Cervical Neoplasms

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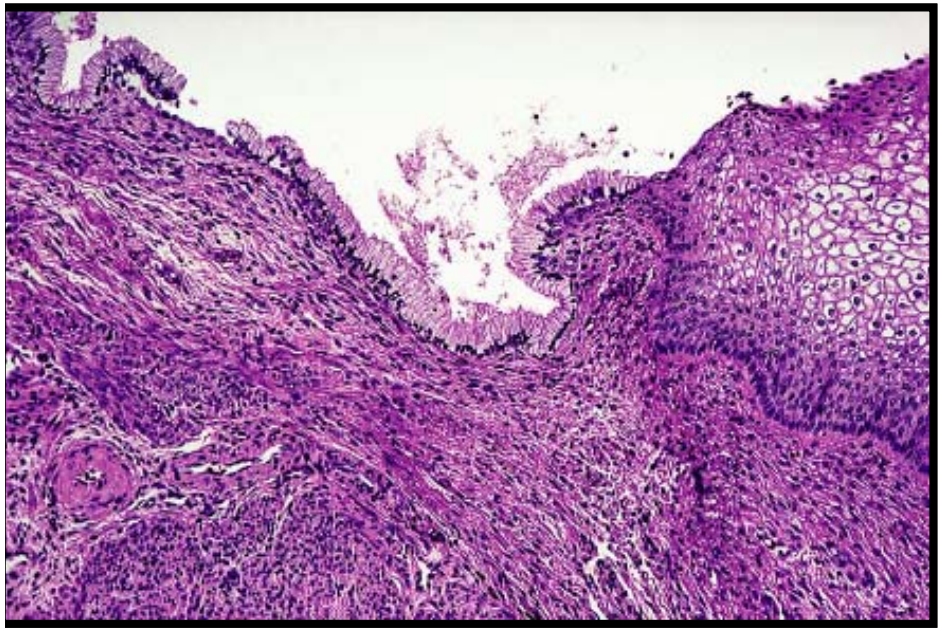
CERVIX : NORMAL HISTOLOGY



- Exocervix covered by non-keratinizing squamous epithelium.
- Endocervix lined by columnar mucus-secreting glandular cells.

Squamo-columnar junction *: the area where squamous and glandular epithelium meet. Also known as* ***transformation zone.***

HUMAN PAPILLOMA VIRUS

- HPV is the dominant factor in cervical oncogenesis.
- HPV DNA is detected in 95% of cervical cancers and precursor lesions.
- Low risk types : 6, 11, 40, 42, 44.
- High risk types : 16, 18, 31, 33, 35, 39 and others.
- Morphological hallmark of HPV infection of the cervical squamous epithelium is koilocytosis or koilocytotic atypia.

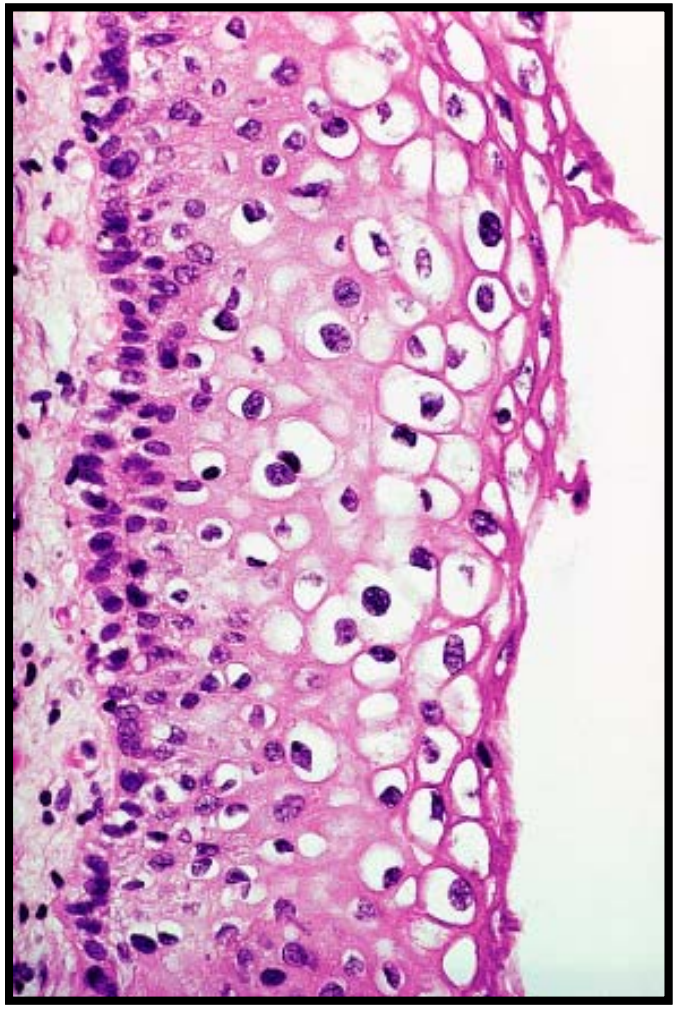
- HPVs infect immature basal cells of the squamous epithelium in areas of epithelial breaks, or immature metaplastic squamous cells present at the squamo-columnar junction.

