Oral Cavity and Oropharyngeal Squamous Cell Carcinoma—An Update

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Oral cavity squamous cell carcinoma (OC-SCC) is the most common malignancy of the head and neck (excluding nonmelanoma skin cancer). Recent trends have shown a dramatic rise in the incidence of oropharyngeal squamous cell carcinoma (OP-SCC), with a marked increase in lesions related to human papillomavirus infection. This update presents the latest evidence regarding OC-SCC and OP-SCC. In particular, the authors compare and contrast tumors at these two sites with respect to epidemiology, etiopathogenesis, clinicopathologic presentation, clinical assessment, imaging, management, and prognosis. It is important for clinicians to be aware of differences between OC-SCC and OP-SCC so that appropriate patient education and multidisciplinary care can be provided to optimize outcomes. **CA Cancer J Clin 2015;65:401-421. © 2015 American Cancer Society.**

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Introduction

In the United States, squamous cell carcinoma (SCC) accounts for approximately 90% of oral and oropharyngeal malignancies. Oral cavity SCC (OC-SCC) is the most common malignancy of the head and neck (excluding nonmelanoma skin cancer). There has been a dramatic rise in the incidence of oropharyngeal SCC (OP-SCC). This article updates a prior review in 2002[1] and presents the latest evidence regarding the incidence, mortality, etiology, risk factors, clinicopathologic presentation, clinical assessment, imaging, staging, and management of OC-SCC and OP-SCC.

Anatomically, the oral cavity and oropharynx are separate regions that border each other but do not overlap. The anatomic subsites of the oral cavity include the labial mucosa, buccal mucosa, floor of mouth, alveolar ridge and gingiva, anterior two-thirds of the tongue (anterior to the circumvallate papillae), hard palate, and retromolar trigone. The oropharynx consists of the soft palate, base (or posterior one-third) of tongue, palatine tonsils, palatoglossal folds, valleculae, and posterior pharyngeal wall. Distinct anatomic borders separate the two sites: from above, the junction of the hard and soft palate, and from below, the circumvallate papillae.

Reviewing the literature and surveillance data on oral and oropharyngeal cancers is difficult because these tumors often are reported in aggregate with other pharyngeal or head and neck malignancies, and anatomic subsite definitions are at times unclear or may not allow for distinction between the oral cavity and the oropharynx. For example, in the Surveillance, Epidemiology, and End Results (SEER) database, the "tongue" is considered a subsite of the oral cavity and pharynx; however, the tongue includes the base of tongue/lingual tonsils (which are part of the oropharynx) as well as the anterior two-thirds of the tongue (which is part of the oral cavity).[2] Also, the SEER database lists the oropharynx and tonsils as distinct subsites, although the tonsils are part of the oropharynx. In the GLOBOCAN database, the oral cavity includes the base of tongue (which is part of the oropharynx) and palate (which may include both the hard palate [part of the oral cavity] and soft palate [part of the oropharynx]); also, "nasopharynx" and "other pharynx" are considered distinct subsites, with the latter referring not only to the oropharynx and tonsils but also to the hypopharynx, pyriform sinus, and "other and ill-defined sites of the lip, oral cavity, and pharynx."[3] In the Cancer Incidence in 5 Continents (CI5) and European Network of Cancer

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Registries (EUREG) databases, the "tongue" includes both the base of tongue (part of the oropharynx) and "other and unspecified parts of the tongue" (presumably the anterior two-thirds of the tongue, which is part of the oral cavity).[4,5] These databases also list the "palate" as a subsite of the "mouth," although the palate may include both the hard palate (part of the oral cavity) and the soft palate (part of the oropharynx). Furthermore, some authors use the term "oral" in reference to both the oral cavity and the oropharynx, whereas others reserve this term solely for the oral cavity.

Current evidence supports that tumors at these two sites are distinct and unique, with differing etiopathogenesis, treatment, and prognosis.[6] Thus, for the purposes of this report, we will clearly separate OC-SCC and OP-SCC, comparing and contrasting tumors at these two sites with respect to epidemiology, etiology, risk factors, early diagnosis, and treatment. Our review does not include SCC of the lip vermilion, which is usually different in etiology (ie, chronic actinic damage) and has a markedly better prognosis than OC-SCC and OP-SCC.

Incidence, Mortality, Etiology, and Risk Factors

According to the most recent GLOBOCAN estimates, worldwide in 2012, there were approximately 300,373 new cases of lip/oral cavity cancer (age-standardized rate [age-standardized to the world population] or ASR[W], 4.0 per 100,000) and 142,387 new cases of "other pharyngeal" (ie, excluding the nasopharynx) cancer (ASR[W], 1.9 per 100,000).[3] Notably, the estimated ASR(W) for lip/oral cavity cancer is highest for the World Health Organization (WHO) South-East Asia region (6.4 per 100,000), followed by the WHO Europe region (4.6 per 100,000), the WHO Eastern Mediterranean region (4.6 per 100,000), the WHO Americas region (4.1 per 100,000), the WHO Africa region (2.7 per 100,000), and the WHO Western Pacific region (2.0 per 100,000). For "other pharyngeal" cancer, the estimated ASR(W) is highest for the WHO South-East Asia region (3.6 per 100,000), followed by the WHO Europe region (2.7 per 100,000), the WHO Americas region (1.9 per 100,000), the WHO Eastern Mediterranean region (1.1 per 100,000), the WHO Africa region (0.8 per 100,000), and the WHO Western Pacific region (0.8 per 100,000). Worldwide mortality estimates for 2012 include an ASR(W) of 2.7 per 100,000 for lip/oral cavity cancer and 2.2 per 100,000 for "other pharyngeal" cancer.[3]

In the United States, the American Cancer Society estimates that, in 2015, there will be 45,780 new cases of oral cavity and pharyngeal cancer (male-to-female ratio, 2.5:1) and 8650 deaths from these tumors.[7] For oral cavity and oropharyngeal cancers combined, the SEER Program reports a median age at diagnosis of 62.0 years (for SEER 18 areas from 2008 through 2012), an age-adjusted incidence of 11.0 per 100,000 (for SEER 18 areas from 2008 through 2012; age-adjusted to the 2000 US standard population), a 0.8% average annual increase in delay-adjusted incidence (for SEER 13 areas from 2008 through 2012), and a 0.5% annual increase in age-adjusted incidence (for SEER 18 areas from 2003 through 2012).[2]

With regard to epidemiologic trends, increasing oropharyngeal cancer incidence has been observed in numerous developed nations over the past few decades (eg, the US annual percentage change [APC] = 3.0 for SEER 9 areas from 1999 through 2012; Canada, APC = 2.7 from 1992 through 2009; Denmark, APC = 3.5 from 1978 through 2007; Portugal, APC = 3.49 from 1998 through 2007; Netherlands, APC = 2.1 for males and APC = 2.7 for females from 1989 through 2011; Korea, APC = 2.35 from 1999 through 2009; and Australia, APC = 1.2 for males and APC = 0.8 for females from 1982 through 2008).[2,8-14] For oral cavity cancer, many regions have reported decreasing or stabilizing trends (eg, Canada, Australia, Bulgaria, Croatia, Slovenia, Ukraine, Slovakia, Netherlands, France, and Germany), whereas others have exhibited markedly increasing trends (eg, Iceland, Finland, and Ireland) (see Table 1).[5,10,14-16] In India, oral cancer trends vary by region, although investigators estimate that the total number of new mouth cancer cases will increase from 45,859 in 2010 to 64,525 in 2020.[17,18] With regard to recent subsite trends in the United States, SEER 9 data from 2008 through 2012 show an average APC in age-adjusted incidence of 3.0 for oropharyngeal cancer, 2.1 for tongue cancer, and −3.6 for floor of mouth/gum/other mouth cancer.[2] In Korea from 1999 through 2010, age-standardized incidence rates increased markedly for cancers of the oral tongue (APC = 2.2 for males, APC = 4.1 for females, and APC = 6.1 for individuals younger than age 40 years) and buccal mucosa (APC = 4.8).[16]

Significant epidemiologic shifts seem to reflect dynamic risk factor trends. Traditional modifiable risk factors include tobacco and alcohol use. In addition, in recent decades, human papillomavirus (HPV) has emerged as a major etiologic factor for OP-SCC.[19-21] These factors and others are discussed in more detail below. In regions such as North America, Australia, and parts of Europe, a dramatic increase in HPV-positive tumors accounts for rising OP-SCC incidence; in contrast, regional variations in trends for OC-SCC and HPV-negative OP-SCC are largely consistent with tobacco use trends.[21,22]

Nevertheless, the underlying cause for increased tongue cancer in the United States and other regions is unclear. In particular, a surprising increase in oral tongue cancer has been observed in young females, often with no significant tobacco and alcohol exposure.[23-25] Also, the vast majority of oral

