

# ORAL CANCER



## Learning Objectives:

- Know the general features of Oral Cancer.
- Identify the risk factors & causes
- Recognize the clinical features
- Establish diagnosis
- Know the histopathological features
- Molecular pathways
- Treatment & prognosis



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Nov.15<sup>th</sup> 2017

# Oral Cancer

Table 1 Age and sex distribution of 1,425 oral squamous cell carcinoma

Age group	Male	Percent from total	Female	Percent from total	Total	Percent from total
11–20	12	0.85	8	0.56	20	1.4
21–30	47	3.29	21	1.47	68	4.77
31–40	70	4.92	56	3.92	126	8.84
41–50	182	12.78	105	7.36	387	20.14
51–60	291	20.44	163	11.43	454	29.82
61–70	244	17.14	82	5.75	326	22.87
71–80	88	6.17	36	2.52	124	8.7
81 and more	14	0.98	6	0.42	20	1.4
Total	948	66.57	477	33.43	1,425	

Clin Oral Invest (2008) 12:15–18

Table 2 Site and sex distribution of 1,425 oral squamous cell carcinoma

Site	Male	Percent from total	Female	Percent from total	Total	Percent from total
Lower lip	279	19.57	87	6.1	366	25.6
Tongue	169	11.85	122	8.56	291	20.42
Alveolar ridge (lower)	100	7.01	65	4.56	165	11.57
Buccal mucosa	92	6.45	49	3.43	141	9.89
Floor of mouth	76	5.33	18	1.26	94	6.59
Retromolar area	61	4.28	28	1.96	89	6.24
Alveolar ridge (upper)	53	3.71	36	2.52	89	6.24
Upper lip	37	2.59	28	1.96	65	4.56
Hard palate	40	2.8	23	1.61	63	4.42
Soft palate	12	0.84	2	0.14	14	0.98
Undefined	29	2.03	19	1.33	48	3.36

## Squamous cell carcinoma of the oral cavity: a case series analysis of clinical presentation and histological grading of 1,425 cases from Iraq

Natheer H. Al-Rawi · Nazar G. Talabani

Table 3 Clinical presentation

Clinical presentation	Number of cases
Ulceration	485
Swelling	324
Pain	74
White lesion	65
Erythroplasia	19
Bleeding	11
Tongue fixation	5
Dysphagia	2
Parasthesia	2
Undefined in patient records	197

# SQUAMOUS CELL CARCINOMA

## Etiological factors

- **Tobacco : Contains > 100 carcinogens  
Polycyclic aromatic hydrocarbons such as**

***Benzo[a]pyrene , arsenic & nitrosamines*** derived

From nicotine.( induce specific changes of the p53 & H-ras)

In addition to the endogenous release of ROS which promotes the destruction & counteract the protective effects of endogenous antioxidants (GSR & SOD) .

**Pipe and cigar smoking** have been

linked with carcinoma of the lip .

**In India** the habit of **reverse smoking** is associated particularly with cancer of the **palate**, one of the rarest sites for oral cancer in other groups.

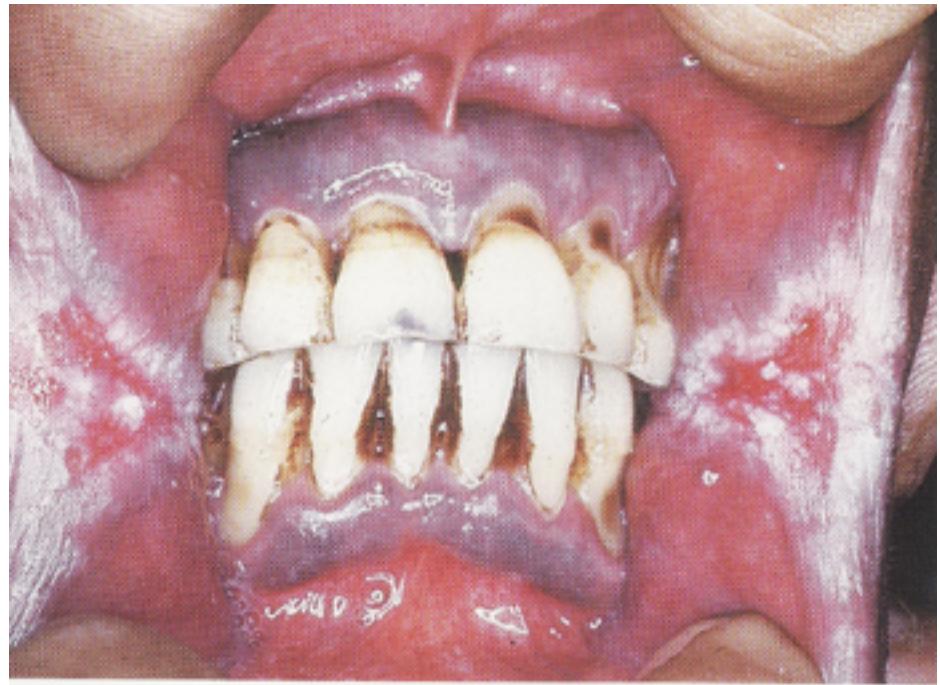
## SMOKELESS TOBACCO

One of the factors that may have led to the increase in oral cancer in young people. Higher risk with dry snuff.

**Betal Quid (Paan):** Psychostimulant (areca nuts, betal leaf, lime & tobacco leaf)



This habit *induces leukoplakia* where the paan is held in the mouth, and *malignant transformation* is usually evidenced clinically by the development of a **papilliferous, ulcerated** mass.



- **Alcohol**
- Ethanol in alcoholic beverages is metabolized to acetaldehyde which is a known carcinogen.  
Pure ethanol can act as a **solvent**, helping harmful chemicals in tobacco to get inside the cells .
- other chemicals in the beverage are responsible for the increased cancer risk like polycyclic hydrocarbones & nitrosamines.

Alcohol acts synergistically to promote the carcinogenic effect of tobacco products (RR=15).

Alcohol may acts directly on epithelial cells of oral mucosa by:

- Increasing permeability &
- Through its dehydrating effect
- Altering the P53 gene.
- Indirect effect of alcohol will be via altered liver metabolism.

The increasing incidence of oral cancer, especially in younger persons, may be linked to the rise in alcohol consumption over the past few decades.



- **Sunlight:**

Actinic radiation has long been associated with cancer of the lower lip.

*UV light* is a potent DNA damaging agent inducing DNA cross-linking, single & double strand DNA breaks and nucleotide substitution.

- **Diet and nutrition**

The increased risk of esophageal, pharyngeal, and oral cancer associated with primary sideropenic anaemia (**Plummer-Vinson or Patterson-Kelly syndrome**) has been recognized for many years.

**Iron** is essential for the maintenance of oral epithelium and it is possible that **atrophic changes in iron-deficiency anemia** render the mucosa more susceptible to chemical carcinogens.

**Vitamin A deficiency:** hyperkeratosis of skin & MM ---Cancer?

## Key points –

**Both** are **independent risk factors** for oral cancer.



- Their effect together is **synergistic**.
- **Relative risk** for tobacco increases with amount and duration of use, as well as method of use and type.
- Main carcinogens in tobacco are **N-nitrosamines** derived from nicotine.
- Alcoholic drinks may include constituents (**congeners**) and/or contaminants that are carcinogenic.
- Alcoholic drinks may **enhance transport of carcinogens** across the mucosal barrier.
- **Nutritional deficiencies** in chronic alcohol abuse may impair the mucosal barrier.
- **Liver disease** in chronic alcohol abuse may impair its ability to **detoxify carcinogens**.
- **Immunosuppression** in chronic alcohol abuse may increase the risk of developing cancer.
- Dietary deficiencies or imbalances may account for 15 % of oral cancer.
- Deficiencies of **iron** and of the antioxidant vitamins A, C, and E increase the risk for oral cancer.
- Diets high in fresh fruit and vegetables decrease the risk of oral cancer

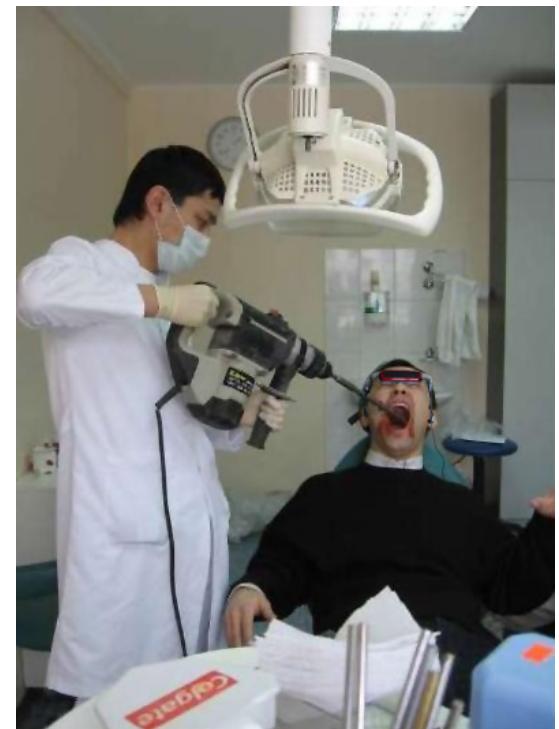
- **Occupational risks**
- ✓ **Outdoor workers** at risk of high exposure to ultraviolet light, which is an important factor in squamous cell carcinoma of the **lip**.
- ✓ It is **rare in dark-skinned races** because of the protection conferred against ultraviolet light by melanin pigment.

**Squamous cell carcinoma of the lip may be preceded by hyperkeratotic and dysplastic changes - solar keratosis.**



# Dental factors

- Poor oral hygiene,
- Faulty restorations,
- Sharp edges of teeth,
- and ill-fitting dentures have all been incriminated in the etiology of oral cancer.

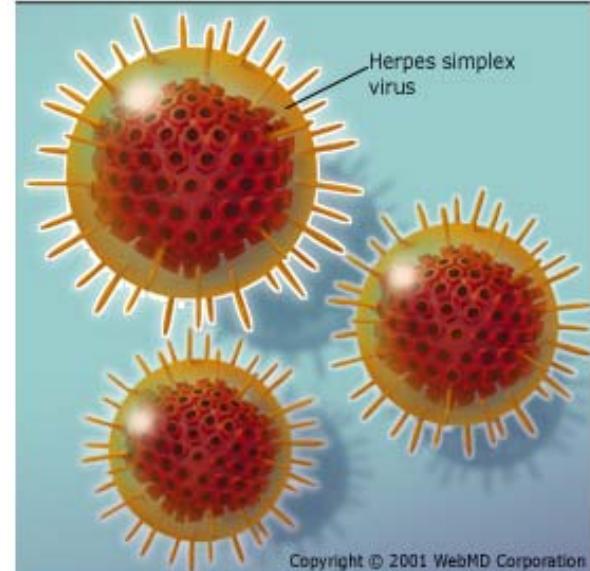


- Oncogenic Viruses

## HERPES SIMPLEX VIRUSES (HSV)

Laboratory experiments have shown that HSV can be carcinogenic or co-carcinogenic under certain circumstances and so must be considered as possible etiological agents in oral carcinoma

