Tumors of the Cervix

Squamous Lesions

Squamous Metaplasia

The process where glandular endocervical cells are replaced with squamous epithelium
The primary importance of this lesion is that it can closely resemble HSIL

In contrast to SIL, metaplasia:
- has uniform chromatin
- has minimal nuclear contour irregularities
- is more likely to have residual mucinous epithelium
- is **p16 negative**

Squamous Intraepithelial Lesion (SIL)

aka **Cervical Intraepithelial Neoplasia (CIN)**

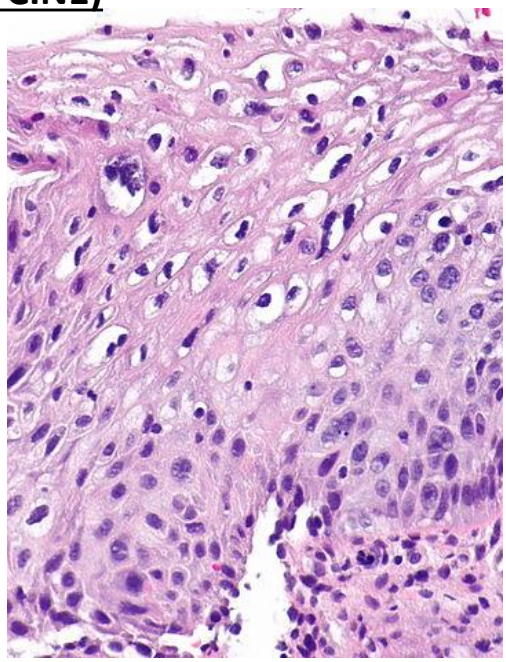
Intraepithelial (in situ, non-invasive), **squamous dysplasia due to HPV infection.**
Maturation abnormalities and/or viral cytopathic changes.
Asymptomatic. Detected by screening. On colposcopy, may be acetowhite.

Low-grade Squamous Intraepithelial Lesion (LSIL; CIN1)

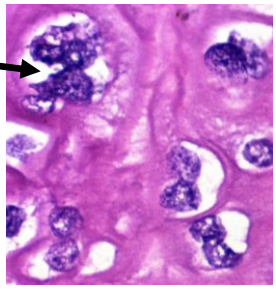
Proliferation of hyperchromatic basal-like cells that extends no more than 1/3 of the way up the epithelium

Cells differentiate (gain cytoplasm) in upper epithelium
Mitoses confined to lower zone

Many nuclei are **hyperchromatic** with **irregular nuclear contours**
(at all levels, but the high N:C ratios cells are just at the bottom)



Koilocytes = large superficial cells with perinuclear halos and large, irregular, "Rasinoid" nuclei. Sometimes binucleated.



Often spontaneously regresses, so just observed clinically with repeat cytology

HPV ISH (+); p16 (-/+)

Condyloma → grossly evident exophytic variant of LSIL. Often composed of papillary fronds.

Human Papilloma Virus (HPV)

Sexually **T**ransmitted **D**isease. Very common (up to 80% of women in early 20s)
Serotypes: **16 &18** → High-risk→ Most associated with **HSIL/SCC**
6 &11 → Low-risk→ Most associated with **LSIL/Condylomas**

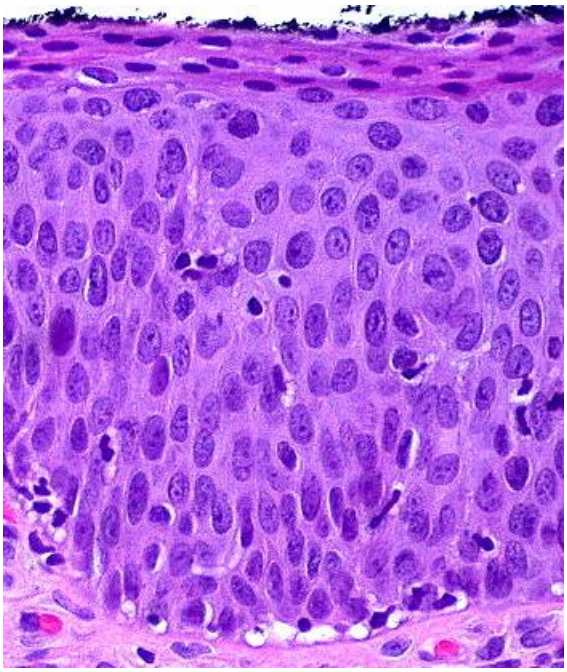
Usually infects transition zone between squamous and glandular mucosa.

HPV can infect epithelium without integrating into the nucleus, creating LSIL/Condyloma (often transient, self-limited, with natural regression) or integrate, where viral oncogene overexpression drives a clonal production of undifferentiated cells causing HSIL (precancerous with persistent infection.)

HPV-associated oncoprotein E6 inactivates p53, E7 inactivates RB1

Squamous Intraepithelial Lesion (SIL) *(Continued…)*

High-grade Squamous Intraepithelial Lesion (HSIL)



Proliferation of hyperchromatic basal-like cells that extend 2/3 of the way up (CIN2) or full-thickness (CIN3/CIS) of the epithelium

Cells (at all levels) have **enlarged, hyperchromatic nuclei with irregular nuclear contours and increased N:C ratios**.

Little (CIN2) to no (CIN3) superficial maturation.
Mitoses common at all levels, including atypical mitoses

Nucleoli are unusual→ raise the possibility of inadequately sampled invasive carcinoma (p16+) or metaplasia (p16-)

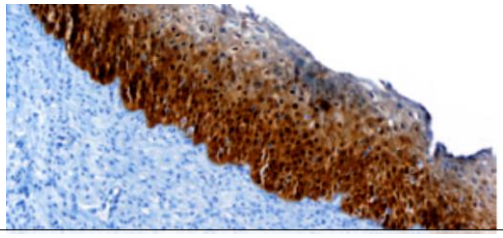
Variants: (of no real clinical significance)
Keratinizing—abnormal surface keratinization
Papillary—papillomatous architecture
Thin—Less than 10 cells thick

Treatment: Given risk of progression to SCC, often treated with LEEP, laser ablation, cryotherapy, or surgical conization.

