

Cervical carcinoma

Etiology · Pathogenesis · Morphology · Spread · Clinicopathologic staging

Histopathology and clinicopathologic correlation

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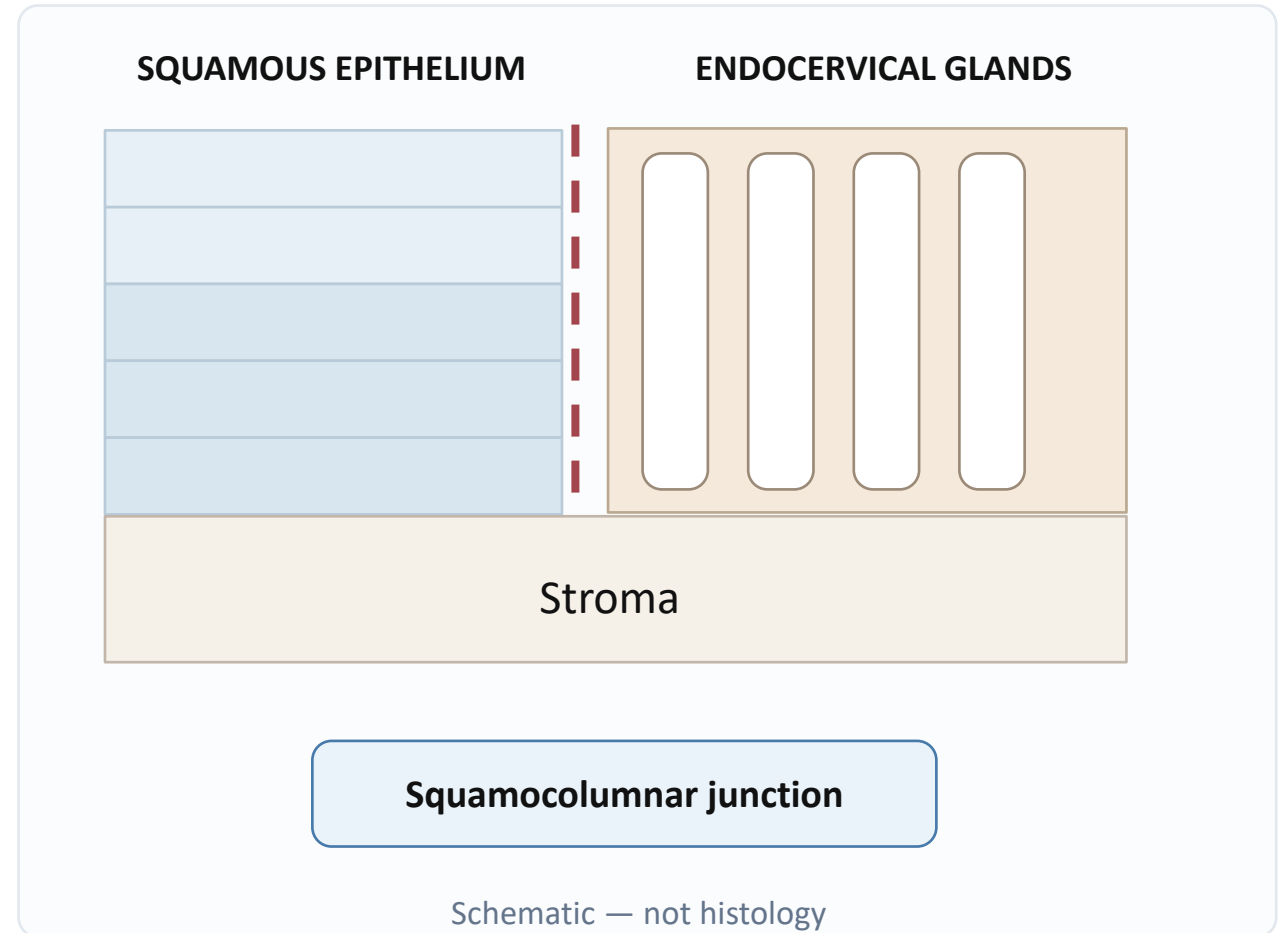
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Learning objectives

- Explain how high-risk HPV disrupts cell-cycle control and predisposes to malignancy.
- Differentiate major cervical carcinoma subtypes by their morphology and pathogenetic associations.
- Relate routes of tumor spread to stage, clinical morbidity, and prognosis.
- Apply invasion and staging concepts to short diagnostic scenarios.

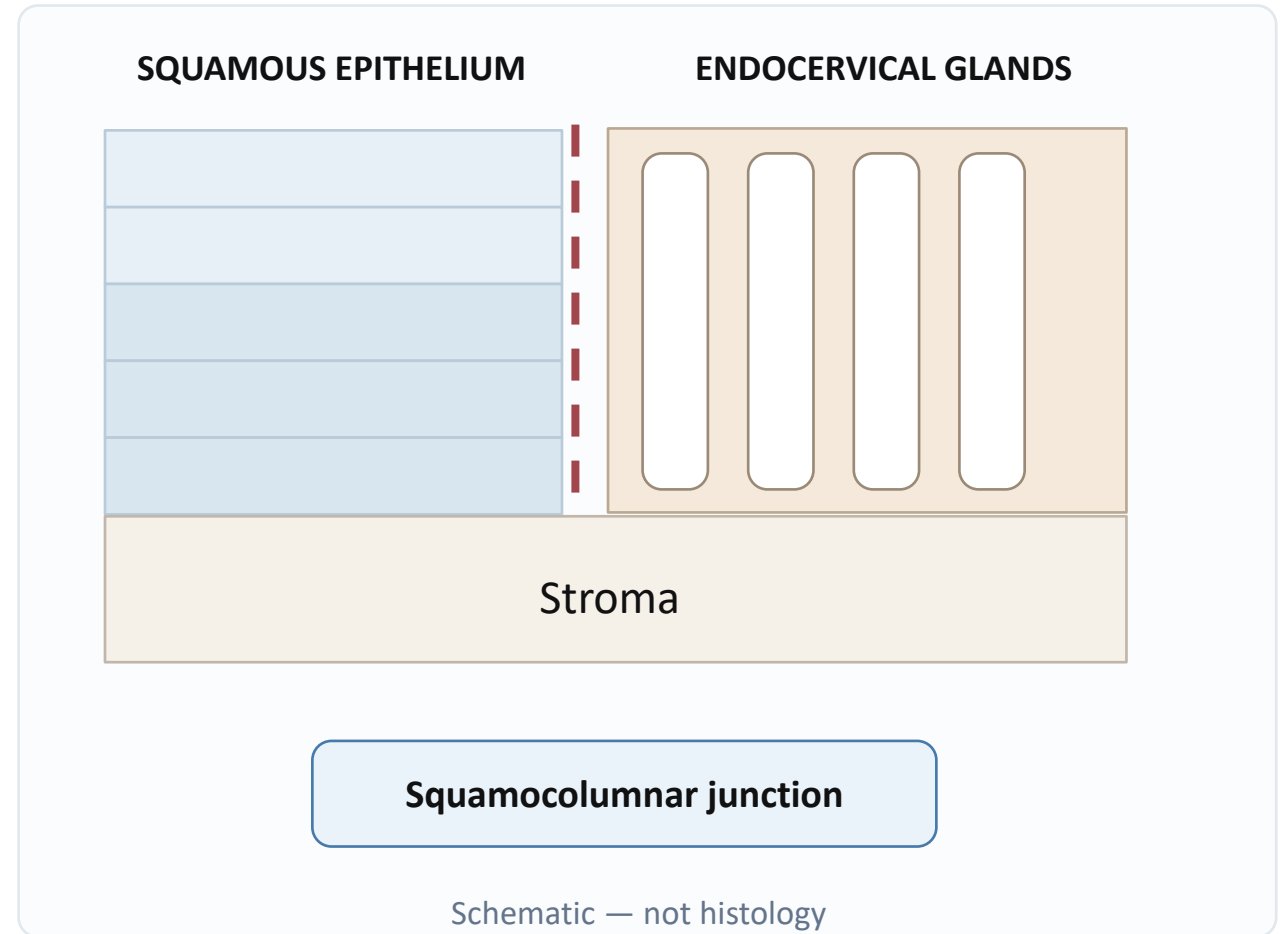
The cervix contains two epithelial compartments

- Ectocervix: Stratified squamous epithelium.
- Endocervical canal: Mucus-secreting columnar epithelium and glands.
- Their interface is the squamocolumnar junction; Adjacent immature metaplastic cells are HPV-susceptible.



Why the transformation zone matters

- Persistent high-risk HPV infection develops in susceptible immature epithelial cells.
- Squamous and glandular malignancies arise in a cervix where epithelial differentiation changes across a narrow zone.
- The cellular site of infection helps connect HPV biology to the distribution of cervical precursor lesions.



Cervical cancer has a major worldwide burden

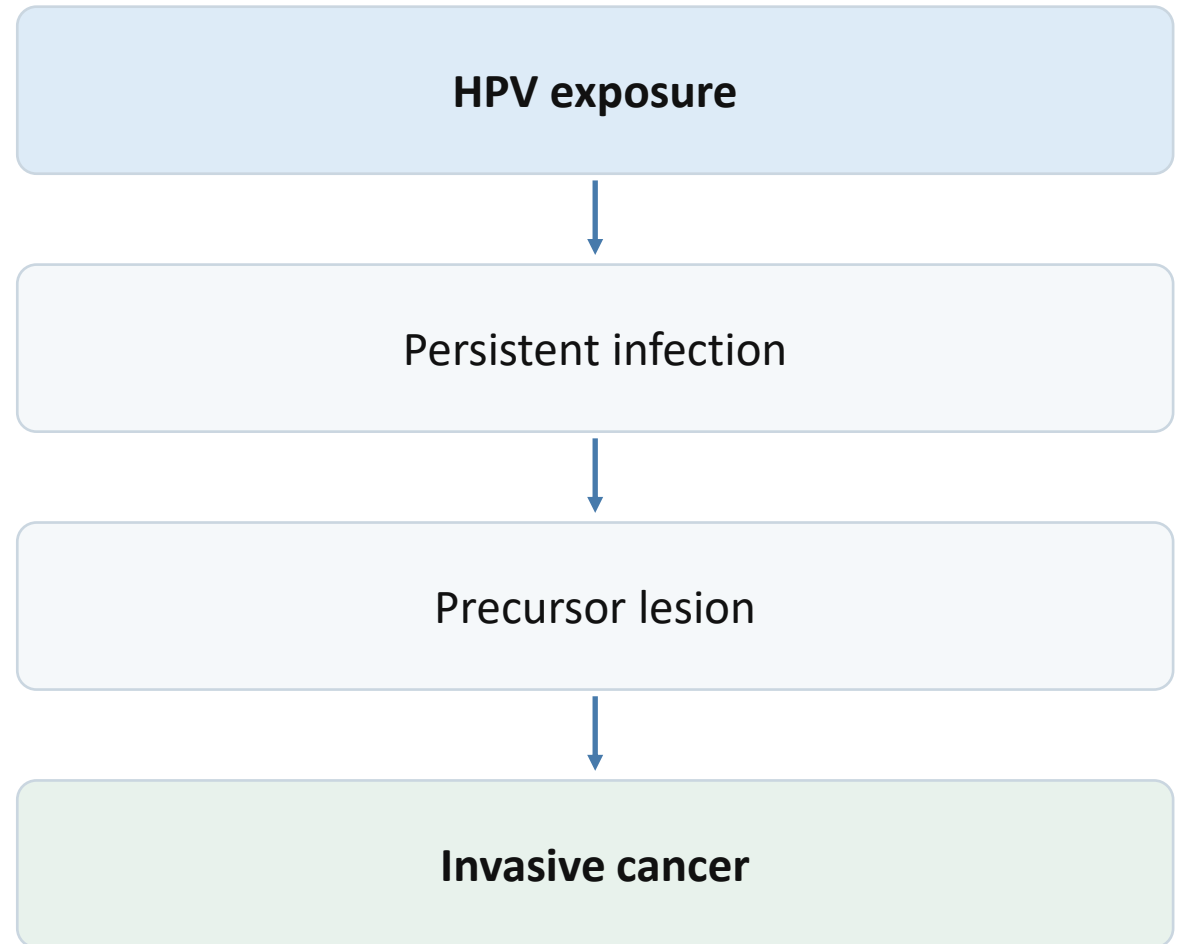
- Cervical carcinoma as the fourth most common cancer in females worldwide.
- The text cites an estimated 604,127 new cases in 2020, with more than half proving fatal.
- These are textbook-reported, year-specific estimates—not a current annual incidence update.

604,127

Estimated global new cases in 2020
(Robbins)

Invasive disease typically presents in mid-adulthood

- Mean patient age is reported by Robbins as approximately 45–50 years.
- This reflects the interval between acquisition or persistence of carcinogenic HPV and the development of invasive disease.
- Individual trajectories vary; HPV acquisition alone does not imply inevitable progression.



Histologic distribution

- Squamous cell carcinoma accounts for approximately 80% of cervical cancer.
- Adenocarcinoma accounts for approximately 15%.
- Adenosquamous and neuroendocrine carcinomas together comprise the remaining approximately 5%.



■ Squamous carcinoma: ≈80%

■ Adenocarcinoma: ≈15%

■ Other: ≈5%

Most cervical carcinomas are HPV-associated

HPV-associated

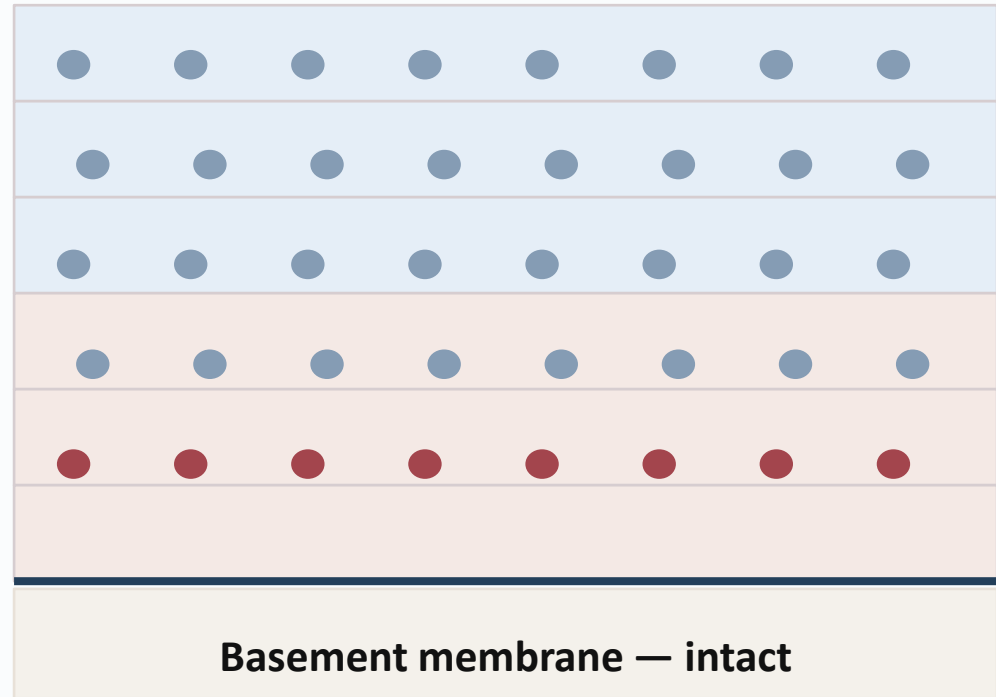
- Squamous carcinoma (majority)
- Usual-type endocervical adenocarcinoma
- Most adenosquamous / neuroendocrine carcinoma

HPV-independent

- Gastric-type adenocarcinoma
- Distinct molecular and clinical behavior
- Not prevented by HPV-directed immune responses

Immature basal and metaplastic cells are susceptible

- Mature superficial squamous cells are not the principal target of productive HPV infection.
- HPV accesses basal cells where epithelium is injured or undergoing repair.
- Immature squamous metaplasia at the squamocolumnar junction creates an important vulnerable field.

