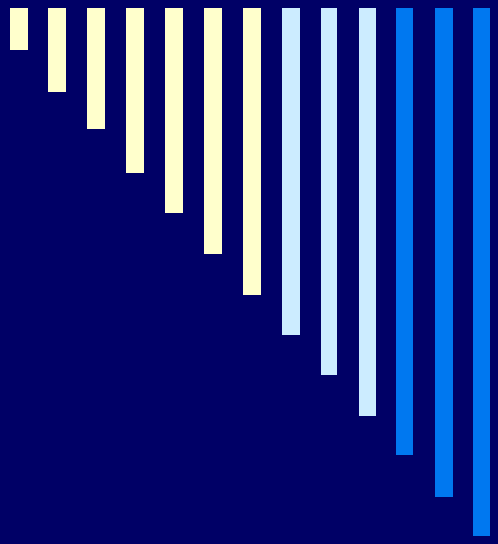


Epithelial malignancies

Squamous cell carcinoma

- In india, it is the most common cancer – 94%
- Risk of oral cancer increases with age especially for males (3:1)
- Multi-factorial etiology
  - Both extrinsic and intrinsic factors play a role – Co-carcinogenesis

Etiology

- Tobacco smoke
- Smokeless tobacco
- Betel quid
- Alcohol
- Radiation
  - Sunlight – for vermilion cancers
  - X-radiation

Etiology

- General malnutrition
  - Iron deficiency anemia
  - Vitamin A deficiency
- Infections
  - Syphilis
  - Candidal infection
  - Oncogenic viruses
- Immunosuppression
- Oncogenes and tumor suppressor genes

Tobacco Smoking

- 2-3 times more risk in smokers than general population
- Increased risk for second primary carcinoma in the upper aerodigestive tract
- More in pipe and cigar smokers
- Dose dependent – increased risk with more cigarettes and longer duration of the habit.
- Higher risk in reverse smoking
- In non-smokers, SCC occurs in tongue/floor of mouth, younger females and mutations in tumor suppressor genes.

Smokeless tobacco

- Four times risk than general population
- 50% of cancers occur at the site of habitual placement

Betel quid

- Slaked lime enhances the absorption of molecules of other products like areca nut, betel nuts and tobacco leaf.
- 8% is the risk of development

Alcohol

- Synergistic effect with tobacco
- Acts as a potentiator or promoter for other causative factors
- Risk is dose dependent and time dependent
- With tobacco, the risk is 15%
- Liver cirrhosis could also be seen.
- With phenols, increased risk for nasal and nasopharyngeal cancer.

Radiation

- X-radiation during radiotherapy and UV rays from sunlight
- Risk of development of new primary oral malignancy
- Effect is dose dependent
- UV rays implicated for lip cancer.

Iron deficiency

- In severe chronic form called Plummer-vinson syndrome, increased risk for SCC in posterior mouth, oropharynx and esophagus.
- Develops in earlier age
- Altered functioning of epithelial cells leading to atrophy
- Presence of esophageal webs

Vit A deficiency

- Vit A leads to excessive keratinization and has a protective role
- In deficiency, there is increased risk for SCC

Syphilis

- Tertiary syphilis strongly associated with development of SCC in tongue.
- 4% is the risk
- This is rare today with the advent of effective antibiotics.

Candidal infection

- Candida could be superimposed on existing precancerous lesions
- Could produce nitrosamines that can promote carcinogenesis.

Oncogenic viruses

- Human papilloma viruses – 16,18,31,33
- Herpes simplex viruses – Type 2
- These agents could integrate into the host DNA and alter the regular growth and proliferation and may immortalize the infected cell.

Immunosuppression

- Lack of immunologic surveillance and attack
- The malignant cells cannot be recognized and detected at the early stage.
- In patients with AIDS, chemotherapy for malignancy or transplants are at increased risk for SCC.

Oncogenes and tumor suppressor genes

- Proto-oncogenes are present in normal cells and they regulate cell growth
- proto-oncogenes are activated by viruses, radiation or chemicals and form Oncogenes which stimulate excessive production of new genetic material
- Tumor suppressor genes regulate cell growth and lack of these genes can lead to malignancy.

Tumor suppressor genes

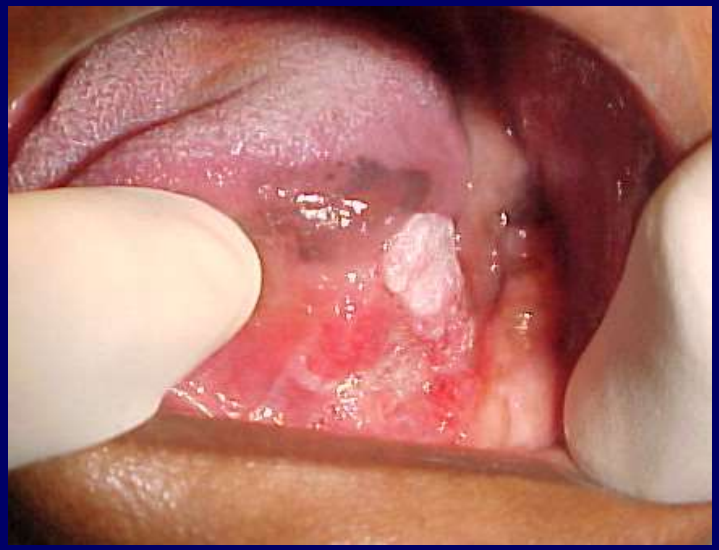
- Ras,
- myc,
- c-erbB,
- p53,
- pRb,
- E-cadherin
- Multiple mutations affecting inter-related components leads to malignancy.

Clinical features

- Usually in older men
- Minimal pain during the early phase
- Presents as
  - Exophytic –
    - As a mass – fungating, papillary or verruciform
    - Color depends on the amount of keratinization and vascularity
  - Endophytic – burrowing – ulcerated
    - Depressed, irregular ulcer with rolled out borders
    - Induration
  - Leukoplakic – white patch
  - Erythroplakic – red patch
  - Erythro-leukoplakic – combined white and red areas,

Clinical features

- Can involve the
  - Gingiva, alveolar mucosa and buccal mucosa – associated with betel quid placement
  - Tongue – posterior, lateral and ventral surfaces
  - Floor of the mouth – more among females, younger age, associated with second primary malignancy
  - Lips – most cases have actinic cheilosis
  - Oropharyngeal – most patients are unaware, tumor size is greater, increased risk for metastasis