TABLE 1. Trends in Oral Cavity Cancer Incidence for Select Countries

COUNTRY	TIME PERIOD	APC[a]	REFERENCE
Australia	1994-2008	Males, −3.1	Ariyawardana & Johnson 2013[14]
	1996-2008	Females, −3.0	Ariyawardana & Johnson 2013[14]
Austria	2000-2009	0.99	Steliarova-Foucher 2013[5]
Bulgaria	2000-2007	−1.5	Steliarova-Foucher 2013[5]
Canada	1992-2007	Males, −2.1; females, −0.4	Johnson-Obaseki 2012[15]
Croatia	2000-2007	−2.7	Steliarova-Foucher 2013[5]
Denmark	2000-2007	0.28	Steliarova-Foucher 2013[5]
Finland	2000-2007	3.27	Steliarova-Foucher 2013[5]
France[b]	2005-2009	−0.7	Steliarova-Foucher 2013[5]
Germany[c]	2003-2007	−0.28	Steliarova-Foucher 2013[5]
Iceland	2000-2007	5.46	Steliarova-Foucher 2013[5]
Ireland	2000-2009	3.24	Steliarova-Foucher 2013[5]
Korea	1999-2010	1.2	Choi 2014[16d]
Netherlands	2000-2007	−0.38	Steliarova-Foucher 2013[5]
Norway	2000-2007	1.04	Steliarova-Foucher 2013[5]
Slovakia	2000-2007	−0.89	Steliarova-Foucher 2013[5]
Slovenia	2000-2007	−1.77	Steliarova-Foucher 2013[5]
Sweden	2000-2009	0.83	Steliarova-Foucher 2013[5]
Switzerland[e]	2003-2007	0.38	Steliarova-Foucher 2013[5]
Ukraine	2003-2007	−1.02	Steliarova-Foucher 2013[5]
United Kingdom[f]	2000-2007	1.49	Steliarova-Foucher 2013[5]

APC indicates annual percentage change. [a]The APC was calculated from age-standardized rates based on the world population standard for References 5, 14, and 16 and based on the Canadian population for Reference 15. [b]Data included are from the 13 registries listed for France in the European Network of Cancer Registries (EUREG) database. [c]Data included are from the 15 registries listed for Germany in the EUREG database. [d]Note that, in this study, the base of tongue (which is actually part of the oropharynx) was considered part of the oral cavity. [e]Data included are from the 7 registries listed for Switzerland in the EUREG database. [f]Data included are from the 11 registries listed for the United Kingdom in the EUREG database.

tongue cancers examined thus far have been negative for high-risk HPV.[26-36] According to SEER 18 data in the United States from 2000 through 2012, the incidence of tongue cancer in adults aged 20 to 44 years increased among females (APC = 1.0) but decreased among males (APC = −0.1).[37,38] In a pooled analysis of case-control studies by the International Head and Neck Cancer Epidemiology Consortium, adults aged 45 years and younger exhibited a higher proportion of oral tongue cancers compared with adults older than 45 years (16% in women/11% in men vs 10.3% in women/5.9% in men, respectively). Also in that study, the associations of smoking and drinking with oral cavity cancer were weaker in young adults compared with older adults (ever-smokers: odds ratio [OR], 1.91 for young adults vs 2.18 for older adults; ever-drinkers: OR, 1.24 for young adults vs 1.61 for older adults).[25] In addition, in a study of 25 young adults diagnosed with oral tongue SCC at a single institution from 1989 through 2007, Harris et al reported that 60% were female and 52% were never-smokers/never-drinkers.[29]

Major Risk Factors

Tobacco

Tobacco consumption continues to be a major risk factor for OC-SCC and OP-SCC. Based on sufficient evidence of carcinogenicity in humans, the International Agency for Research on Cancer classifies tobacco smoking as a group 1 carcinogen for both the oral cavity and the pharynx and classifies smokeless tobacco as a group 1 carcinogen for the oral cavity.[39] Although tobacco use has been declining or stabilizing in many high-income countries, it has been increasing in many low-income and middle-income countries, where nearly 80% of the world's one billion smokers currently reside.[40] A meta-analysis by Gandini et al noted a relative risk of 6.76 for OP-SSC and 3.43 for OC-SCC among current tobacco smokers compared with nonsmokers.[41] This smoking-associated risk appears to be dose-dependent and correlates with daily or cumulative cigarette consumption. For patients who quit smoking, the risk for OC-SCC and OP-SCC declines over time and may

approach that of nonsmokers after 10 or more years of cessation.[42]

Although cigarettes represent the predominant form of tobacco used worldwide, tobacco types abound and vary in popularity by region. In the United States, there has been increased large cigar and pipe tobacco consumption over the past decade, likely in part because of federal excise tax increases in 2009, which made large cigars less expensive than small cigars and made pipe tobacco less expensive than roll-your-own tobacco and manufactured cigarettes.[43] The Centers for Disease Control and Prevention reported changes in the total annual number of these products consumed from 2008 to 2011 as follows: consumption increased for large cigars from 5.7 billion to 12.9 billion, decreased for small cigars from 5.8 billion to 0.8 billion, increased for pipe tobacco from 2.6 billion to 17.5 billion, and decreased for roll-your-own tobacco from 10.7 billion to 2.6 billion.[43] Data are limited, but some studies suggest that the relative risk for head and neck SCC (HN-SCC) among pipe or cigar smokers is comparable to or greater than that for cigarette smokers.[42,44] In parts of Asia, other popular forms of combustible tobacco include the bidi (tobacco hand-rolled in a tendu or temburni leaf), kretek (clove cigarette), and water pipe (hookah, nargile). Despite the need for further research regarding alternative combustible tobacco products, all forms of tobacco use are unsafe.

In Western countries, major types of smokeless tobacco include wet snuff, dry snuff, and chewing tobacco. The risk for OC-SCC appears to be greater with dry snuff (relative risk, 4-13) compared with moist snuff and chewing tobacco (relative risk, 0.6-1.7).[45] The development of oral cancer from long-term smokeless tobacco use has been largely attributed to tobacco-specific nitrosamines. However, tobacco-specific nitrosamine levels are relatively low in Swedish moist snuff (snus) and in contemporary American moist snuff, with recent analyses detecting no risk or a minimally elevated risk for HN-SCC among users of such products.[46-49] Nevertheless, the use of snus as a safer alternative to smoking and the effects of snus on initiation or cessation of smoking require further research. A recent meta-analysis found no statistically significant association between snus consumption and various cancer types, heart disease, or stroke[49]; however, in a cohort study of >40,000 Swedish male construction workers, an increased risk for cancer-specific death was observed both among exclusive smokers (hazard ratio, 1.15; 95% confidence interval [CI], 1.10-1.21) and never-smoking snus users (hazard ratio, 1.15; 95% CI, 1.05-1.26).[50] In a recent systematic review (based largely on Swedish males), dual use of snus and cigarettes was more common among adolescents than adults, more often began with cigarette than snus consumption, and was hypothesized to increase smoking quit rates.[51] In contrast, other investigators suggest that snus use may interfere with attempts to quit smoking.[52] In parts of Asia, smokeless tobacco often is combined with betel quid, which is discussed separately below.

Alcohol

After adjusting for tobacco smoking and other confounding factors, most studies from the United States, Europe, and Asia have reported an increased risk for oral cavity/pharyngeal cancers in association with heavy alcohol consumption (typically defined as >60 grams [or 4 drinks] per day or >4 to 7 drinks per week), with point estimates of adjusted ORs ranging from 4.1 to 8.8.[53] Alcohol also appears to be an independent risk factor, with studies of nonsmokers noting both a strong association and a dose-response relationship between alcohol consumption and oral cavity/pharyngeal SCC.[53] Recent meta-analyses have estimated that the relative risk for HN-SCC is 1.3 for 10 grams of ethanol per day compared with 13.0 for 125 grams of ethanol per day, with higher risk estimates for OP-SCC than for OC-SCC.[54]

Underlying carcinogenic mechanisms are not entirely clear, although several have been proposed. Ethanol is metabolized by epithelial cells and microflora into acetaldehyde, which is a known carcinogen. Accordingly, risk polymorphisms in alcohol-metabolizing genes (eg, alcohol dehydrogenase 1B gene [*ADH1B*], alcohol dehydrogenase 1C gene [*ADH1C*], aldehyde dehydrogenase 1 gene [*ALDH1*], and aldehyde dehydrogenase 2 gene [*ALDH2*]) have been identified; studies have reported reduced head and neck cancer risk with *ADH1B*2* (meta-OR, 0.5; 95% CI, 0.37-0.68) and *ADH1C*2* (meta-OR, 0.87; 95% CI, 0.76-0.99) alleles and an increased risk with *ADH1B(*1/*1 + *1/*2)* plus *ALDH2(*1/*1)* (OR, 2.31 for current regular drinkers; 95% CI, 0.77-6.95) and *ADH1B(*1/*1 + *1/*2)* plus *ALDH2(*1/*2 + *2/*2)* (OR, 4.01 for current regular drinkers; 95% CI, 2.06-7.81).[55,56] In addition, alcoholic beverages may contain aldehyde itself and various carcinogenic contaminants, such as polycyclic aromatic hydrocarbons and nitrosamines.[57,58] Nutritional deficiencies may contribute to an increased risk of HN-SCC in heavy drinkers as well.

