Oral epithelial tumors.

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Human papillomavirus (HPV)

- **Infect keratinocytes**

- **HPV infection associated with abnormal epithelial proliferation**
  - Benign epithelial lesion (squamous cell papiloma, verruca vulgaris, focal epithelial hyperplasia)
  - Oral precancerous/premalignant lesions
  - Malignant tumours (squamous cell carcinomas/SCC)

- **May be present in normal epithelium**

Benign epithelial lesions associated with human papillomavirus (HPV)

low risk HPV infection (2,4,6,11,13,32,…)

- **Squamous cell papilloma**
- **Verruca vulgaris (common wart)**
- **Condyloma acuminatum (venereal wart)**
- **Focal epithelial hyperplasia (Heck´s disease)**

  - ethnic occurance (Inuits, Indians) + immunosuppressed
  - lower lip, buccal mucosa

Squamous cell papilloma

- Usually solitary, in adults and children
- Pedunculated or sesile
- May be warty or cauliflower-like
- Finger-like processes of proliferating stratified squamous epithelium supported by fibrovascular cores; hyperkeratosis
- No dysplasia, no premalignant lesion

- **Verruca vulgaris (HPV 2, 4)**

- sesile, pedunculated; single, multiple
- papillary processes of proliferating stratified squamous epithelium supported by fibrovascular cores; hyperkeratosis

- **Condyloma acuminatum (HPV 6, 11)**

- **Focal epithelial hyperplasia (HPV 13, 32)**

Squamous cell carcinoma - epidemiology

- Incidence varies around the world
- One of the 10 commonest cancers
- Incidence in developed countries now on the increase
- M>F, usually in people over the age 40
- Increasing incidence in people aged under 40 years
- Fatal clinical outcome in 30-40 per cent

Aetiological factors in oral cancer

- **Tabacco smoking**
- **Smokeless tabacco** (inhalation of powdered tabacco, tabacco chewing)
- **Betel chewing, betel quid, areca nut**
- **Alcohol** (spirit, wine, beer; alcohol and tabacco synergism)
- **Diet and nutrition** (iron deficiency, vit A, C; nutritional deficiencies, alcoholism)
- **Dental factors**
- **Ultraviolet light**
- **Viruses** (**HPV**, HSV, HIV, EBV)
- **Immunosuppression**
- **Chronic infection** (candidosis, syphilis)
- **Occupation** (in agriculture, forestry, fishing – UV light – ca lips; chemicals, dust???)

Tabacco and alcohol

- Independent risk ofooral cancer
- Synergistic effecr
- Relative risk increases with amount and duration of use
- Relative risk influenced by method of use and type
- Main carcinogens in tabacco: N-nitrosamines from nicotine
- Carcinogenic constituents and/or contaminants in alcoholic drinks
- Alcoholic drinks may enhance transport of carcinogens across the mucosal barrier
- Mucosal barriers impaired by nutritional deficiences in chronic alcohol abuse
- Liver disease in alcoholism impair its ability to detoxify carcinogens
- Immunosupression in chronic alcohol abuse may increase the risk of developing cancer

Diet and oral cancer

- Dietary deficiences or imbalances may account for 15 per cent of oral cancer
- Deficiences of iron and of the antioxidant vitamins A, C, and E increase the risk of oral cancer
- Diets high in fresh fruit and vegetables decrease the risk of oral cancer

Genetic abnormalities in oral cancer

- Accumulation of 6 to 10 genetic alterations in an epithelial cell leading to uncontrolled proliferation and clonal expansion
- Activation of oncogenes; inactivation of tumor suppressor genes
- Genetic progression model: normal epithelium→dysplasia→carcinoma *in situ*→invasive cancer
- Loss of chromosomal material from specific areas of a chromosome: LOH (loss of heterozygosity)
- LOH at 9p – predysplastic lesion

  LOH at 3p, 17p (p53 gene)– leading to dysplasia

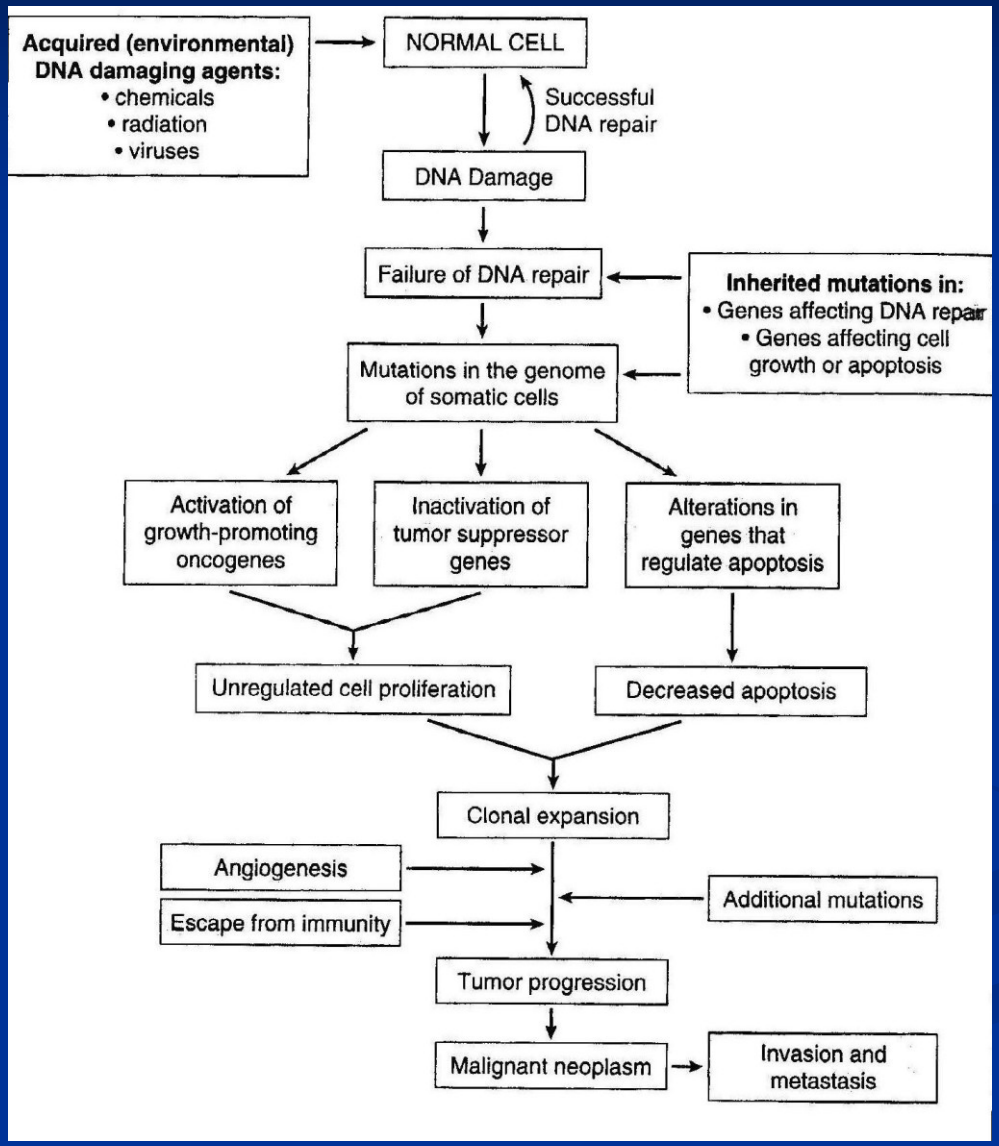
  LOH at 11q, 13q (retinoblastoma gene), 14q – leading to carcinoma *in situ*