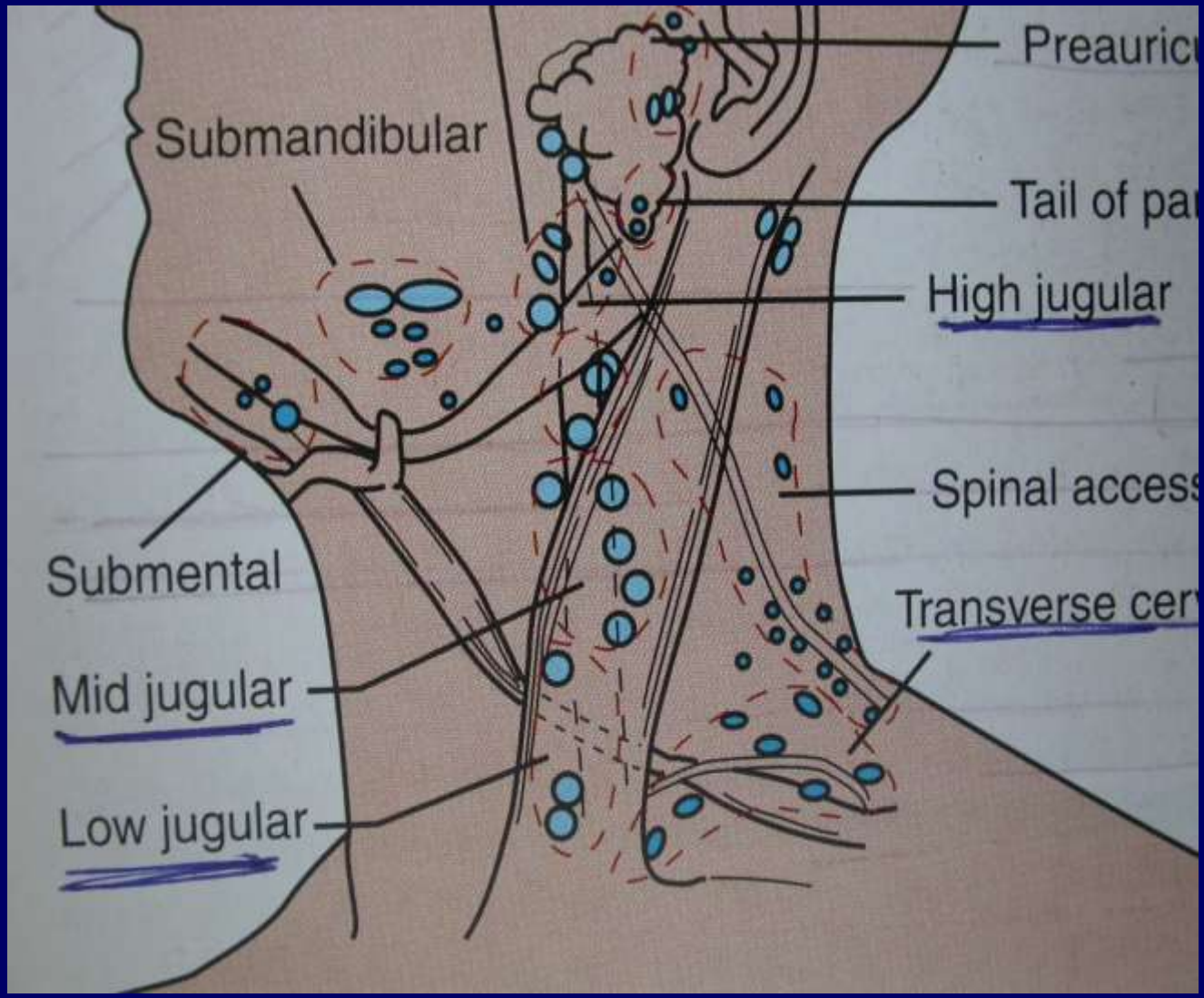


Metastasis

- The posterior or inferior location, larger lesions – increased risk for metastasis.
- Spreads largely through lymphatics to the ipsilateral cervical lymphnodes
- Metastatic nodes are firm to stony hard in consistency, non-tender and enlarged,
- In advanced stages, the nodes are fixed and multiple nodes (contralateral or bilateral nodes) may be involved.

Metastasis

- Ca of lower lip and oral floor – submental nodes
- Posterior portions of the mouth – superior jugular and digastric nodes
- Oropharynx – jugulo-digastric nodes or retropharyngeal nodes


Preauric
Submandibular
Tail of par
High jugular
Spinal access
Submental
Transverse cer
Mid jugular
Low jugular

Staging of disease

- Based on
  - the tumor size and
  - the extent of metastatic spread,
- Used to assess the prognosis and clinical outcome.
- TNM staging is widely used
  - T- Primary tumor size
  - N – Regional lymph node involvement
  - M – Involvement by distant metastasis

(TNM)- Primary tumor size

Tx	No available information on primary tumor
T0	No evidence of primary tumor
T1s	Only carcinoma in situ at primary site
T1	Tumor is less than 2cm in greatest diameter
T2	Tumor is 2 - 4cm in greatest diameter
T3	Tumor is greater than 4cm in greatest diameter
T4	Massive tumor greater than 4cm in diameter, with involvement of antrum, ptergygoid muscles, base of tongue or skin.

(TNM)- Regional LN inv

Nx	Nodes could not be or were not assessed
N0	No clinically positive nodes
N1	Single, clinically positive, homolateral node, less than 3cm in diameter.
N2a	Single, clinically positive, homolateral node, 3 - 6cm in diameter.
T2b	Multiple, clinically positive, homolateral nodes, none more than 6 cm in diameter
N3a	Clinically positive, homolateral node or nodes, one more than 6 cm in diameter
N3b	Bilateral, clinically positive nodes
N3c	Contralateral, clinically positive node or nodes.

(TNM)- Distant metastasis

Mx	Distant metastasis was not assessed
M0	No evidence of distant metastasis
M1	Distant metastasis is present.

TNM clinical staging

Stage	TNM classification	5 year survival rate
Stage I	T1 N0 M0	85%
Stage II	T2 N0 M0	66%
Stage III	T3 N0 M0 T1,T2, T3 with N1 M0	41%
Stage IV	Any T4 lesion Any N2 or N3 lesion Any M1 lesion	9%

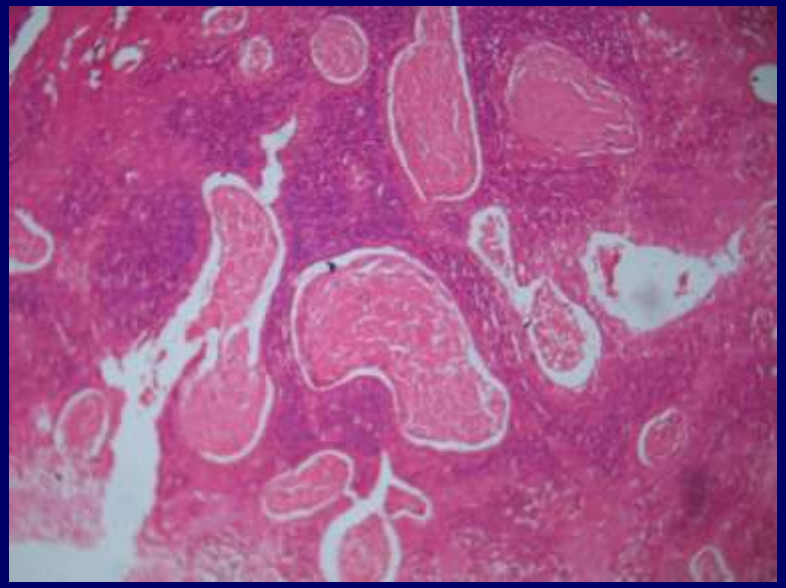
Histopathology

- Grading of tumors is done to assess the degree of resemblance to parent tissue and production of their normal product – epithelium and keratin
- Can be grouped into
  - Low grade / Well differentiated
  - High grade/ Anaplastic / Poorly differentiated
  - Intermediate grade / Moderately differentiated

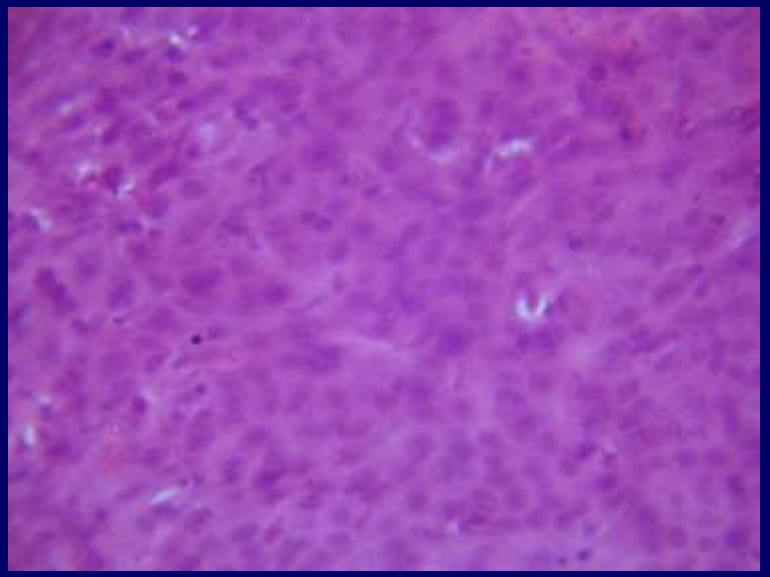
Histopathology

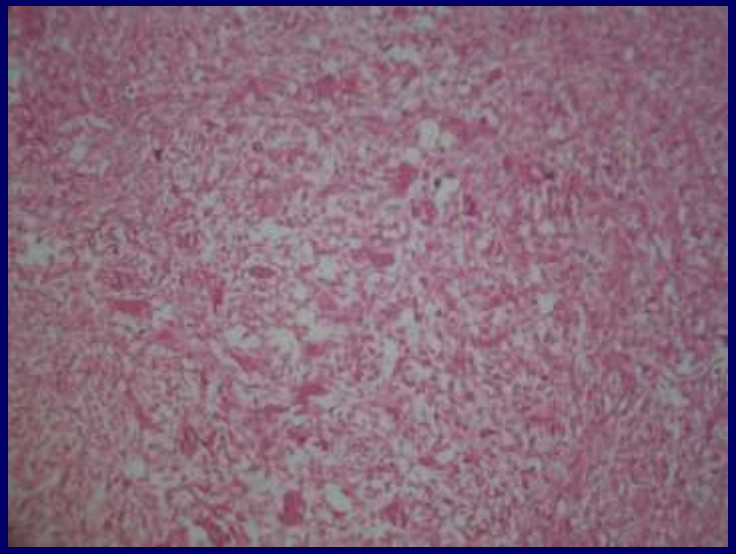
- Shows dysplastic epithelium with malignant cells in the connective tissue stroma in the forms of sheets, islands or cords
- Angiogenesis and inflammatory response
- Hyperchromatic nuclei with keratin pearl formation, individual cell keratinization,