- HPVs cannot infect the mature superficial squamous cells that cover the ectocervix, vagina, or vulva. Establishing HPV infection in these sites requires damage to the surface epithelium, which gives the virus access to the immature cells in the basal layer of the epithelium.

- Although the virus can infect only the immature squamous cells, replication of HPV occurs in the maturing squamous cells and results in a cytopathic effect, “koilocytic atypia”.

Koilocytotic atypia = HPV infection

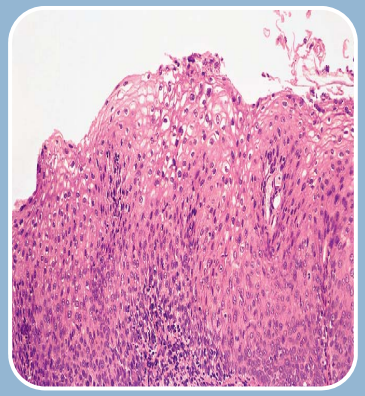
- Perinuclear vacuolation
- Dense and irregular-staining peripheral cytoplasm
- Enlarged nucleus
- Undulating nuclear membrane (raisin-like)
- Rope-like chromatin pattern
- Binucleation/multinucleation may occur



RISK FACTORS

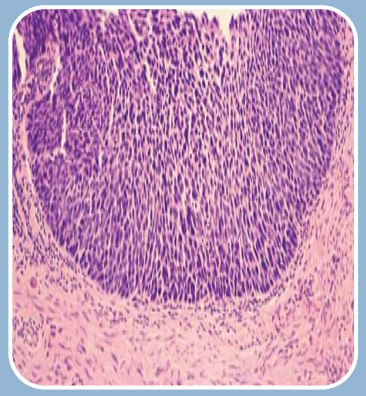
- Multiple sexual partners
- A male partner with multiple previous or current sexual partners
- Young age at first intercourse
- High parity
- Persistent infection with a high oncogenic risk HPV- HPV 16,18
- Immunosuppression
- Use of oral contraceptives
- Use of nicotine

SQUAMOUS INTRAEPITHELIAL NEOPLASIA



Low-Grade Squamous Intraepithelial Lesion

- Exophytic condyloma (condyloma acuminatum)
- Immature condyloma (squamous papilloma, papillary immature metaplasia)
- Flat condyloma (CIN I)



High-Grade Squamous Intraepithelial Lesion

- CIN II
- CIN III

CLASSIFICATION OF HPV-ASSOCIATED INTRAEPITHELIAL LESIONS OF CERVIX

Term	HPV risk category	Comparison of classification systems		
		Two-tiered CIN	Dysplasia/CIS	SIL
Exophytic condyloma	Low risk	-	-	LGSIL
Squamous papilloma	Low risk	-	-	LGSIL
Flat condyloma	Low and high risk	-	-	LGSIL
CIN I	Low and high risk	Low grade CIN	Mild dysplasia	LGSIL
CIN II	High risk	High grade CIN	Moderate dysplasia	HGSIL
CIN III	High risk	High grade CIN	Severe dysplasia / CIS	HGSIL

LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION

- Cervical cancer precursor lesion associated with both low and high-risk HPV subtypes.
- Includes exophytic, immature and flat condyloma. (CIN I)
- Peak incidence in mid-20s, decreases thereafter.
- Most commonly occurs at the transformation zone.
- Usually asymptomatic.
- Only 15% of LGSIL progress to HGSIL.