Interaction between tobacco and alcohol

Notably, combined cigarette smoking and alcohol consumption exhibits a synergistic effect, with a reported relative risk for HN-SCC of 15 or more among heavy users of both products.[53] Large-scale multicenter studies in Europe and Asia, as well as pooled analysis of European and American case-control studies, have attributed more than half of oral and oropharyngeal cancer cases to tobacco and/or alcohol.[59-61]

Betel quid

Betel quid (paan) chewing is a common practice in many parts of Asia as well as in migrant Asian communities around the world, with 600 to 1200 million users estimated globally.[62] The habit produces pleasing psychostimulatory

effects and is deeply entrenched in many cultures.[61,63] Betel quid consists of a mixture of areca nut, slaked lime, and betel leaf, which may be combined with tobacco, sweeteners, and/or spices. Regional variations include mawa, naswar, khaini, and zarda. In addition, prepackaged, freeze-dried betel quid substitutes (eg, gutka, pan masala) are widely available.

The carcinogenicity of betel quid traditionally has been attributed to tobacco, although areca nut itself is carcinogenic.[63] Recent large-scale studies, meta-analyses, and systematic reviews have reported ORs for HN-SCC of approximately 7 to 8 for betel quid with tobacco and 3 to 6 for betel quid without tobacco.[64-67] Among individuals who smoke, drink alcohol, and chew betel quid, OC-SCC risk is exceptionally high (approximate pooled OR, 40). Indeed, all three habits are prevalent in South-East Asia, where 75% of the approximately 59,000 males annually affected by oral cancer have a history of combined smoking-drinking-betel quid exposure.[68]

HPV

Over the past several decades, accumulating evidence from epidemiologic, clinicopathologic, and molecular studies has established HPV as a major etiologic factor in a subset of HN-SCC. The majority of HPV-related HN-SCC arises in the oropharynx, particularly the palatine and lingual tonsils. In contrast, only a small proportion of OC-SCC appears to be caused by HPV. Specifically, the high-risk genotype HPV-16 accounts for the vast majority (approximately 90% to 95%) of HPV-positive OP-SCCs, whereas greater variability in HPV types is seen in OC-SCC.[69]

Interestingly, the prevalence of high-risk HPV DNA in oropharyngeal and oral cancers appears to vary by geographic region. For OP-SCC, prevalence has been reported to be highest (approximately 60%) in North America; intermediate (approximately 36% to 45%) in Asia, Oceania, and Europe; and low (approximately 15%) in South and Central America.[70-72] Also, prevalence within Europe varies by subregion from approximately 17% in Southern Europe to 38% to 39% in Northern, Western, and Eastern Europe.[70,71] In contrast, for OC-SCC, high-risk HPV DNA prevalence has been reported to be highest in Asia (25% for HPV-16).[72]

Determining the HPV-attributable fraction of HN-SCC is somewhat problematic because of confounding factors (especially from tobacco use) and limitations in methodology. In particular, many large-scale studies have assessed the presence of high-risk HPV DNA without concurrently evaluating biomarkers of HPV carcinogenesis (ie, E6 and E7 messenger RNA [mRNA], p16 cellular protein), thereby failing to distinguish between "passenger" versus carcinogenic HPV infection. Nevertheless, with attempts to correct for some of these limitations, a recent systematic review and meta-analysis of studies reported worldwide from 1990 to 2004 estimated that the HPV-attributable fraction is approximately 40% for OP-SCC and 7% to 16% for OC-SCC.[72] Similarly, in North America and Europe, transcriptionally active, high-risk HPV (as evidenced by either quantitative reverse-transcriptase polymerase chain reaction or in situ hybridization-based methods for high-risk HPV E6 and E7 mRNA) has been detected in only about 0% to 9% of OC-SCC cases examined.[69]

Particularly in developed nations, a recent dramatic rise in HPV-related oropharyngeal cancer incidence has raised concerns of an emerging cancer epidemic.[6,8,73] Remarkably, in the United States, HPV has been estimated to account for approximately 16% of OP-SCCs in the early 1980s compared with >60% of cases in more recent studies.[74] In addition, recent data suggest that the HPV-positive fraction of OP-SCC in Europe is increasing at an especially rapid rate and, thus, may be approaching that of North America.[75] The risk profile for HPV-positive oropharyngeal carcinomas differs from that for HPV-negative tumors. In both groups, there is a male predilection. However, HPV-positive tumors are more likely to occur in patients who are white, somewhat younger (median age, 54 years vs 58 years), and of higher socioeconomic status. HPV-positive OP-SCC also is strongly associated with an increased number of lifetime sexual or oral sexual partners.[76,77] Compared with HPV-negative tumors, HPV-positive tumors are more likely to arise in individuals with a history of marijuana use and are less likely to arise in individuals with heavy tobacco and alcohol exposure.[76] Nevertheless, in various recent studies, 47% to 71% of patients with HPV-positive OP-SCC have had some history of tobacco use.[78-82] In addition, 61% to 75% of patients with HPV-positive OP-SCC have reported current alcohol use, although only 9% to 18% have been classified as daily or heavy consumers.[79,80,82] More research is needed to clarify interactions between HPV, tobacco, and alcohol.

Molecular evidence in support of HPV-driven HN-SCC includes the following observations: 1) high-risk, tumorigenic HPV-16 is present in 90% of HPV-positive HN-SCCs; 2) in situ hybridization demonstrates localization of HPV-16 within the nuclei of HN-SCC cells; 3) HPV-16 DNA is present in high copy numbers in HPV-positive HN-SCC cells; and 4) HPV-16 genomic DNA is frequently integrated into HPV-positive HN-SCC cells, with active transcription of the major viral oncoproteins E6 and E7.[19,83] Differences in molecular genetic profile support that HPV-related HN-SCC is biologically distinct from HN-SCC related to tobacco and alcohol. In the early stages of HPV-negative carcinogenesis, there are frequent losses of chromosomes 9p, 3p, and 17p[84]; in particular, the tumor suppressor genes tumor protein 53 (*TP53*) (which encodes p53) and cyclin-dependent kinase inhibitor 2A (*CDKN2A*) (which encodes p16) are located at 17p13 and 9p21, respectively. Thus, frequent p53 and p16 mutations result in cell cycle dysregulation and genomic instability. In contrast, HPV-related HN-SCC often lacks such chromosomal losses,

exhibits decreased expression of wild-type p53 (because of inactivation and degradation by E6), and exhibits increased p16 (because of E7 binding retinoblastoma protein [pRb], thereby interfering with cell cycle arrest and allowing accumulation of the p16 tumor suppressor protein).[85,86]

It is not entirely clear why HPV-related HN-SCC preferentially develops within the oropharynx. Traditionally, investigators have proposed that HPV infection occurs via microtrauma and exposure of basal epithelial cells to viral entry. Notably, the oropharynx is analogous to the uterine cervix and anus, in that it exhibits a squamocolumnar transition zone. Thus, the accessibility of metaplastic basal/reserve cells within the transition zone may explain the susceptibility of these sites to carcinogenic HPV infection.[87]

Others have theorized that the tendency for OP-SCC to originate specifically within the palatine and lingual tonsils may be related to the following: 1) the deep invaginations of the tonsillar crypts may function as a reservoir for HPV and other pathogens, 2) the reticulated epithelium in these sites is attenuated with a discontinuous basement membrane, and 3) the deep crypts within this lymphoid tissue represent immune-privileged sites that favor persistent HPV infection and allow tumors to evade immune surveillance.[69,88]

Additional Factors

Other microorganisms

With recent advances in high-throughput genetic-based assays, there has been a growing body of research concerning the relationship between the oral microbiome and OC-SCC. Several studies have demonstrated differences in the oral microbiome between normal individuals and patients with OC-SCC. However, it is not entirely clear whether such microbial shifts play a direct role in carcinogenesis or merely reflect differences in adaptability of microbial species to the cancer microenvironment.[89] Possible mechanisms by which oral flora may contribute to cancer development include the following: 1) metabolism of procarcinogens (eg, conversion of ethanol to acetaldehyde by *Candida*, *Neisseria*, and streptococci), 2) production of carcinogens (eg, production of nitrosamine by *Candida*), 3) induction of chronic inflammation (eg, by periodontal disease-causing bacteria) with production of cytokines that enhance cell proliferation and inhibit apoptosis, 4) direct influences of bacteria on cell cycle signaling, and 5) direct DNA damage by bacterial toxins.[89,90] Although it is difficult to control for confounding factors (eg, tobacco use, alcohol consumption, nutrition, socioeconomic status), some studies suggest an association between oral/pharyngeal cancer and measures of bacterial load (eg, poor oral hygiene, poor dental status, chronic periodontitis).[91-93]

Dietary factors and vitamin/mineral deficiencies

Several epidemiologic studies have noted that a diet rich in fruits and vegetables and low in animal products is associated with a reduced risk for oral cavity, pharyngeal, and other cancers.[94-96] The protective effects of plant foods might be attributed to various substances, such as carotenoids, vitamins C and E, folate, flavonoids, fiber, and lycopene. In addition, there is an increased risk for SCC of the upper alimentary tract among iron-deficient patients—most notably those with untreated Plummer-Vinson syndrome.[97] Some investigators have noted high rates of vitamin D deficiency in oral/head and neck cancer patients; a weak inverse association between oral/pharyngeal cancer and dietary vitamin D intake; and correlations between smoking, alcohol, and vitamin D deficiency.[98-100] However, further research regarding the potential role of vitamin D metabolism in HN-SCC development is needed.

