Last updated: 3/6/2025

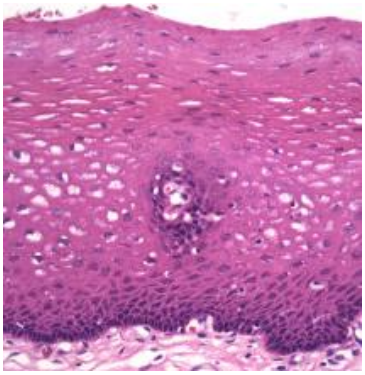
Upper Aerodigestive Tract Squamous Lesions

Prepared by Dr. Kurt Schaberg

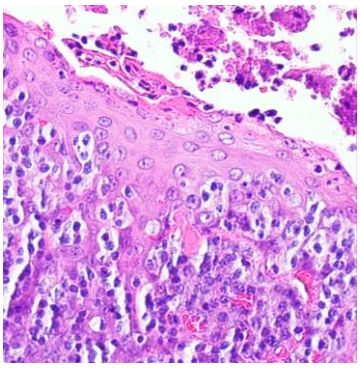
General

The "Upper Aerodigestive Tract" (UADT) is lined by non-keratinizing squamous mucosa and includes the oral cavity, pharynx, larynx and esophagus. The most common malignancy is squamous cell carcinoma (SCC).

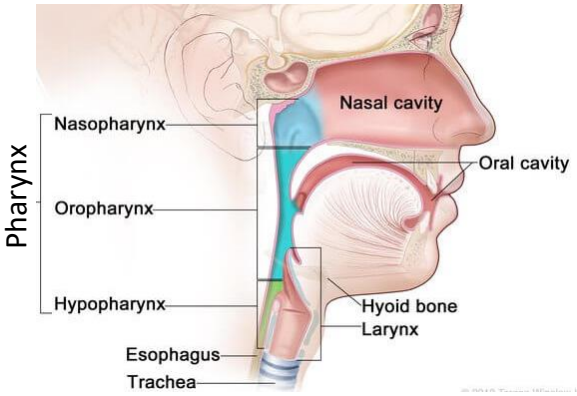
Anatomy is very important with etiology and staging! Know where you are and use the correct staging.
In the *oropharynx*, SCC is often HPV-associated.
In the *oral cavity and larynx*, SCC is often due to smoking and alcohol (HPV-independent).



Normal oral mucosa
(lines most of UADT)
Virtual vocal cords slide



Normal tonsil crypt epithelium
(reticular epithelium with abundant lymphocytes)
Virtual tonsil slide



Both benign and malignant conditions can have similar *clinical* appearances.
"**Leukoplakia**"—clinical term for a **white** plaque on a mucous membrane
"**Erythroplakia**"—clinical term for a **red** plaque. Much higher risk of dysplasia.
"Speckled Erythroplakia"—clinical term for a mixed red and white lesion.

May represent a wide spectrum of histologic changes often falling within the general category of keratosis (abnormal presence and/or excessive keratin) with or without dysplasia.

Any type of lesion may be biopsied to evaluate for malignancy/dysplasia.

Non-neoplastic Lesions

May mimic cancer clinically, often with leukoplakia or ulceration

Candidiasis

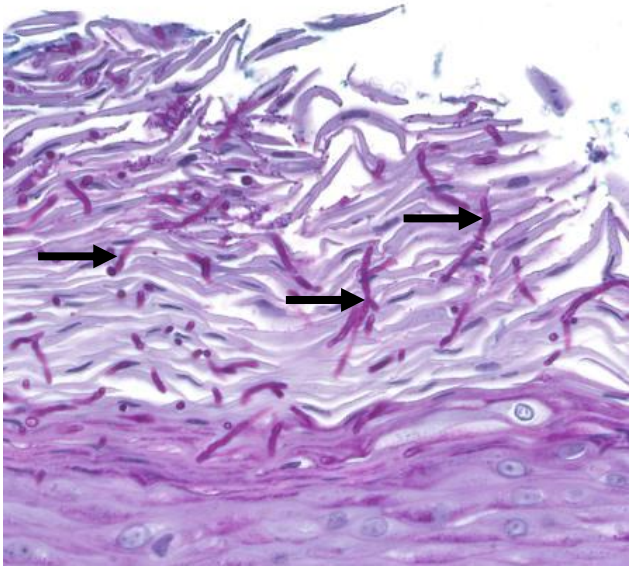
Most common oral fungal infection.
Often occurs in **immunocompromised** patients, but can occur in healthy individuals.
Often appears clinically like a **white plaque**.

Dimorphic fungi with yeast forms and hyphae/pseudohyphae→ **hyphal form causes tissue invasion/symptoms** so look for hyphae to make Dx (yeast only is not good enough!)

Often seen with **parakeratosis and acute inflammation** (so consider this Dx and do stains whenever you see this).

Can **highlight with PASd or GMS**

May see accompanying reactive epithelial changes like hyperplasia. Virtual slide



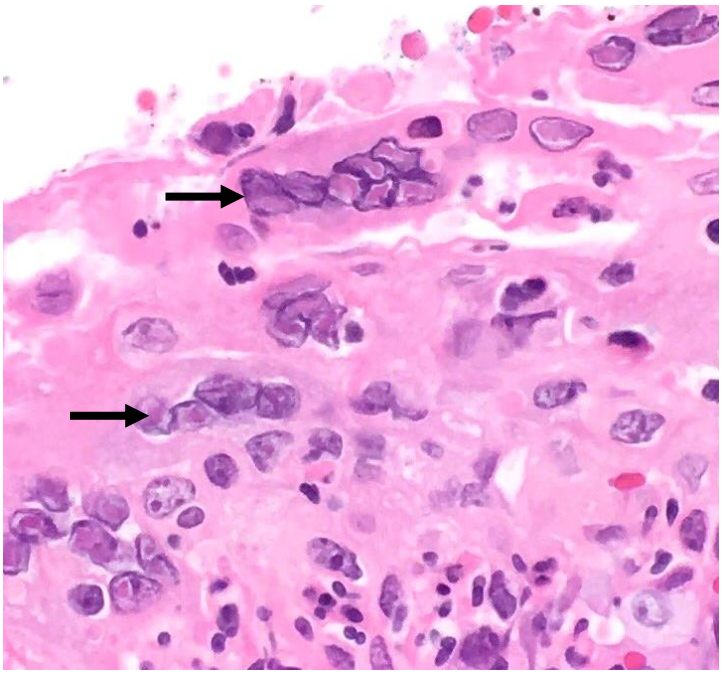
Herpes Simplex Virus

Virus **infects epithelial cells** and ganglion cells.
Two types classically infecting different sites:
Type 1= Oral, Type 2=Genital, but not always true.

Infected cells show classic **ground glass intranuclear inclusions** with "**3 M's**": ***M***olding, ***M***argination, ***M***ultinucleation.

Often associated **ulceration** with acute and chronic inflammation. Virtual slide

CMV can cause similar ulcers, but is much rarer, usually only seen in the immunocompromised, and the eosinophilic intranuclear inclusions are seen in mesenchymal cells.