Herpes Simplex

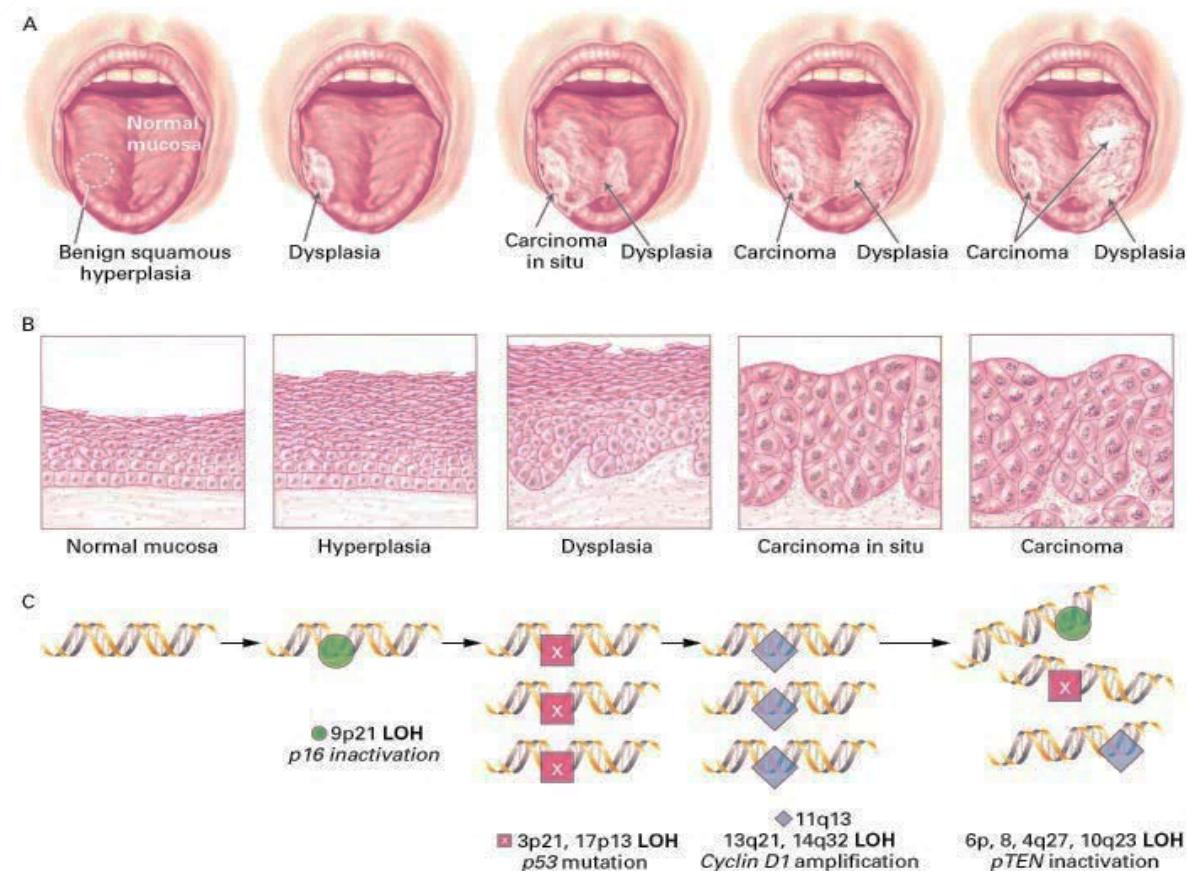


## ❑ HUMAN PAPILLOMAVIRUSES (HPV)

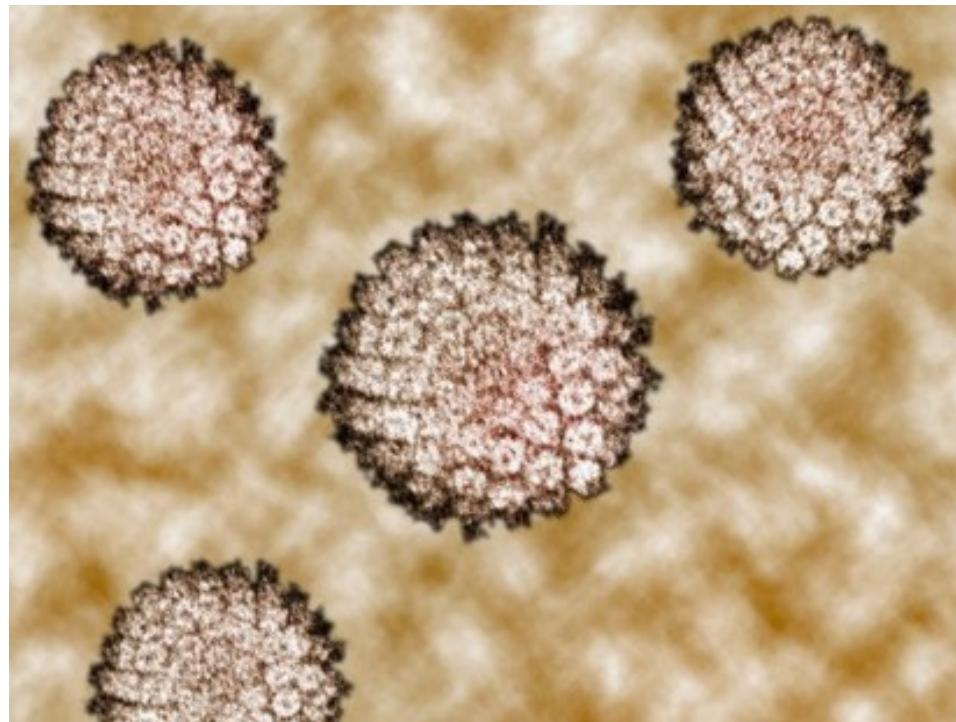
✓ HPV types **16** and **18** are important factors in the etiology of squamous cell carcinoma of the uterine cervix, but their role in oral carcinomas and oral pre malignancy is less clear.

✓ HPV have been identified with increasing frequency in the progression from normal mucosa, through dysplasia to carcinoma.

In 2020 the annual number of HPV-positive oropharyngeal cancers would be expected to surpass the annual number of cervical cancers. Why?



- ✓ However, certain **HPV oncogenes (E6 & E7)** code for proteins which can bind and inactivate the products of the tumor-suppressor genes p53 (E6 effect) and Rb (retinoblastoma gene) (E7 effect).
- ✓ Mutation or inactivation of these genes, from whatever cause, is thought to be a significant step in the development of oral cancer , and for this reason HPV are likely to be an **important cofactor** in the etiology of at least some oral cancers.



- **EPSTEIN-BARR VIRUS (EBV)**

EBV has an etiological role in the development of some nasopharyngeal carcinomas and some malignant lymphomas, but a similar role in the development of oral squamous cell carcinoma has not been established.



Oral « hairy » leukoplakia

- **Immunosuppression**

Oral squamous cell carcinoma has been reported as an oral lesion associated with HIV infection



- **Chronic infections**

### ***CHRONIC CANDIDAL INFECTION***

This is often associated with **speckled leukoplakias**, and such lesions are particularly prone to undergo malignant transformation

Chronic hyperplastic candidiasis also presents as a leukoplakic lesion and may have premalignant potential.

The role of candidal infection in malignant transformation must be regarded as uncertain.” certain strains may produce nitrosamines (which activates certain proto oncogens) or convert ethanol into acetaldehyde”



# **Oncogenes & tumor Suppressor genes:**

**Genetic aberrations** includes:

ras, myc & EGFR (oncogenes) &

TP53, pRb, P16 & e-cadherin (tumor suppressor genes)

## Clinical presentation

It take many forms.

□ **Early lesions** are usually

asymptomatic.

□ Common modes of presentation

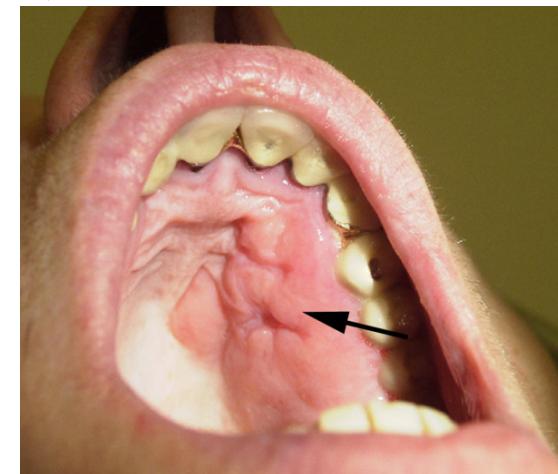
are a **white patch**, a small exophytic growth which in the early stages may show **no ulceration or erythema**,

□ a small **indolent ulcer**, or

□ an area of **erythroplakia** .

□ Pain is seldom

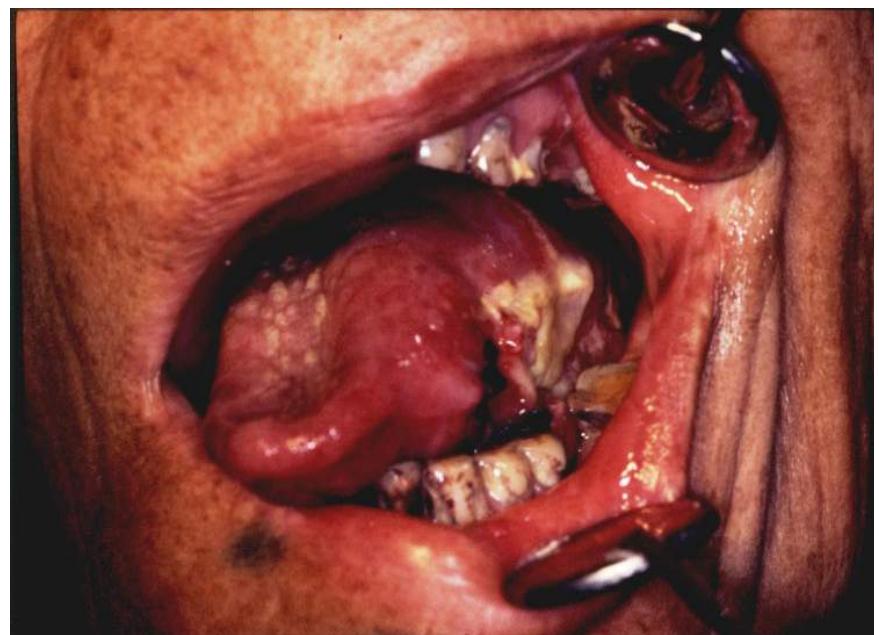
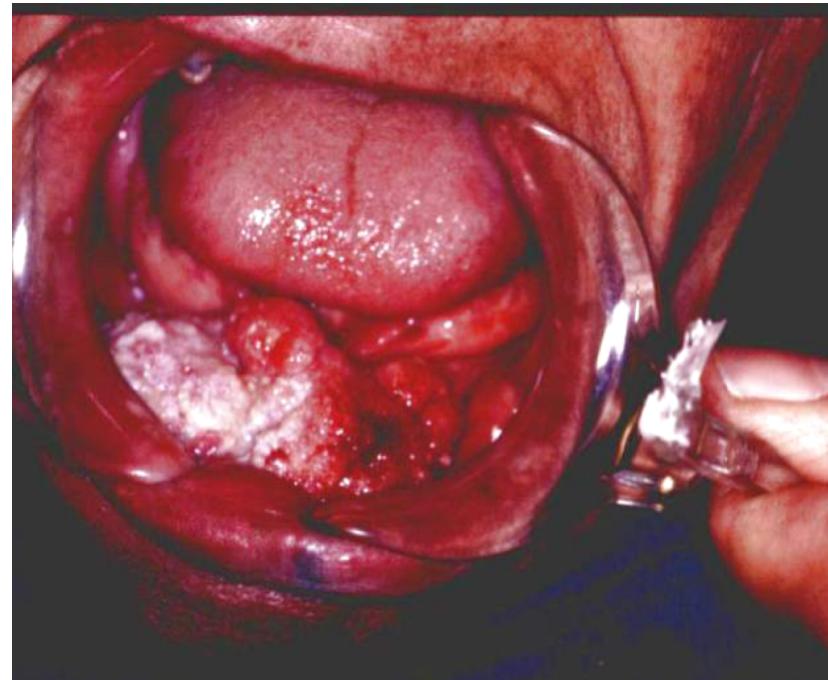
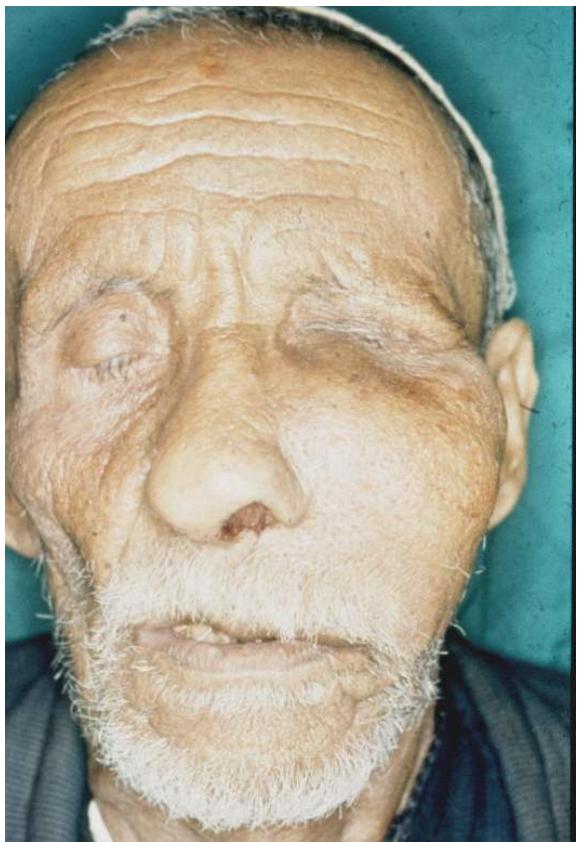
present.