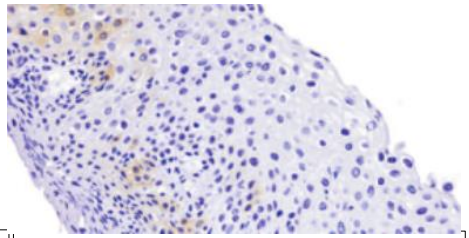
When to use P16 Immunohistochemistry

Used as surrogate marker of High-risk HPV infection

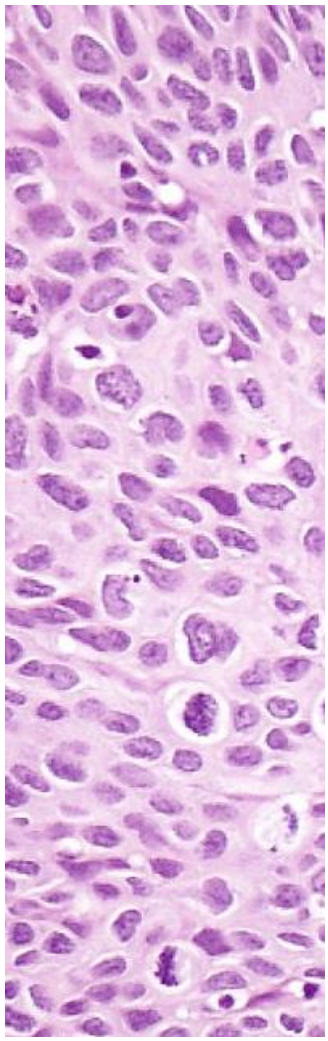
- When the morphologic **DDX is between HSIL (P16 +) and a mimic**, such as squamous metaplasia (P16 -)
- When you are considering a **Dx of CIN2**, which should be P16+ (vs. LSIL, which should be P16 -)
- When there is **disagreement** between pathologists
- When there is a **high-risk** for missed HSIL disease (e.g., HPV +)



P16 Positive
Strong, diffuse, nuclear and cytoplasmic, block staining along the basal layer going at least 1/3 of the way up



P16 Negative
Weak/Patchy
i.e., Anything but "Block" positive



When P16 Immunohistochemistry will NOT help

- When the biopsy is unequivocally LSIL, HSIL, or Negative morphologically
- When the DDX is between LSIL and Negative, as both processes are P16 negative.

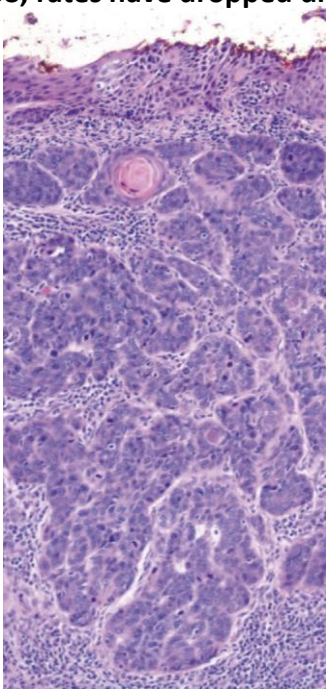
Just Remember:

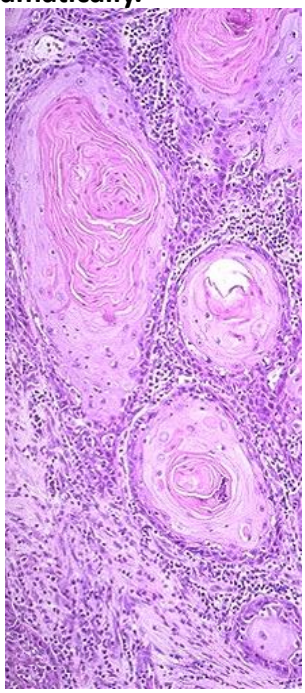
- p16 has no value outside of morphologic context (LSIL can be + !)
- p16 has a very good negative predictive value for HSIL

Squamous Cell Carcinoma, HPV-associated

An **invasive** epithelial tumor composed of squamous cells of varying degrees of differentiation.
~95% of cervical SCC is HPV-associated. Most commonly HPV types 16 or 18, and arise from HSIL

World-wide, 4th most common cancer in women, **mostly in low resource countries** without cervical cancer screening programs (Pap smears) and vaccinations. **In the US, rates have dropped dramatically.**





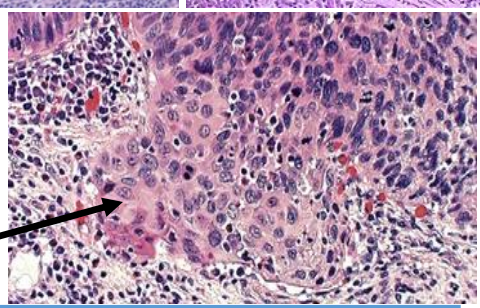
Infiltrating, angulated, irregularly sized and shaped nests, anastomosing cords, and solid sheets.
Nuclear pleomorphism and increased mitoses.
Often desmoplastic/inflammatory stroma
Can be non-keratinizing (more common) or keratinizing.
IHC: Overexpression of p16 is an acceptable surrogate for HPV infection.

With invasion can see "paradoxical maturation" with increased cytoplasmic eosinophilia

Multiple histologic patterns have been described (and do not impact treatment) including, keratinizing, non-keratinizing, basaloid, Verrucous, papillary, and lymphoepithelioma-like

Treatment depends on stage, but often involves chemoradiation.

Tumor depth of invasion must be calculated for all Stage 1 carcinomas. This is measured from the base of the HSIL origin (or nearest dysplastic epithelium if the site of origin is not apparent) to the deepest point of invasion.
Note: if tumors are severely ulcerated or largely exophytic, measuring depth of invasion may be hard/impossible.

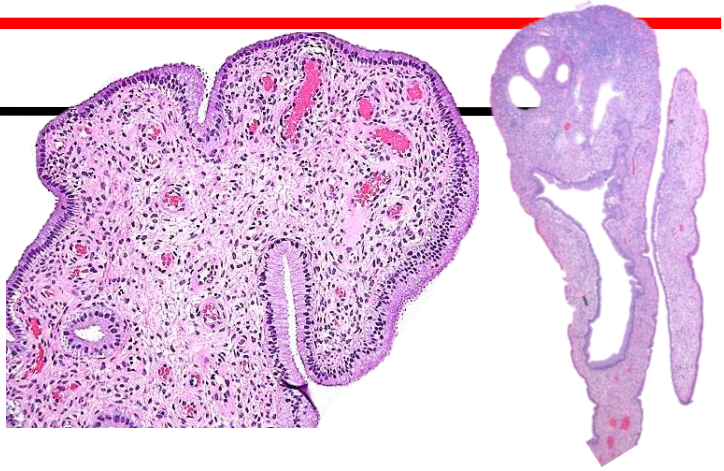


Invasive Squamous Cell Carcinoma	HSIL colonization of endocervical glands
Paradoxical maturation of cells from high N:C ratio HSIL to invasive cells with more abundant eosinophilic cytoplasm	Paradoxical maturation absent. Same cells throughout lesion
Stromal reaction present with edema, desmoplasia, and/or inflammation	No stromal reaction
Irregular contours of nests: angulated, wavy, or bulging, resulting in unusual shapes	Regular, rounded nests
Anastomosing nests of atypical cells (after tangential sectioning is excluded)	Anastomosing absent
No nearby uninvolved glands	Often residual uninvolved glands nearby

Squamous cell carcinoma, HPV-independent: Requires Negative P16 and molecular testing for HPV.
~5% of SCC of the cervix. Frequently keratinizing type, but can have any histologic pattern.
Often advanced stage and poor prognosis.

