oropharyngeal cancers, especially those among individuals without a significant history of tobacco use and/or alcohol consumption.¹⁻⁷

Epidemiology

Surveillance, Epidemiology, and End Results data reveal that the annual incidence of base-of-tongue and tonsil cancers increased by 2.1% and 3.9%, respectively, from 1973 to 2001 among white men and women age 20–44 years, whereas the incidence at other sites declined.^{8,9} There was also an increase by 2–3% per year in the incidence of tonsillar cancer among African-American and white men younger than 60 years through 1998.^{8,10} An increase in sexual behaviors associated with HPV transmission through this period, indirectly demonstrated by the increase in herpes-simplex seroprevalence over these years, may account for this rise. Specifically, in the United States, herpes simplex-2 seroprevalence increased by 30% between the periods 1976–1980 and 1988–1994, and the relative increase was more significant in younger individuals.¹¹ Sev-

Keywords

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eral studies support the evidence of sexual transmission of oral HPV infection.^{12,13} Individuals with a history of HPV-associated anogenital cancers, husbands of women with in situ and invasive cervical cancer, posttransplant patients, and HIV-infected men are all at increased risk of developing HPV-associated oropharyngeal squamous cell carcinoma (OSCC).^{4,8,14-16} A recent hospital-based case-control study of 100 newly diagnosed patients with oropharyngeal cancer and 200 control patients without cancer revealed that a high (ie, ≥ 26) lifetime number of vaginal sex partners and 6 or more lifetime oral sex partners were associated with subsequent development of oropharyngeal cancer (odds ratios, 3.1 and 3.4, respectively).¹² The authors found that there was a strong association between oral HPV infection and OSCC among individuals with or without tobacco or alcohol use, the well-recognized causative agents for this disease. Although oral-genital contact may be responsible for HPV transmission, transmission through direct mouth-to-mouth contact or other means cannot be excluded.

There has also been an association between markers of HPV infection and increased risk of OSCC. Oral high-risk HPV infection significantly increased the risk of developing oropharyngeal cancer (odds ratio, 230; 95% confidence interval [CI], 44–1,200) after adjustment for alcohol and tobacco in a Swedish study.¹⁷ A nested case-control study from Norway demonstrated that HPV 16–seropositive individuals had a greater than 14-fold increased risk of oropharyngeal cancer.¹⁸ Oropharyngeal cancer was linked to oral HPV infection and HPV 16 L1 seropositivity among patients with or without history of heavy tobacco and alcohol use in a study by D'Souza and colleagues.¹² Studies that do not show an association between sexual practices, oral HPV infection, and head-and-neck cancer include patient populations in which less than 25% of the cases have detectable HPV DNA; thus, the risk association might be attenuated.^{15,19} Studies that reduced etiologic heterogeneity by limiting enrollment to patients with oropharynx cancer, showed a clear association between sexual behaviors, oral HPV infection, and head-and-neck squamous cell cancer (HNSCC).^{3,12,20} Tonsillar crypts resemble the transformation zone of the cervix and appear particularly susceptible to transformation by HPV.²¹

Clinical Presentation

Clinical characteristics of HPV-positive HNSCC differ from those of HPV-negative HNSCC.⁶ Similar to tobacco-associated OSCC, there is a male predominance in HPV-associated OSCCs, which are more frequent in nonsmokers and nondrinkers. Patients with HPV-associated OSCC are on average 5 years younger than smokers

with oropharyngeal cancer. The epithelium of the lingual and palatine tonsils is the most frequent site of infection. HPV-associated OSCC tends to be poorly differentiated, often basaloid in histology, and frequently present at advanced tumor, node, metastasis (TNM) stage.²