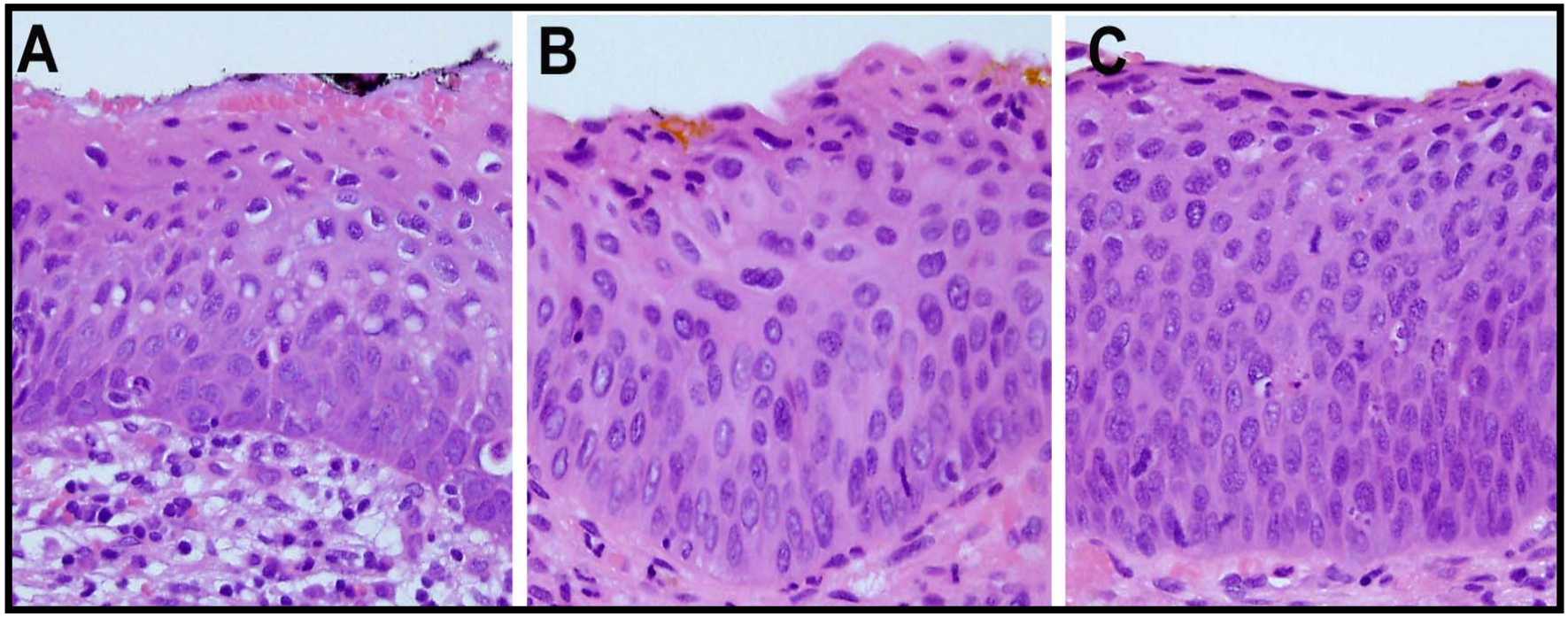
HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION

- Cervical cancer precursor lesion mainly associated with high-risk HPV subtypes.
- Includes cervical intraepithelial neoplasia II and III. (CIN II and CIN III)
- Peaks at 35–39 years, decreases thereafter.
- Predominantly occurs at the transformation zone.
- Usually asymptomatic.
- Treatment : Wide excision of transformation zone.
- If untreated, high risk of developing invasive cancer.

