

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

Squamous cell papilloma

- Usually solitary, in adults and children
- Pedunculated or sessile
- 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 of oral cancer
- Synergistic effect
- Relative risk increases with amount and duration of use
- Relative risk influenced by method of use and type
- Main carcinogens in tobacco: 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 deficiencies in chronic alcohol abuse
- Liver disease in alcoholism impairs its ability to detoxify carcinogens
- Immunosuppression in chronic alcohol abuse may increase the risk of developing cancer

Diet and oral cancer

- Dietary deficiencies or imbalances may account for 15 per cent of oral cancer
- Deficiencies 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

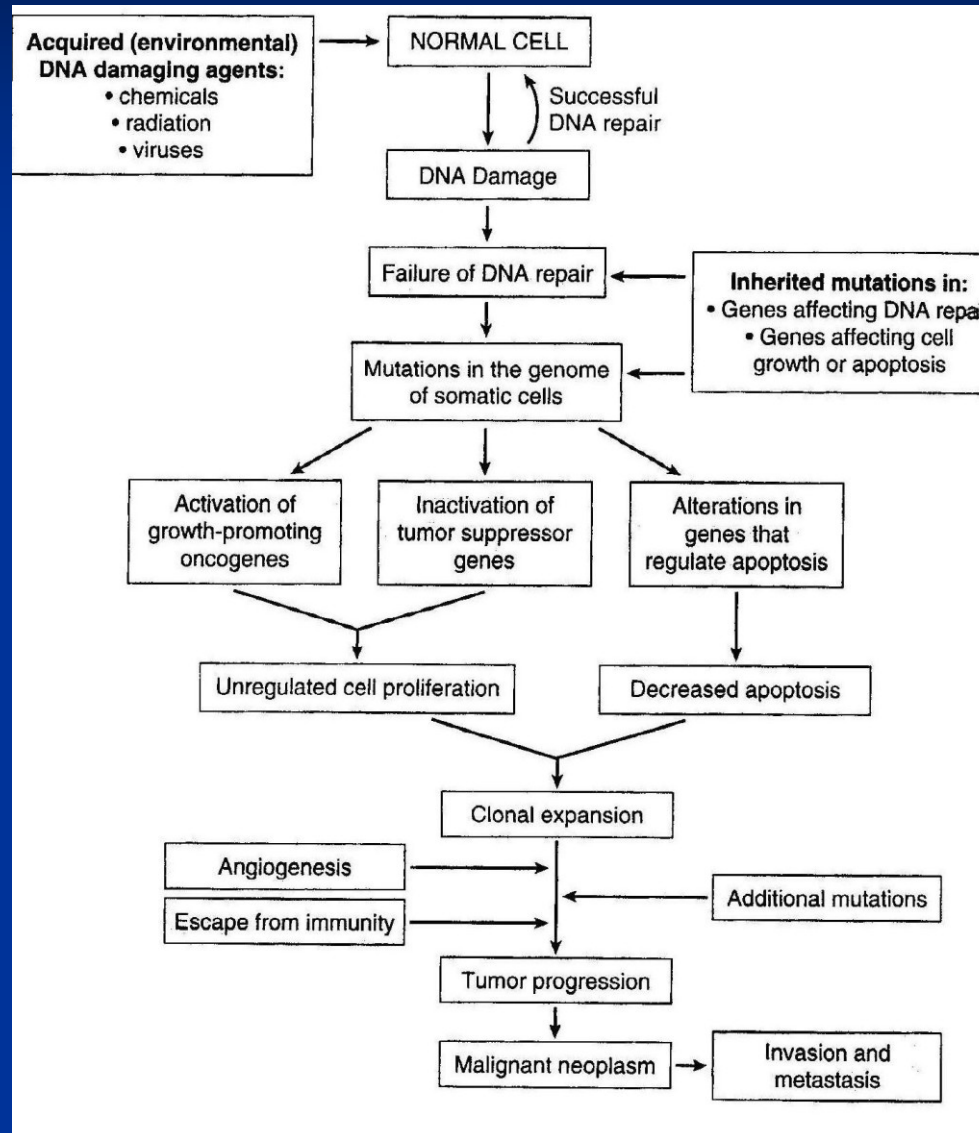
■ **Oncogenes**

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

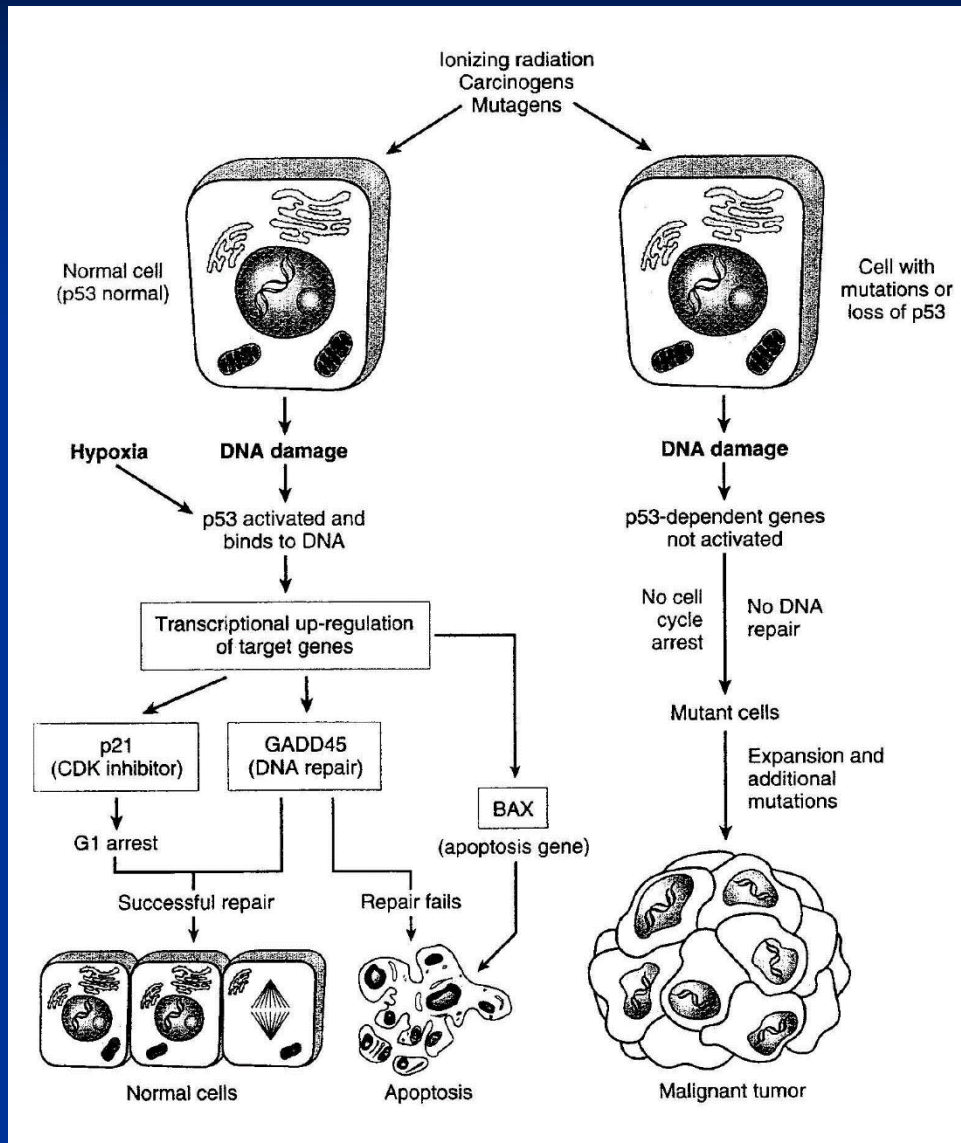
■ **Tumor suppressor genes**

- 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: pre-malignant 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

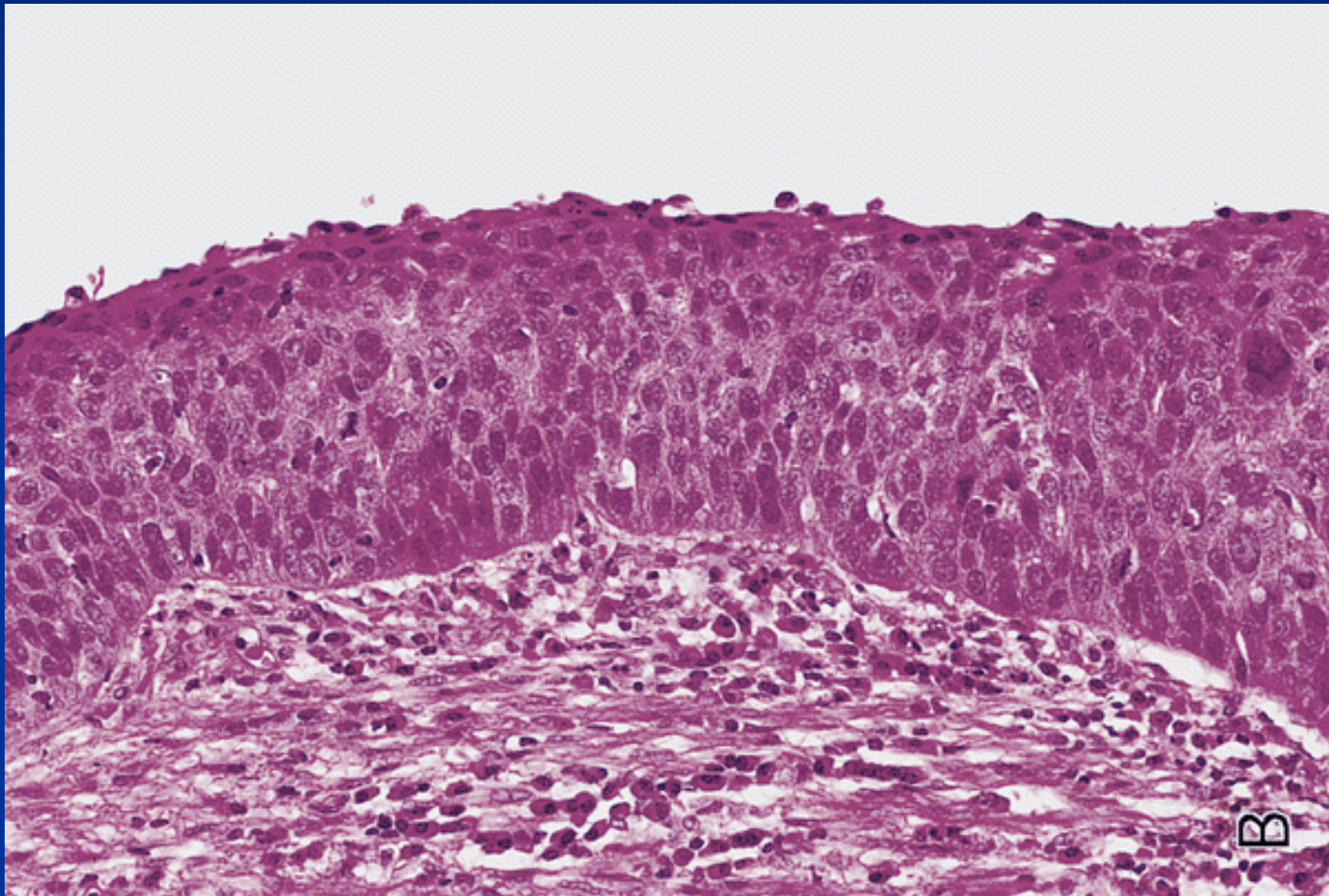
Precancerous/premalignant lesions:

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



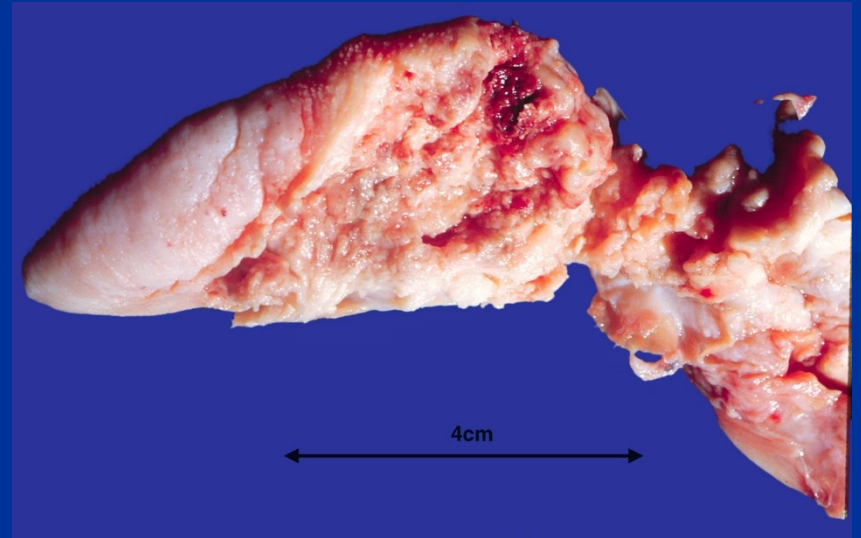
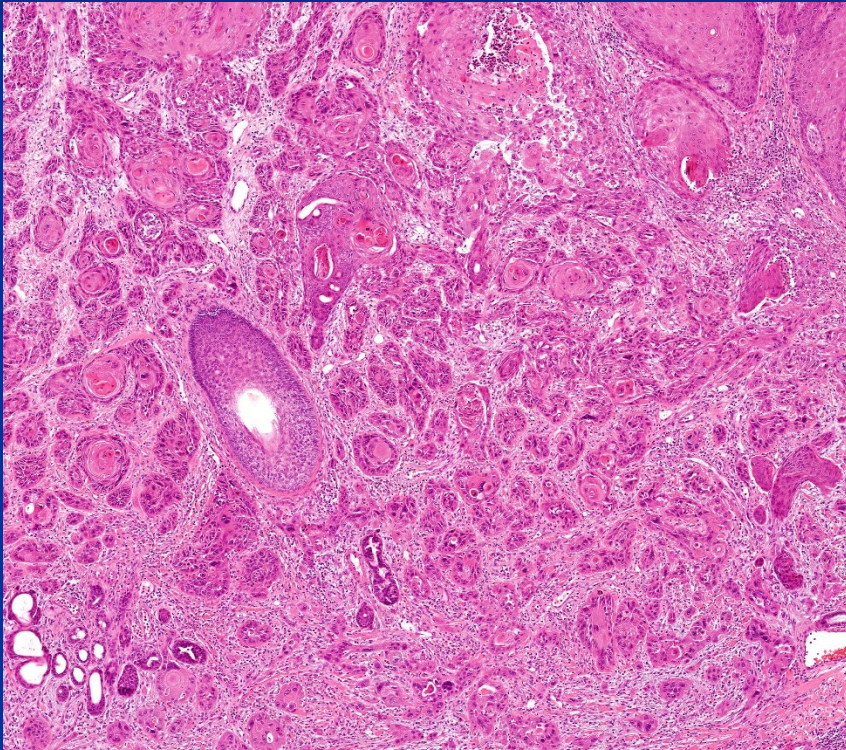
Clinical features of invasive oral squamous cell carcinoma

- **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
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- 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