Well differentiated



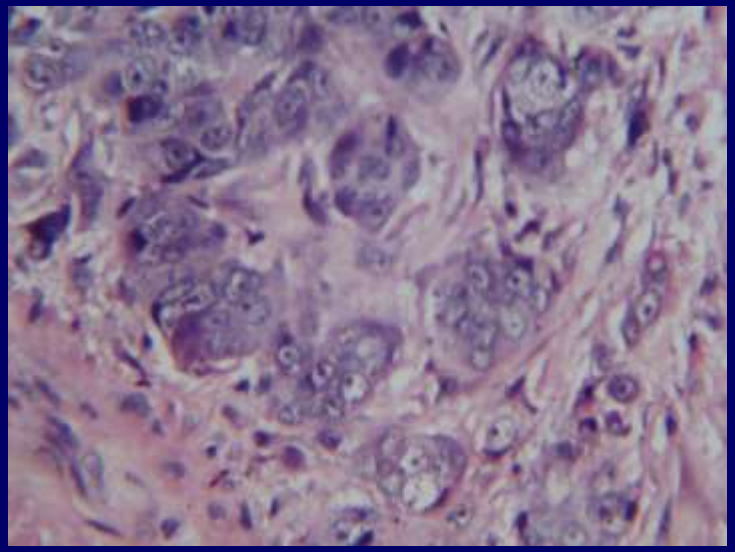
Moderately differentiated

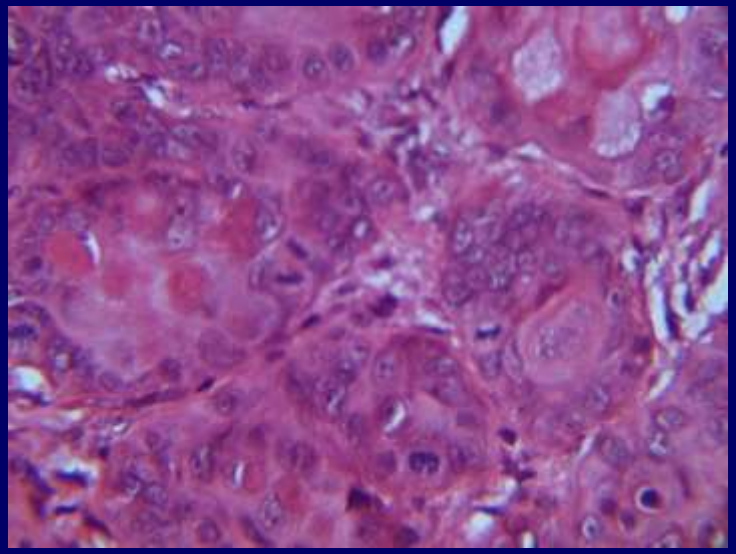




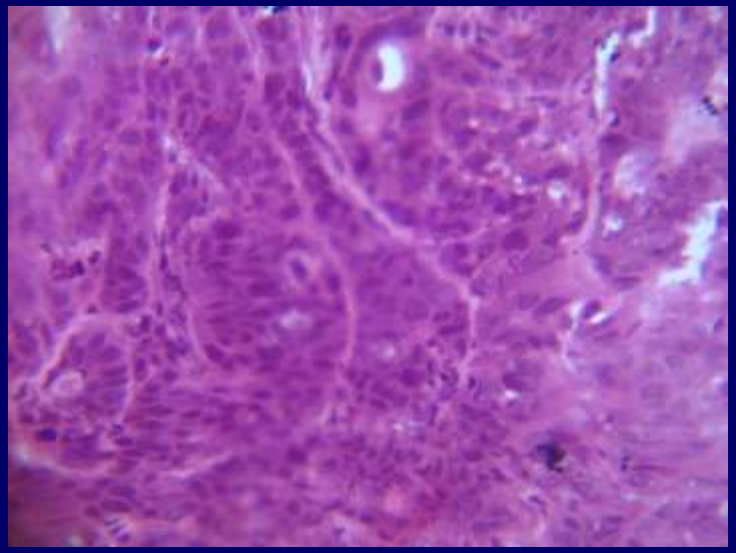
Poorly differentiated

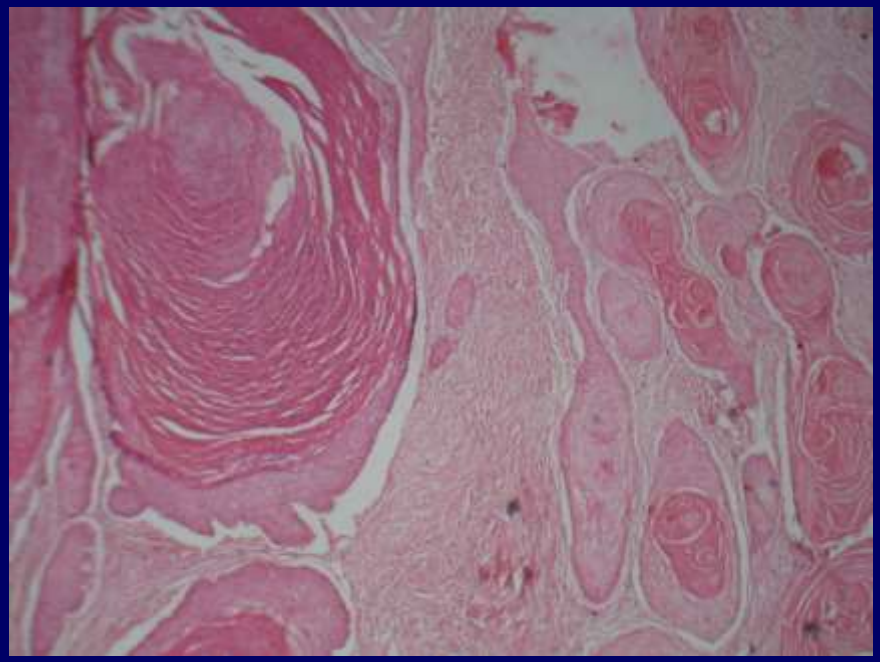
Epithelial islands



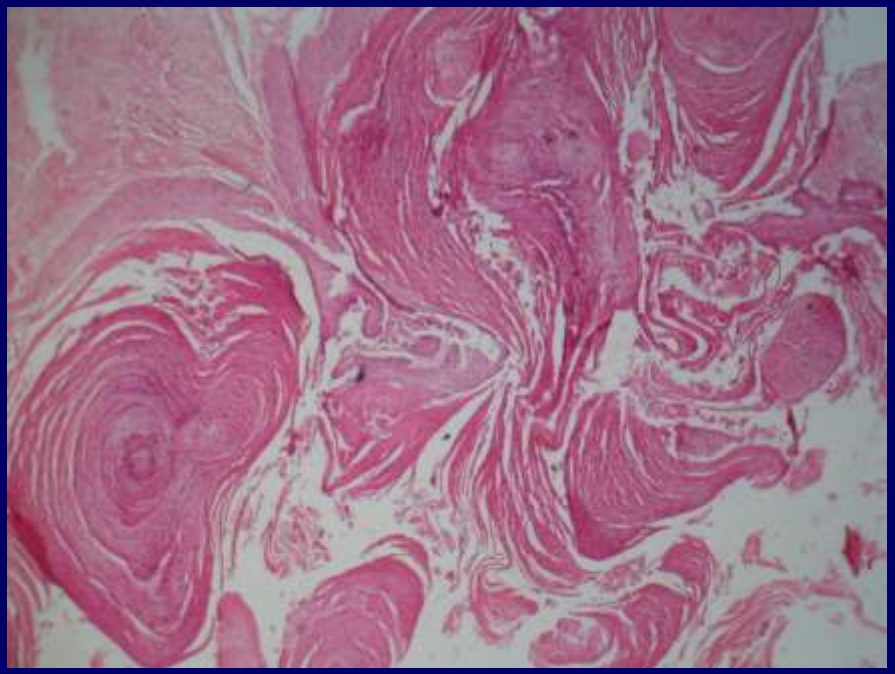


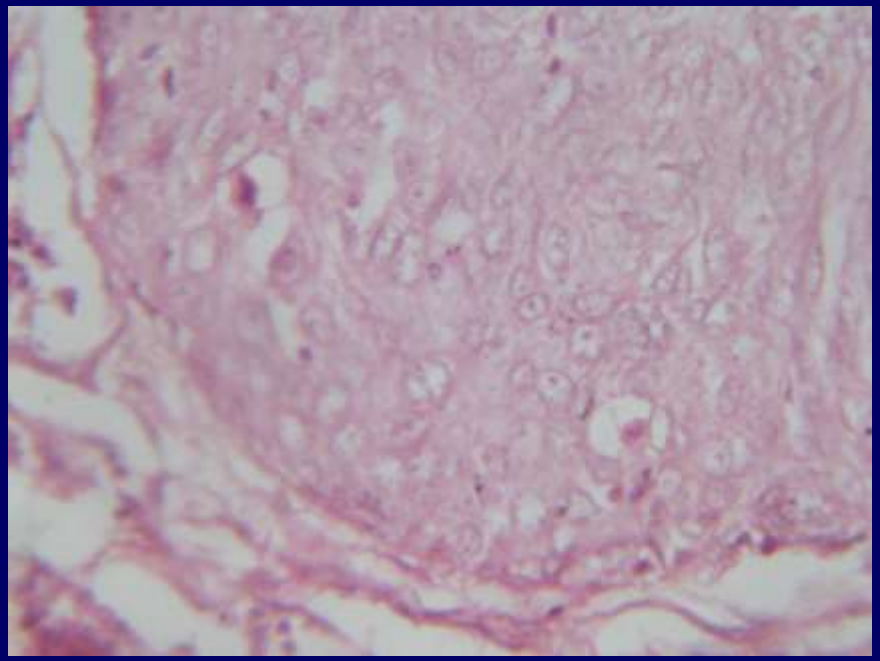
Epithelial cords



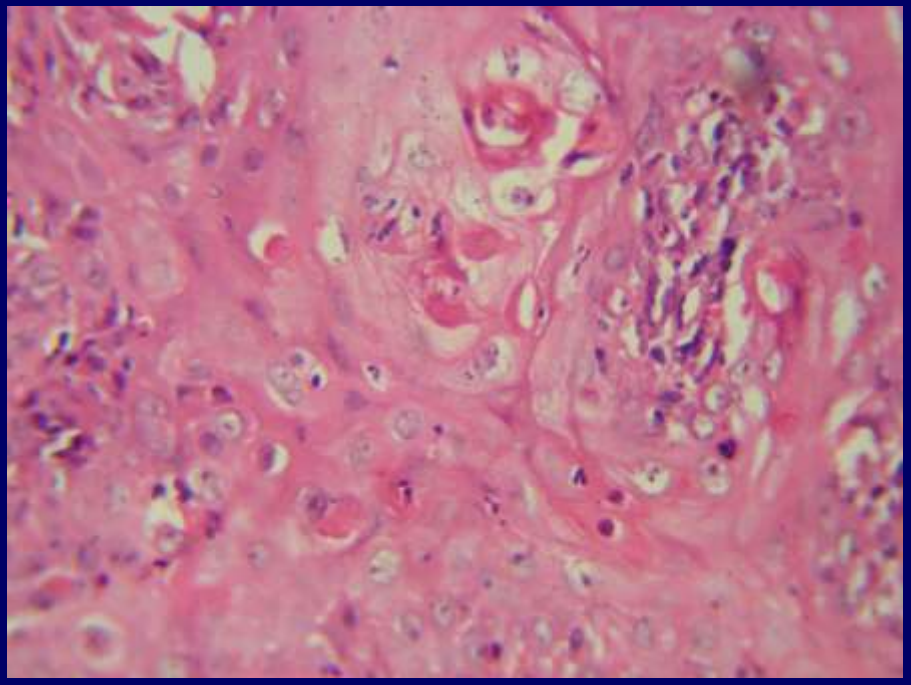


Keratin pearls

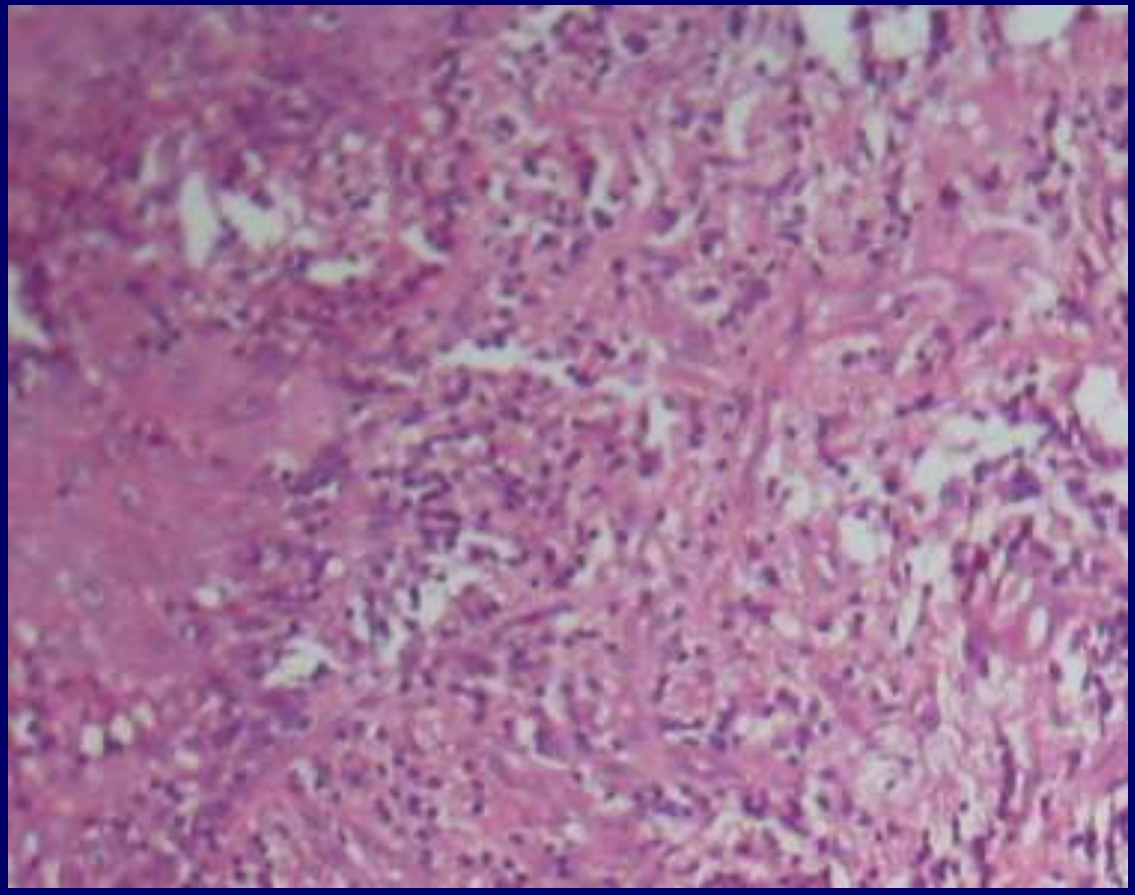