Benign Lesions

Endocervical Polyp



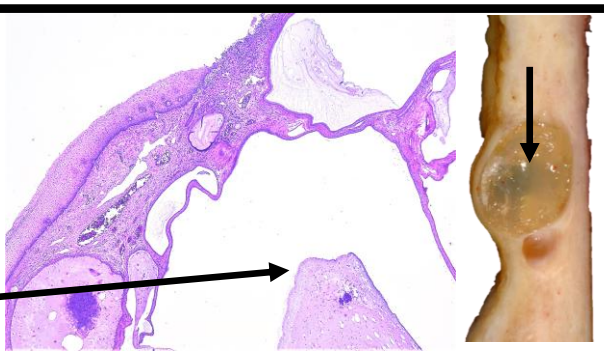
Benign. Most common growth of cervix.

Focal hyperplastic protrusions of **benign endocervical glands** and **loose fibrous stroma**

May have cystic change of glands
Frequently associated inflammation.
May have surface squamous metaplasia

Mullerian papilloma: Rare. Cervical or upper vaginal lesion of children. Branching fibrous papillae lined by a single layer of benign glandular epithelium.

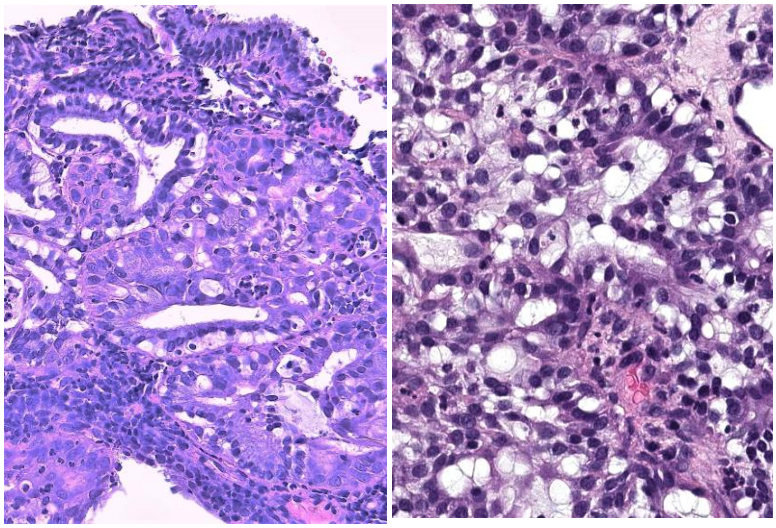
Nabothian Cyst



Common. Non-neoplastic.
Usually incidental and asymptomatic.
Endocervical gland dilation after outlet obstruction

Grossly dilated cysts filled with translucent mucoid material. Lined by a single layer of columnar mucinous endocervical epithelium, but may be flattened due to atrophy.

Microglandular Hyperplasia



Benign. Very common. Usually premenopausal

Tightly packed glands/tubules lined by flattened to cuboidal cells with eosinophilic cytoplasm sometimes a small mucin vacuole. Uniform small nuclei with rare mitoses. Subnuclear vacuoles.

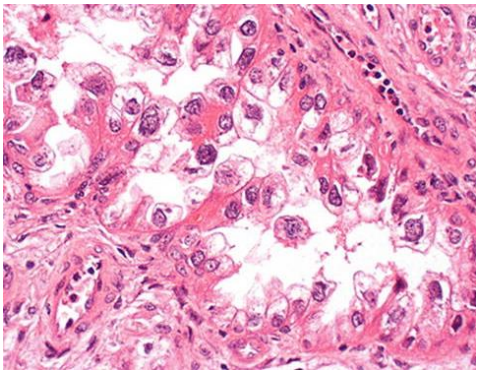
In florid cases, can have **reticular** ("net-like") or solid growth with increased atypia.

No invasive growth.

Often associated **inflammation**

p63 highlights a subset of the cells. Ki67 <10%. Usually vimentin negative and ER/PR positive

Arias Stella Reaction



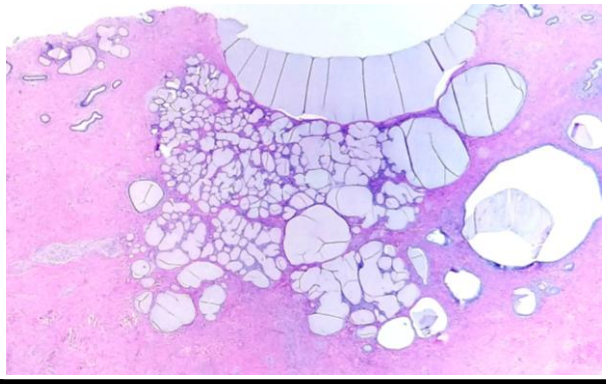
Benign change seen usually during **pregnancy** (high progestin states)

Glandular cells are **markedly enlarged with irregular, hyperchromatic nuclei and abundant vacuolated cytoplasm**. Hobnail and papillary architecture with nuclear pseudostratification

Often only focal within cervix. Does not form a mass.

Main importance is that it can be **confused** with clear cell carcinoma. In contrast though, this reactive condition lacks mitotic figures, does not form a mass, and is seen only during pregnancy.

Tunnel Clusters



Benign. Common. Incidental.

Clusters of benign, lobularly arranged endocervical glands often near the surface.
Can be cystically dilated.

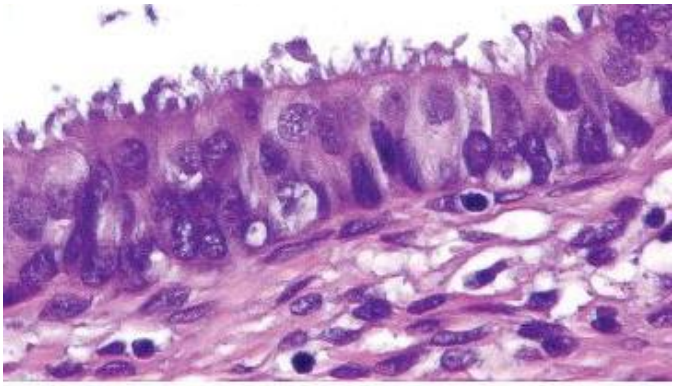
Endocervical Glandular Hyperplasia

Both confined to the inner 1/3–1/2 of the cervical wall with no mitoses or atypia.