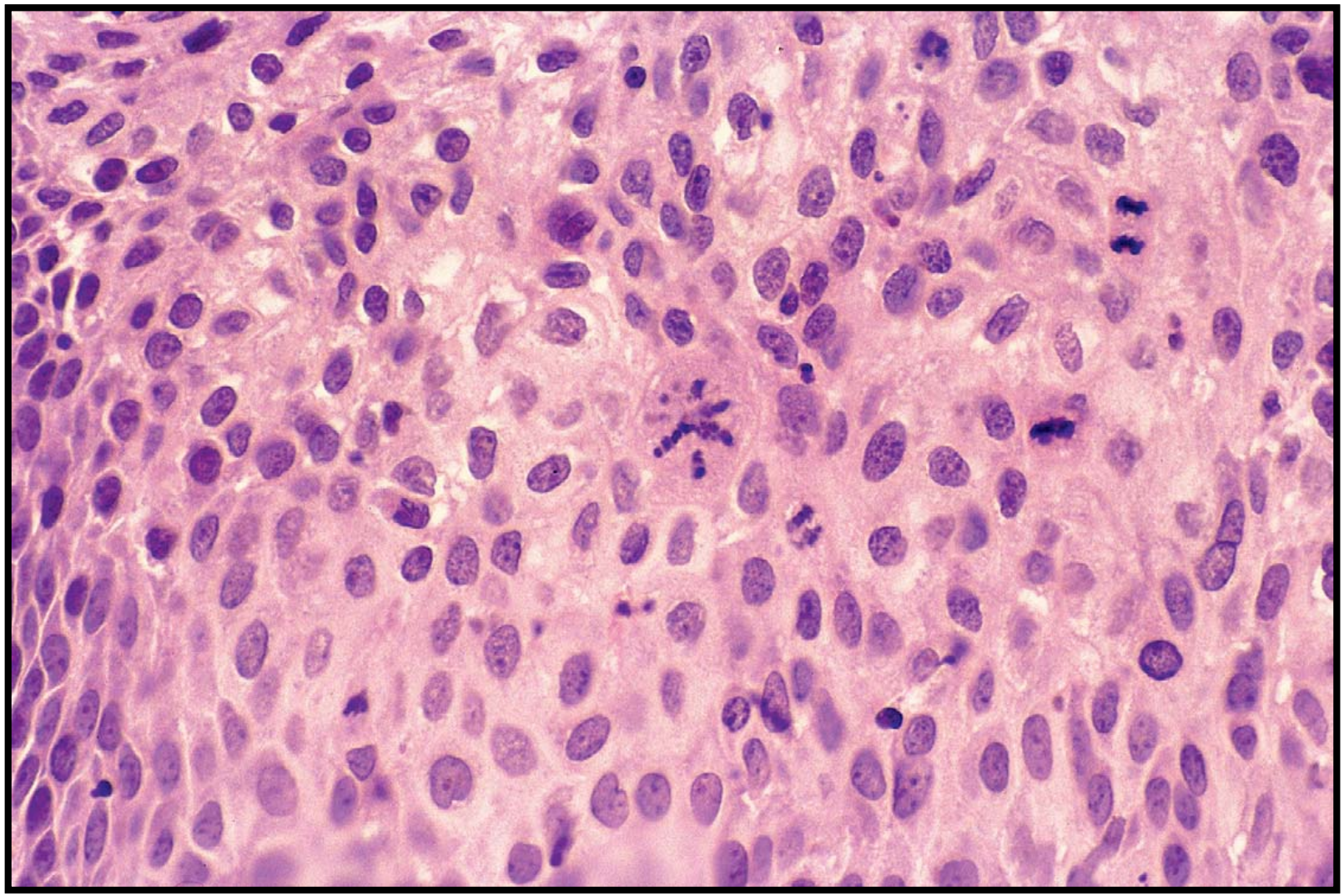
- Diagnosis of SIL is based on identification of nuclear atypia characterized by nuclear enlargement, hyperchromasia, presence of coarse chromatin granules, and variation of nuclear sizes and shapes.

- The nuclear changes may be accompanied by cytoplasmic halos indicating disruption of the cytoskeleton before release of the virus into the environment.

- The grading of SIL into low or high grade is based on expansion of the immature cell layer from its normal, basal location. If the atypical, immature squamous cells are confined to the lower one third of the epithelium, the lesion is graded as LSIL; if they expand to two thirds of the epithelial thickness, it is graded as HSIL.



CIN I CIN II CIN III



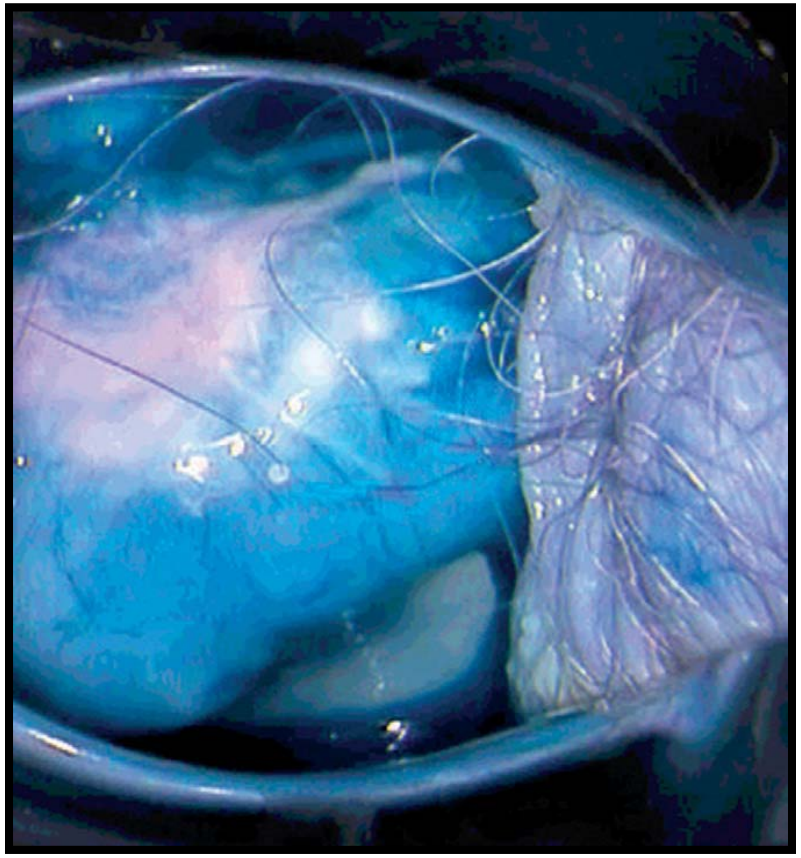
HGSIL showing prominent syncytial growth in basal layers, increased NC ratio and brisk mitotic activity. (including an abnormal form)