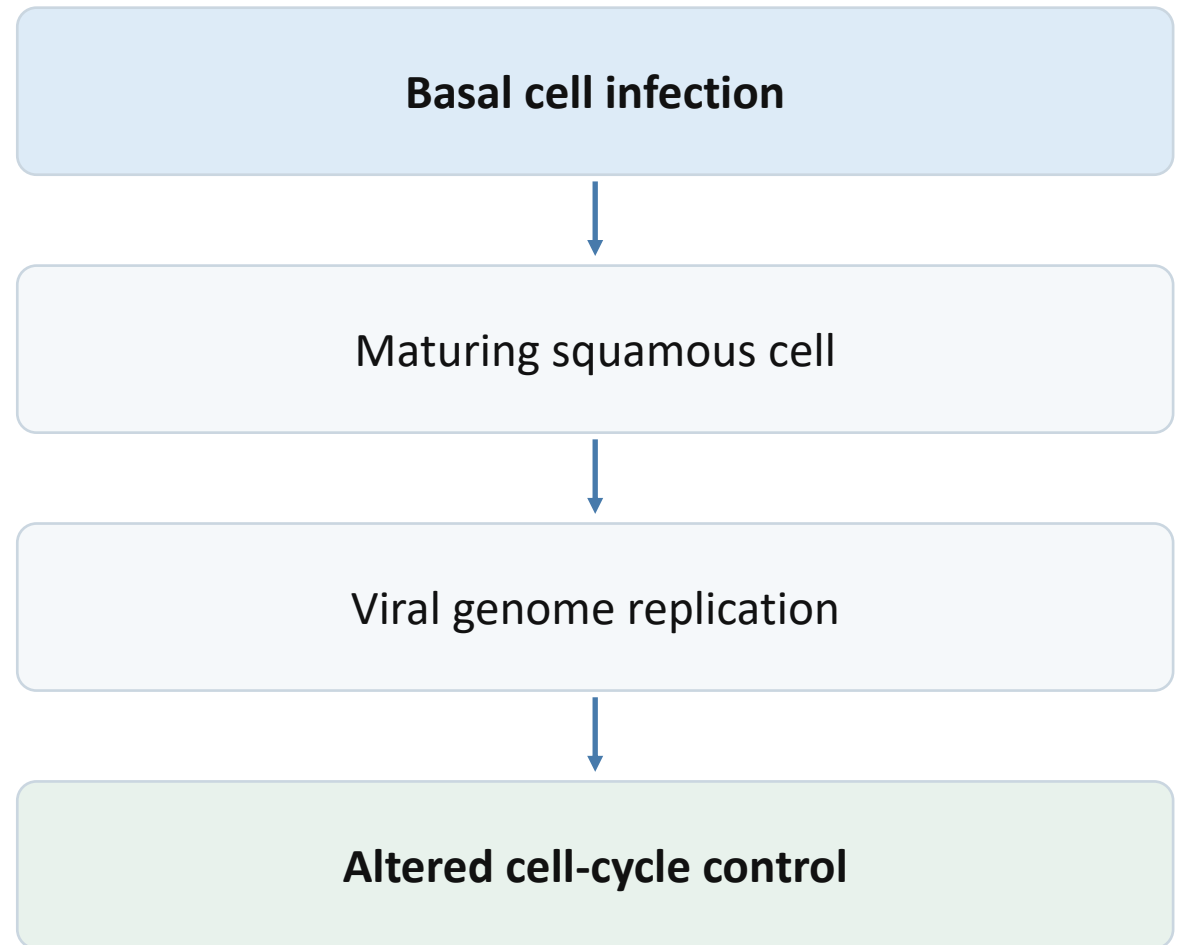


Basal proliferative compartment

Schematic (not a micrograph)

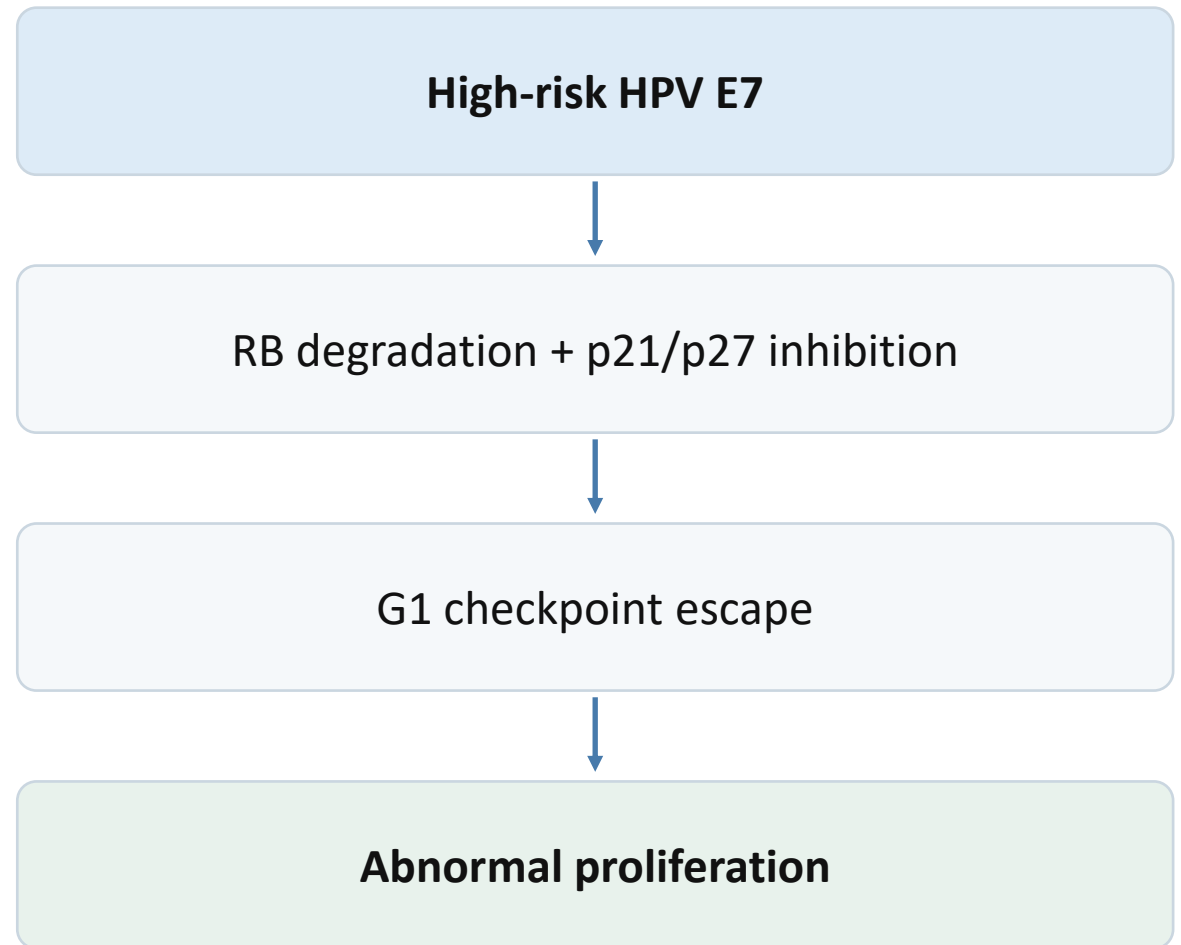
Viral replication depends on host-cell division

- HPV infection begins in immature epithelial cells.
- Viral replication becomes prominent in maturing squamous cells.
- HPV oncogenic proteins sustain cellular-cycle progression in cells that would ordinarily arrest during maturation.



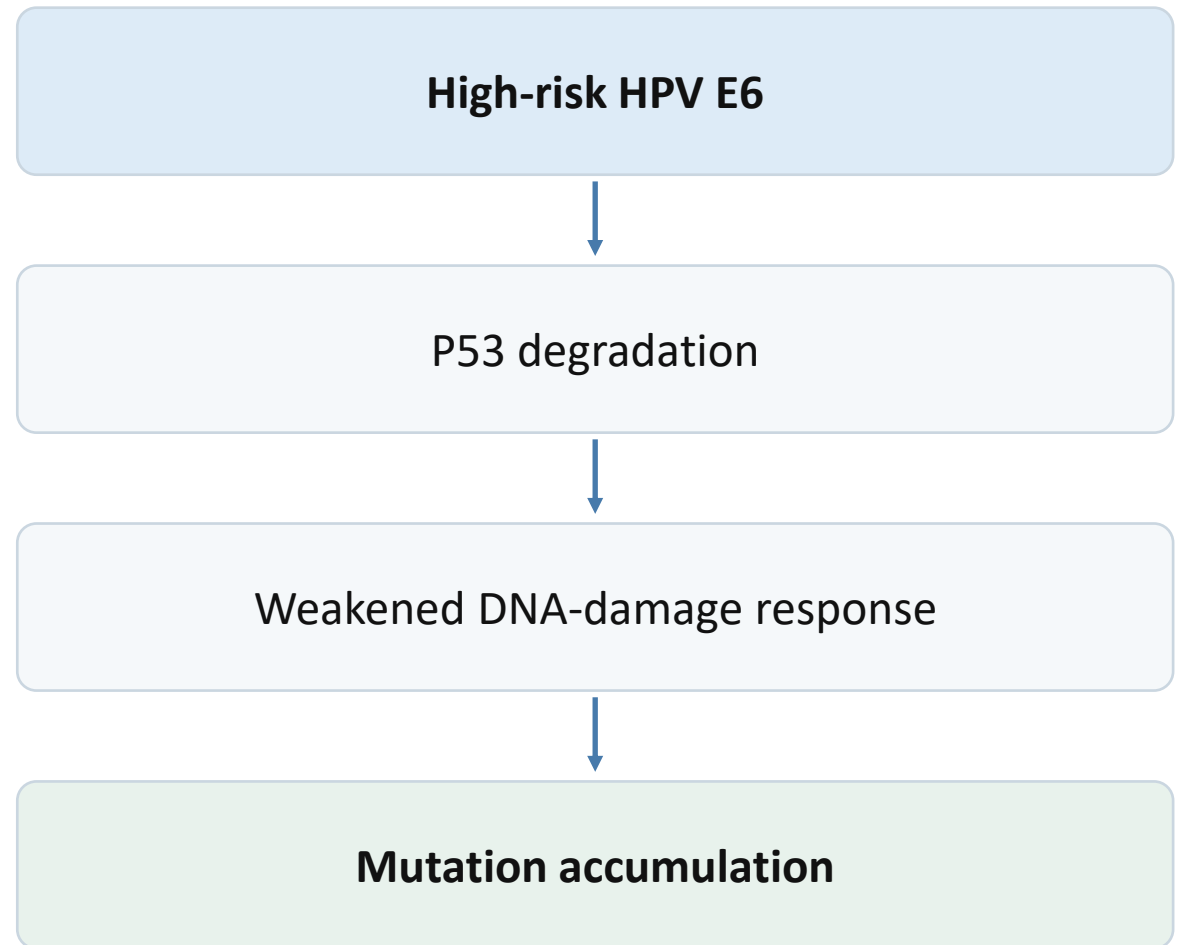
High-risk HPV E7 disables the RB pathway

- E7 promotes proteasomal degradation of the RB tumor suppressor.
- E7 also inhibits the CDK inhibitors p21 and p27.
- Reduced G1 restriction promotes proliferation and contributes to genomic instability.



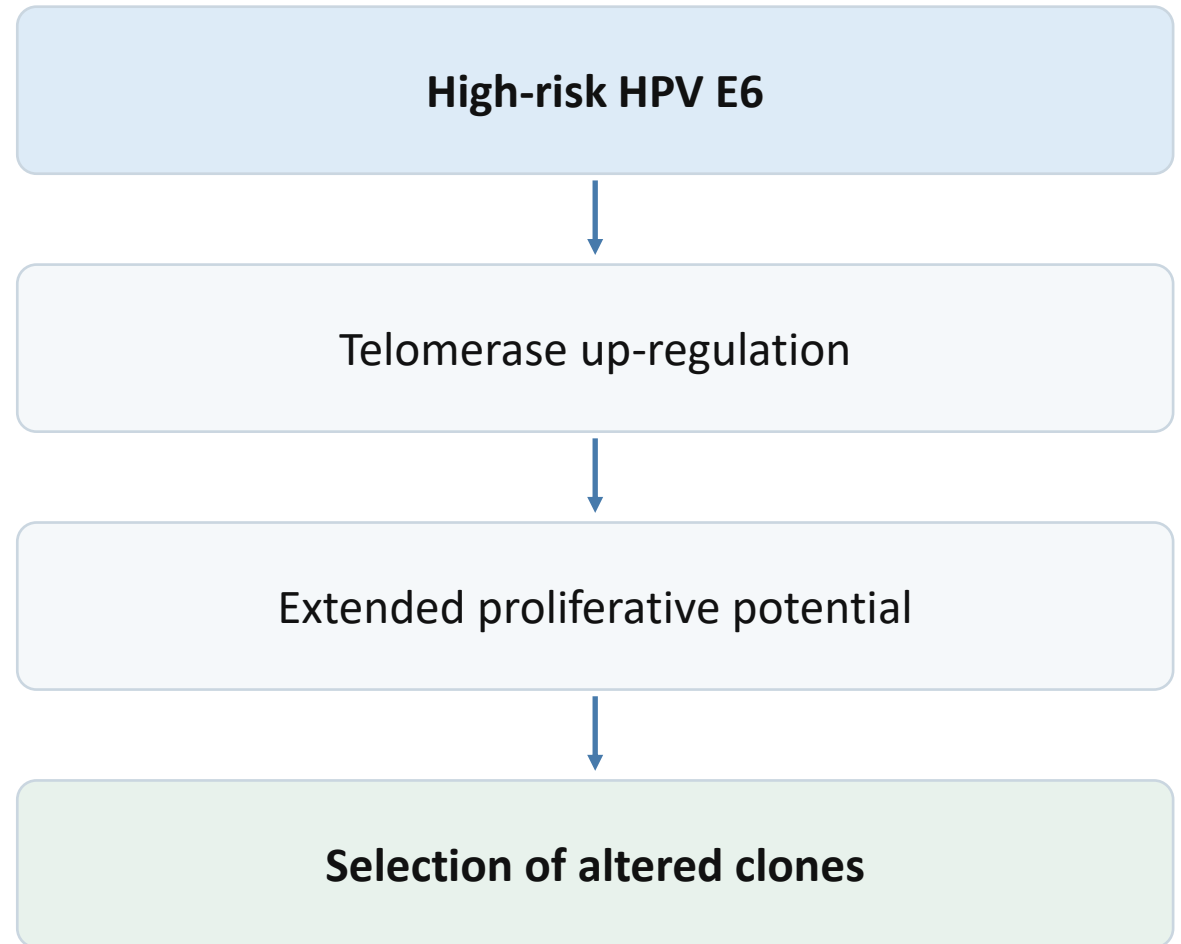
High-risk HPV E6 disables p53 protection

- E6 binds p53 and promotes its proteasomal degradation.
- Compromised p53 signaling weakens responses to DNA damage.
- Unrepaired lesions may accumulate while infected epithelial cells continue cycling.



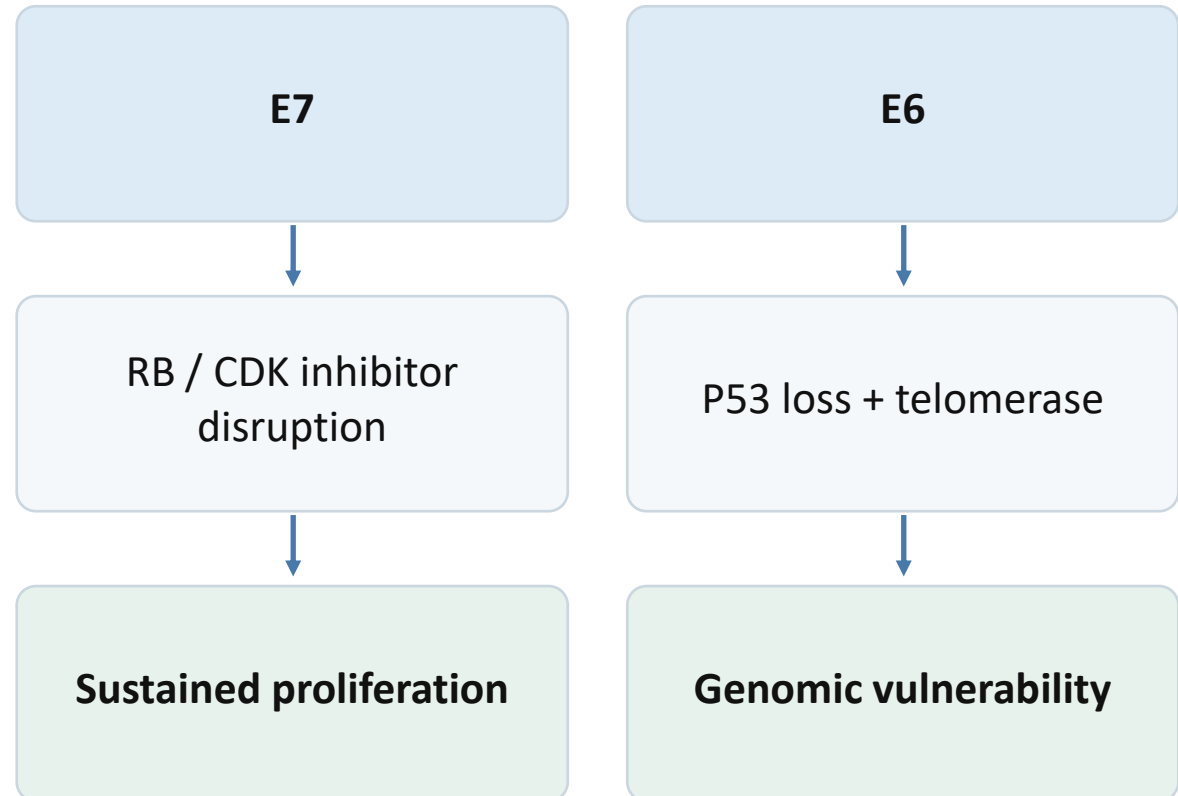
E6 also supports cellular immortalization

- High-risk HPV E6 up-regulates telomerase expression.
- Telomere maintenance extends proliferative capacity.
- Immortalization cooperates with loss of checkpoint surveillance but is not sufficient alone to explain cancer.



