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Estd. 1999
Vadodara
SUMANDEEP VIDYAPEETH
Deemed to be University

BDS Year 4 Regular batch
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Subject: Oral Medicine and Radiology
Topic: Oral cancer- I

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विद्या विनयेन शोभते

LECTURE CONTENT

- Introduction
- Epidemiology
- Classification
- Etiological factors and pathogenesis
- Clinical features
- Investigations
- MCQS

INTRODUCTION

- Oral cancer is a broad term that includes various malignant diagnoses that present in the oral tissues.
- It is traditionally defined as a squamous cell carcinoma (OSCC), because 90% of cancers are histologically originated in the squamous cells.
- It has different levels of differentiation and a propensity for lymph node metastasis.

EPIDEMIOLOGY

- Sixth most common cancer Worldwide.
- Cancer of the oral cavity and pharynx affects 10.8 of every 100,000 individuals in the United States, based on the National Cancer Institute data, and 7.2 of every 100,000 individuals will have cancer in oral cancer.
- Based on the data from Surveillance, Epidemiology, and End Results program for 2003 to 2009 the 5-year survival in the United States was 62.2%.
- In India, the incidence of oral cancer for males and females was highest in the central region of India. For males, it was 64.8% and for females it was 37.2% at 70 years of age.
- The next highest magnitude was observed in west and northeast regions (58.4%) at 60 years of age.

EPIDEMIOLOGY

- The majority of oral cancers are squamous cell cancers
- Majority of oral cancers involve the lateral borders and base of the tongue. The lips, gingiva, dorsal tongue, palate, and salivary glands are less common sites.

WHO Classification of Oral Cancer

- Epithelial cancer
  - Squamous cell carcinoma
    - Verrucous carcinoma
    - Basaloid squamous cell carcinoma
    - Papillary squamous cell carcinoma
    - Spindle cell carcinoma (sarcomatoid SCC)
    - Acantholytic squamous cell carcinoma
    - Adenosquamous carcinoma
    - Carcinoma cuniculatum
  - Lymphoepithelial carcinoma
- Salivary gland cancer
  - Salivary gland carcinoma
    - Acinic cell carcinoma
    - Mucoepidermoid carcinoma
    - Adenoid cystic carcinoma
    - Polymorphous low-grade adenocarcinoma
    - Basal cell adenocarcinoma
    - Epithelial-myoepithelial carcinoma
    - Clear cell carcinoma, NOS
    - Cystadenocarcinoma
    - Mucinous adenocarcinoma
    - Oncocytic carcinoma
    - Salivary duct carcinoma
    - Myoepithelial carcinoma
    - Carcinoma ex pleomorphic adenoma
  - Salivary gland adenomas[a]

WHO Classification of Oral Cancer

Soft tissue cancer[b]
Kaposi sarcoma
Hematolymphoid cancer
Diffuse large B-cell lymphoma
Mantle cell lymphoma
Follicular lymphoma
Extranodal marginal zone B-cell lymphoma of MALT type
Burkitt lymphoma
T-cell lymphoma
Extramedullary plasmacytoma
Langerhans cell hystiocytosis
Extramedullary myeloid sarcoma
Follicular dendritic cell sarcoma
Secondary tumors

TABLE 8-2 WHO Classification of Odontogenic Cancer[24]
Odontogenic carcinomas
Metastasizing (malignant) ameloblastoma
Ameloblastic carcinoma—primary type
Ameloblastic carcinoma—secondary type (dedifferentiated), intraosseous
Ameloblastic carcinoma—secondary type (dedifferentiated), peripheral
Primary intraosseous squamous cell carcinoma—solid type
Primary intraosseous squamous cell carcinoma derived from keratocystic odontogenic tumor
Primary intraosseous squamous cell carcinoma derived from odontogenic cysts
Clear cell odontogenic carcinoma
Ghost cell odontogenic carcinoma
Odontogenic sarcomas
Ameloblastoma fibrosarcoma
Ameloblastic fibrodentino- and fibro-odontosarcoma
Other tumors
Melanotic neuroectodermal tumor of infancy

SQUAMOUS CELL CARCINOMA OF THE ORAL CAVITY AND OROPHARYNX

Etiology and risk factors

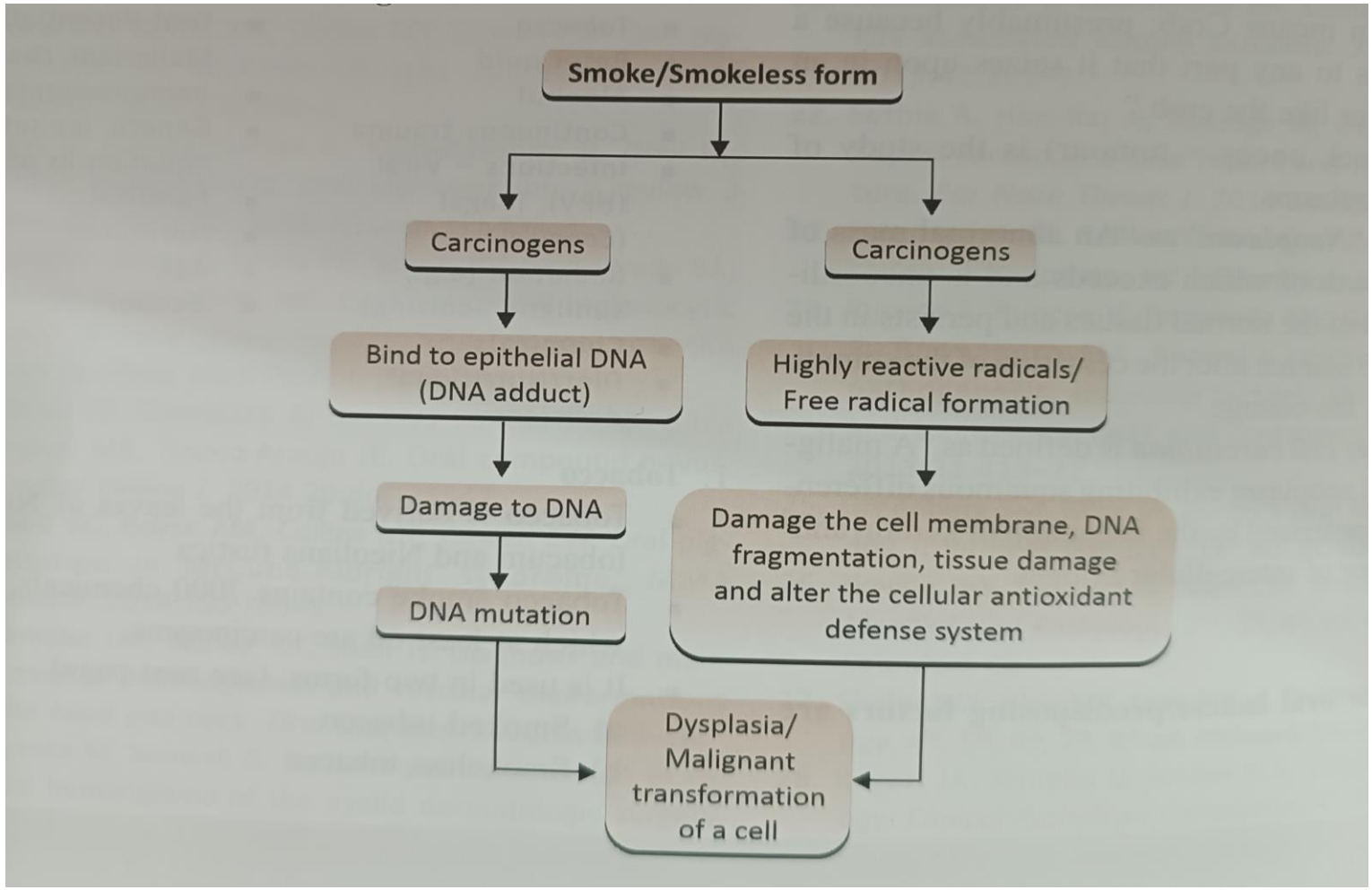
Tobacco Areca Nut and Betel Leaf Alcohol Trauma Infections – viral (HPV), fungal (candida) Radiation Chemicals Nutritional Factors	Oral potentially malignant Disorders Immunosuppression Gene mutation Hormonal Age Gender

Tobacco

Form of tobacco	Constituents	Risk
Tobacco (Smokeless)	**Nitrosamines**, Polycyclic aromatic hydrocarbons Nitrosodiethanolamine Nitrosoproline Polonium	**Short term**-Benign hyperkeratosis and epithelial dysplasia **Chronic use**-risk of malignant lesions
Tobacco (smoke)	Carbon monoxide Thiocyanate Hydrogen cyanide Nicotine	80%- primary oral cancer Risk of recurrent and second primary oral cancer

- Nicotine is a powerful and addicting drug.