SQUAMOUS CELL CARCINOMA

- Cervical carcinoma is the most common malignancy of the female genital tract.
- ***Worldwide, it represents the second most common malignancy in females following breast cancer.***
- ***In developing countries, squamous cell carcinoma of the cervix is the most common cancer in women.***
- Over the past few decades, the incidence of cervical SCC has been declining in developed countries – attributable to cervical cancer screening programmes.
- ***Squamous cell carcinoma is the most common type of carcinoma of the cervix.***
- Occurs from third to fifth decades.
- Causally related to HPV infection – HPV 16 conferring the greatest risk

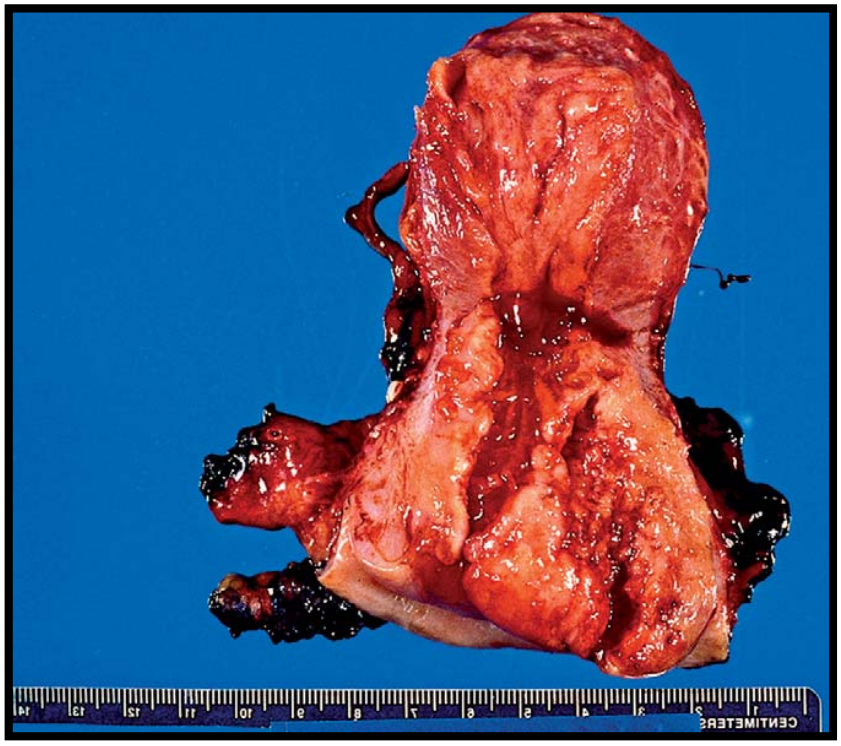
CLINICAL FEATURES

- Abnormal Pap smear in early invasive carcinoma (stage IA).
- Postcoital or intermenstrual bleeding in stage IB or higher.
- Obstructive uropathy, pain, hematuria, or rectal bleeding in advanced stages.



Squamous cell carcinoma. A large exocervical mass obliterates the exocervix on colposcopy.

