Oral Cancer Detection: The Role of Adjunctive Technology

Written by Denis P. Lynch, D.D.S., Ph.D.

Educational Objectives
1. Know the incidence of oral cancer in the United States and understand the risk factors
2. Understand screening methods available for the detection of oral cancer
3. Understand the role of chromosomal aberrations in the risk of malignant transformation

Abstract
In the United States in 2007, over 34,000 new cases of oral cavity and oropharyngeal cancer will be diagnosed. With a five-year relative survival rate estimated at 59.1% overall during 1996–2003. Early detection based on diagnoses of suspicious lesions is increased through regular screening of patients. In recent years, screening technologies have become available that supplement the visual examination. The ultimate goals are to reduce mortality and morbidity, and to improve patients’ quality of life.

Introduction/Overview
In the United States in 2007, over 34,000 new cases of oral cavity and oropharyngeal cancer will be diagnosed. During the same time period, over 7,000 affected individuals will die of these cancers. In the United States, the most common sites for oral cancer are the tongue and lip.

Risk Factors
The single greatest risk factor for oral cancer in the United States is the use of tobacco, with combustible and smokeless tobacco being associated with 75% of all cases of oral cancer. Oral cancer is also six times more likely to develop in alcohol drinkers than in non-drinkers. The combination of tobacco use and alcohol abuse is particularly hazardous, posing a fifteen-fold risk of oral cancer compared to non-users. Other factors associated with increased oral cancer risk include ultraviolet radiation (lip exposure) and HIV seropositivity (Table 1). A strong association has been found with the presence of HPV in oral tissues, independent of smoking or drinking habits. One study of 143 patients found HPV-16, present in 16.8% of head and neck squamous cell carcinomas. A reduced risk of oral cancer has been associated with a high dietary fruit and vegetable intake.
Table 1. Risk factors for oral cancer

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Predisposing risk factors</th>
<th>Negative association</th>
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<tbody>
<tr>
<td>Smoking and/or chewing tobacco</td>
<td>Increasing age</td>
<td>High dietary fruit and vegetable intake</td>
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<tr>
<td>Drinking alcohol</td>
<td>Male gender</td>
<td></td>
</tr>
<tr>
<td>Betel quid chewing</td>
<td>Genetics</td>
<td></td>
</tr>
<tr>
<td>Areca nut use</td>
<td>Socioeconomic status</td>
<td></td>
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<tr>
<td>HPV</td>
<td></td>
<td></td>
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<tr>
<td>HIV seropositivity</td>
<td></td>
<td></td>
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<tr>
<td>Use (abuse) of narcotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sunlight exposure (lower lip)</td>
<td></td>
<td></td>
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<tr>
<td>Previous oral or other cancer</td>
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Morbidity and mortality

Oral cancer is associated with significant morbidity and mortality. The five-year relative survival rate for oral and pharyngeal cancer is estimated at 59.1% overall for cases diagnosed during 1996–2003. Survival rates vary with the stage of the disease and site. The best prognosis exists for lip cancer, with a 97% five-year relative survival rate if the tumor is localized and completely excised. Oral cancers in other anatomic sites can be clinically occult and asymptomatic. Fifty percent of tongue carcinomas have metastasized by the time they are diagnosed. Early diagnosis significantly improves the patient’s long-term survival and reduces morbidity. The excision of an oral cancer, depending on the site and size of the tumor, can severely compromise the patient’s quality of life and in some cases may not even be possible.

Initial lesions

Preventing disease progression relies on early detection, a diagnosis, and appropriate treatment. Early detection of oral cancer is complicated by the fact that many lesions in their earlier stages may be completely asymptomatic.

Clinically, cancerous and pre-cancerous lesions may present as ulcers, leukoplakia, erythroplakia, erythroleukoplakia, soft tissue masses, or other lesions that will not heal even after removal of the presumptive etiology (Figures 1–2).
Leukoplakia, erythroplakia, and erythroleukoplakia (speckled leukoplakia) are clinical terms for white, red, or mixed red/white lesions, respectively, that cannot be wiped off, do not have an obvious clinical diagnosis, and have an unclear etiology. An estimated 85% of oral premalignant and malignant lesions present clinically as leukoplakias and the rate of malignant transformation of leukoplakia is estimated to be 7%, occurring on average seven years following initial diagnosis.

Non-homogenous leukoplakia has been found to have a seven times greater risk of malignant degeneration than homogenous leukoplakia. Lesions greater than 2 cm in size had a 5.4 times greater risk of developing malignancy than smaller lesions. In the case of erythroplakias, 70% to 90% have been found to be severely dysplastic or frankly malignant at the time of initial biopsy. The definitive diagnosis of oral cancer can only be determined by histopathologic examination of a biopsy specimen and ranges from normal, through varying degrees of dysplasia, to carcinoma-in-situ to invasive malignancy.