E6 and E7 cooperate in carcinogenesis

- E7 releases cell-cycle restrictions through RB pathway dysfunction.
- E6 reduces p53-mediated genome protection and supports telomerase activity.
- The combined effect favors persistence and expansion of cells that acquire further oncogenic alterations.



Viral integration can intensify oncogene expression

Episomal HPV DNA

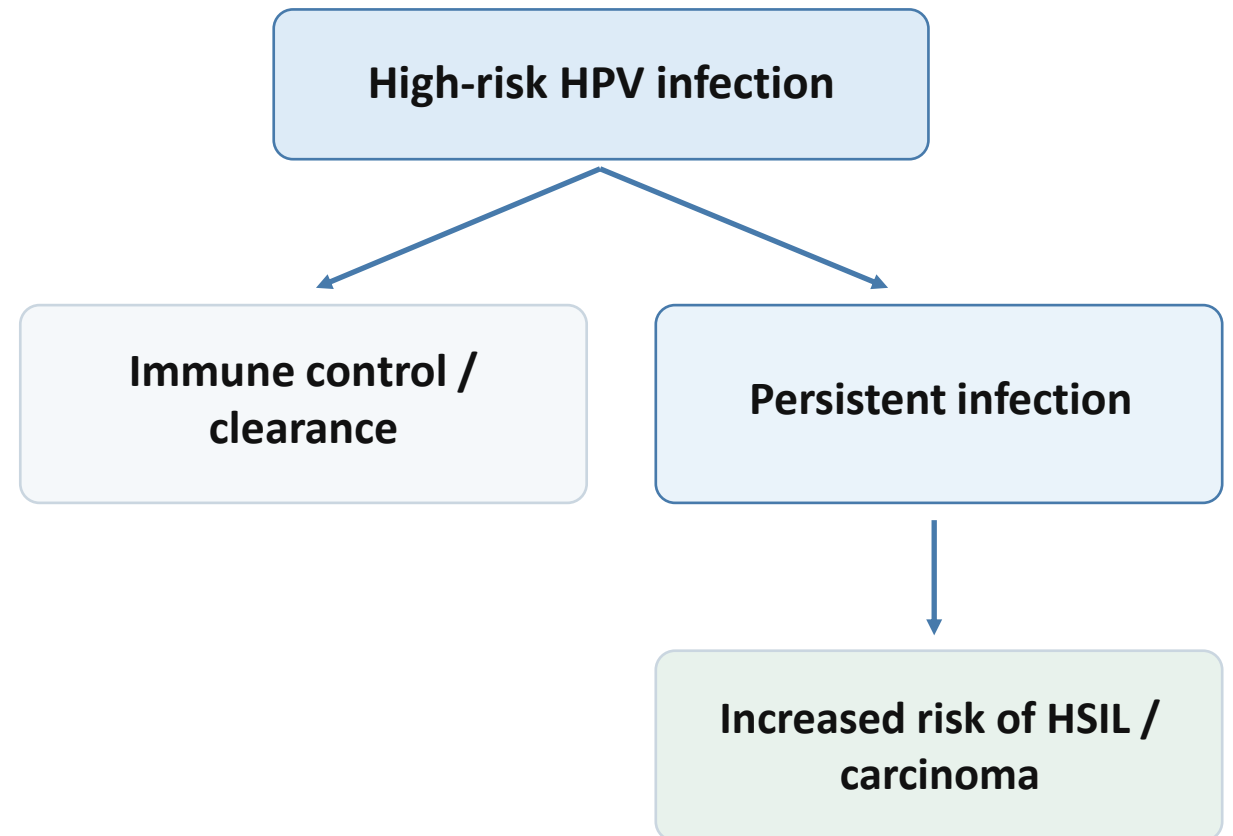
- Extrachromosomal viral genome
- Typical in productive infection
- Often identified in precursor lesions

Integrated HPV DNA

- Viral DNA inserted into host genome
- E6/E7 expression may increase
- Potential effects on nearby host genes

Persistence—not exposure alone—drives cancer risk

- HPV infection is common, but only a small fraction of infected individuals develop invasive cancer.
- Host immune status and additional co-carcinogenic exposures influence regression versus persistence.
- Type-specific viral risk is important but cannot reliably predict an individual outcome.



Alternative outcomes — schematic

Low-risk and high-risk HPV differ mechanistically

Lower-risk HPV

- Less effective RB disruption
- No high-risk-type p53 degradation
- Commonly productive benign lesions

High-risk HPV

- E7 drives RB pathway disruption
- E6 drives p53 degradation
- Persistent infection may transform cells

Squamous precursor lesions use a two-tier system

LSIL (CIN 1)

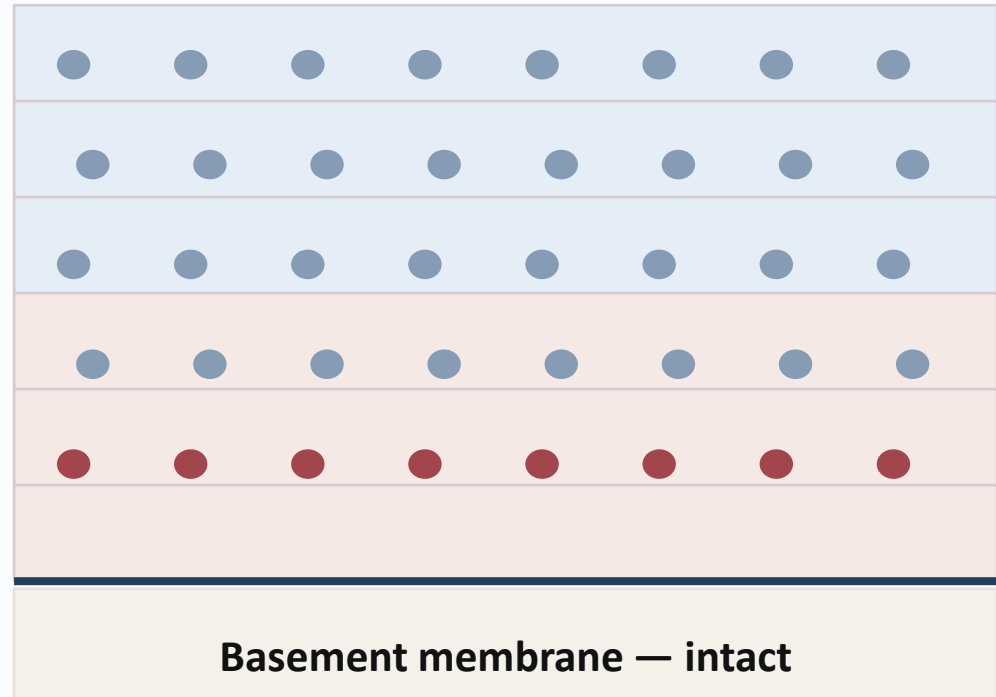
- Productive HPV infection
- Maturation largely preserved
- Frequent spontaneous regression

HSIL (CIN 2/3)

- More pronounced cell-cycle dysregulation
- Immature cells occupy greater thickness
- Substantial malignant potential

LSIL reflects a productive HPV infection

- Viral replication is high in differentiating epithelial cells.
- The basal proliferative compartment is modestly expanded.
- Koilocytic changes and largely retained maturation distinguish many LSILs from HSILs.

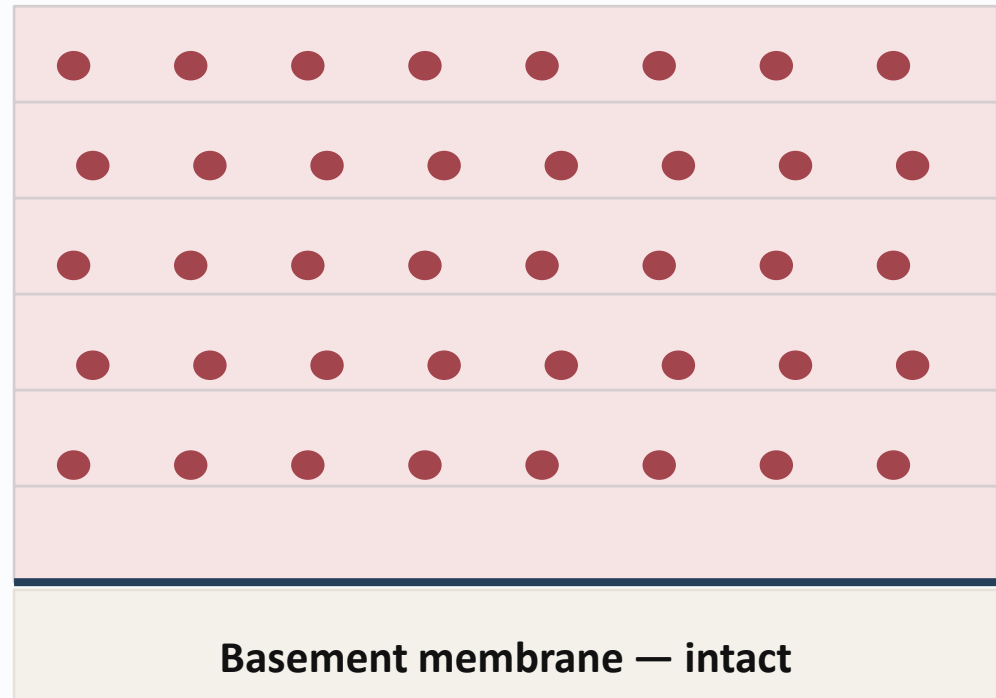


LSIL: Productive HPV changes

Schematic (not a micrograph)

HSIL reflects a transforming epithelial lesion

- Epithelial maturation becomes progressively reduced.
- Immature atypical cells expand into the middle or upper epithelial layers.
- The lesion remains intraepithelial until malignant cells breach the basement membrane.

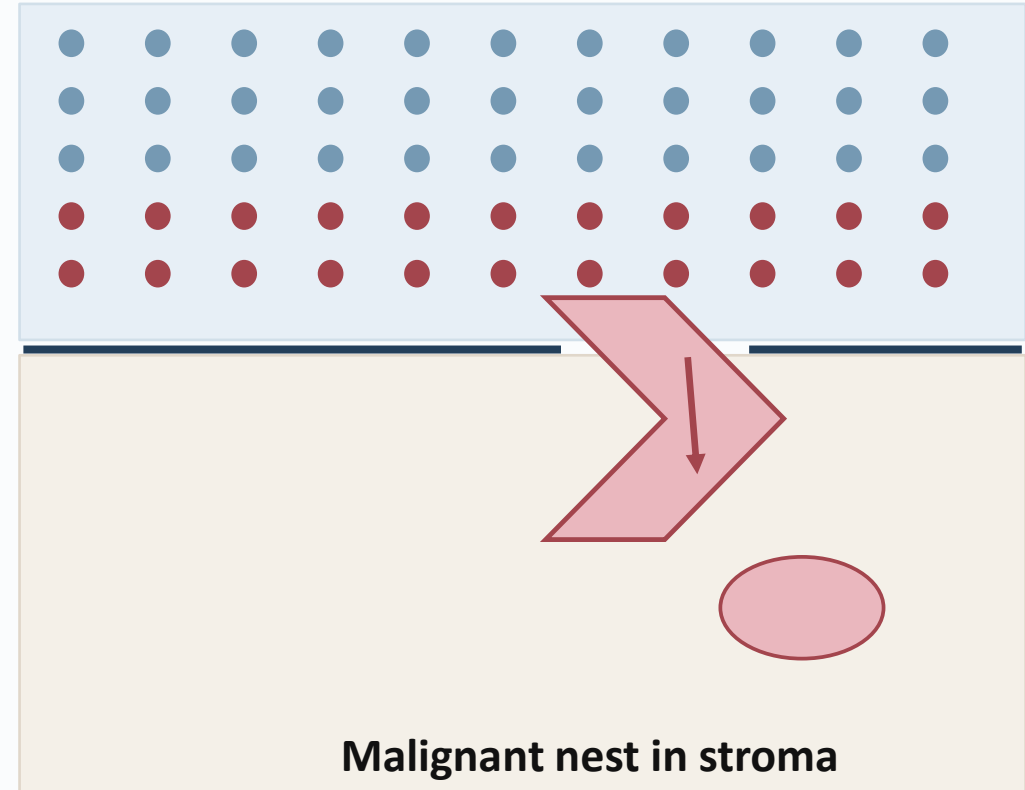


HSIL: Expanded immature cells

Schematic (not a micrograph)

The invasion threshold is the key diagnostic boundary

- HSIL shows dysplastic full-thickness or partial-thickness epithelial changes with an intact epithelial–stromal interface.
- Invasive carcinoma is defined by malignant epithelium infiltrating cervical stroma.
- Surface severity alone does not establish stromal invasion.



Schematic — epithelial–stromal boundary

Koilocytic atypia signals HPV-related cytopathic change

- Characteristic findings include nuclear enlargement and irregularity.
- Hyperchromatic nuclei and perinuclear cytoplasmic halos occur in affected squamous cells.
- The morphologic context and epithelial maturation pattern determine LSIL versus HSIL classification.

P16 and Ki-67 provide supportive information

P16

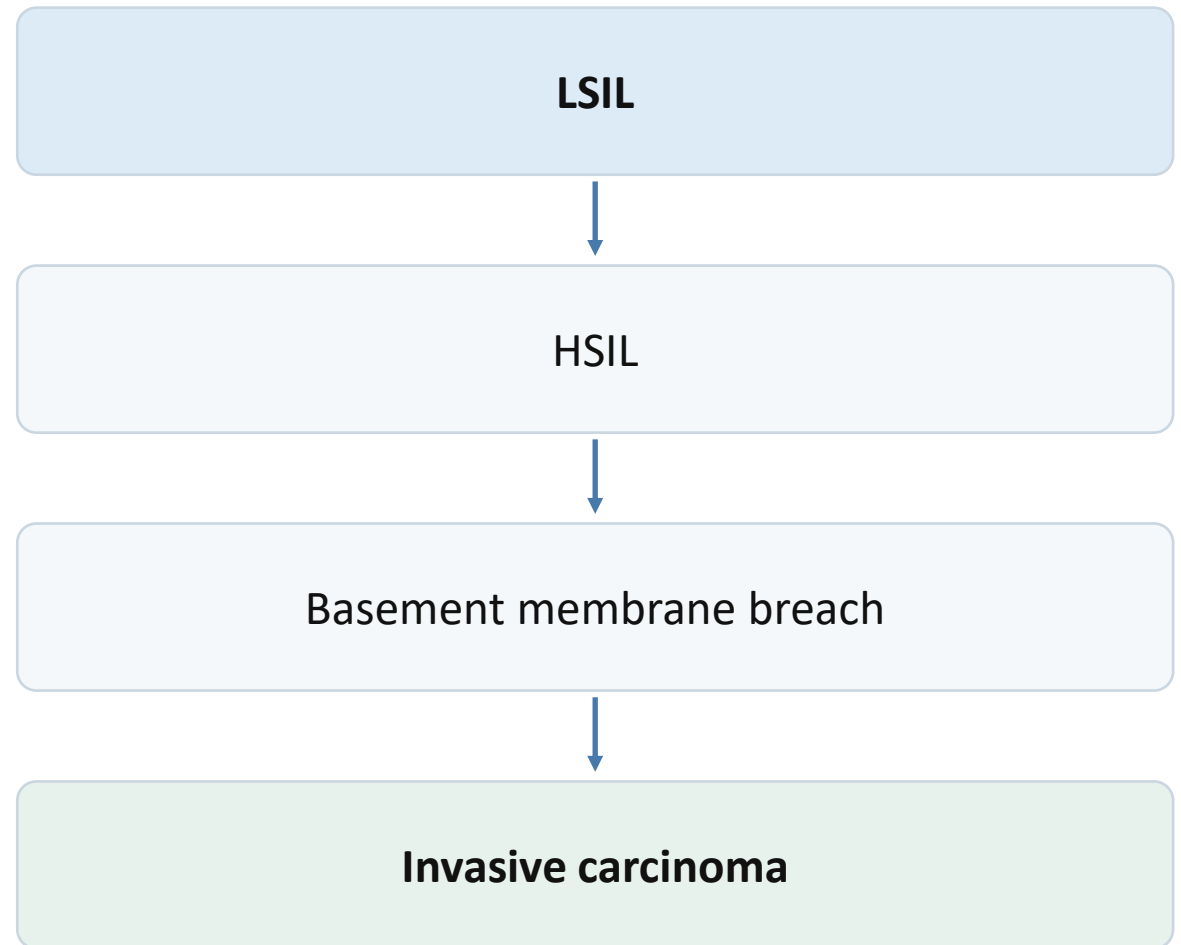
- Cell-cycle dysregulation surrogate
- Often increased in high-risk HPV lesions
- Interpret with morphology