GROSS FEATURES



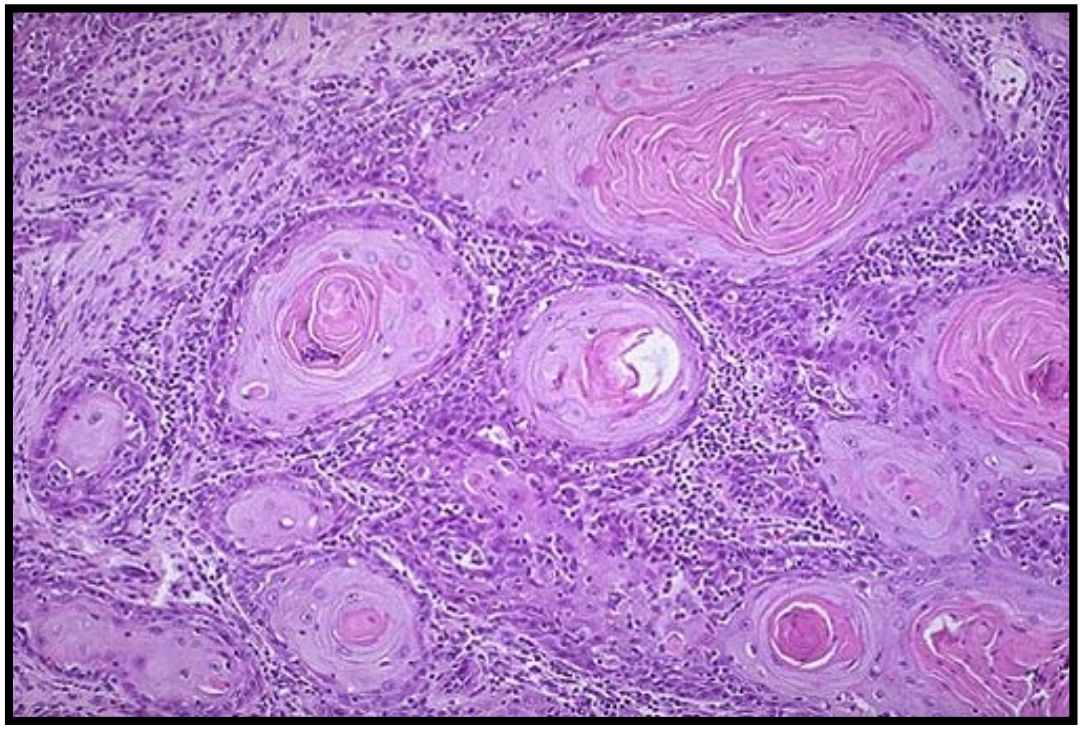
Squamous cell carcinoma. A large fungating mass is centered in the transformation zone and grows into the endocervical canal.

- Exophytic friable polypoid or papillary tumor frequently in the exocervix.
- Nodular, ulcerated, endophytic mass with extensive infiltration of the cervical wall. (Barrel cervix)
- An ulcerative lesion.

HISTOLOGICAL SUBTYPES

Large Cell Keratinizing type (well differentiated) :

- Conspicuous keratinization (keratin pearls, keratohyaline granules, nests of squamous cells with central keratinization)
- Pushing border of invasion

