

Oral Cavity Squamous Cell Carcinoma – An Overview

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Abstract

Inhaled or chewed tobacco is equally addictive and harmful and used daily by over 1 billion people. In addition to increased rates of coronary artery disease, stroke, peripheral vascular disease, congestive heart failure, chronic obstructive pulmonary disease and lung cancers, tobacco is the leading preventable cause of oral cavity squamous cell carcinoma. In addition to tobacco, consumption and abuse of alcohol, and betel nut quid significantly contribute to the burden of oral cavity squamous cell carcinoma. Dental visits are excellent opportunities to identify primary lesions in the oral cavity. This review highlights relevant anatomy, epidemiology, pathogenesis, evaluation and treatment options for oral cavity squamous cell carcinoma.

Key Words: Oral cavity, Squamous cell carcinoma, Tobacco

Epidemiology

As the gateway to the alimentary and respiratory tract, the oral cavity has repeated exposure to many carcinogenic agents, specifically tobacco, alcohol, betel nut and Human Papillomavirus (HPV). Worldwide, approximately 275,000 oral cavity malignancies are diagnosed each year and the predominant malignancy is squamous cell carcinoma [1,2]. In Sri Lanka, India, Pakistan and Bangladesh, nearly a quarter of total cancer diagnoses are oral cavity squamous cell carcinoma. In western countries, oral cavity squamous cell carcinoma represents approximately 3% of new cancer diagnoses annually [3]. Globally, oral cavity squamous cell carcinoma primarily affects males (1.5:1); however, in regions where female tobacco and betel nut consumption is common, the gender difference normalizes [3]. Worldwide the mortality rate is estimated to be nearly 50% [1].

Anatomy

The oral cavity has strict anatomic boundaries and extends from the lips to a vertical plane at the junction of the hard and soft palate that extends through the circumvallate papillae and ends in the hyoid bone (*Figure 1*) [4]. For staging and treatment purposes, the oral cavity is further subdivided (*Table 1*) [4,5].

The oral cavity is frequently and incorrectly combined or mixed with the oropharynx; however, the oral cavity and oropharynx are distinct anatomical sites with important distinctions in staging, etiology, treatment and prognosis. The oral cavity transitions to the oropharynx at a plane that transverses the anterior tonsillar pillars, the junction of the hard and soft palate, the circumvallate papillae and the hyoid bone. The vertical boundary of the oropharynx is an imaginary plane that extends from the inferior surface of the soft palate to the superior surface of the hyoid bone.

Pathogenesis

The use of tobacco products is the leading cause of preventable disease worldwide [6]. It is estimated that 1 billion men and

250 million women consume tobacco daily [7]. Nicotine is rapidly absorbed through the oral cavity mucosa or pulmonary epithelium and provides individuals with increased energy, reduced anxiety, reduced stress and appetite suppression [8]. Within 30 minutes, abstinence results in somatic symptoms such as bradycardia, gastrointestinal distress, increased appetite as well as depressed mood, irritability, anxiety, and frustration [8,9]. The highly rewarding effects of tobacco along with the negative effects of cessation make prolonged abstinence from tobacco the exception rather than the rule, even for individuals who are motivated to quit [10].

Tobacco use has been demonstrated to increase rates of coronary artery disease, stroke, peripheral vascular disease, congestive heart failure, chronic obstructive pulmonary disease and a variety of cancers [11-13]. While tobacco inhalation is implicated in greater than 90% of lung cancers, it is also a causative factor in other cancers throughout the aerodigestive tract [14]. At least 25% of oral cancers are directly attributed to tobacco use [15].

While over 60 carcinogenic substances have been identified in tobacco smoke, the levels of known carcinogens are generally lower in smokeless tobacco; however, nitrosamines 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-Nitrososnicotine (NNN) are present in both smokeless and inhaled tobacco products. NNK and NNN form covalent bonds with genomic DNA resulting in genomic instability and are thought to be the primary mediators of malignant transformation [7].