Ki-67

- Proliferation marker
- Expansion beyond basal layer
- Supports abnormal proliferation

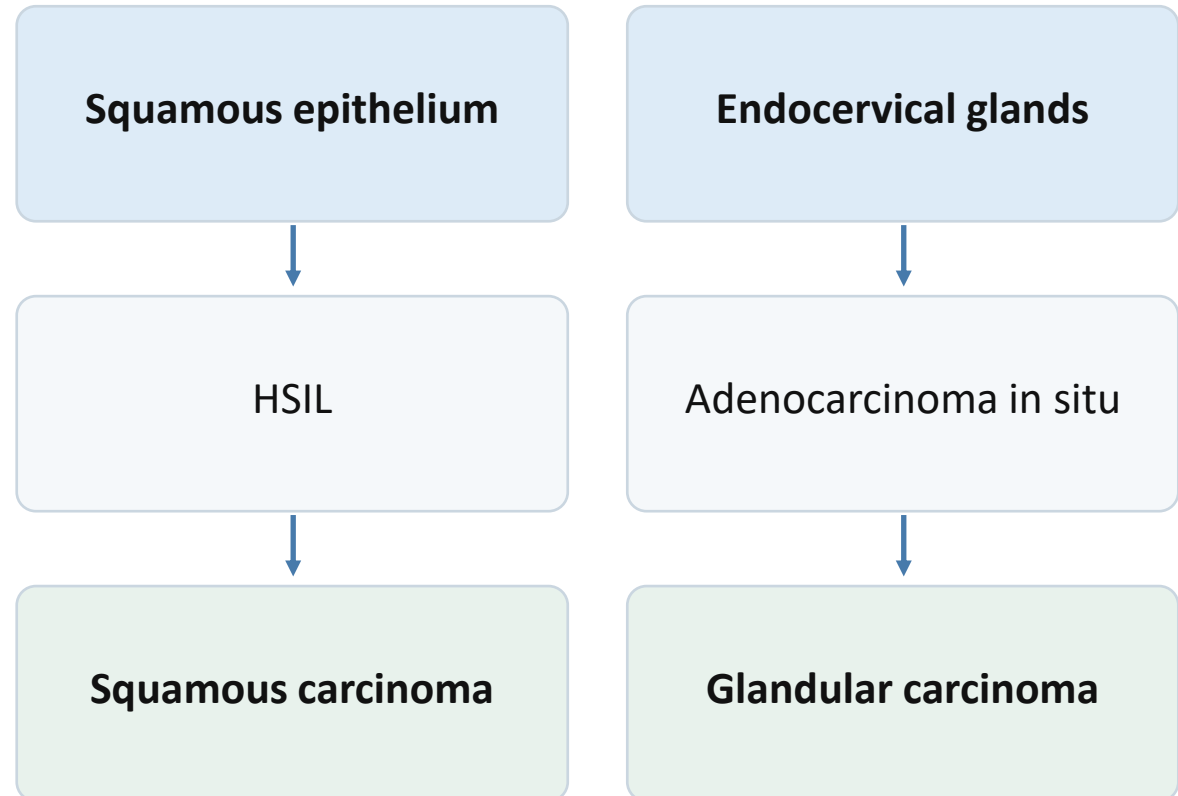
A precursor is not yet a carcinoma

- LSIL is usually managed as a productive viral lesion, not as established malignancy.
- HSIL is a premalignant lesion with potential to progress.
- Invasive carcinoma adds the ability to infiltrate stroma and access lymphovascular channels.



Squamous and glandular routes differ

- Squamous lesions commonly progress through LSIL and HSIL states.
- Most HPV-associated endocervical adenocarcinomas develop from adenocarcinoma in situ (AIS).
- The relevant epithelial architecture differs, but invasion remains a defining event for both pathways.



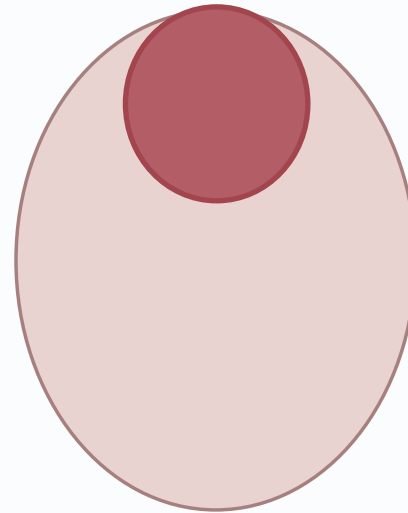
Cervical carcinoma: Principal histotypes

- Squamous carcinoma forms invasive nests and tongues of malignant squamous cells.
- Adenocarcinoma forms malignant glandular epithelial structures.
- Adenosquamous carcinoma combines both; Neuroendocrine carcinoma is characterized by small- or large-cell morphology.

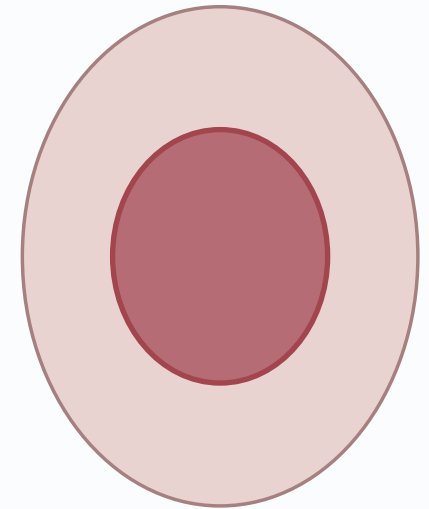
Squamous	Glandular	Other
Keratinizing	Adenocarcinoma	Adenosquamous
Nonkeratinizing	Gastric-type exception	Neuroendocrine

Gross growth may be exophytic or infiltrative

- Exophytic tumors may form fungating lesions that project from the cervix.
- Infiltrative tumors extend into cervical tissue with a less surface-dominant configuration.
- Gross configuration does not replace microscopic assessment of type and depth.



Exophytic projection



Infiltrative growth

Gross-form schematic — not a specimen

Exophytic growth does not determine histologic subtype

Gross descriptor

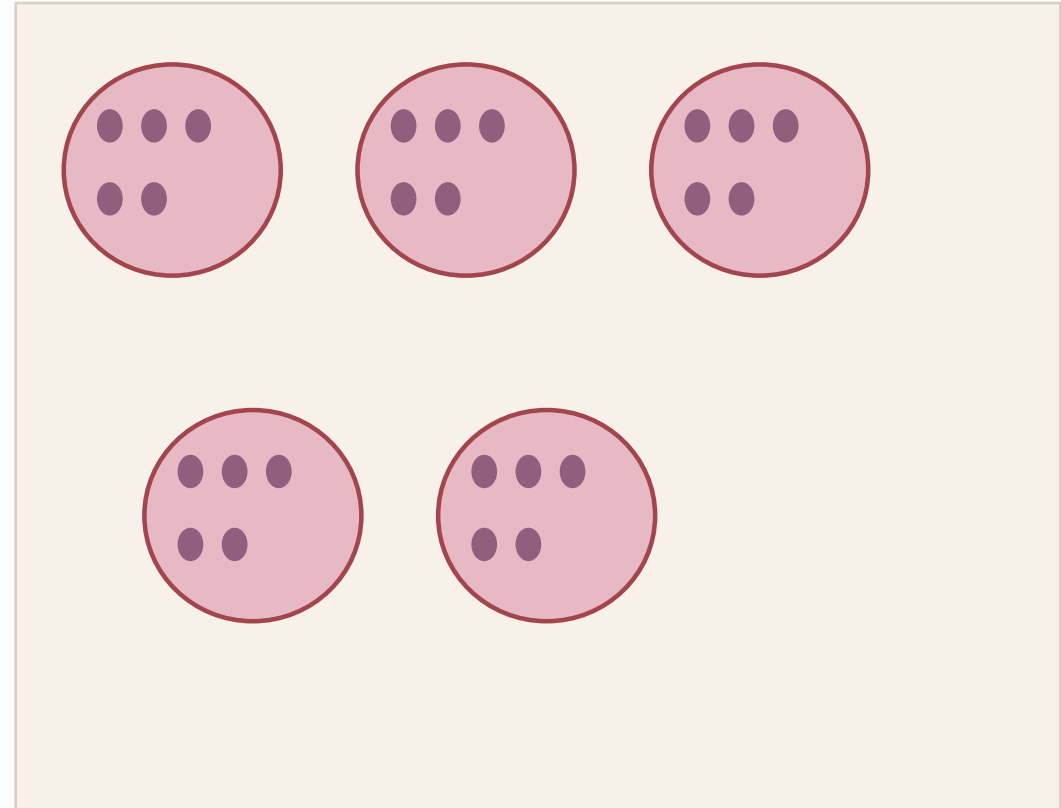
- Visible mass configuration
- Exophytic / fungating
- Infiltrative extension

Microscopic descriptor

- Squamous / glandular differentiation
- Tumor–stroma relationship
- Pattern of invasion

Squamous carcinoma invades as nests and tongues

- Cohesive malignant squamous epithelial cells form irregular nests or tongues in cervical stroma.
- The tumor may be keratinizing or nonkeratinizing.
- Stromal location, rather than mere cytologic atypia, establishes invasive behavior.



Separate malignant squamous nests infiltrating stroma

Original schematic — not observed histology

Keratinizing and nonkeratinizing patterns coexist

Keratinizing SCC

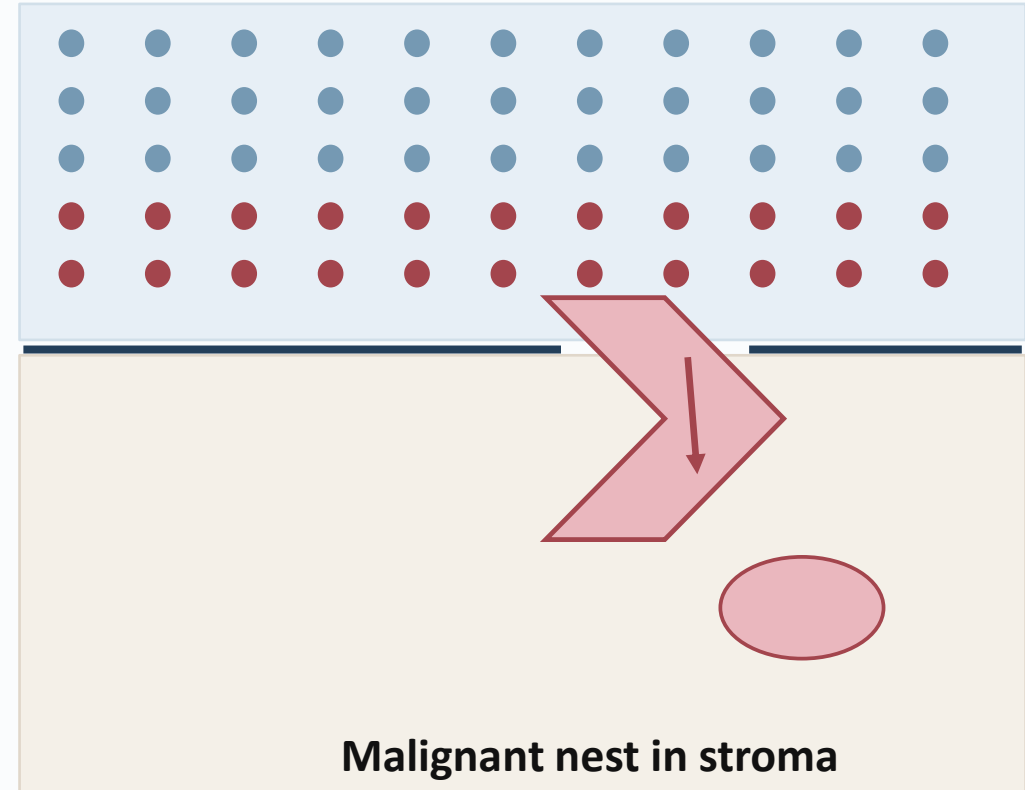
- Squamous differentiation
- Conspicuous keratin production
- May form keratin pearls

Nonkeratinizing SCC

- Malignant squamous cells
- Keratin less apparent
- Invasive nests remain diagnostic

The basement membrane separates in situ from invasion

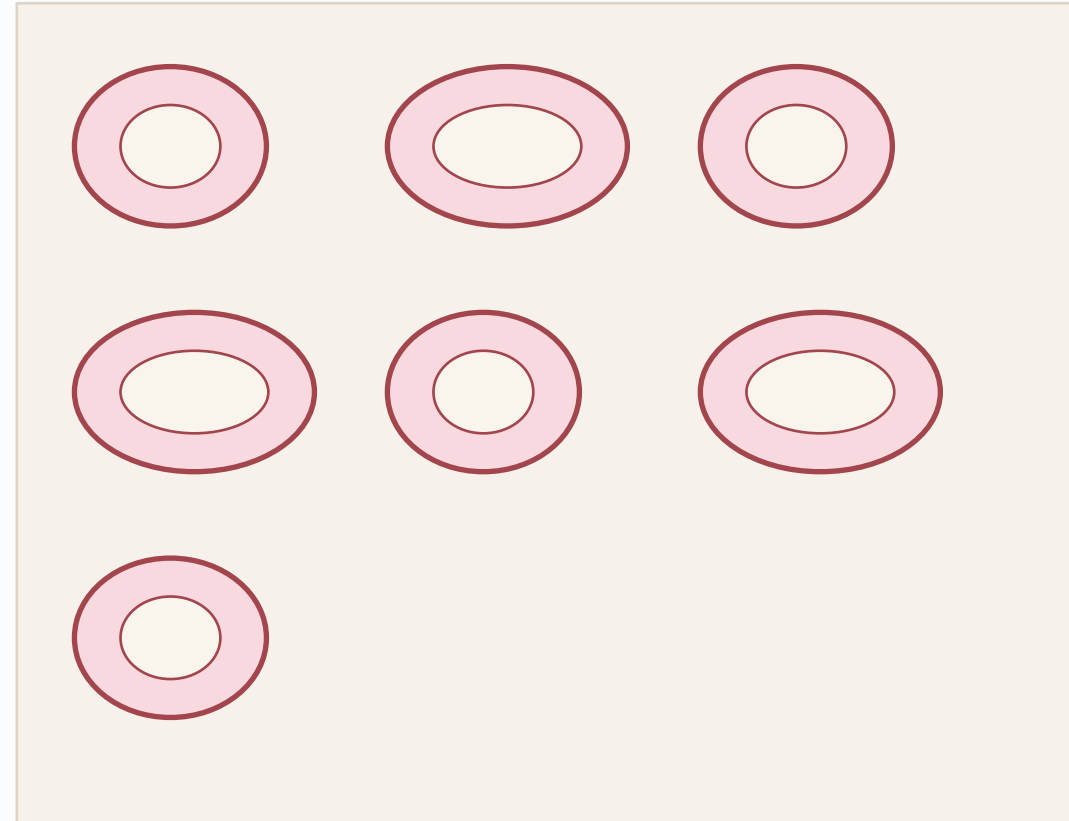
- Preinvasive cells remain on the epithelial side of the basement membrane.
- Tumor cells penetrating the interface enter the cervical stromal compartment.
- Measured invasion depth becomes important in superficially invasive carcinoma.



Schematic — epithelial–stromal boundary

Adenocarcinoma creates abnormal malignant glands

- Invasive glandular tumors comprise malignant endocervical cells with enlarged hyperchromatic nuclei.
- Cytoplasm is relatively mucin depleted in typical HPV-associated lesions.
- Darkly staining neoplastic glands contrast with normal paler endocervical epithelium.

