MALIGNANT TUMOR OF ORAL CAVITY (EPITHELIAL LAYER)

Oral Squamous Cell Carcinoma (OSCC)

Oral squamous cell carcinoma begins in the squamous cells, which are the cells that line the lips and the inside of the mouth. Symptoms can include sores or a lump in the mouth, a sore throat, and white patches in the mouth.Oral cancer affects the back of the mouth and the throat lining. It may also affect the tongue and the floor of the mouth.

What causes oral squamous cell carcinoma?

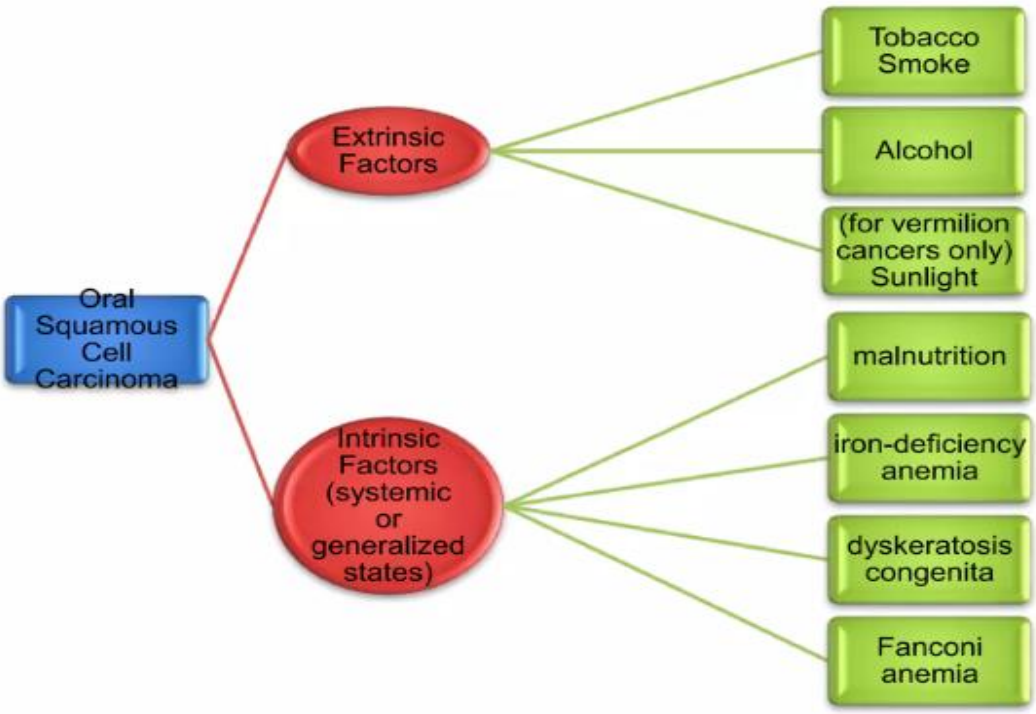
Medical professionals do not fully understandTrusted Source what causes oral squamous cell carcinoma.

However, they do know that cancer typically happens as a result of genetic mutations. The body usually requires changes in a number of different genes for oral squamous cell carcinoma to develop

Etiology

- Multifactorial
- No single causative agent or factor (carcinogen) has been clearly defined or accepted
- more than a single factor is needed to produce such a malignancy (cocarcinogenesis)

Etiology



Etiology and Risk Factors

The incidence of oral cancer is age related, which may reflect time for the accumulation of genetic changes and duration of exposure to initiators and promoters.
These include chemical and physical irritants, viruses, and hormonal effects.
In addition, decreased immunologic surveillance over time may be another explanation for the age relation.
Furthermore, immunosuppressed patients following solid organ and hematopoietic stem cell transplantations, patients treated with chemotherapy, and HIV patients have an increased risk.

Tobacco and Alcohol

Tobacco contains potent carcinogens, including nitrosamines, polycyclic aromatic hydrocarbons, nitrosodiethanolamine, nitrosoproline, and polonium.
Tobacco smoke contains carbon monoxide, thiocyanate, hydrogen cyanide, nicotine, and metabolites of these constituents. Nicotine is a powerful and addictive drug.
Epidemiologic studies have shown that up to 80% of oral cancer patients were smokers.
In addition to the risk of primary cancers, the risk of recurrent and second primary oral cancers is related to continuing smoking after cancer treatment.

The effect of smoking on cancer risk diminishes 5–10 years after quitting.
Most studies have focused on cigarette use; however, other forms of tobacco use have been associated with oral cancers.
Benign hyperkeratosis and epithelial dysplasia have been documented after short-term use of smokeless tobacco products, and it is implied that chronic use will be associated with an increasing incidence of malignant lesions.

Areca Nut and Betel Leaf

People who use betel quid, with or without added tobacco, are at a higher risk for developing oral cancer. In parts of Asia and Southeast Asia (e.g., India, Taiwan), use is historically widespread and accounts for the higher incidence of oral cancer. oral submucous fibrosis of the buccal mucosa and periodontium may develop secondary to alkaloid damage to fibroblasts.