  LOH at 6p, 8p, 4q – invasive cancer

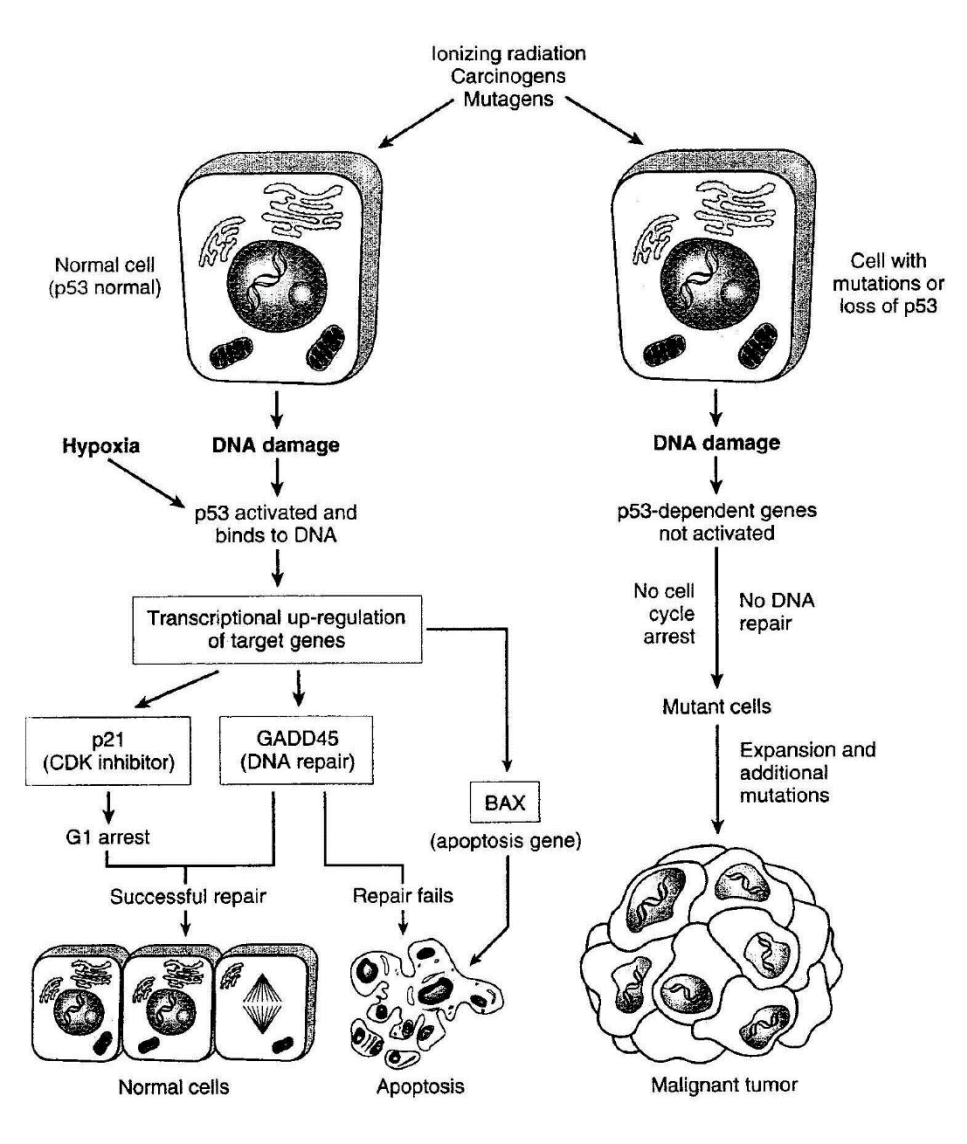
- **Oncogenes**
  - Derived from mutated proto-oncogenes in normal cells
  - Mutation results in enhanced or inappropriate gene expression which may lead to uncontrolled cell growth

- **Tumor suppressor genes**
  - Present in normal cells
  - Regulatory protein of cell proliferation
  - Mutation/deletions→defective/deficient protein→uncotrolled celll growth
  - Mutations in p53 also in oral cancer

Molecular basis of cancer



The role of tumor suppressor p53



Precancerous and premalignant lesions and conditions:
premalignant and tissue lesions and changes with statistically increased risk of progression to cancer

- **Precancerous/premalignant lesions:**

- dysplasia/intraepithelial neoplasia
- *in situ* carcinoma
- actinic keratosis (lips)

- **Precancerous conditions/facultative precanceroses**

- morphologically and cytologically still no signs of neoplastic transformation, but in these lesions statistically significant increased risk of cancer

Precancerous/premalignant lesions:

- **Dysplasia/intraepithelial neoplasia: loss of uniformity and architectural arrangement of epithelial cells**

- Progression of dysplastic changes/intraepitelial neoplasias in invasive cancer:

low grade dysplasia → high grade dysplasia → *carcinoma in situ* → invasive carcinoma (with invasion through basement membrane)