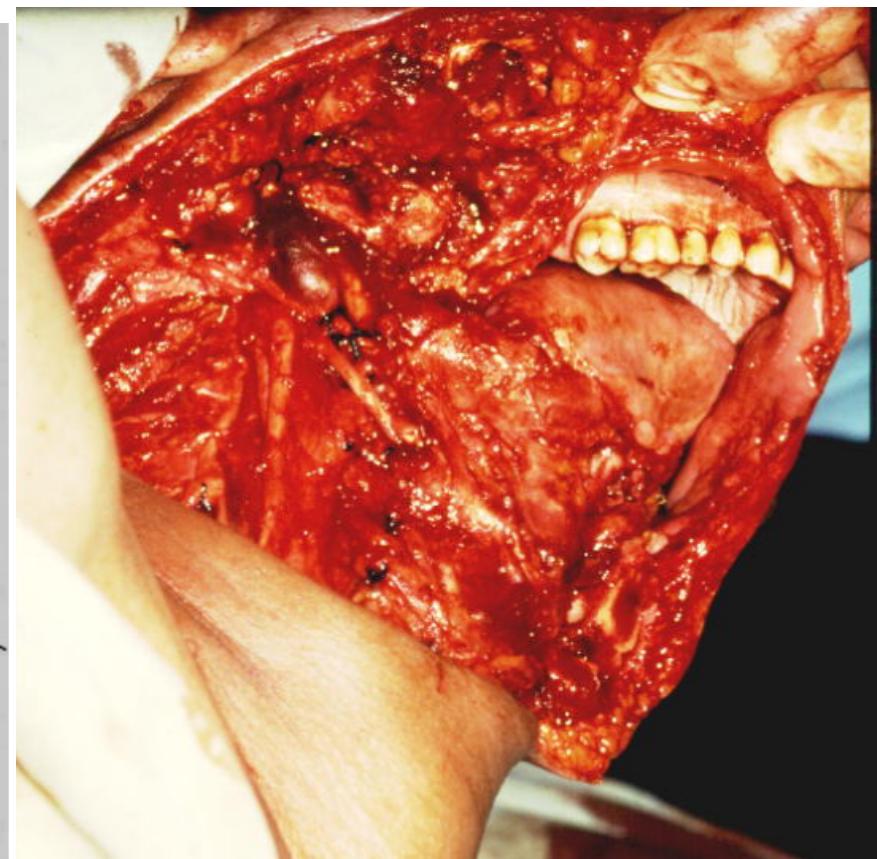
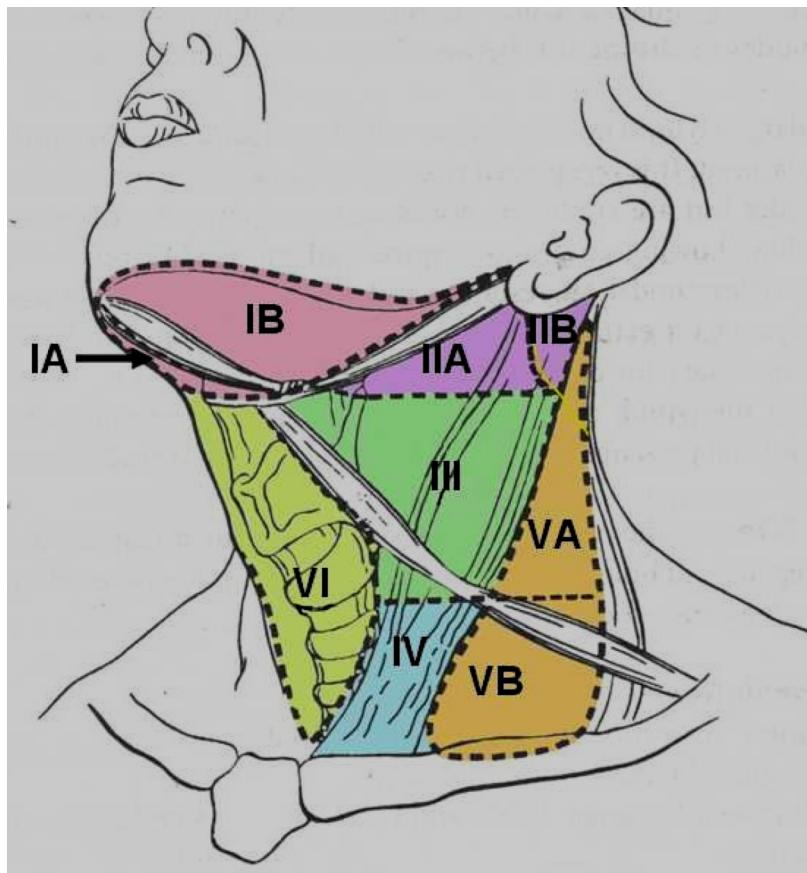
**Clinical features arouse suspicion of an early carcinoma are**

- ***persistent ulceration***,
- ***induration***, and
- ***fixation of affected tissue to underlying structures.***
- **Underlying bone destruction** may also be detected in the case of carcinomas arising from the alveolar mucosa.





❑ **Lymph node involvement** may occur early in oral carcinomas, but enlarged regional nodes do not necessarily indicate metastatic spread as they may show only non-specific changes of **reactive hyperplasia**.



## **Metastasis:**

- Via Lymphatics “ Local or Regional”
- Carcinoma of lower lip: Metastatic cells travels via superior jugular vein & digastric nodes.
- Oropharyngeal carcinoma: Found in jugulo-digastric or retropharyngeal nodes.
- Distant metastasis: Lungs & liver.

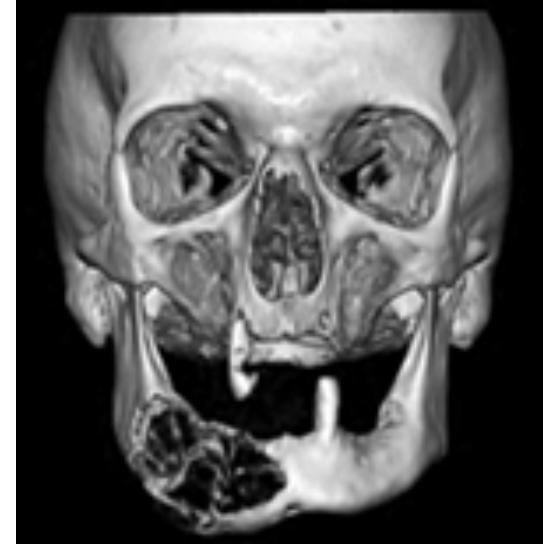
- An advanced or late lesion may present as a **broad-based, exophytic mass** with a *rough, nodular, warty, hemorrhagic, or necrotic surface* , or
- as a *deeply destructive and crater-like ulcer with raised, rolled averted edges* .

Infiltration of the oral musculature may result in functional disturbances, particularly if the tumor involves the tongue or floor of mouth.



- Pain may be a feature of an advanced lesion.
- Extra capsular spread “ extension of metastatic deposits outside of the lymph nodes” { associated with poorer prognosis}
- Bone invasion may be detected on radiographs and may be suggested clinically by **mobility of teeth**, and in the mandible, by **altered sensation** over the distribution of the mental nerve, or **pathological fracture**.

**It is important to note that the size of the surface lesion does not indicate the extent of underlying invasion.**



## **Pathology**

- SCC arises from dysplastic surface epithelium
- At earliest moment of invasion, the term superficially invasive or micro-invasion is often used.
- Tumor cells may destroy tissue and extend deeply into underlying adipose tissue, muscles and bones.
- Peri -neural invasion, vascular invasion (via lymphatic vessels), desmoplasia and angiogenesis.

## **Grading of Oral dysplasia:**

### ***Architectural characteristics***

- Irregular epithelial stratification
- Loss of polarity of basal cells
- Drop-shaped rete ridge
- Increased number of mitotic figures
- Abnormally superficial mitoses
- Keratin pearls within rete pegs

### ***Cellular characteristics***

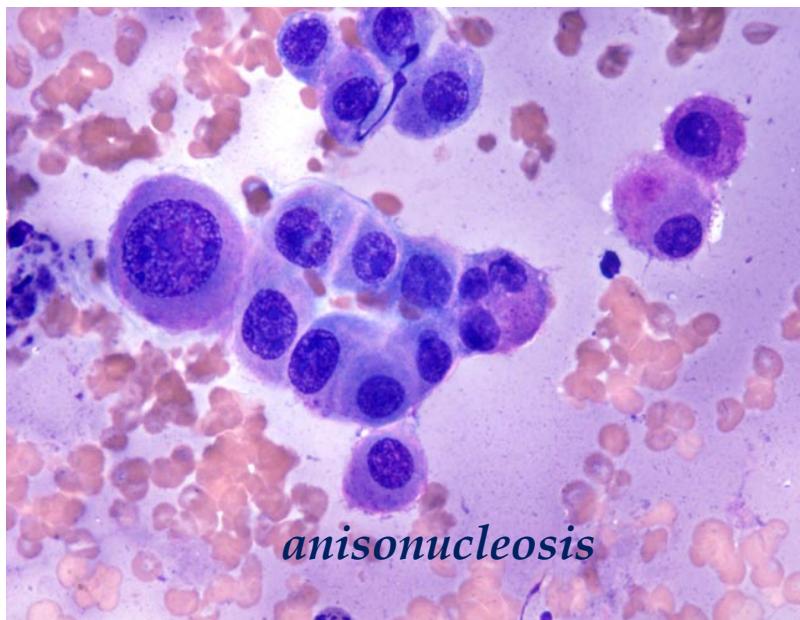
- Anisonucleosis
- Nuclear pleomorphism
- Anisocytosis
- Cellular pleomorphism
- Increased nuclear-cytoplasmic ratio
- Dyskeratosis
- Atypical mitotic figures
- Increased number and size of nucleoli

**Mild dysplasia:** Architectural changes limited to the lower third of the epithelium along with the cytological atypia

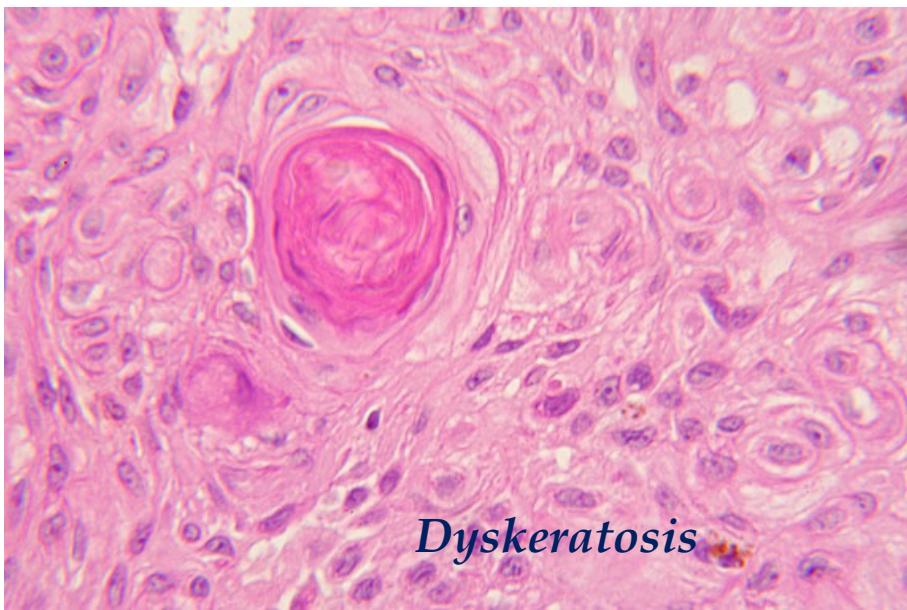
**Moderate dysplasia:** Architectural changes extending to the middle third of the epithelium. Degree of cytologic atypia requires upgradation

**Severe dysplasia:** Greater than 2/3rd of the epithelium exhibits architectural disturbances and the increased number of the cytologic atypia.