Mechanism of Tobacco Chewing



Areca Nut and Betel Leaf

- With or without added tobacco, are at a higher risk to develop oral cancer.
- In parts of Asia (e.g., India, Taiwan)--(betel nut + lime) the incidence of oral cancer is high
- More commonly involves the buccal mucosa.
- Gutkha and pan masala- are potential carcinogenic as well

a) *Damage of DNA by areca nut alkaloids*

Nitrosation of areca nut alkaloids

↓

Leads to the formation of areca nut specific nitrosamine (Namely nitrosoguvacoline, nitrosoguvacine & 3-methyl nitrosominopropionitrile)

↓

Metabolism of these areca nut specific nitrosamines lead to formation of cyanoethyl, which binds with o-methyl-guanine in DNA

↓

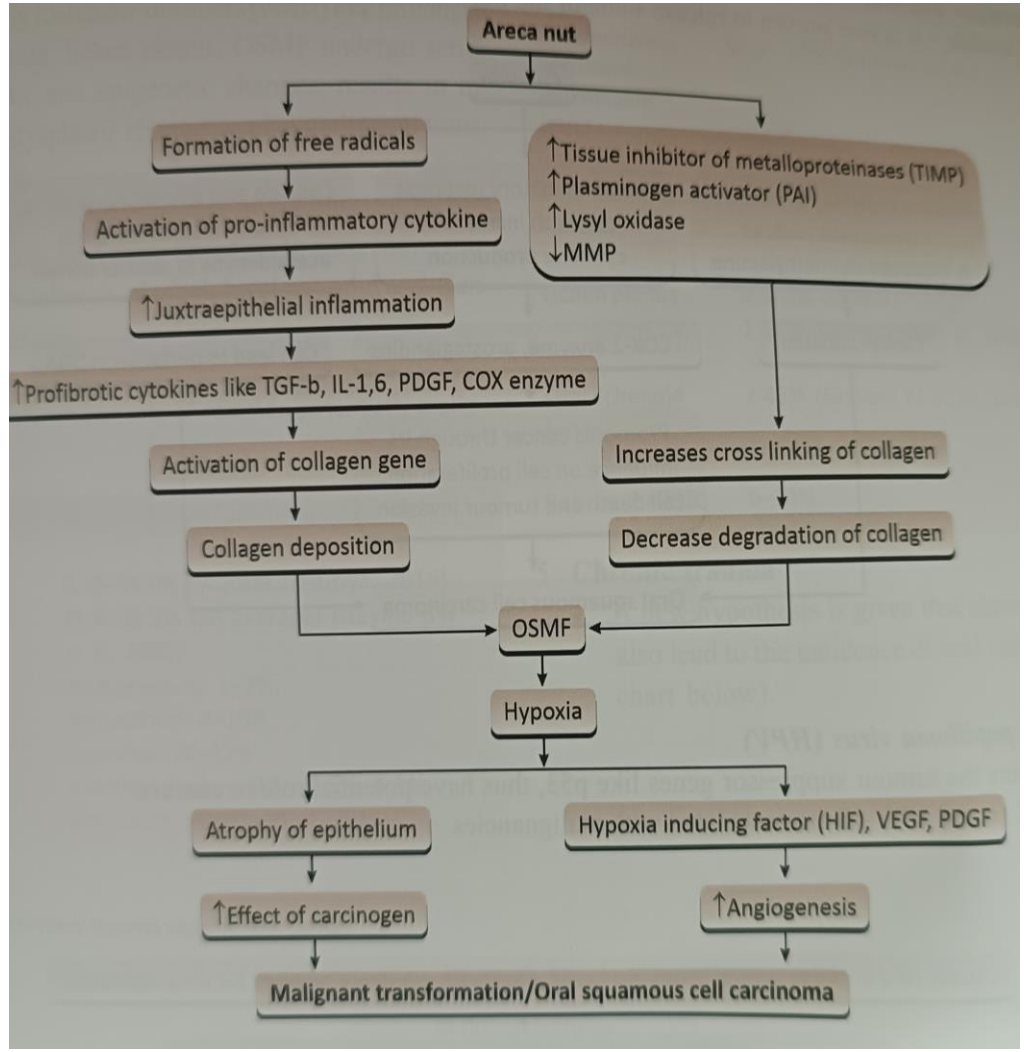
This leads to DNA damage and tumour induction

↓

Prolonged exposure to this irritant leads to malignant transformation

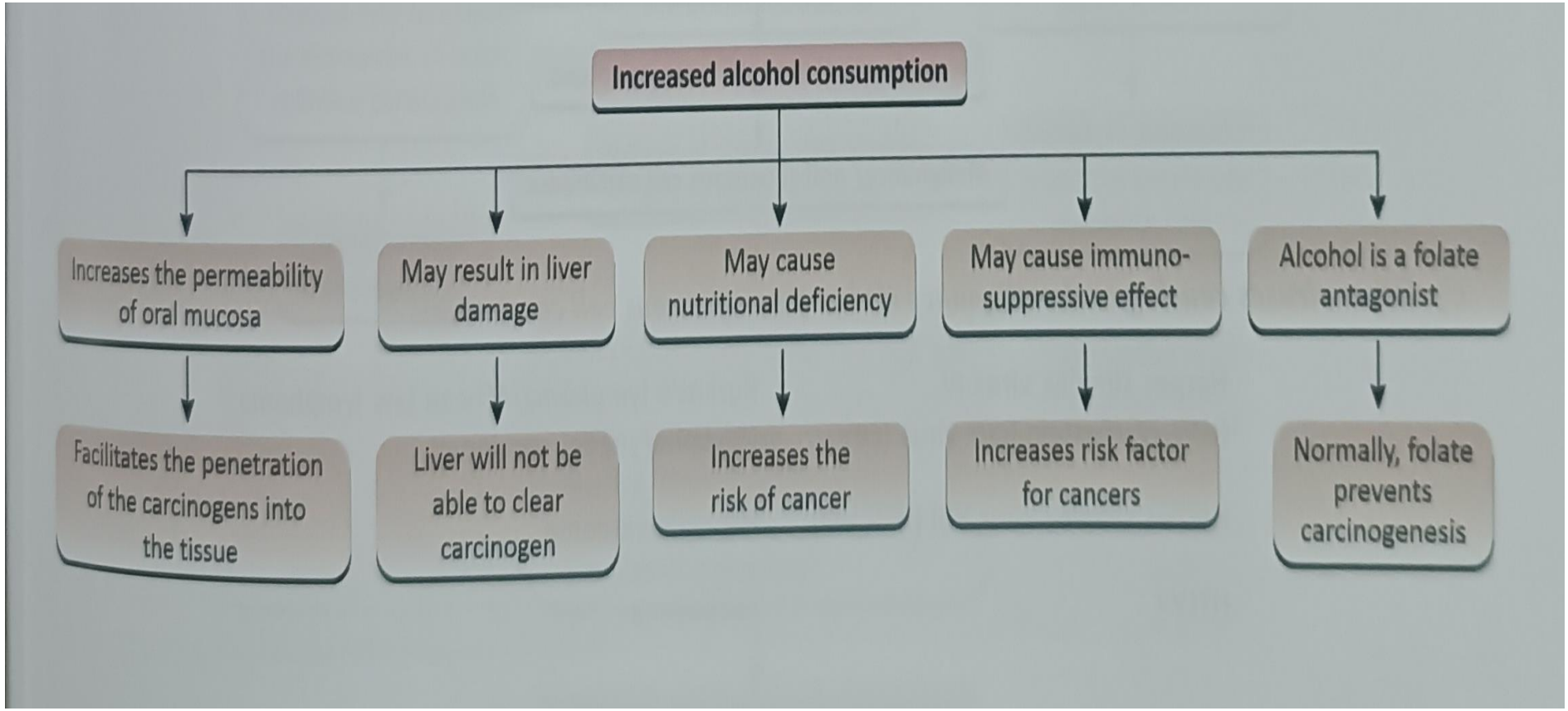
↓

Additionally, its genotoxic (tumour suppressor genes) and mutagenic effects leads to malignant transformation