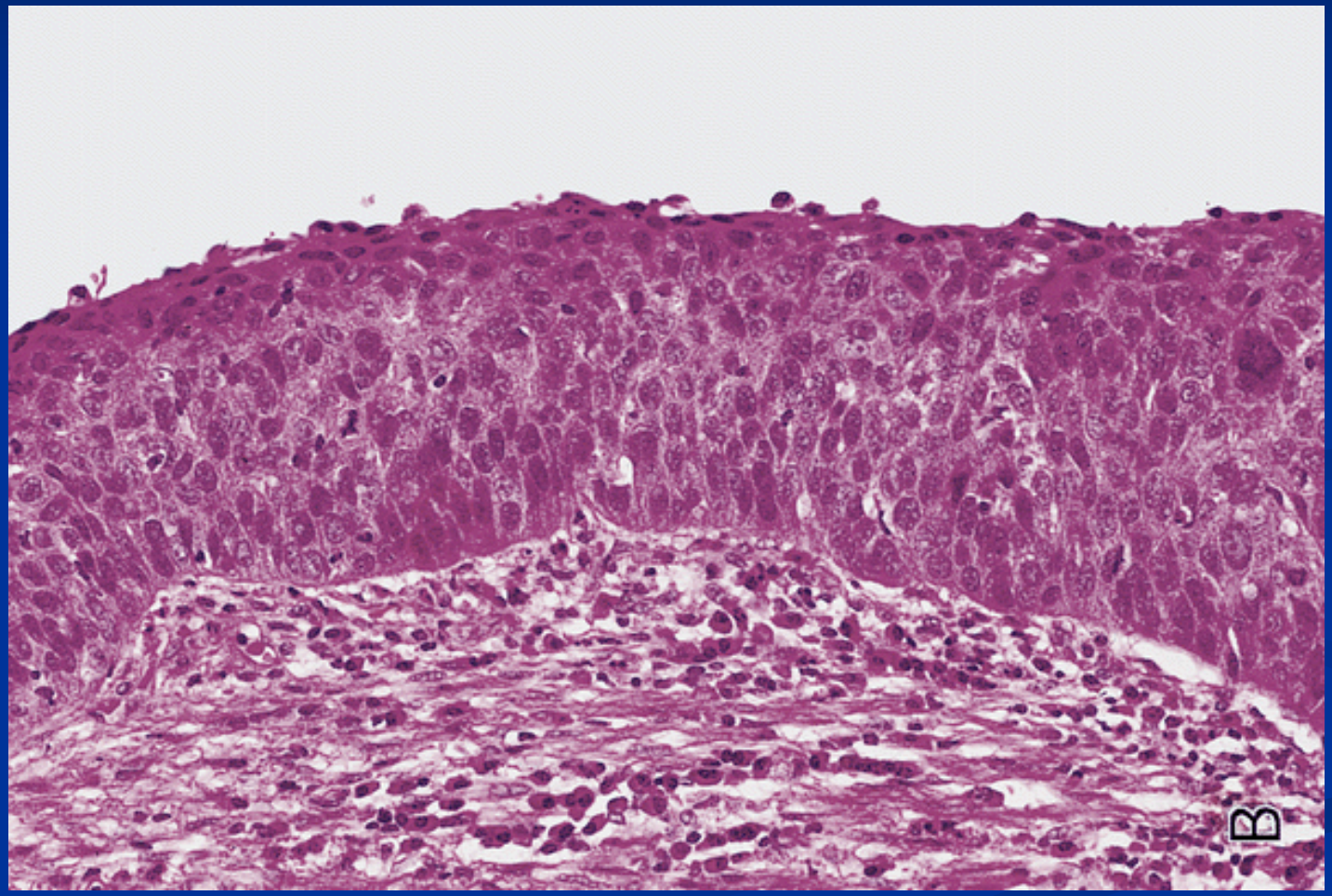
- *carcinoma in situ:* dysplastic changes involve all thickness of the epithelium – preinvasive neoplasia – high risk of progression into invasive carcinoma

- most low grade dysplasias do not progress into carcinoma, but the risk of progression of high grade dysplasias and in situ carcinomas is very high

Precancerous conditions/facultative precanceroses

- **Conditions assoc. with epithelial atrophy (e.g. siderophenic dysphagia)**
- **Oral submucous fibrosis**
- **Lichen planus**
- Lupus erytematodes
- Epidermolysis bullosa
- Xeroderma pigmentosum (AR, defect of DNA reparation)

Carcinoma in situ



Clinical features of invasive oral squamous cell carcinoma

- **Early lesion usually asymptomatic; early detection – determination of prognosis**

- **Local invasion**
  - Induration and fixation of tissues
  - Destruction of tissues
  - Distortion of tissues
  - Dysfunction of tissues

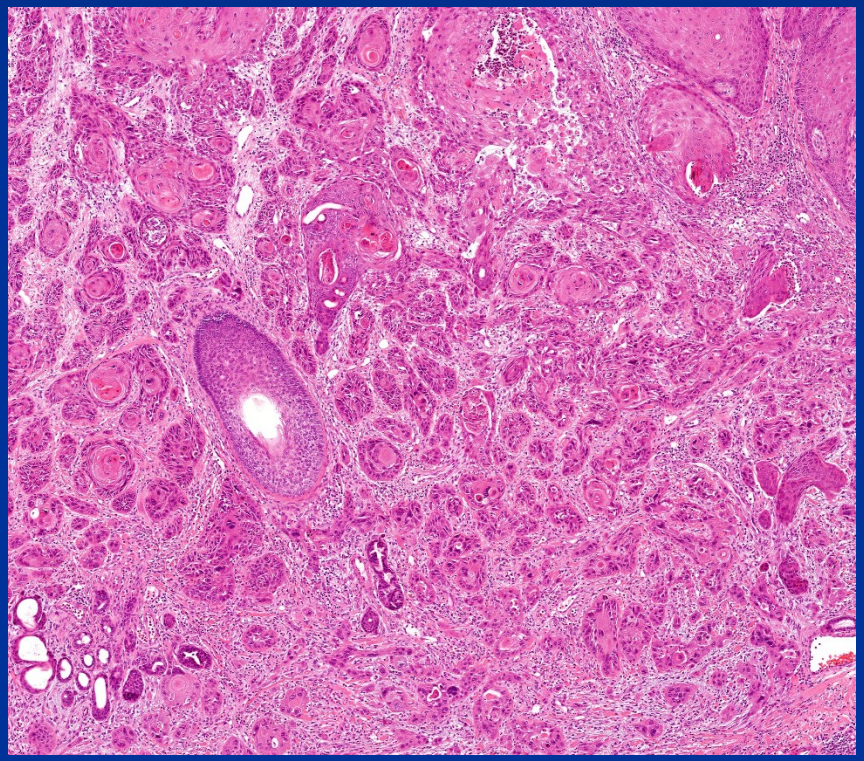
- **Metastatic spread to regional lymph nodes**
  - Enlarged, firm nodes
  - Mobile or fixed nodes