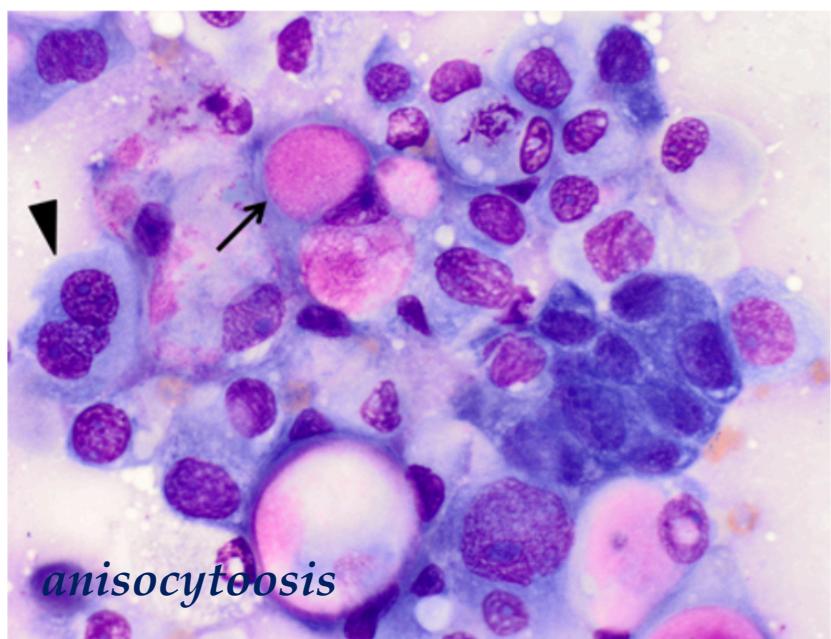
**Carcinoma *in situ*:** Full thickness of the epithelium exhibits architectural disturbances. Abnormal superficial mitosis and atypical figures are seen commonly.



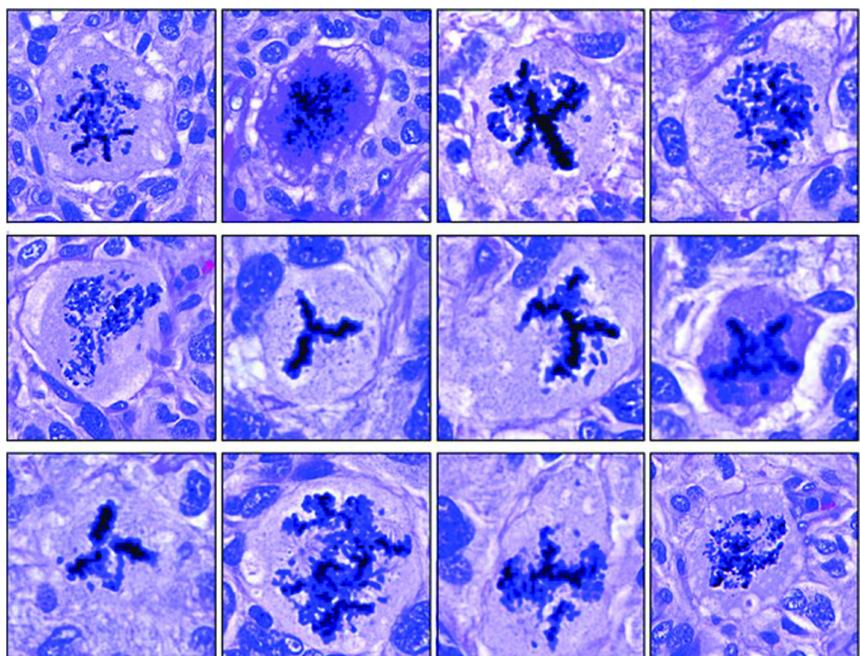
*anisonucleosis*

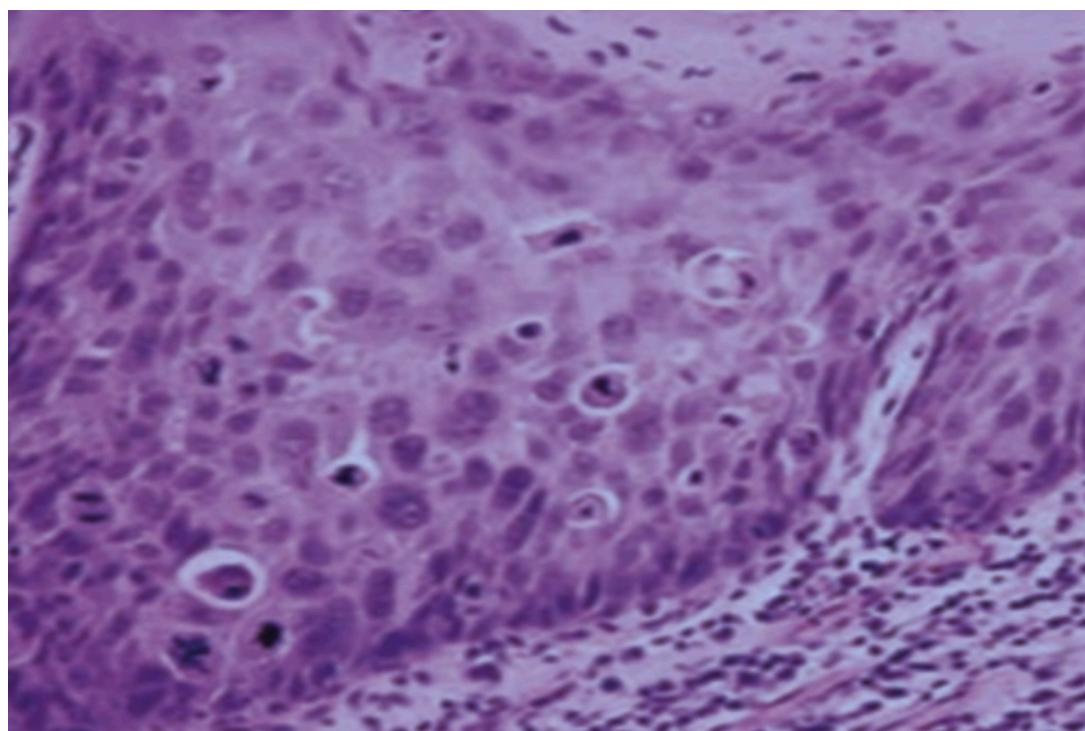
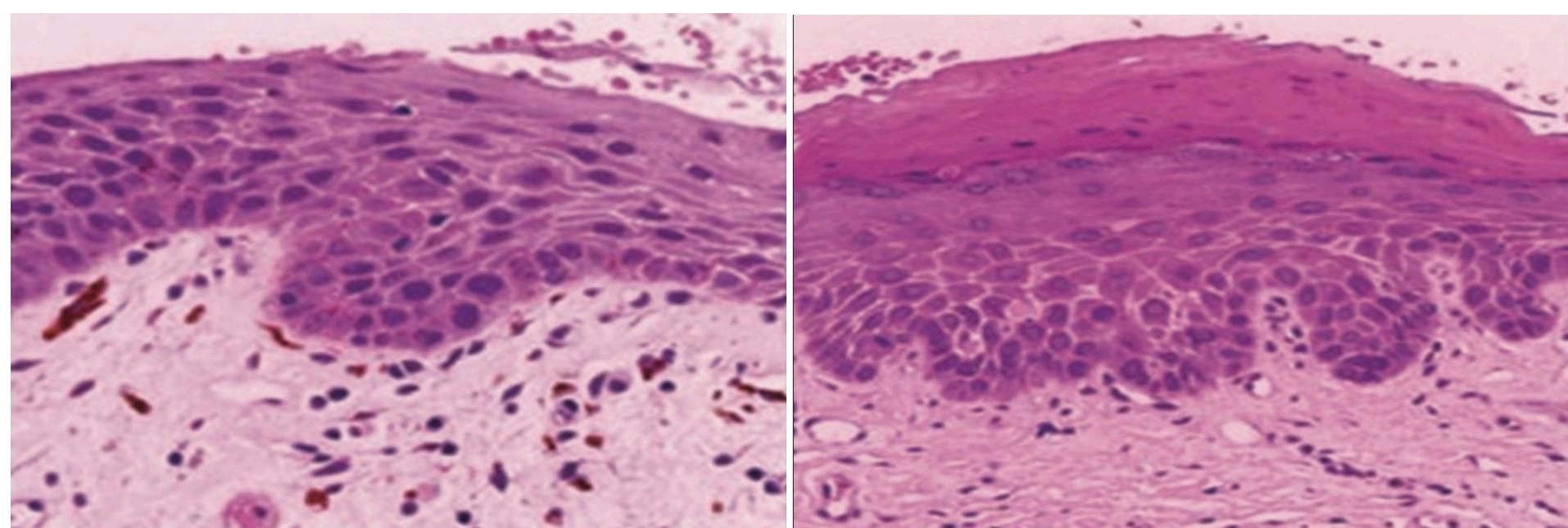