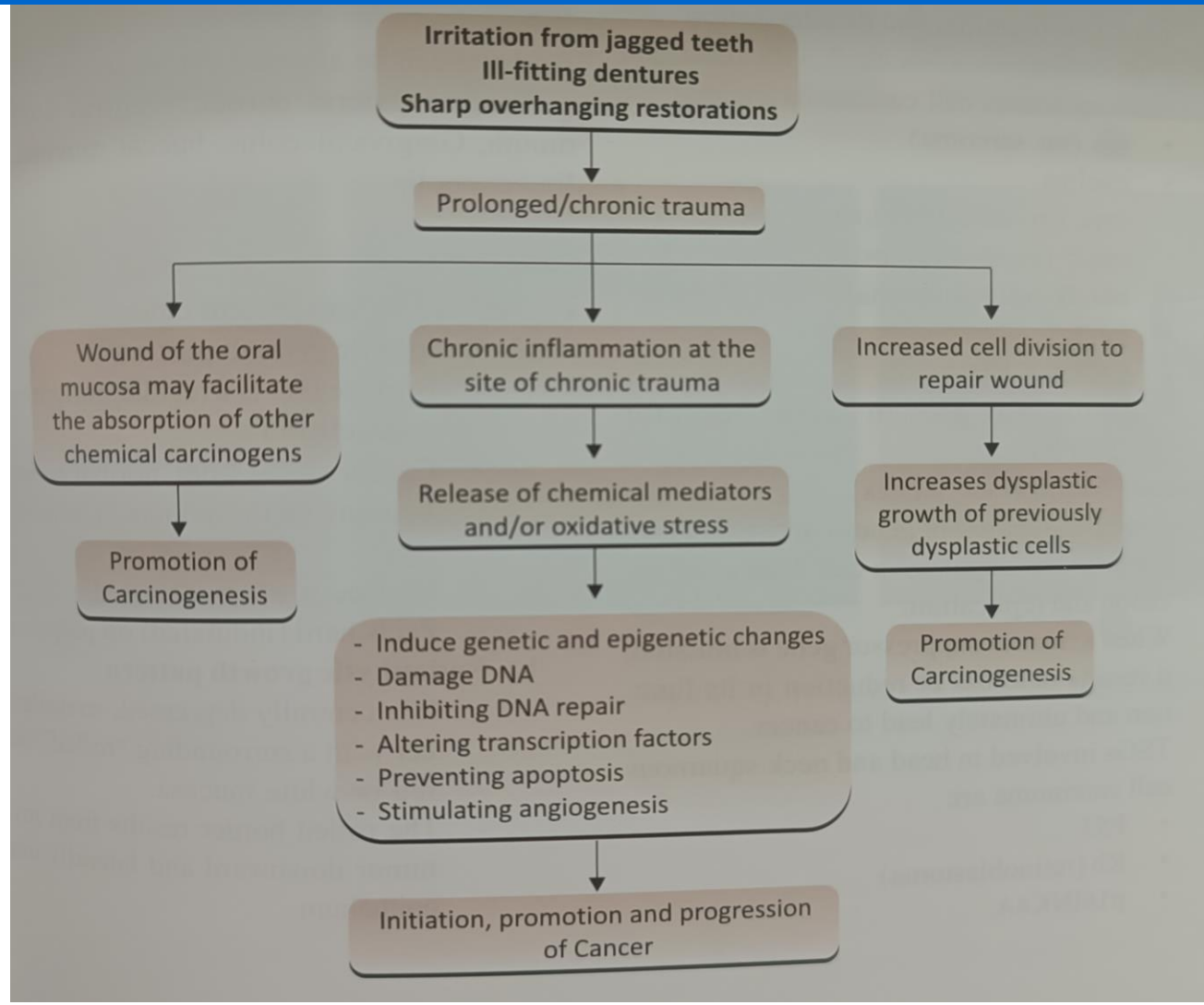


Alcohol

- Hard liquor and wine
- The combined effects of tobacco and alcohol-synergistic effect on the development of oral cancer.
- Mechanism: Alcohol is shown to increase the permeability of oral mucosa producing an alteration in morphology characterized by epithelial atrophy, which in turn leads to easier penetration of carcinogens into the oral mucosa
- Smoking and alcohol interaction may influence central nervous system activity

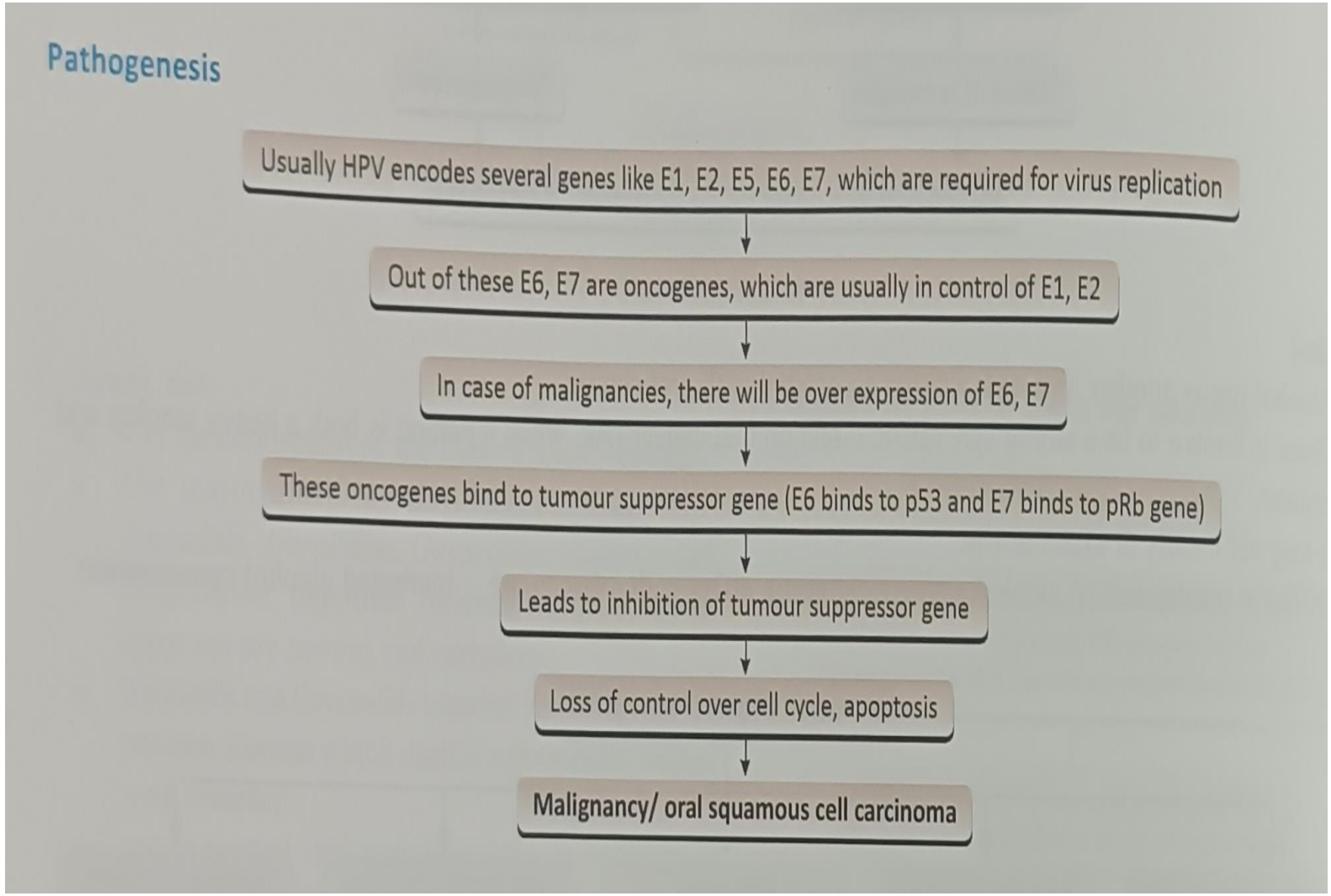

Increased alcohol consumption
Increases the permeability of oral mucosa
Facilitates the penetration of the carcinogens into the tissue
May result in liver damage
Liver will not be able to clear carcinogen
May cause nutritional deficiency
Increases the risk of cancer
May cause immuno-suppressive effect
Increases risk factor for cancers
Alcohol is a folate antagonist
Normally, folate prevents carcinogenesis