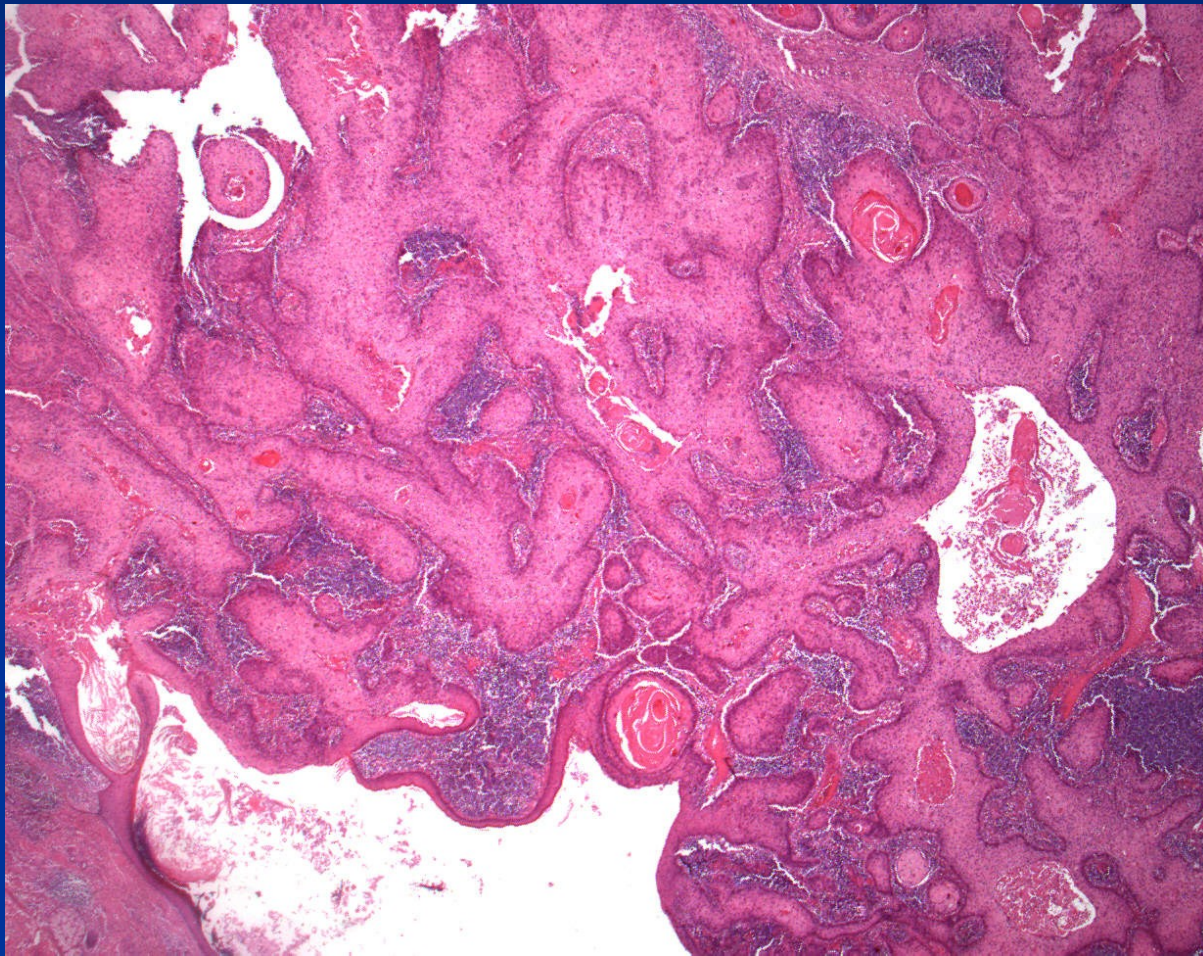
- **Level I:** nodes of submandibular and submental triangles
- **Level II:** nodes of upper cervical (jugular) chain
- **Level III:** nodes of mid-cervical (jugular) chain
- **Level IV:** nodes of the lower cervical (jugular) chain
- **Level V:** nodes of posterior triangle of the neck

Oral squamous cell carcinoma

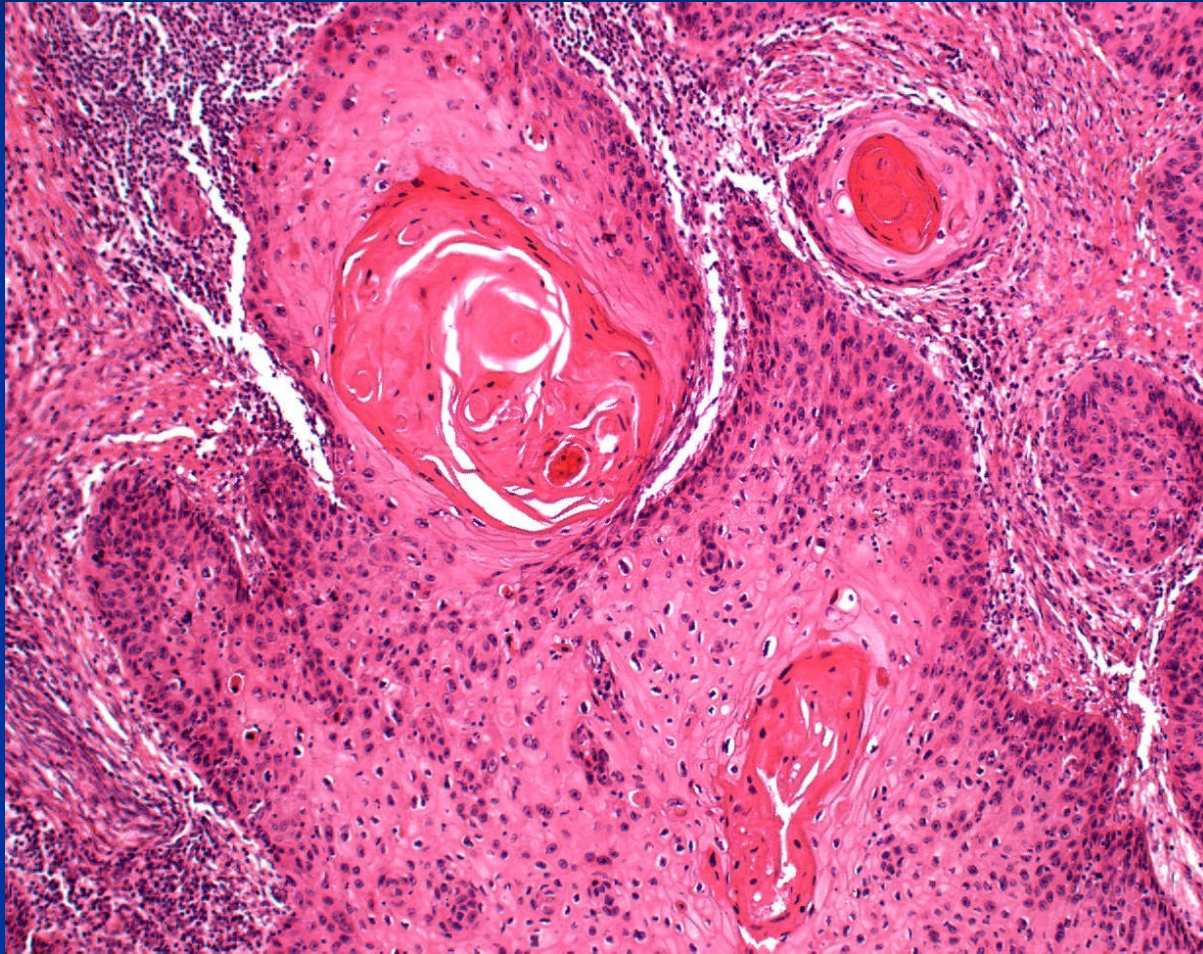
- Well differentiated
- Moderately differentiated
- Poorly differentiated