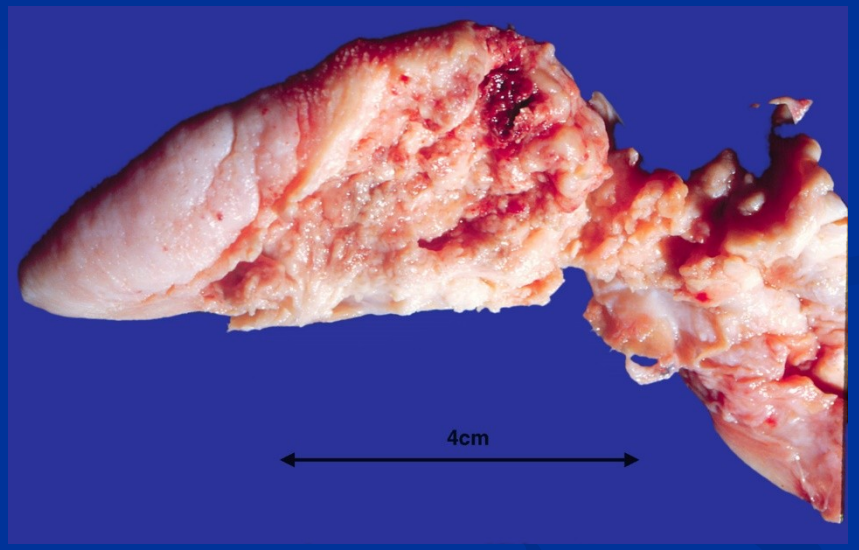
Histopathological features related to prognosis of oral SCC

- Diameter of tumor (clinical T stage)
- Depth of invasion, incl. bone invasion
- Non-cohesive pattern of invasion
- Perineural invasion
- Lymphatic and vascular invasion
- Metastatic disease (clinical N and M stage)
- Extracapsular spread of nodal metastases

- Prognosis decreases with increasing clinical stage
- Site and late onset adversely affect early diagnosis
- Worse prognosis in SCC at the back of the mouth: late diagnosis, rich lymphatic drainage around the base of the tongue

Squamous cell carcinoma.





Carcinoma of the tongue.

Lymph node metastases

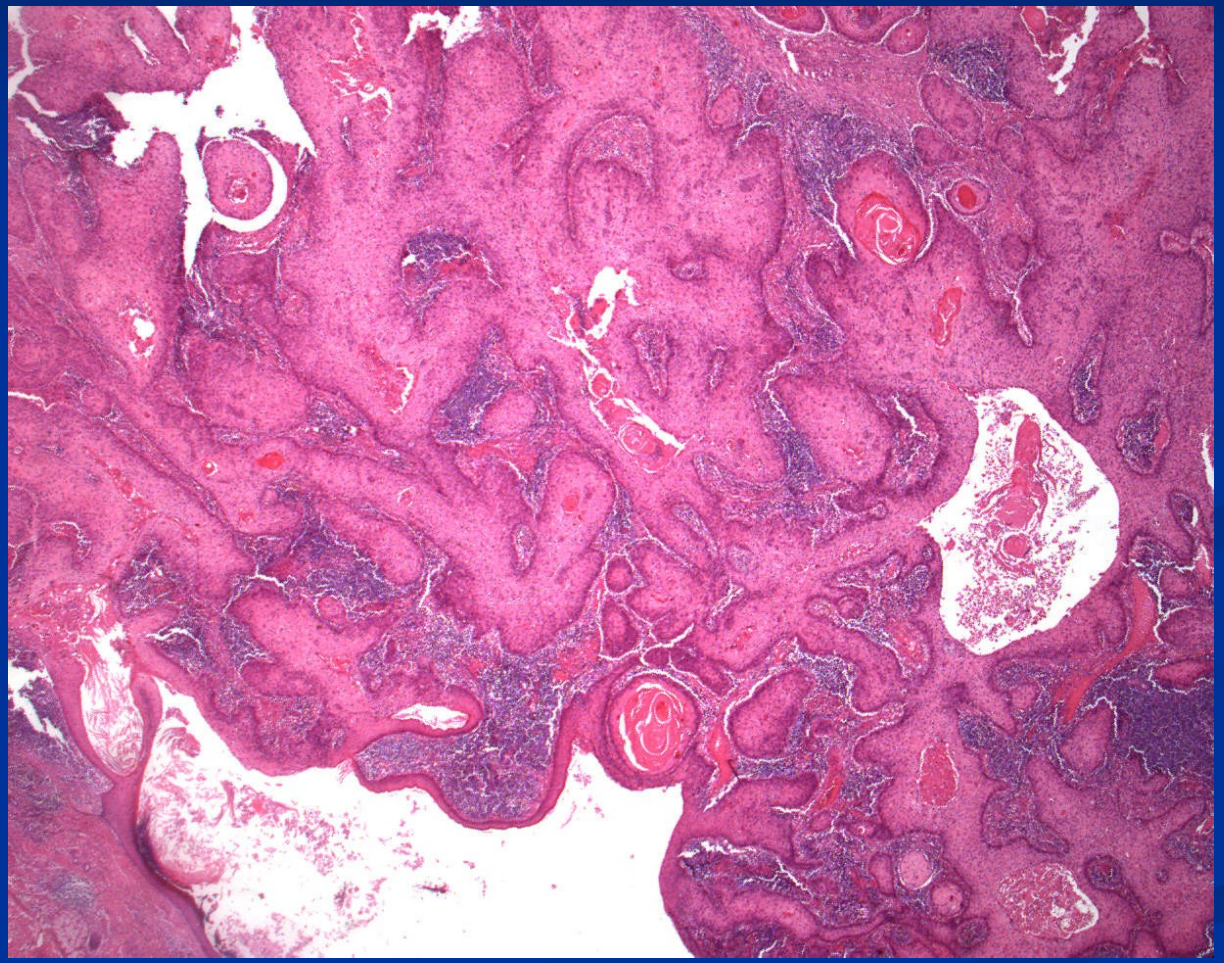
- **Level I:** nodes of submandibular and submental triangles
- **Level II:** nodes of upper cervical (jugular) chain
- **Level III:** nodes of mid-cervical (jugular) chain
- **Level IV:** nodes of the lower cervical (jugular) chain
- **Level V:** nodes of posterior triangle of the neck