Areca Nut

The resulting fibrosis may cause a decreased intraoral aperture, interfering with speech, swallowing, and oral care, which may lead to an increase in periodontal disease risk.
Submucous fibrosis is considered a premalignant condition and other deleterious health effects including increased risk of non-head and neck primary cancers have been reported.

The combined effects of tobacco and alcohol result in a synergistic effect on the development of oral cancer. The mechanisms by which alcohol and tobacco act synergistically may include

Dehydrating effects of alcohol on the mucosa, increasing mucosal permeability, and the effects of potential carcinogens in alcohol or tobacco.

Various enzymatic pathways were suggested as having a role in the mechanism of the synergistic effect of smoking and alcohol on the oral mucosa.The combined effects of tobacco and alcohol result in a synergistic effect on the development of oral cancer. The mechanisms by which alcohol and tobacco act synergistically may include Dehydrating effects of alcohol on the mucosa, increasing mucosal permeability, and the effects of potential carcinogens in alcohol or tobacco.

Human Papillomavirus

HPVs are DNA viruses that infect various epithelial surfaces. There are more than 120 types of HPV. HPV 16, 18, 31,33, and 35 are considered high-risk subtypes due to their association with malignant tumors. HPV 16 alone is associated with about 90% of HPV-positive oropharyngeal cancers.

The virus penetrates the host cell and integrates into the host cell genome, where it can replicate. Malignant transformation occurs through the expression of two HPV Viral oncogenes, E6 and E7, which downregulate p53 and Rb, two critical cell regulators of cell cycle progression.

Nutritional Factors

Low consumption of fruits and vegetables and high consumption of meat, tobacco, and alcohol is associated with an increased risk of cancer. Foods high in vitamins A, C, E, and selenium have antioxidant protective effects, particularly for epithelial cancers. High abdominal adipose composition combined with low consumption of nutritionally dense foods is a concern for increased cancer rates in Western countries. Some reports have demonstrated that vitamin A may cause regression of premalignant leukoplakia.

Other Risk Factors

There is conflicting evidence on the causality of other risk factors related to oral health, including alcohol-based mouthwashes, poor dental status, denture use, chronic mucosal trauma, and microorganisms. These factors com-
bined with exposure to known carcinogens likely work in a synergistic fashion. In lip cancer, sun exposure, fair skin, pipe smoking, and alcohol are identified risk factors. Recurrent herpes sim-plex virus of the lip has not been associated with increased cancer risk.

Environmental exposure to indoor and outdoor pollution from wood smoke and coal combustion, leading to inhaled toxins such as mercury, lead, sulfur dioxide, nitrogen, and other particulates, is related to numerous deleterious health effects globally.
The IARC has classified air pollution as a carcinogen and it is a leading environmental cause of cancer deaths.
Certain inherited cancer syndromes show an increased risk for oral cancer. For example, patients with Fanconi anemia. Cowden syndrome, xeroderma pigmentosum, and dyskeratosis congenita were reported in association with oral cancer
as well.

Oral Potentially Malignant Disorders

The WHO listed several oral conditions as having the potential to transform into oral cancer, including
lichen planus,
leukoplakia,
discoid lupus erythematosus,
inherited disor-ders,
tobacco-related lesions,
erythroplakia,
actinic cheilitis,
submucous fibrosis.

Under the term “leukoplakia,” it is worthwhile mentioning proliferative verrucous leukoplakia which behaves more aggressively than other leukoplakias and has a high risk of progression to SCC.

Keratotic epithelium with dysplasia has a 3–5 times increased risk of malignant transformation with severe dysplasia.

Clinical and histologic features may help the oral medicine provider stratify risk for malignant progression.
These high-risk factors include large size, nonhomogeneous texture, red or speckled in color, tongue or floor of mouth location, tobacco use, and histologic severe dysplasia.

Pathogenesis

Carcinogenesis is a genetic process that leads to a change in molecular function, cell morphology, and, ultimately, cellular behavior.
Carcinogenesis is not limited to the epithelium but involves a complex epithelial, connective tissue, and immune function interaction.
Major genes involved in OSCC include oncogenes and tumor suppressor genes (TSGs).
Epigenetic changes such as deoxyribonucleic acid (DNA) methylation or histone deacetylation. Extracellular enzymes, cell surface molecules, and immune function play a role in the development and spread of oral cancer; viruses and carcinogens are involved as well.