*Dyskeratosis*



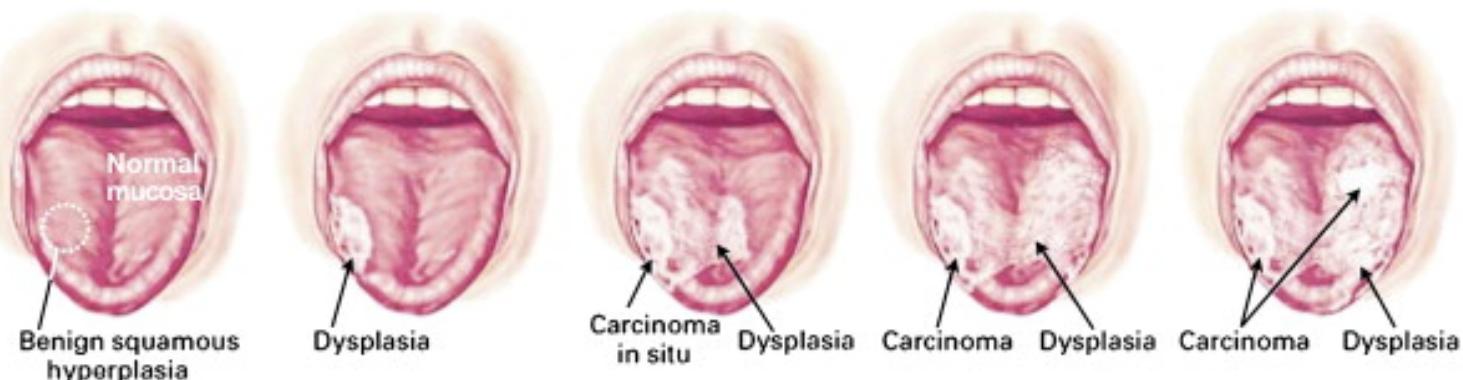
*anisocytosis*



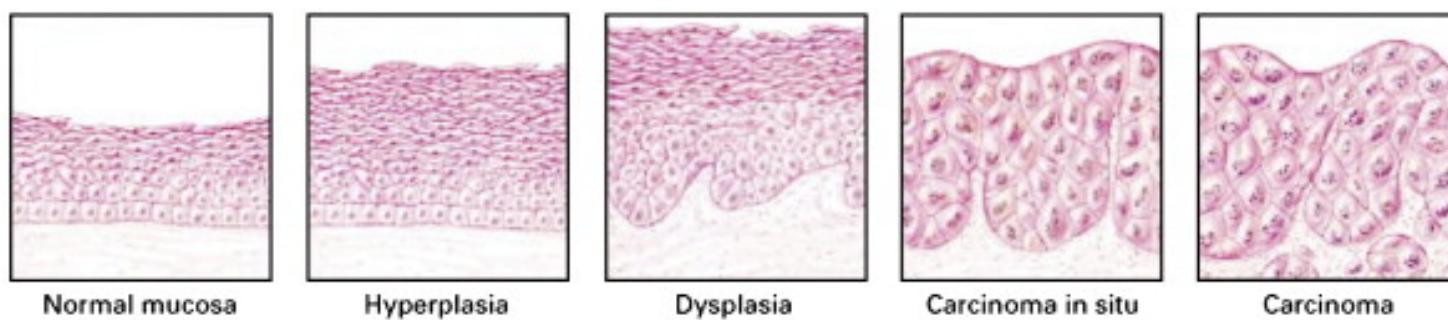


# Clinical, Pathological, and Molecular Progression of Oral Cancer

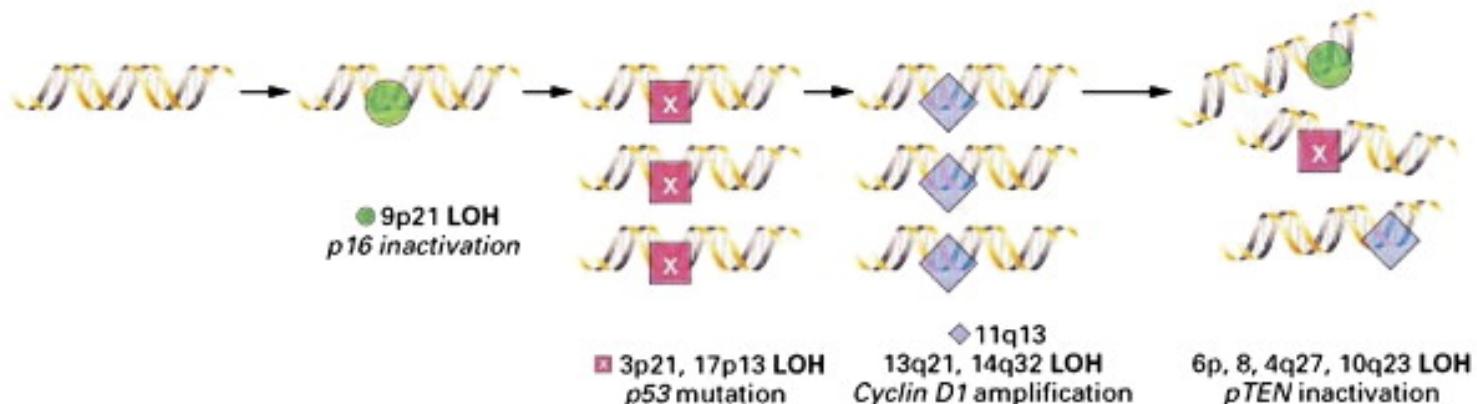
A



B



C



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## **Pathology**

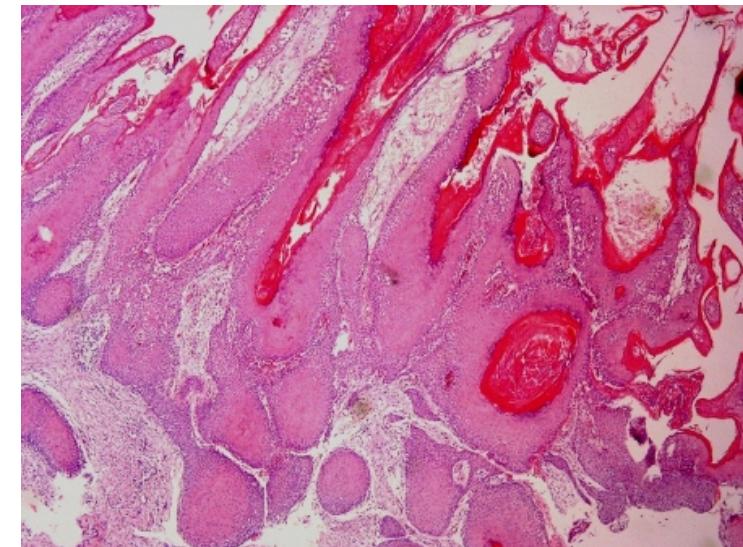
- SCC arises from dysplastic surface epithelium
- At earliest moment of invasion, the term superficially invasive or micro-invasion is often used.
- Tumor cells may destroy tissue and extend deeply into underlying adipose tissue, muscles and bones.
- Peri -neural invasion, vascular invasion (via lymphatic vessels), desmoplasia and angiogenesis.

**Squamous cell carcinoma can be graded into :**

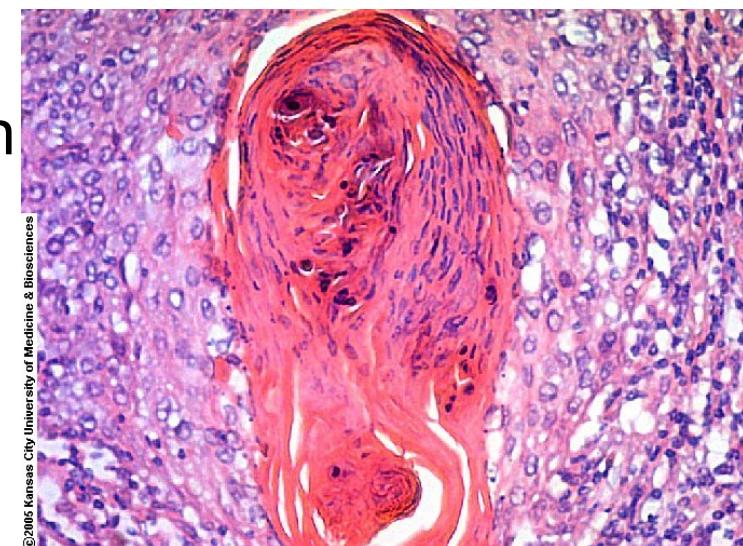
- Well differentiated,
- Moderately differentiated,
- and Poorly differentiated types.

In well-differentiated tumors “ low grade or grade 1”:

- **Neoplastic epithelium** is obviously **squamous** in type and consists of **masses of prickle cells** with a limiting layer of basal cells around the periphery.



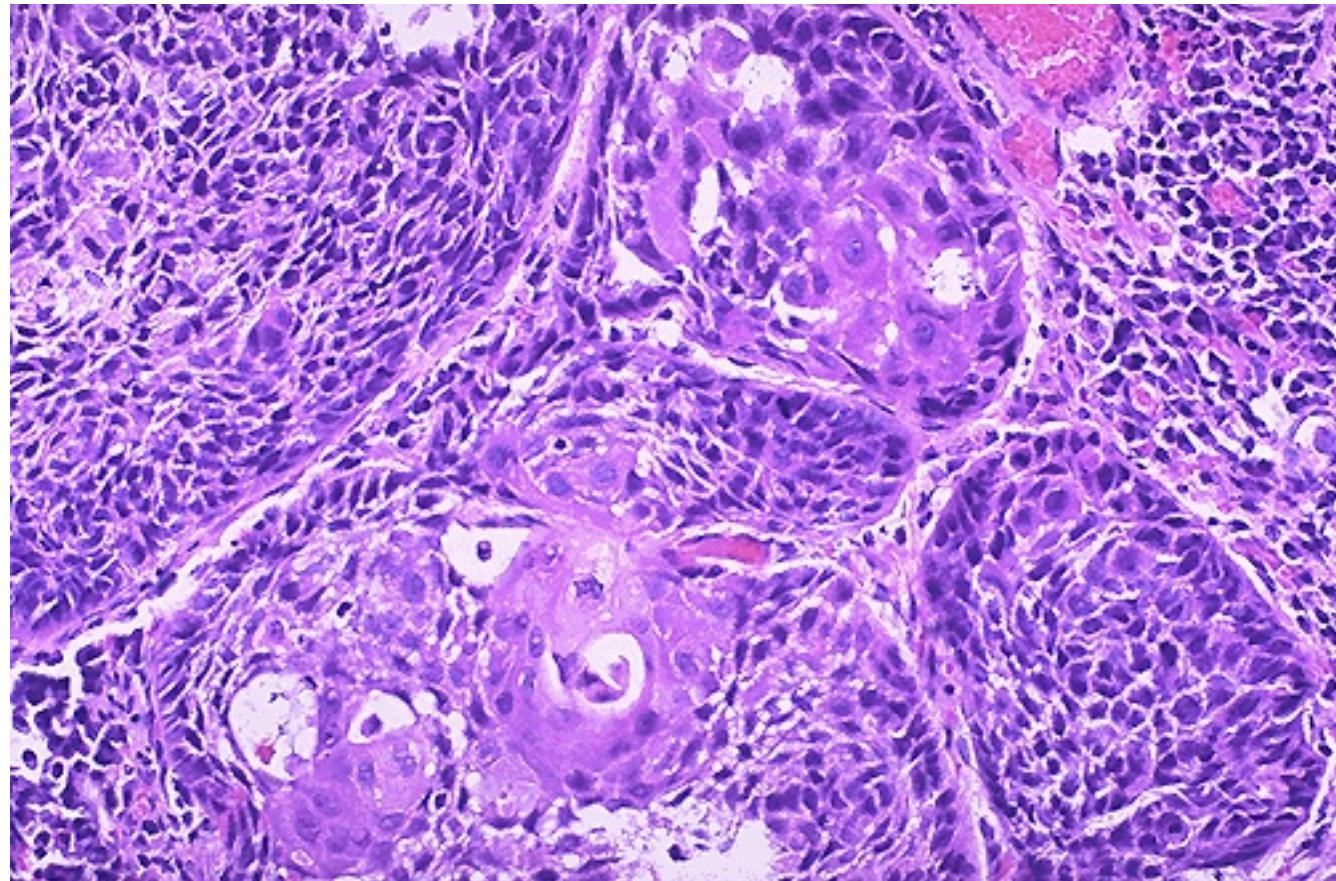
- **Intercellular bridges** are readily recognizable.
- **Keratin pearls** are often found within the masses of infiltrating cells, each pearl consisting of a central area of keratin surrounded by whorls of prickle cell .



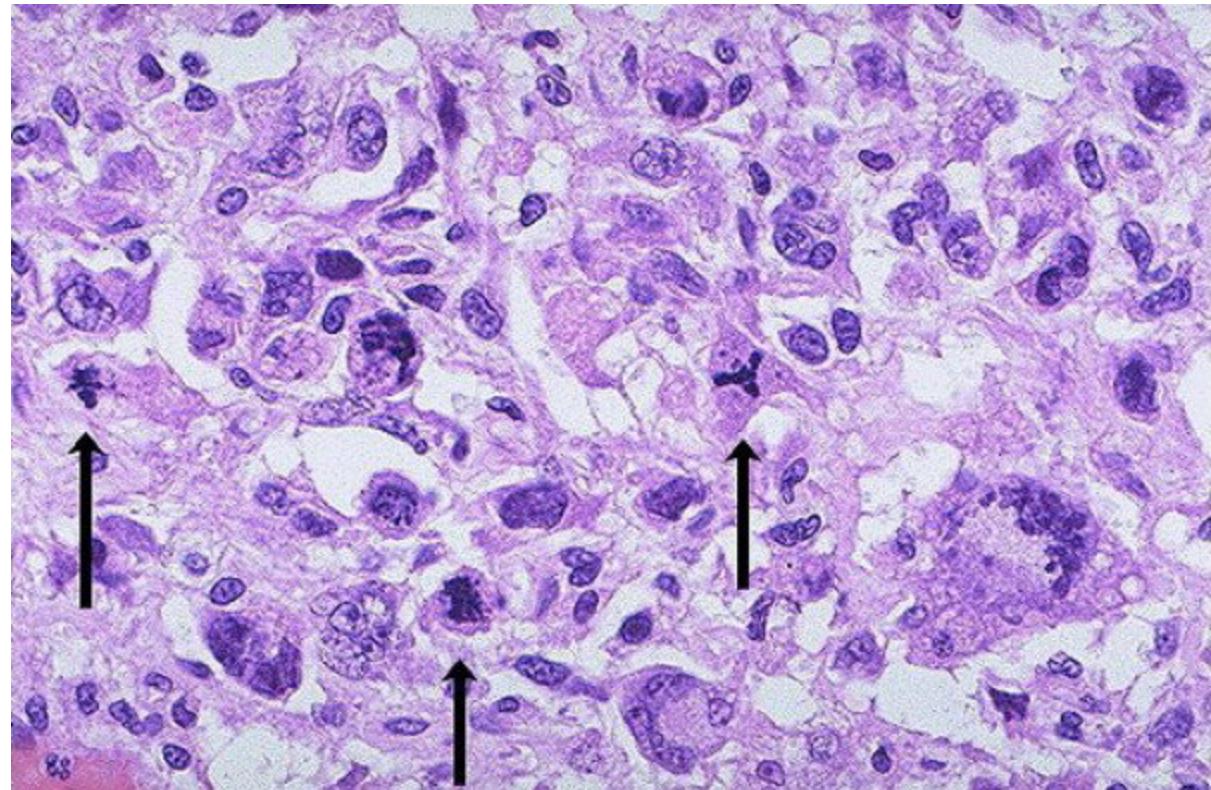
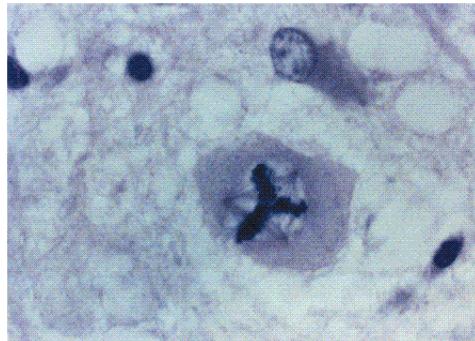
- **Nuclear and cellular pleomorphism is not prominent and there are relatively few mitotic figures.**

Moderately differentiated tumors" Grade 2 or moderate grade"

- Show less keratinization and more nuclear and cellular pleomorphism and mitotic activity, but are still readily identified as **squamous** in type.