The oral cavity is the initial conduit for tobacco, and also serves as the entryway for alcoholic beverages. The mechanism of alcohol addiction is complex; however, it is well established that ethanol directly affects N-methyl-D-aspartate receptor (NMDA), γ -aminobutyric acid type A GABA_A and 5-hydroxytryptamine 3 (serotonin; 5-HT₃) receptors resulting in addiction [16]. Heavy consumption of alcohol increases the risk of oral cavity cancer 2-3 times, and alcohol use is implicated in 15% of oral cancers [9]. At least part of the carcinogenic effects of alcohol is mediated by the initial metabolite acetaldehyde, which forms DNA adducts

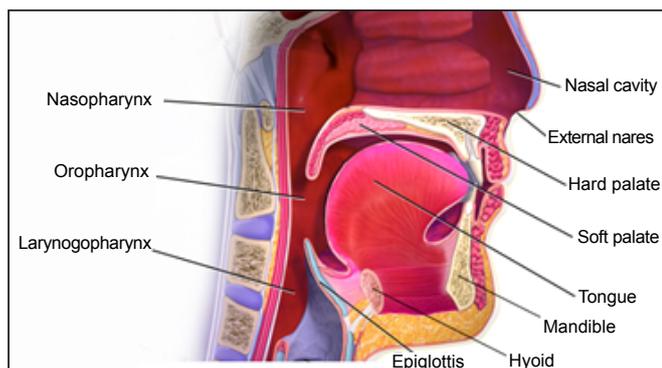


Figure 1. Sagittal rendering of the oral cavity. Adapted from [5].

and results in aberrant DNA methylation patterns [17,18]. Additionally, alcohol may lead to malignant transformation by acting as a solvent to increase permeability of tobacco carcinogens, impairing immunity and causing nutritional deficiencies [19].

While tobacco and alcohol are independent risk factors for oral cavity cancer, the risks are not simply additive. In a US based study, patients who consumed 4 or more alcoholic drinks a day and smoked 2 packs per day had a 35 fold increase in oral cavity cancer compared to drinkers or smokers alone who had a ~9 fold and ~4 fold respectively [20].

While worldwide chewing and smoking tobacco are highly prevalent, in South-East Asia it is estimated that up to 600 million people chew betel quid. Betel quid is the 4th most commonly consumed psychoactive drug after caffeine, alcohol, and nicotine [21]. While the betel quid has regional variation, a typical preparation consists of betel leaves (*Piper betle*) wrapped around the fruit of the *Areca catechu* tree [9]. The principal psychoactive and addictive components of betel quid are arecoline and arecaidine, which act as muscarinic agonists and GABA antagonists respectively [22-24]. While some regions incorporate tobacco into betel quid, there is strong evidence that betel quid alone increases the risk of cancer by up to 9 fold [25]. The carcinogenic compounds have been less clearly defined than in tobacco and alcohol but NNK, NNN, and reactive oxygen species are thought to be the main drivers of oncogenesis [26,27].

The synergistic effects of smoking and drinking on the development of oral cavity squamous cell carcinoma are further amplified among individuals who regularly consume tobacco, alcohol, and betel quid. In a Taiwanese study, individuals who regularly consumed tobacco, alcohol, and betel quid had a 46-fold increase in oral cavity cancer [28].

While tobacco use declines in the United States, the number of head and neck squamous cell carcinomas driven by HPV is on the rise [29]. HPV is a family of DNA viruses whose genome codes for 8 proteins [30]. Carcinogenesis is thought to be driven by expression of three of these proteins, E5, E6 and E7, which alter the host cell cycle (reviewed in [30]). HPV associated oropharyngeal (Table 1) squamous cell carcinoma has been associated with improved outcomes, resulting in efforts to de-intensify treatment [31,32]. However, the prognosis of HPV positive oral cavity squamous cell carcinoma has been shown to be worse than HPV negative tumors [33-35].

Table 1. Subdivisions of the oral cavity.

Oral Cavity
Lips
Oral Tongue (anterior 2/3's)
Floor of Mouth
Buccal Mucosa
Upper Gingiva (alveolar ridge)
Lower Gingiva (alveolar ridge)
Retromolar Trigone
Hard Palate



Figure 2. A. Patient with beefy red lesions consistent with erythroplakia on lateral aspect of oral tongue. B. Grossly the lesion appears beefy red consistent with erythroplakia but pathology demonstrates carcinoma in situ.