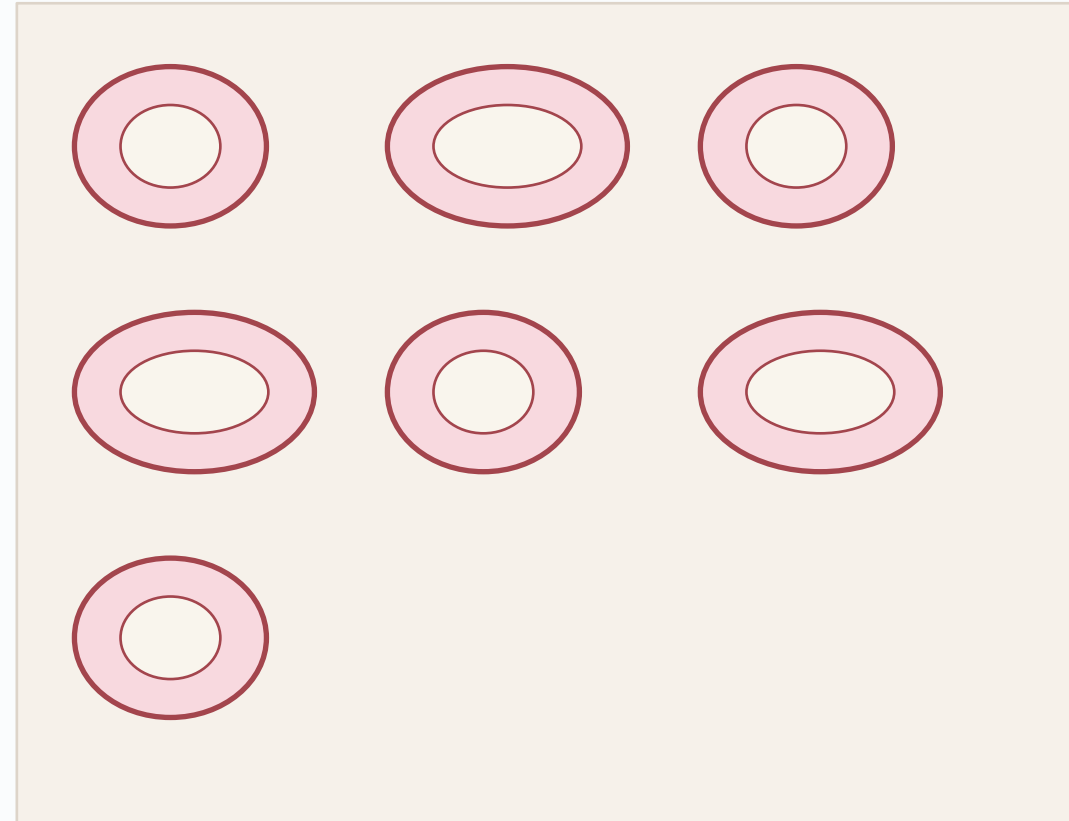


Irregular malignant gland profiles in stroma

Original schematic — not observed histology

Mucin depletion explains the “dark gland” appearance

- Normal endocervical glands contain mucin-rich, relatively pale columnar cells.
- Neoplastic glands in typical cervical adenocarcinoma show greater nuclear crowding and less cytoplasmic mucin.
- The visual contrast reflects altered differentiation and nuclear-to-cytoplasmic balance.



Irregular malignant gland profiles in stroma

Original schematic — not observed histology

AIS differs from invasive adenocarcinoma

Adenocarcinoma in situ

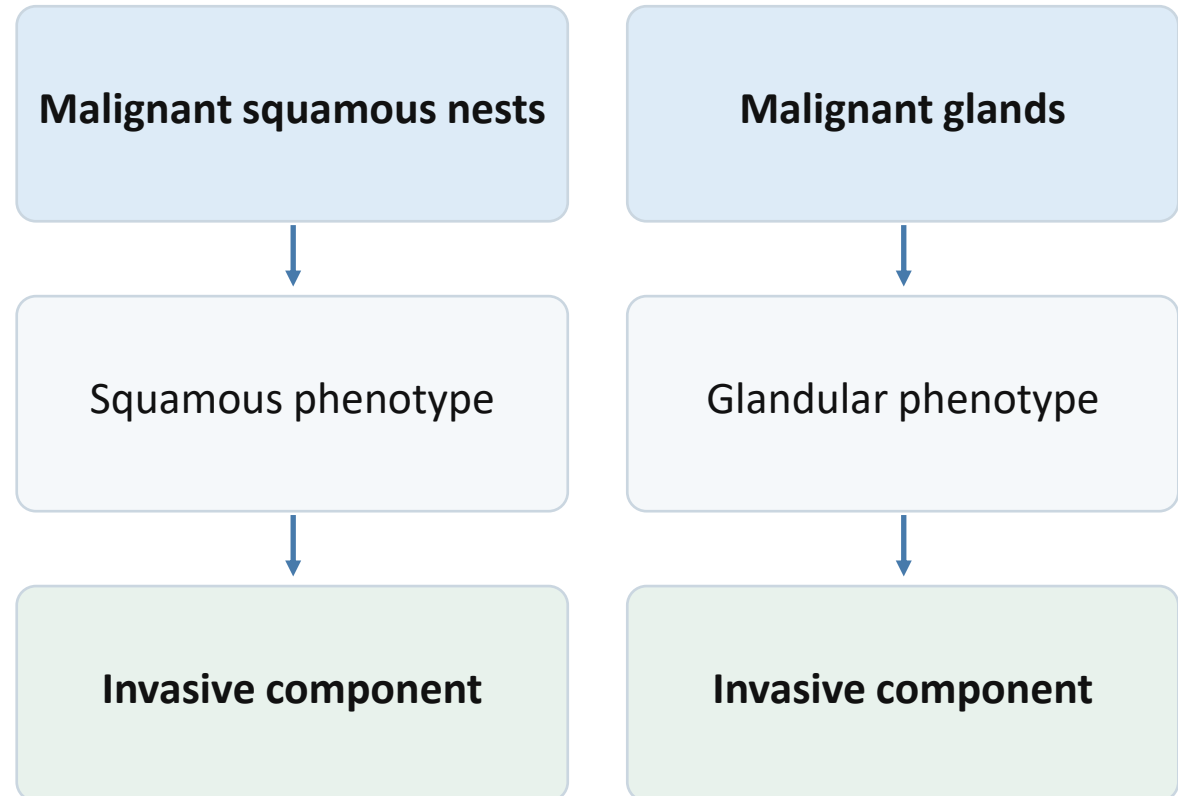
- Atypical endocervical glands
- No destructive stromal invasion
- Glandular precursor

Invasive adenocarcinoma

- Malignant glands in cervical stroma
- Invasive growth established
- Potential local and metastatic spread

Adenosquamous carcinoma shows dual differentiation

- Tumor contains admixed malignant squamous epithelium and malignant glandular epithelium.
- Both components should be recognized within the malignant lesion.
- Robbins groups it among rare cervical epithelial malignancies.



Neuroendocrine carcinomas: Small- and large-cell types

Small-cell morphology

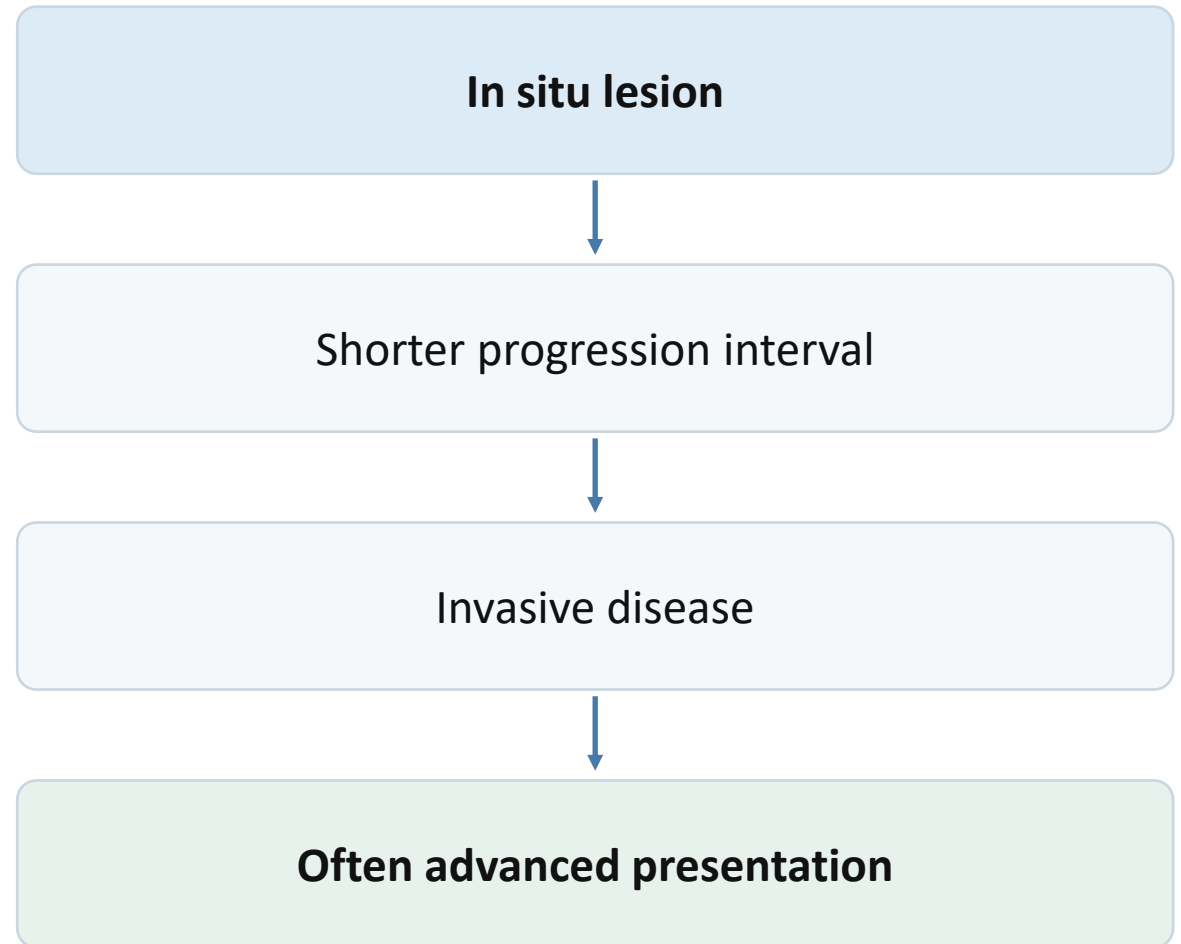
- Small malignant tumor cells
- Neuroendocrine carcinoma category
- High-risk HPV association

Large-cell morphology

- Larger malignant tumor cells
- Neuroendocrine carcinoma category
- High-risk HPV association

A shorter preinvasive interval changes presentation

- More rapid progression for adenosquamous and neuroendocrine carcinomas than for typical SCC.
- These tumors may be detected at a more advanced stage.
- Shorter evolution and advanced presentation contribute to unfavorable clinical behavior.



Gastric-type adenocarcinoma is HPV-independent

HPV-associated adenocarcinoma

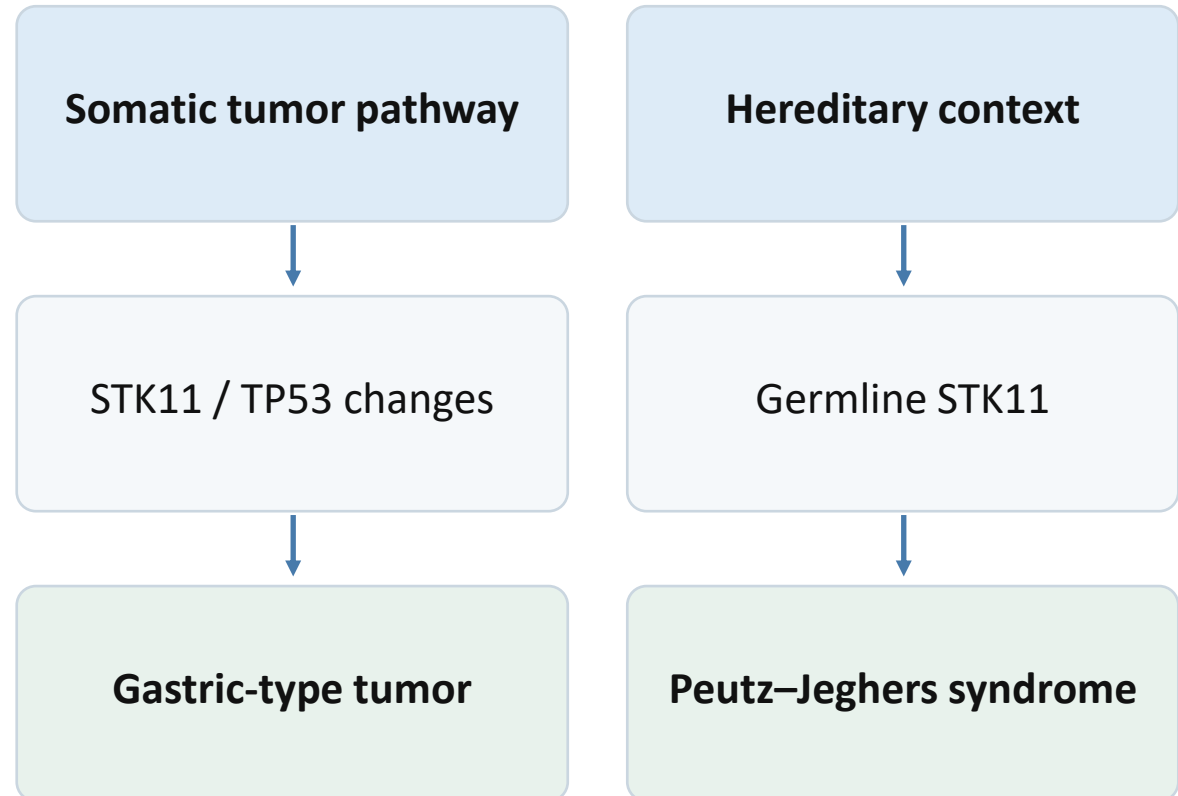
- Usual type is common
- Often AIS precursor
- HPV-driven cell-cycle changes

Gastric-type adenocarcinoma

- HPV-independent
- Gastric-type differentiation
- Often aggressive behavior

STK11 and TP53 in gastric-type adenocarcinoma

- Frequent somatic alterations involving STK11 and TP53.
- Some tumors occur with Peutz–Jeghers syndrome, associated with germline STK11 alteration.
- Somatic tumor changes and inherited susceptibility are distinct genetic contexts.



WHO 2020 emphasizes HPV etiologic classification

- The WHO 2020 classification distinguishes HPV-associated and HPV-independent cervical carcinomas.
- Gastric-type adenocarcinoma is included among HPV-independent glandular malignancies.
- This classification is a contemporary supplement to the Robbins tumor descriptions.

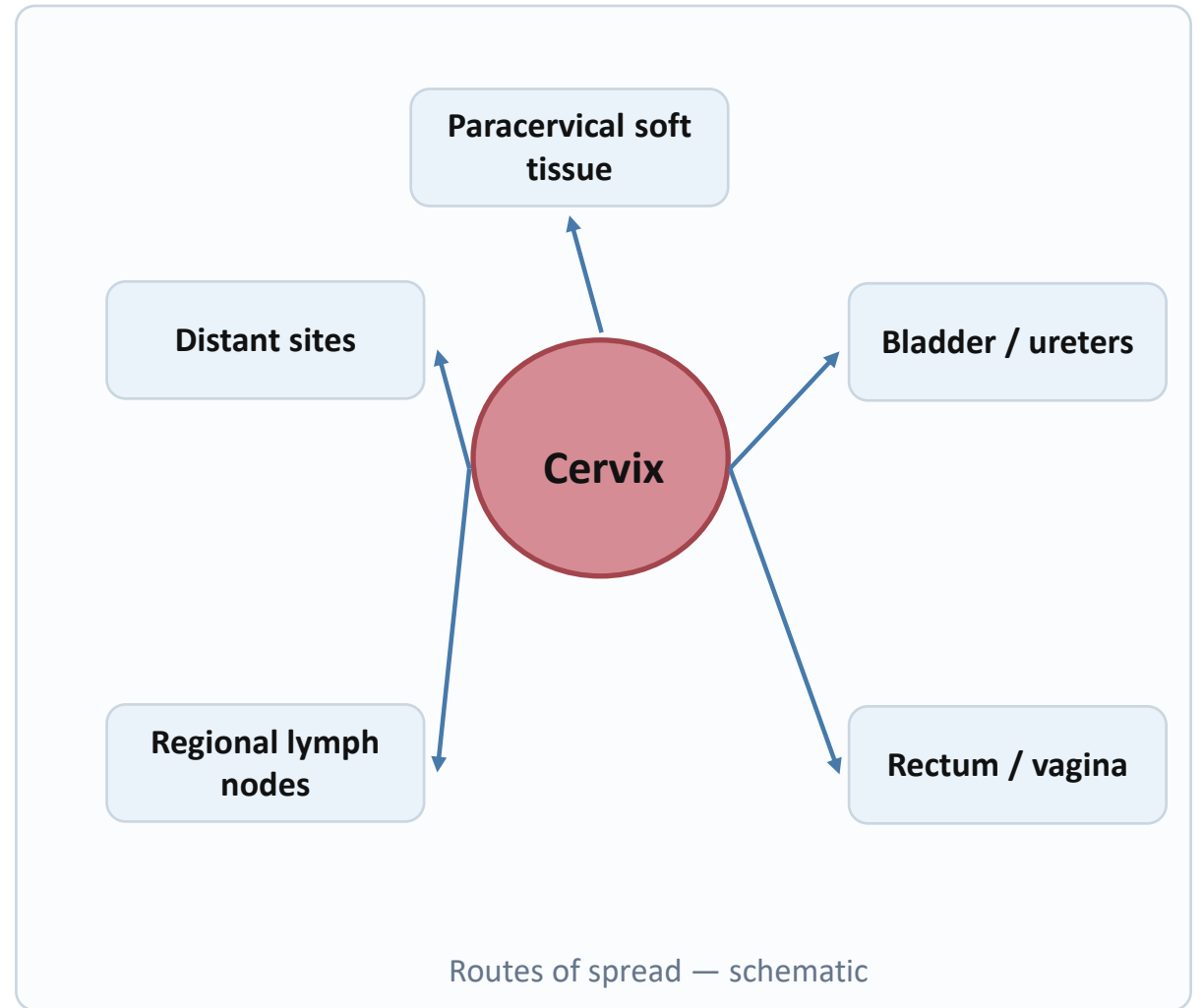
HPV-associated	HPV-independent
Squamous carcinoma	Gastric-type adenocarcinoma
Usual-type adenocarcinoma	Other defined glandular types