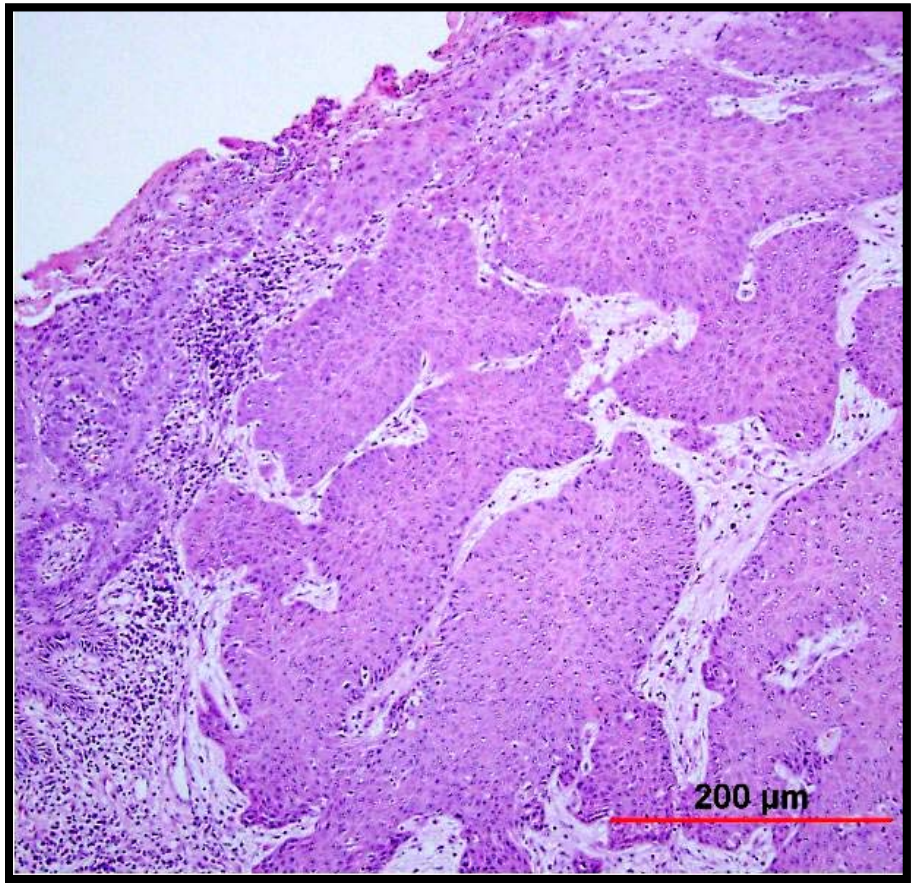


Large cell keratinizing squamous cell carcinoma

HISTOLOGICAL SUBTYPES

Large cell non-keratinizing (moderately differentiated) : *most common subtype*

- Large polygonal squamous cells with eosinophilic cytoplasm.
- Lack keratin pearl formation, keratohyaline granules.
- Individual cell keratinization may be present.
- Greater degree of nuclear pleomorphism.
- Infiltrative border associated with inflammation.

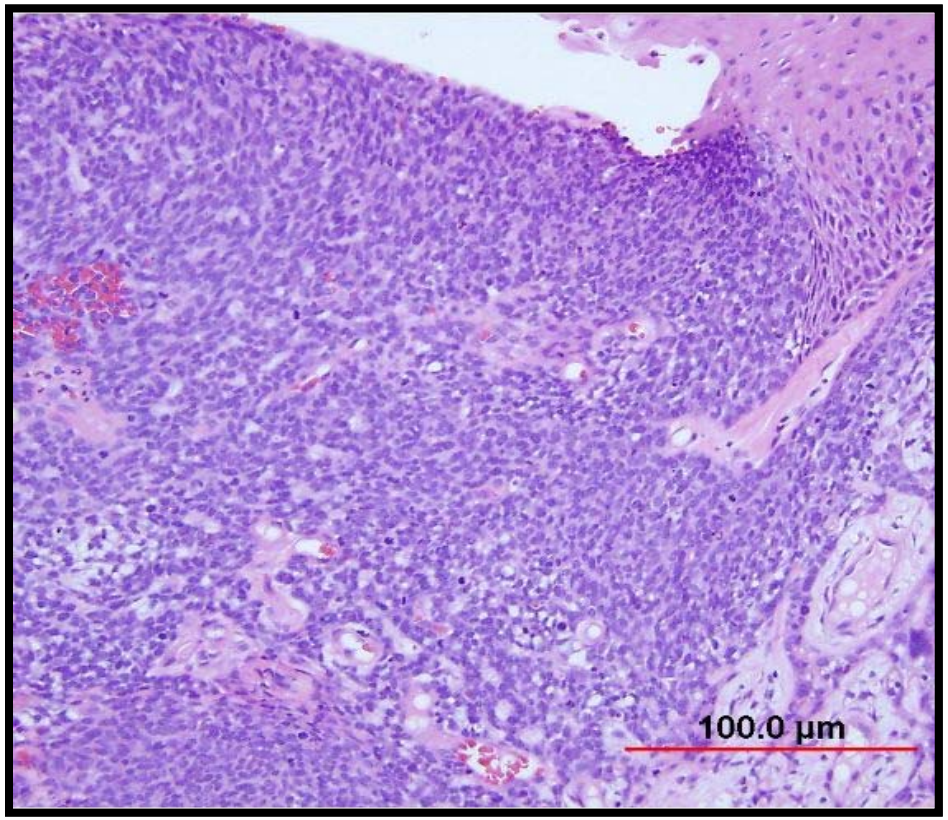


Large cell non-keratinizing squamous cell carcinoma

HISTOLOGICAL SUBTYPES

Small cell non-keratinizing (poorly differentiated) :

- Small cells with high NC ratio
- Hyperchromatic nuclei, increased mitoses.
- Minimal evidence of squamous differentiation.
- Poor prognosis



SPREAD AND METASTASES

- Direct extension : vagina, uterus (endometrium or myometrial wall), parametrium, lower urinary tract, and uterosacral ligaments
- Lymph node metastases are also common
- Haematogenous metastases : lungs and bone

STAGING OF CERVICAL CARCINOMA

Stage 0. Carcinoma in situ (CIN III, HSIL)

Stage I. Carcinoma confined to the cervix

Ia. Preclinical carcinoma, that is, diagnosed only by microscopy

Ia1. Stromal invasion no deeper than 3 mm and no wider than 7 mm (so-called microinvasive carcinoma)

