**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)**

Intraepithelial (in situ, non-invasive), squamous dysplasia due to HPV infection.

**Low-grade Squamous Intraepithelial Lesion (LSIL)**

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)

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

Often spontaneously regresses, so just observed clinically with repeat cytology

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

**Human Papilloma Virus (HPV)**

Sexually Transmitted Disease

Serotypes: 16 & 18 → Most associated with HSIL/SCC

6 & 11 → 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) or integrate, where viral oncogene overexpression drives a clonal production of undifferentiated cells causing HSIL (precancerous)

HPV-associated oncoprotein E6 inactivates p53, E7 inactivates Rb
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 have enlarged, hyperchromatic nuclei with irregular nuclear contours and increased N:C ratios.

Little to no 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:
Keratinizing—abnormal surface keratinization
Papillary—papillomatous architecture

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 +)

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.
Squamous Cell Carcinoma

An **invasive** epithelial tumor composed of squamous cells of varying degrees of differentiation. **Virtually all associated with HPV infection**, most commonly types 16 or 18, and arise from HSIL.

World-wide, 2\textsuperscript{nd} or 3\textsuperscript{rd} most common cancer in women, **mostly in low resource countries** without cervical cancer screening programs (Pap smears) and programs to manage precursor lesions.

**In the US, rates have dropped dramatically** in recent history due first to screening, and now to HPV immunizations.

Morphologically, **most are non-keratinizing and basaloid**

Sheet-like growth with infiltrating bands and single cells **Often desmoplastic/inflammatory stroma**

Can be keratinizing or non-keratinizing

With invasion can see “paradoxical maturation” with increased cytoplasmic eosinophilia

Several subtypes 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

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

**Napothian 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.
Tightly packed glands/tubules lined by flattened to cuboidal cells with eosinophilic cytoplasm sometimes a small mucin vacuole.
Uniform small nuclei with rare mitoses.
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.
Usually vimentin negative and ER/PR positive

**Arias Stella Reaction**
Benign change seen during pregnancy
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

**Clusters of benign endocervical glands** often near the surface. Can be cystically dilated.

Main importance—can be confused with minimal deviation adenocarcinoma (but in contrast, tunnel clusters are superficial and have no atypia or mitotic activity)

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.
Thought to be the precursor lesion to Gastric-type/Minimal deviation adenocarcinoma

**Diffuse Laminar Endocervical Glandular Hyperplasia (DLEG)**
Rare. Proliferation of tightly packed small to medium-sized endocervical glands. No lobular architecture, but has a clearly defined base.

Tubal Metaplasia

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: GATA-3 and TTF-1 frequently +
P16, ER negative
If large collection ➔ Mesonephric hyperplasia (still maintains lobular growth though)
**Adenocarcinoma In Situ (AIS)**

Non-invasive adenocarcinoma, so **confined to normal, pre-existing glandular epithelium on surface and in endocervical glands.** Maintained lobular architecture. Often nearby HSIL.

Cell crowding, **pseudo-stratification, mucin-depletion**

**Enlarged nuclei** with variable size/shape

**Hyperchromasia.** Sometimes large nucleoli

“**Floating” mitoses** (near surface, see arrows).

Atypical mitoses

**Apoptotic debris**

IHC: **P16 diffuse/strong positive.** Loss of ER/PR staining

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.

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**Endocervical Adenocarcinoma, 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+

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### Site of Origin | Immunohistochemical stain
---|---
Endocervical | P16+, ER/PR-, Vimentin-
Endometrial | ER/PR+, Vimentin+ (cup-like), P16-
Both | PAX8
Patterns of Invasion (Silva system):