Evaluation & Differential Diagnosis

Regular dental visits are an ideal time for identification of suspicious lesions in the oral cavity. Oral cavity squamous cell carcinoma can present as an innocuous rough patch, but more commonly presents as leukoplakia or erythroplakia. Erythroplakia is generally described as red velvety plaques, which cannot be characterized clinically or pathologically as any other recognizable condition (Figure 2) [36]. Reports of the malignant potential for leukoplakia vary widely in the literature; however, transformation rates of 1% per year are generally cited [37]. In contrast to the low malignant potential of leukoplakia, erythroplakia has a high propensity to degenerate into malignancy [38] and we recommend routine excisional biopsy. While we often advocate for an excisional biopsy of leukoplakia, if a dental amalgam or other cause of chronic irritation can be identified and remedied, follow-up for resolution of the lesion is reasonable.

In addition to lesions identified during dental exams, patients will also frequently present with painful ulcerative lesions. Lesions that have been present for more than 3 weeks are concerning for malignancy. Additionally, newly loose teeth, unprovoked bleeding, or exophytic lesions are highly concerning for underlying malignancy (Figure 3).

Patients with biopsy proven cancer should be referred for evaluation to a Head and Neck surgeon (Figure 4). We routinely obtain a contrast enhanced computed tomography of the neck to assist the physical exam in determining extent of the primary lesion and lymph node status (Figure 5A). We obtain a computed tomography of the chest with contrast as well to assess for distant metastasis or a second pulmonary primary malignancy. For low risk patients without smoking history, hemoptysis, weight loss, or obvious palpable lymphadenopathy, a chest X-ray is a reasonable alternative. Magnetic Resonance Imaging (MRI) with contrast is also



Figure 3. A large exophytic lesion on right buccal mucosa.

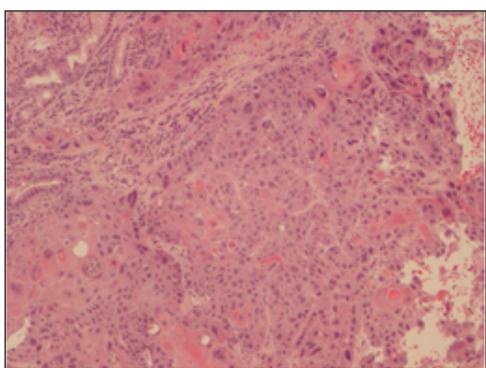


Figure 4. Hematoxylin and eosin stain of a biopsy of an oral cavity lesion demonstrating moderately differentiated squamous cell carcinoma.

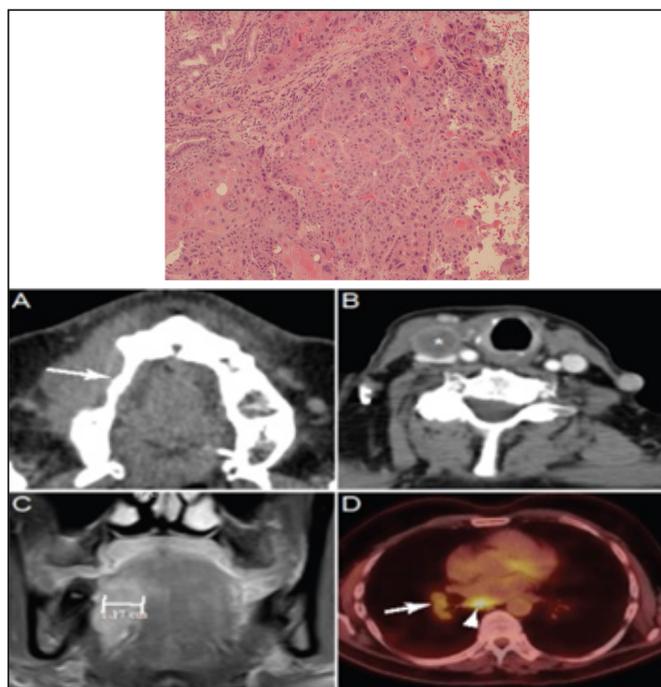


Figure 5. Imaging is a diagnostic adjuvant for assessing patient. **A.** Computed tomography with contrast demonstrates a squamous cell carcinoma of alveolar ridge eroding maxillary bone (arrow) **B.** A level IV, 2 cm lymph node (*) is noted to be compressing the internal jugular vein by computed tomography with contrast. **C.** T1 weighted magnetic resonance image provides robust localization of the extent of an oral tongue squamous cell carcinoma. **D.** F-fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography identifies avid subcarinal lymph node (triangle) and right hilar lymph nodes (arrow).