3: In contrast, in poorly differentiated tumors “ high grade or grade Keratinization is usually **absent** and the cells show prominent nuclear and cellular pleomorphism and abundant, often bizarre, mitoses.

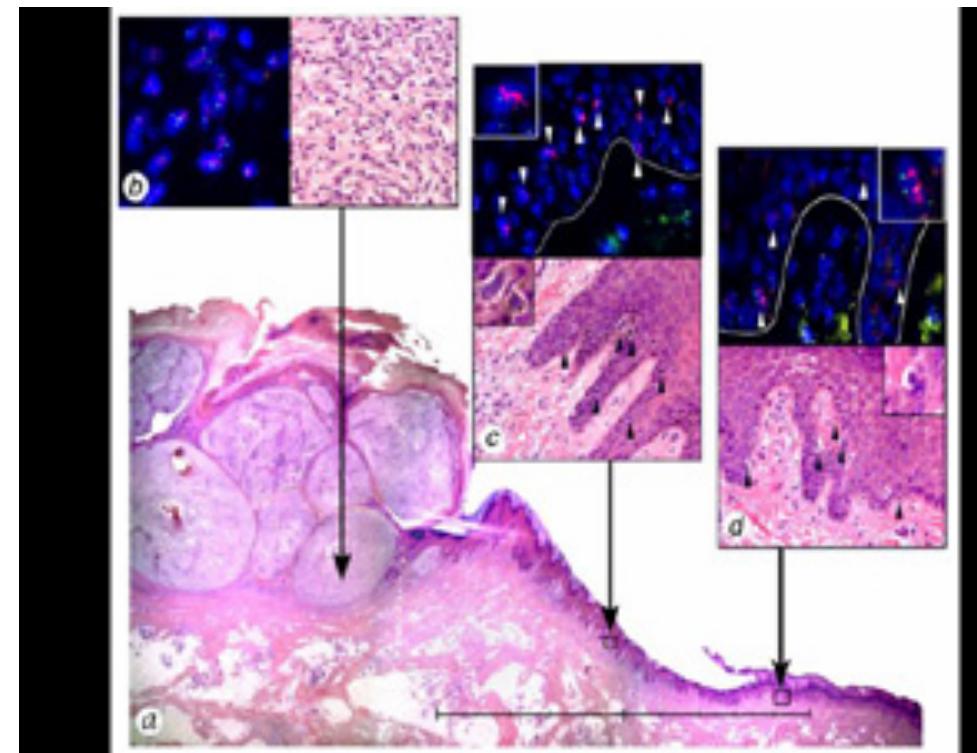


It must be appreciated that the assessment of grade is entirely subjective and that a degree of overlap between them is inevitable.

- There is **variable lymphocytic and plasma cell infiltration** in the stroma supporting the invasive malignant epithelium, which probably represents a reaction by the **host's immune system** to tumor antigens as well as a response to **tumor necrosis and ulceration**.

Most oral squamous cell carcinomas are **extremely locally destructive**.

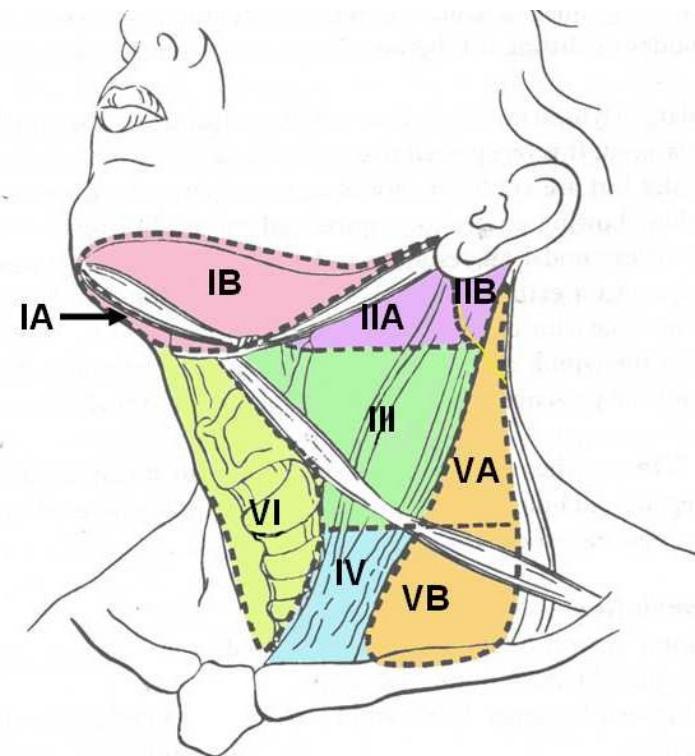
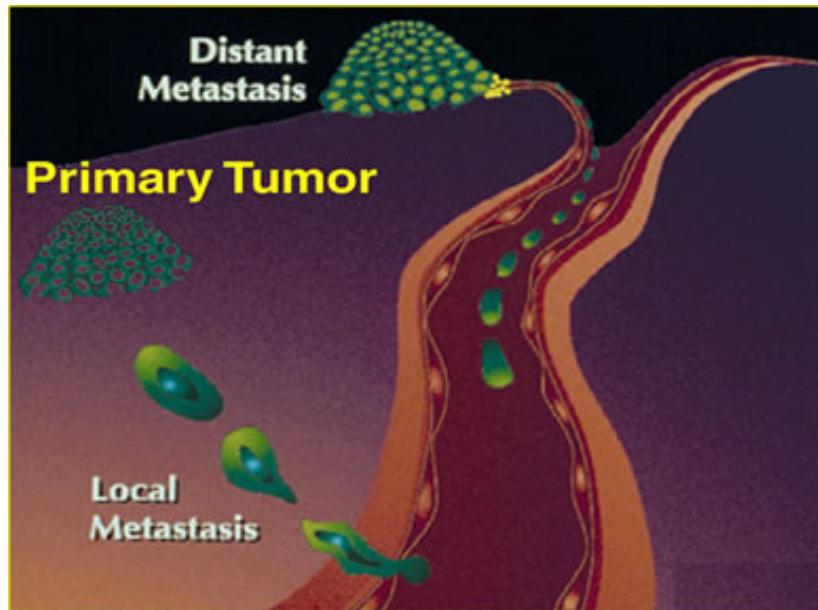
- The **pattern of infiltration** of the adjacent tissues by the neoplastic epithelium is variable.
- **broad front of invasion** ( better prognosis), in others separate islands of carcinoma or even individual malignant cells may be seen well in advance of the main growth.



Invasion of bone occurs as a result of local spread.

- The main **route of entry** is through the crest of the ridge in edentulous.
- In the dentate patient, tumor may also invade via the **periodontal ligament**.

- The cervical lymph nodes are usually divided into five groups .
- The risk of distant metastases increases with increasing involvement of nodal metastases in the neck.



# Prognosis

**The further back in the mouth the tumor, then the worse the prognosis, why?**

- ✓ Tend **not to be diagnosed** at an early stage,
- ✓ The **rich lymphatic drainage** around the base of the tongue may also favor early metastatic spread.

❖ Carcinomas in **females** have a **better prognosis** than carcinomas in males, why?

➤ **tend to be diagnosed and treated at an earlier stage.**

➤ **Age** affects prognosis, partly, why?

- ✓ With increasing age the patient becomes less well able to withstand extensive surgery or radiotherapy.
- ✓ **Reduction in the effectiveness of cell-mediated immune responses** may also be involved.

**Local recurrence at the primary site, or within the neck in patients with metastatic disease, is the major cause of death.**

The major factors thought to influence prognosis have been incorporated into **clinical staging** systems which assess the extent of disease in the patient.

The most widely used is the **TNM system** which is based on three parameters:

- **T**, the size of the primary lesion;
- **N**, the extent and distribution of metastases in the regional lymph nodes;
- **M**, the presence or not of distant metastases.

Primary Tumor Size	Description
T0	No evidence of primary site
Tis	Carcinoma in situ
T1	2cm or less in greatest diameter
T2	More than 2cm but less than 4 cm
T3	More than 4 cm
T4a	Oral cavity: Tumor invade cortical bone or extrinsic tongue muscles, or maxillary sinus or skin of face. (Resectable)
T4 b	Tumor involve masticator space, pterygoid plate, or skull base and/or encases internal carotid artery (unresectable)

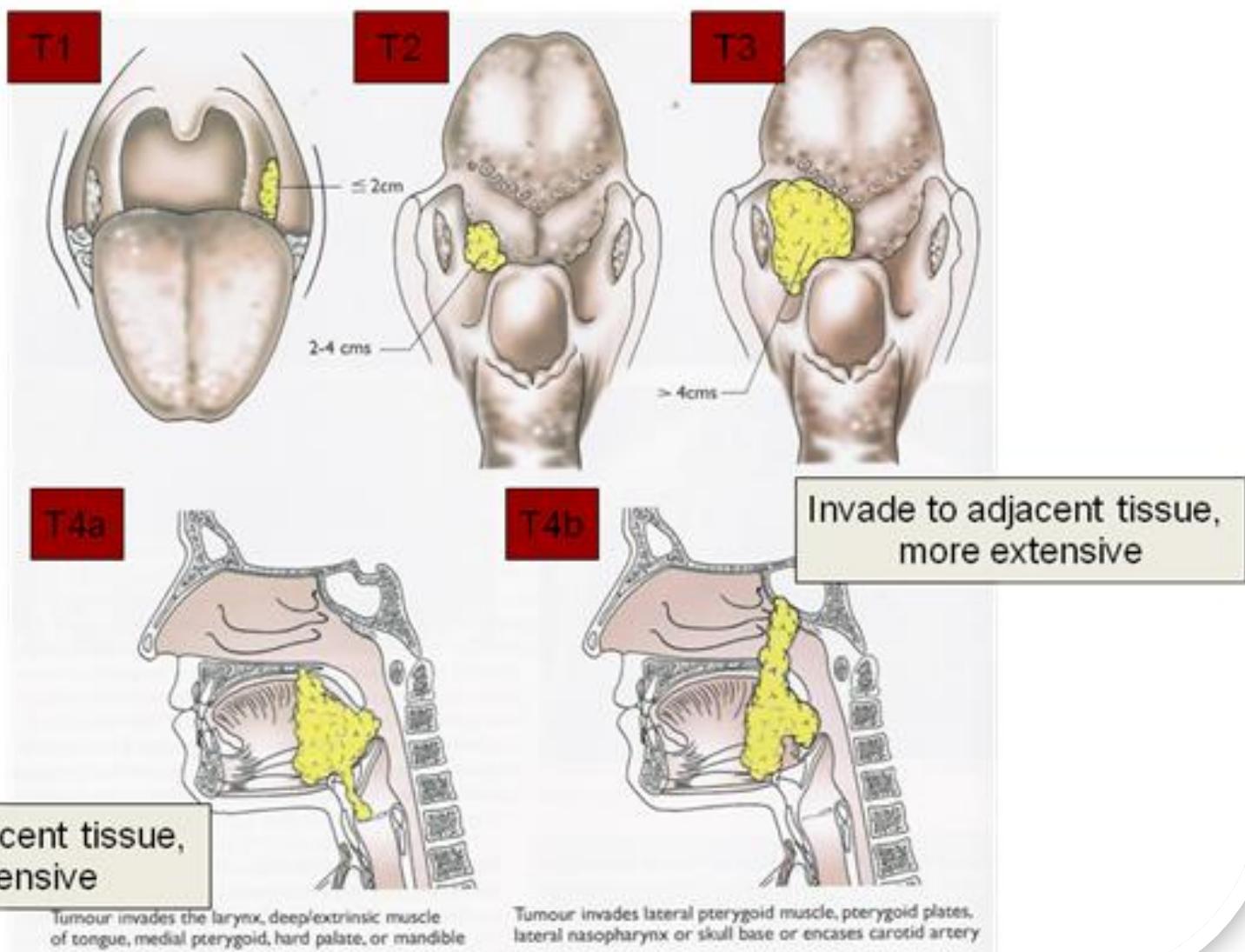
Regional LN involvement	Description
NX	Nodes could not be or were not assessed
N0	No regional LN metastasis
N1	Metastasis in single ipsilateral node 3 cm or less in greatest dimension
N2 a	Metastasis in single ipsilateral node 3 cm ,but not greater than 6 cm in greatest diameter;
N2 b	Metastasis in multiple ipsilateral node , none more than 6 cm in greatest diameter;
N2 c	Metastasis in bilateral or contralateral nodes, none more than 6 cm in greatest diameter.
N3	Metastasis in a node more than 6 cm in greatest diameter