- 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

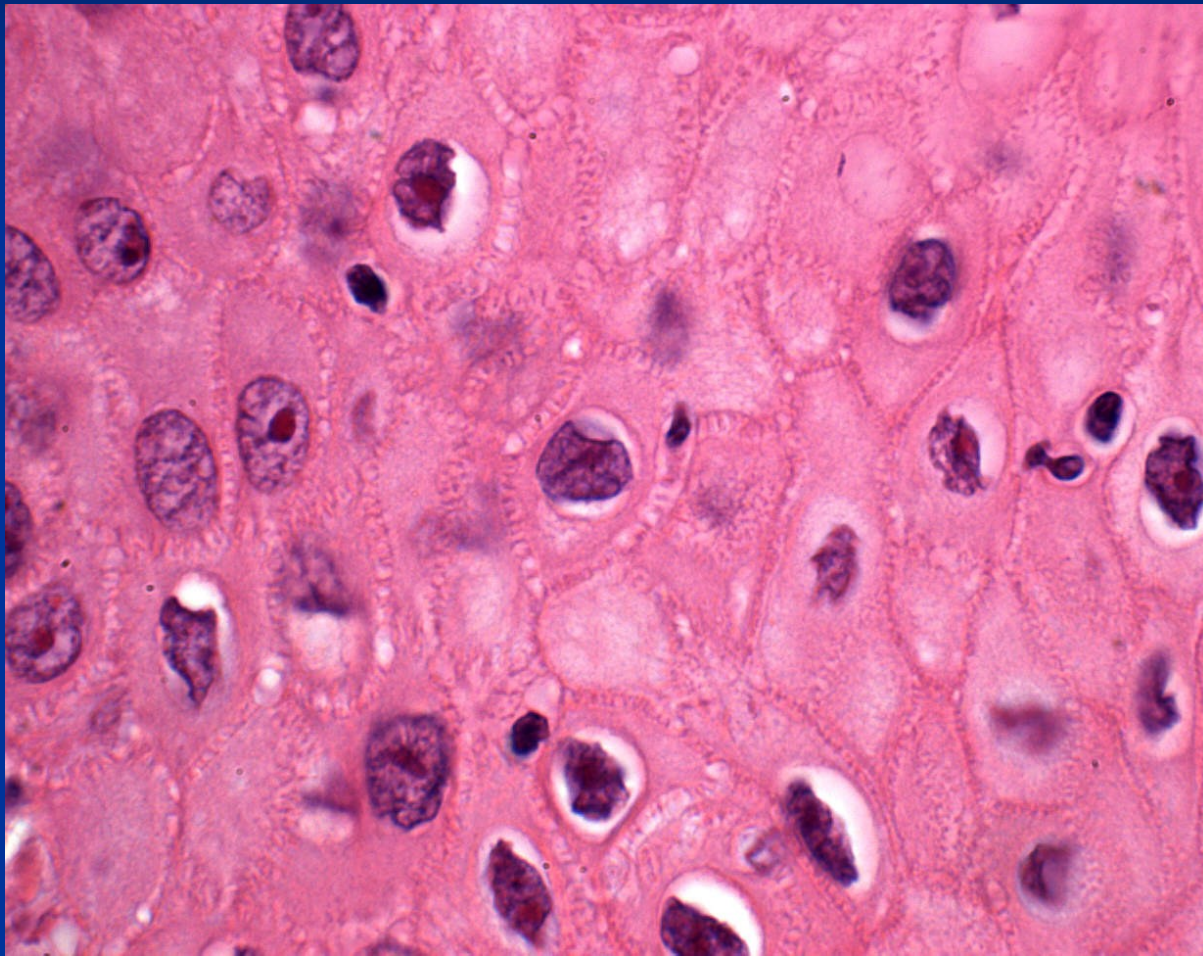
Squamous cell carcinoma



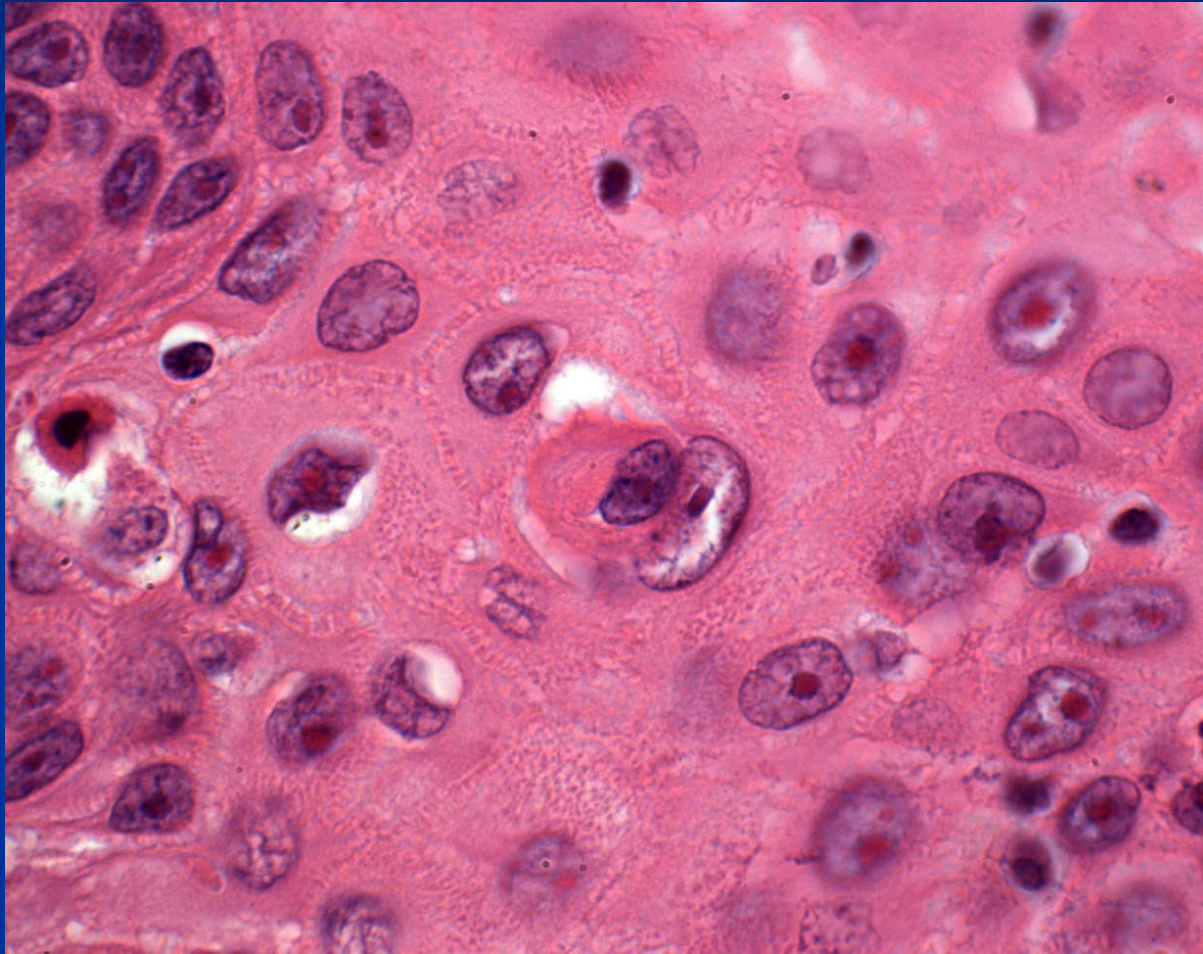
Squamous cell carcinoma



Squamous cell carcinoma



Squamous cell carcinoma