- Proto-oncogenes may be transformed into activated oncogenes by environmental agents (e.g., viruses, irradiation, and chemical carcinogens) or inherited changes

Oncogenes

Oncogenes may encode for growth factors, growth factor receptors, protein kinases, signal transducers, nuclear phosphoproteins, and transcription factors.
Although proto-oncogenes increase cell growth and effect differentiation and are likely involved in carcinogenesis,.
Proto-oncogenes associated with HNSCC include ras (rat sarcoma), cyclins, myc (myelocytomatosis), erb-b (erythroblastosis), bcl (B-cell lymPhoma)

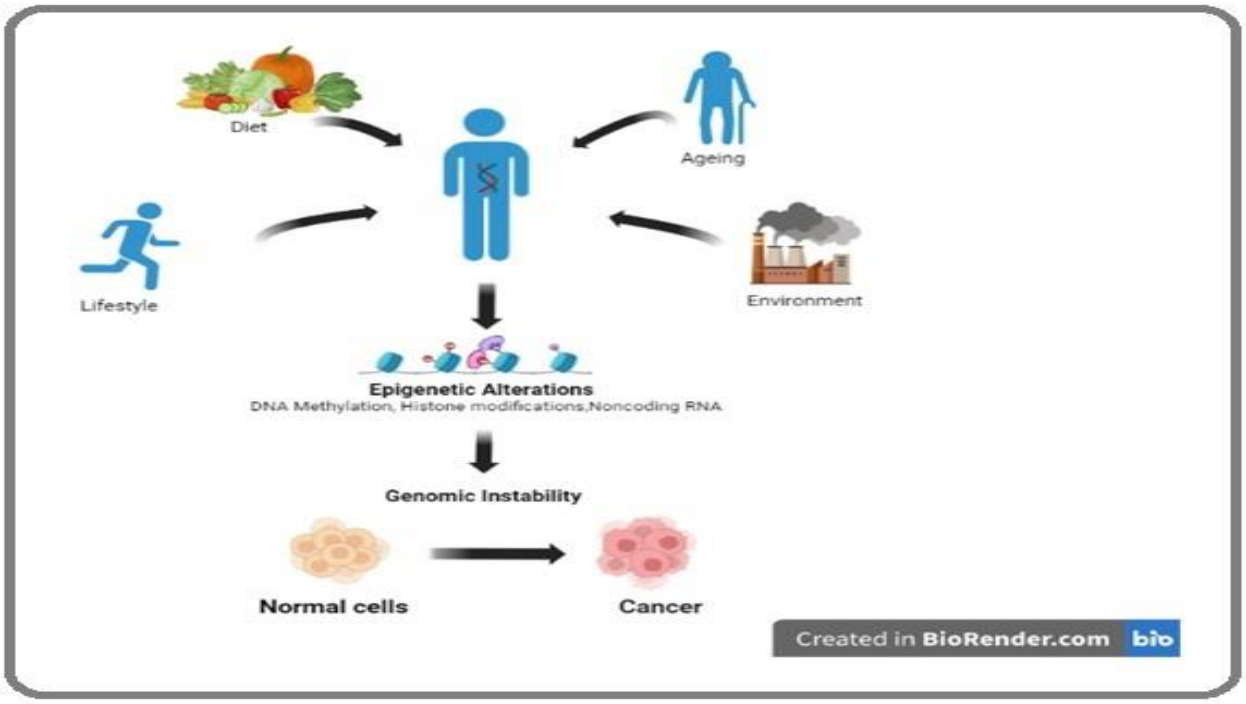
Each of these oncogene families has several genes and isoforms with potential roles in carcinogenesis. For example, the ras family has three genes (Hras, Kras, Nras) and represents one of the most mutated oncogenes in human cancer, including oral cancer.

Tumor Suppressor Genes

TSGs negatively regulate cell growth and differentiation. Functional loss of TSGs is common in carcinogenesis and in OSCC. Both copies of a TSG must be inactivated or lost for loss of function (the "two-hit" hypothesis).
TSGs have been associated
TSGs involved in HNSCC are P53, Rb (retinoblastoma), and p16INK4A

Gene-Regulating Proteins

Part of the oncogenic gene regulation is performed by transcription factors. These are proteins binding to DNA sequences to permit or inhibit co-binding to RNA polymerase, which in turn regulates the activation of the DNA-segment respective gene. Transcription factors that were identified from oral tumors and their potential contribution to oral cancer



Hypermethylation

The role of promoter hypermethylation of CpG islands is being investigated in OSCC, as methylation of epigenetic DNA has been shown to result in a loss of function in some genes involved in cell cycle regulation and DNA repair that may lead to loss or change in TSGs involved in carcinogenesis. Changes in DNA methylation of six genes and a significantly higher frequency of methylation in a number of TSGs, including cyclin A1 and p16 promoter sequences, have been seen

Immunosuppression

The development of malignant disease at a higher rate in immunosuppressed patients indicates the importance of an intact immune response

Mononuclear cell infiltration correlates with prognosis, and more aggressive disease is
associated with limited inflammatory response. Total numbers of T cells may be decreased in patients with head and neck cancer.
Clusters of differentiation 8 (CD8) lymphocytes (T-suppressor cells) predominate tumor infiltrates, suggesting that immunosuppression

is associated with progression of disease.
Programmed cell death-1 (PD-1) is currently the target of many cancer immunotherapy agents aimed at interference with specific
immune checkpoints.