Immune status

Compared with the general population, HIV-positive patients and organ transplant recipients exhibit a higher incidence of lip, oral cavity, and pharyngeal cancer.[101-103] Interestingly, a few large-scale case-control studies have noted an inverse relationship between allergies and head and neck cancer risk. Some investigators have hypothesized that heightened T-helper 2 immunity in individuals with allergies and asthma might protect against tumor growth, although further studies are needed.[104,105]

Environmental pollutants

In parts of Taiwan with alarmingly high oral cancer rates, some researchers have noted elevated soil concentrations of carcinogenic heavy metals (such as arsenic, chromium, and nickel). However, the strength of association between regional oral cancer mortality rates and heavy metal soil concentrations has varied across studies.[106-108]

Occupational exposures

Some studies have reported an association between oral/pharyngeal cancer and various occupations (including construction, painting, carpentry, metalworking, and machine operating).[109] In such occupations, exposures to high levels of solvents and metal/wood/cement dusts have been hypothesized to confer an increased risk for oral and/or pharyngeal cancer. However, supporting data are limited and often inconsistent, with likely a small contribution to the overall occurrence of these cancers.

Heritable conditions

There is an increased risk for oral/pharyngeal SCC in patients with certain rare heritable conditions, including Fanconi anemia, dyskeratosis congenita, and Bloom syndrome.[110-114]

Clinicopathologic Presentation

Squamous Cell Carcinoma of the Oral Cavity

OC-SCC often is preceded by a white or red mucosal change known as *leukoplakia* or *erythroplakia*. Some lesions will show a combination of red and white features, termed

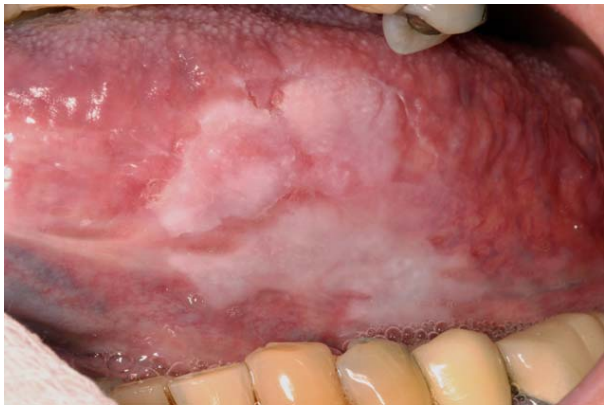

FIGURE 1. Leukoplakia. This diffuse white patch on the lateral border of the tongue showed hyperkeratosis with mild epithelial dysplasia.

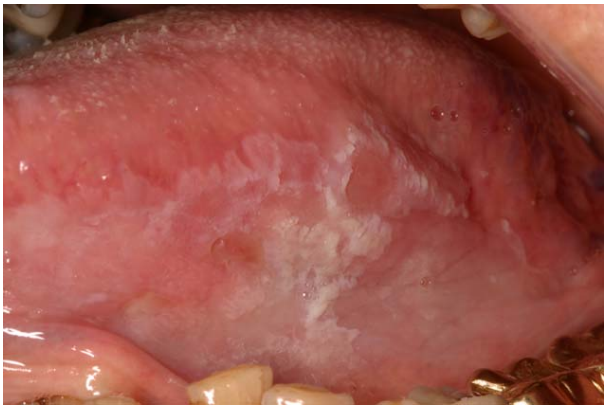

FIGURE 3. Leukoplakia. This diffuse white patch on the lateral border of the tongue showed carcinoma in situ.

erythroleukoplakia, *speckled leukoplakia*, or *speckled erythroplakia*. Because these white and/or red mucosal lesions have an increased risk of becoming or already harboring invasive carcinoma, they have collectively been classified as "potentially malignant disorders."[115,116]

Oral leukoplakia traditionally has been defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease (ie, excluding pseudomembranous candidiasis, lichen planus, tobacco pouch keratosis, nicotine stomatitis, oral hairy leukoplakia, etc) (Fig. 1).[117,118] Unfortunately, this "negative" definition, which is based on the exclusion of other white lesions rather than specific clinicopathologic features, has resulted in variations in data reported across studies over the years.

Microscopically, leukoplakias demonstrate hyperkeratosis and/or epithelial thickening (acanthosis). In most studies, the reported prevalence of epithelial dysplasia in leukoplakias ranges from 16% to 39% (Figs. 2 and 3).[1] This variation probably is caused by differences in populations studied and definitions of leukoplakia. In addition, a large retrospective study by Waldron and Shafer showed that 3.1% of biopsied cases were unsuspected SCC.[119] The risk for dysplasia or carcinoma is higher for leukoplakias of the lateral tongue and floor of mouth compared with those in other oral sites.

Although the majority of leukoplakias will not progress to cancer, the potential for malignant transformation is well known. More recent studies suggest a malignant transformation rate from 8% to nearly 18%.[120-124] Factors associated with an increased risk for progression to malignancy include the presence of dysplasia on initial biopsy, subsite (tongue or floor of mouth), nonhomogeneous clinical appearance (ie, speckled or verrucous surface), large size (>200 mm^2), older age, female gender, and the absence of known risk factors (Fig. 4).[116,125-127] However, even the most innocuous leukoplakias can show significant dysplastic changes or even invasive carcinoma; therefore, biopsy is usually recommended for most unexplained oral white lesions (Fig. 5).

An especially worrisome variant of leukoplakia, *proliferative verrucous leukoplakia* (PVL), tends to exhibit multifocal lesions with slow, relentless growth.[128-131] PVL is unusual

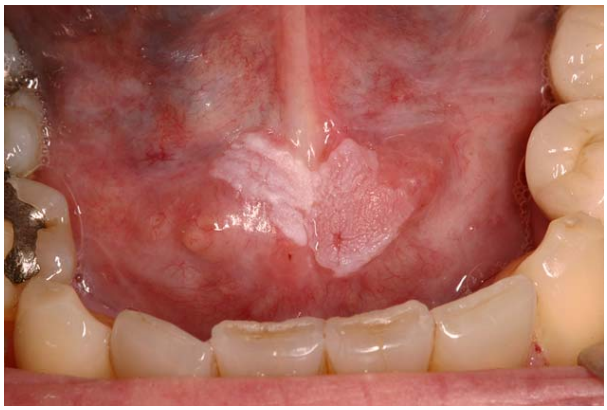

FIGURE 2. Leukoplakia. This discrete white patch on the floor of the mouth showed hyperkeratosis with severe epithelial dysplasia.

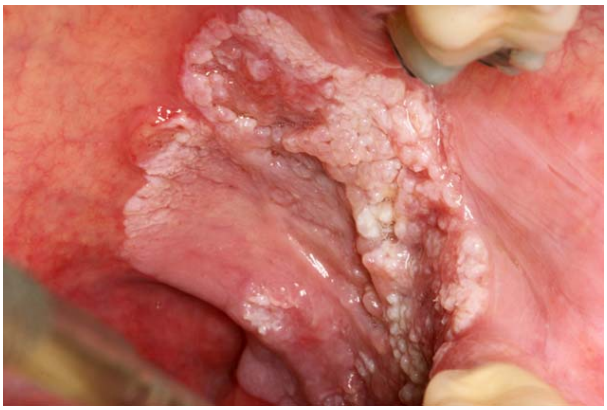

FIGURE 4. Leukoplakia. A rough, papillary, white patch of the retromolar trigone and soft palate. The large size and nonhomogeneous nature of this lesion are particularly worrisome for malignancy. Biopsy showed invasive squamous cell carcinoma.

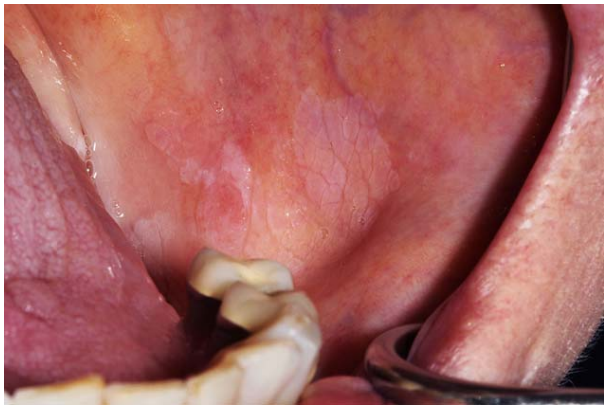

FIGURE 5. Leukoplakia. This subtle, thin, white patch on the left buccal mucosa showed early invasive squamous cell carcinoma.