Histotype provides information beyond anatomic stage

Stage	Histotype
• Local extension • Regional lymph nodes • Distant dissemination	• Cell lineage / morphology • HPV association • Subtype-associated prognosis

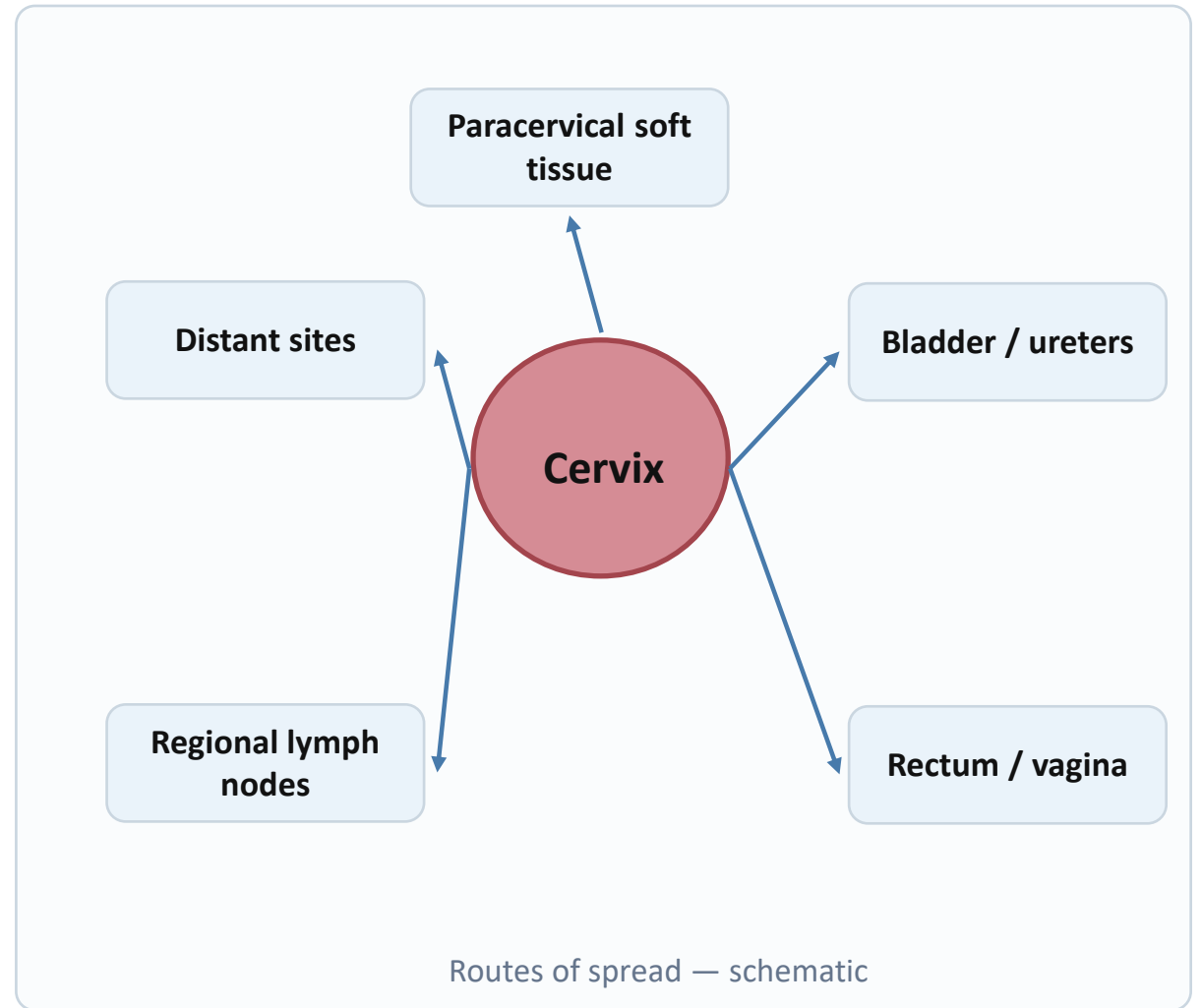
Locoregional extension is a major route of spread

- Advanced lesions may extend into paracervical soft tissue.
- Contiguous spread can involve vagina, urinary bladder, ureters, and rectum.
- Local invasion itself is a major driver of late complications.



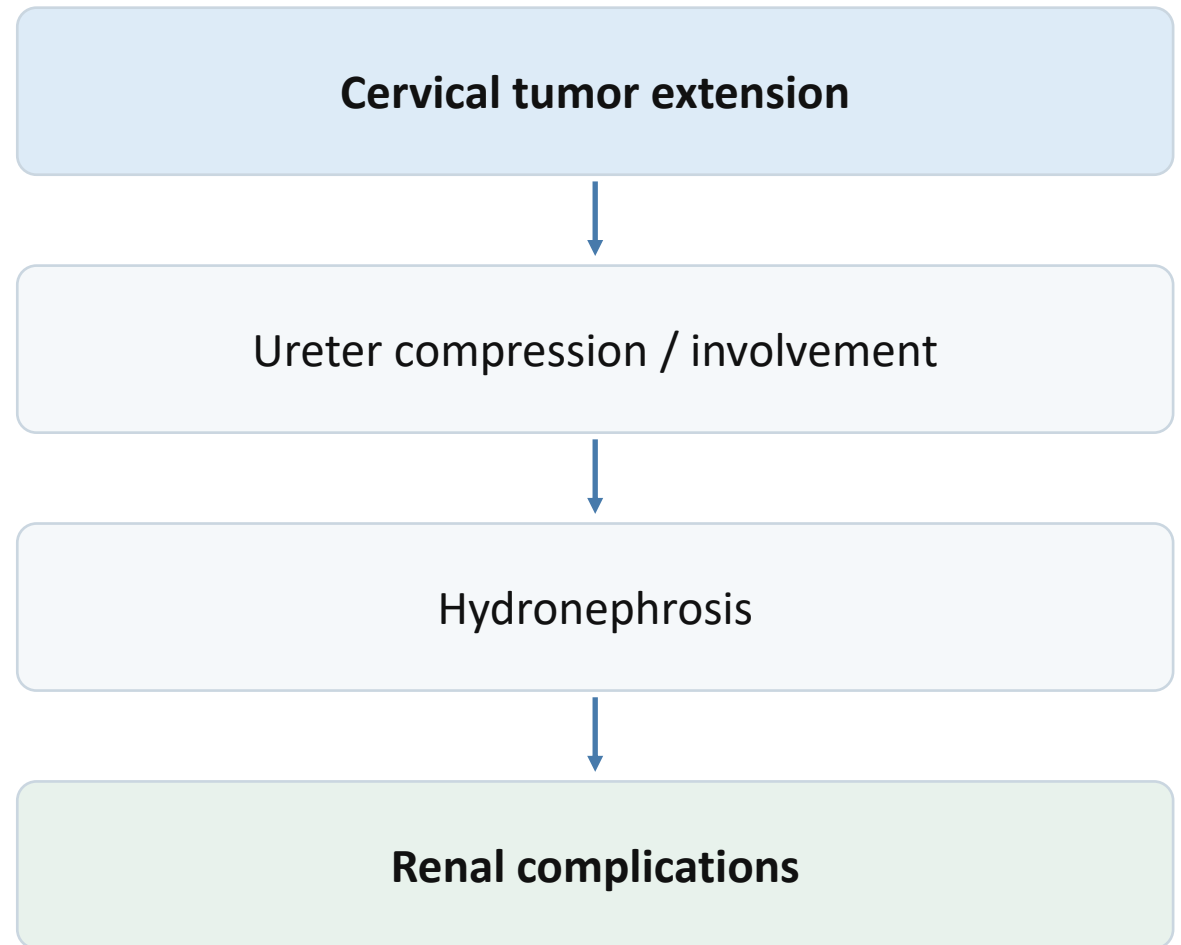
Paracervical extension reflects loss of confinement

- Cervix-confined disease differs from tumors extending beyond the cervix.
- Tumor infiltration of adjacent soft tissue expands the anatomic field requiring treatment.
- Regional extent is central to clinical staging.



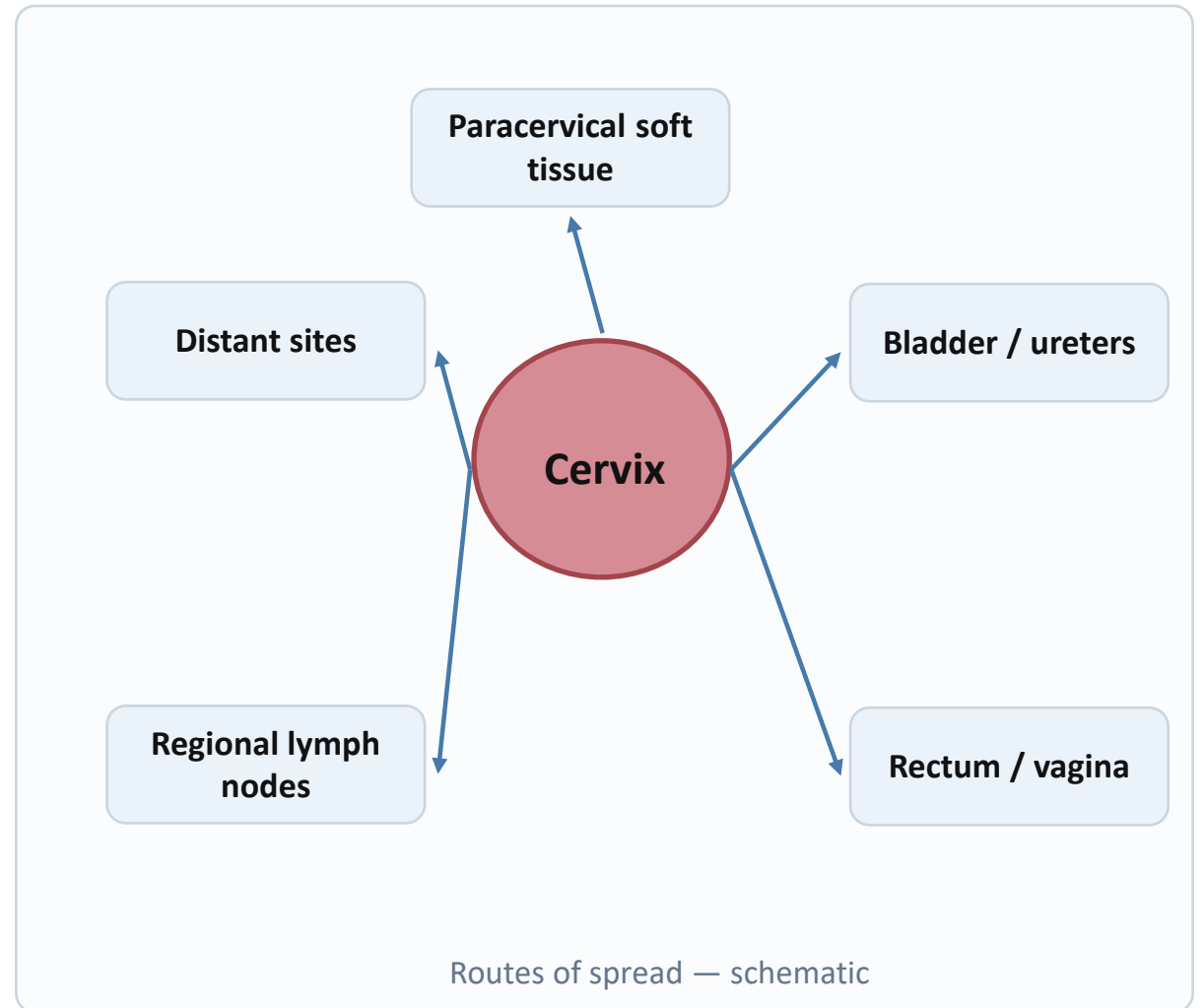
Ureteral obstruction can cause hydronephrosis

- Tumor encroachment on a ureter can impede urinary drainage.
- Urine pressure backs up into the collecting system, producing hydronephrosis.
- Advanced obstruction may lead to infection and renal dysfunction.



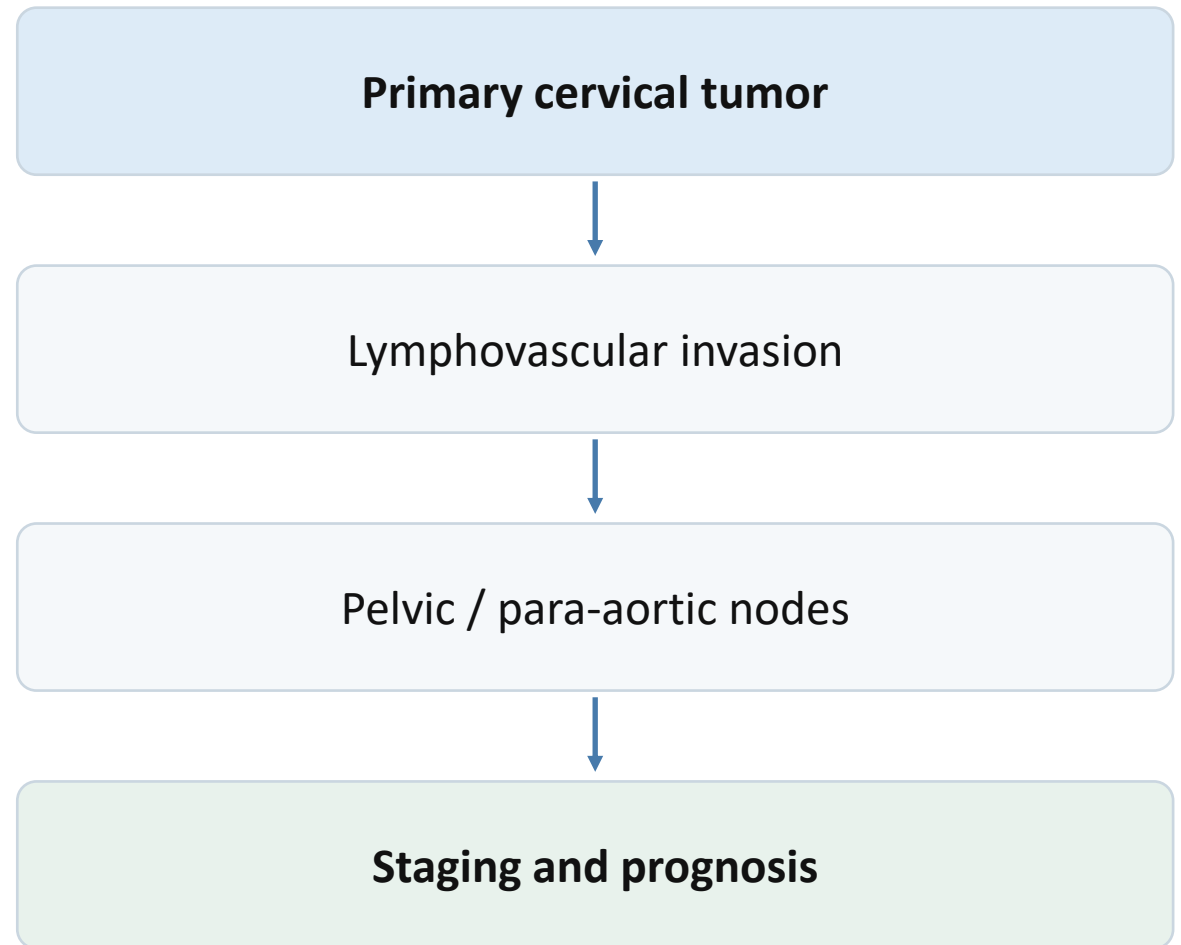
Bladder and rectal involvement signal advanced spread

- Direct growth into adjacent pelvic organs may occur with advanced disease.
- Mucosal invasion of bladder or rectum is a major staging distinction.
- Symptoms and morbidity may arise from local organ invasion rather than distant tumor deposits.



Lymphovascular invasion enables nodal metastasis

- Malignant cells entering lymphovascular channels can disseminate beyond the primary cervical lesion.
- Pelvic and para-aortic nodes are clinically important regional sites.
- Nodal status affects modern cervical-cancer stage assignment.



