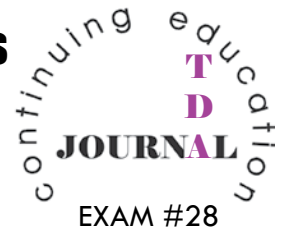


Oral Cancer: Enduring Characteristics and Emerging Trends

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Introduction

Patients diagnosed with oral cancer have a rather poor five-year survival rate. Approximately 36,000 new cases of oral cancer will be reported this year in the United States; it will cause over 8,000 deaths.¹ Dental professionals have the opportunity to perform intraoral examinations on their patients and it is critical that members of the dental team are familiar with the current knowledge and clinical manifestations of oral cancer.

Oral cancer is generally classified into cancers of the oral cavity and of the oropharynx. The oral cavity includes the lips, buccal mucosa, gingiva, hard palate, floor of mouth and anterior 2/3s of the tongue, whereas the oropharynx consists of the posterior 1/3 of the tongue, soft palate, tonsils and posterior pharyngeal wall. About 94% of oral cancers are squamous cell carcinoma,² a malignancy derived from the surface epithelial cells that line the oral cavity and oropharynx. Oral squamous cell carcinoma (OSCC) is primarily a disease of adults. The average age at diagnosis is 62, and 97% of cases occur in patients 35 and older.¹ Men are more than twice as likely to be affected by OSCC as women. In the U.S., black males have the greatest risk for developing OSCC of any population group, making it a major health concern in the Mid-South area. While the overall incidence of OSCC is declining, the incidence of oropharyngeal SCC is on the rise. Many of these new cases of oropharyngeal cancer are occurring in a younger adult population that does not exhibit the traditional risk factors for the development of OSCC.

Etiology

Most experts believe that oral cancer is a multifactorial disease, and many well-established risk factors have been identified. Tobacco use is universally regarded as the single biggest risk factor. About 80% of OSCC patients have a history of smoking tobacco,²

ABSTRACT

Oral cancer is arguably the most serious condition that dental providers may encounter in their practice. The relatively poor prognosis associated with oral cancer highlights the importance of the dental team's awareness of the disease. While many characteristics of oral cancer have endured over time, new research is revealing trends that are changing the way we approach its screening, diagnosis and treatment. In this report, we provide a translational overview of oral cancer, including risk factors, signs and symptoms, clinical management, as well as our recent findings on the role of chronic inflammation in the development of the disease. In addition, our recent genetic profiling approach in both cancer cell lines and in patients has identified potential biomarkers, molecular pathways and therapeutic drugs (Velcade® and Aspirin®) for oral squamous cell carcinomas. This comprehensive review should be of interest to all dental professionals.

and a person's risk of developing OSCC increases with heavier daily use and longer duration of use. While relative risk data regarding OSCC specifically is lacking, the risk of head and neck SCC for cigarette smokers is estimated to be 10-fold over that of people who have never smoked cigarettes.³ Smokeless tobacco (chewing tobacco, moist snuff and dry snuff) has also been implicated in OSCC. Recent epidemiologic studies have found that smokeless tobacco users are about twice as likely to develop OSCC as those who have never used.⁴ It should be noted that dry snuff, which is used most often in the southern U.S., including Tennessee, appears to be more dangerous than moist snuff or chewing tobacco. Current literature indicates that the association between OSCC and smokeless tobacco is not as strong as the relationship between OSCC and tobacco smoking.

Excessive alcohol consumption is another important risk factor for OSCC. While it is unclear whether alcohol abuse alone can cause cancer, the risk of alcohol and tobacco in combination is well established. Tobacco and alcohol appear to have a synergistic effect, and their

combined use increases a person's risk for OSCC by a factor of at least 15.²

Radiation to the head and neck may also contribute to the development of OSCC. Long-term exposure to ultraviolet radiation is the primary causative factor in SCC of the lip vermillion. A different type of radiation, X-irradiation, is a common treatment for many malignancies and other diseases. X-irradiation generates cellular abnormalities in the area of exposure that cause a dose-dependent increased risk of developing another primary malignancy in the future. Post-irradiation malignancies of the oral region may be either SCCs or sarcomas. Importantly, there is no association between oral cancers and the small amount of radiation generated by routine dental radiographs.