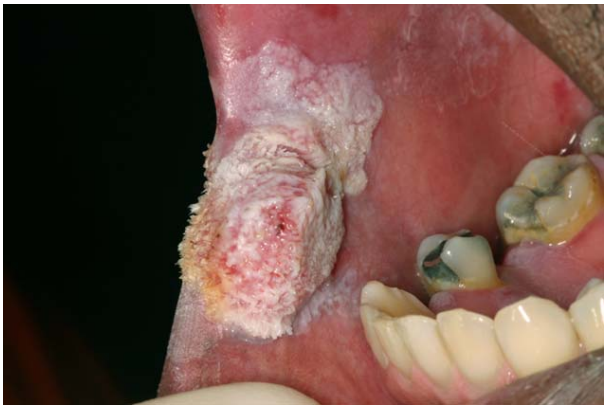

FIGURE 7. Verrucous Carcinoma Arising in Proliferative Verrucous Leukoplakia. A papillary exophytic tumor of the anterior buccal/labial mucosa from a patient with multifocal oral lesions.

because it often occurs in patients without traditional risk factors for OC-SCC. Recognition of PVL is difficult in the early stages, and the diagnosis often requires retrospective clinicopathologic correlation. Early lesions appear similar to conventional leukoplakia. Over time, however, PVL tends to become multifocal, with the development of a rough, verrucous surface (Fig. 6). Eventually, the lesions may transform into verrucous carcinoma (a well-differentiated subtype of OC-SCC that classically has been associated with long-term use of chewing tobacco or dry snuff) (Fig. 7) or conventional SCC. Recurrence after excision is common.

Erythroplakia is defined as a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease.[115,118,132] In contrast to leukoplakia, almost all true erythroplakias will show evidence of high-grade dysplasia, carcinoma in situ, or invasive SCC. Clinically, the lesion appears as a red, velvety patch that often is well-demarcated. Some lesions may have a rough, granular surface (speckled erythroplakia) (Fig. 8). Many erythroplakias are asymptomatic, although some examples can be associated with burning or tenderness.

In addition, some OC-SCCs appear as ulcers without adjacent white or red mucosal change (Fig. 9). As invasion occurs, the mucosal surface usually exhibits an increasingly irregular, granular, and ulcerated appearance. Continued growth can result in an exophytic or endophytic mass with a raised, rolled border. Pain or tenderness often develops, although this may not occur until later in the course of the disease.

In the Western world, the most common site for OC-SCC is the tongue, which accounts for approximately 40% to 50% of all cases (Fig. 10).[118,133] The vast majority of tongue lesions occur on the lateral and ventrolateral aspects; carcinomas of the dorsal tongue are distinctly rare. The second most common oral site is the floor of the mouth (Fig. 11). Tumors of the buccal mucosa, gingiva, and hard palate are less common (Fig. 12). However, in areas of the world where betel quid usage is prevalent, the tongue and buccal mucosa are the most common sites for OC-SCC.[134–136]

Squamous Cell Carcinoma of the Oropharynx

OP-SCC develops most frequently in the tonsillar region and base of the tongue, often appearing as an ulcerated mass, fullness, or irregular erythematous mucosal change

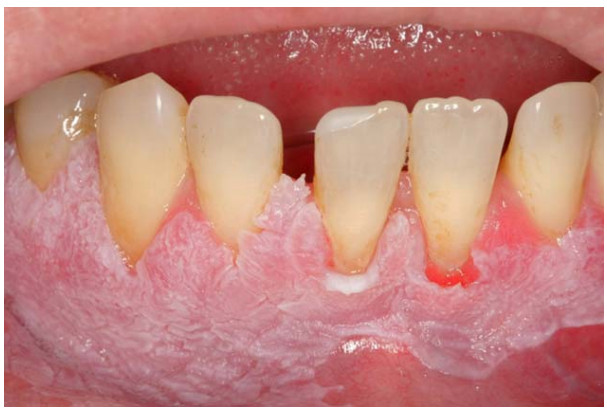

FIGURE 6. Proliferative Verrucous Leukoplakia. A diffuse, rough, white lesion of the anterior mandibular gingiva (courtesy of Dr. Lynn Wallace).

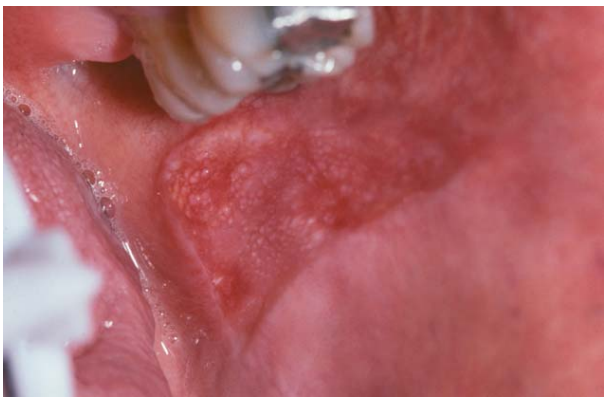

FIGURE 8. Speckled Erythroplakia. A red patch with a speckled surface on the left posterior buccal mucosa. Biopsy showed invasive squamous cell carcinoma.

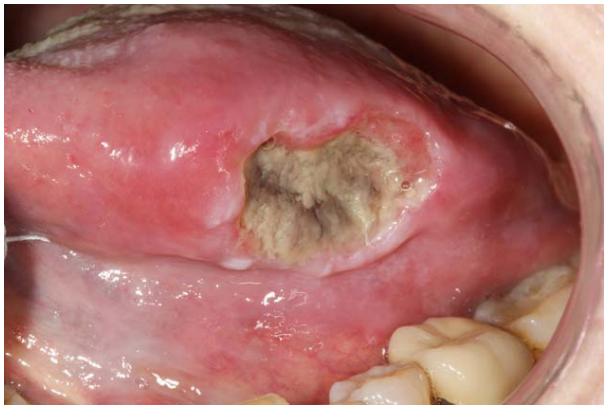

FIGURE 9. Squamous Cell Carcinoma. A deep, necrotic ulceration on the left lateral border of the tongue (courtesy of Dr. Marty Steed).

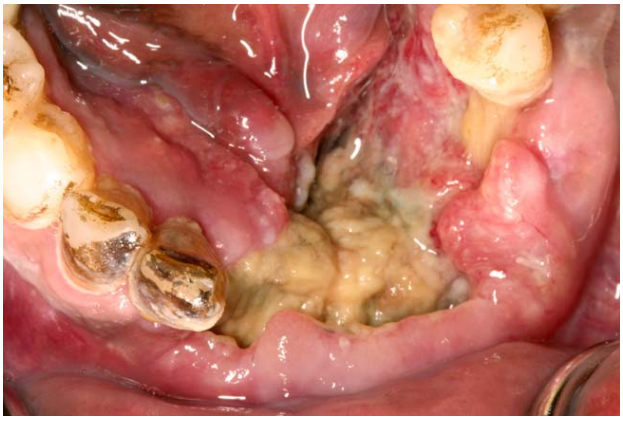

FIGURE 11. Squamous Cell Carcinoma. An ulcerated mass in the anterior floor of the mouth and lingual mandibular alveolar mucosa.

(Fig. 13).[82] Such tumors often present at a more advanced stage than OC-SCC because of their ability to grow undetected and their propensity for metastasis. The most common chief complaints are the presence of a neck mass (from metastatic disease), sore throat, and dysphagia. However, significant differences are noted with respect to the HPV status of the tumor.[137] In patients with HPV-related OP-SCC, the most common complaint is development of a neck mass (51%), followed by sore throat (28%), and dysphagia (10%). It is not unusual for a patient to present with significant metastatic neck disease yet to have a small primary tumor that remains hidden or undetectable. In contrast, the most common symptom in HPV-negative OP-SCC is sore throat (53%), followed by dysphagia (41%), and neck mass (18%).