Oral squamous cell carcinoma

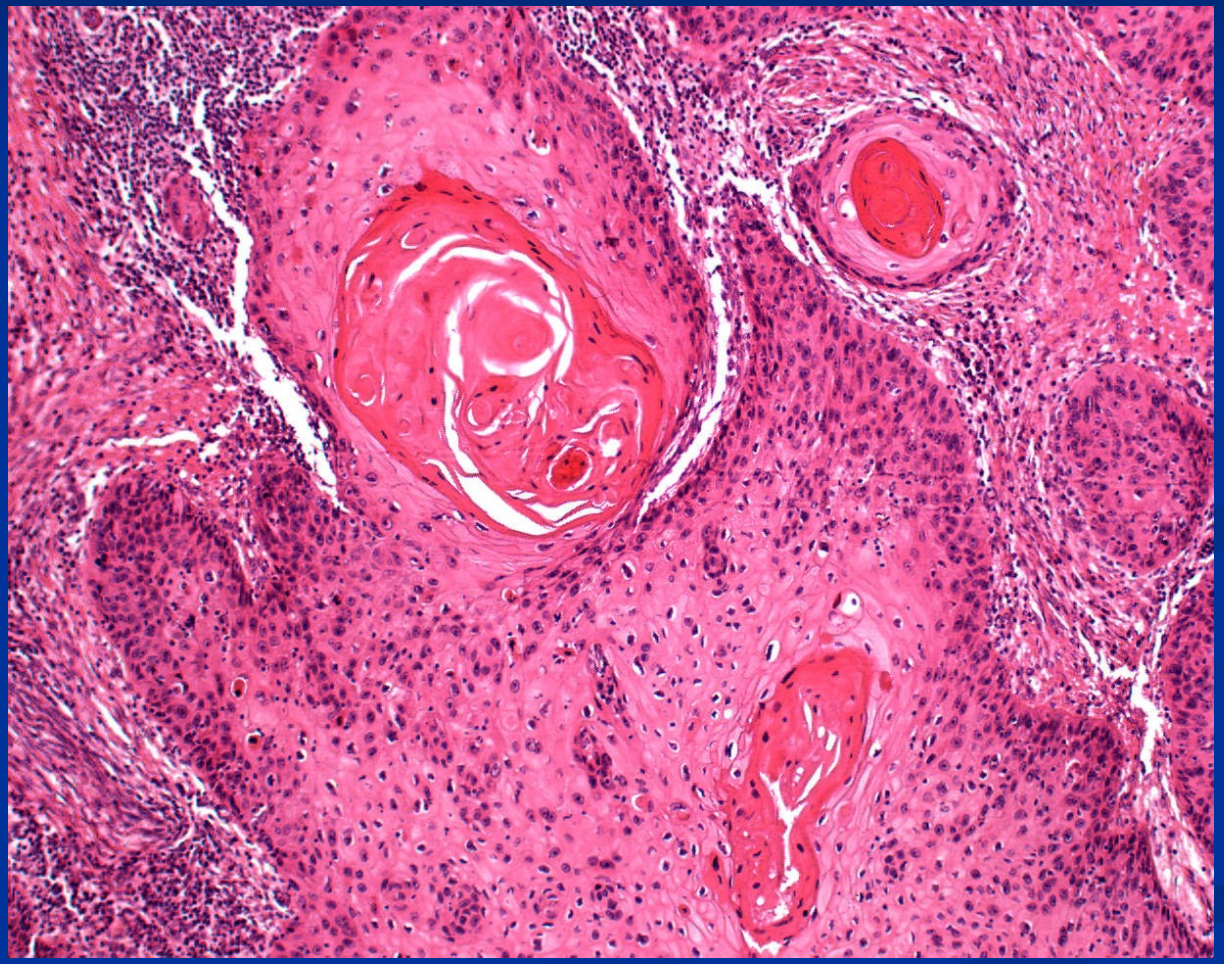
- **Well differentiated**
- **Moderately differentiated**
- **Poorly differentiated**

- Cytologically malignant squamous epithelium
- Keratinization varies with degree of differentiation
- Verrucous carcinoma (distinctive pathological variety of LG SCC)
- Basal cell carcinoma (lips, older people (or in younger with naevoid BCC sy), UV exposure