Molecular Progression of Oropharyngeal Cancer

In tobacco-induced HNSCC, loss of 9p21–22 is the most frequent event and is also present in the earliest definable lesions, including dysplasia and carcinoma in situ.²² The p16 (CDKN2) protein resides within this chromosomal region and is a candidate tumor suppressor gene.²³ The p16 protein binds to the cyclin D1 CDK4/CDK6 complex, preventing phosphorylation of the retinoblastoma (Rb) protein (pRb).²⁴ p105Rb and the Rb family members p107 and p130 in turn regulate the activity of E2F transcription factors.^{25,26} E2F forms complexes with hypophosphorylated p105Rb and represses the transcription of genes required for cell cycle progression such as cyclin A, and this repression is relieved by cyclin-dependent kinase (CDK)-mediated phosphorylation of p105Rb.²⁷ Thus, p16 is a CDK inhibitor that preserves the integrity of the G1/S checkpoint and also regulates the transcriptional program involved in cell proliferation. Abrogation of p16 function in HNSCC occurs rarely via point mutations of the p16 gene and more frequently via homozygous deletions and methylation of the 5' CpG promoter region of p16.²⁸⁻³⁰ Tobacco use may account for loss of p16 function.^{31,32}

p53 mutations occur in approximately 50% of HNSCC cases. Abrogation of p53 function via mutation results in progression of lesions from preinvasive to invasive.³³⁻³⁵ Amplification of cyclin D1 gene occurs in approximately one third of tobacco-induced HNSCC and is usually associated with invasive disease.³⁶ Therefore, in tobacco-associated head and neck cancers, functional abrogation of p16 leads to inactivation of the Rb pathway (one of the earliest events in the carcinogenic progression model). Abrogation of the function of p53 tumor suppressor protein occurs via p53 gene mutation. Heavy smokers and those with a history of excess alcohol consumption may present with multiple precancerous and cancerous lesions of the upper aerodigestive tract, a phenomenon called field cancerization.³⁷ Individuals with tobacco-induced OSCC are also prone to developing second primary cancers.

The molecular events in HPV-induced carcinogenesis also lead to functional abrogation of p53 and pRb pathways that is mediated through expression of viral oncoproteins. The molecular events of HPV-driven malignant conversion have extensively been studied in cervical

cancer, the most thoroughly studied HPV-associated malignancy. After viral DNA integration into the host genome, expression of the main viral transcription/replication factor E2, the transcriptional repressor of E6 and E7 oncogenes, is disrupted. Disruption of E2 expression leads to unconstrained expression of the E6 and E7 oncogenes. The E6 and E7 genes of oncogenic HPVs encode oncoproteins that bind and degrade p53 and Rb tumor suppressors, respectively.³⁸ p53 and Rb tumor suppressor genes are wild-type in most cervical carcinomas. Thus, the tumor suppressor pathways are active but dormant in these cells due to the continuous expression of E6 and E7 genes. Introduction of the bovine papillomavirus E2 gene into HeLa cervical carcinoma cells via an SV40-based viral vector represses expression of the HPV18 E6 and E7 genes and the cells rapidly become senescent.^{39,40} Antisense strategies to repress expression of viral oncogenes in cervical carcinoma cell lines typically result in a several-fold inhibition of proliferation.⁴¹ Collectively these findings indicate that proliferation of cervical cancer cell lines requires continuous HPV oncogene expression.

Establishing the link between HPV and a subset of OSCC has been more difficult than in cervical cancer. Since 1985, when for the first time HPV 16 DNA was detected in an invasive HNSCC by Southern blot hybridization,⁴² HPV DNA has been repeatedly detected in a variable proportion of HNSCCs, from less than 10% to up to 100%, probably influenced by the anatomic location of tumors, HPV detection techniques, and the population studied.⁴³ In HPV-associated OSCC, viral oncoprotein-mediated abrogation of the p53 and pRb pathways obviates the need for mutational inactivation of p53 and Rb genes. Thus, HPV-induced cancers are associated with wild-type p53 gene and pRb genes. Wild-type p53 and pRb genes are associated with low levels of p53 and pRb proteins, respectively. pRb is a negative regulator of p16 protein at the transcriptional level.^{44,45} Therefore, low pRb levels lead to subsequent p16 upregulation. Overexpression of p16 protein has been repeatedly found in HPV-associated cancers. In one study of cervical and genital lesions, HPV oncogenic potential was directly associated with p16 protein levels.⁴⁶ A study of lymph node metastases in HNSCC reported that p16 overexpression is a surrogate marker for oropharyngeal primary site and HPV association.⁴⁷ As previously mentioned, in tobacco-related HNSCC, loss of p16 protein expression is a common and early event.