helpful to assess soft tissue involvement, especially of tumors of the oral tongue and where dental artifact limits the quality of the study (*Figure 5B*).

Patients will likely undergo formal endoscopy for staging and assessment of synchronous tumors. While the role of panendoscopy (laryngoscopy, bronchoscopy and esophagoscopy) has been called into question given low rates of metachronous lesions, improvements in computed tomography and ^{18}F -fluoro-2-deoxy-D-glucose positron emission tomography-computed tomography, we still routinely perform panendoscopy in all patients taken to the operating room for formal excision of malignant lesions [39,40].

While squamous cell carcinoma accounts for over 90% of oral cavity malignancies, other pathologies of minor salivary glands, major salivary glands, sarcomas, lymphomas, mucosal melanoma, nerve sheath tumors and metastases from other sites have been identified in the oral cavity [41-44]. The behaviors of these malignancies are highly variable, and given their rarity, warrant immediate referral to multidisciplinary team for further evaluation and treatment.

Staging

The American Joint Committee on Cancer (AJCC) has detailed a comprehensive staging system for oral cavity squamous cell carcinoma using the standard Tumor, Nodes and Metastasis (TNM) classification system. An overview of the staging system is presented in *Table 2* and *Table 3* [4].

In addition to TNM staging, histologic tumor depth has been shown to be an important prognostic variable. Tumors with less than 2 mm as compared to tumors with more than 2 mm of invasion have 13% and 46% chance of nodal metastasis at diagnosis [45]. Furthermore, their respective rates of disease-free survival are 95% and 85% respectively at 2 years [45].

Primary Site Treatment

Management options include radiation, chemotherapy, surgery, or a combination of these modalities. In our institution, a multi-disciplinary tumor board of medical oncologists, radiation oncologists, pathologists, social workers and head and neck surgeons meet weekly to discuss management of all patients diagnosed with head and neck cancer. The input of this multidisciplinary panel has been shown to affect management options in 1 in 5 patients [46].

Despite a lack of evidence from randomized control trials, stage I and II oral cavity squamous cell carcinoma can be treated with single modality radiation or surgery with similar efficacy. In our practice, primary radiation therapy is reserved for poor surgical candidates and we consider primary surgery with possible adjuvant radiation therapy the standard of care. Primary surgical resection spares patients the long-term morbidity associated with radiation therapy such as xerostomia, osteoradionecrosis, dysgeusia, dysphagia, and dental caries. The majority of oral cavity T1 and T2 tumors can be resected through a transoral approach. For larger or posterior tumors, lip split approaches with or without mandibulotomy may be necessary to gain adequate exposure.

For larger tumors, T3 or T4, tumors with close margins

Table 2. Oral cavity squamous cell carcinoma classification using the standard Tumor, Nodes and Metastasis (TNM) classification system, given by AJCC.

Primary Tumor		Regional Lymph Nodes		Distant Metastasis	
TX	cannot be assessed	NX	cannot be assessed	M0	absent
T0	no evidence of tumors	N0	none	M1	present
Tis	carcinoma <i>in situ</i>	N1	single, ipsilateral, < 3 cm		
T1	< 2cm	N2a	single, ipsilateral, 3-6 cm		
T2	2-4 cm	N2b	multiple, ipsilateral, < 6 cm		
T3	> 4 cm	N2c	bilateral or contralateral, < 6 cm		
T4a	invades adjacent structure	N3	> 6 cm		
T4b	invades distant structures				

Table 3. An overview of the staging system of oral cavity squamous cell carcinoma.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T1-3	N1	M0
	T3	N0	M0
IV	T1-3	N2	M0
	T4	N1-2	M0
	T1-3	N0-3	M0
	T1-3	N0-3	M1

Table 4. Anatomical divisions of nodal basins.