<table>
<thead>
<tr>
<th>Silva Group</th>
<th>Morphology</th>
<th>Risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><strong>Well-demarcated glands with rounded contours</strong>, usually forming groups.</td>
<td>Low</td>
<td>No need for nodal sampling</td>
</tr>
<tr>
<td></td>
<td><em>No</em> destructive stromal invasion, single cells, or lymphovascular invasion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complex intraglandular growth acceptable (cribriform, papillae), but no solid growth. May be hard to separate from AIS. <strong>THINK:</strong> “AIS-like”</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td><strong>Localized (limited, early) destructive stromal invasion</strong> arising from pattern A glands (well-demarcated glands). Individual or small groups of tumor cells, separated from pattern A-type glands, frequently in desmoplasic or inflamed stroma. LVI acceptable. Lack of solid growth (well-moderately differentiated).</td>
<td>Middle</td>
<td>Sentinel lymph node sampling</td>
</tr>
<tr>
<td>C</td>
<td><strong>Diffuse destructive stromal invasion</strong>, characterized by: Diffusely infiltrative glands, with associated extensive desmoplasic 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)</td>
<td>High</td>
<td>Need nodal resection</td>
</tr>
</tbody>
</table>


**Gastric Type**

**NOT** related to high-risk HPV.

Diffuse infiltration (without a distinct mass) of stroma

Infiltrating glands lined by cells with **abundant pale to eosinophilic cytoplasm and distinct cell borders.**

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 desmoplasic 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, HNF-1β, and NapsinA.

Putative precursor lesion: LEGH.

Prognosis: **Significantly WORSE than usual-type adenocarcinoma**
**Minimal Deviation (“Adenoma Malignum”)**

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.**

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**

**Mucinous Carcinoma**

**HPV-associated.**

**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, and iSMILE (Invasive stratified mucin-producing carcinoma, which has peripheral palisading)

**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.**

Relatively **bland, uniform cytology**


**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.**
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 or invasive carcinomas.

Other Subtypes

**Adenoid basal carcinoma**—Rare. Composed of small, well-differentiated rounded nests of basaloid cells that have scant cytoplasm and which resemble basal cell carcinoma. Only focal gland formation. Good prognosis.

**Adenoid cystic carcinoma**—Rare. Resemble salivary gland tumor: cribriform and tubular patterns of growth with basement membrane-like material.

**Serous carcinoma**—Rare. Resembles Serous carcinoma of the uterus/ovary. Must exclude secondary involvement/metastasis.

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

**Adenosquamous carcinoma**—Rare. Contains malignant squamous and glandular components. Must have good gland formation. May arise from SIL or AIS. Similar behavior to usual-type adenocarcinoma.

**Glassy Cell carcinoma**—Rare. Variant of adenosquamous carcinoma characterized by cells with sharp cytoplasmic margins, “ground glass” appearing eosinophilic cytoplasm, and large round nuclei with prominent nucleoli. Often in young women. Aggressive with frequent metastases at presentation. Frequently eosinophilic inflammation.

**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, cystic, or papillary architecture.
Frequent “hobnail” appearance

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

NOTE: This journal article also contains great IHC tables with % staining of each tumor for each marker.

### IHC

<table>
<thead>
<tr>
<th>Marker</th>
<th>Endocervical adenocarcinoma, usual type</th>
<th>Endocervical adenocarcinoma, gastric type</th>
<th>Endometrial endometrioid carcinoma</th>
<th>Serous carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16</td>
<td>Block positive</td>
<td>Negative or patchy</td>
<td>Patchy, variable</td>
<td>Block positive</td>
</tr>
<tr>
<td>P53</td>
<td>Wild-type</td>
<td>Some mutated</td>
<td>Wild-type (usually)</td>
<td>Mutated</td>
</tr>
<tr>
<td>ER/PR</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative (usually)</td>
</tr>
<tr>
<td>High-risk HPV</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>
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 **Embryonal subtype.**

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 **smooth muscle** differentiation.

Resemble uterine leiomyomas.

Well-circumscribed.

Intersecting fascicles of spindled cells.

“Cigar-shaped” nuclei.

No significant mitoses, atypia, or necrosis.

Can also get leiomyosarcomas.