In summary, tobacco/alcohol-associated OSCC is associated with downregulation of p16 protein, p53 gene mutation, and cyclin D1 amplification. HPV-associated OSCC is associated with wild-type p53 and pRb genes and upregulation of p16 protein levels.^{2,48}

As discussed, HPV DNA detection by itself in an OSCC does not prove causal association; only transcriptionally active HPV DNA is biologically and clinically relevant in the causation of OSCC. We analyzed a cohort of 107 cases of OSCC for HPV 16 DNA viral load by real-time polymerase chain reaction (PCR).² In addition, we constructed a tissue array composed of these tumors and studied expression of p53, pRb, and p16 proteins using a quantitative in situ method of protein analysis. We hypothesized that for HPV DNA-positive cancers, p16 expression status would differentiate the biologically relevant cases.

Our results delineated three biologically and clinically distinct classes of OSCCs based on HPV DNA determination and p16 expression status: one class of HPV-negative/p16-nonexpressing, one class of HPV-positive/p16-nonexpressing, and one class of HPV-positive/p16-expressing oropharyngeal tumors. Overall survival in the third class was 79% compared to the other two classes (20% and 18%; $P=.0095$). Disease-free survival for the same class was 75% versus 15% and 13% ($P=.0025$). The 5-year local recurrence rate was 14% in the third class versus 45% and 74% ($P=.03$) in the other two classes. Only patients in the third class had significantly lower p53 and pRb expression ($P=.017$ and $P=.001$, respectively). Multivariable survival analysis confirmed the prognostic value of the three class model. We were able to show that only the HPV-positive/p16-expressing tumors fit the cervical carcinogenesis model and are the tumors associated with favorable prognosis.

Diagnosis of HPV-associated OSCC

HPV association should be considered in all oropharyngeal tumors, particularly those arising from the tonsils. HPV causal association should especially be suspected in oropharyngeal cancer patients with little or no tobacco or alcohol exposure, immunocompromised patients, and patients with basaloid or poorly differentiated tumors.

As mentioned, only the transcriptionally active HPV-associated tumors are biologically and clinically relevant. Detection of high-risk E6/E7 mRNA or protein would identify the true HPV-associated tumors. However, this determination is difficult in formalin-fixed paraffin-embedded tissue. p16 protein expression status determined by immunohistochemistry is a reasonable surrogate marker for HPV transcriptional activity in these cancers. Therefore, the addition of p16 immunohistochemistry to existing protocols for determination of HPV DNA presence may distinguish the transcriptionally active HPV-positive OSCC.²

In situ hybridization with an HPV 16 probe (Dako) has a sensitivity of one to two copies of integrated HPV

DNA. The HPV hybridization signal when the virus is integrated is seen as punctate nuclear staining. Some investigators use HPV in situ hybridization to determine the integration status and, presumably, the transcriptional activity of HPV in oropharyngeal tumors. They interpret punctate staining in tumors as a marker of integrated transcriptionally active virus. However, transcription of HPV 16 E6/E7 mRNA in tonsillar carcinomas is not necessarily dependent on viral DNA integration and the virus may be present predominately in episomal form.⁴⁹ How the virus remains in cancer tissues as episomes with high copy number is not fully understood. A report by Van Tine and associates revealed that HPV E2 protein may serve as an “anchor” to bind episomal HPV to cellular mitotic spindles.⁵⁰ Detection of HPV 16 DNA in plasma or HPV 16 E6 and E7 antibodies in serum may prove useful diagnostic tests in the future.

Prognosis of HPV-associated OSCC

HPV-associated OSCCs have improved prognosis compared to stage-matched HPV-negative tumors in the majority of studies.^{1,2,7,49,51-54} HPV positivity confers a 60–80% reduction in risk of death from cancer relative to comparably treated HPV-negative tumors.^{1,2,13} Reports that fail to demonstrate a better prognosis in the literature may be explained by the molecular heterogeneity of the HPV-positive group. Knowledge of the p16 protein status may clarify delineation of the proportion of HPV-induced oropharyngeal cancers.²

The favorable outcome of HPV-induced oropharyngeal cancers may be due to the absence of field cancerization or enhanced radiation sensitivity.^{1,13} In addition, HPV-associated oropharyngeal cancers bear wild-type p53 and their apoptotic mechanism in response to radiation and chemotherapy might be intact.