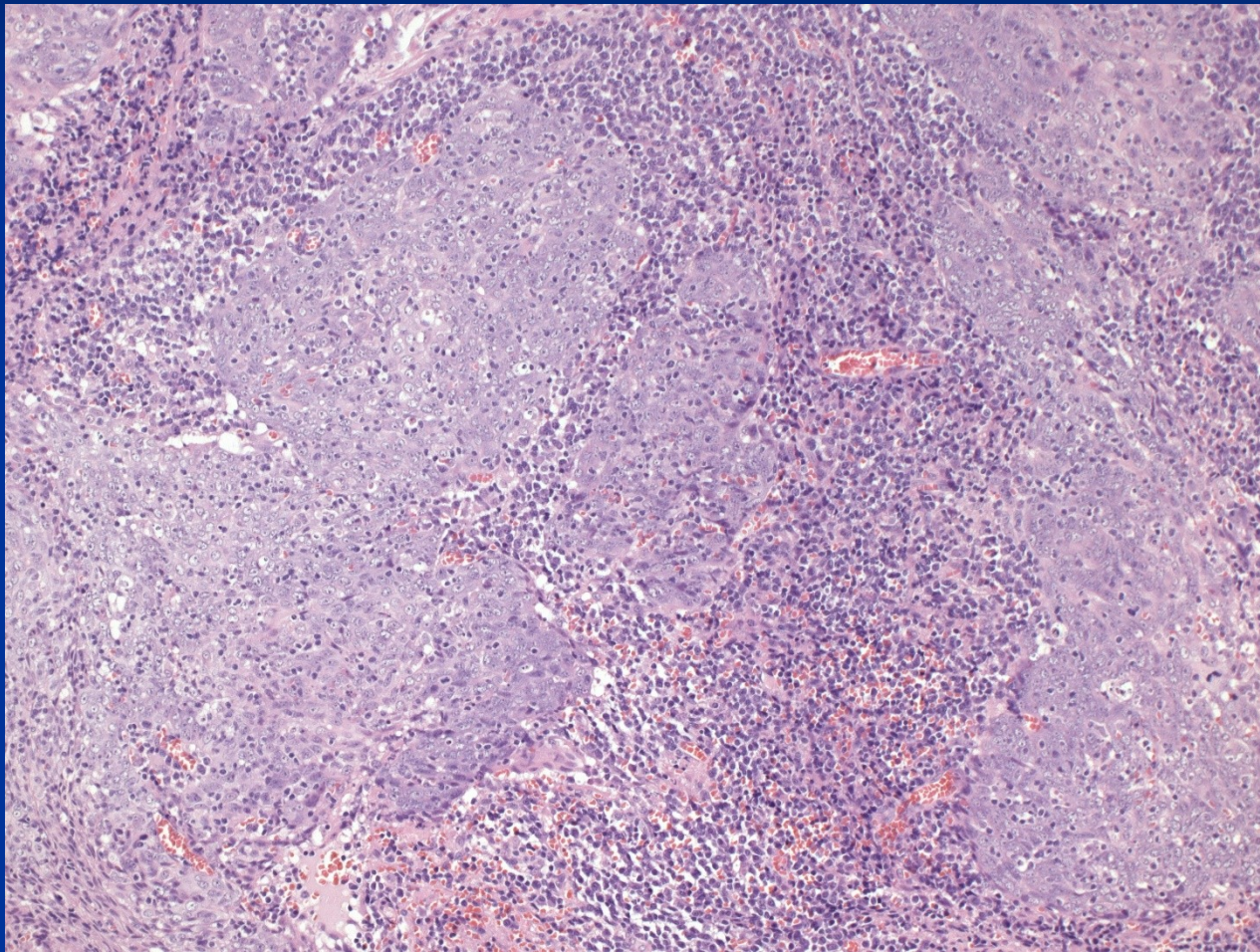
Oral SCC

- **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

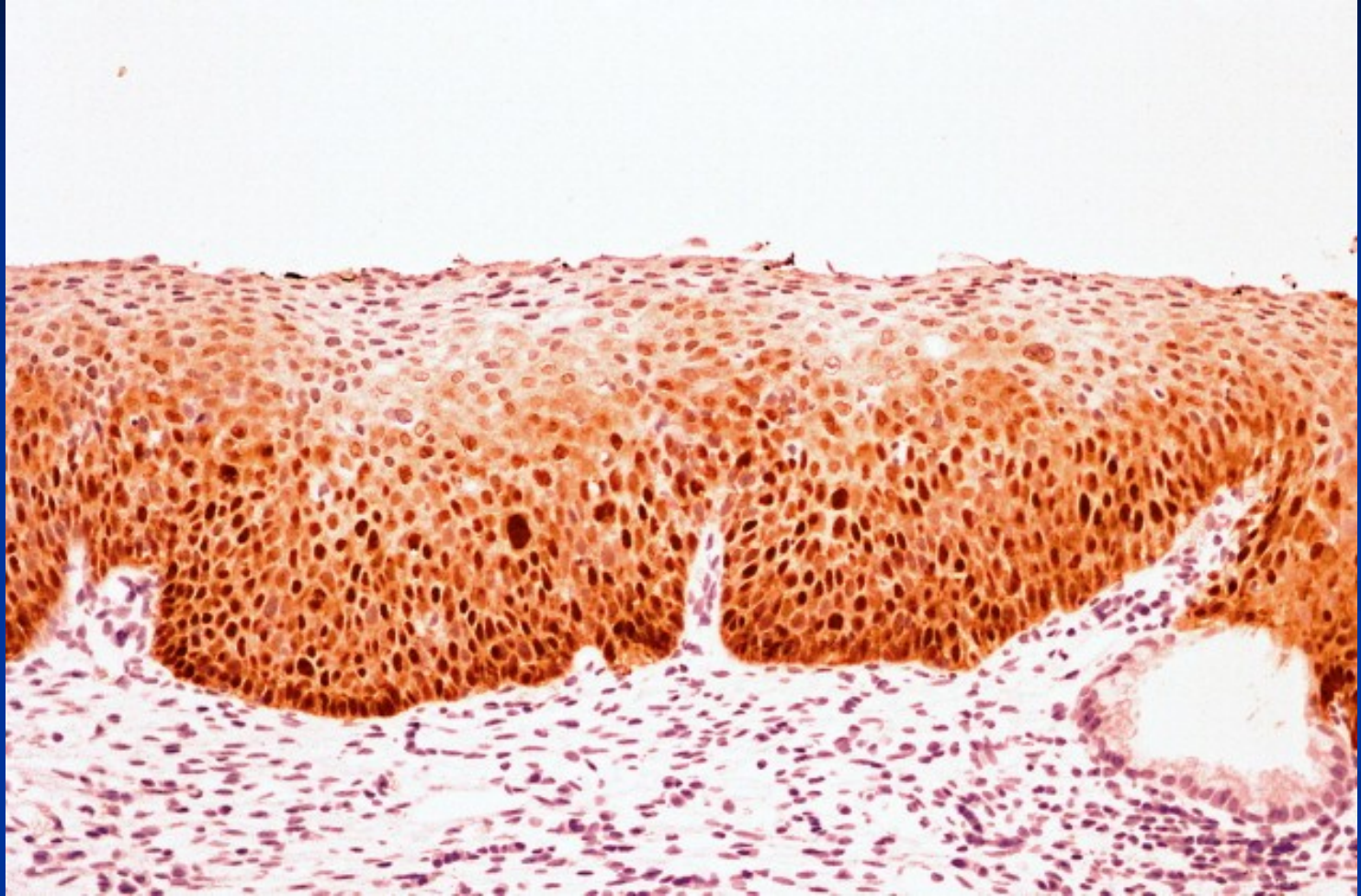
- HPV: assoc. with a subgroup of head and neck SCC (most common HPV 16)
- Younger patients, non-smokers, non-alcoholics
- Better prognosis, better response to chemotherapy and chemoradiotherapy
- Better clinical status of patients at diagnosis, earlier diagnosis
- HPV+ carcinomas – half risk of death 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