Trauma



Infections

- **Viruses**
- HPV are the most common viruses implicated in oral carcinogenesis.
- High-risk HPV types - 16, 18, 31,33, 35, and 39- associated with OSCC and oral premalignant lesions.
- HPV encodes two major oncoproteins - E6 and E7.
- HPV-16 and -18 --malignant tumors.
- HPV-16 alone is associated with about 85% to 95% of HPV-positive OPCs

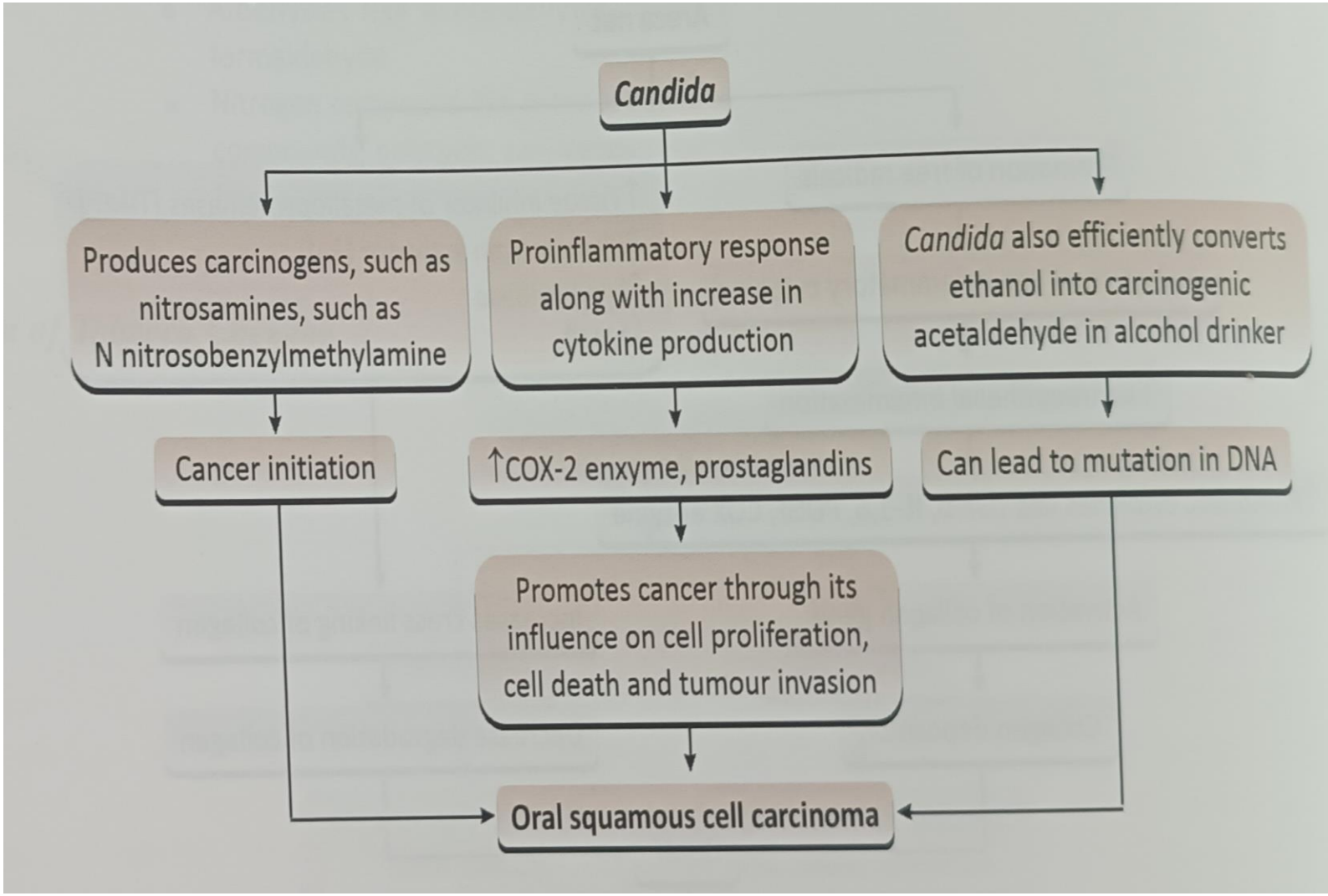

Pathogenesis
Usually HPV encodes several genes like E1, E2, E5, E6, E7, which are required for virus replication
Out of these E6, E7 are oncogenes, which are usually in control of E1, E2
In case of malignancies, there will be over expression of E6, E7
These oncogenes bind to tumour suppressor gene (E6 binds to p53 and E7 binds to pRb gene)
Leads to inhibition of tumour suppressor gene
Loss of control over cell cycle, apoptosis
Malignancy/ oral squamous cell carcinoma

Evidence

Authors	Schwartz SM, Daling JR, Doody DR, Wipf GC, Carter JJ, Madeleine MM, Mao EJ, Fitzgibbons ED, Huang S, Beckmann AM, McDougall JK, Galloway DA.
Title	**Oral cancer risk in relation to sexual history and evidence of human papillomavirus infection.** J Natl Cancer Inst. 1998 Nov 4;90(21):1626-36. CEBM 3a
Aim	Population-based, case-control study to determine whether the risk of this cancer is related to HPV infection and sexual history factors.
Results	Among males only, oral SCC risk increased with self-reported decreasing age at first intercourse, increasing number of sex partners, and a history of genital warts. Approximately 26% of the tumors in case subjects contained HPV DNA; 16.5% of the tumors contained HPV type 16 DNA. The prevalence of oncogenic HPV types in exfoliated oral tissue was similar in case and control subjects.
Interpretation	HPV type 16 infection may contribute to the development of a small proportion of oral SCCs in this population, most likely in combination with cigarette smoking.

Infection

- Candida albicans has been implicated in the pathogenesis of oral premalignant lesions.
- Superficial fungal hyphae of Candida albicans have been found superimposed on leukoplakia, especially nodular leukoplakia, many of which have undergone malignant transformation.
- Besides immunocompromised individuals, Candida infection can coexist or be associated with other risk factors like iron deficiency and in chronic smokers which may prove synergistic in the development of oral cancer.
- There is evidence that Candida possesses necessary enzymes from dietary substances to produce nitrosamines and chemicals that have been implicated in carcinogenesis.


Candida
Produces carcinogens, such as nitrosamines, such as N nitrosobenzylmethylamine
Proinflammatory response along with increase in cytokine production
Candida also efficiently converts ethanol into carcinogenic acetaldehyde in alcohol drinker
Cancer initiation
↑COX-2 enxyme, prostaglandins
Can lead to mutation in DNA
Promotes cancer through its influence on cell proliferation, cell death and tumour invasion
Oral squamous cell carcinoma

Nutritional factors

- Consumption of fruits and vegetables is associated with a reduced risk for oral cancer.
- Diets high in eggs and butter and meats-Elevated but inconsistent risk of oral cancer
- Vitamins A ,C and E; carotenoids (β-carotene); potassium, lycopene, selenium-decrease the risk of oral cancer development
- Vitamin D deficiency - associated with oral cancer