Lobular Endocervical Glandular Hyperplasia (LEGH)
Rare. Proliferation of tightly packed small endocervical glands in a lobular pattern, resembling gastric pyloric gland epithelium, surrounding a central cleft. Bland, basal nuclei. Thought to be the precursor lesion to Gastric-type/Minimal deviation adenocarcinoma.

Diffuse Laminar Endocervical Glandular Hyperplasia
Rare. Proliferation of tightly packed small to medium-sized endocervical glands. No lobular architecture, but has a clearly defined base. Can have associated edema and chronic inflammation.

Tubal Metaplasia



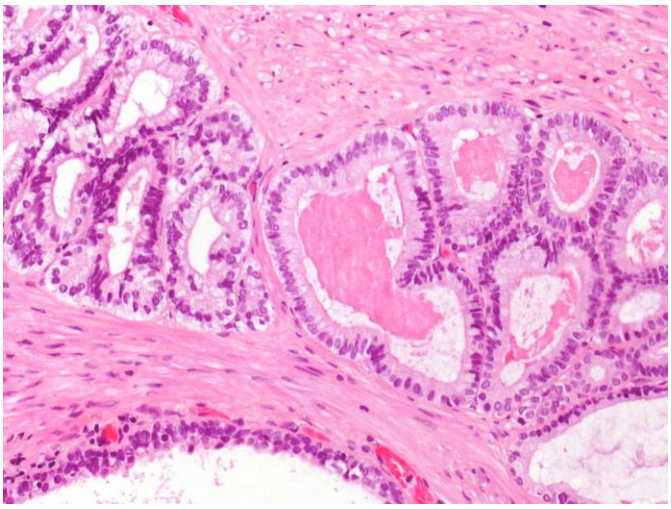
Benign. Non-neoplastic. Incidental.

Endocervical glandular epithelium is **replaced by tubal epithelium, which is ciliated with intercalated "peg" cells**

Main significance—can be confused with AIS. However, tubal metaplasia shouldn't have mitoses, has no significant atypia, and should be 1 cell layer thick.

Can also have endometrioid or tuboendometrioid metaplasia (with varying resemblance to normal endometrium)

Mesonephric Remnants



Benign vestigial embryologic remnants from the mesonephric duct.
Most common in lateral aspect of the cervix

Small tubules/cysts deep within the wall of the cervix, often arranged in clusters.
Tubules lined by **cuboidal cells** and have central characteristic **pink PAS-positive secretions**.

IHC: (+)GATA3, TTF1, PAX8, Calretinin, CD10 (luminal)
P16, ER negative

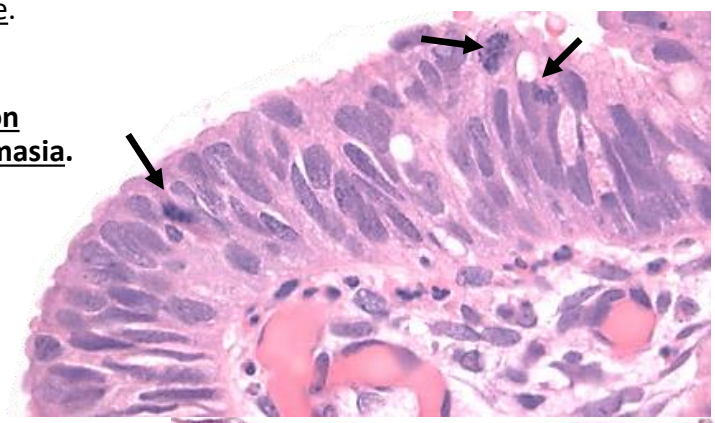
If large collection→ Mesonephric hyperplasia (still maintains lobular growth though)

HPV-Associated Adenocarcinomas

Adenocarcinoma In Situ (AIS), HPV-associated

Non-invasive adenocarcinoma, so **confined to normal, pre-existing glandular epithelium on surface and in endocervical glands**. Maintained lobular architecture.
Caused by High-risk HPV, classically type 18
Often nearby HSIL.

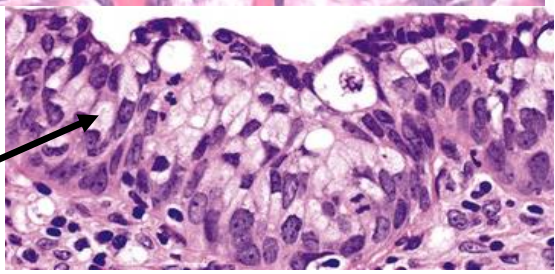
Cell crowding, **pseudo-stratification, mucin-depletion**
Enlarged nuclei with variable size/shape **Hyperchromasia.**
Sometimes large nucleoli
"**Floating" apical mitoses** (near surface →).
Atypical mitoses
Apoptotic debris (karyorrhexis)



IHC: **P16 diffuse/strong positive.** Loss of ER/PR.
Ki67 higher than adjacent normal endocervix

Uncommon features:
Cribriform growth, Goblet cells
Intraglandular tufting, branching, papillary

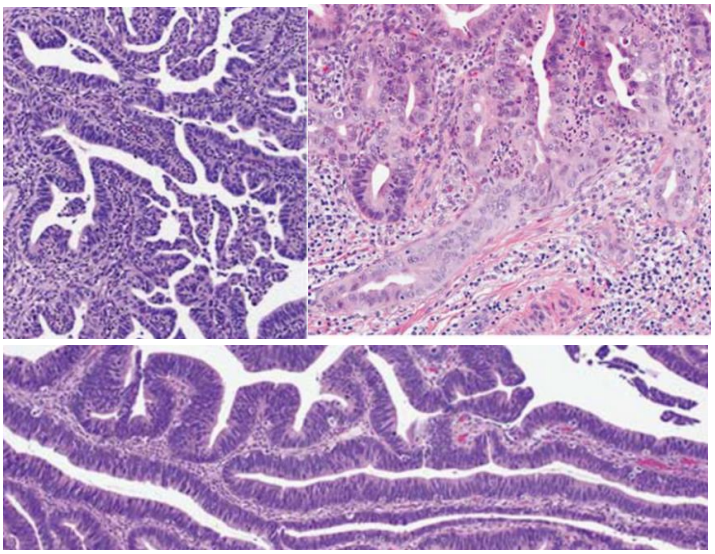
Unique Variant:
Stratified Mucin-producing Intraepithelial Lesion (SMILE)
☺ Stratified epithelium with nuclear atypia, hyperchromasia, and mitotic figures. Has mucin vacuoles at all cell layers.