The detection of suspicious lesions is increased through routine, regular screening of patients. Early detection will result in earlier diagnosis, less aggressive treatment, and decreased need for complicated post-treatment management.

**Early detection and technology**

Historically, unaided visual examination, palpation, and radiographs were available for oral cancer screening. Supplemental screening technologies now available that help the clinician identify suspicious lesions include the use of special wavelength lights and chemiluminescence, as well as dyes that selectively stain lesions. Stand-alone screening devices include the Microlux/DL (AdDent), VELScope (LED Dental, Inc.), and ViziLite and ViziLite Plus (Zila Pharmaceuticals, Inc.).

**Microlux/DL**

Microlux/DL is a hand-held device that uses light-emitting diodes (LEDs) as the illumination source. The patient rinses for 30–60 seconds with 1% acetic acid, and upon illumination the abnormal tissue will appear white ("aceto-white").
**VELScope**
VELScope is a hand-held device that emits a blue light to fluoresce the mucosa. No pre-rinse is required. When exposed to the blue light, normal mucosa emits a pale green autofluorescence, while abnormal tissue appears dark green to black (Figures 3a, b). Highly inflamed mucosa results in a loss of fluorescence which may result in a false positive. The VELScope has been found to help delineate the extent of visible lesions, as well as to identify lesions that were difficult to appreciate with unaided visual examination. In one study, 12 of 19 VELScope-positive lesions were biopsied and found to exhibit loss of heterozygocity.

![Figure 3a. Lesion prior to use of VELScope](image)

![Figure 3b. Appearance following autofluorescence](image)

**ViziLite and ViziLite-Plus**
ViziLite is a hand-held device that emits chemiluminescent light. The patient rinses for 30–60 seconds with 1% acetic acid and the ViziLite device is used to illuminate the oral cavity. Abnormal areas will appear white (“aceto-white”). The light increases both the brightness and the sharpness of lesions.

Chemiluminescence has been found to significantly assist the clinician in identifying white and erythroleukoplakic lesions. In one study of 134 patients, use of ViziLite identified two lesions that were not found by unaided visual examination, one of which was a squamous cell carcinoma of the tongue. Kerr et al. studied 501 patients and ninety-eight lesions found in when ViziLite was used with 77 of these considered suspicious, including six that had been missed with unaided visual examination. The adjunctive use of T-Blue is a feature specific to the ViziLite-Plus system. This is the only FDA-cleared device and in-vivo staining system for the marking and identification of oral lesions. After using the ViziLite to identify abnormal “aceto-white” areas, T-Blue can be used to mark suspicious areas for further evaluation (Figures 4a, b).

![Figure 4a. Lesion prior to use of T-Blue](image)

![Figure 4b. Lesion after use of T-Blue](image)
T-Blue® is the brand name for pharmaceutical-grade tolonium chloride, a toluidine blue dye. Generic toluidine blue is not FDA-cleared for human use.

**Screening protocol**

Early detection of oral cancer and related premalignancy requires an appropriate screening and diagnosis protocol (Figure 5). All oral structures must be thoroughly examined, and any abnormalities should be recorded on a mouth map. If suspicious lesions are found, the lesion must be biopsied or the patient referred to a specialist for further evaluation. It has been recommended that all adult patients 18 and over be screened annually, even if medical and dental histories elicit no risk factors. Known-risk patients should be screened every six months.

Figure 5. Screening and biopsy protocol

**Biopsy protocol**

The two basic biopsy techniques for definitive diagnosis of oral mucosal lesions are incisional biopsy and excisional biopsy. The brush biopsy (CDx) is a less-invasive, preliminary diagnostic tool and may also be useful as an intermittent preliminary diagnostic technique in patients under observation, but is insufficient to provide a definitive diagnosis. Incisional or excisional biopsy is the standard-of-care for definitive diagnosis.
The ability to predict risk of a benign lesion undergoing malignant transformation could help determine the frequency of follow-up and/or earlier intervention.

**Risk differentiation and prediction**

**Dysplasia and risk prediction**
The conventional wisdom is that the more severe a lesion’s dysplasia, the more likely it is that it will undergo malignant transformation. A number of recent studies do not support this presumption.\(^{26,27}\)

While dysplasia can be predictive, that is not always the case. Rosin et al. found that forty-seven percent of leukoplakias classified as having either no dysplasia or mild dysplasia developed into a secondary oral malignancy. Primary tumor stage, grade, and location were not significantly associated with the outcome.\(^{29}\)