Distant metastasis can involve several organs

Regional disease

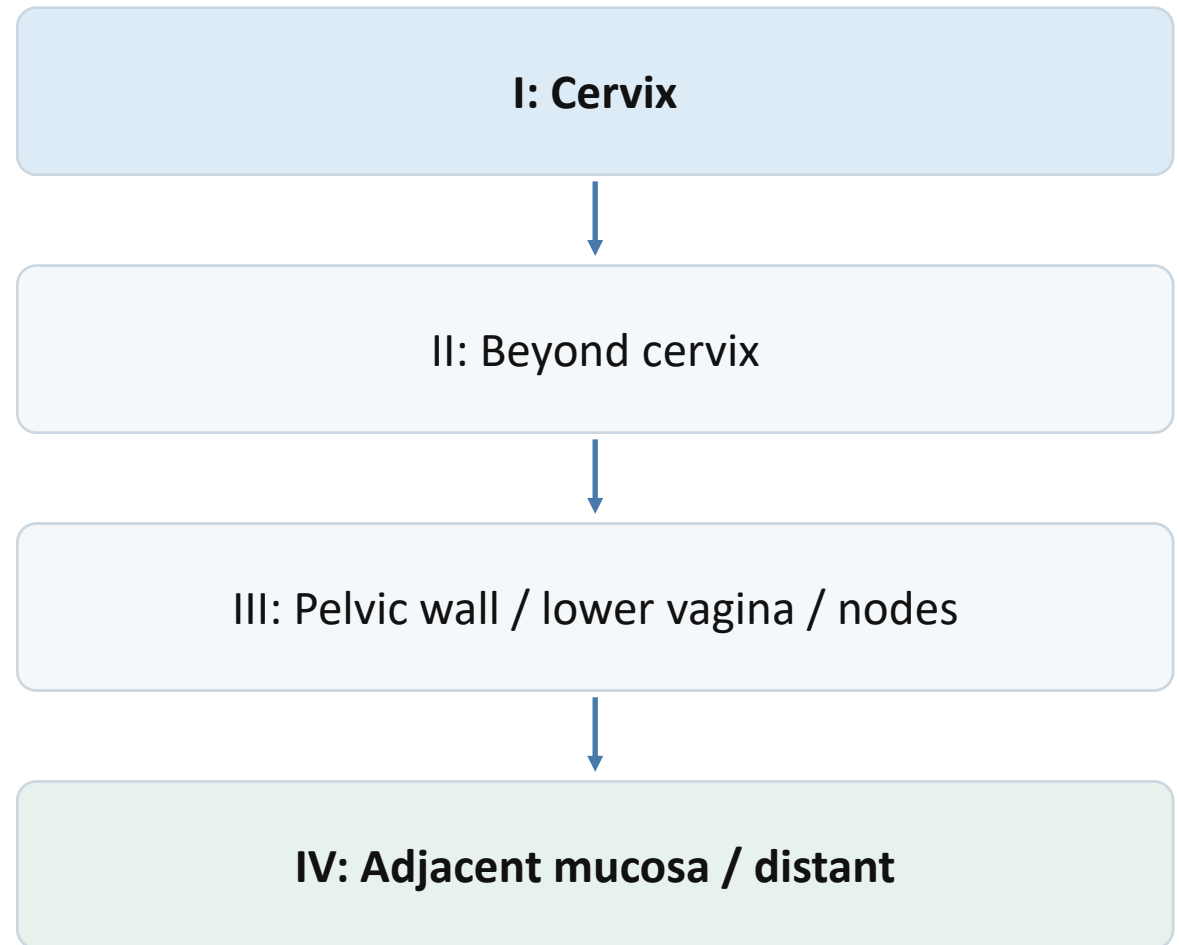
- Paracervical tissue
- Pelvic structures
- Regional lymph nodes

Distant disease

- Lung
- Liver
- Bone marrow / other organs

Extent of disease underlies staging

- Localized invasive carcinoma remains confined to cervix.
- Higher stages describe progressively wider local extension, nodal involvement, or distant dissemination.
- Stage is a structural description, not a proxy for tumor histology.



FIGO 2018 stage I: Disease confined to cervix

- Stage IA is diagnosed only microscopically; The maximum depth of stromal invasion is 5 mm.
- IA1: Invasion ≤ 3 mm; IA2: Invasion > 3 mm and ≤ 5 mm.
- Stage IB represents invasive carcinoma confined to cervix beyond IA; Size subdivisions apply.

I **Confined to cervix**

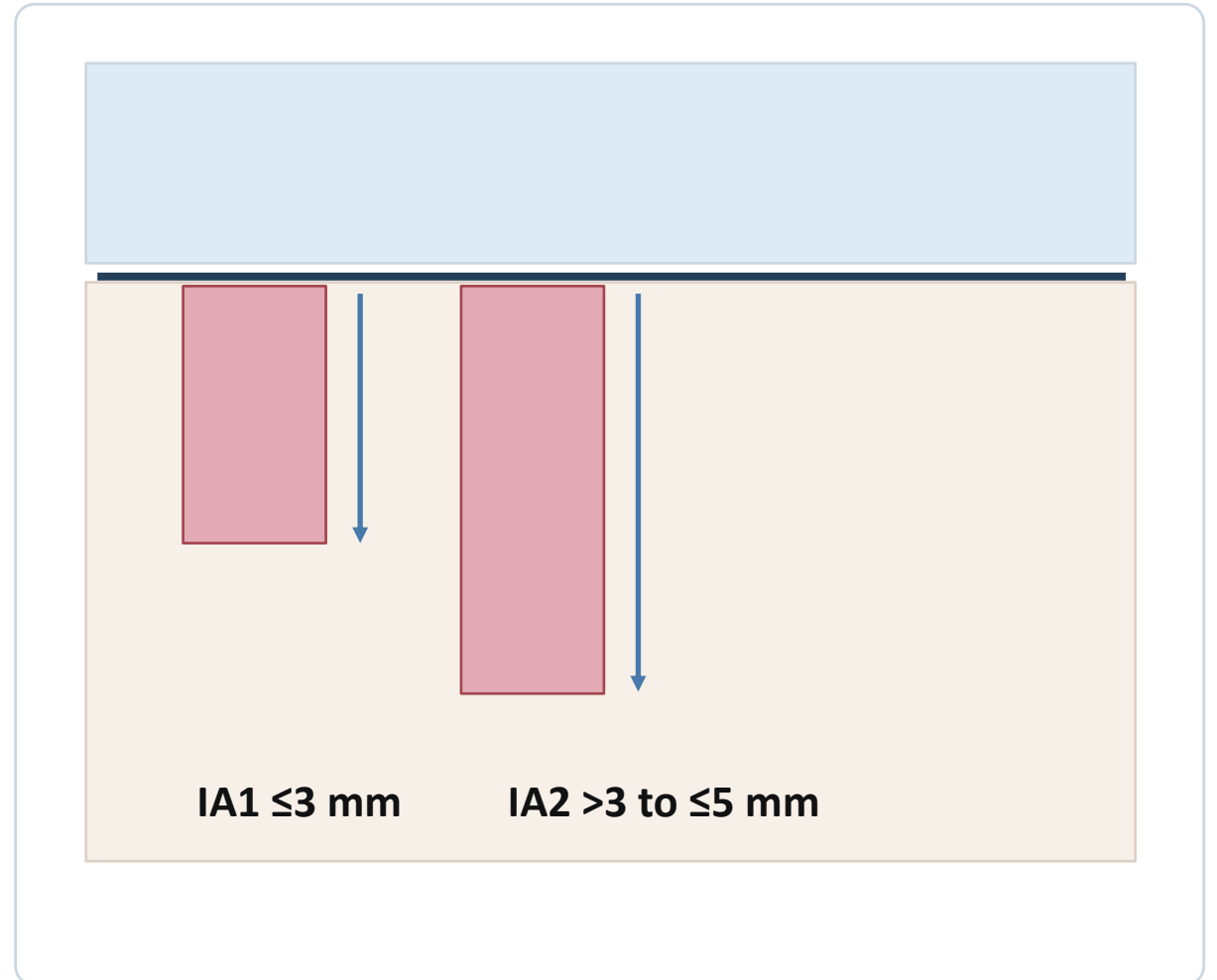
II Beyond cervix, not pelvic wall / lower vagina

III Lower vagina, pelvic wall, obstruction and/or nodes

IV Bladder/rectal mucosa, beyond pelvis or distant

Invasion depth distinguishes IA1 and IA2

- Stage IA1 includes stromal invasion of at most 3 mm.
- Stage IA2 includes invasion deeper than 3 mm but not deeper than 5 mm.
- Measurement refers to the maximum depth of stromal invasion, not the size of an exophytic surface mass.



FIGO 2018 stage II: Beyond cervix, not pelvic wall

- Disease extends beyond uterus/cervix without reaching the pelvic wall or lower vaginal third.
- IIA involves the upper two-thirds of vagina without parametrial involvement.
- IIB denotes parametrial involvement short of the pelvic wall.

I Confined to cervix

II **Beyond cervix, not pelvic wall / lower vagina**

III Lower vagina, pelvic wall, obstruction and/or nodes

IV Bladder/rectal mucosa, beyond pelvis or distant

FIGO 2018 stage III includes nodes and obstruction

- Extent to lower vaginal third or pelvic wall is included.
- Tumor-related hydronephrosis or nonfunctioning kidney qualifies (unless due to another cause).
- IIIC captures pelvic or para-aortic lymph node metastases, regardless of primary tumor size.

I Confined to cervix

II Beyond cervix, not pelvic wall / lower vagina

III Lower vagina, pelvic wall, obstruction and/or nodes

IV Bladder/rectal mucosa, beyond pelvis or distant

FIGO 2018 distinguishes pelvic from para-aortic nodes

IIIC1

- Pelvic nodal metastasis
- Any primary tumor size
- FIGO 2018

IIIC2

- Para-aortic nodal metastasis
- Any primary tumor size
- FIGO 2018

FIGO 2018 stage IV: Adjacent mucosa or distant spread

- IVA: Extension to the mucosa of bladder or rectum or beyond the true pelvis (without distant spread).
- IVB: Distant metastasis.
- Superficial adjacency to an organ is not automatically equivalent to mucosal invasion.

I Confined to cervix

II Beyond cervix, not pelvic wall / lower vagina

III Lower vagina, pelvic wall, obstruction and/or nodes

IV Bladder/rectal mucosa, beyond pelvis or distant

Why “stage 0” needs careful terminology

Noninvasive precursor

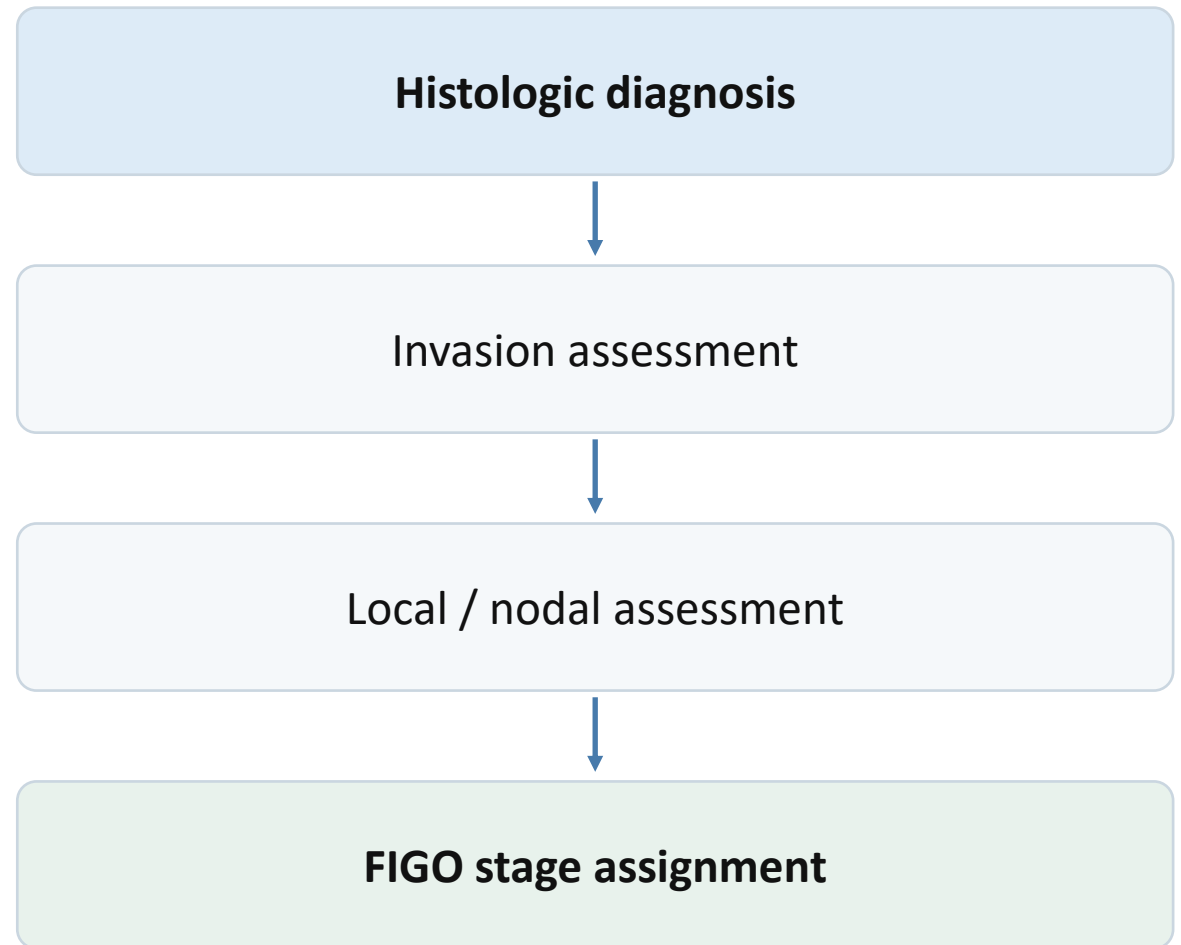
- CIN 3 / HSIL
- Adenocarcinoma in situ
- No stromal infiltration

Invasive staged cancer

- FIGO stage I–IV
- Stromal invasion or greater extent
- Extent determines stage

Staging integrates morphology and anatomic extent

- Histology establishes the malignant subtype and confirms invasion.
- Local extent, ureteral obstruction, regional nodes, and distant spread refine stage.
- Staging cannot be inferred from grade, p16 staining, or tumor type alone.



Screening participation changes detection patterns

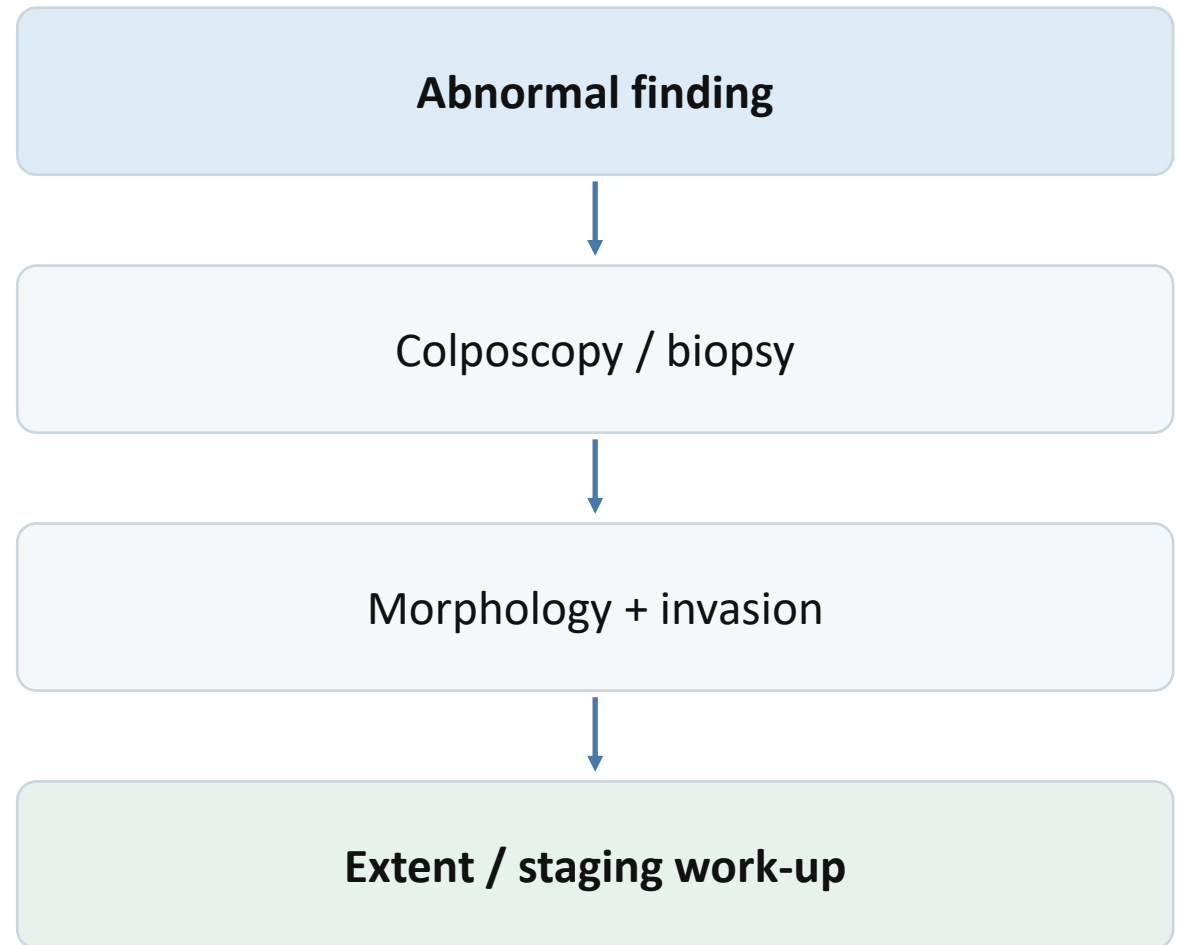
- More than half of invasive cases occur in people not participating in regular screening.
- Cervical precursors often persist for years before invasion, enabling detection.
- Screening and prevention are the subject of the adjacent Robbins topic; This lecture emphasizes invasive disease.