Lichen Planus

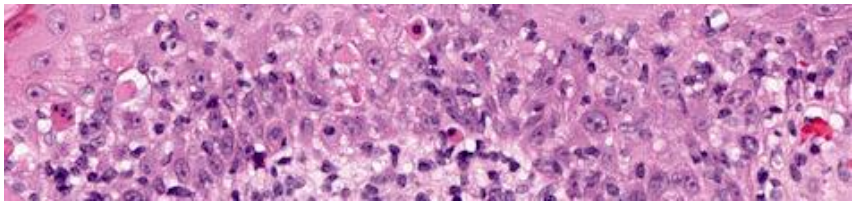
Same as on the skin (often also involves mucous membranes).
Chronic, self-limited inflammatory reaction.
Multifocal (if focal → consider *Lichenoid keratosis*)

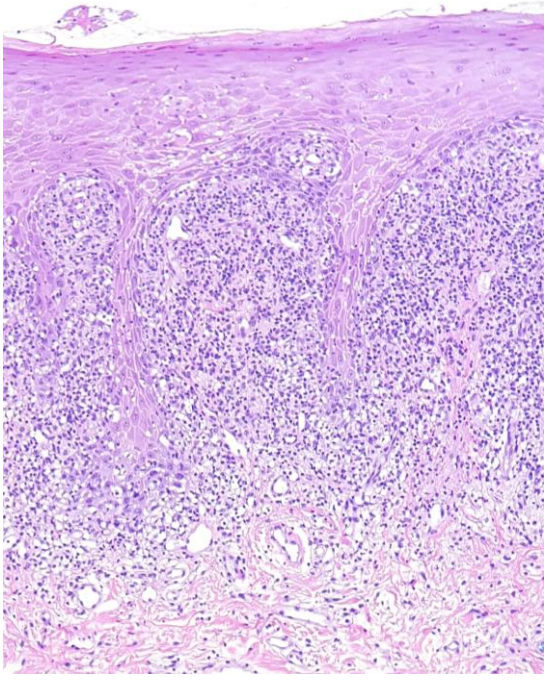
"Band-like" T-cell infiltrate below epithelium
"Saw-tooth" rete ridges

Often hydropic degeneration and/or degenerating keratinocytes
NO **significant atypia** (otherwise consider dysplasia)
Variable thickness and keratinization. Virtual slide

Unknown etiology. Associated with many medications and Hep C.

Clinical 5P's: **P**urple, **P**ruritic, **P**olygonal, **P**lanar, **P**apules.



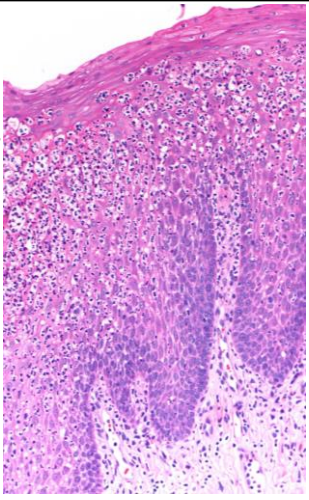


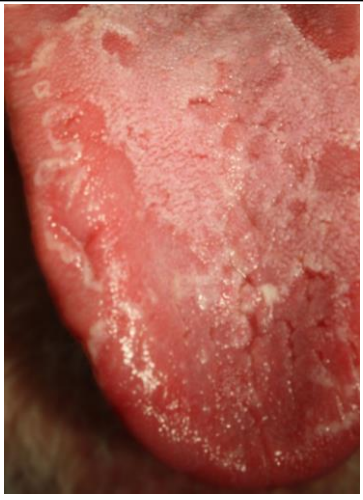
Geographic Tongue

aka "Benign migratory glossitis" Virtual slide
Idiopathic inflammatory condition, primarily on **tongue**.
Often asymptomatic→ self-resolves

Multiple, well-defined erythematous islands with raised whitish yellow borders that rapidly appear→ migrate around tongue.

Epithelium with hyperparakeratosis, acanthosis, spongiosis, elongated rete ridges, and collections of neutrophils (Monro abscesses).
Lamina propria acute and chronic inflammation

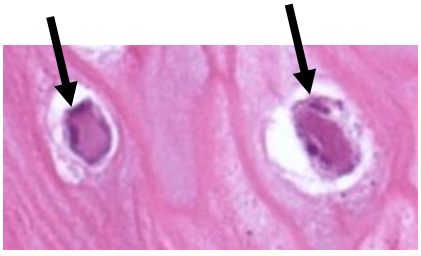


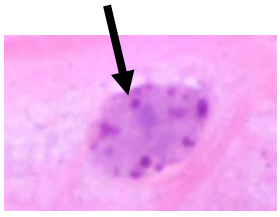


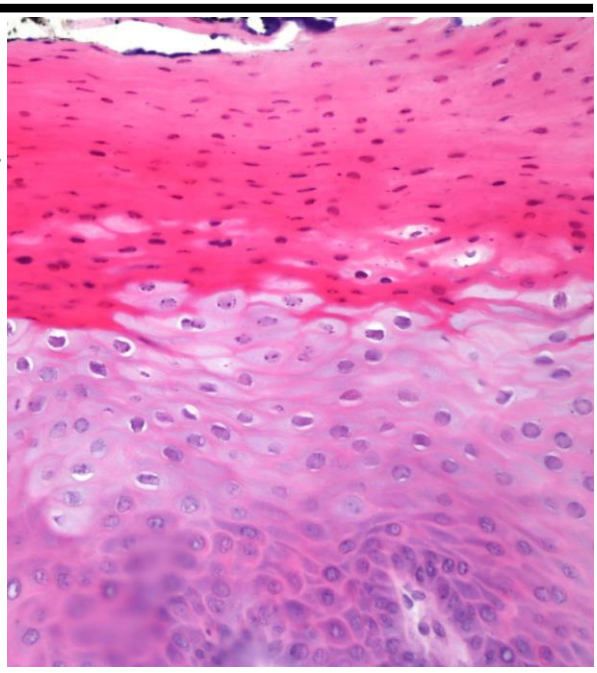
Hairy Leukoplakia

Epithelial hyperplasia induced by Epstein-Barr virus (**EBV)**.
Often on the **lateral tongue** of **immunocompromised patients**.

Acanthosis and **parakeratosis**
"Balloon" cells in spinous layer with viral cytopathic effect including eosinophilic nuclear inclusions and ballooning degeneration→ highlighted by EBER in situ hybridization
Often coinfected with candida.
Little inflammation. No dysplasia.





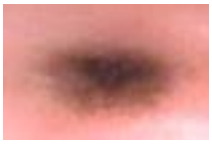


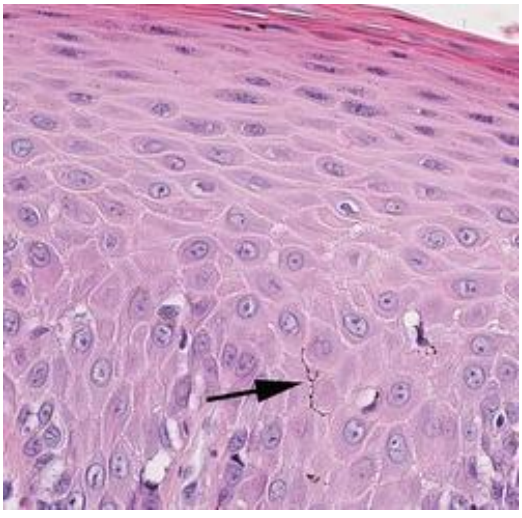
Oral Melanoacanthoma

Non-neoplastic. Likely trauma-related.
Dual proliferation of epithelial and melanocytic cells
Rapidly growing pigmented, smooth lesion.
Often regresses.

Acanthotic epithelium with dendritic melanocytes throughout the epithelium(→). Increased melanin in basal layer.

No atypia or invasion of melanocytic nests.
(Important clinical DDX: oral melanoma!)



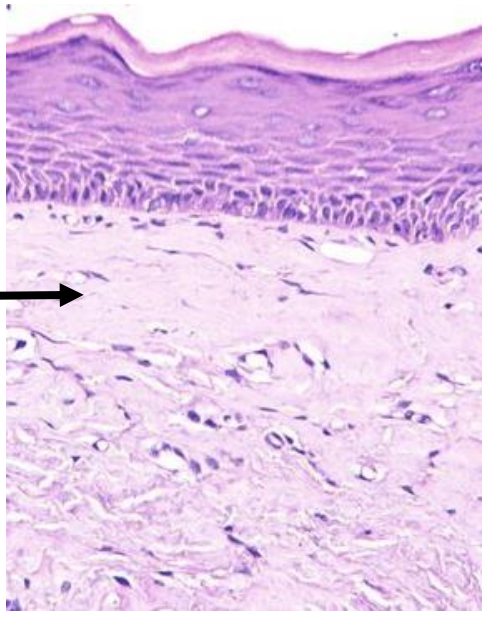


Submucosal fibrosis

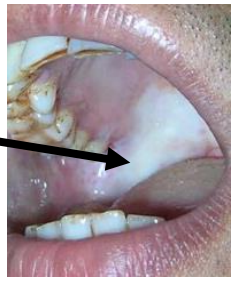
Chronic, insidious disease characterized by progressive fibrosis of submucosal tissues of the oral cavity and oropharynx.