Infection by tumor-producing (oncogenic) viruses is an independent risk factor for many different types of cancers. Human papillomavirus (HPV) is a well-known risk factor for cervical cancer and has recently been established as a risk factor for SCC of the oropharynx.^{5,6} In contrast, HPV has not proven to be an important risk factor for SCC of the

oral cavity. Specifically, HPV type 16 is present in up to 90% of all HPV-positive oropharyngeal SCCs.⁵ These tumors appear to represent a unique subset of OSCCs that accounts for the recent increase observed among a relatively younger adult, non-smoking population. Among these patients, a high number of sexual partners and history of oral-genital and/or oral-anal sex are significant risk factors,⁶ suggesting the possibility that HPV-positive oral cancers could represent a type of sexually transmitted disease. As more subjects are vaccinated with Gardasil® and later generations of HPV vaccines, there could be a decline in the number of HPV-positive oral cancers.

These various risk factors have the ability to initiate chronic inflammatory conditions that could potentially cause DNA damage.⁷ This altered DNA changes the expression level of certain genes involved in DNA repair and stability. Reported genetic alterations in oral cancer include deletions of tumor suppressor genes, amplifications of oncogenes and/or mutations. Oncogenes promote cancer when they are stimulated, and tumor suppressor genes contribute to cancer when they become inactivated.

Mutations of these genes in a cell can result in DNA damage leading to uncontrolled proliferation, inability to repair DNA or impairment of programmed cell death (apoptosis), resulting in tumor formation.

Recent scientific reports strongly suggest that inflammation is a major cause of certain epithelial cancers.⁸ Through our own experiments at the Center for Integrative Cancer Research at the University of Tennessee Health Science Center, it is becoming clear that chronic inflammation influences tumor progression and development in OSCC.⁹ We confirmed that a special subclass of genes [CXC family members including interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF α) and CXCL10] is over-expressed/amplified during chronic inflammatory conditions. The

CXC family members can contribute to cancer by activating other genes involved in tumor formation, such as epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF). The pro-inflammatory cytokine IL-8 is one of the over-expressed genes in our studies and has been reported to be present at high levels in the saliva of OSCC patients.¹⁰ Elevated levels of IL-8 have been observed in many other malignancies as well.^{11,12,13,14} These findings suggest a role for IL-8 as an important inflammatory modulator in OSCC. In fact, utilization of specific molecules that reduce the expression of IL-8 leads to significant death of oral cancer cells. In addition, aspirin

Recently CSCs were isolated in head and neck squamous cell carcinomas,¹⁶ and our own results are indicative of the presence of CSCs in carcinoma cell lines (**Figure 1A and B**). Our research on the genetic signature of CSCs from OSCC cell lines suggests that they could be involved in a process called epithelial to mesenchymal transition (EMT). EMT occurs physiologically (during normal development), but also pathologically in some cancers where it is important for metastasis. Interestingly, inflammation in the tumor microenvironment could stimulate the EMT process. We are currently investigating the influence of inflammation on EMT in OSCC CSCs to develop potential novel therapeutic approaches.

Clinical Features and Diagnosis

Upon identification and biopsy of a suspicious lesion, an oral pathologist or general pathologist will diagnose the OSCC lesion microscopically (see **Figure 1C** for an example). Early OSCCs are often asymptomatic, which can result in a delay in the patient seeking care. This is emphasized by the fact that most people diagnosed with OSCC have been aware of an abnormality in their mouth for an average of four to eight months.² The most common symptom is a non-healing sore or ulcer. Other potential signs

and symptoms include pain, numbness, a persistent lump or thickened area, a persistent red or white patch, dysphagia, sore throat or the sensation of something “caught” in the throat. The most common site for OSCC is the tongue, especially the lateral and ventral surfaces. Interestingly, OSCC of the dorsal surface of the tongue is rare. The floor of the mouth, soft palate, and tonsils are other common locations. OSCC of the gingiva is somewhat unique in that it is predominantly observed in elderly females, especially those with no known risk factors. SCC of the lip vermilion is almost always located on the lower lip, usually in fair-skinned individuals.