Oncoviruses
An estimated 12% of cancers can be caused by an oncovirus, including Epstein–Barr virus (EBV), HPV, human T-cell lymphotropic virus-1 (HTLV-1, hepatitis B and C viruses (HBV and HCV), and Kaposi sarcoma (KS) herpesvirus (HHV8).
HPV is the most critical oncovirus in the pathogenesis of head and neck cancer
OSCC have been associated with high-risk HPV, showing a
. The most common HPV subtypes detected in OPC are HPV 16 and 18 (68% and 34%, respectively).

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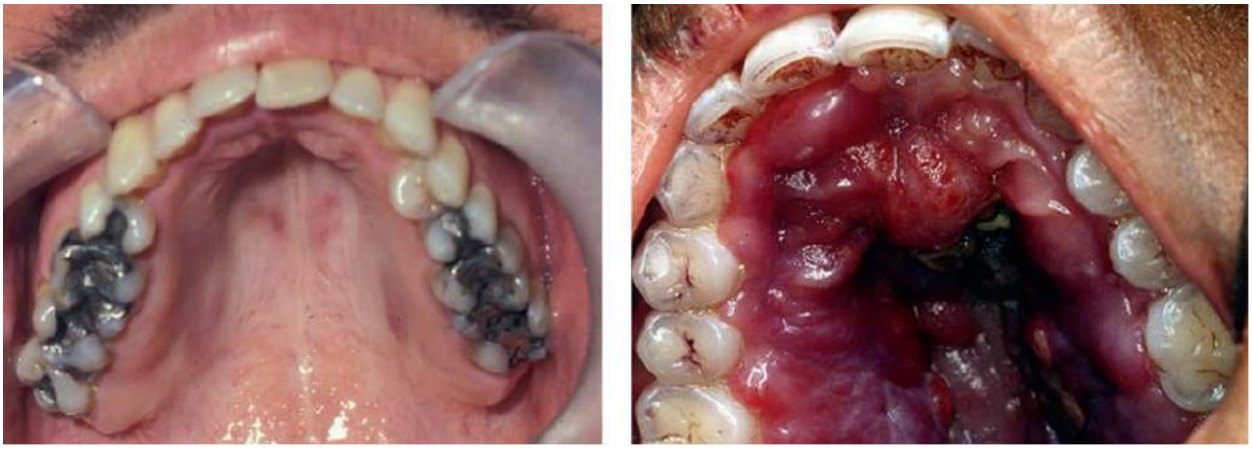
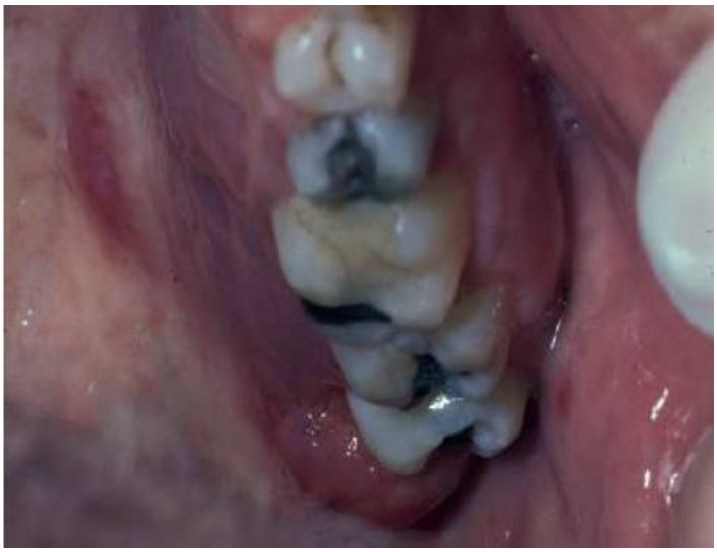
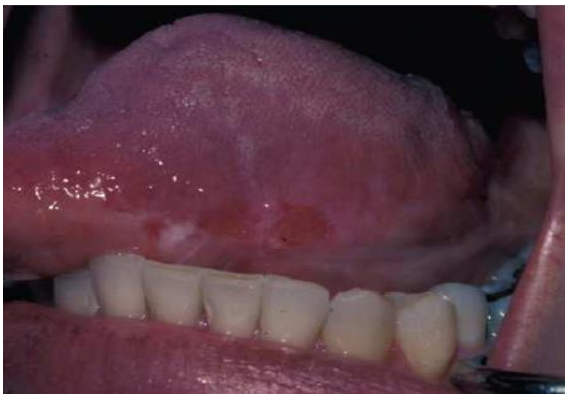
EBV and HHV8 are of particular importance to understanding head and neck cancer.
EBV infection is noted in malignant transformation of nasopharynx and specific salivary gland cancers.
KS continues to impact immunosuppressed individuals
and can occur in the oral cavity. (Figures 7-2 and 7-3)



Bilateral involvement of the anterior and posterior hard palate with purple discolorations consistent with Kaposi sarcoma



Gingival involvement by Kaposi sarcoma, with discoloration and enlargement and soft tissue mass on the maxillary tuberosity.