Treatment of OSCC

Clinical trials that stratify to more or less intense therapy based on HPV status are only now being undertaken. Standard of care for these cancers is currently determined by stage and anatomic site. Early stage tumors (TNM stages I and II) are treated with single modality therapy, surgery alone, or radiation alone. Treatment selection relies on organ-sparing/-preserving approaches, taking into consideration the potential side effects, quality of life, and patients' performance status and preferences.

Surgery followed by radiotherapy was historically the cornerstone in the management of locally advanced OSCC. However, cure rate and functional outcome associated with these approaches remain poor. Currently, radiation therapy combined with chemotherapy for organ

preservation and increase in cure is a widely accepted standard. In addition, breakthrough advances in the molecular biology of head and neck carcinogenesis have furnished newer therapeutic agents, such as growth factor receptor antagonists.

The main goals of chemotherapy should be to enhance locoregional control and reduce distant metastases while offering better overall survival and quality of life for the patient. Chemotherapy has been shown in multiple randomized studies and three meta-analyses⁵⁵⁻⁵⁷ to reduce local and distant recurrence rates,⁵⁸⁻⁶⁰ preserve organs,⁵⁸⁻⁶⁰ and improve survival.^{57,61-64} The exact sequence and content of the different components of combined modality therapy remain an area of study and, sometimes, controversy.⁶⁵

The different strategies for combining chemotherapy with radiotherapy and surgery include induction chemotherapy, which consists of several courses of chemotherapy before surgery or radiotherapy; the concomitant administration of chemotherapy and radiation therapy; and adjuvant chemotherapy administered after definitive local therapy with the assumption that the patient has been rendered disease-free.

Concurrent chemoradiation has been tested in the treatment of locally advanced HNSCC with success. Carboplatin and 5-fluorouracil (5-FU), administered over 4 days, twice during a course of once-daily radiation therapy, resulted in a significant increase in overall survival (from 31% to 51% at 2 years) in patients with resectable and unresectable oropharyngeal cancer.⁶⁶ Chemoradiotherapy is reported to enhance radiation-induced cell death not only through cytotoxic mechanisms but also by direct radiosensitization.

Recognizing the pitfalls of meta-analysis, there is evidence for a survival advantage in patients receiving chemoradiotherapy, though at the expense of increased toxicity. The survival advantage associated with chemoradiotherapy is 8% at 5 years⁶⁷ ($P < .001$) in the meta-analysis performed by Pignon and associates. A previous meta-analysis of 42 prospective and randomized trials in HNSCC, including 11 trials of concurrent chemoradiotherapy, by El-Sayed and coworkers had also shown a statistically significant reduction of the mortality rate by 22% with concurrent chemoradiotherapy.⁵⁶ A third meta-analysis by Munro and coauthors,⁵⁵ which preceded the others, showed that concurrent chemoradiotherapy increased survival by 12.1%, whereas induction chemotherapy resulted in a survival-rate advantage of only 3.7%. As a result of these findings, chemoradiotherapy has become the standard of care for the conservative management of locally advanced oropharyngeal cancers.

There is compelling evidence from randomized phase III trials and meta-analyses that chemoradiotherapy

improves survival in patients with locally advanced HNSCC, increases local control rate, and may permit organ preservation. Induction chemotherapy provides high-dose systemic therapy, which effectively treats distant dissemination, improves locoregional control, and increases survival in patients with unresectable tumors. With induction chemotherapy, toxicity is transient, whereas chemoradiotherapy may enhance the long-term toxic effects of radiation. On the other hand, induction chemotherapy is associated with delay in the delivery of definitive treatment. After treatment with induction chemotherapy, it is possible to assess prognosis and adjust therapy accordingly. It is not feasible to assess prognosis and adjust treatment once chemoradiotherapy has started. Recent data extracted from several randomized trials and from a meta-analysis support the application of induction therapy in the combined modality treatment of patients with advanced HNSCC.