Risk of transformation to SCC.
Etiologic agent: Areca nut chewing.
Almost exclusive to Southeast Asia (India, Pakistan, Taiwan, etc..)

Subepithelial hyalinization and fibrosis.
Epithelial atrophy.



Palpable fibrous bands in oral mucosa that limits mouth opening
Loss of tongue papillae.



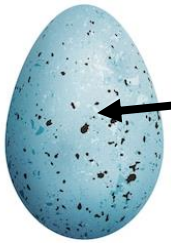
Reactive vs Dysplastic Changes

Benign/Reactive

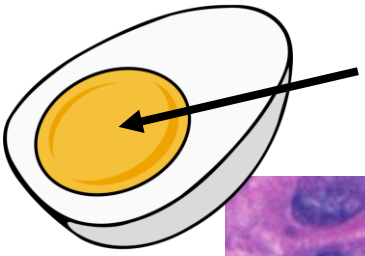
"Think Eggs"

Cytology: Although they may enlarge, nuclei are still **rounded** with **smooth nuclear contours**.

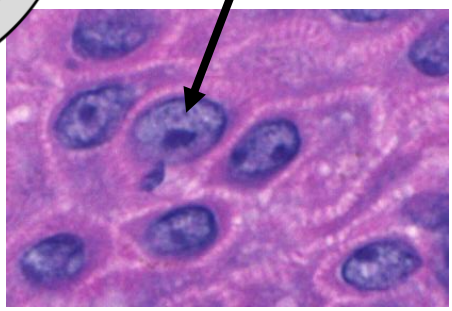
Low N:C ratios (More cytoplasm)



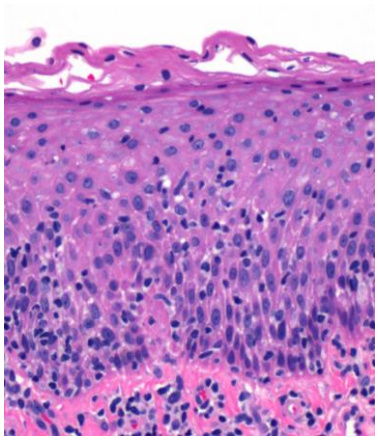
Nuclei are smooth **Round/oval**, often with **speckled chromatin**



Sometimes have a prominent nucleolus *(think Yolk)*



Lots of *inflammation*? If so, raise your threshold to account for reactive changes!



Maturating

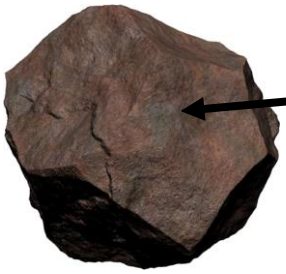
Architecture: Often matures towards surface, with highest N:C ratio cells confined to the base. Cells seem to "Know which way is up."

Dysplastic

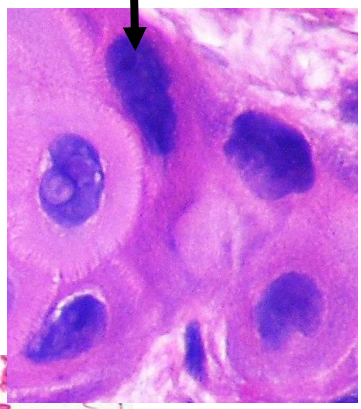
"Think Boulders"

Cytology: Nuclei are **big, irregular, jagged, rough, and dark.**

High N:C ratios (mostly nucleus!)

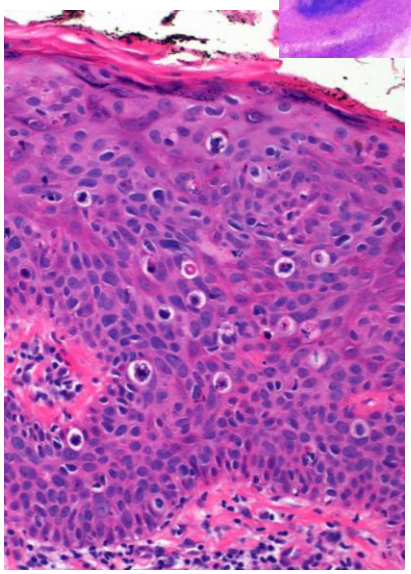


Nuclei are **Dark** with **Irregular** crinkled contours



Dyskeratotic cells

Usually *no* nucleoli (unless perhaps invasive)



Architecture: No maturation in traditional High-grade dysplasia. Many cells don't know which way is up.

However, can see maturation in low-grade dysplasia and keratinizing dysplasia.

Squamous Neoplasms, Non-HPV related

Majority of oral cavity, larynx, and pharynx cancers are squamous cell carcinoma.

Major risk factors: <u>smoking</u> (most important cause), **<u>alcohol</u>**, and chewing *<u>(Carcinogens!)</u>*
→ DNA damage accumulation with frequent p53 mutations → chromosomal instability and aneuploidy
→ <u>synergistically</u> increase risk together exponentially (not just additive)

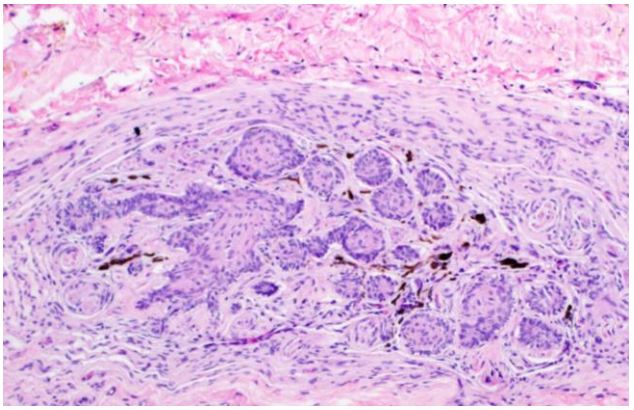
Often **clinically appear white to erythematous**. Erythematous lesions are more frequently dysplastic.

<u>"Oral Potentially Malignant Disorders (OPMD)"</u>
Heterogeneous group of clinically defined conditions associated with a variable risk of progression to squamous cell carcinoma. Most produce visible lesions (i.e., leukoplakia, erythroplakia, etc…)
Relatively low annual transformation rate to cancer = ~1.5%

OPMD Includes: Erythroplakia, Leukoplakia, Proliferative Verrucous Leukoplakia, Submucosal Fibrosis, Palatal lesions associated with reverse smoking, Lichenoid lesions, Smokeless tobacco keratosis, GVHD, Lupus, etc…

Note: Although the WHO doesn't formally endorse using a two-tiered dysplasia grading system in the oral cavity, they don't forbid it either and don't offer an alternative, so I think it's the best system to use for the time.

<u>Warning!</u> Mimic to know about:
"Juxtaoral organ of Chievitz"
Normal structure consisting of bland, lobular squamous epithelium closely associated with nerves.
Located bilaterally in oral cavity on buccal mucosa medial surface of mandible near the angle of the jaw.
<u>Can be mistaken for SCC on frozen section analysis of margins!</u>



Proliferative Verrucous Leukoplakia

Multifocal, progressive disorder→ <u>very high rate of recurrence</u> and <u>transformation to SCC</u>. Often older females. Unknown etiology.