Oral Potentially malignant Disorders

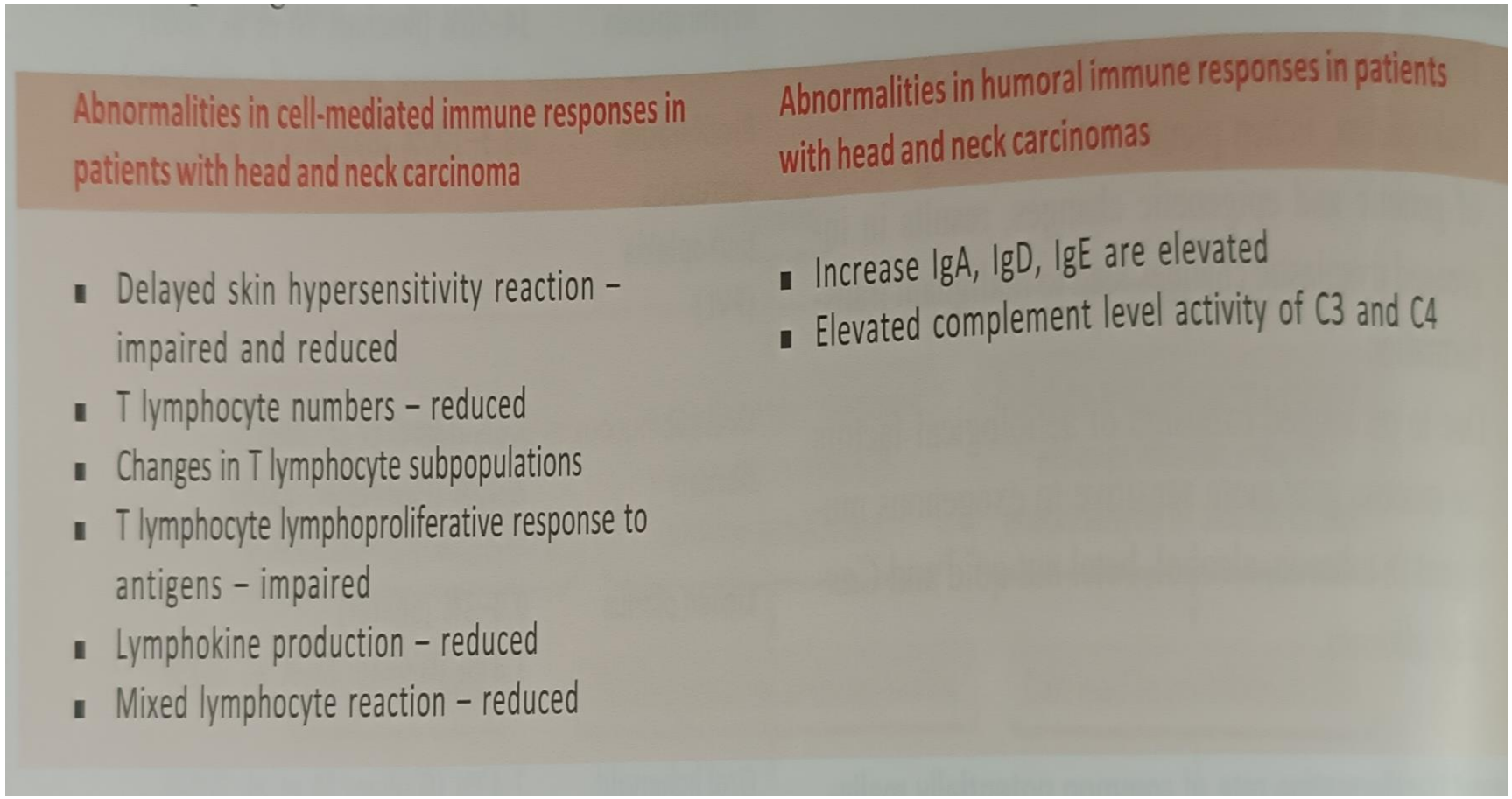
- WHO listed several oral conditions as having the potential to transform into oral cancer, including

- Lichen planus
- Leukoplakia
- Discoid lupus erythematosus
- Inherited disorders
- Tobacco-related lesions
- Erythroplakia
- Actinic cheilitis

Immunosuppression

- HIV infected - Kaposi's sarcoma and lymphomas.
- Immunosuppressed organ transplant -lip cancers
- Due to increased exposure to solar radiation and other risk factors such as smoking.

Immunopathogenesis of oral cancer



Abnormalities in cell-mediated immune responses in patients with head and neck carcinoma

- Delayed skin hypersensitivity reaction – impaired and reduced
- T lymphocyte numbers – reduced
- Changes in T lymphocyte subpopulations
- T lymphocyte lymphoproliferative response to antigens – impaired
- Lymphokine production – reduced
- Mixed lymphocyte reaction – reduced

Abnormalities in humoral immune responses in patients with head and neck carcinomas

- Increase IgA, IgD, IgE are elevated
- Elevated complement level activity of C3 and C4

Genetic pathogenesis of oral cancer

- Alter the normal function of oncogenes and tumor suppressor genes
- Oncogenes : genes promote autonomous cell growth in cancer cells
- Protooncogenes : physiological regulators of cell proliferation and differentiation (CK8,CK19,EGFR, BCL)
- Tumor suppressor genes : gene that regulates a cell during cell division and replication (p53, p16INK4A, retinoblastoma)

Others

- Poor oral hygiene,
- Poor dental status (sharp/fractured teeth due to caries/trauma)
- Chronic ulceration from an ill-fitting denture has been suggested to promote neoplasm in the presence of other risk factors.

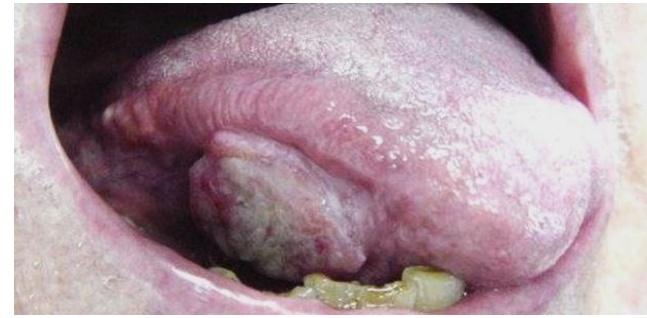
Clinical Signs and Symptoms

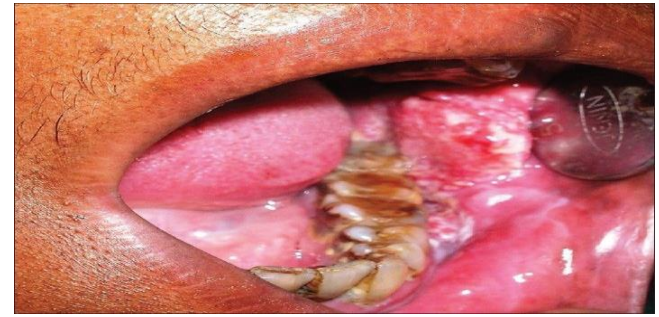
- Discomfort
- Individuals presents with mass in the mouth or neck.
- Dysphagia
- Odynophagia
- Otalgia
- Limited movement
- Oral bleeding
- Weight loss may occur with advanced disease.
- Loss of sensory function – unilateral - indicate neural involvement
- Loss of function involving the tongue can affect speech, swallowing, and diet.

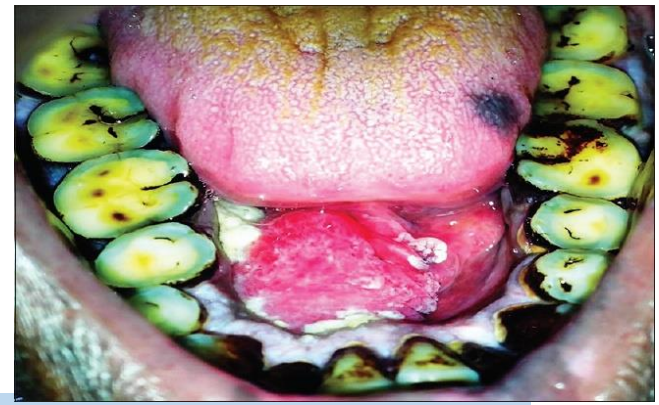
Clinical Signs and Symptoms

- Tissue changes –
- 1) Red, white, or mixed red-and-white lesion
- 2) Surface texture: smooth, granular, rough, or crusted lesion
- 3) Presence of a mass or ulceration
- 4) The lesion may be flat or elevated and may be minimally palpable or **indurated**

- High-risk sites - lower lip, the anterior floor of the mouth, and the lateral borders of the tongue.







Lymphatic spread

- Submandibular and digastric nodes, and the upper cervical nodes and also remaining nodes of the cervical chain.
- Enlarged and firm to hard in texture, and with progression may become fixed and not mobile.
- Nontender , if tender they are associated with secondary infection or an inflammatory response is present, which may occur after a biopsy.
- The fixation of nodes to adjacent tissue due to invasion of cells through the capsule is a late occurrence and is 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.
- Spread of tumor is critical for prognosis and for selection of treatment.