Irregular erythroleukoplakia of the left lateral border of the tongue.

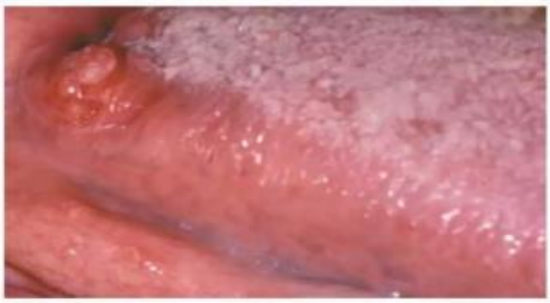
PRESENTING SIGNS AND SYMPTOMS

Discomfort is the most common symptom that leads a patient to seek care and may be present at the time of diagnosis in oral cavity tumors. However, oropharynx cancers often present with an awareness of a mass in the neck.
Dysphagia, odynophagia, otalgia, limited movement, oral bleeding, neck masses, and weight loss may occur with advanced disease.
Paresthesia or dysesthesia, especially when it is unilateral, is a red flag that may indicate neural involvement and requires that cancer be ruled out.
Loss of function involving the tongue can affect speech, swallowing, and diet.

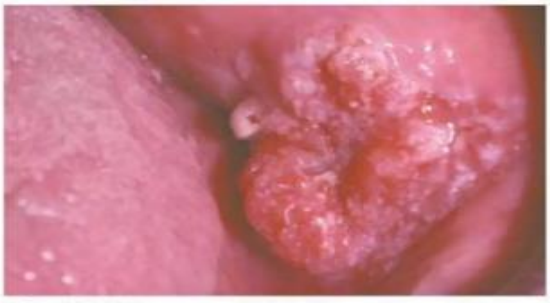
Possible tissue changes may include a red, white, or mixed red and white lesion; a change in the surface texture producing a smooth, granular, rough, or crusted lesion; or the presence of a mass or ulceration.
The lesion may be flat or elevated and may be minimally palpable or indurated. The high-risk sites for oral carcinoma include the lower lip, the anterior floor of the mouth, and the lateral borders of the tongue.
The clinical presentation may take a different shape in verrucous carcinoma, a subtype of OSCC with characteristic clinical findings

. It can be described clinically as grainy, papillary, verruciform, fungating, or cauliflower-like.
Verrucous carcinoma may develop from the progression of proliferative

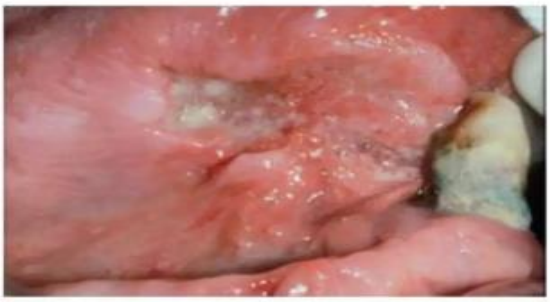
verrucous leukoplakia and develop into carcinoma.
Lymphatic spread of oral carcinoma most commonly involves the submandibular and digastric nodes and the upper cervical nodes, and can involve the remaining nodes of the cervical chain.
The nodes most commonly involved are those that are ipsilateral to the primary tumor, although the closer the tumor is to the midline and the more posterior in the oral cavity or oropharynx, the more common is the involvement of the bilateral and contralateral nodes.



• **Fig. 10-99 Squamous Cell Carcinoma.** An exophytic lesion of the posterior lateral tongue demonstrates surface nodularity and minimal surface keratin production. It is painless and indurated.



• **Fig. 10-100 Squamous Cell Carcinoma.** An exophytic buccal lesion shows a roughened and irregular surface with areas of erythema admixed with small areas of white keratosis. Surface ulceration is evident.



• **Fig. 10-101 Squamous Cell Carcinoma.** Chronic ulcerated lesion on the right ventral surface of the tongue. The rolled anterior margin felt indurated on palpation.

Clinical Features

- An exophytic lesion - surface that is irregular, fungating, papillary, or verruciform
- color - normal to white or red (depending on the amount of keratin and vascularity)
- surface is often ulcerated
- feels hard (indurated) on palpation

Lymph nodes associated with cancer become enlarged and firm to hard in texture, and with progression may become fixed.
The fixation of nodes to adjacent tissue due to invasion of cells through the capsule is a late occurrence and evidence of aggressive disease

The fixation of the primary tumor to adjacent tissue overlying bone suggests the involvement of the periosteum and possible spread to bone.
Nodes are not tender unless they are associated with secondary infection or an inflammatory response is present, which may occur after a biopsy.
Spread of tumor is critical for prognosis and for selection of treatment.