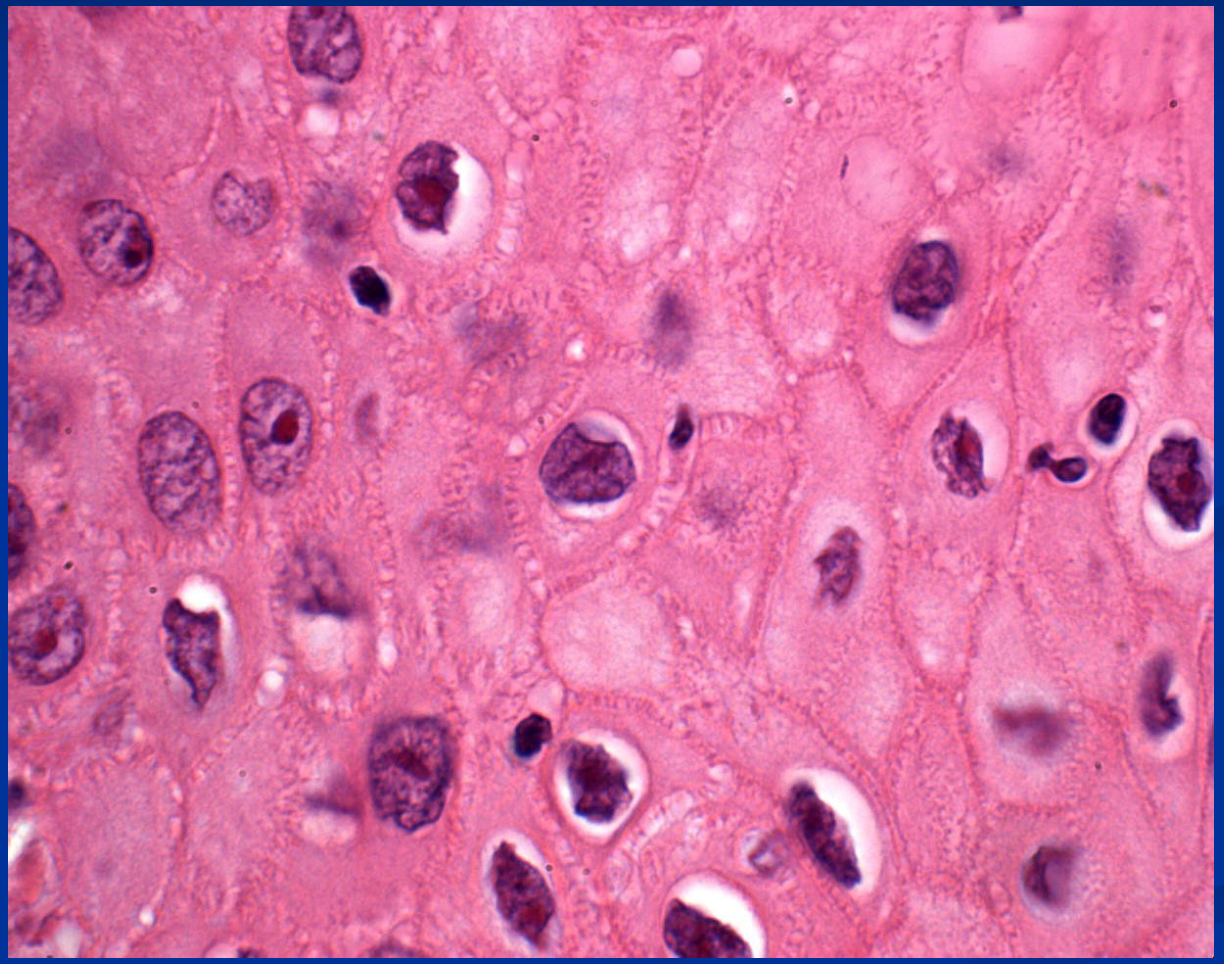
Squamous cell carcinoma



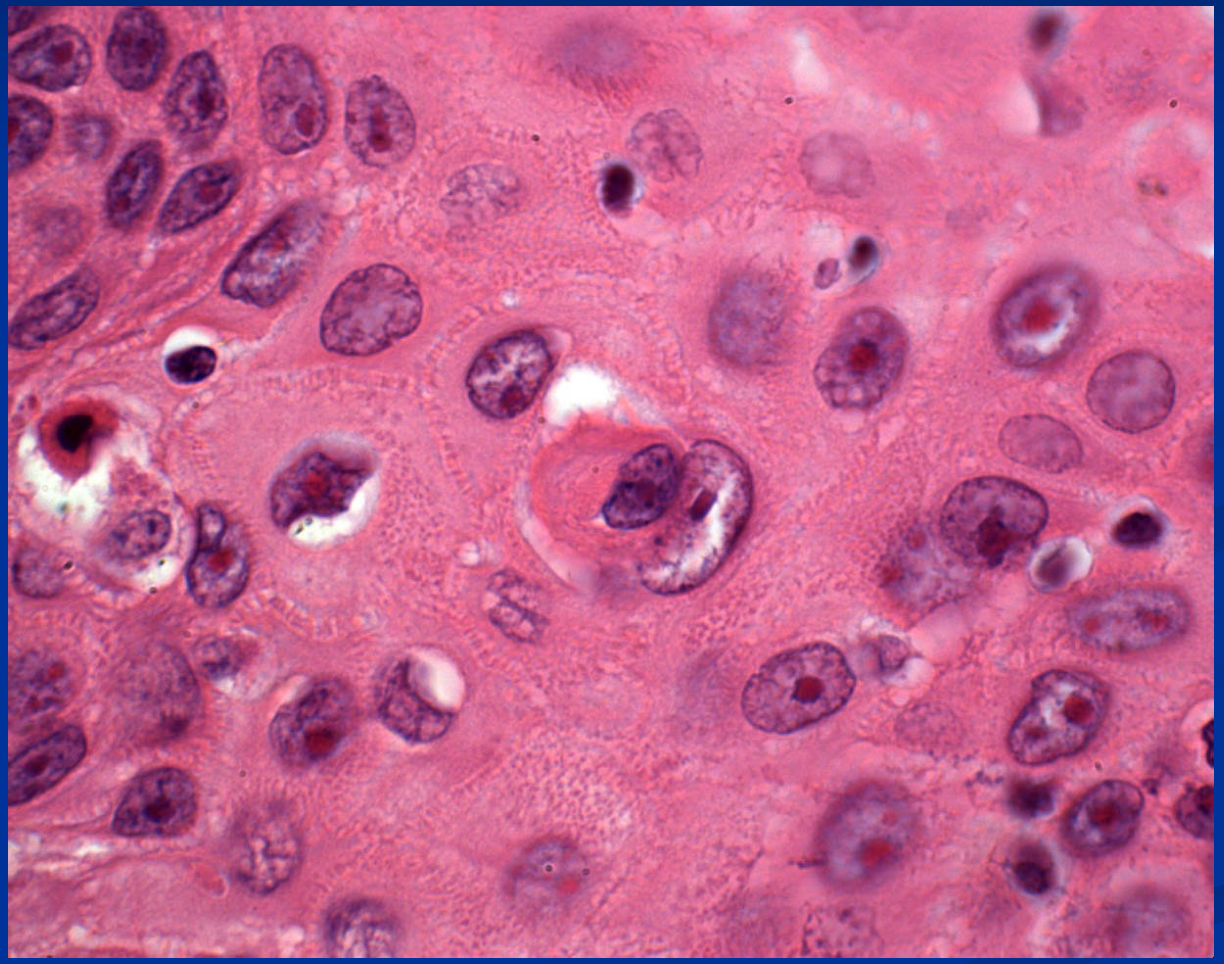
Squamous cell carcinoma



Squamous cell carcinoma



Squamous cell carcinoma



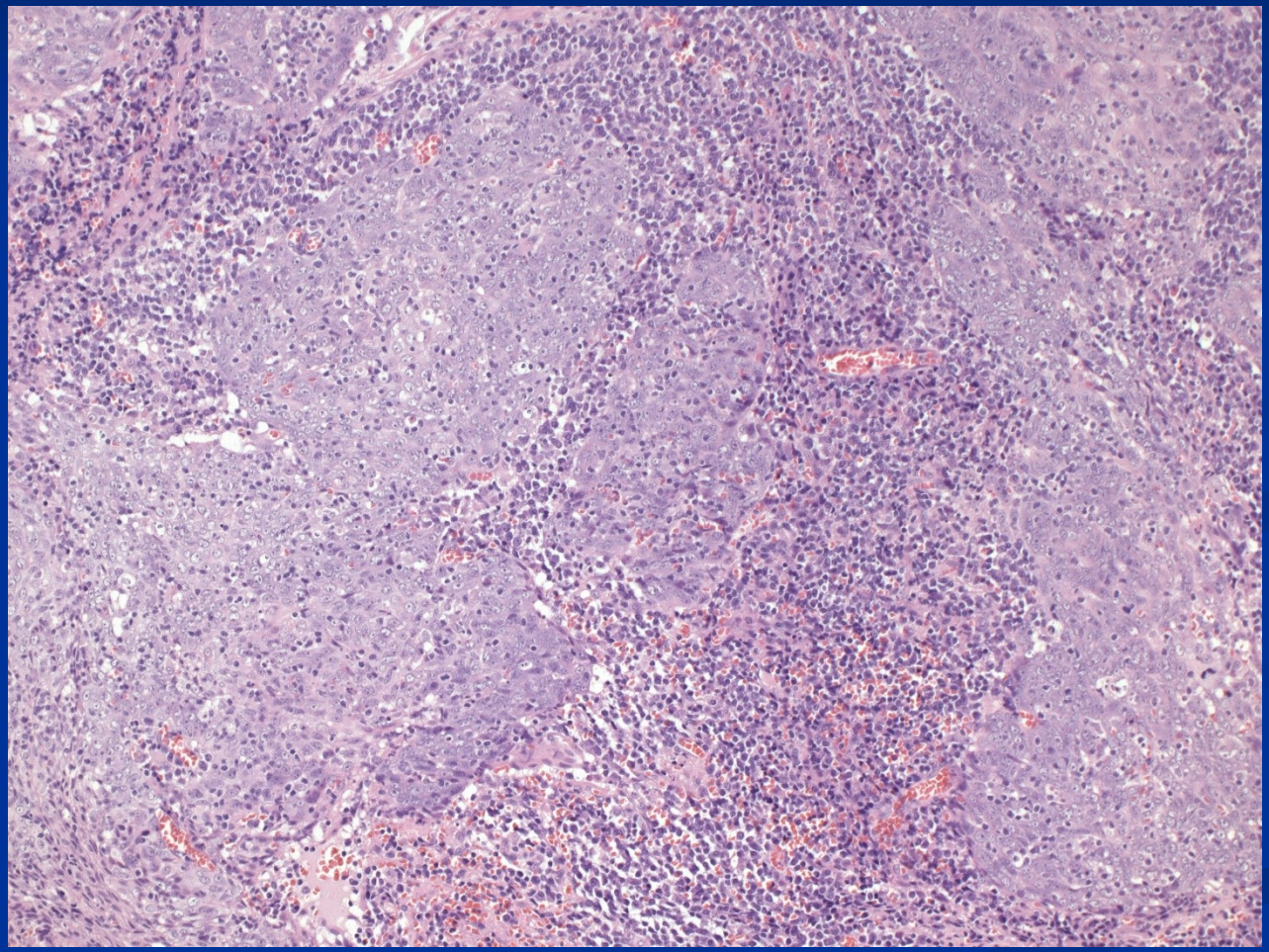
Oral SCC

- **Tongue, base of the oral cavity:** the worst prognosis, rapid spread into deep cervical lymph nodes and hematogeneously into lungs
- **Lips:** late metastatic spread into submandibular and submentl lymph nodes
- **Gingiva:** most frequent at 3rd molar, slower progression

HPV and head and neck SCC