Involvement of distant metastasis	Description
MX	Distant metastasis was not assessed
MO	No evidence of distant metastasis
M1	Distant metastasis is present

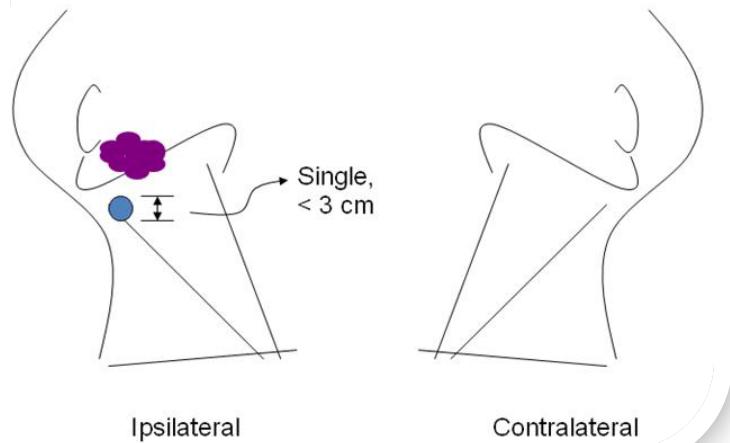
# **TNM clinical stages of oral SCC**

Stage	Classification	5yrs. survival
I	T1N0M0	72%
II	T2N0M0	58%
III	T3N0M0, or T1, T2, or T3, N1M0	45%
IVA	T4aN0 or N1M0, or T1,T2,T3 or T4 N2M0	22 %
IVB	Any TN3M0 or T4b any NM0	
IVC	Any T Any N & M1 lesion	

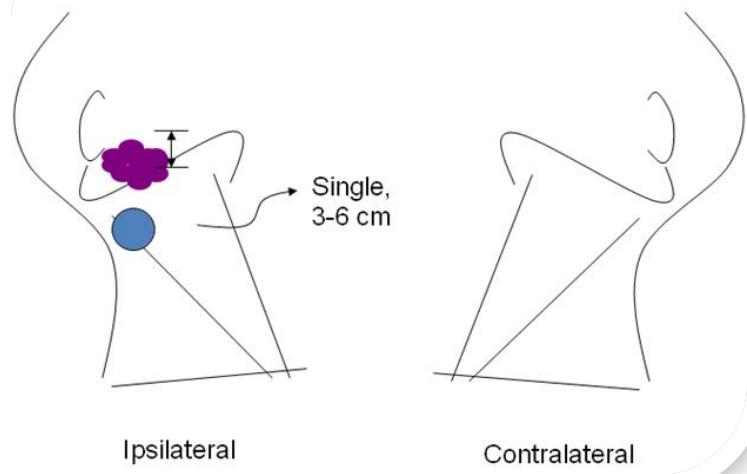
## T stage of oropharyngeal cancer



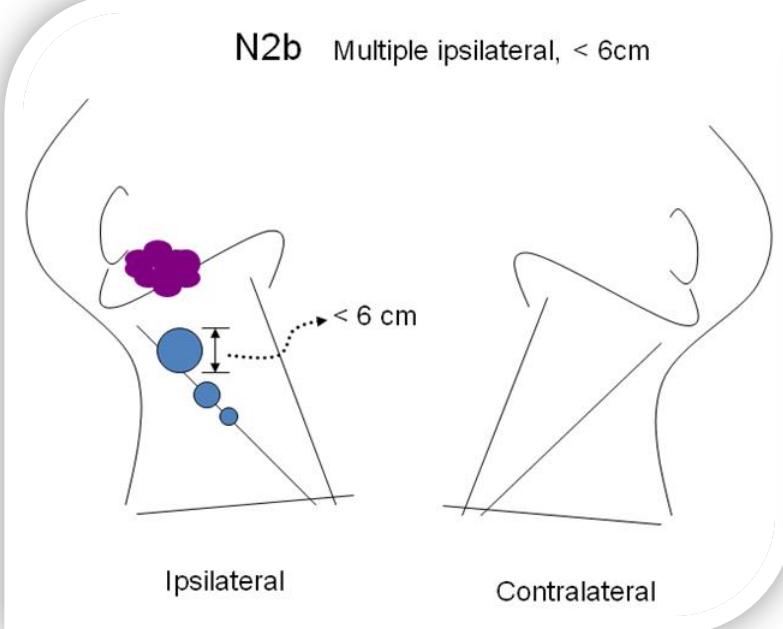
**N1** Single ipsilateral, < 3cm



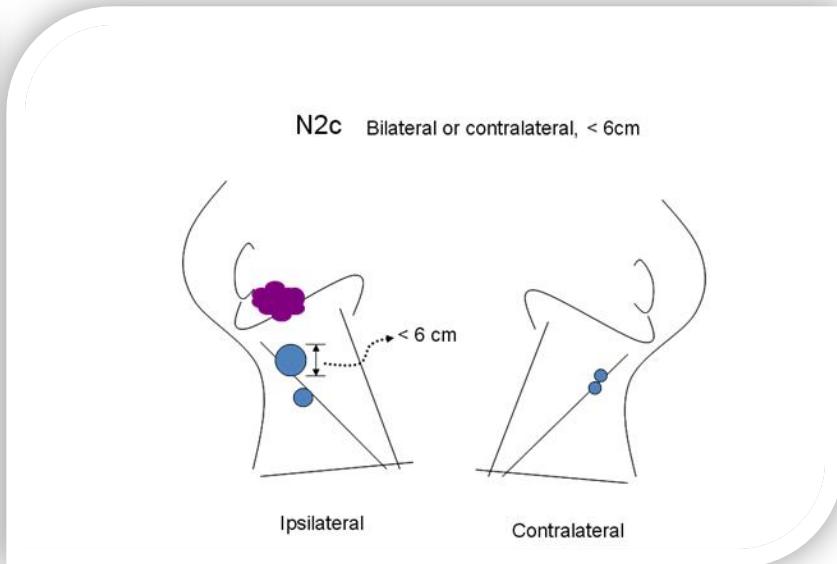
**N2a** Single ipsilateral, 3-6cm



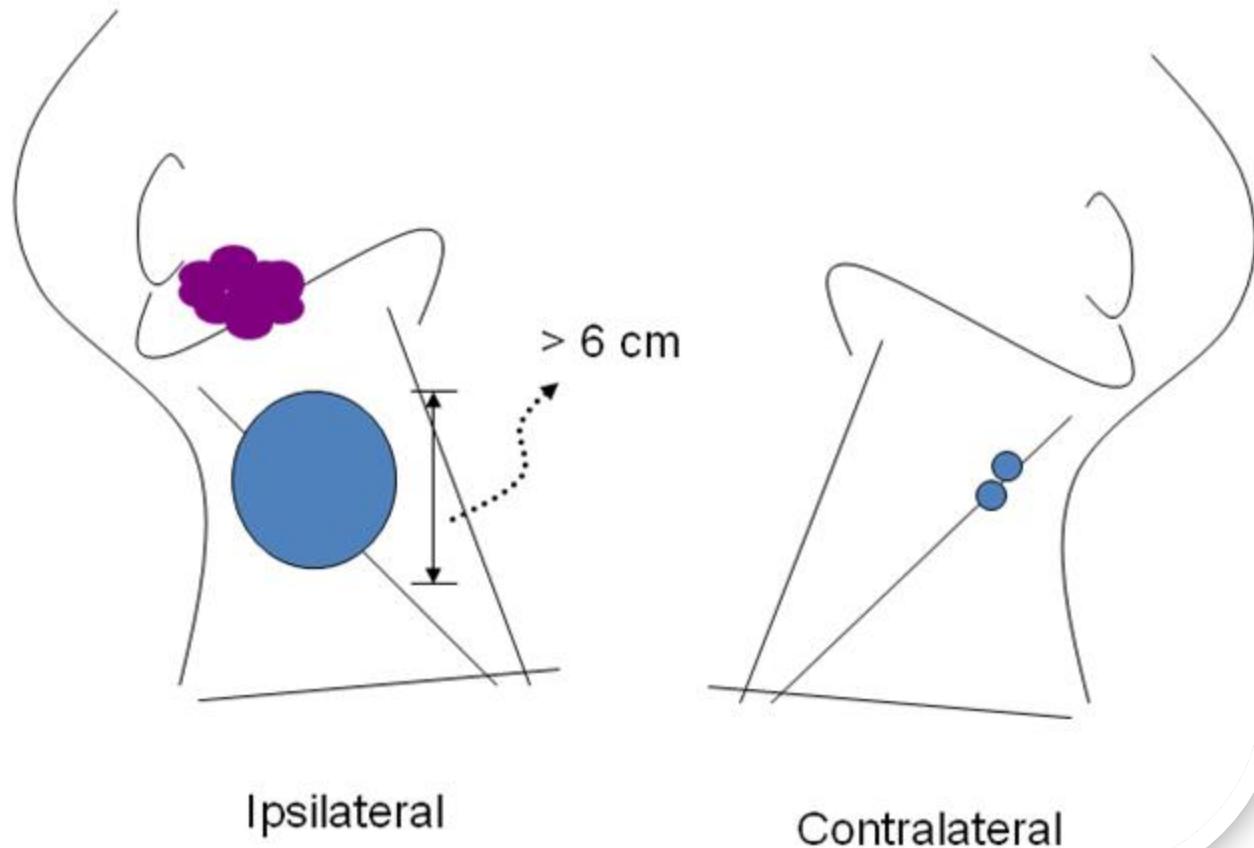
**N2b** Multiple ipsilateral, < 6cm



**N2c** Bilateral or contralateral, < 6cm



**N3 Any LN > 6cm**



## Field Concretization

The term field cancerization has been utilized to explain the followings:

- (a) Oral cancer developing in multifocal areas of a pre-cancerous change;
- (b) abnormal tissues surrounding the tumor;
- (c) oral cancer often consisting of multiple independent lesions that may coalesce;
- (d) the persistence of abnormal tissue even after surgery may explain secondary primary tumor and recurrences.