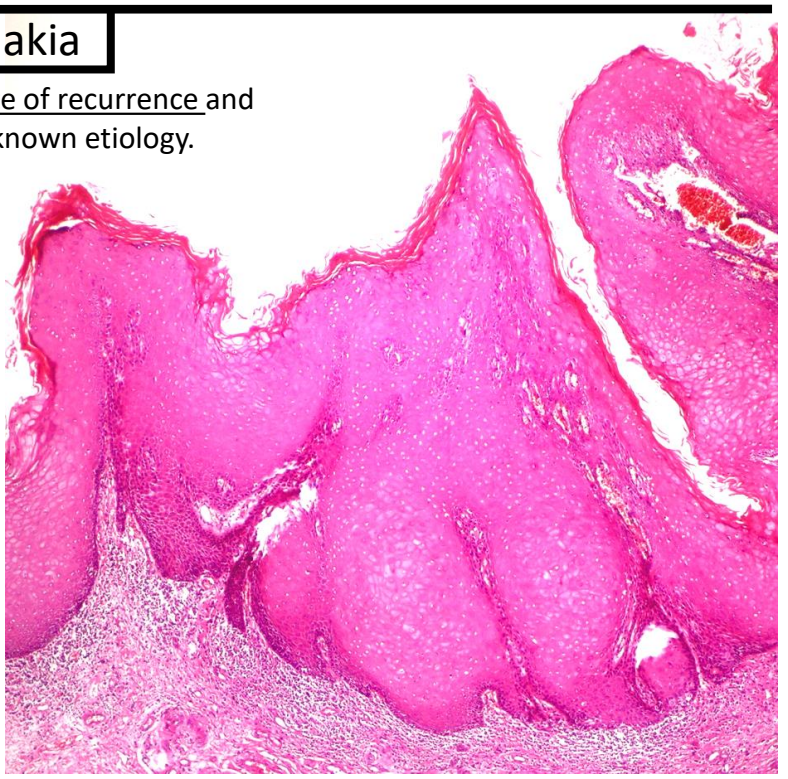
Oral cavity: often involves gingival, alveolar mucosa, and palate.

Appearance changes with time:
Starts with **localized** flat or verrucous **hyperorthokeratosis,** prominent granular layer, and loss of rete ridges. Bulky architecture. Often lichenoid reaction.

Eventually becomes **multifocal**, has increasingly thick epithelium, and develops **dysplasia**.

Dx often requires <u>clinical</u> and pathologic correlation as findings on one biopsy are not diagnostic (must know <u>multifocal, progressive</u>).

May progress to conventional or "Barnaculate" SCC (better prognosis, like verrucous).



Squamous Dysplasia

Epithelium with accumulated genetic changes→ **risk of progression to squamous cell carcinoma**.
Non-obligate precursor→ most cases of dysplasia do *not* progress to SCC (higher grade = higher risk)

Features of nuclear/cellular "atypia": marked variation in size/shape (pleomorphism), marked hyperchromasia, and high N:C ratios.

May be atrophic or acanthotic.

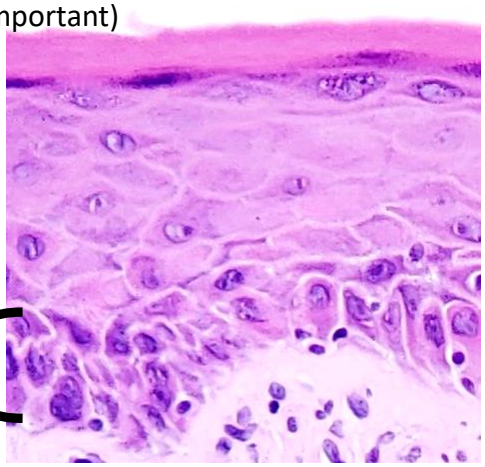
Grade using scheme below based on maturation, but if there is severe atypia it is acceptable to upgrade to high-grade dysplasia even if it matures at the surface.

Not always reproducible! (So consider showing another person if it's important)

Low-Grade Dysplasia/SIL
(previously mild dysplasia)

Low Malignant Potential (may regress or not advance) Virtual slide
Limited to LOWER half of epithelium, with surface maturation

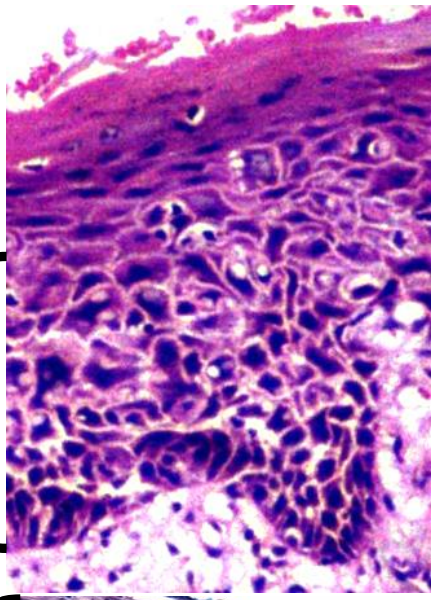
Architectural criteria	Stratification preserved with retained orientation (vertical cells at bottom, horizontal cells at top)
Cytologic Criteria	Hyperchromasia. Minimal cellular atypia Rare mitoses, in or near basal layer. Few dyskeratotic cells



High-Grade Dysplasia/SIL
(previously moderate to severe dysplasia)

Pre-malignant lesion
Involves at least half of the epithelium Virtual slide 1 2

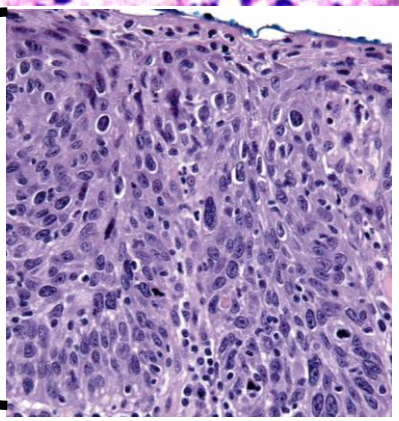
Architectural criteria	Abnormal maturation Altered cells involve ≥1/2 of thickness Disordered stratification Can be keratinizing or non-keratinizing Intact basement membrane No stromal alterations
Cytologic Criteria	Conspicuous cellular atypia. Pleomorphism. Marked hyperchromasia. Increased N:C ratio. Increased mitoses at or above basal layer Dyskeratotic or apoptotic cells throughout



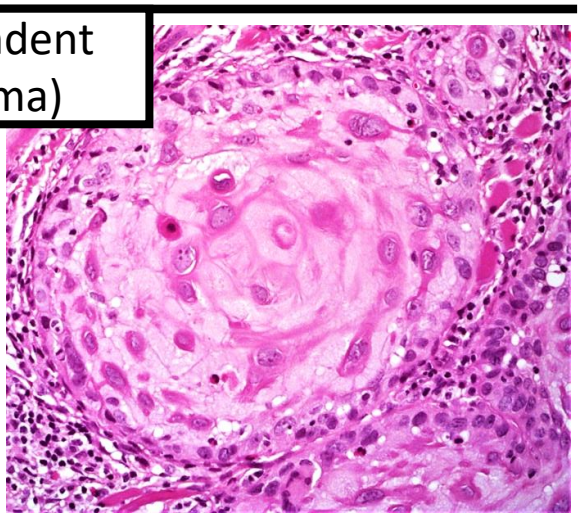
Carcinoma in situ

Changes occupy the entire thickness of the epithelium

Architectural criteria	Complete loss of stratification and polarity Preserved basement membrane (not infiltrative)
Cytologic Criteria	Severe cellular and nuclear atypia Atypical mitoses



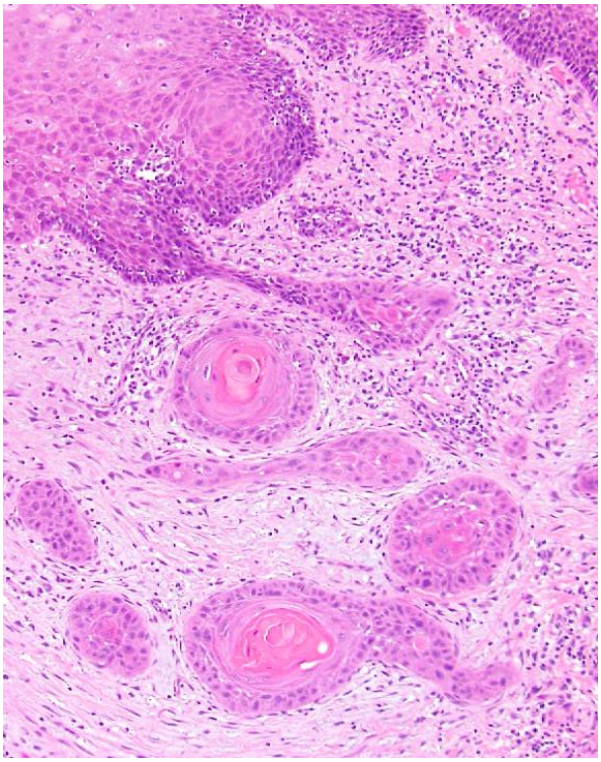
Squamous cell carcinoma, HPV-independent (Conventional Squamous Cell Carcinoma)



Malignant epithelial tumor with squamous differentiation arising from mucosal epithelium.
→ **Keratinization** (±keratin pearls) and/or **intercellular bridges**

Frequently keratinizing

Features of invasion: downward growth of islands, cords and isolated tumor cells with complex growth, irregular interface, desmoplastic response, lymphovascular invasion, perineural invasion, and paradoxical maturation (deep keratinization).