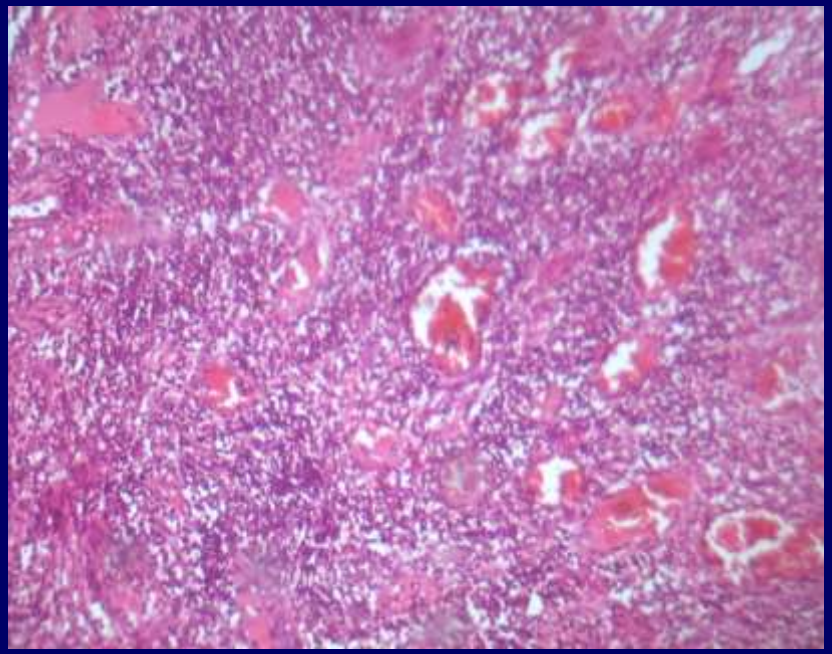


Individual cell keratinization

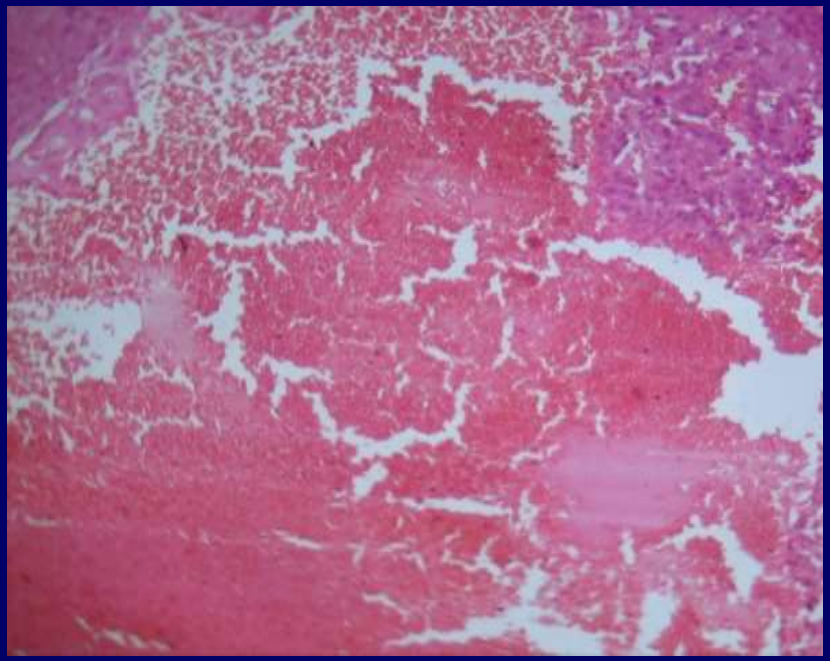


Inflammatory cells

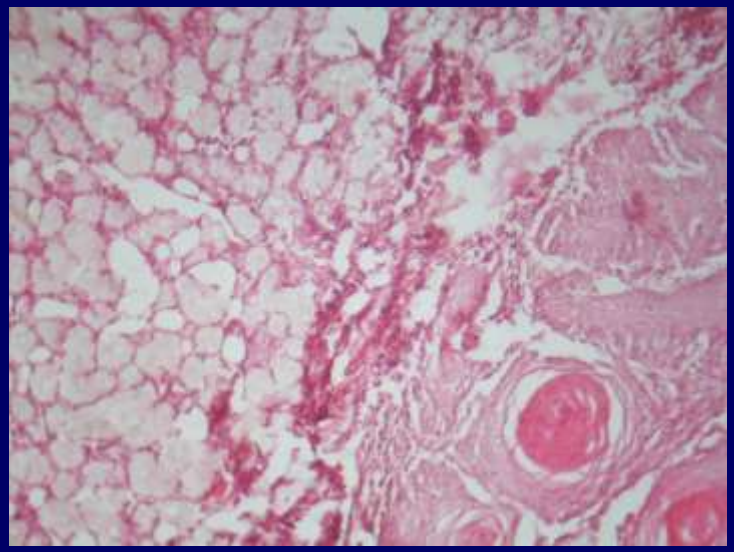


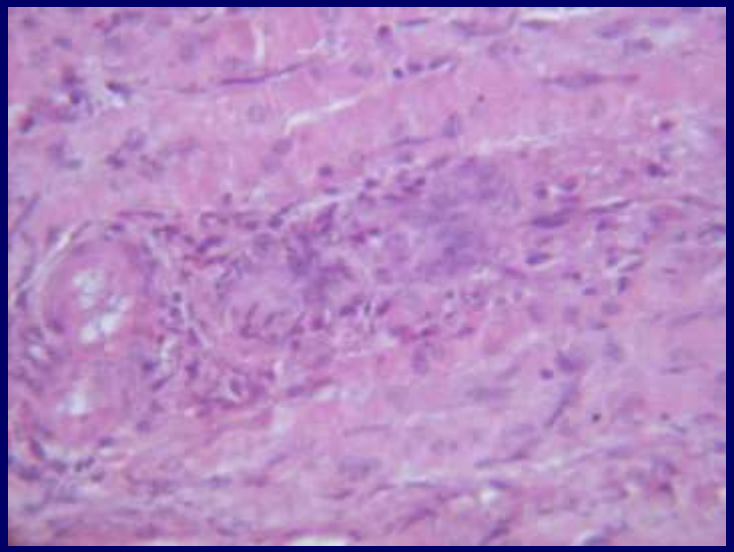


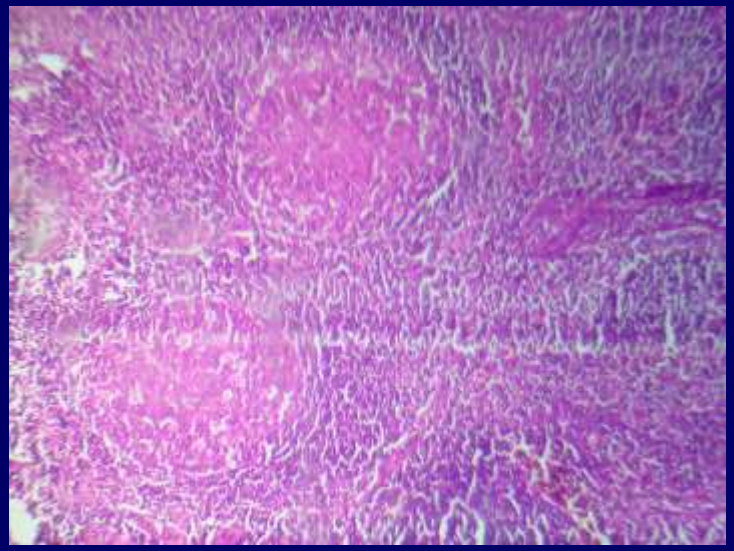
Vascularity & haemorrhage

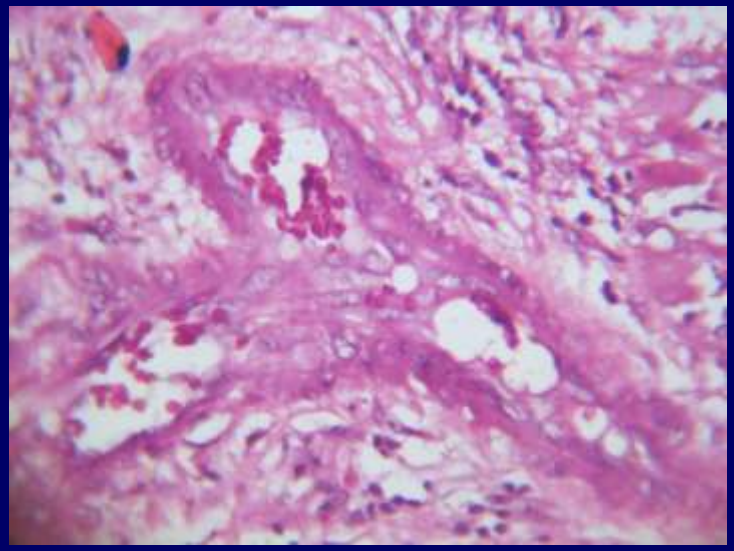


Invasion









Treatment and prognosis

- Surgery
- Chemotherapy
- Radiation therapy
- Based on clinical staging – prognosis assessment

Recurrences

- Improper management
- Recur at the same site
- Occur at different sites other than the primary
- Occur at distant site

Multiple carcinomas

- Synchronous tumors – additional concurrent tumors
- Metachronous tumors – additonal tumors at a later time
- Involvement of esophagus, upper aerodigestive tract, stomach, lungs and other sites
- Highest incidence in patients who continue smoking and alcohol abuse after therapy.