The clinical appearance of OSCC is variable (**Figure 2**). It can be

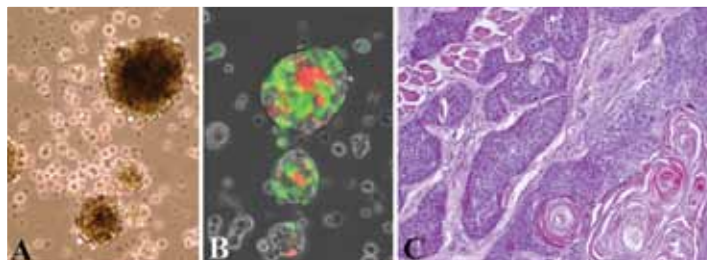


Figure 1 - Oral squamous cell carcinoma (OSCC) cell lines grown under specific stem cell conditions form spherical clusters (tumospheres) that contain cancer stem cell-like cells. A) OSCC-25 cell line grown in stem cell medium forms tumospheres. B) OSCC-9 cells form tumospheres. Different colors indicate different origins for the cells within the same cluster. Labeling was performed using a lentivirus construct containing mKate (red) or green fluorescent protein (green). C) Invasive OSCC-25 cells grown subcutaneously in a special strain of immunocompromised mice. Keratinized islands are found throughout the xenografted solid tumor biopsy.

and another anti-inflammatory drug (Bortezomib, Velcade®) inhibit cell proliferation and viability in OSCCs. These results suggest that IL-8 could serve as a potential therapeutic target in the treatment of OSCC.

Interestingly, some cancers become more aggressive and invasive after drug treatment. A hypothesis proposed to explain this clinical behavior is the presence of a subset of cells within a tumor known as “cancer stem cells.”¹⁵ Cancer stem cells (CSCs) have unique markers compared to other cancer cells and are proposed to be highly tumorigenic and potentially metastatic, with resistance to most forms of radiation and chemotherapy. Cancer therapy may remove most but not all cancer cells, leaving an enriched population of CSCs.

exophytic (growing outward) or endophytic (growing inward), and may have an ulcerated surface. OSCCs are characteristically firm on palpation, which can be a helpful diagnostic clue. The color of OSCC can be white, red or, in many cases, speckled red and white. Many OSCCs are associated with an adjacent leukoplakia, the most common oral precancerous lesion. Leukoplakia is defined as a white patch or plaque that cannot be characterized clinically as any other disease.² In other words, there are no apparent local etiologic factors (such as a source of frictional irritation) that might explain its presence. Similarly, erythroplakia is a red patch that cannot be diagnosed clinically as another disease. While leukoplakia and erythroplakia are clinical terms only, their risk factors are the same as OSCC. Both lesions tend to have sharply-demarcated borders, unlike most reactive lesions which tend to have margins that blend gradually into the surrounding normal mucosa. Erythroplakia is less common than leukoplakia but much more likely to demonstrate significant epithelial dysplasia. **Any lesion that persists longer than two weeks after removal of potential etiologic factors should be biopsied to evaluate for epithelial dysplasia.** Dysplasia represents an alteration in the morphology of the surface epithelial cells and is evidence of precancerous change.

Conventional oral examination continues to be the standard method of oral cancer screening. Oropharyngeal cancers are more difficult to detect on conventional oral exam due to their location. Referral to an otolaryngologist or oral and maxillofacial surgeon is warranted for further evaluation of any persistent oropharyngeal symptoms for which there is no clinically visible abnormality. Many diagnostic aids have been developed and marketed recently to potentially assist in the detection of cancerous and precancerous oral lesions. These adjuncts include cytology and devices that utilize tissue reflectance, autofluorescence, or both. Recently, a panel of experts was convened by the American Dental Association to provide evidence-based recommendations regarding screening for OSCCs. The panel found that there was “insufficient

evidence that the commercially available devices based on tissue reflectance (ViziLite and ViziLite Plus) and autofluorescence (VELscope) improved the detection of potentially malignant lesions beyond that of a conventional visual and tactile examination.”¹⁷ These devices have high sensitivity but low specificity, meaning a propensity for false positive results. Cytology (Oral CDx BrushTest) has validity in the identification of dysplastic cells but does not provide a definitive diagnosis.¹⁷ The ADA panel suggested surgical biopsy to determine a definitive diagnosis. There is currently no published evidence regarding Identafi 3000, which utilizes both tissue reflectance and autofluorescence.



Figure 2 - An extensive squamous cell carcinoma of the lateral tongue. The diagnosis for this lesion was confirmed histopathologically after biopsy. College of Dentistry at UTHSC provides biopsy service and histopathological analysis. Department of Pathology and Laboratory Medicine at the College of Medicine offers a repository service for oral cancer biopsy samples.