Because HPV-positive OP-SCCs have a better prognosis than HPV-negative tumors, HPV tumor status is routinely assessed at most institutions for patients who have oropharyngeal carcinoma or metastatic head and neck carcinoma with an unknown primary site. Upon histopathologic examination, HPV-related OP-SCC tends to be nonkeratinizing with a somewhat basaloid appearance recapitulating tonsillar crypt epithelium.[138] Methods for evaluating HPV tumor status include quantitative reverse-transcriptase polymerase chain reaction for high-risk HPV E6 and E7 mRNA, DNA or RNA in situ hybridization-based methods, and p16 immunohistochemistry.[139] The use of p16 immunohistochemistry as a surrogate marker for HPV status has been validated by many studies, albeit only for carcinomas of the oropharynx and mainly for tumors with nonkeratinizing morphology.[140,141] Accordingly, the College of American Pathologists recommends the following protocol for assessing HPV status in OP-SCC: 1) for entirely or predominantly nonkeratinizing tumors, strong and diffuse (ie, >70% cytoplasmic and nuclear) immunohistochemical expression of p16 is sufficient to indicate HPV positivity, and HPV DNA testing (ie, in situ hybridization or polymerase chain reaction) is not required; 2) for entirely or predominantly nonkeratinizing tumors with negative or focally positive immunohistochemical expression of p16, HPV DNA testing is required; 3) for keratinizing tumors with strong and diffuse immunohistochemical expression of p16, HPV DNA testing is required; 4) for keratinizing tumors, negative or focally positive immunohistochemical expression of p16 is sufficient to indicate negative HPV status, and HPV DNA testing is not required.[140] Also, the

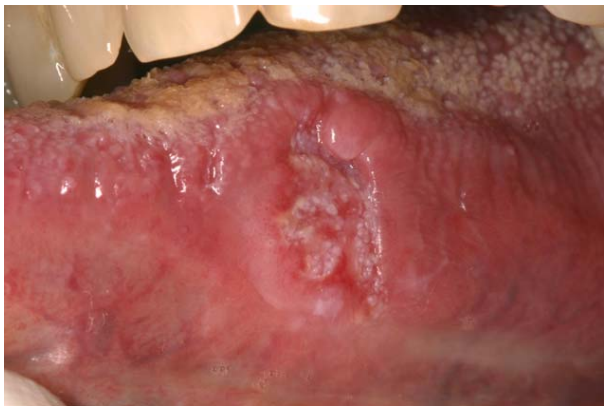

FIGURE 10. Squamous Cell Carcinoma. A granular, ulcerated lesion with a raised, rolled border on the left lateral border of the tongue.

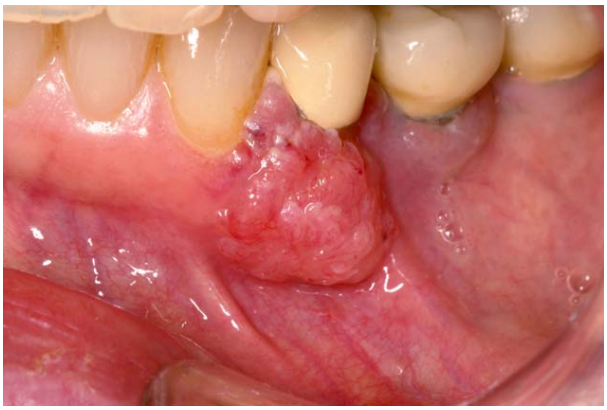

FIGURE 12. Squamous Cell Carcinoma. An irregular, granular, ulcerated mass on the mandibular gingiva.

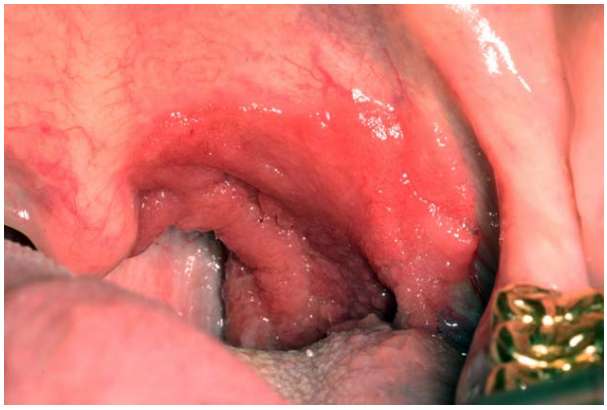

FIGURE 13. Squamous Cell Carcinoma. This human papillomavirus-positive tumor presented as a diffuse erythroplakia of the left soft palate and tonsillar region.

College of American Pathologists protocol advocates p16 immunohistochemistry or in situ hybridization as a reliable predictor of oropharyngeal origin in the evaluation of lymph node biopsies or fine-needle aspirations showing metastatic cervical carcinoma with an unknown primary.

Imaging and Clinical Assessment

Imaging aids in determining the extent of the primary tumor, regional lymph node spread, and distant metastasis. Because the oral cavity and oropharynx are amenable to visual examination (either transorally or endoscopically), initial diagnosis and staging may rely primarily on clinical examination. However, for tumors that are not visible or palpable (eg, OP-SCC arising in a tonsillar crypt), imaging studies are especially important.

Imaging of oral and oropharyngeal cancers most commonly involves an enhanced contrast and noncontrast computed tomographic (CT) scan of the head and neck, magnetic resonance imaging (MRI), and/or fused CT/positron emission tomography (CT/PET) for complete assessment and staging (Figs. 14 and 15).[142] For patients at risk for distant metastasis, plain radiography and/or CT of the chest as well as full-body CT/PET are often required.

Imaging and Clinical Assessment for Oral Cancer

Because early OC-SCCs usually are superficial lesions, they are often not evident on any radiologic studies. This applies to almost all stage I OC-SCCs because, by definition, they are less than 2 cm in size and do not involve deep (extrinsic) tongue muscles or the mandible. However, T2 cancers are 2 to 4 cm in size and, thus, may involve adjacent structures and have a higher incidence of occult lymph node metastasis. Therefore, additional imaging is necessary to assess primary tumor extent as well as to evaluate the regional lymph nodes. CT provides fast image acquisition and excellent resolution of bony involvement. MRI is superior in characterizing the degree of local soft tissue invasion, perineural

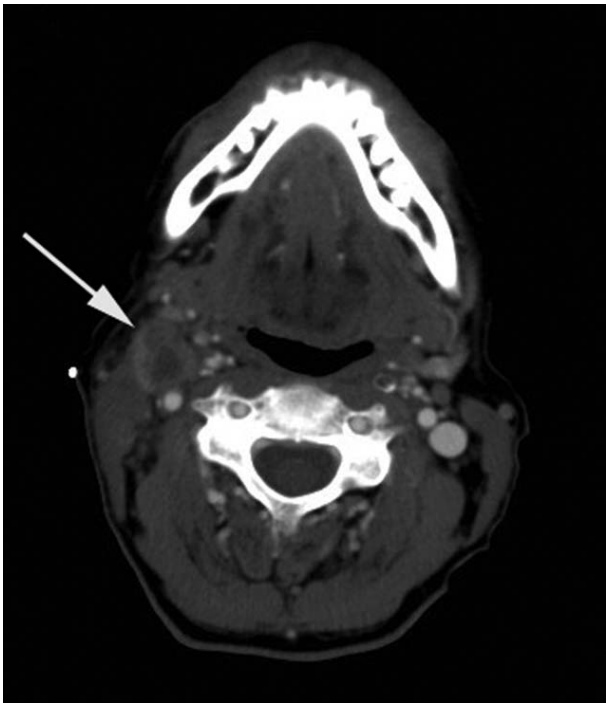

FIGURE 14. Contrast-enhanced Computed Tomography Scan. This image shows the typical appearance of a cystic lymph node metastasis (arrow) involving levels 2 and 3 of the neck in a patient with human papillomavirus-positive oropharyngeal carcinoma.

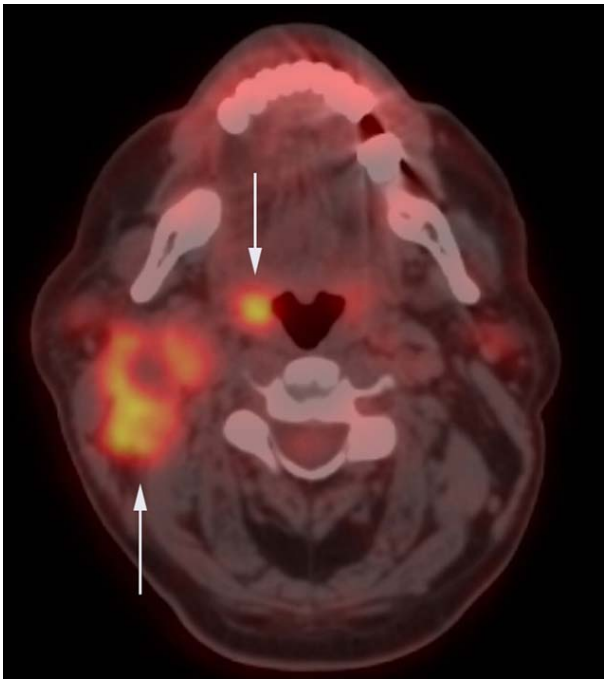

FIGURE 15. Computed Tomography/Positron Emission Tomography Fusion Study. This image is from a patient with a small (T1), human papillomavirus-positive primary cancer in the tonsil (top arrow). In addition, there is a large, cystic lymph node metastasis (bottom arrow) with radiographic evidence of extracapsular extension; the cystic component shows minimal 18F-fluorodeoxyglucose (FDG) uptake, whereas the surrounding solid component shows increased FDG uptake (courtesy of Dr. Zoran Rumboldt).

invasion, and bone marrow involvement.[143] In particular, for tongue cancers, MRI is the best modality for determining primary tumor extent (including whether or not the tumor crosses the midline), deep muscle invasion, and resectability.[144] Also, intraoral ultrasound has emerged in recent literature as an acceptable alternative to MRI for preoperative assessment of tongue tumor thickness.[145] In addition, panoramic or periapical dental imaging may be used to assess possible invasion of the mandible or maxilla. These films also can be helpful to evaluate the dental and bone health in patients who may require radiation therapy as part of their treatment, in an effort to avoid loss of dentition or prevent the subsequent development of osteoradionecrosis of the mandible.