Adenocarcinoma, HPV-mediated (Usual type)

An invasive adenocarcinoma of the cervix with relative mucin-depletion. **HPV-mediated** (P16-positive).
Most common type of endocervical adenocarcinoma by far (~90%)
Often presents with vaginal bleeding and a mass. May be exophytic or ulcerated.

Most tumors are well- to moderately-differentiated
Cribriform to papillary architecture
Characteristic morphology with mucin-poor glands and pseudostratified, enlarged, hyperchromatic nuclei. Must have <50% of cells with mucin.
Frequent floating **mitotic figures** and **apoptoses**.

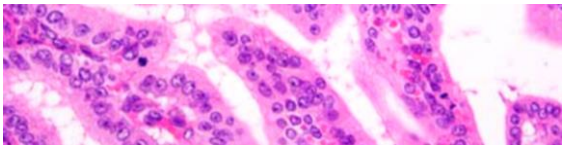


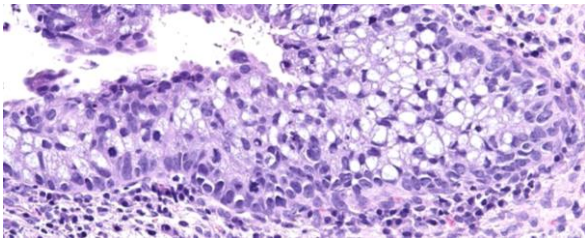
Hints for invasion (beyond "infiltrating" growth):
- Very complex architecture
- Haphazard growth
- Extension of glands beyond the depth of normal endocervical glands, esp. if near thick-walled blood vessels
- Stromal reaction (edema, chronic inflammation, or desmoplasia)
- Increased eosinophilic cytoplasm and prominent nucleoli
- Exophytic villoglandular surface growth

IHC: **P16 block positive**. PAX8+. HPV ISH+

Site of Origin	Immunohistochemical stain
Endocervical	P16+, ER/PR-, Vimentin-
Endometrial	ER/PR+, Vimentin+ (cup-like), P16-
Both	PAX8

Mucinous Carcinoma



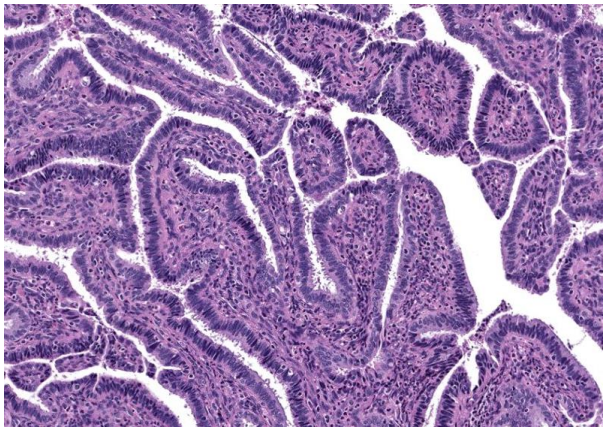


HPV-associated. **Worse prognosis.**
Typical HPV-morphology: "floating" mitoses, frequent apoptoses, but with **>50% of cells with intracytoplasmic mucin**, often in a **background of usual-type adenocarcinoma.**

Subtypes: NOS, Signet ring cell type, Intestinal, iSMILE.

Invasive Stratified Mucin-Producing Intraepithelial Lesion
"iSMILE"→ solid nests of stratified mucinous cells

Villoglandular Carcinoma



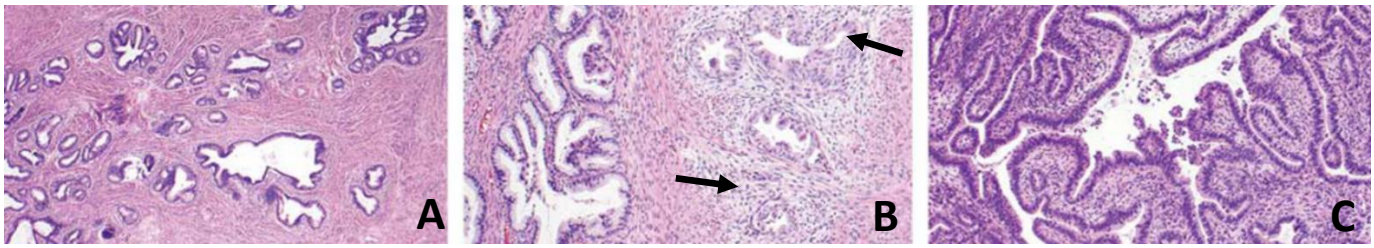
Well-differentiated variant of **usual-type.**
Often occurs in **young women**.

Exophytic surface component of **papillae** lined by epithelium that has only mild atypia.
Papillae can be thin or thick.

Similar staining pattern to usual-type endocervical adenocarcinoma (p16-positive)

Excellent prognosis.

Patterns of Invasion (Silva system):



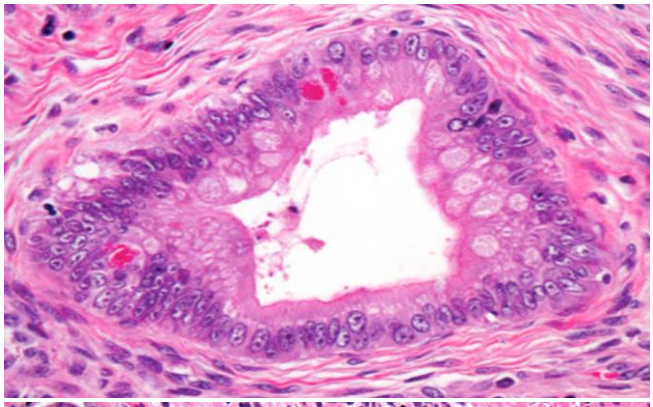
Silva Group	Morphology	Risk	Treatment
A	**Well-demarcated glands with rounded contours**, usually forming groups. ***No*** destructive stromal invasion, single cells, or lymphovascular invasion. Complex intraglandular growth acceptable (cribriform, papillae), but no solid growth. May be hard to separate from AIS. *THINK*:**"AIS-like"**	**Low** (No LN mets)	No need for nodal sampling
B	**Localized (limited, early) destructive stromal invasion** arising from pattern A glands (well-demarcated glands). Individual or small groups of tumor cells, separated from pattern A-type glands, frequently in desmoplastic or inflamed stroma. LVI acceptable. Lack of solid growth (well-moderately differentiated).	**Middle** (Rare LN mets)	Sentinel lymph node sampling
C	**Diffuse destructive stromal invasion,** characterized by: Diffusely infiltrative glands, with associated extensive desmoplastic response. Glands often angulated or with canalicular pattern, with interspersed open glands Confluent growth filling a 4x field (5 mm). Solid, poorly differentiated component (architecturally high grade)	**High** (Frequent LN mets)	Need nodal resection