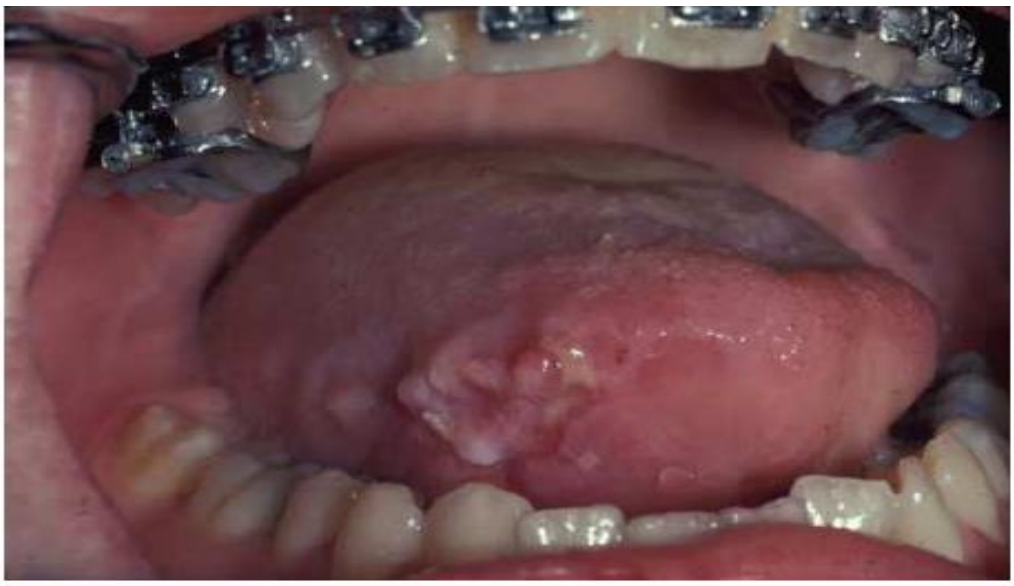


Figure 7-6 Indurated and ulcerated lesion of the right anterior tongue in a 15-year-old girl, persisting after removal of orthodontic appliances, proven to be squamous cell carcinoma on biopsy.

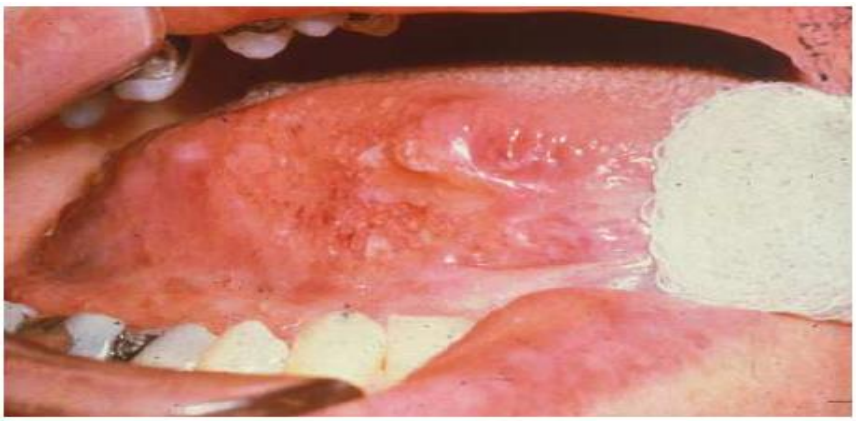
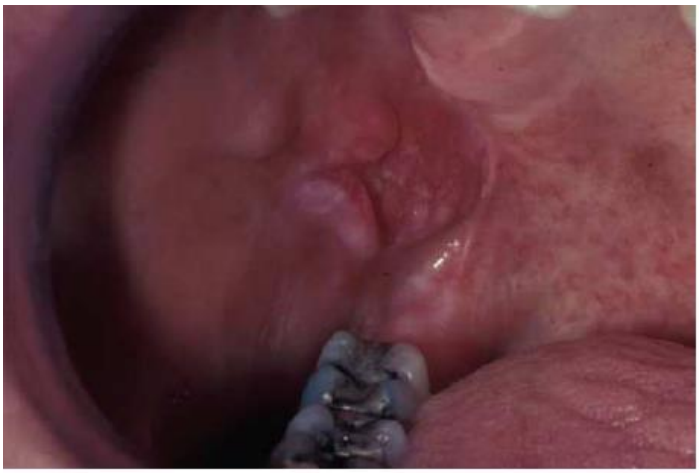


Figure 7-8 Eroded, erythroleukoplakic, indurated lesion in the right posterior third of the lateral border of the tongue, diagnosed as squamous cell carcinoma.



Nonpainful, irregular indurated exophytic and ulcerated buccal mass; histopathology revealed squamous cell carcinoma.

DIAGNOSIS AND HISTOPATHOLOGY

Diagnosis is primarily based on histopathology. Within the epithelial tumors, SCC is the most prevalent oral malignancy.
It has several subtypes based on histopathology. Some of the variants may have a unique clinical presentation.
For the diagnosis of OSCC, dysplasia involves the full thickness of the epithelium and the basement membrane is violated.