Grading is irrespective of keratinization.
Well-differentiated: closely resemble normal squamous mucosa (matures somewhat normally), few mitoses.

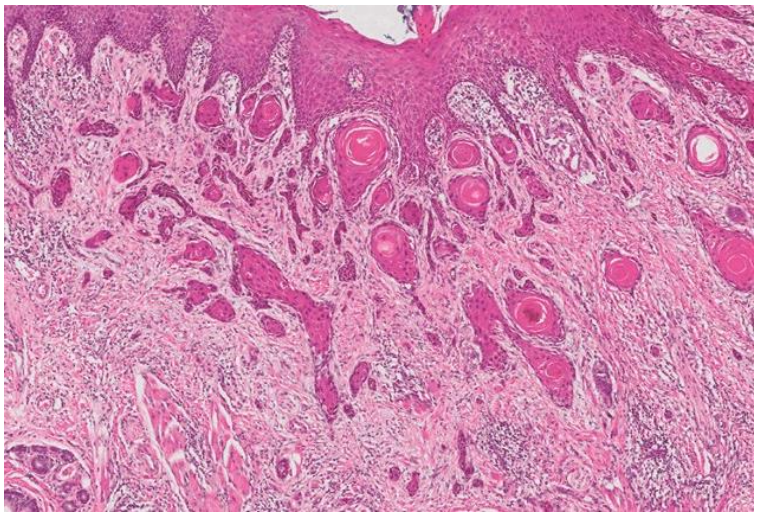
Moderately-differentiated: more pleomorphism and mitoses.

Poorly-differentiated: May be difficult to Dx as squamous, requiring IHC. Basal-type cells predominate with lots of mitoses. Often lose expression of HMWCKs.

Depending on location, can present with mass (oral cavity), hoarseness (supraglottic larynx) or dyspnea/stridor (subglottic larynx), etc..

Usually white and firm. Can be endophytic or exophytic.

Frequently metastasizes to cervical lymph nodes→ lymph node mets is the single most adverse prognostic factor. Extracapsular extension is a particularly associated with regional recurrence and worse survival.



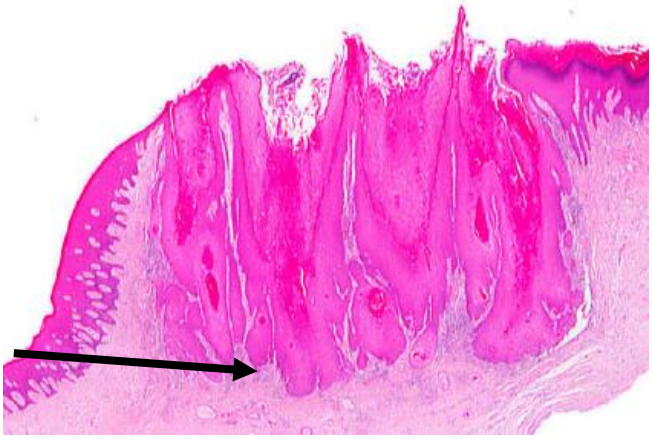
Negative for HPV: P16 negative, Negative ISH

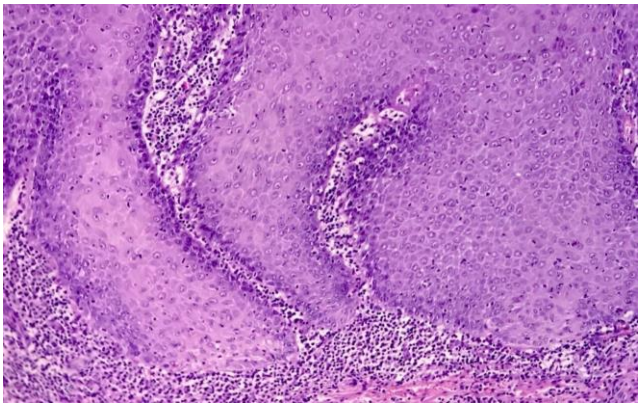
IHC: (+) AE1/AE3, CK5/6, p40, p63
(-) CK7, NUT, Neuroendocrine markers

Virtual slide 1
Virtual slide 2
Virtual slide 3

Important (HPV-independent) Squamous cell carcinoma variants:

Verrucous Squamous Cell Carcinoma





Variant of Well-differentiated Squamous Cell Carcinoma

Dramatic **acanthosis** with club-shaped spiky projections and invaginations. Marked "church-spire" keratinization. Broad-based, papillary.
No significant cytologic atypia
Proliferative basal cell layer only 1-2 cells thick.
Only very rare mitoses in basal layer.
Dense eosinophilic "glassy" cytoplasm.

Well-defined "Pushing" invasion, often with associated **lymphocytic inflammation**. Intact basement membrane.
NO infiltrative growth.
Often need to see nearby epithelium to show *relative* invasion beneath basal layer of nearby epithelium.

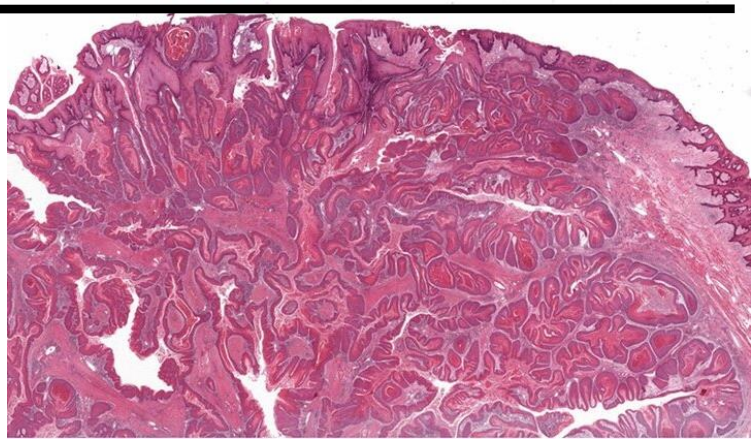
Good prognosis: Locally destructive/invasive, but does not metastasize

Grossly fungating exophytic. Virtual slide

May be very hard to Dx on small biopsies, requiring clinical correlation. If clinically concerned for malignancy, but biopsy looks like benign→ consider this Dx! Consider saying "Atypical Verrucous Lesion"

If infiltrative growth→ conventional SCC

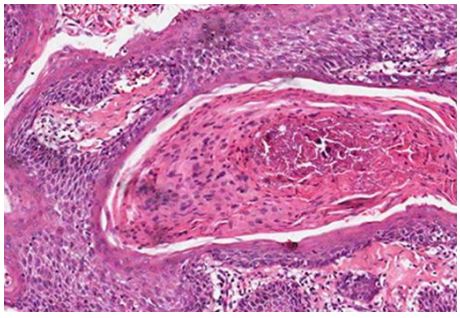
Carcinoma cuniculatum

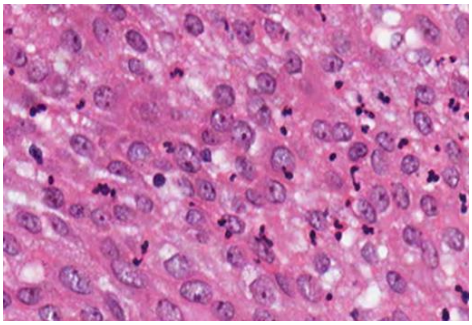


Rare, well-differentiated, locally destructive, non-metastasizing squamous cell carcinoma type.