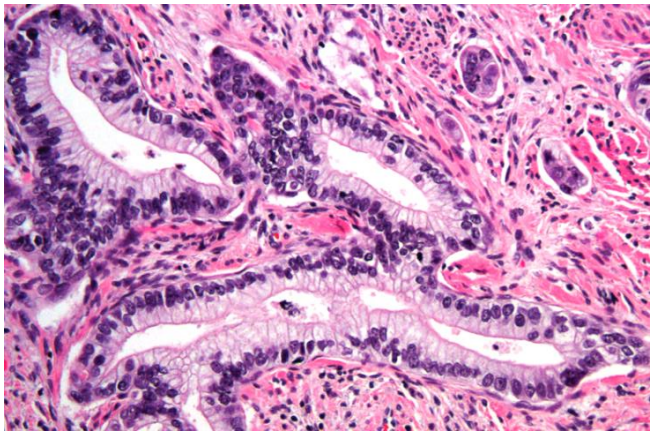
Modified from: Roma AA, et al. New pattern-based personalized risk stratification system for endocervical adenocarcinoma with important clinical implications and surgical outcome. Gynecol Oncol. 2016;141(1):36-42.

HPV-Independent Adenocarcinomas

Usually present at later age than HPV-mediated.

Gastric Type





Infiltrating glands lined by cells with **abundant pale to eosinophilic cytoplasm and distinct cell borders (gastric phenotype).** NOT related to high-risk HPV.

Diffuse infiltration (without a distinct mass) of stroma
Malignant cytologic features: Round, vesicular nuclei, often with prominent nucleoli
Glands show marked variation in size and shape.
Tumor is usually **deeply invasive**, often with a desmoplastic response.

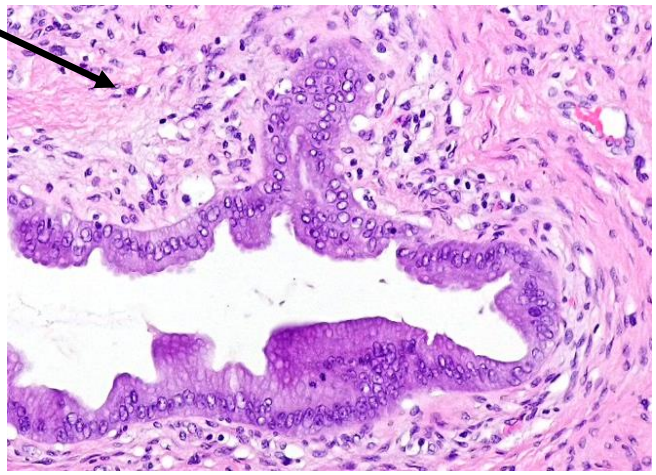
Typical presentation: profuse watery discharge and "barrel-shaped" cervix

IHC: **p16 usually negative**. P53 is sometimes mutated.
Loss of hormone receptor expression.
Often express: PAX8, CK7, CAIX

Prognosis: **Significantly WORSE than usual-type adenocarcinoma**

Minimal Deviation ("Adenoma Malignum")

(old name, no longer recommended, but perhaps useful to know for historical/remembering purposes)



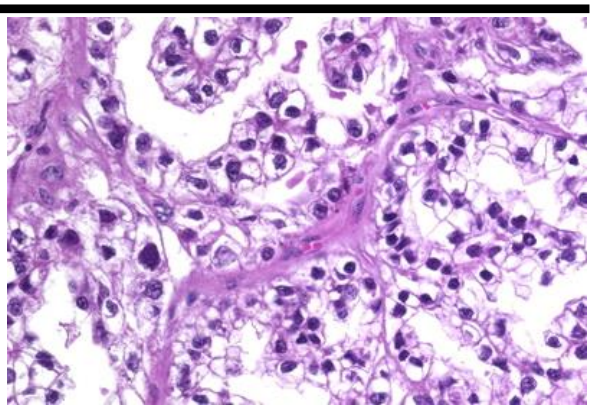
Highly differentiated form of gastric-type adenocarcinoma

Numerous **deceptively bland glands, which often *lack* surrounding stromal desmoplasia**.
Deeply invasive with haphazard distribution
Architectural abnormalities: intraglandular papillary protrusions and **irregular profiles** ("Claw-like").

At least focally, some glands display malignant cytologic features (vesicular nuclei with distinct/prominent red nucleoli) and are associated with stromal desmoplasia

Associated with **Peutz-Jegher's syndrome** and/or STK11 mutations. Putative precursor: LEGH

Clear Cell Carcinoma



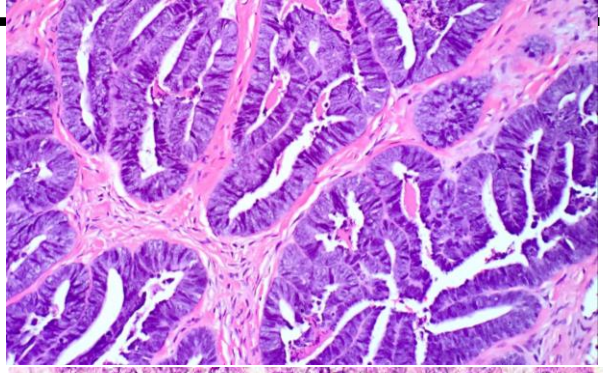
NOT associated with high-risk HPV. Associated with **DES**.

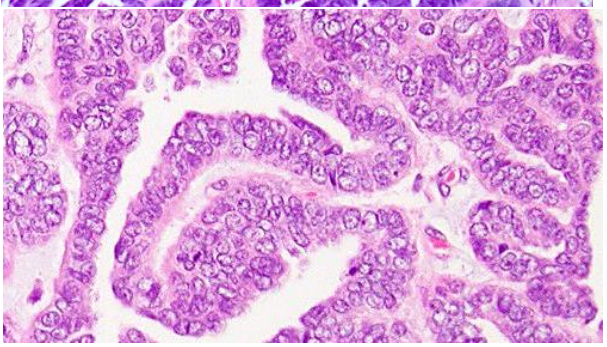
Cells with abundant clear to granular eosinophilic cytoplasm
Large, hyperchromatic, pleomorphic nuclei.