The clear benefits of chemotherapy in HNSCC have been demonstrated in four randomized trials in patients with locally advanced disease who received 5-FU/cisplatin. The incorporation of 5-FU/cisplatin into therapy of locally advanced HNSCC resulted in organ preservation and an increase in distant control rate compared to the control populations. In a meta-analysis of 5,269 patients enrolled in 31 randomized clinical trials comparing induction chemotherapy followed by locoregional treatment with locoregional treatment alone,⁵⁷ induction therapy was shown to offer a nonsignificant 2% survival benefit for patients receiving induction therapy of varied regimens. In 15 trials 5-FU/cisplatin was used, whereas in the 16 other trials, cytotoxics such as bleomycin, bleomycin with vincristine, and various 3- to 5-drug regimens with and without cisplatin were studied. Despite the analysis of 2,782 patients in the 16 trials using cytotoxics other than 5-FU/cisplatin, no survival benefit was detected. In the 15 trials using the 5-FU/cisplatin regimen; although no single study had sufficient power to demonstrate survival advantage, the meta-analysis showed a significant survival gain of 5% at 5 years ($P=.05$) in favor of the 5-FU/cisplatin combination. Recent data suggest that combination chemotherapy regimens incorporating taxanes⁶⁸⁻⁷⁰ (paclitaxel or docetaxel [Taxotere, Sanofi-Aventis] with 5-FU/cisplatin improve outcome.^{69,70} Posner and colleagues reported on 501 patients with stage III or IV HNSCC who were randomly assigned to receive either docetaxel, cisplatin, and fluorouracil (TPF) or 5-FU/cisplatin. Chemoradiotherapy was given following induction in both of the groups. Survival was significantly higher with TPF than 5-FU/cisplatin (hazard ratio [HR] for death, 0.7; $P=.006$). Patients receiving TPF had significantly higher 3-year (62% vs

48%; $P=.002$) and median survival (71 vs 30 months; $P=.006$). In this study, however, the survival advantage appeared to be driven more by improvement in locoregional control with the addition of docetaxel to 5-FU/cisplatin, whereas a small reduction in the development of distant metastases was not statistically significant. A randomized phase III trial led by Vermorken⁶⁹ showed significantly higher progression-free survival (PFS) with TPF than 5-FU/cisplatin (11 vs 8.2 months; HR for disease progression or death 0.72; $P=.007$). In this study, radiotherapy alone, instead of chemoradiotherapy, followed the induction chemotherapy. Adverse effects were less evident with TPF than the 5-FU/cisplatin combination in this trial.

In summary, taxane-containing induction chemotherapy can change the natural history of HNSCC, and is currently being studied in definitive comparisons of chemoradiation with or without induction chemotherapy or chemobiotherapy. It seems likely that this will become the standard of care for patients with more advanced primary or nodal disease.

Some concurrent chemoradiation studies found that as local control improved, distant metastatic failure became a more frequent event. This finding suggests not only that the use of intensive chemoradiation programs has altered the natural history of locally advanced disease but that the low doses of drugs used to enhance radiation may not be adequate to sterilize micrometastatic disease.

As cure of locally advanced HNSCC may necessitate different approaches to prevent locoregional recurrence and metastatic disease, there has recently been an increased interest in the use of programs in which induction therapy is followed by concomitant chemoradiotherapy in the treatment of advanced disease. This strategy seems particularly attractive in tumor sites associated with a high incidence of metastatic disease, such as the base of the tongue and hypopharynx. Several sequential treatment plans have been investigated in phase II/III trials. At Yale University, 42 patients with stage III-IV resectable HNSCC and nasopharyngeal tumors (NPC) received induction chemotherapy with two courses of PFL (cisplatin 20 mg/m²/day continuous infusion [CI], 5-FU 800 mg/m²/day CI, and leucovorin 500 mg/m²/day CI \times 4 days) followed by concurrent therapy with cisplatin (100 mg/m²/day; day 1 and 22) and 7,000 cGy of external-beam radiation therapy (EBRT). The 5-year PFS was 60% and the 2- and 5-year overall survival rates were 67% and 52%, respectively.⁷¹

Machtay and associates⁷² used induction chemotherapy composed of carboplatin (area under the curve [AUC] formula = 6) and paclitaxel 200 mg/m² for two cycles to select patients with technically resectable oropharyngeal cancer for organ preservation. Patients with major response

subsequently underwent definitive radiotherapy (70 Gy over 7 weeks) plus concurrent once-weekly paclitaxel (30 mg/m²). Fifty-three patients were enrolled. The major response rate to induction chemotherapy was 89%, whereas 90% of patients achieved a complete response after concurrent chemoradiotherapy. Actuarial survival was 70% at 3 years, and 3-year disease-free survival was 59%. The 3-year actuarial locoregional control was 82% and the 3-year actuarial distant control was 81%. Organ preservation was feasible in 77% of all patients. Twenty-four percent of patients experienced late toxicity, consisting mainly of chronic dysphagia/aspiration and/or radiation soft-tissue ulceration. The treatment-related mortality rate was 4%, as 2 patients died from respiratory failure.