. Well-differentiated carcinoma retains some anatomic features of epithelial cells, including their ability to produce keratin,
whereas poorly differentiated carcinoma involves a loss of the anatomic pattern and function of epithelium.

Histologically, verrucous carcinoma is characterized by piling up of keratin on the surface, with downgrowth of club-shaped fingers of hyperplastic epithelium with a pushing front rather than infiltration into the connective tissue.
Dysplasia may be mild. Usually, a dense infiltrate of lymphocytes and plasma cells is present.
Verrucous carcinoma rarely spreads to lymph nodes and typically remains locally destructive.
The difficulty in diagnosis and treatment is due to a benign histology or mild dysplastic changes that may be seen despite progressive and recurrent disease.

While histopathology is the gold standard in diagnosis, it is a subjective assessment of tissue, with inter- and intrarater variability. However, phenotypic changes appear following molecular change, and it is expected that as molecular markers become defined, they will provide additional information and may ultimately become the gold standard in diagnosis.

Staging and Grading of Oral Cancer: Tumor–Nodes–Metastasis System **(TNM)**
The American Joint Committee on Cancer (AJCC) Tumor–Nodes–Metastasis (TNM) staging system is the most widely used system for clinical and pathologic staging of cancer.
Staging reflects prognosis, and is therefore a determinant of treatment strategy..

TNM Staging

Tx	no available information on primary tumour
T0	no evidence of primary tumour
TIS	only carcinoma *in-situ on primary sites*
T1	<2 cm
T2	2 to 4 cm
T3	>4 cm
T4	>4 cm, involvement of natrum, pterygoid muscles, base of tongue or skin

Mx	Not assessed
M0	No evidence
M1	Distant metastasis present

Nx	Cannot be assessed
N0	No clinical positive nodes
N1	Single, ipsilateral, <3 cm
N2a	Single, ipsilateral, 3-6 cm
N2b	Multiple, ipsilateral, <6 cm
N3	Massive ipsilateral/bilateral/contralateral
N3a	Ipsilateral node(s), one more than 6 cm
N3b	bilateral
N3c	contralateral

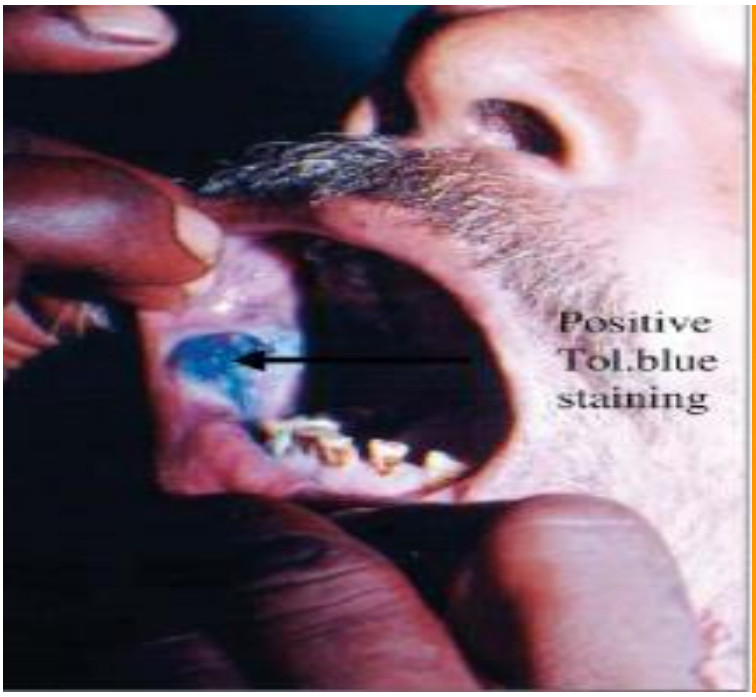
Adjunctive Diagnostic Aids and Screening Tools

Early detection of potentially malignant and malignant lesions is associated with improved treatment outcomes and a reduction in morbidity of treatment.
Patient history and thorough head and neck and intraoral examinations are prerequisites. The definitive test for diagnosis remains tissue biopsy.
Several aids to the oral examination were suggested in the past, including light technologies, vital tissue staining using toluidine blue (TB), and computer-assisted cytology of oral brush biopsy specimens.
Additional markers based on blood and saliva samples are under investigation for use in early detection, diagnosis, and surveillance for recurrence.
That these techniques are adjunctive aids for screening and tools for early detection and are not a replacement for surgical tissue sample collection and histopathologic diagnosis.