The concept of field cancerization can be interpreted in different ways to explain phenomenon of secondary primary tumors:

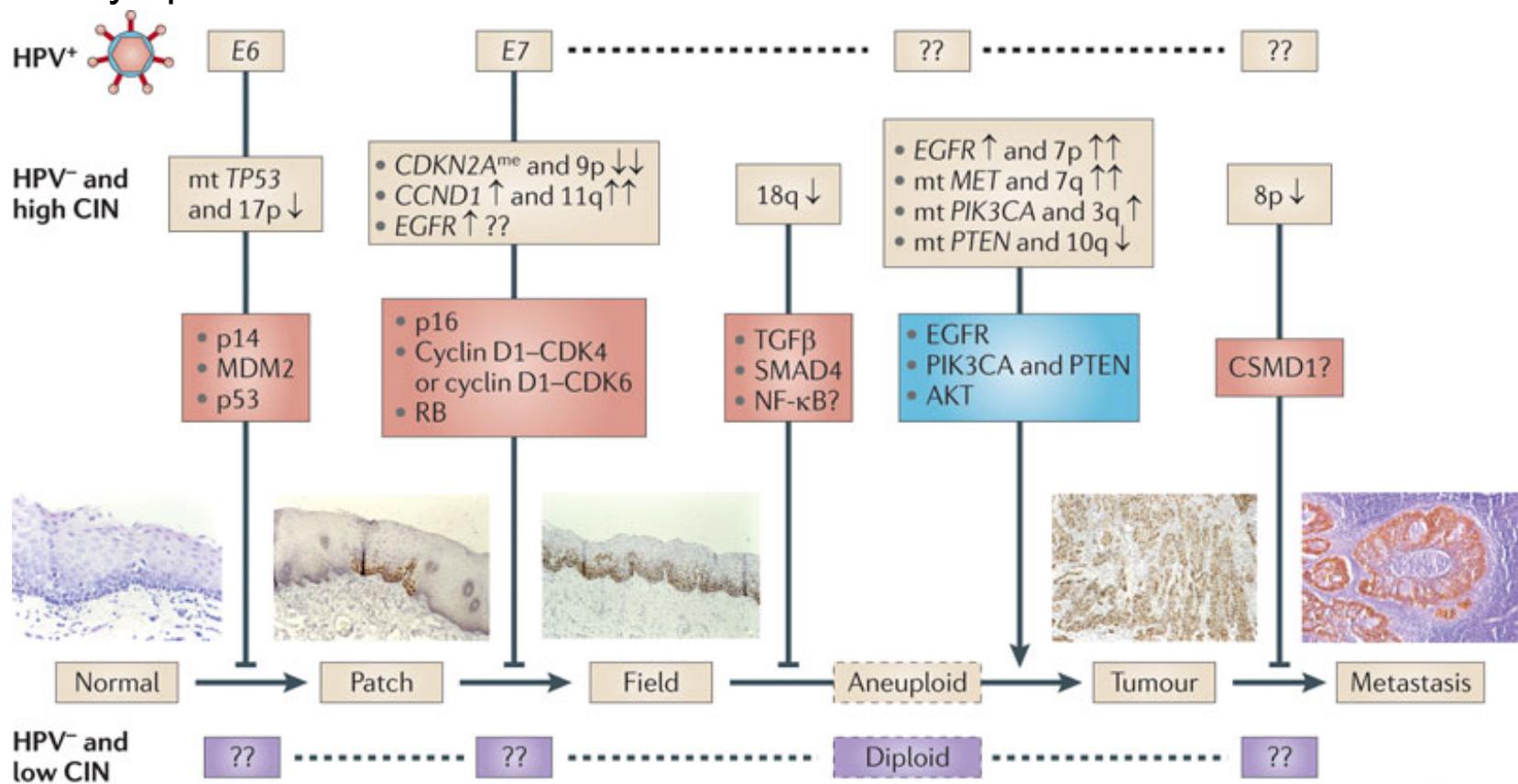
- (a) **In classic view**, large areas of aero -digestive tissue are affected by long-term exposure to carcinogens.

*In this pre-conditioned epithelium, multifocal carcinomas can develop as a result of independent mutations;*

- (b) **in terms of clonal theory**, a single cell is transformed and gives rise to one large, extended, pre-malignant field by clonal expansion and gradual replacement of normal mucosa.

## Risk Factors:

- Oral lichen planus (OLP)**, Activated inflammatory cells and cytokine network promote squamous tumorigenesis, influence clonal spreading, and thus support process of field cancerization.
- Tobacco** can cause morphological changes in cells of normal buccal mucosa in patients with malignant disease. The changes include increase in nuclear size, discontinuous nuclear membrane,, absence of a single large nucleolus and altered nuclear-cytoplasmic ratio.



## **Early detection and prevention**

### Potential Biomarkers for Oral Carcinogenesis

<b>Category of biomarkers</b>	<b>Measurements</b>
Genomic	Micronuclei, DNA adduct, DNA content, Chromosomal aberration
Oncogenic	Oncogenic expression, Modified tumor suppressor genes, Src genes
Proliferation	Nuclear and cyclin-related antigens, Mitotic frequency, Ornithine decarboxylase (ODC), Polyamines
Differentiation	Cytokeratins, Transglutaminase Type I, Transcription factor (AP)-1
Oxidative stress	Glutathione S-transferase, Stress proteins (HSPs), Superoxide dismutase
Apoptosis	Bcl-2 family, Chromatin condensation factors, Caspases, Mitochondrial pathway
Immunologic	Various cytokines

***Field cancerization can be identified by molecular analyses of various markers like:***

- LOH, microsatellite alterations, TP53 mutation & X chromosome inactivation.
- Field cancerization does not appear to be associated with malignancies attributed to HPV infection.

## Prognostic and Predictive Markers for Oral Squamous Cell Carcinoma

1	Demographic Data	<ul style="list-style-type: none"> <li>• Young Vs Old</li> <li>• Married Vs Single or divorced</li> <li>• Poor Vs wealthy</li> <li>• Tobacco &amp; alcohol Vs none</li> </ul>	Better Better Better Poor
2.	Tumor Stage	<ul style="list-style-type: none"> <li>• High tumor stage</li> <li>• Nodal metastasis <math>&gt; 1\text{cm}</math></li> <li>• Contralateral vs ipsilateral</li> <li>• Extracapsular spread</li> </ul>	Poor
3	Tumor thickness	<ul style="list-style-type: none"> <li>• Tumor thickness <math>&gt; 4\text{mm}</math></li> </ul>	Worse prognosis
4	Tumor differentiation	<ul style="list-style-type: none"> <li>• Well differentiated vs poorly differentiated</li> </ul>	Better
5	Pattern of infiltration	<ul style="list-style-type: none"> <li>• Infiltrative vs smooth pushing margin</li> </ul>	Worse prognosis
6	Perineural infiltration	<ul style="list-style-type: none"> <li>• sensitive indicator for regional recurrence and distant metastasis</li> </ul>	Worse prognosis
7.	Excised margin	<ul style="list-style-type: none"> <li>• a margin <math>&gt; 5\text{ mm}</math> is clear, 1-5 mm is close and <math>&lt; 1\text{ mm}</math> is involved</li> </ul>	
8	HPV Infection	<ul style="list-style-type: none"> <li>• favorable outcome attributable to an increased sensitivity toward radiotherapy</li> </ul>	
9	Genetic Mechanism	<ul style="list-style-type: none"> <li>• See the table next page</li> </ul>	

**Table 1: Gene-expression changes and prognosis of oral squamous cell carcinoma**

Pathways affected	Genes studied	Changes in expression	Prognostic effect
Signaling pathways	pEGFR	Over	Poor prognosis
	c-erb-2,3,4	Coexpression	Decreased survival
Cell cycle/apoptosis	TP53	Over	Poor survival
	P16 (INK 4A)	High expression	Improved survival
	P14 (ARF)	Expression	Improved survival
	P21 WAF1	Expression	Poor prognosis
	Cyclin D1	Over expression	Poor survival
	P63	Over	Poor survival
	Suvivin	Expression	Poor prognosis
Adhesion/mobility degradation	E-cadherin	Reduced	Local regional failure
	P-cadherin	Reduced	Local regional failure
	S100 A4	Loss	Poor prognosis
	CD44	Loss	Metastasis
	MMPs 2 and 9	Increased	Poor prognosis
	TIMPs 1 and 2	Expression	Poor prognosis
	Ezrin	Over	Shorter survival
	Maspin	Loss	Improved survival
	Nm23H1	Deregulation	Poor outcome
	VEGF	Elevation	Increased severity
Angiogenesis			
Immortalization	Telomerase	Activation	Invasive
Prostaglandin synthesis	COX2	Increased expression	Poor outcome

## Treatment & Prognosis:

Clinical Staging guides the treatment of SCC.

**Lip Carcinoma:** Wedge resection

**Intraoral Carcinoma:** Early stage: Surgery &/or Radiotherapy

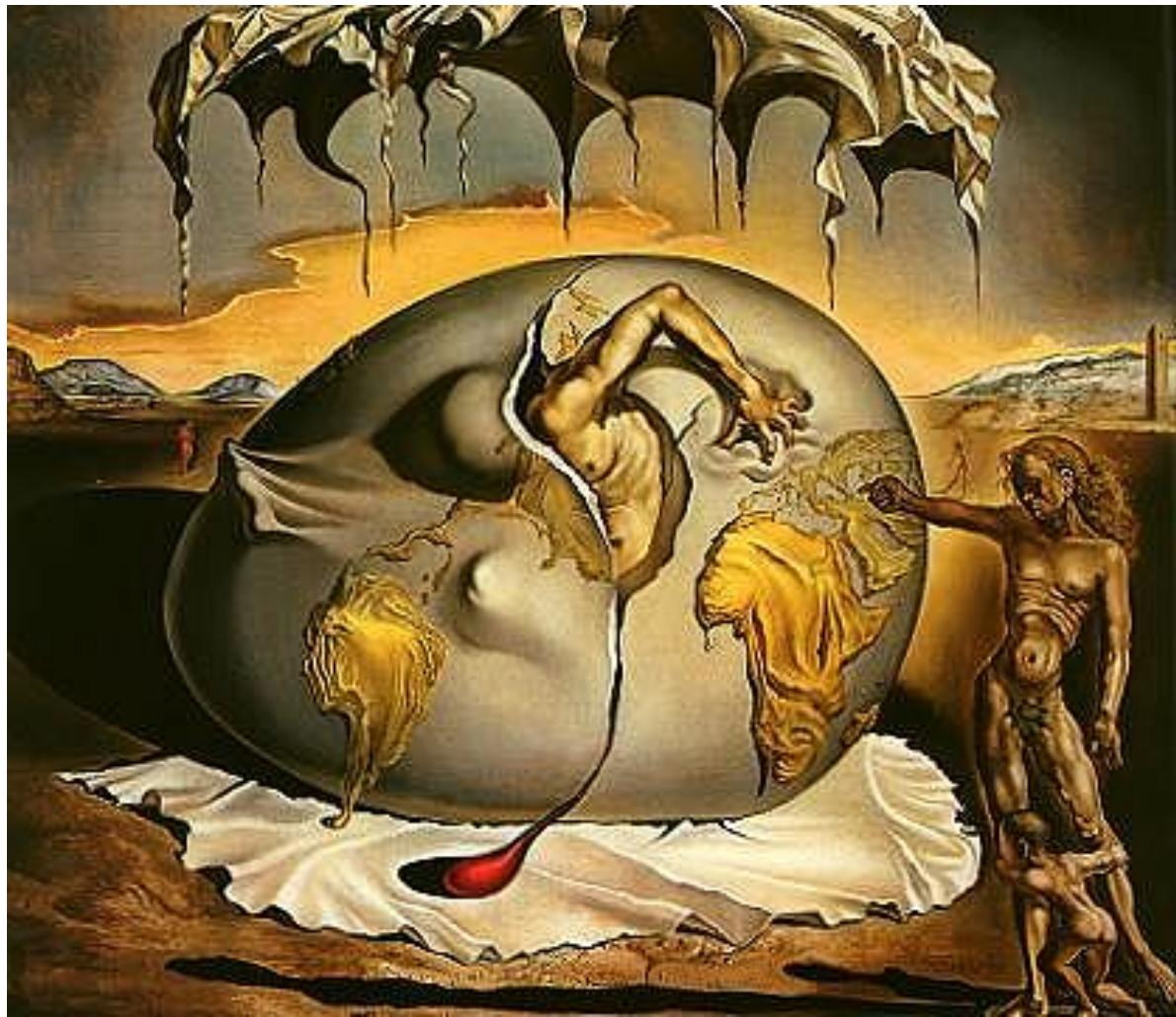
**Cervical lymph nodes involvement:** Radical Neck dissection or modified or selective neck dissection.

**Chemotherapeutic agents:** Platinum containing compounds “ cisplatin”, 5 FU.

**Neoadjuvant chemotherapy** could be used initially to shrink the tumor prior to additional therapy.

**Targeted therapy:** Cetuximab & Panitumomab (monoclonal Abs)

Tyrosine kinase inhibitors (Erlotinib) directed against EGFR, anti VEGF & mTOR inhibitors



Thank You