Novel agents are being added to conventional induction regimens. The Eastern Cooperative Oncology Group (ECOG) recently completed a phase II trial using induction cetuximab (Erbix, Bristol-Myers Squibb/ImClone), carboplatin, and paclitaxel followed by the same drugs concurrently with radiotherapy. Primary site response rate was excellent; 72% of the enrolled patients had negative biopsy at the primary site after completion of treatment, although survival analysis is pending. Kies and coworkers⁷³ reported on 47 treatment-naïve patients with stage T0–4, N2b/c/3, M0 with any primary site within the head and neck treated with induction chemotherapy consisting of six weekly cycles of paclitaxel 135 mg/m², carboplatin (AUC=2) and cetuximab. Following induction chemotherapy, patients underwent local therapy, including surgery with or without postoperative radiotherapy or radiotherapy alone, or concomitant chemoradiation; the different treatment itineraries were selected on the basis of tumor stage and site at diagnosis. The primary endpoint was clinical complete response. Most patients (n=42) had oropharyngeal primary disease. All evaluable patients responded in the primary site, and 83% had a complete response in the primary site. Twenty-seven percent of patients had clinical complete response in the nodal sites. At follow-up of more than 3 years, there had been two local and two distant recurrences.

Organ-preservation strategies may be more successful in HPV-associated OSCC than in HPV-negative cancers. The ECOG conducted a trial of taxane-based induction and chemoradiation therapy for organ preservation, and outcome has been compared for HPV-positive and HPV-negative cases. Patients with locally advanced squamous cell carcinoma of the oropharynx or larynx received two cycles of paclitaxel/carboplatin induction chemotherapy followed by paclitaxel chemoradiotherapy. HPV status was determined by in-situ hybridization and multiplex PCR. HPV-positive patients had superior response rates after induction therapy and chemoradiotherapy.⁷⁴ After a

median follow-up of 39.1 months, HPV-positive patients had a 72% lower risk of progression and a 79% lower risk of death compared to patients with HPV-negative tumors after adjustment.

Novel Therapies

HPV-targeted Strategies

The potential application of HPV-targeted therapies in HPV-associated cancers is an active research area. As detailed, HPV-associated oropharyngeal cancers harbor wild-type p53 and pRb genes and display excellent response to chemotherapy and radiation. A clinical trial using an HPV 16-specific therapeutic vaccine aiming to potentiate the cytotoxic T-cell response to the HPV 16 oncoproteins is ongoing. The vaccine is used as adjuvant therapy.⁷⁵

Preventive HPV vaccines have been developed based on recombinant expression and self-assembly of the major capsid protein L1 into immunogenic virus-like particles that are similar to authentic virions but are noninfectious. One such vaccine (Gardasil, Merck) protects against HPV types 6, 11, 16, and 18, and another vaccine (Cervarix, GlaxoSmithKline) protects against types 16 and 18. Several randomized, placebo-controlled trials in human volunteers demonstrated that these prophylactic vaccines significantly reduce the incidence of persistent HPV 16 and 18 infections and associated moderate-to-high grade cervical intraepithelial neoplasia CIN2/3.^{76,77} The impact of these vaccines on the incidence of persistent oral HPV infection has not been investigated. However, data from animal models immunized against HPV 16 have shown a reduction in the development of HPV oral lesions.⁷⁸