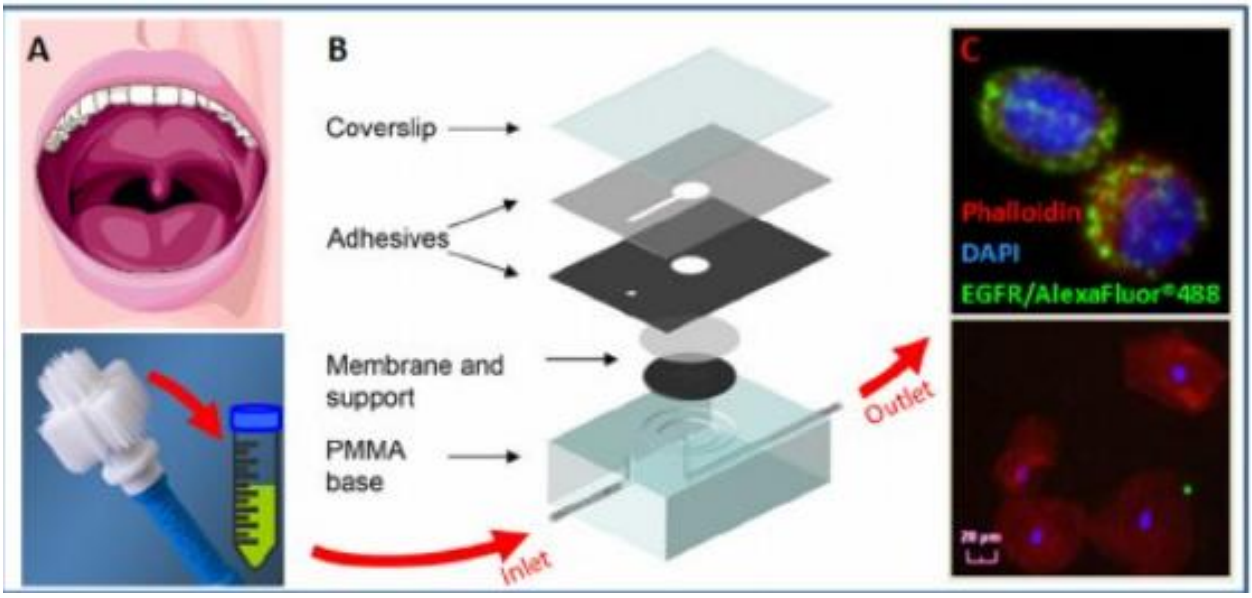
Vital Tissue Staining with Toluidine Blue

Vital staining with TB may be used as an adjunctive aid in the assessment of potentially malignant oral mucosal lesions.
TB is a basic thiazine metachromatic dye with high affinity for acidic tissue components, thereby staining tissues rich in DNA and RNA.

TB can be applied directly to suspicious lesions or used as an oral rinse.
The assessment of dye uptake depends on clinical judgment and experience . Positive retention of TB, particularly in areas of leukoplakia, erythroplakia, and uptake in a peripheral pattern of an ulcer, may indicate the need for biopsy or assist in identifying the site of biopsy.
False-positive dye retention may occur in inflammatory and ulcerative lesions, but false-negative retention is uncommon.



cytopathology
Brush cytology, such as the OralCDx® system (OralScan Laboratories, Suffern, NY, USA), combines the cytobrush with a computer-assisted analysis of the cytologic sample, assessing the cell morphology and keratinization. The final diagnosis is made
by an examining pathologist on the basis of standard histomorphologic criteria.
Further developments in cytology include
molecular evaluation of exfoliated cells for molecular markers of dysplasia or carcinoma to improve the diagnostic and prognostic value.



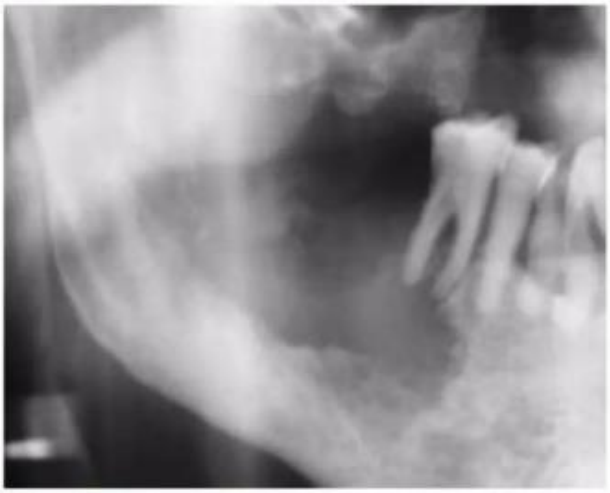
Clinical Features

D/D of endophytic growth pattern :

- Traumatic granulomas,
- deep fungal infections,
- tuberculosis,
- tertiary syphilis, and
- oral lesions of Wegener granulomatosis or Crohn's disease

Radiological Features

- Destruction of underlying bone appears on radiographs as a "moth-eaten" radiolucency with ill-defined or ragged margins (an appearance similar to osteomyelitis)



• **Fig. 10-103 Squamous Cell Carcinoma.** Bone involvement is characterized by an irregular, "moth-eaten" radiolucency with ragged margins—an appearance similar to that of osteomyelitis.