DIAGNOSTIC AIDS

- Include:

1. For frank carcinoma:

- Exfoliative cytology , brush biopsy (oral CDx)
- Toluidine blue staining

- Biopsy: Histopathology, tumor markers

- Imaging: OPG, CT, MRI, PET, USG

- Blood investigations, salivary investigations: Immunological, biochemical, genetic markers

DIAGNOSTIC AIDS

2. For potentially malignant disorders (screening test)

Conventional

Toluidine blue staining

Lugol's iodine

Advance

Vizilite

Vizilite plus with toluidine blue

Tissue fluorescence spectroscopy

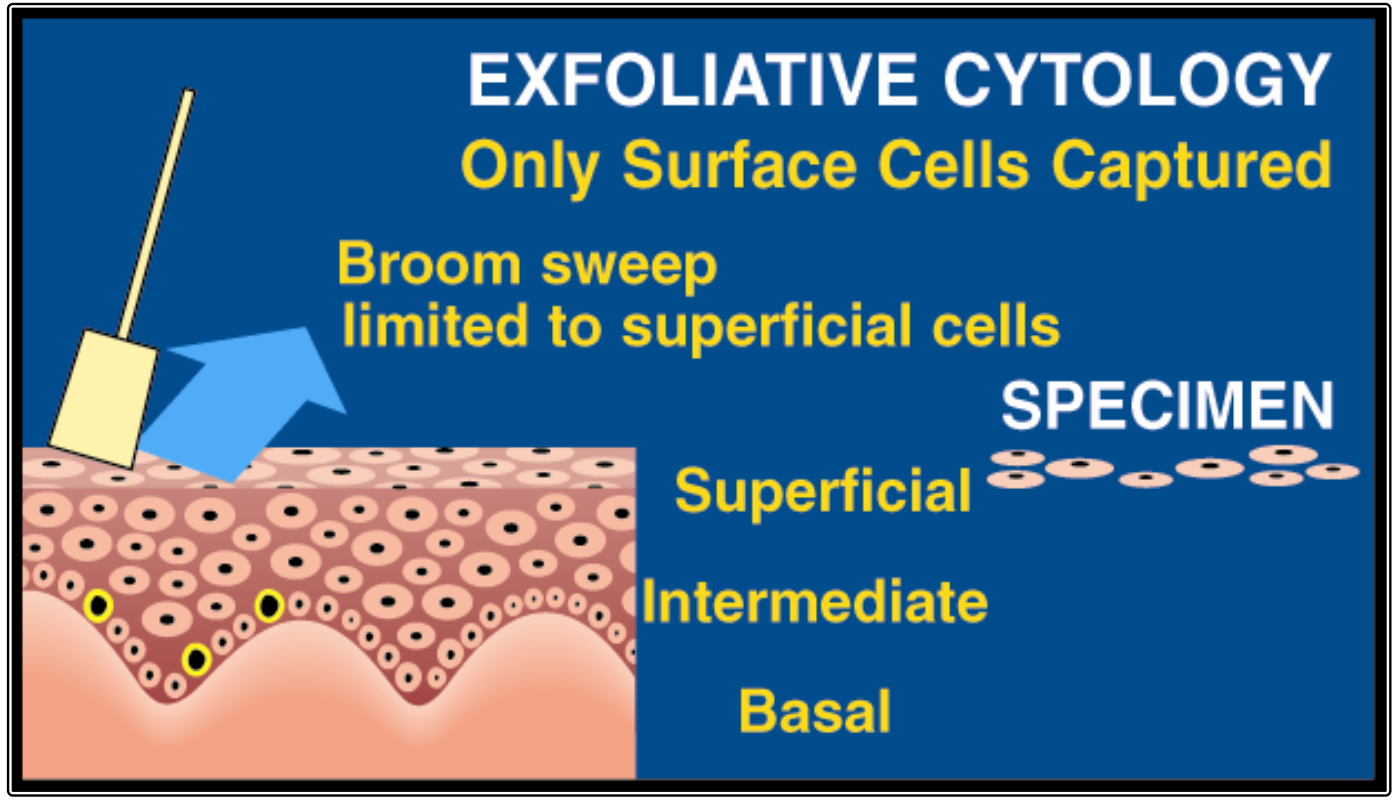
Laser induced fluorescence spectroscopy

Enhance/ dye fluorescence

Optical coherence tomography

Exfoliative Cytology

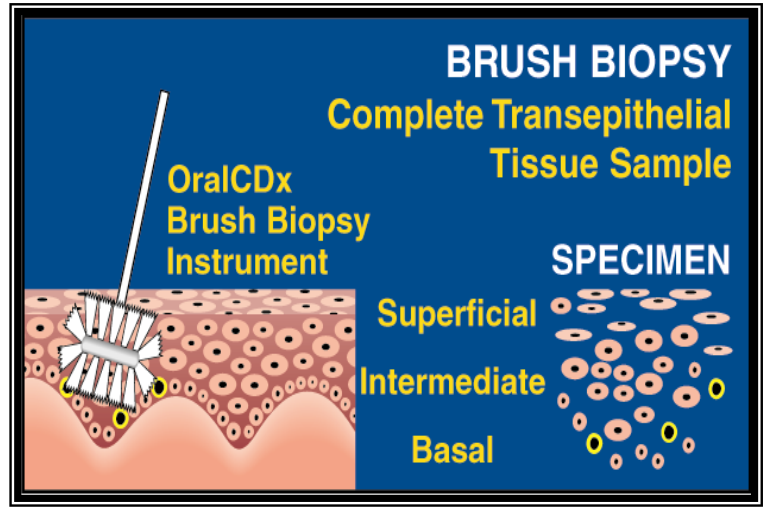
- Microscopic examination of cells
- Spread on slide
- Fixed
- Stained



OralCDx® brush biopsy

- Computer-assisted analysis of oral brush biopsy
- Evaluate benign appearing lesions
- High accuracy
- Does not replace scalpel biopsy

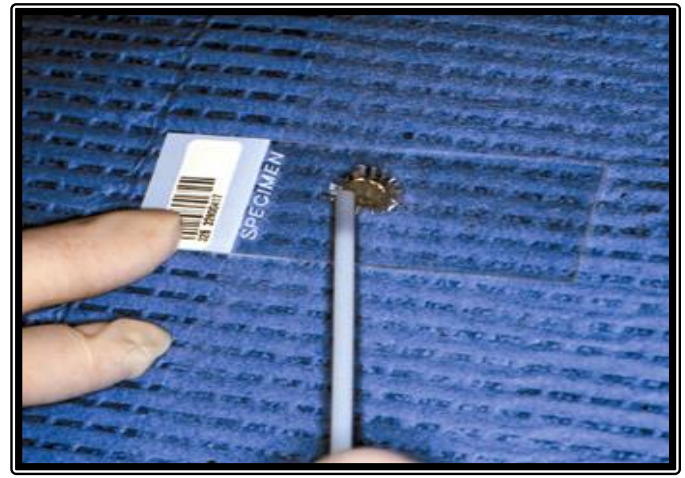
- **OralCDx kit contents include the following items:**
- **Oral brush biopsy instrument**
- **Precoded glass slide**
- **Matching coded test requisition form**
- **Alcohol/carbowax fixative pouch**
- **Prepaid mailer**



OralCDx® brush biopsy

Steps:

- Place brush against lesion
- Rotate brush 10 times (bleeding)
- Transfer cellular material to slide
- Immediately apply fixative
- Allow slide to air dry
- Place slide in prepaid mailing container
- Mail specimen to laboratory

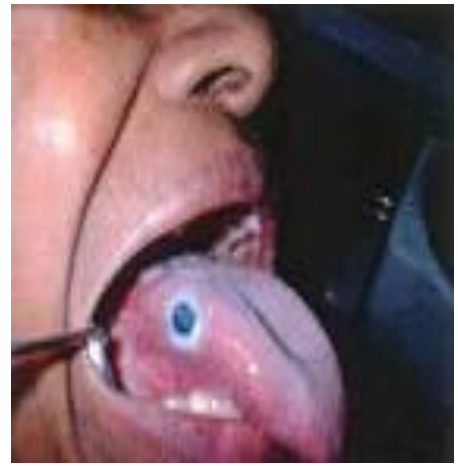


OralCDx® Results

Negative:	No cellular abnormalities
Positive:	Definitive cellular evidence of epithelial dysplasia or carcinoma
Atypical:	Abnormal epithelial changes warranting further investigation