>50%

Invasive cancers detected in persons without regular screening (Robbins)

Diagnosis requires tissue assessment

- An abnormal screening or examination result may prompt colposcopy and targeted biopsy.
- Histologic review determines whether the lesion is intraepithelial or invasive.
- When invasion is identified, depth and subtype influence further assessment and planning.



Superficially invasive SCC may permit local excision

Excision pathology

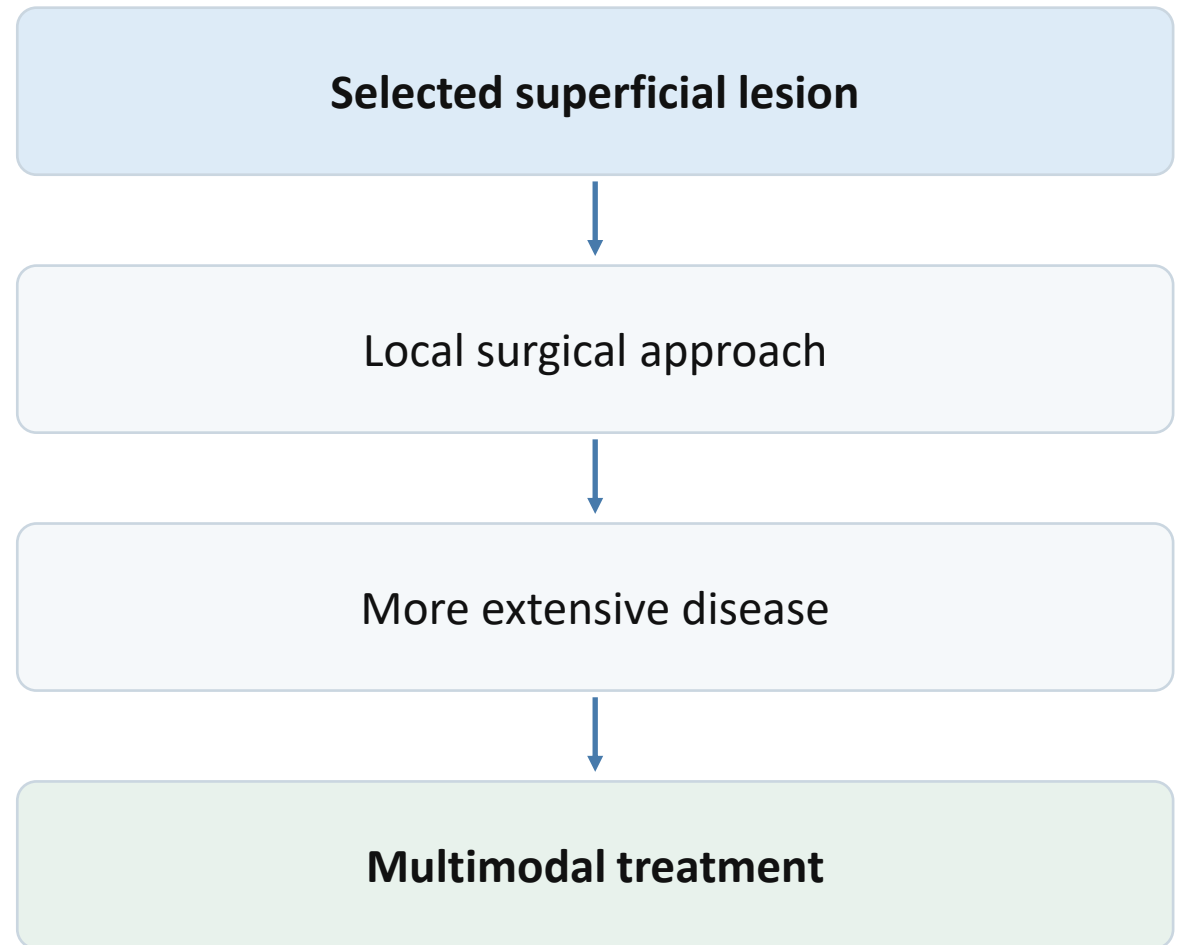
- Depth of invasion
- Margins and lesion extent
- Tumor morphology

Clinical decision

- Stage and risk features
- Individual circumstances
- Specialist-directed management

Treatment intensity generally rises with extent

- Hysterectomy with lymph-node dissection for many invasive tumors.
- Advanced disease may require radiation and chemotherapy.
- Specific contemporary treatment protocols are beyond the scope of this source-anchored pathology lecture.



Stage is the strongest prognostic determinant

Superficially invasive SCC

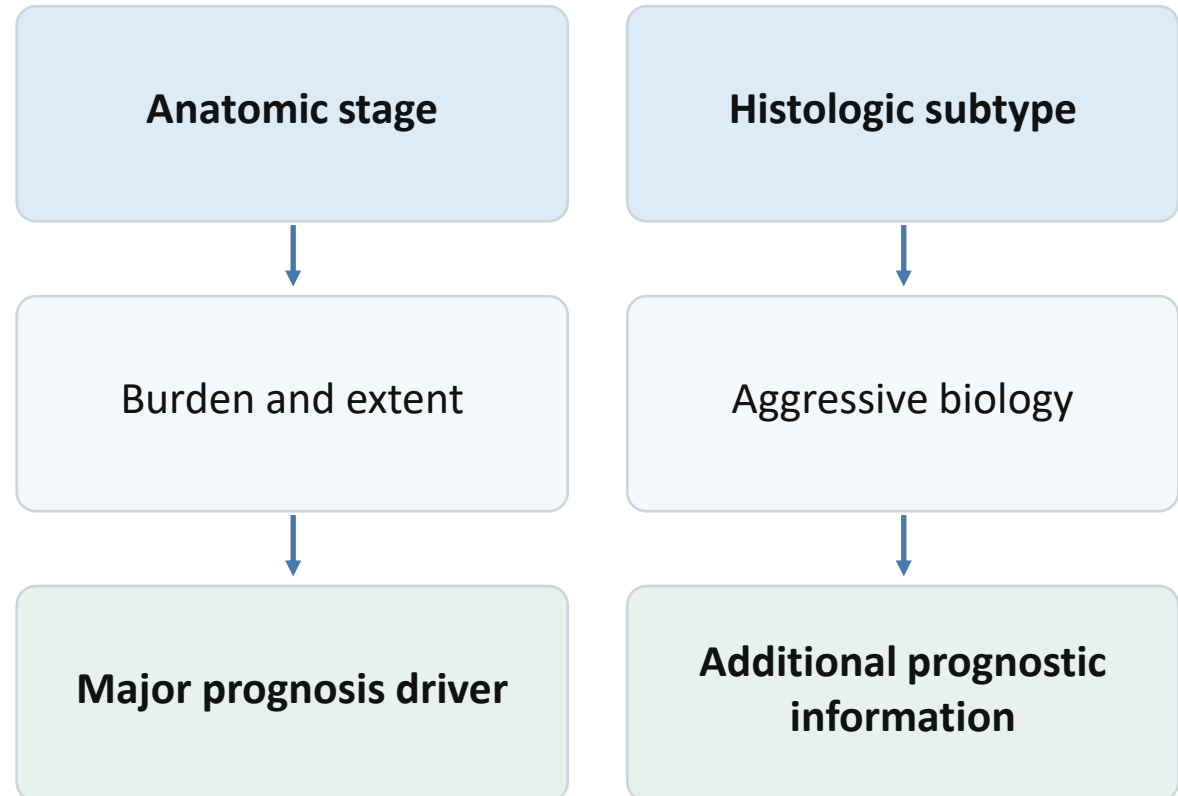
- Robbins: 100% five-year survival
- Favorable when appropriately treated
- Localized disease

Beyond-pelvis extension

- Robbins: <20% five-year survival
- Very advanced extent
- Poor outcome

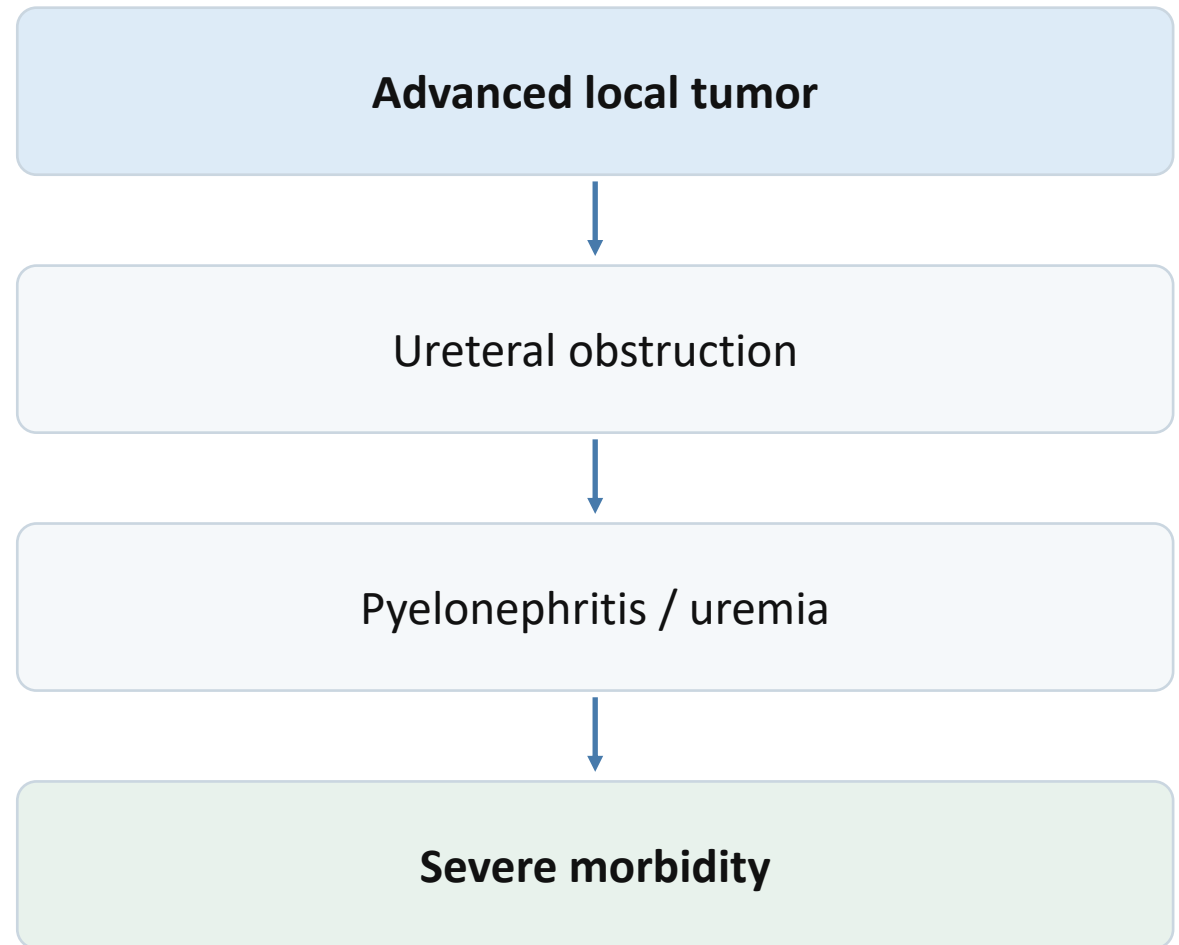
Aggressive histotypes modify prognosis

- Neuroendocrine carcinoma is associated with particularly unfavorable clinical behavior.
- Gastric-type HPV-independent adenocarcinoma has a poor prognosis.
- Stage and histologic subtype provide complementary prognostic information.



Local complications often cause late mortality

- Ureteral obstruction, pyelonephritis, and uremia in advanced cervical cancer.
- Local extension can severely disrupt pelvic-organ function.
- Distant metastasis is not the only, or necessarily the dominant, cause of death in advanced cases.

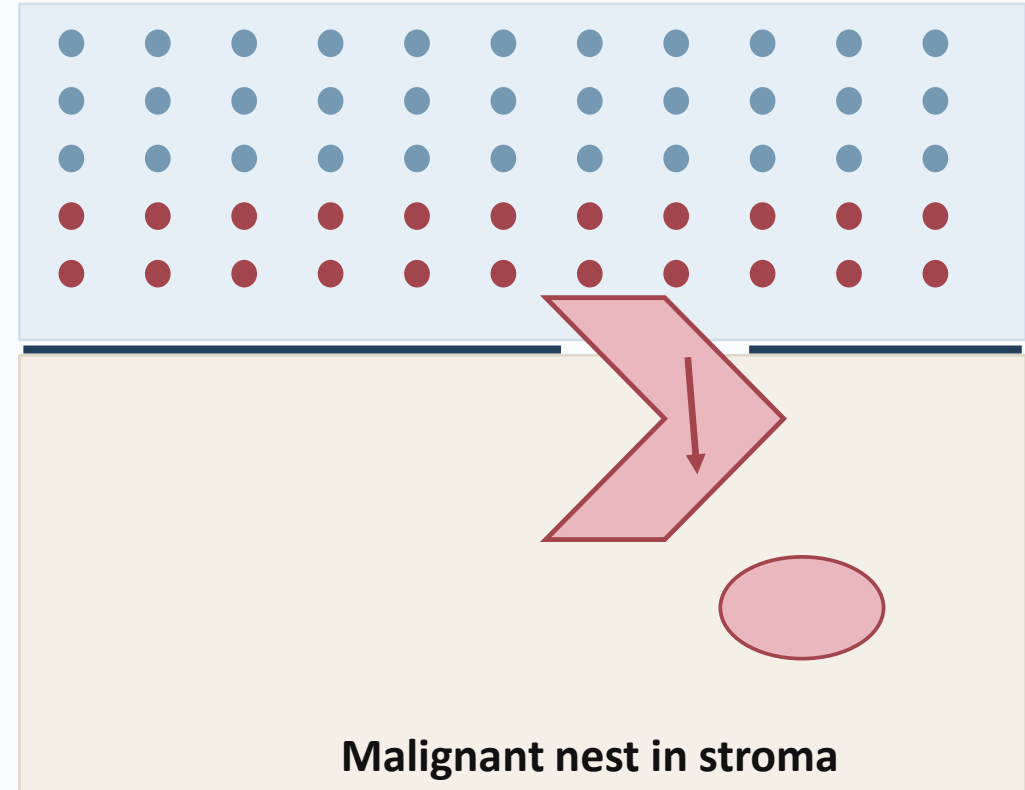


Case: Dysplasia versus invasion

- A biopsy shows a high-grade atypical squamous epithelium with loss of maturation.
- An irregular malignant nest is identified beyond the epithelial basement membrane in cervical stroma.
- Question: Is the correct diagnostic category HSIL alone, or invasive squamous carcinoma?

Case analysis: Stromal invasion changes diagnosis

- HSIL describes atypia confined above the basement membrane.
- A malignant squamous nest in cervical stroma establishes invasion.
- Correct conclusion: Invasive squamous cell carcinoma; Further extent assessment is required.



Schematic — epithelial–stromal boundary

Case: Ureteral obstruction and nodal spread

- A cervical tumor extends toward the pelvic wall and causes tumor-related hydronephrosis.
- Imaging also identifies metastatic pelvic lymph nodes.
- Question: Which category of FIGO 2018 stage is relevant, and why?

Case analysis: The stage III mechanisms

- Tumor-related hydronephrosis qualifies as FIGO 2018 stage IIIB.
- Pelvic lymph node metastasis qualifies as IIIC1 under FIGO 2018.
- The final stage designation integrates the nodal information; Identify the basis of nodal detection.

I Confined to cervix

II Beyond cervix, not pelvic wall / lower vagina

III **Lower vagina, pelvic wall, obstruction and/or nodes**

IV Bladder/rectal mucosa, beyond pelvis or distant

Cervical carcinoma: Pathology synthesis

- Most cases involve high-risk HPV-driven disruption of RB and p53 pathways.
- Invasion distinguishes carcinoma from LSIL, HSIL, and AIS.
- Squamous, glandular, mixed, neuroendocrine, and gastric-type tumors have different morphology and biology.
- Disease extent, nodal involvement, and local complications dominate staging and much of prognosis.

Primary textbook and verified supplements

- Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Female genital tract: cervical carcinoma section.
- WHO Classification of Tumours: Female Genital Tumours. 5th ed. 2020 (HPV-associated versus HPV-independent categories).
- FIGO 2018 revised cervical cancer staging; IARC/WHO World Cancer Report staging table (2018 schema).
- Historical and source-specific epidemiology and survival values are identified on relevant slides.