Field cancerization

- Diffuse exposure to local carcinogens, increases the malignant transformation potential of all exposed epithelial cells
- Genetic alterations could be detected.
- Additional tumors are not clones of original – they have not migrated from the original tumor cells.

Variants of SCC

- Verrucous carcinoma – low grade
- Spindle cell carcinoma – high grade
- Adenosquamous carcinoma – high grade
- Basaloid squamous cell carcinoma – high grade

Verrucous carcinoma

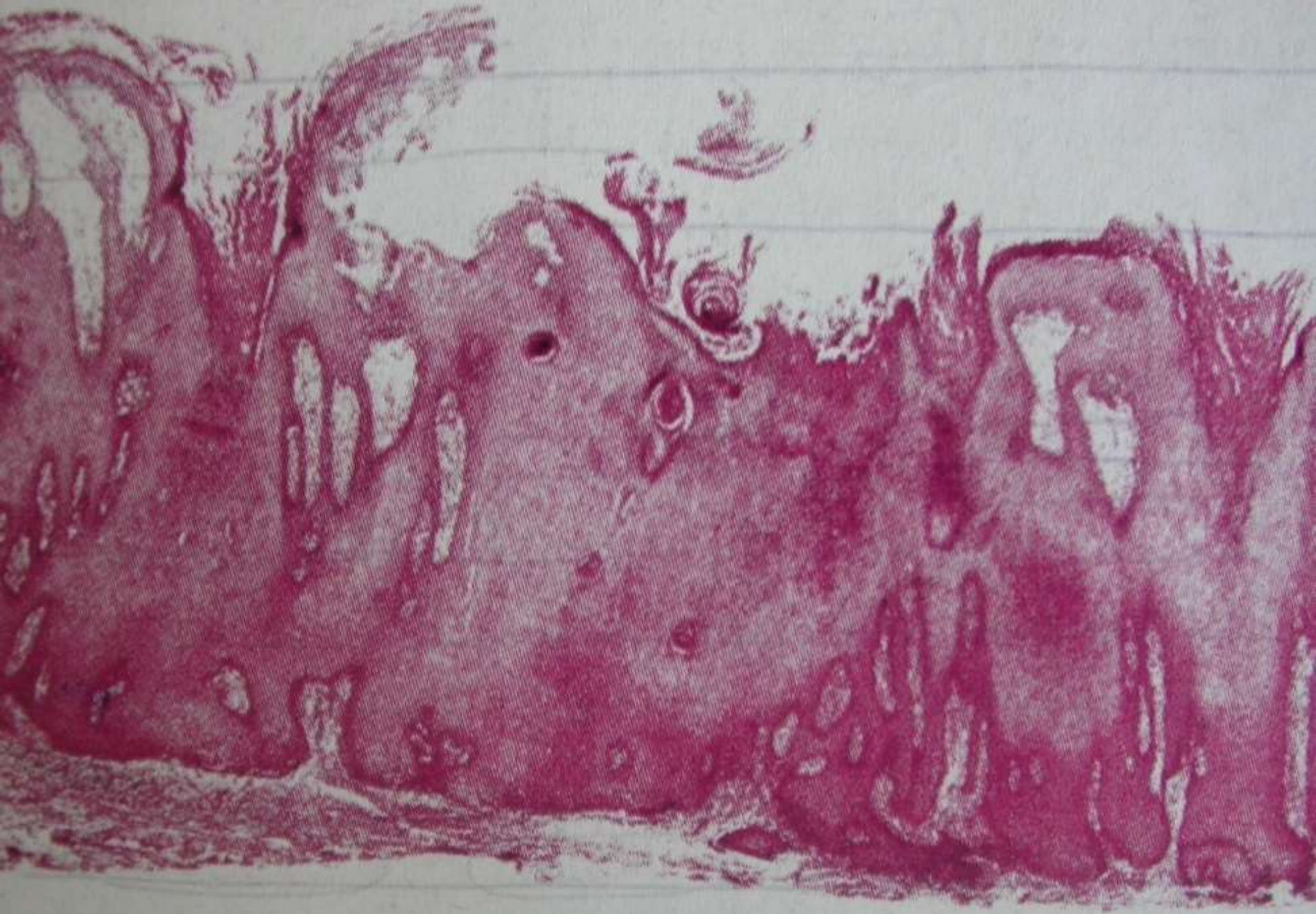
- Also called snuff dippers cancer, Ackerman's tumor
- Low grade variant of SCC
- First reported by Ackerman in 1948 is association with tobacco usage
- Also occurs in larynx, vagina, rectum, breast, axilla, ear canal and soles of feet.
- HPV 16 & 18 can be seen in these lesions.

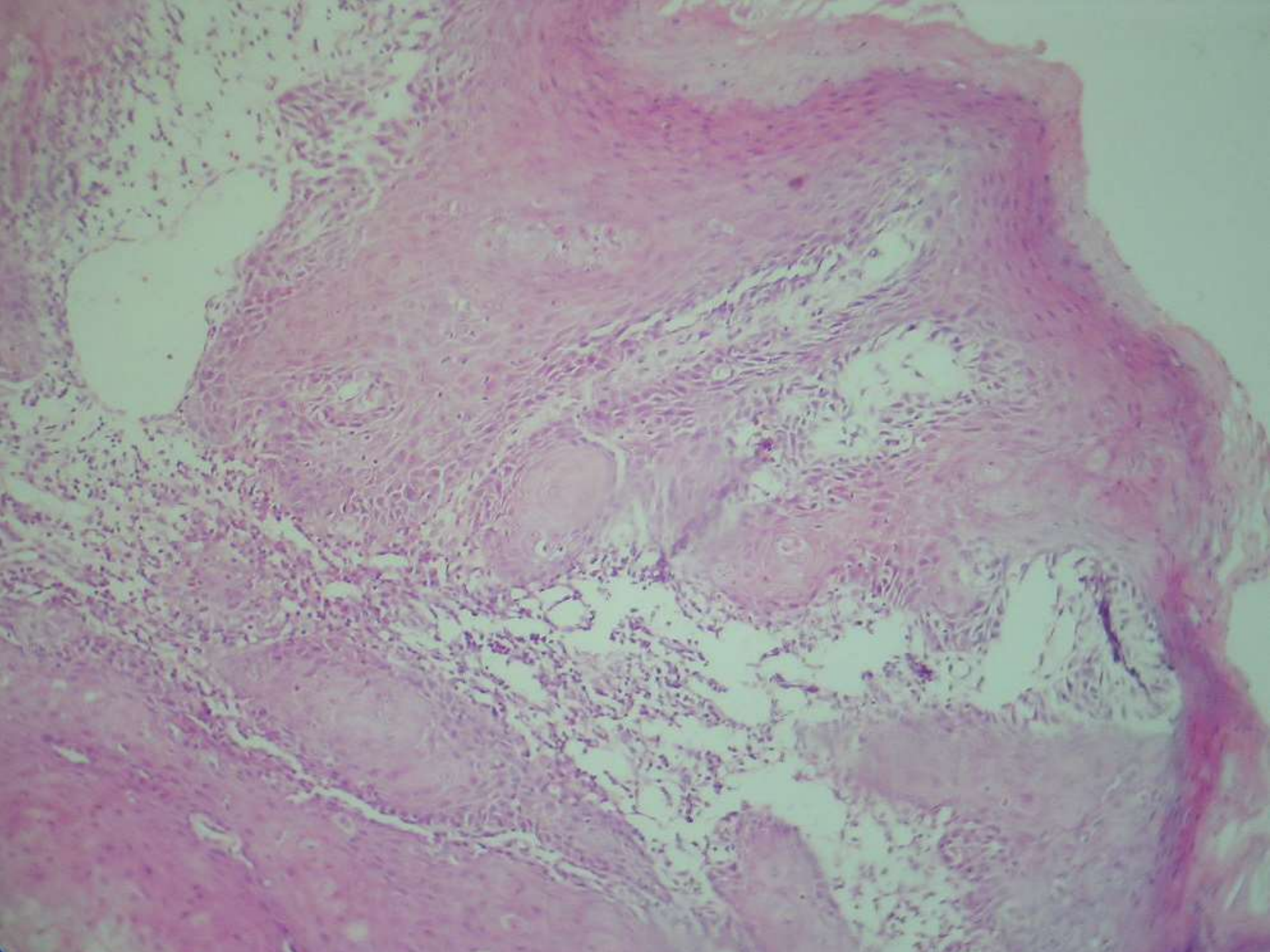
Clinical features

- In men older than 55 yrs
- In mandibular vestibule, buccal mucosa and hard palate
- Often corresponds to the site of chronic tobacco placement
- Diffuse, well demarcated, painless, thick plaque with papillary or verruciform surface projections
- Typically white
- It can develop as a component of proliferative verrucous leukoplakia

Histopathology

- Benign microscopic appearance
- Wide, elongated rete ridges which push into the underlying connective tissue
- Show abundant keratin production
- Parakeratin plugs – keratin filling the numerous clefts and crypts
- Lesional cells show normal maturation
- Intense chronic inflammatory infiltrate
- SCC could be seen in association.