Burrowing, labyrinthine invasive pattern.
Heavily keratinizing with Keratin-containing crypts ("Keratin microabscesses")
Minimal cytologic atypia.
Stromal neutrophils. Microsequestra;

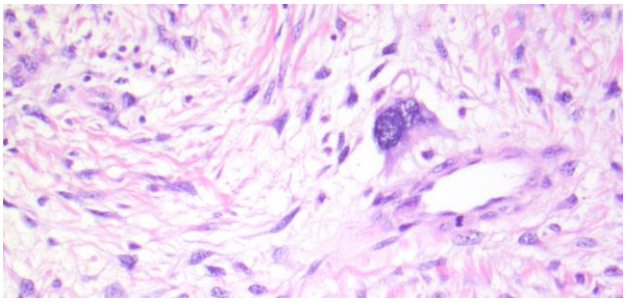
Excellent prognosis.
Treated with excision.





Spindle Cell Squamous Cell Carcinoma

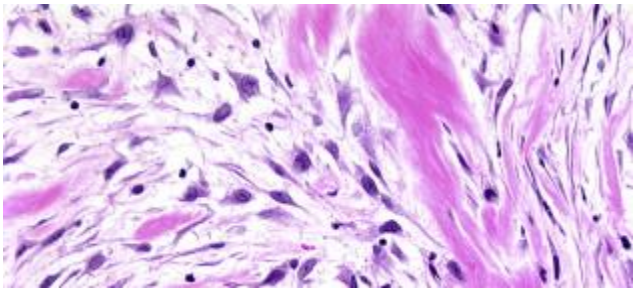
aka "Sarcomatoid carcinoma" or "Carcinosarcoma"



Squamous cell carcinoma variant with predominantly **malignant spindle and/or epithelioid pleomorphic cells**.

Often a **polypoid mass** with ulceration.
Epithelial→ mesenchymal transition

Spindle cells often have overt pleomorphism, hyperchromasia, and increased mitoses.
Can have heterologous differentiation.

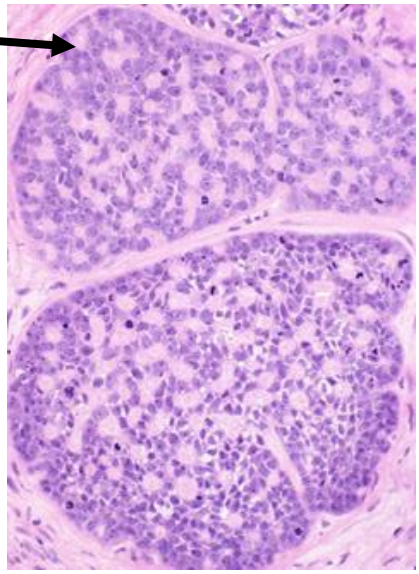


Must have evidence of epithelial differentiation, either by morphology (e.g., adjacent conventional SCC or dysplasia) or by IHC (e.g., CK, p40, etc..)

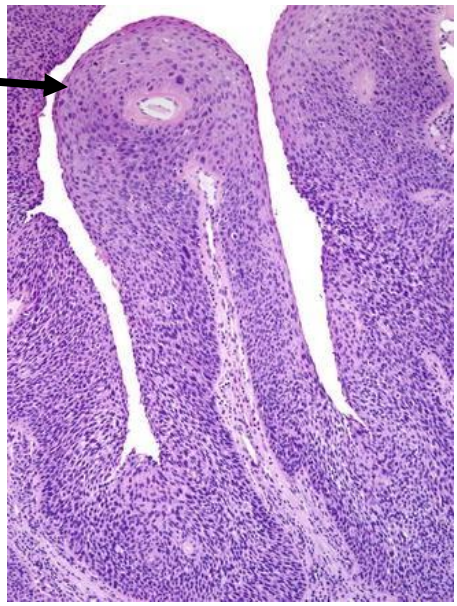
Often worse prognosis.

Virtual slide 1
Virtual slide 2

Basaloid Squamous Cell Carcinoma:
Basaloid, hyperchromatic appearance (high N:C ratio) often with a conventional component. HPV-negative. Rounded nests with peripheral palisading and admixed hyalinized stroma. Frequent mitoses and comedonecrosis. May mimic a salivary gland neoplasm and be SOX10 positive, but diffuse p63/p40 (which is often patchy in adenoid cystic carcinoma). Also, must be negative for neuroendocrine markers. More aggressive. Virtual slide
IHC: (+) p63/p40, SOX10, CK5/6; (+/-) MYB, CD117
(-)S100, TTF1, Synaptophysin, SMA



Papillary Squamous Cell Carcinoma:
Exophytic papillary growth pattern with thin fibrovascular cores covered by non-keratinizing malignant stratified squamous epithelium or, in the keratinizing type, by high-grade atypia. Uncommon. May be HPV-related in oropharynx, but not elsewhere. Better prognosis. Ideally see stromal invasion to make Dx. Virtual slide
On biopsy may call "Papillary keratosis with dysplasia."

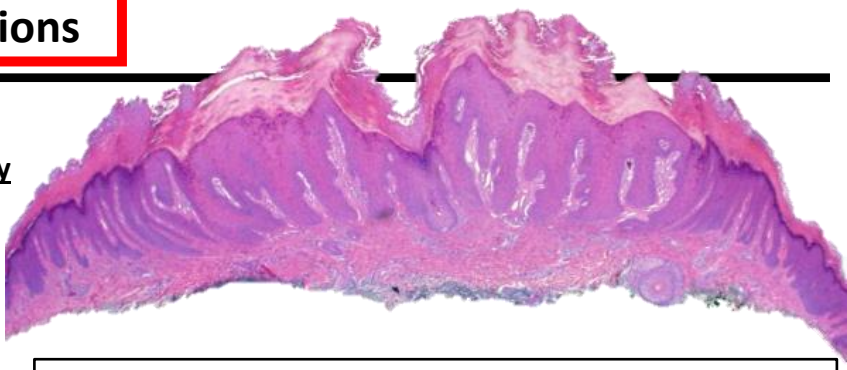


Adenosquamous Carcinoma:
Arises from squamous epithelium and shows *both* squamous and glandular differentiation. (Must consider/exclude mucoepidermoid carcinoma) Virtual slide

Lymphoepithelial Carcinoma:
Syncytial sheets of pleomorphic cells with a prominent intratumor chronic inflammatory infiltrate. Vesicular nuclei with prominent nucleoli. Like nasopharyngeal carcinoma, but not often associated with EBV. Virtual slide

HPV-related Squamous Lesions

Verruca Vulgaris



Benign squamous proliferation in **oral cavity**
Caused by **low-risk HPV** (e.g., Type 2 and 4)
Identical to on the skin.

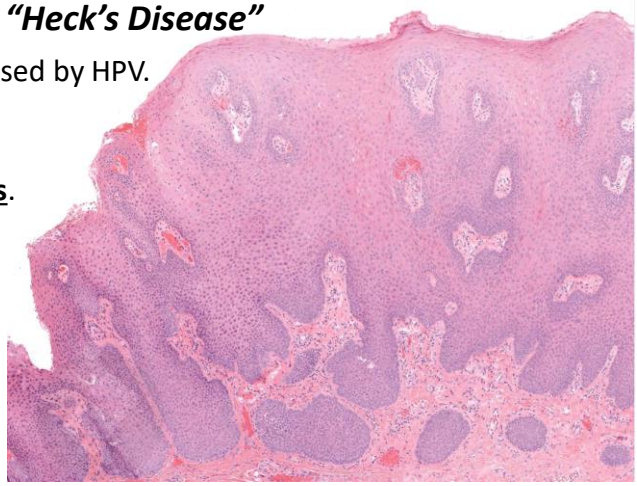
Exophytic and papillomatous.
Hyperkeratosis and acanthosis.
Elongated and **"cup-like" rete ridges.**

Cytologically bland with prominent granular layer and occasional **koilocytes**.

Condyloma Acuminatum: Oral equivalent of anogenital condyloma. HPV types 6 or 11. Often sexually transmitted. Often larger than verruca vulgaris.