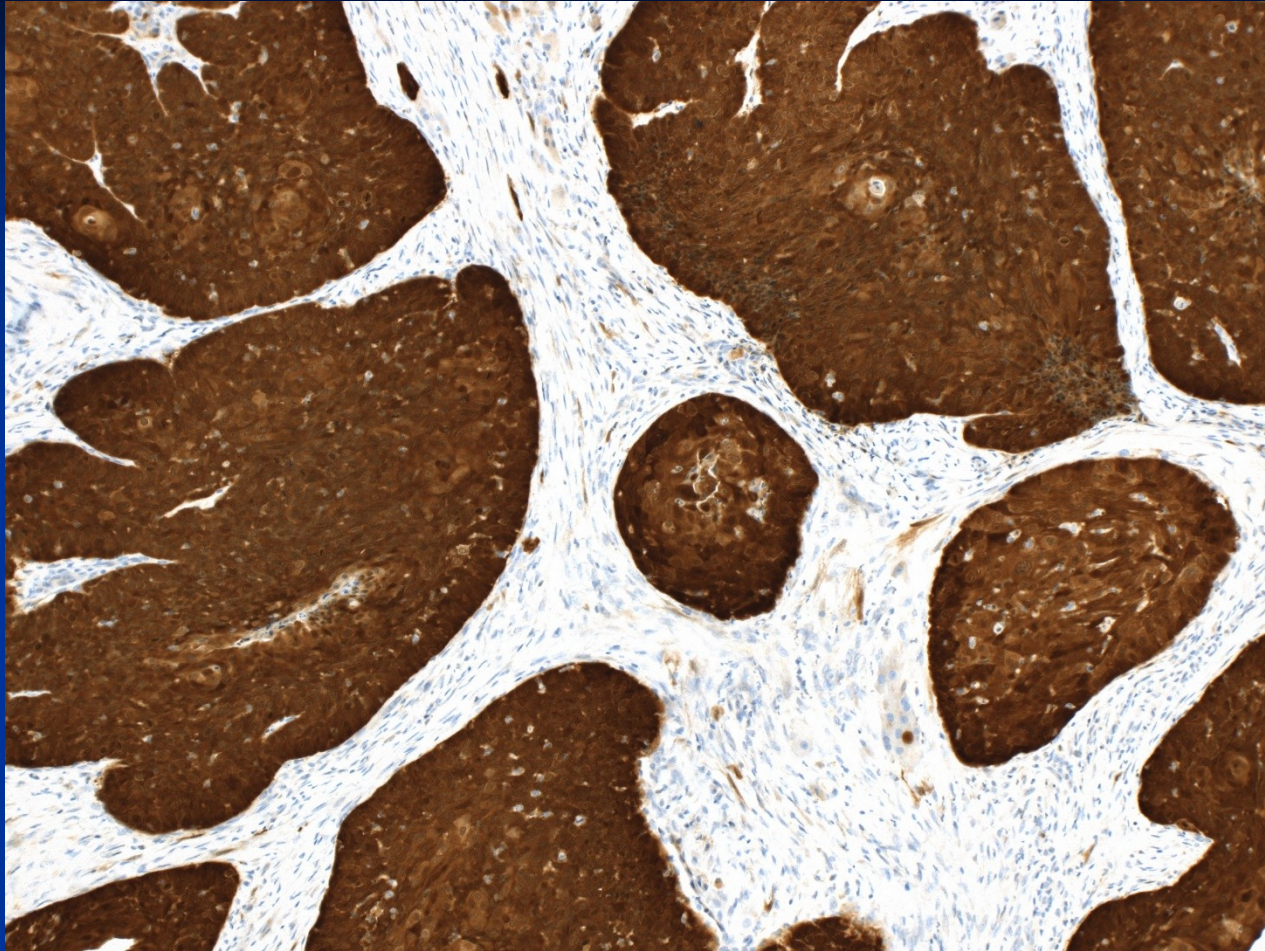


Expression of p16 in SCC

- 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