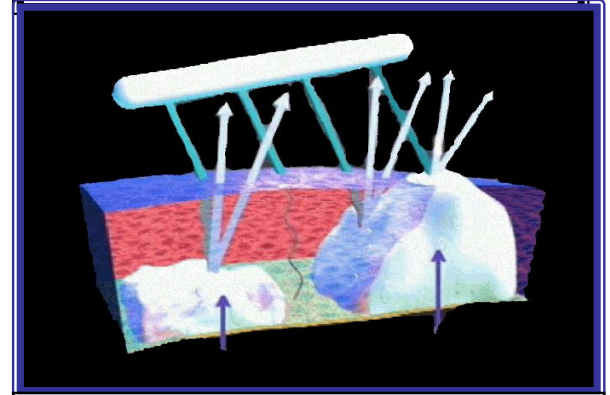
Tolonium Chloride

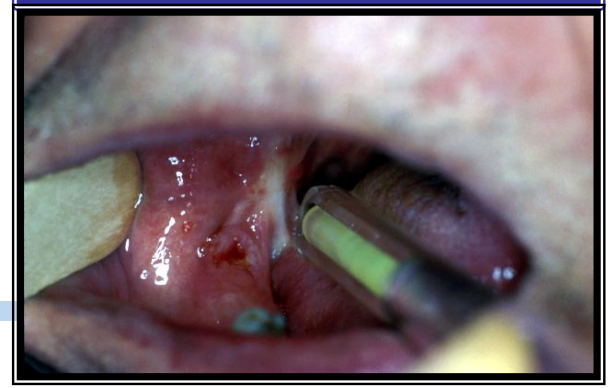
- Toluidine blue
- Stains nuclear DNA
- 1% aqueous solution followed by 1% acetic acid to decolorize lesion
- Abnormal tissue retains the blue dye



Visualization Adjunctive Tools

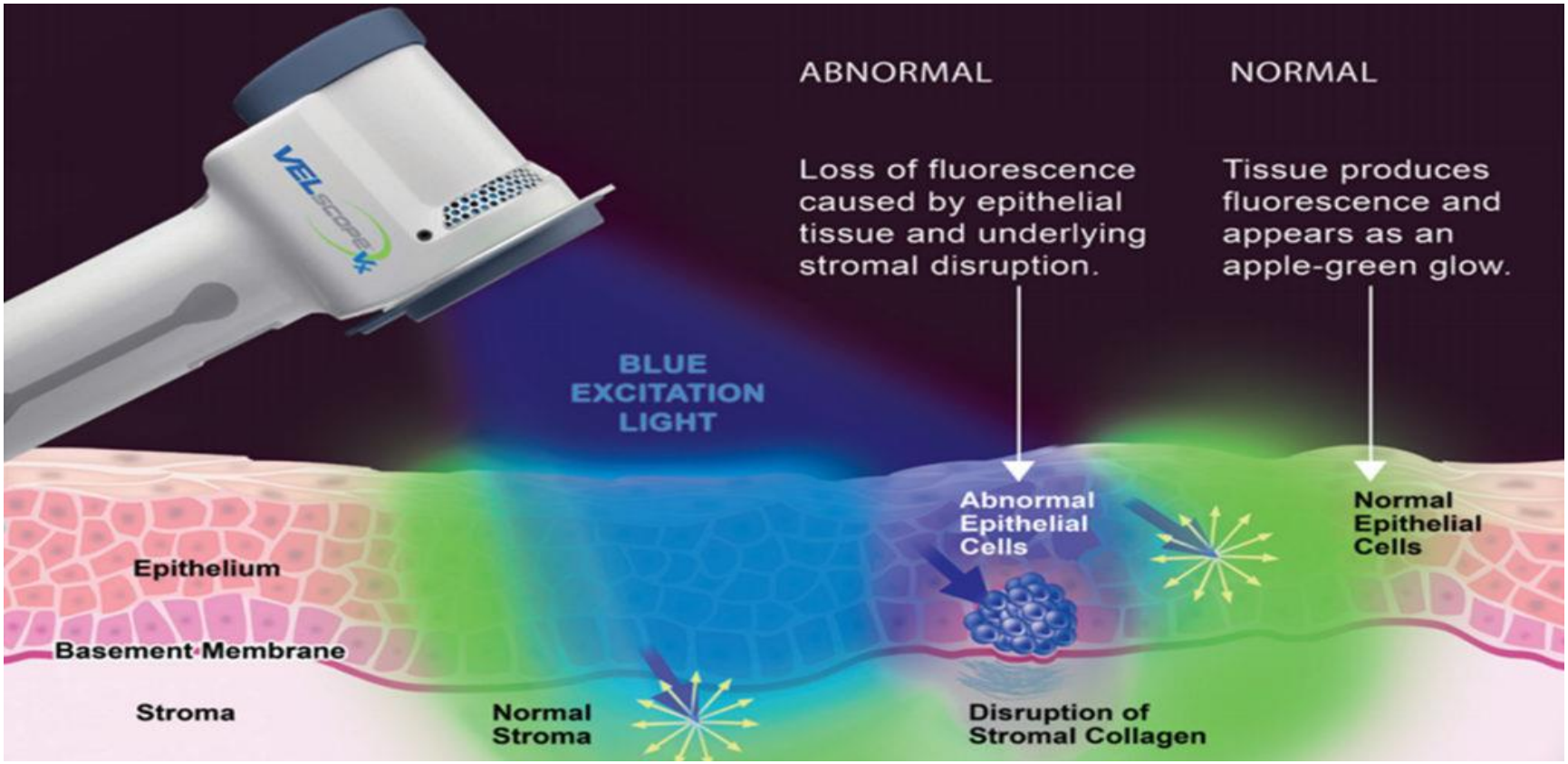
- Chemiluminescent devices
- **ViziLite®**
- Generate light based on chemical reaction.
- The suspected area of mucosa appears brightly lit.
- Normal epithelium absorbs the light and appears dark
- Abnormal tissue reflects light and appears bright white





Visualization Adjunctive Tools

- **VELscope®**
- Generate fluorescent light using an LED source

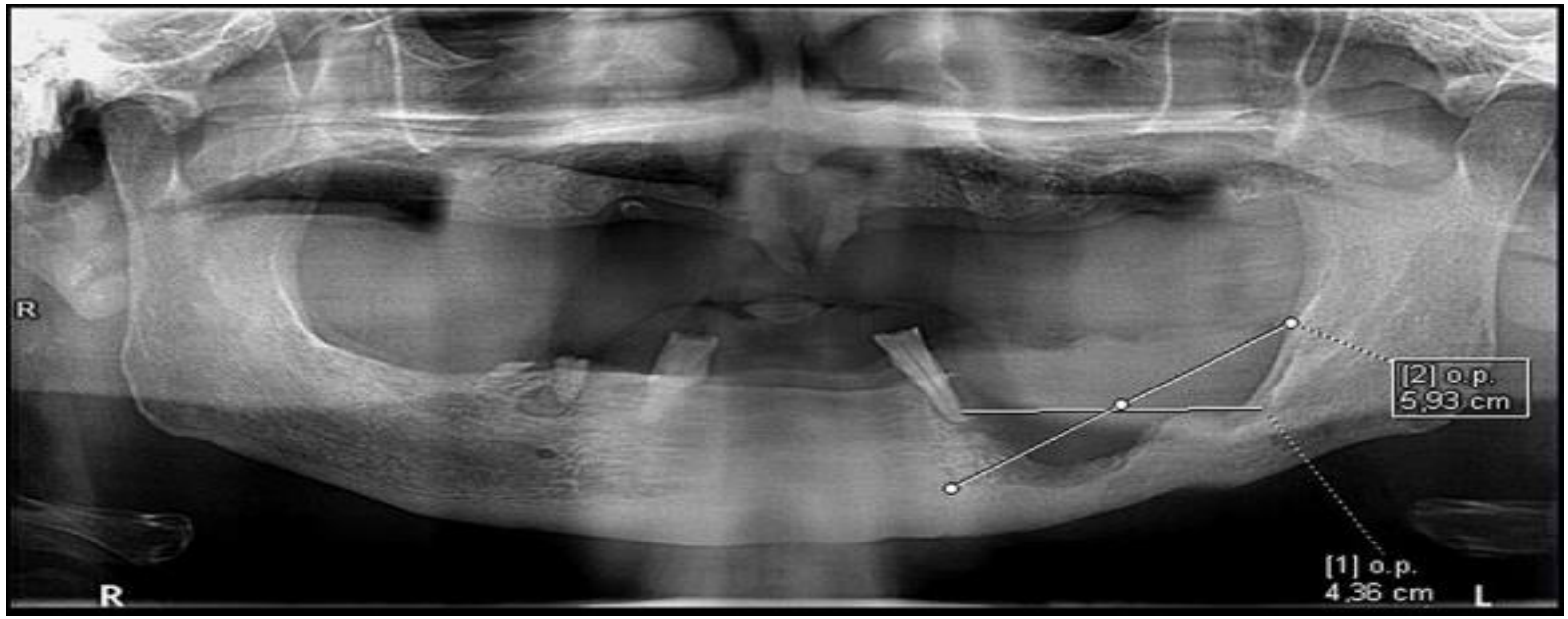


IMAGING MODALITIES

- 1)Plain radiography
- 2)Orthopantomography (OPG)
- 3) Cone beam computed tomography (CBCT)
- 4) Multidetector computed tomography (MDCT),
- 5)Computed tomography perfusion (CTP)
- 6)Diffusion-weighted MRI (DW-MRI)
- 7)Dynamic contrast-enhanced MRI (DCE-MRI)
- 8)Whole body MRI (WB-MRI)
- 9) Ultrasonography (USG)
- 10)Single-photon emission computed tomography (SPECT)
- 11)Hybrid techniques such as SPECT/CT, CT/MRI, PET/CT, PET/MRI with radiopharmaceuticals – (^{18}F-FDG), (^{18}F-FAMT), (C-TYR)