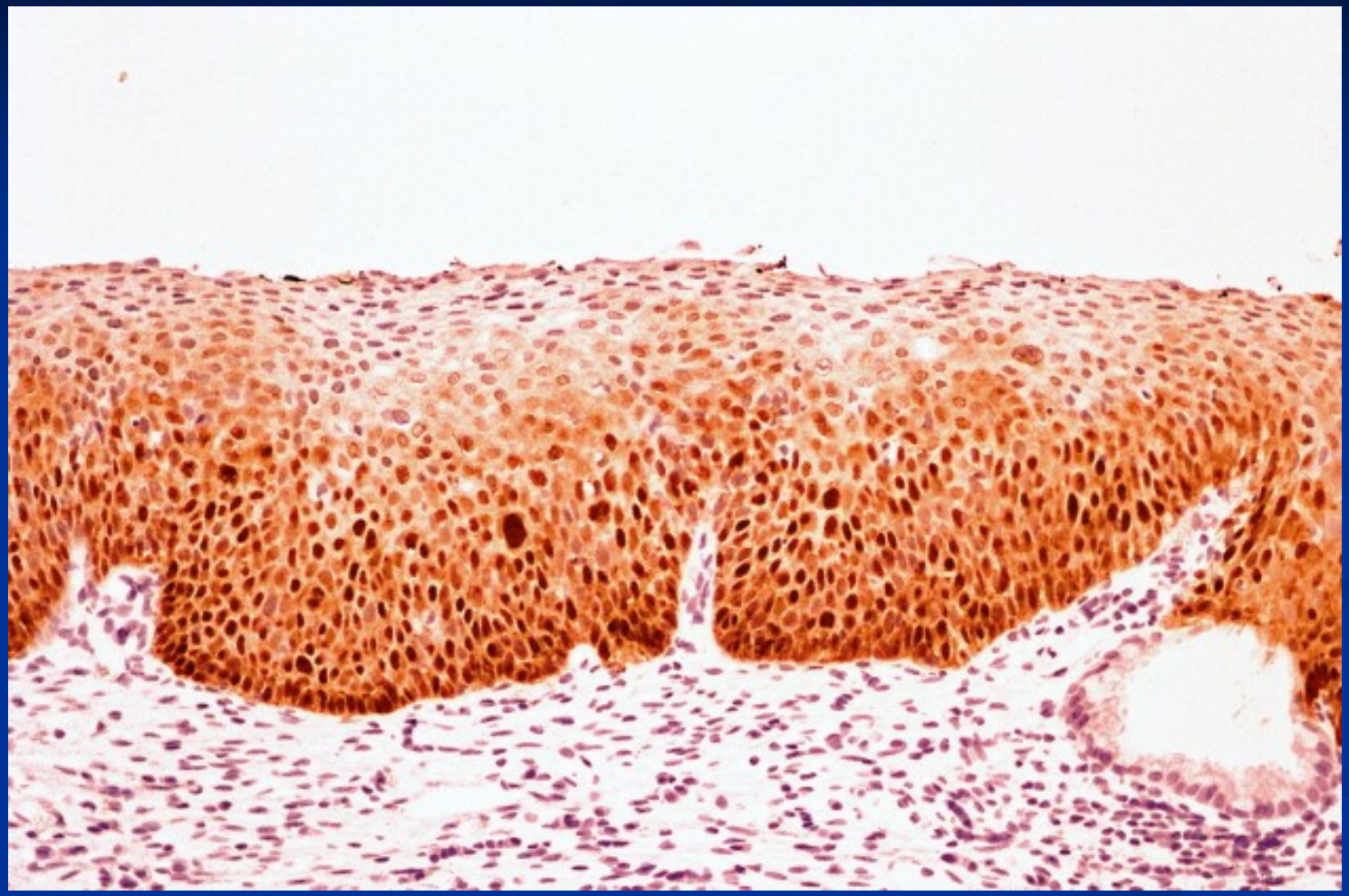
- HPV: assoc. with a subgroup of head and neck SCC (most common HPV 16)
- Younger patients, non-smokers, non-alcoholics
- Better prognosis, better responce to chemotherapy and chemoradiotherapy
- Better clinical status of patients at diagnosis, earlier diagnosis
- HPV+ carcinomas – half risk of death compared with HPV- carcinomas
- Basaloid morphology, non-keratinising
- HPV associated carcinomas most common arising from tonsilla lingualis and tonsillae palatinales - oropharyngeal squamous cell carcinoma (OSCC)