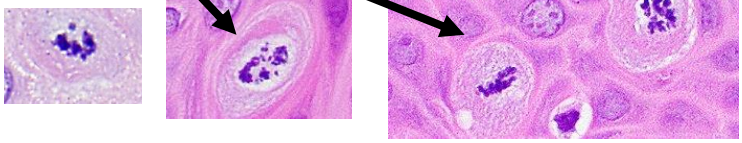
Multifocal Epithelial Hyperplasia

aka "Heck's Disease"

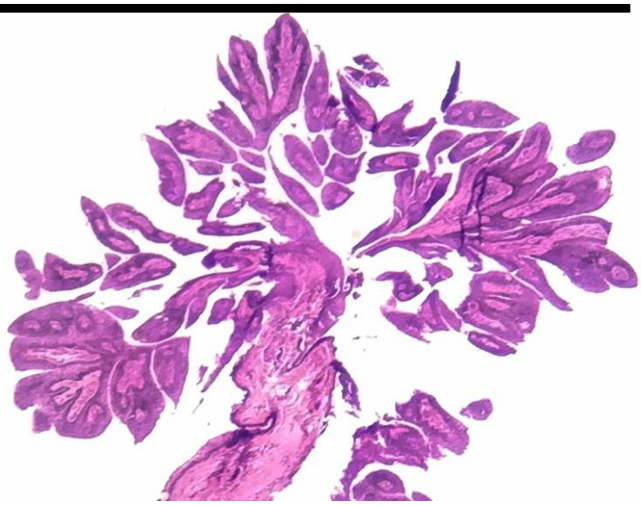


Multifocal benign squamous proliferation in **oral cavity** caused by HPV.
Most common in **children/adolescent girls**.
HPV types 13 or 32 often.
Often located on **lips or buccal mucosa**→ **multiple papules**.

Mild **hyperkeratosis**, prominent **acanthosis**, normal cell maturation. Occasional koilocytes.
"Mitosoid" figures are hallmark (not often seen in other conditions)



Squamous Papilloma

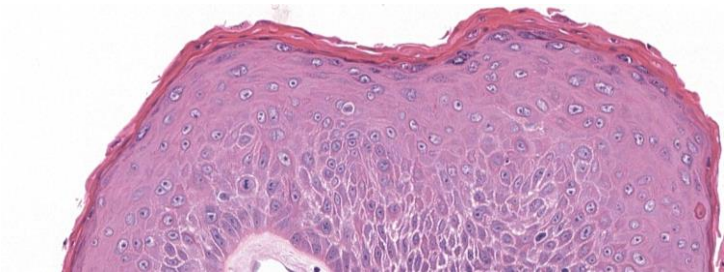


Benign exophytic squamous proliferations with branching papillary fibrovascular cores.

Usually associated with HPV types 6 or 11 (Low-risk).
Can get through sexual or non-sexual contact.

Infrequent koilocytes.
Epithelial hyperplasia. No dysplasia.

Often solitary, cauliflower-like.
Malignant transformation is very rare.



If multiple, especially if young, consider:
Recurrent Respiratory Papillomatosis (RPR)— multiple, recurrent papillomas in the respiratory tract of children and young adults→ high morbidity as can obstruct breathing, swallowing, etc…

Squamous Cell Carcinoma, HPV-associated

Sometimes also called "HPV-positive" or "P16-positive" SCC.

Squamous cell carcinoma associated with <u>High-risk HPV</u>
>90% caused by **HPV type 16** → associated with **oral sex**
Incidence rising: Frequently white men in 50's

Strong predilection to **<u>oropharynx</u>**: **Base of Tongue** (BOT) and **Tonsils** (usually arises from tonsillar crypts)

Often presents at <u>high clinical stage</u> with a **<u>small/occult oropharyngeal primary</u> and cervical lymph node <u>metastases</u>**, which are often large and cystic.

Typical distinct morphology:
Non-keratinizing, high N:C ratios → basaloid appearance.
Frequent mitoses and/or apoptotic figures.
Frequent associated lymphocytes/lymphoid stroma.
Some morphologic spectrum as can be papillary, etc…

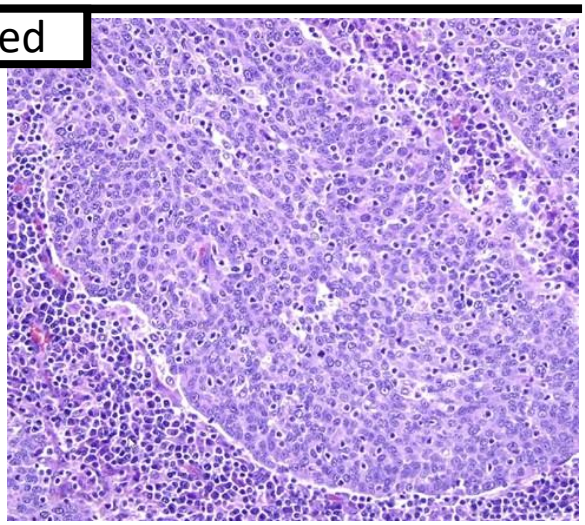
Arises is crypts of tonsils → grows/invades as nests/lobules.
<u>No</u> recognizable in situ component/background dysplasia.

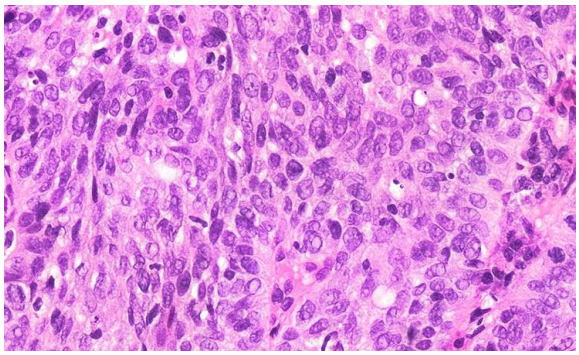
Grading is *<u>NOT</u>* applicable!!

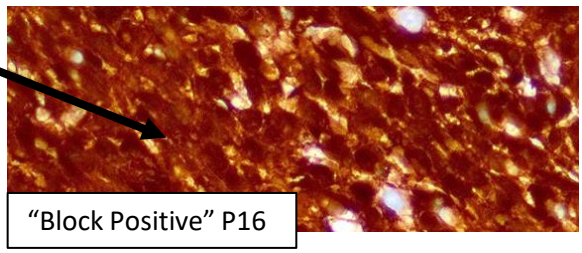
HPV can be detected by: In situ hybridization or PCR.
Diffuse "block positive" staining with p16 (>70% epithelium nuclear and cytoplasmic staining cut-off) is used as a reliable surrogate marker for the presence of high-risk HPV in oropharyngeal carcinomas (if appropriate morphology).

IHC: **(+) p40,** p63; (-) synaptophysin

Significantly **<u>better prognosis</u>** than conventional SCC







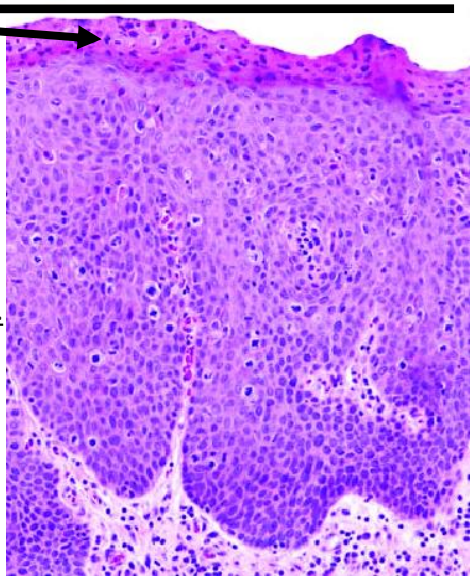
"Block Positive" P16

Virtual slide (H&E) P16

Characteristic	HPV-associated SCC	HPV-independent SCC
Median Age	~50 yrs	~65 yrs (older)
Risk Factors	Sexual behavior	Smoking and Alcohol
Background Dysplasia	Not recognized	Frequent
Morphology	Commonly non-keratinizing with high N:C ratio	Conventional, often keratinizing
Grading	Not Applicable	Applicable
P16 IHC	Positive ("Block")	Negative
Lymph node metastases	Frequently cystic	Uncommonly cystic
Postulated origin	Reticulated epithelium of invaginated crypts	Surface epithelium
3-year survival	~80% (Better survival)	~60% (Worse survival)

Adapted from: WHO Classification of Head and Neck Tumors. 2017 and 2024.