EGFR-targeted Therapies

The epidermal growth factor receptor (EGFR) is a membrane tyrosine kinase receptor that regulates multiple functions, including cell growth, differentiation, and development. EGFR is as an attractive molecular target for therapy in HNSCC. Overexpression of EGFR is one of the most common molecular alterations in HNSCC. First, the level of EGFR expression on head and neck cancers is elevated relative to expression on normal adjacent squamous mucosa in 83–100% of cases.⁷⁹ Second, increased receptor content is often associated with increased production of ligands, such as transforming growth factor alpha (TGF- α), by the HNSCC.⁷⁹ Furthermore, treatment with EGFR-targeted therapy, such as the chimeric monoclonal antibody cetuximab or the quinazoline gefitinib (Iressa, AstraZeneca), inhibits EGFR signaling and potentiates the effects of chemotherapy or radiation.^{80–82} EGFR is frequently overexpressed in HPV-associated dysplasias and carcinomas, implying

that it is important for the progression of keratinocytes to malignancy.⁸³⁻⁸⁵ The mechanism of HPV-mediated upregulation of EGFR is not clear, but likely involves HPV E5 protein. The function of the HPV E5 protein is not well characterized and controversies exist about its role in the viral life cycle.

A phase III study comparing high-dose radiation with or without cetuximab in patients with locally advanced HNSCC showed that the addition of cetuximab significantly prolonged overall survival.⁸² In this trial, 424 patients were randomized; 60% had oropharyngeal, 25% laryngeal, and 15% hypopharyngeal primary tumors. The two arms were well balanced with respect to radiation, dose and fractions received, use of postradiotherapy neck dissection, and secondary cancer therapy. Minimum and median durations of follow-up were 24 and 38 months, respectively. Median survival times, from Kaplan-Meier estimates, were 54 months versus 28 months ($P=.02$), favoring the cetuximab arm. Subset analysis showed that the effect of cetuximab treatment was more pronounced in the oropharyngeal primary site, but that the analysis had inadequate power and the difference was not statistically significant. The overall toxicity profile was dominated by classic known effects of high-dose and head and neck radiation, although some additional toxicity was attributed to cetuximab. Late functional outcomes from this trial have not been reported, although a quality of life analysis failed to show a benefit in the cetuximab treated arm.⁸⁶ The Bonner study, along with the aforementioned phase II study by Kies and coworkers, in which the overwhelming majority of patients had oropharyngeal primary disease, give some hints that HPV-associated HNSCC responds better to EGFR-targeted therapies.

In the recurrent or metastatic setting, the combination of cetuximab with cisplatin as first-line therapy resulted in higher response rates compared to cisplatin alone as first-line therapy in an ECOG phase III randomized trial, with a HR for progression of 0.78. The study was underpowered for outcome and permitted crossover to cetuximab on progression, obscuring the impact on survival.⁸¹ A subsequent European randomized phase III trial (EXTREME) examined the addition of cetuximab until disease progression in patients receiving six cycles of a cisplatin or carboplatin/5-FU chemotherapy regimen as first-line treatment in recurrent or metastatic HNSCC. A preliminary oral report of significantly improved survival in cetuximab-treated patients has been presented.⁸⁴ Cetuximab alone is an acceptable second-line therapy in recurrent/metastatic HNSCC.⁸⁷

ONYX-015

The tumor suppressor gene p53 is the most frequently mutated gene in HNSCC, with a frequency close to

50%.⁸⁸ Replication-competent adenoviruses have been developed that selectively replicate in and cause lysis of cells deficient in p53 tumor suppressor function. ONYX-015 (Onyx) is an adenovirus that is constructed with a deletion of the E1b protein and will proliferate only in p53-deficient cells. Phase I and II trials of ONYX-015 alone or combined with chemotherapy have shown safety and efficacy, as well as durable responses at injectable tumor sites.^{89,90}

Conclusions

OSCC represents a heterogeneous group of cancers in terms of etiology, biology, and clinical behavior. It is now clear that a growing subset of OSCC is a sexually transmitted disease, as high-risk HPVs, especially type 16, account for their etiology. Although the incidence of tobacco/alcohol-associated HNSCC is declining, the incidence of HPV-associated OSCC is rising, parallel to changes in sexual behaviors over the past two decades.

Presently, HPV-associated OSCC is treated similarly to stage-matched tobacco-associated cancers. However, questions such as whether HPV-positive OSCC requires less radiotherapy or whether they respond better to organ-preserving strategies are active areas of research. Therapeutic vaccines against HPV 16 oncoproteins are being tested in HPV-associated OSCC in the adjuvant setting. Prophylactic HPV 16 vaccines reduce the incidence of persistent viral infection and cervical dysplasias and may reduce the incidence of HPV-associated lesions. Future therapy of OSCC should be individualized according to etiology.

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