Advanced OC-SCCs (stage III and IV) require CT of the head and neck, with and without contrast, to assist with both T and N staging. Patients with severe pain or trismus may have nerve involvement (lingual, hypoglossal) or pterygoid muscle invasion, which also would be an indication for such imaging.

Imaging and Clinical Assessment for Oropharyngeal Cancer

Patients with OP-SCC may present to their primary care provider for evaluation of an enlarged cervical lymph node, which initially may be treated with antibiotics. However, if there is no resolution within 2 weeks, then referral to a specialist for fine-needle aspiration biopsy and further clinical evaluation may be appropriate. Advanced clinical examination by an otolaryngologist/head and neck surgeon or head and neck surgical oncologist typically includes fiberoptic endoscopic examination of the nasopharynx, oropharynx, hypopharynx, and larynx. A CT scan or MRI of the primary tumor and neck typically is indicated for accurate locoregional staging. Cystic lymph node metastases are not unusual for HPV-related tumors (see Figs. 14 and 15).[146] Furthermore, according to recent studies, ultrasound may be a useful adjunct, not only for guiding fine-needle aspiration biopsy of lymph nodes but also for the identification of unknown primary tumor sites in patients with metastatic lymph node disease of the head and neck region.[147,148] HPV testing of cytopathologic samples from cervical lymph nodes may aid in determining the etiology and predicting the location of unknown primary tumors; the use of liquid-phase cytologic assays for HPV determination is especially promising but requires further studies for clinical validation.[139,149,150]

There is controversy regarding the utility of posttreatment imaging to assess response to therapy and/or to serve as a baseline for future surveillance imaging. Several studies have shown that a CT/PET scan is most effective when scheduled at 12 weeks postchemoradiation to determine treatment response and, if lymph node disease persists, the need for neck dissection. A common approach is to perform neck dissection on any lymph node that is persistently enlarged on CT and has elevated uptake on PET at 12 weeks posttreatment.[151-153] The timing of surveillance imaging is important, because waiting too long may miss the optimal window for salvage surgery. Studies have shown that CT/PET scans performed too early have an unacceptably high rate of false-positives and false-negatives.[154,155] A recent retrospective study of 247 HN-SCC patients found very similar positive predictive values and negative predictive values among scans performed from 7 to 11 weeks and from 11 to 14 weeks posttreatment, thereby concluding that CT/PET performed as early as 2 months posttreatment is acceptable without affecting accuracy.[156] Nevertheless, there is no consensus regarding the use of imaging at specific time points after treatment to assess for recurrence.[157-161]

Staging

The American Joint Committee on Cancer staging system for both oral and oropharyngeal cancers requires an assessment of the primary tumor (T), lymph nodes (N), and distant metastasis (M) (Tables 2 and 3).[162,163] Prognosis traditionally has been linked to tumor stage. However, evidence supports that HPV-associated OP-SCC, despite often exhibiting lymph node disease at diagnosis, has a more favorable prognosis compared with HPV-negative disease.[164-166] Conversely, a history of cigarette smoking portends a worse prognosis.[167,168] Accordingly, some investigators propose that staging criteria for oropharyngeal cancer also should include HPV status and smoking history.[164,165] For example, in a retrospective analysis of the effect of HPV tumor status on survival among patients with OP-SCC enrolled in a Radiation Therapy Oncology Group trial, Ang et al used recursive-partitioning analysis to identify factors (including HPV tumor status, pack-years of cigarette smoking, T classification, and N classification) that were most predictive of overall survival.[78] Accordingly, patients were classified into the following categories: low-risk (HPV-positive tumors with $\leq$10 pack-years of smoking or N0-N2a HPV-positive tumors with >10 pack-years of smoking), intermediate-risk (N2b-N3 HPV-positive tumors with >10 pack-years of smoking or T2-T3 HPV-negative tumors with $\leq$10 pack-years of smoking), and high-risk (T4 HPV-negative tumors or HPV-negative tumors with >10 pack-years of smoking). The 3-year overall survival rates for the low-risk, intermediate-risk, and high-risk groups were 93%, 70.8%, and 46.2%, respectively. Subsequently, investigators have confirmed these findings or have proposed other prognostic risk models.[164,169-171] Further validation studies for proposed risk models are needed, although clinical trials evaluating deintensified radiation and chemotherapy protocols are

TABLE 2. TNM Definitions for Oral Cavity and Oropharyngeal Carcinoma According to the American Joint Committee on Cancer, 7th Edition[a]

CATEGORY	DEFINITION
Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Oral cavity: Tumor more than 4 cm in greatest dimension
	Oropharynx: Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease
	Oral cavity: Tumor invades adjacent structures only (eg, through cortical bone [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face) *Note*: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4
	Oropharynx: Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible (*Note*: mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx)
T4b	Very advanced local disease
	Oral cavity: Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery
	Oropharynx: Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base, or encases carotid artery
Regional lymph node involvement (N)[b]	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

[a]Source: American Joint Committee on Cancer (AJCC). Lip and Oral Cavity. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010:29-40[162]; and American Joint Committee on Cancer (AJCC). Pharynx. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010:41-56.[163] [b]Note: For the oropharynx, metastases at level VII are considered regional lymph node metastases.

underway for patients considered to have a favorable prognosis based on HPV-positive tumor status and other parameters (see Treatment section below).

Also of interest, retrospective studies by Mroz et al have found that increased mutant-allele tumor heterogeneity (MATH) (a quantitative measure of an individual tumor's genetic heterogeneity based on next-generation sequencing data) correlates with an adverse prognosis in HN-SCC patients, with high MATH values significantly associated with shorter overall survival (hazard ratio, 2.2-2.5), decreased survival among patients receiving primary or adjuvant chemoradiation therapy (hazard ratio, 5.2), HPV-negative tumor status, and disruptive *TP53* mutations.[172,173] Despite a strong association between HPV-positive tumors and low MATH values, bivariate Cox proportional hazards analysis suggests that the role of intratumor heterogeneity in HN-SCC mortality is independent of HPV tumor status. The investigators propose that MATH

TABLE 3. Staging and TNM Classification for Oral and Oropharyngeal Carcinoma According to the American Joint Committee on Cancer, 7th Edition[a]

STAGE	TNM CLASSIFICATION
0	Tis N0 M0
I	T1 N0 M0
II	T2 N0 M0
III	T3 N0 M0
	T1 N1 M0
	T2 N1 M0
	T3 N1 M0
IV	
IVA	T4a N0 M0
	T4a N1 M0
	T1 N2 M0
	T2 N2 M0
	T3 N2 M0
	T4a N2 M0
IVB	T4b Any N M0
	Any T N3 M0
IVC	Any T Any N M1

[a]Source: American Joint Committee on Cancer (AJCC). Lip and Oral Cavity. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010:29-40[162]; and American Joint Committee on Cancer (AJCC). Pharynx. In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. AJCC Cancer Staging Manual. 7th ed. New York: Springer; 2010:41-56.[163]

may be useful not only for clinical trials evaluating deintensified organ-preservation therapy for OP-SCC but also for the stratification of patients who have head and neck cancers unrelated to HPV.

Treatment

The standard of care should follow the National Comprehensive Cancer Network guidelines whenever possible and as appropriate for a given patient.[174] Multidisciplinary care may include specialists in surgery, radiation oncology, medical oncology, dental oncology, nursing, and speech pathology. Current National Comprehensive Cancer Network treatment guidelines remain stage-dependent, although modifications based on HPV tumor status may be recommended in the future.