HPV+ OPSCC

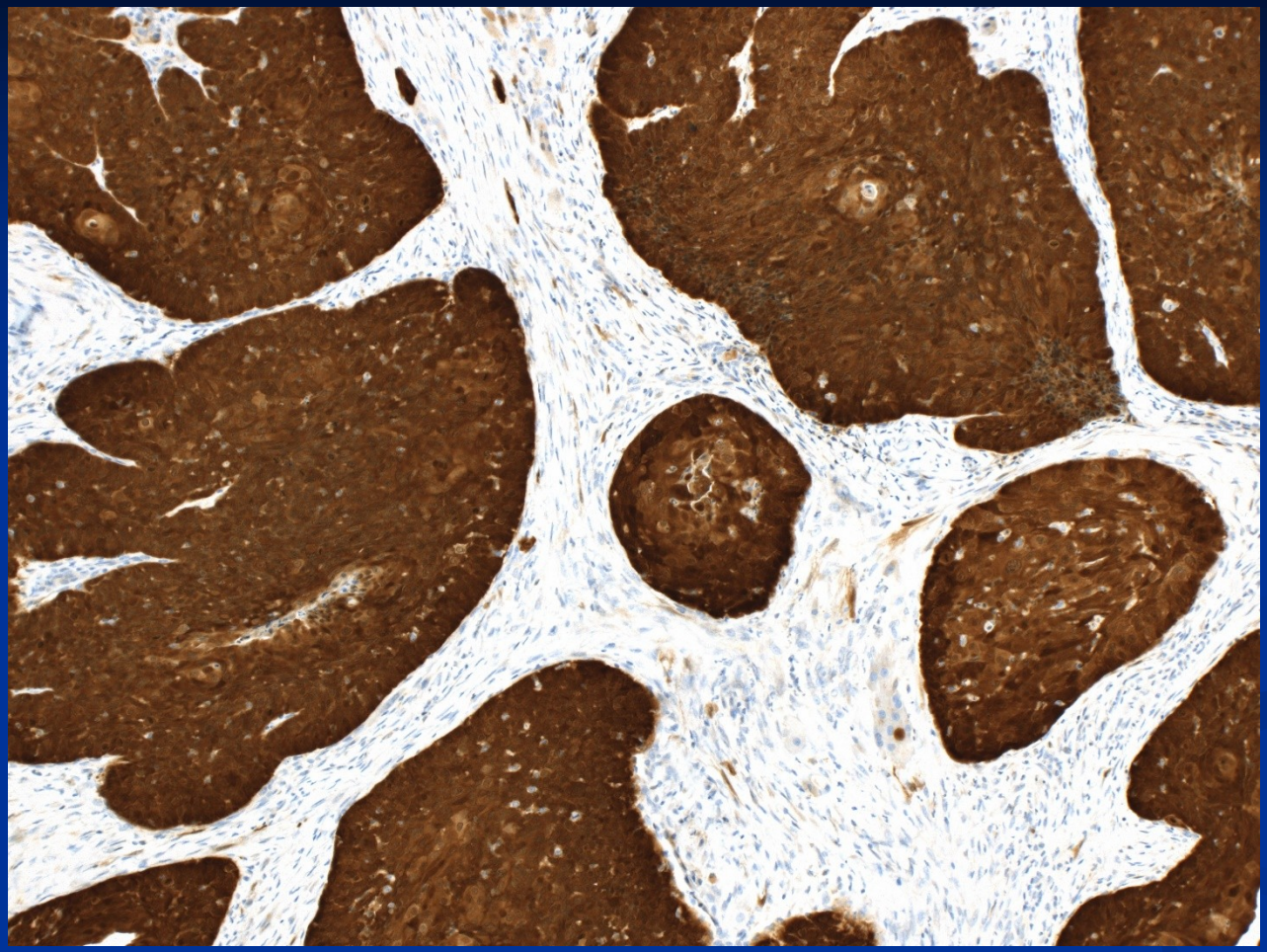


Expression of p16 in SCC

- TSG product, cyclin-dependent kinase 4A inhibitor
- Production of p16 normally inhibited by pRB (repression of transcription)
- Degradation of pRB in HPV+ tumours → ↑p16 expression
- p16 expressed HPV+ tumours and premalignant lesion
- p16 = surrogate marker of high risk HPV



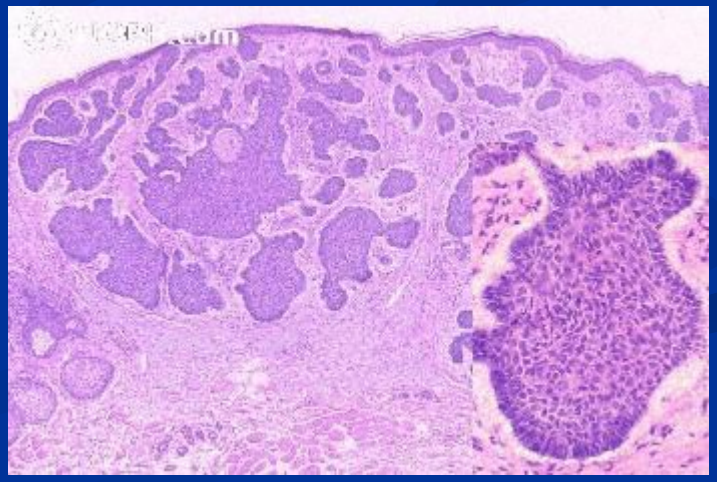
High grade dysplasia, HPV+, p16 expression in 2/3 epithelial thickness.



p16+/HPV mediated OPSCC: strong nuclear and cytoplasmic p16 expression

Basal cell carcinoma (rodent ulcer)

- Usually on the skin of the face in elderly patienty (UV exposure)
- Occasionally lips (upper)
- Multiple naevoid BCC in naevoid BCC syndrome
- Slow-growing nodule
- centrally ulcerated



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