Solid, tubulocystic, or papillary architecture.
Frequent "hobnail" appearance

IHC: Positive HNF-1β, and NapsinA (but not all that specific!)
P16 +/-, p53 wild-type, ER/PR -

Mesonephric Carcinoma





Rare. Develop from mesonephric remnants.

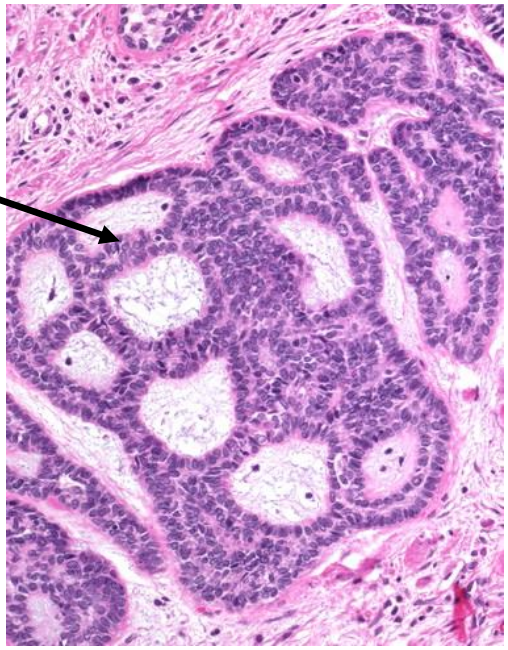
Often **located deep in lateral cervical stroma.**

Characteristic glandular spaces with **eosinophilic PAS-D positive secretions.**
Variable architectural patterns: tubular, papillary, etc…
Often small, tightly-packed glands with low-cuboidal cells.
Uniform nuclei with coarse or vesicular chromatin.
Frequent nuclear grooves, inconspicuous nucleoli.
NO mucinous or squamous differentiation.
Frequent sarcomatous differentiation.

IHC: Similar to mesonephric remnants, express **CK7, PAX8, TTF-1, GATA3**, apical CD10. Negative P16, HPV, ER/PR

Frequent KRAS mutations.

Other Subtypes



Adenoid basal carcinoma—Rare. HPV-mediated (so often nearby SIL or carcinoma). Composed of small, well-differentiated rounded nests of bland basaloid cells that have scant cytoplasm and which resemble basal cell carcinoma. Only focal gland formation. No stromal reaction. Good prognosis (no metastatic potential). Non-mass forming, asymptomatic, incidental.
(vs Adenoid cystic carcinoma—Rare. Resemble salivary gland tumor: cribriform and tubular patterns of growth with basement membrane-like material. MYB rearrangements)

Endometrioid—Rare. Resembles uterine endometrioid adenocarcinoma. Must consider secondary involvement/metastasis. May arise from endometriosis.

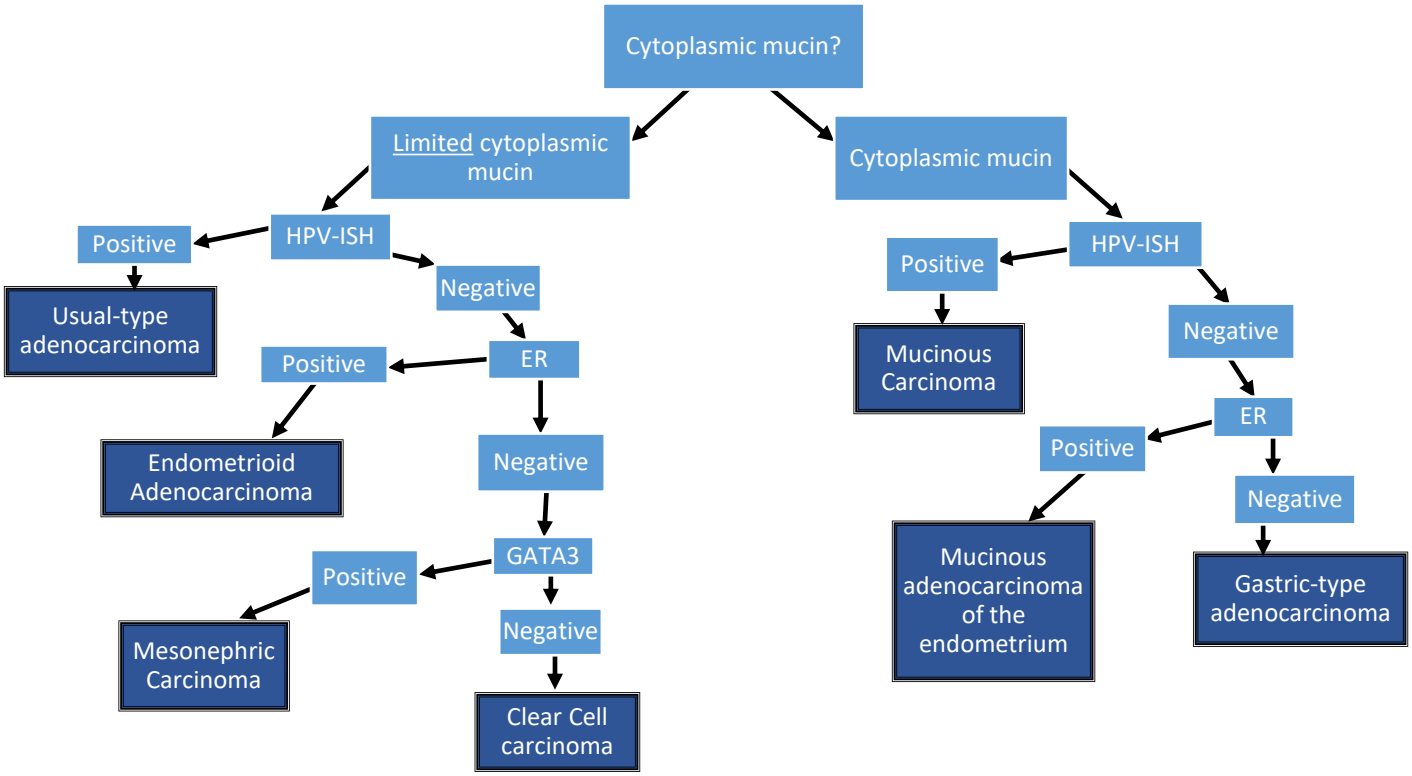
Adenosquamous carcinoma—Rare. HPV-mediated. Contains malignant squamous and glandular components. Must have good gland formation. May arise from SIL or AIS. Similar behavior to usual-type adenocarcinoma.
(vs Mucoepidermoid carcinoma which much rarer and, like in the salivary gland, has 3 cell types and MAML2 gene rearrangements)

Neuroendocrine Tumors/Carcinomas

Use same classification system as **GI tract** (see separate GI guide with more info).