Most early and late-stage OC-SCCs are treated surgically with clear 1-cm to 2-cm margins; in addition, neck dissection typically is performed when lymph node disease is evident or when there is an elevated risk of occult regional metastasis. Stage III or IV OC-SCC typically requires combined treatment, with surgery as the primary modality, and the need for adjuvant radiation or chemoradiation therapy often dictated by adverse findings (eg, positive surgical margins, perineural or lymphovascular invasion, N2 or N3 lymph node disease, lymph node disease in levels IV or V, extracapsular extension of tumor in lymph nodes).[174-176]

Although optimal treatment of the clinically lymph node-negative (cN0) neck for OC-SCC remains controversial and requires further study, management is based on assessing the risk for occult regional lymphatic spread. Factors associated with increased risk for occult lymph node disease include increased T classification, higher tumor grade, increased depth of invasion (eg, >4 mm for tongue lesions) or increased tumor thickness, and the presence of perineural or lymphovascular invasion.[177] In reported series of patients with cN0 early stage OC-SCC treated universally by elective neck dissection, the prevalence of occult lymph node disease ranged from 6% to 25% for T1 lesions and 20% to 32% for T2 lesions; in addition, although subject to patient selection bias, studies comparing observation with elective neck dissection have reported a prevalence of occult lymph node disease in cN0 early stage OC-SCC as high as 40% to 50%.[177] With regard to subsite, oral tongue carcinomas exhibit a higher likelihood of regional metastasis compared with floor of mouth cancers.[178] Management options include observation, elective neck dissection, sentinel lymph node biopsy, and radiation therapy. Sentinel lymph node biopsy has been shown to be a reliable means of assessing the cN0 neck in T1/T2 OC-SCC, with reported negative predictive values ranging from 88% to 100%.[179-184]

Compared with the treatment of OC-SCC, management of OP-SCC is somewhat more complex and controversial, with various proposed combinations and sequences of chemotherapy, radiation therapy, and/or surgery. For early stage cancers, either radiation alone or surgery alone is indicated, whereas advanced cancers typically require combinations of either surgery followed by radiation or initial concomitant chemotherapy and radiation therapy. Decision making in this scenario is difficult, because one cannot always predict the functional and curative outcome before treatment. Current evidence supports the use of either chemoradiation therapy or surgery.[185-187] The latter may be followed by adjuvant therapy, depending on the surgical pathology findings and the final pathologic stage.

For both OC-SCC and OP-SCC, several surgical techniques are available, including open resection, transoral robotic surgery, and transoral laser microsurgery. Recent advances have resulted in a trend away from an open surgical approach and toward a transoral approach without external incisions. Despite these technologic advances, the general surgical principle remains the same: removal of the entire cancer with at least 1-cm margins.

The authors recommend nonsurgical therapy when the expected functional or cosmetic outcome of surgery could

result in higher morbidity or lower quality of life than that for nonsurgical therapy. Examples of such situations include bilateral involvement of the base of tongue, extensive soft palate disease, or limited surgical access. A neck dissection typically is performed when there is clinically evident lymph node disease or a significant risk for occult metastasis. The findings of the neck dissection can lead to upstaging or downstaging of the tumor and help to determine the need for adjuvant treatment. Whenever radiation therapy is performed, either intensity-modulated radiation therapy or 3-dimensional conformal radiation therapy is recommended.

The current 5-year survival rate for oral cavity/pharyngeal cancer in the United States is 63%.[133] However, many centers have reported 5-year survival rates for HPV-positive OP-SCC as high as 78% to 93%.[74,188] In particular, the more favorable prognosis of HPV-related HN-SCC, compared with HPV-negative disease, seems to result from a better response to chemotherapy and radiation therapy. The mechanisms underlying chemoradiation sensitivity have yet to be fully elucidated but may be due in part to an increased frequency of intact p53. Also, apparently because of a lack of field cancerization, the risk for developing a second primary malignancy of the head and neck is lower among patients who have HPV-related HN-SCC compared with those who have HPV-negative, tobacco-related disease.[189,190] For HPV-related OP-SCC, current areas of clinical investigation include transoral robotic surgery (National Clinical Trial 01898494 [NCT01898494], NCT02072148, NCT02159703), deintensified chemotherapy and/or radiation therapy (NCT02281955, NCT01530997, NCT01663259, NCT01088802, NCT01687413), immunotherapy (NCT02002182, NCT01585428, NCT02280811), and biomarkers for predicting response to therapy (NCT02128906).[73]

Reconstruction and Rehabilitation

An important issue related to treatment and outcomes in head and neck oncology is reconstruction and rehabilitation. Because cancers of the oral cavity and oropharynx can have a direct impact on function of the teeth, tongue, mandible, palate, and pharynx, patients often present with disruption of their abilities to eat, drink, chew, and swallow.[191-193] In addition, surgical and radiation treatments of these cancers may result in further loss of function and major cosmetic changes, which often require extensive reconstruction and/or rehabilitation. Accordingly, advocacy organizations and specialists recommend multidisciplinary and interprofessional care, which incorporates head and neck surgery, radiology, pathology, medical oncology, radiation oncology, microvascular reconstructive surgery, nutrition, tobacco cessation, general dentistry, prosthodontics, and speech/swallowing pathology.[194,195]

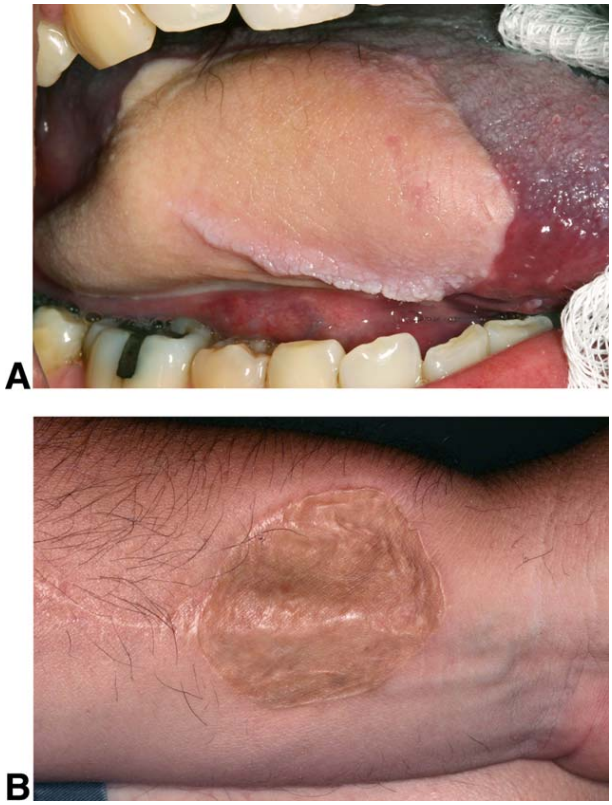

FIGURE 16. Images From a Patient After Right Partial Glossectomy With Healed Radial Forearm Free Flap (RFFF) Reconstruction. (A) This intraoral photograph shows a patient after right partial glossectomy with healed RFFF reconstruction. Note that the linear ridge along the skin is a result of biting the flap. (B) In the same patient, the forearm shows the RFFF donor site with healed skin graft.

Common problems and side effects of treatment for OC-SCC include xerostomia, mucositis, and speech deficits. Severe side effects are uncommon but can include marked fibrosis and trismus, malocclusion, dysphagia, and osteoradionecrosis.[196-200] Surgery is the mainstay of treatment for OC-SCC, often requiring removal of parts of the tongue, mandible, teeth, palate, buccal mucosa/cheek, lips, and chin. This requires significant mandibular and tongue reconstruction along with dental rehabilitation. The tongue may be reconstructed with tissue grafting, primary closure, or secondary intention healing when the cancer is small. However, large or recurrent cancers may require free tissue transfer using tissue transplantation from the arm or leg; this may include a free flap from the radial forearm, fibula, or anterolateral thigh (Fig. 16A,B).[201,202]

Common side effects of treatment for OP-SCC include dysphagia, mucositis, and xerostomia. Severe side effects include velopharyngeal insufficiency, aspiration, fibrosis, and osteoradionecrosis.[191,197,198,203-205] Transoral robotic and/or laser surgery may result in defects of the base of tongue, tonsil, soft palate, and/or pharynx. When the defects are small, healing typically occurs secondarily—similar to a tonsillectomy; however, if defects are large or involve the soft palate, then velopharyngeal insufficiency may occur, which may

require reconstruction with palatoplasty, velopharyngoplasty, and/or a palatal obturator. For large defects, free tissue transfer with soft tissue flaps (eg, radial forearm free flap, anterolateral thigh flap) may be ideal.[201]

HPV Vaccination for OP-SCC Prevention

The availability of vaccines targeting high-risk HPV types offers great promise in controlling the rise of OP-SCC in the future. HPV vaccination currently is approved by the US Food and Drug Administration for the prevention of carcinoma of the uterine cervix and anogenital warts.[206,207] In a clinical trial including over 7400 young Costa Rican women randomized to receive either the bivalent HPV-16/HPV-18 vaccine or the hepatitis A vaccine as control, Herrero et al reported vaccine efficacy of 93% against oral HPV-16/HPV-18 infection approximately 4 years after vaccination.[208] However, prevention of OP-SCC is not yet an approved indication for HPV vaccination, and further studies are ongoing.[208-210] In addition, there is a need to address barriers to vaccination.[211]

Summary

With regard to HN-SCC, the oral cavity and oropharynx represent more than just different anatomic sites. The etiopathogenesis, diagnosis, treatment, and outcomes for tumors involving these sites have been diverging for over a decade. It is important for clinicians to be aware of these differences, so that appropriate patient education and multidisciplinary care can be provided to optimize outcomes. HPV vaccines may have the greatest potential to reduce the morbidity and mortality from OP-SCC, which has been increasing in incidence in the United States and other developed nations. ■

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