HPV-associated oral epithelial dysplasia

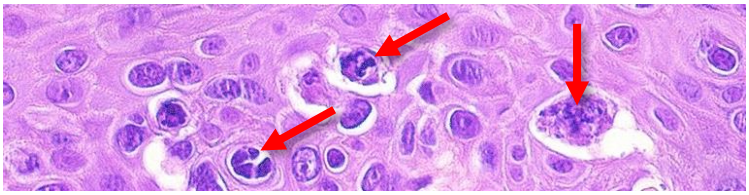


In *oral cavity* (only!) a form of HPV-mediated dysplasia is recognized.

High-risk HPV-associated lesion. (Usually, type 16)
Epithelial dysplasia with prominent viral cytopathic changes, including prominent karyorrhectic/apoptotic debris and Pericellular halos (→)
Brightly eosinophilic parakeratosis. (→)
Monotonous population of basaloid keratinocytes with high N:C ratios.

Usually men. Flat **tongue** or **floor of mouth lesion**.
(Notably, *NOT* oropharyngeal!)
Can progress to Squamous cell carcinoma.

IHC: Strong, diffuse "block positive" p16 IHC; Positive HPV ISH.



Important Staging Details:

Use the right Checklist!

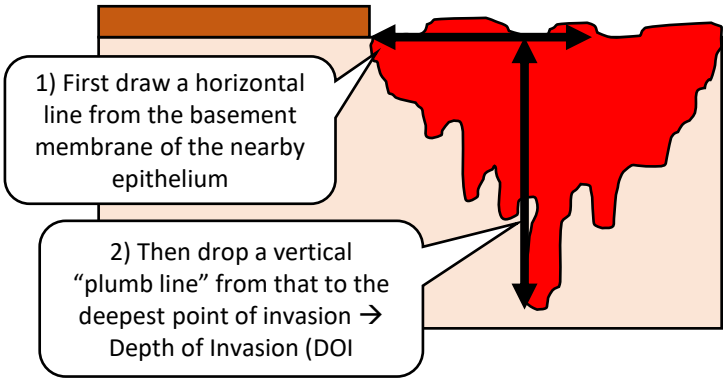
There are separate checklists and staging criteria for the Oral Cavity & Lip, Pharynx, and Larynx. Make sure you use the right one as they are very different!

Depth of Invasion (DOI):

Particularly in oral cavity, DOI is predictive of regional lymph node metastasis.

Measure by drawing a horizontal line from the basement membrane of adjacent epithelium and then dropping a "plump line" from this (see →)

In oral cavity, 5 mm is often an important cut-off

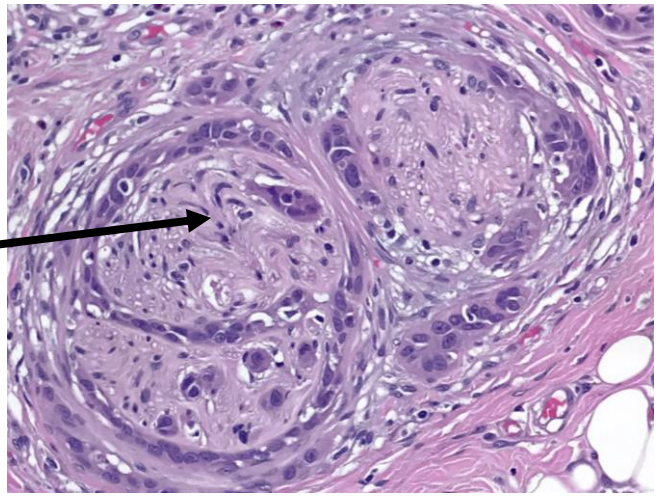


Perineural invasion (PNI):

Neurotropism.
Poor prognosis at all sites (associated with recurrence and metastasis), so concurrent chemoradiation is often considered.
Any size nerve counts.

Tumor should "have a *relationship*" with the nerve
(not just be near the nerve or passing by the nerve)

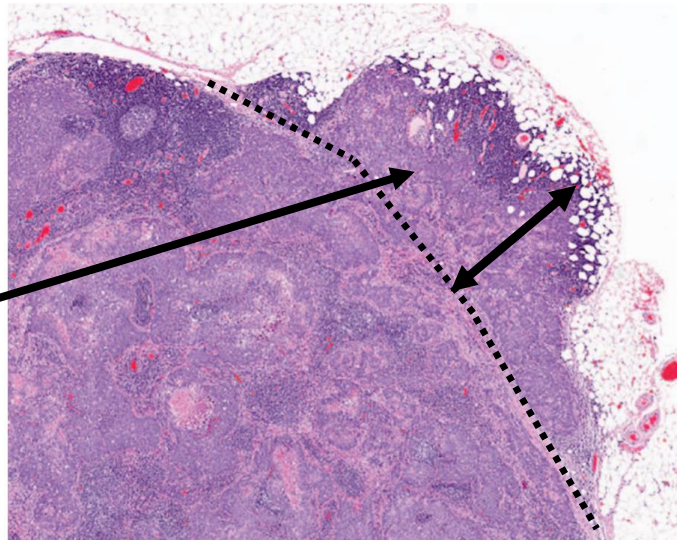
One definition: Tumor within any layers of the nerve sheath *or* in close proximity to a nerve and involving at least 1/3 of its circumference.



Extranodal extension (ENE):

Nodal status is the most important prognostic factor in upper aerodigestive tract SCC. All macroscopically negative or equivocal lymph nodes should be entirely submitted.

ENE is defined as of extension of metastatic tumor, present within the confines of the lymph node, **through the lymph node capsule into the surrounding connective tissue**, with or without associated stromal reaction.



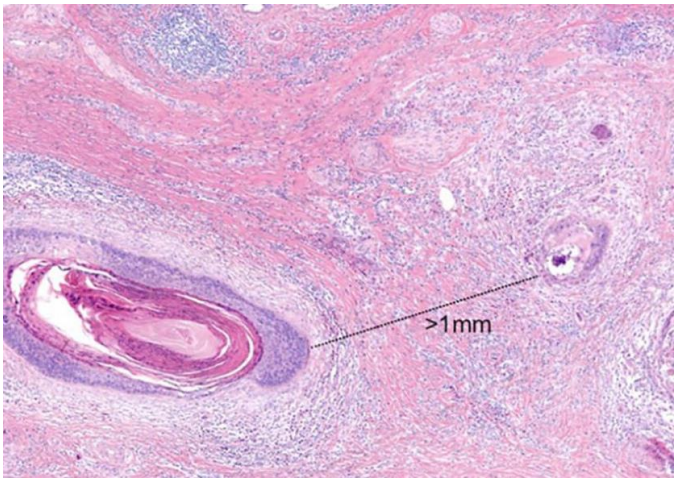
Soft tissue deposits appear to be the equivalent of a positive lymph node with ENE and should be recorded as such

A distance of extension from the native lymph node capsule is now suggested (but not yet required) with the proposed stratification of ENE into ENEma (>2 mm) and ENEmi (≤2 mm).

Worst Pattern of Invasion (WPOI):

Validated prognosticator for *oral* SCC.
Although there are 5 patterns noted, distinction between WPOI-5 and other patterns is what is most relevant.

WPOI-5 is defined by tumor dispersion ≥1 mm between tumor satellites (that is, very infiltrative with lots of tongues of tumor extending far out). PNI and LVI count as WPOI-5.



Tumor Budding:

Presence of nests composed of ≤4 cells.
Worse prognosis

Bone Invasion:

Associated with a worse prognosis.
I want to see tumor appearing to get *into* the bone(→), not just eroding the surface.

In the oral cavity, invasion “through the cortical bone” significantly upgrade the tumor to pT4a, so you want to be “sure.” Ideally, you should have tumor with bone on 3 or 4 sides of it.