IMAGING MODALITIES

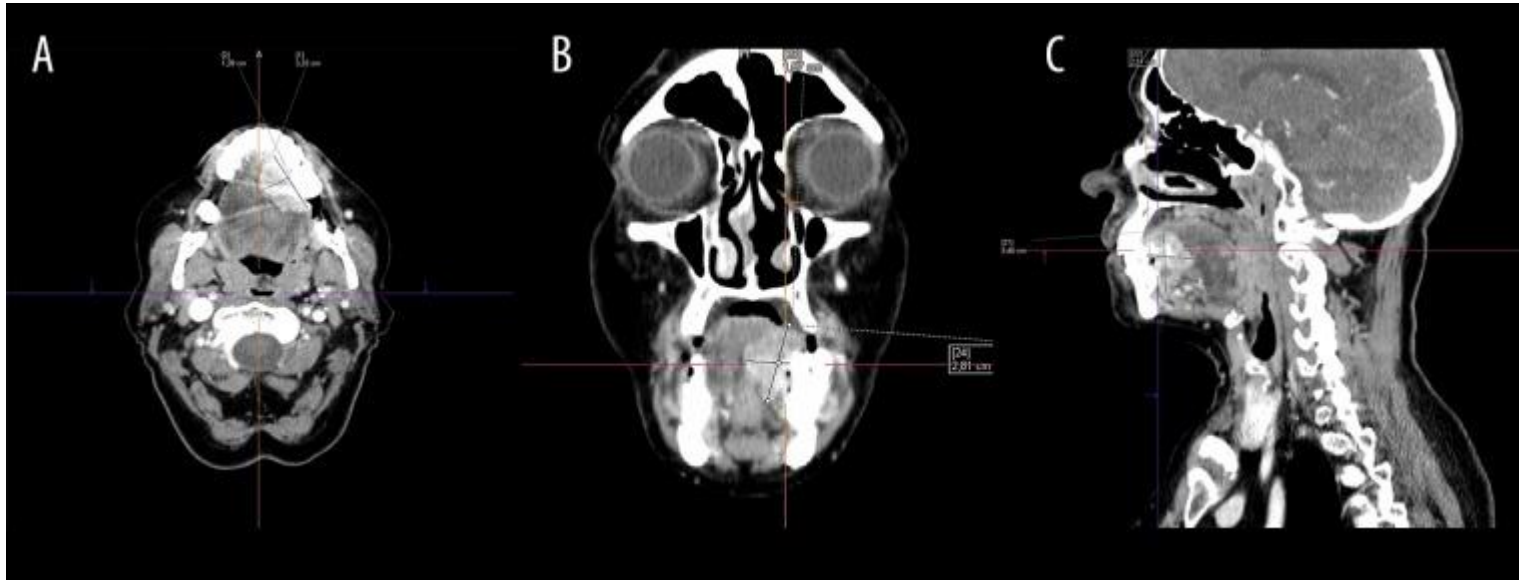
- Panoramic radiograph is used to see involvement of bone specially in gingival and vestibular malignancies.
- Show moth eaten appearance (bone destruction), ragged edges (malignant process rapidly expanding into bone).



Bowl-shaped bone defect in the left part of the mandibular body

Computed Tomography

- Computed tomography is a standard tool for detecting the primary tumors as well as their local bone infiltration.



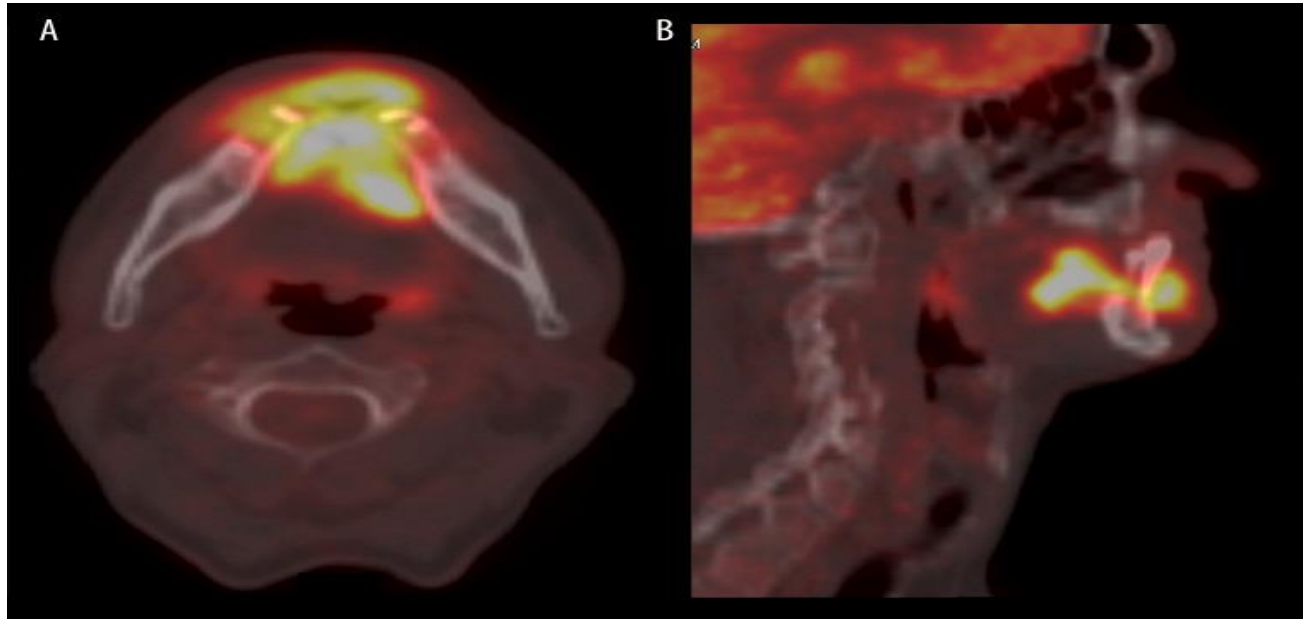
Contrast-enhanced computed tomography (CECT) tumor in the tongue.

Cone beam computed tomography (CBCT)

- Isovolumetric tomography is an intensely developed diagnostic tool.
- The usefulness of CBCT in detecting osteolysis has been confirmed (sensitivity 89–93%, specificity 60–96.5%).
- CBCT is more accurate than panoramic radiography and comparable to MRI, CT and bone scintigraphy
- CBCT is increasingly used by dentists in everyday practice which can result in an improved detection of oral cancers.
- CBCT is limited by a poor assessment of soft tissues.

Positron emission tomography (PET)

- Evaluates tissue metabolic activity .
- Used for the detection of metastatic lymph nodes.
- It allows for an estimation of the risk of recurrence.



- **^{18}F-FDG PET. Tumor of the tongue infiltrating the mandible (T4a stadium).**

CCES MCQS

1. Etiology for oral cancer are all of the following except:
    a. Tobacco
    b. Alcohol
    c. Pigmented fruits
    d. HPV

2. In vizilite screening test following occurs
    a. abnormal cells absorbs light and appears dark.
    b. abnormal cells reflects light and appears white.
    c. Both of the above
    d. None of the above

3. Definitive diagnosis of oral cancer is made by
    a. Radiographic survey
    b. Biopsy
    c. Exfoliative cytology
    d. Pantograph

CCES MCQS

4. Major genes involved in HNSCC:
    a. proto-oncogenes
    b. tumor suppressor genes (TSGs)
    c. Both of the above
    d. None of the above

5. Virus involved in head & neck sq.cell ca is
    a. HZV
    b. CMV
    c. pox virus
    d. HPV

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THANK YOU