Treatment and prognosis

- Surgical excision without radical neck dissection
- Metastasis is extremely rare

Spindle cell carcinoma

- Rare variant with dysplastic epithelial cells with an invasive spindle cell element.
- Considered to be anaplastic type of carcinoma cells.
- Lesional cells have the ability to produce mesenchymal intermediate filaments.
- Can occur as recurrences after radiotherapy – dedifferentiation

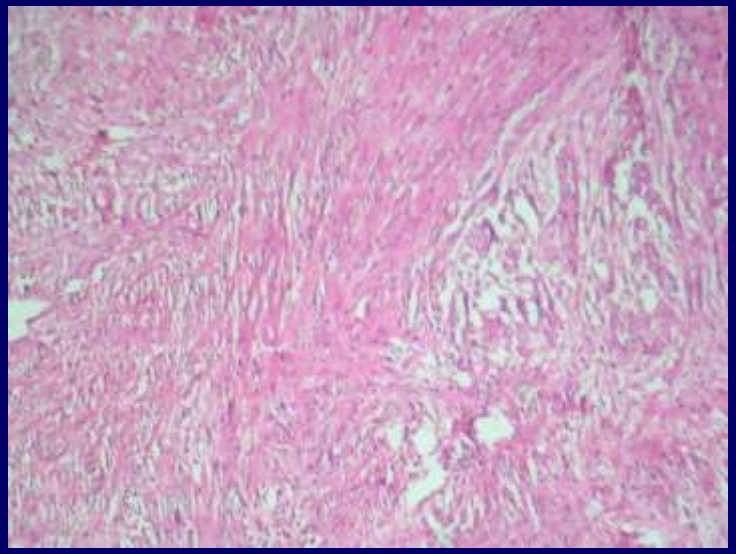
Clinical features

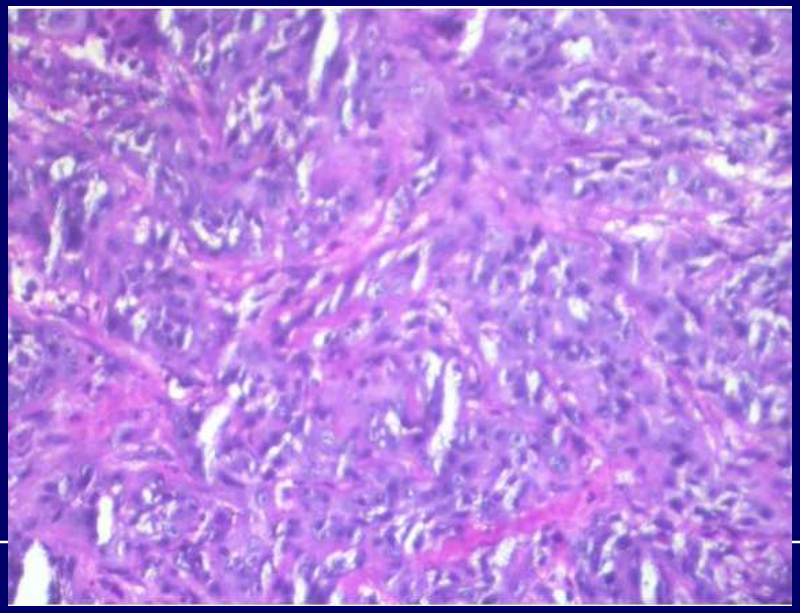
- In older people
- In the upper aerodigestive tract
- Involve lower lip, tongue and alveolar ridges
- Pedunculated, polypoid mass associated with pain and paresthesia
- Grows rapidly, metastasize early and travels along nerves

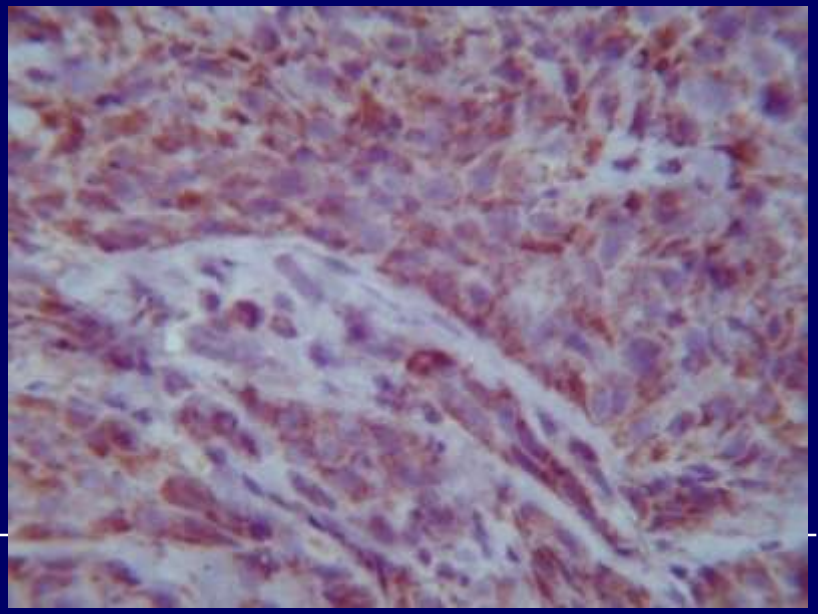
Histopathology

- Fascicles of anaplastic spindle shaped cells along with squamous cells
- Numerous mitotic figures
- Confirmed with cytokeratin expression by IHC.

Spindle cell variant







Adenosquamous carcinoma

- Rare variant, high grade tumor
- Combination of adenocarcinoma in deeper regions and surface squamous cell carcinoma
- Adenocarcinoma shows glandular pattern with mucus production
- Occurs in tongue, floor of mouth of older adults
- Metastasis to cervical nodes is more common
- Radical therapy and poor prognosis

Basaloid squamous carcinoma

- High grade, aggressive tumor in upper aerodigestive tract
- Most recently described variant
- In men, abusers of alcohol and tobacco
- Involves base of tongue and larynx
- Cervical metastasis is more common
- Has well differentiated or moderately differentiated superficial epithelial cells and invasive basaloid epithelium with palisading peripheral cells and central necrosis
- Radical surgery

Carcinoma of maxillary sinus

- Uncommon malignancy
- Weak association with tobacco use
- Strong relationship – wood & leather dust exposure
- 3% of H & N carcinomas
- Remains asymptomatic or mimic sinusitis for long periods and fills up the sinus

- Usually squamous cell carcinoma
- Disease of elderly person & male predilection
- 80% cases are in advanced stage (stage 3 & 4) at time of diagnosis.
- Nasal stiffness or an ulcer or mass of the hard palate or alveolar bone
- Intense pain or paraesthesia mimicking toothache

- Loose teeth
- “Moth eaten” appearance & cloudy sinus appearance (CT & MRI)
- Cervical & submandibular lymph node metastasis
- H / P – squamous cell carcinoma (moderately or poorly differentiated)
- Treatment & Prognosis
  - Radical surgery & radiotherapy

Nasopharyngeal carcinoma

- Arise from lining epithelium of lymphoid tissue-rich nasopharynx
- Involves the lateral pharyngeal wall and shows cervical lymph node enlargement
- Aggressive tumor with three variants,
  - Keratinizing squamous cell carcinoma
  - Non-keratinizing squamous cell carcinoma
  - Undifferentiated non-keratinizing carcinoma

Basal cell carcinoma

- Also called rodent ulcer
- Most common skin cancer
- Locally invasive, slowly spreading primary epithelial malignancy
- Arises from basal cell layer of skin and its appendages.
- 85% in the skin of head and neck – result of chronic exposure to UV light
- Treated by surgery

Clinical features

- In adult whites
- Five clinical forms,
  - Nodular – nodule with central umbilication, telangiectatic vessels on the border
  - Pigmented – uneven melanin
  - Sclerosing – resembles a scar
  - Superficial – multiple lesions
  - Association with Nevoid basal cell carcinoma syndrome

Histopathology

- Uniform ovoid, dark staining basaloid cells with moderate sized nuclei and little cytoplasm
- Well demarcated islands and strands invading into the connective tissue
- Palisading of peripheral cells surrounded by a clear zone

Merkel cell carcinoma

- Rare, aggressive primary malignancy with neuroendocrine features
- In older people in sun-exposed skin
- Dome shaped nodule with a smooth surface and telangiectatic blood vessels
- Infiltrating sheets and strands of moderately sized, uniform, undifferentiated basophilic cells.
- Numerous mitotic figures and intracytoplasmic argyrophilic granules.