**Chromosomal abnormalities and risk prediction**
Recent microscopic studies have investigated loss of heterozygocity (LOH) in tumor cells and its potential role as a risk predictor for malignant transformation. LOH has been found to indicate high risk of transformation or conversion to malignancy. In particular, aberrations in the 3p, 9p, and 17p chromosomal arm sites have been implicated as high-risk predictors.\(^{30,31,32,33,34}\) LOH in multiple chromosome arms, and in particular in 3p and 9p sites, has also been found to be predictive of a secondary malignancy.\(^{35}\)

**Summary**
The importance of routine screening to improve early diagnosis of oral malignancies cannot be overemphasized. It is incumbent upon the clinician to screen all adult patients for oral cancer. Available screening technologies include the use of LED lights, autofluorescence, chemiluminescence, and the combined use of chemiluminescence and T-Blue.\(^{630}\) Recent advances have shown that the risk of malignant transformation is associated with chromosomal aberrations. The ability to identify lesions and to predict which lesions will undergo malignant transformation would facilitate early diagnosis and subsequent disease management.

**References**
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17


Author Profile

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Dr. Lynch received his Doctor of Dental Surgery degree from the University of California at San Francisco in 1976. He subsequently completed a residency in oral and maxillofacial pathology at the University of Alabama at Birmingham, as well as a Ph.D. in Experimental Pathology. Dr. Lynch is currently Professor of Oral and Maxillofacial Pathology and Associate Dean for Academic Affairs at Marquette University School of Dentistry in Milwaukee, as well as Professor of Dermatology at the Medical College of Wisconsin. He is the author of numerous scientific articles and book chapters, as well as the coauthor of The Mouth: Diagnosis and Treatment.

Disclaimer

Dr. Lynch lectures on oral cancer for Zila Pharmaceuticals, Inc.

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1. In the United States, more than _____ new cases of oropharyngeal cancer will be diagnosed in 2007.
   a. 17,000
   b. 26,000
   c. 34,000
   d. 42,000

2. The most common site for oral cancer in patients in the United States is _____.
   a. the tongue
   b. the cheek
   c. the lip
   d. a and c

3. The single greatest risk factor for oral cancer in the United States is _____.
   a. drinking
   b. use of tobacco
   c. use of narcotics
   d. a and c

4. A reduced risk of oral cancer has been associated with a high dietary fruit and vegetable intake.
   a. True
   b. False

5. The overall five-year relative survival rate for oral and oropharyngeal cancer diagnosed between 1996 and 2003 is estimated to be _____.
   a. 51.1%
   b. 59.1%
   c. 62.3%
   d. none of the above

6. Leukoplakia is estimated to _____.
   a. be found in approximately 15% of adults
   b. be the clinical presentation in 85% of oral premalignant and malignant lesions
   c. have a 7% rate of malignant transformation
   d. a and b

7. Non-homogenous leukoplakia has a greater risk of malignant degeneration than homogenous leukoplakia.
   a. True
   b. False

8. The definitive diagnosis of oral cancer can be determined by _____.
   a. brush biopsy
   b. incisional or excisional biopsy
   c. visual and clinical examination
   d. all of the above

9. The detection of suspicious lesions is increased through regular screening.
   a. True
   b. False

10. Stand-alone oral cancer screening devices currently available include _____.
    a. ViziLite Plus
    b. VELScope
    c. Ultrascope
    d. a and b

11. _____ is cleared by the FDA as a stain for the marking of oral lesions.
    a. Toluidine blue
    b. Methylene blue
    c. T-Blue630
    d. all of the above

12. Studies have shown that use of ViziLite aids identification of lesions not found with unaided visual examination.
    a. True
    b. False

13. Adjunctive use of T-Blue630 can _____.
    a. help identify abnormal lesions
    b. stain tissue pink
    c. provide a definitive diagnosis
    d. none of the above

14. If a lesion does not stain with toluidine blue and remains clinically suspicious after two weeks, _____.
    a. it should still be biopsied
    b. it does not need to be biopsied
    c. it should be biopsied if it is still present in six months
    d. none of the above

15. Known-risk patients should be screened more often than patients with no known risk.
    a. True
    b. False

16. A screening protocol should include _____.
    a. a medical and dental history
    b. visual examination
    c. palpation
    d. all of the above

17. Rosin et al. found that _______ of leukoplakias in previously treated sites with either no dysplasia or mild dysplasia developed into a secondary oral malignancy.
    a. 25%
    b. 38%
    c. 47%
    d. 53%

18. Aberrations on certain chromosomal arms have been found to be high-risk predictors of malignant transformation.
    a. True
    b. False

19. The clinician should screen all adult patients for oral cancer.
    a. True
    b. False

20. The ability to predict lesions at high risk of malignant transformation would _____.
    a. facilitate disease management
    b. be relatively unimportant
    c. facilitate early diagnosis
    d. a and c*
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3. Understand the role of chromosomal aberrations in the risk of malignant transformation.

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**Educational Objectives**

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3. Understand the role of chromosomal aberrations in the risk of malignant transformation.

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