Level	Superior	Inferior	Medial	Lateral
I	mandible	inf. border of hyoid bone	ant. belly of digastric	stylohyoid muscle
II	skull base	inf. border of hyoid bone	stylohyoid muscle	lateral border of SCM muscle
III	inf. border of hyoid bone	cricoid cartilage inf. border	sternohyoid lateral border	lateral border of SCM muscle
IV	cricoid cartilage inf. border	clavicle	sternohyoid lateral border	lateral border of SCM muscle
V	SCM & trapezius convergence	clavicle	sternohyoid lateral border	Anterior border of the trapezius
VI	hyoid bone	suprasternal notch	common carotid	common carotid
VII	suprasternal notch	innominate artery	sternum	trachea, esophagus and prevertebral fascia

after resection, bone invasion, deeper depth of invasion, and multiple lymph node involvement, adjuvant postoperative radiation is routinely performed [47]. Despite increased morbidity, chemotherapy, specifically cisplatin, is indicated for patients with positive margins or extracapsular spread. For detailed treatment strategy by subsite we refer the reader to reference [48]. In addition to management of the primary site, the rich network of lymphatics in the oral cavity and a propensity of these tumors to metastasize make management of the neck another consideration for health care providers.

Treatment of the Neck

The oral cavity has a rich lymphatic network that results in general trends but not rules regarding location of nodal metastasis. For treatment and staging purposes the nodal basins of the neck are anatomically broken down into 7 levels (Table 4) [4]. In a large study of over 1000 patients with clinical nodal metastasis, oral tongue, floor of mouth, and retromolar trigone primary site tumors metastasized primarily to ipsilateral levels I, II, and III [49]. Soft palate lesions were slightly different with metastases primarily to levels I and II, with a greater than 10% rate of metastasis to the contralateral side in level I [49].

The importance of resection of nodal metastatic disease in the treatment of head and neck cancers was recognized in the early 1900's by George Crile who subsequently

developed the radical neck dissection, which removed all of the lymphatic tissue from the lateral neck and was further refined by Hayes Martin in the 1950's [50]. The clinical importance of the neck is paramount. The presence of positive lymph nodes with extracapsular spread is the single-most important determinant of prognosis, cutting survival in half when present [51,52]. Clinical evidence of nodal metastatic disease in the neck requires treatment with neck dissection. However, while we routinely obtain computed tomography of the neck with contrast and perform rigorous head and neck exams, large series have demonstrated that approximately 30% of clinically negative necks will harbor lymph node metastasis [53]. Institutional treatment for the N0 neck varies, with a balance of the risk of disease recurrence versus the morbidity associated with neck dissection. We routinely perform a selective neck dissection on any N0 neck with a primary tumor with 4mm or more of invasion, and tumors greater than T2.

Surveillance

The majority, up to 80%, of recurrences occur within the first 4 years [54]. Therefore, we routinely follow patients every 1-2 months for the first year after treatment followed by every 3-4 months in the 2nd year followed by every 6 months from years 3-5. Five years after the completion of treatment, patients should undergo lifelong yearly follow-

up. Besides identifying recurrent disease, every encounter with medical and dental providers should emphasize the importance of abstaining from tobacco, ethanol, and betel quid. It is well established that patients who continue these highly addictive habits have worse local control rates and outcomes in general [46].

Conclusions

Worldwide, oral cavity squamous cell carcinoma causes significant mortality and morbidity. As the majority of cases

worldwide are linked to consumption of alcohol, tobacco, and betel quid, public health efforts aimed at cessation and discouraging initial use of these addictive substances will have the greatest impact in decreasing the burden of this disease. If trends that have been seen in the United States continue worldwide with public health campaigns, the makeup of oral cavity squamous cell carcinoma will be drastically different in 50 years and suggests that we need additional research efforts into the treatment and prevention of HPV associated oral cavity and oropharyngeal squamous cell carcinoma.

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