Malignant melanoma

- Melanocarcinoma
- Melanocytic origin that arises from a
  - Benign melanocytic lesion
  - Denovo from melanocytes of normal skin / mucosa
- Most occur on the skin, caused by UV radiation
- MORE INCEDENCE – Light comlexioned people as they approach equator
- Acute sun exposure than chronic – greater importance

- Oral lesions – no relation to sun exposure
- 3rd most common skin cancer with high mortality rate
- Mucosal melanomas are common in H/N area, followed by urogenital & rectal
- Mucosal melanomas aggressive than cutaneous
- Genetic alterations – BRAF protein kinase

Clinical features

- In white adults, 50-55 yrs
- ABCDE – clinical features
  - A – asymmetry
  - B – border irregularity
  - C – color variegation (brown, black, white, red, blue)
  - D – diameter greater than 6mm (pencil eraser)
  - E - evolving (change wrt size, shape, color, surface or symptoms over time)

Growth phases

- Radial growth phase – malignant melanocytes spread horizontally through the basal layer of the epithelium
- Vertical growth phase – malignant melanocytes invading the underlying connective tissue

Clinical features

- In white adults
- Four types
  - Superficial spreading – interscapular area, satellite macules or nodules of malignant cells around the primary lesion.
  - Nodular – in head and neck region, more aggressive and short radial phase, deeply pigmented lesion
  - Lentigo maligna M – long radial phase arising from precursor LM
  - Acral lentiginous M – in blacks, most common oral melanoma, in palms and soles,

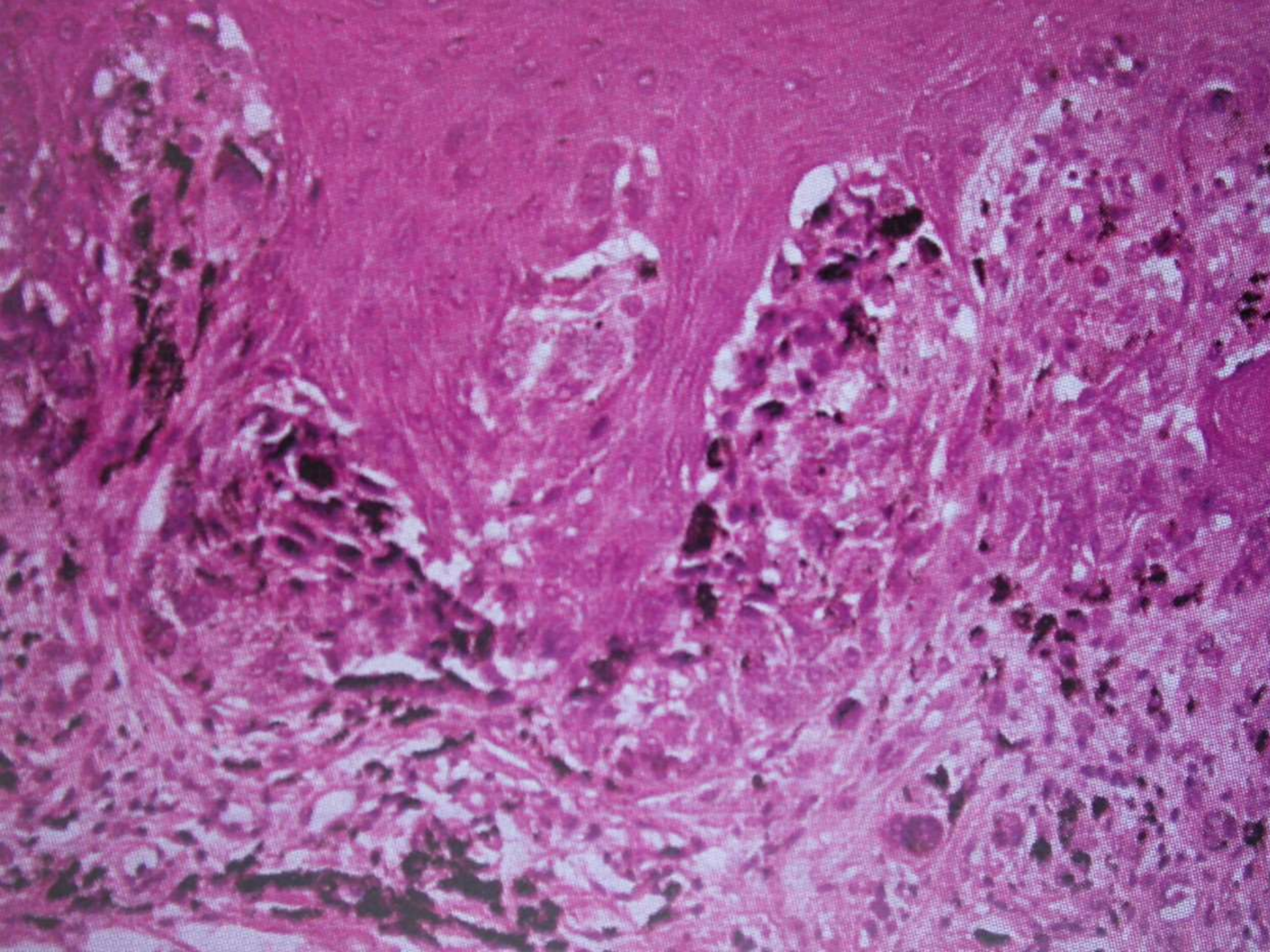
Oral findings

- Often nodular
- In 6^{th} – 7^{th} decades, male predominance
- Hard palate and maxillary alveolus
- Brown to black macule with irregular borders and a lobular exophytic mass develops with the vertical growth phase
- Soft on palpation
- “Moth-eaten destruction”

Histopathology

- Atypical melanocytes at the epithelial and connective tissue junction
- These cells are larger than normal melanocytes with varying degrees of pleomorphism and hyperchromatism
- Pagetoid spread is seen in superficial spreading melanomas.
- The invasive melanoma cells appear spindle shaped or epitheloid and arranged in cords and sheets.
- Invasion into blood vessels and lymphatics

- Few oral melanomas – Bone & Cartilage – misdiagnosed as Pl. Adenoma, ost. Sarcoma & mes. Chondrosarcoma
- Some cases do not express melanin within the melanocytes – Amelanotic melanoma
- IHC for S-100 protein, MART-1 and HMB-45 to confirm the diagnosis



Treatment and prognosis

- Clinical staging is based on TNM
- Histopathological grading is based on two systems,
  - Clark system - assigns a level based on the deepest anatomic tissue invaded by the tumor cells
  - Breslow system - measures the distance form the top of granular cell layer to the deepest identifiable point of tumor invasion
- Surgery with radical neck dissection
- Prognosis is extremely poor and most patients usually die due to distant metastasis

Treatment and prognosis

Clark's defintion	Clark's classification	Breslow's depth of invasion $(mm)^2$
Cells confined to epithelium	Level I	N/A
Cells penetrating papillary dermis	Level II	0.00 to 0.75mm
Cells filling papillary dermis	Level III	0.76 to 1.69mm
Cells extending into reticular dermis	Level IV	1.70mm to 3.59mm
Cells invading subcutaneous fat	Level V	>3.6mm