Cervical Neuroendocrine Tumors (NETs) are extremely rare.
Neuroendocrine carcinomas (NECs) may be seen in association with other in situ of invasive carcinomas.

Cervical Adenocarcinoma Typing Algorithm



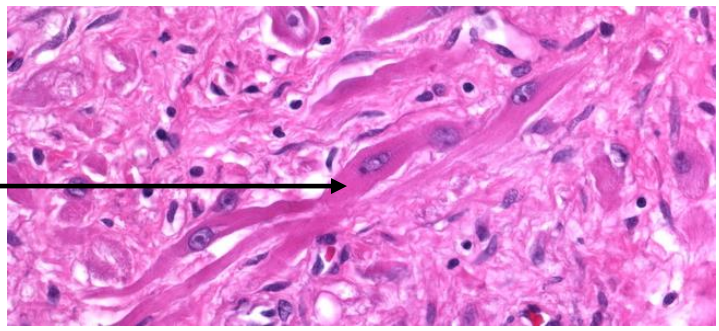
Modified from: Stolnicu S, Barsan I, Hoang L, et al. Am J Surg Pathol. 2018;42(8):989-1000.
NOTE: This journal article also contains great IHC tables with % staining of each tumor for each marker.

HPV-status	Unifying morphology	Tumors included
HPV-Positive	Apical mitotic figures and apoptotic bodies easily appreciable at scanning magnification	Usual-type Mucinous Villoglandular
HPV-Negative	Absence of usual findings (Diverse histology)	Gastric Clear Cell Endometrioid Serous Mesonephric

IHC	Endocervical adenocarcinoma, usual type	Endocervical adenocarcinoma, gastric type	Endometrial endometrioid carcinoma	Serous carcinoma (from Uterus)
p16	Block positive	Negative or patchy	Patchy, variable	Block positive
P53	Wild-type	Some mutated	Wild-type (usually)	Mutated
ER/PR	Negative	Negative	Positive	Negative (usually)
High-risk HPV	Positive	Negative	Negative	Negative

Non-Epithelial/Mesenchymal Lesions

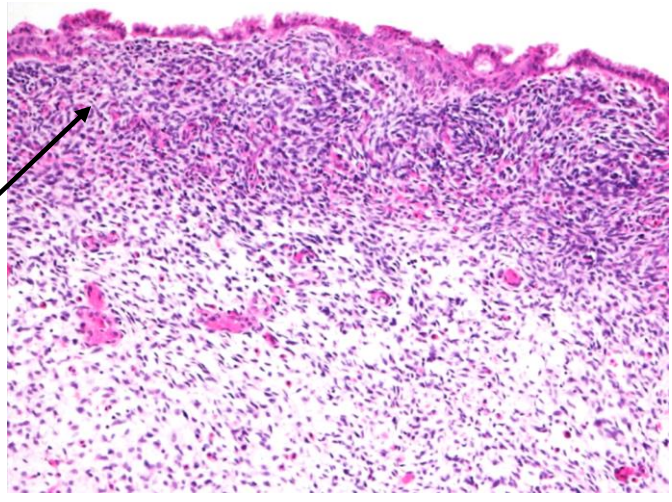
Rhabdomyoma



Benign. Non-recurring.

Haphazardly-arranged, interlacing, mature, bland-appearing **rhabdomyoblasts** with oval or tubular shape.
Cytoplasmic striations. No mitoses or necrosis.
IHC: +Desmin, Myogenin, MyoD1

Rhabdomyosarcoma

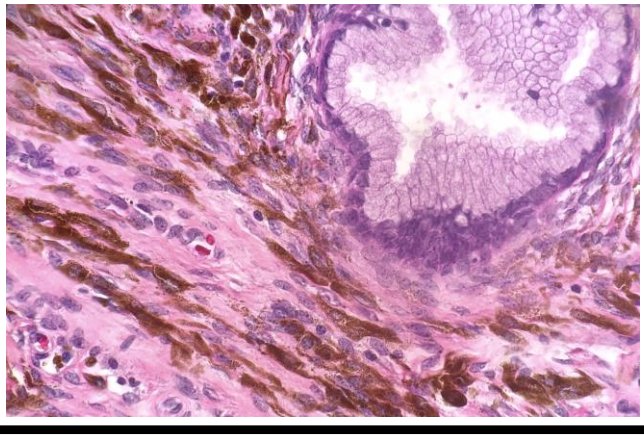


Malignant tumor with skeletal muscle differentiation.

Most commonly **<u>Embryonal subtype</u>**.
Polypoid tumors of small, round or spindled hyperchromatic cells.
Subepithelial condensation→ "Cambrium layer"
Variable skeletal muscle differentiation (e.g., strap cells, rhabdomyoblasts). Frequent cartilage nodules.

IHC: +Desmin, Myogenin, MyoD1

Blue Nevus



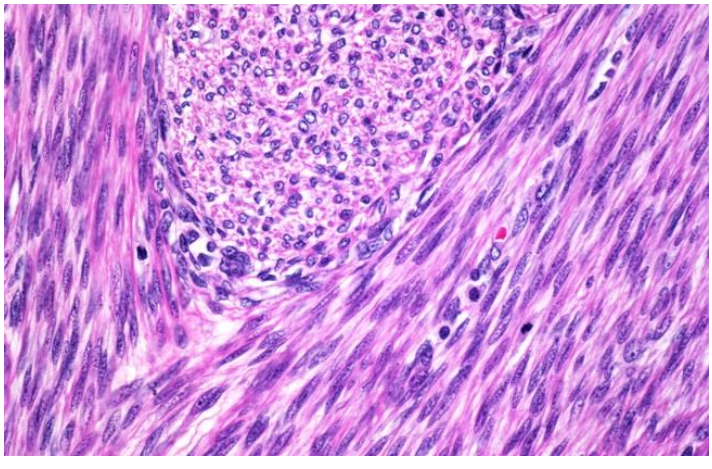
Benign, melanocytic lesion.

Grossly appear as blue/black flat nodules, often 2-3mm.

Markedly elongated spindle cells in submucosa.
Often **heavily pigmented** dendritic projections.
Often organized parallel to surface

IHC: +S100, SOX10, HMB45, MelanA, MiTF

Leiomyoma



Benign tumor with <u>smooth muscle</u> differentiation.

Resemble uterine leiomyomas.
Well-circumscribed.
Intersecting fascicles of spindled cells.
"Cigar-shaped" nuclei.
No significant mitoses, atypia, or necrosis.

Can also get leiomyosarcomas.