Treatment and Prognosis

SCC of the lip vermilion is a distinct type of cancer that behaves similarly to SCC of the skin. Surgical excision is the treatment of choice, and the prognosis is very good. A 96% 5-year survival rate is reported among patients diagnosed with localized disease.¹⁸

The treatment of all other OSCCs may consist of surgery, radiation and/or chemotherapy. Surgery may include a neck dissection if regional lymph node metastasis is suspected. A lymph node with metastatic OSCC will usually be enlarged, firm and non-tender. About 20% of patients with SCC of the oral cavity have cervical lymph node metastases at the time of diagnosis.² SCC of the oropharynx is prone to earlier metastasis,

with 50% of patients having involved cervical lymph nodes when diagnosed.² These figures highlight the importance of a thorough head and neck exam as a component of the oral cancer screening process.

The precise treatment regimen that a given patient receives depends largely on the location and stage of their disease. Staging is a quantification of the size and metastatic spread of a tumor. This determination is made with the help of imaging tests such as x-ray, CT, MRI and PET scans. The TNM protocol is the preferred method of staging OSCCs, where T indicates the size of the primary tumor, N stands for involvement of local lymph nodes and M for distant (below the clavicles) metastasis. Once each of these factors is evaluated, a stage of I, II, III or IV is assigned to the cancer, with stage IV having the worst prognosis. In general, surgery is the initial treatment for SCCs of the oral cavity, which may be followed by radiation, chemotherapy or both. Oropharyngeal SCCs are usually treated by a combination of radiation and chemotherapy. New therapeutic regimens continue to be developed with the goal of maximizing the desired effect on cancer cells while minimizing patient morbidity and thus improving survival and quality of life. Examples of these new techniques include intensity modulated radiation therapy, induction chemotherapy and new drugs that target specific components of cancer cells (targeted therapy). Clinical trials are constantly being conducted to evaluate the utility of promising new therapies.

The prognosis for patients with OSCC varies based on stage and other factors. According to the most recent epidemiologic data available, the overall 5-year survival rate for OSCC is around 60%.¹ This figure varies significantly by race, with only 38% of black males surviving 5 years (compared to 62% for white males).¹ This discrepancy is largely due to the relatively greater proportion of black males who are diagnosed at later stages. The 5-year survival rate for stage I SCCs of the oral cavity varies slightly by location, but is approximately 75%.¹⁸ Only 30-40% of patients diagnosed in stage IV survive 5 years.¹⁸ For oropharyngeal SCCs, tumor HPV status appears to be

an important and independent prognostic factor. Patients with HPV-positive tumors have significantly better survival rates compared to persons with HPV-negative tumors.¹⁹

Summary


Enduring characteristics

- Men remain twice as likely as women to develop OSCC
- Tobacco use is still the single greatest risk factor
- Conventional oral examination remains the standard screening method
- Prognosis depends on the stage but is still poor, owing to the proportion of cancers diagnosed at late stages

Emerging trends

- The incidence of oropharyngeal SCC is increasing, especially among younger, non-smoking patients
- Infection with HPV is a newly identified risk factor and positive prognostic factor for oropharyngeal SCC
- Chronic inflammation appears to influence OSCC by promoting DNA damage and possibly stimulating epithelial to mesenchymal transition for metastasis
- Inflammatory modulators such as IL-8 could serve as future therapeutic targets in the treatment of OSCC

Acknowledgement

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Questions for Continuing Education Article - CE Exam #28

1. Oral cancer is generally divided into two general categories:
 - a. Cancers of the oral cavity
 - b. Oropharynx
 - c. Esophagus
 - d. a. and b.
2. The risk of head and neck squamous cell carcinoma (SCC) for cigarette smokers is estimated to be increased over those who never smoked by:
 - a. There is no measurable difference
 - b. Two-fold
 - c. Fifty-fold
 - d. Ten-fold
3. Of all oral cancers, the percentage of oral squamous cell carcinoma (OSCC) is approximately:
 - a. 100%
 - b. 25%
 - c. 50%
 - d. 94%
4. An important risk factor for OSCC is:
 - a. Excessive alcohol consumption
 - b. High triglycerides
 - c. High cholesterol
 - d. Oral antibiotics
5. An important oncogenic virus in oropharyngeal (SCCs) is:
 - a. Human papilloma virus (HPV)
 - b. Herpes simplex
 - c. Hepatitis c

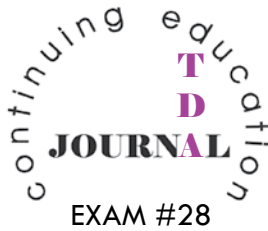
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2.	a	b	c	d
3.	a	b	c	d
4.	a	b	c	d
5.	a	b	c	d

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