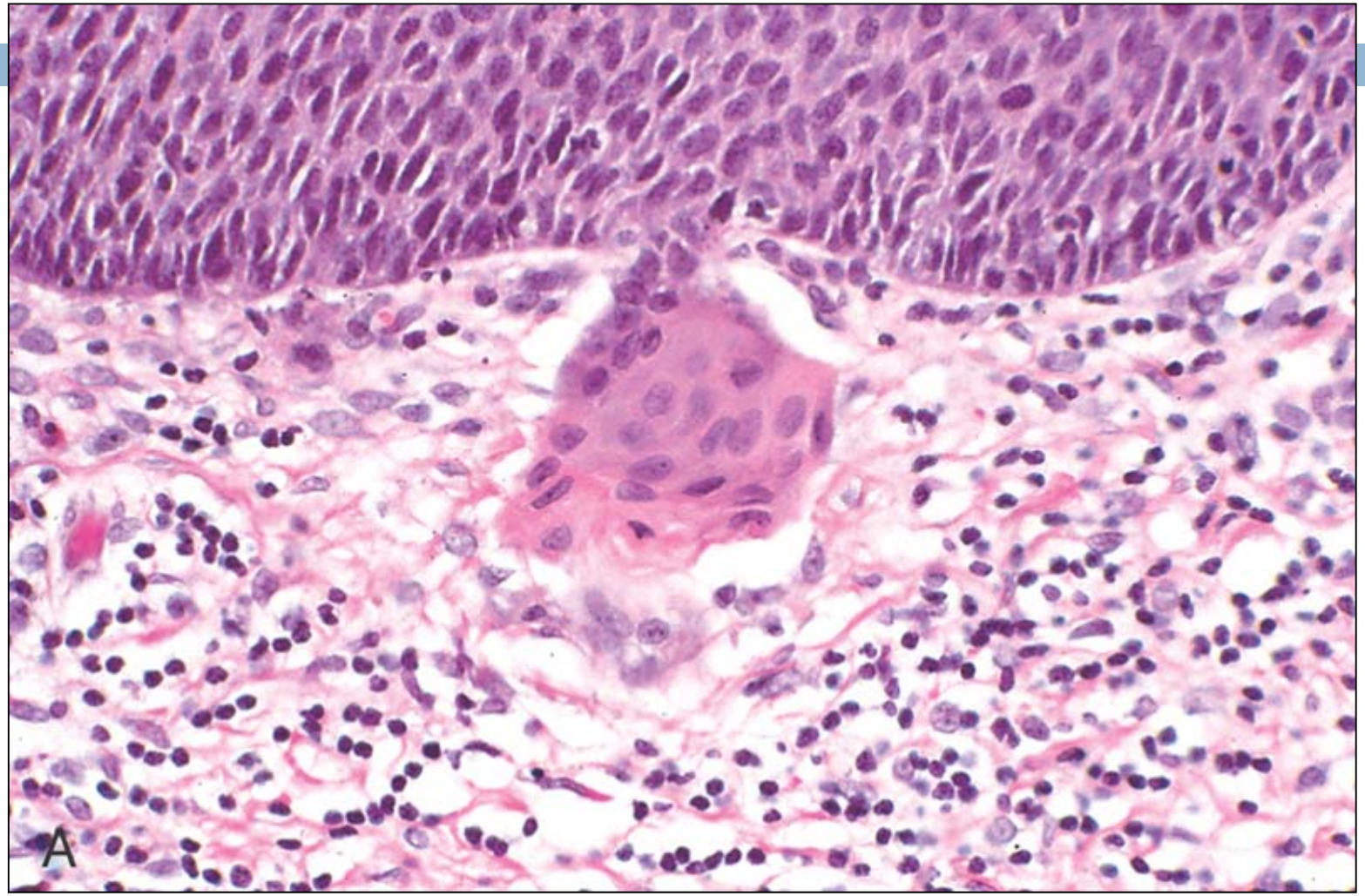
Ia2. Maximum depth of invasion of stroma deeper than 3 mm and no deeper than 5 mm taken from base of epithelium; horizontal invasion not more than 7 mm

Ib. Histologically invasive carcinoma confined to the cervix and greater than stage Ia2

Stage II. Carcinoma extends beyond the cervix but not to the pelvic wall. Carcinoma involves the vagina but not the lower third.

Stage III. Carcinoma has extended to the pelvic wall. On rectal examination there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina.

Stage IV. Carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. This stage also includes cancers with metastatic dissemination.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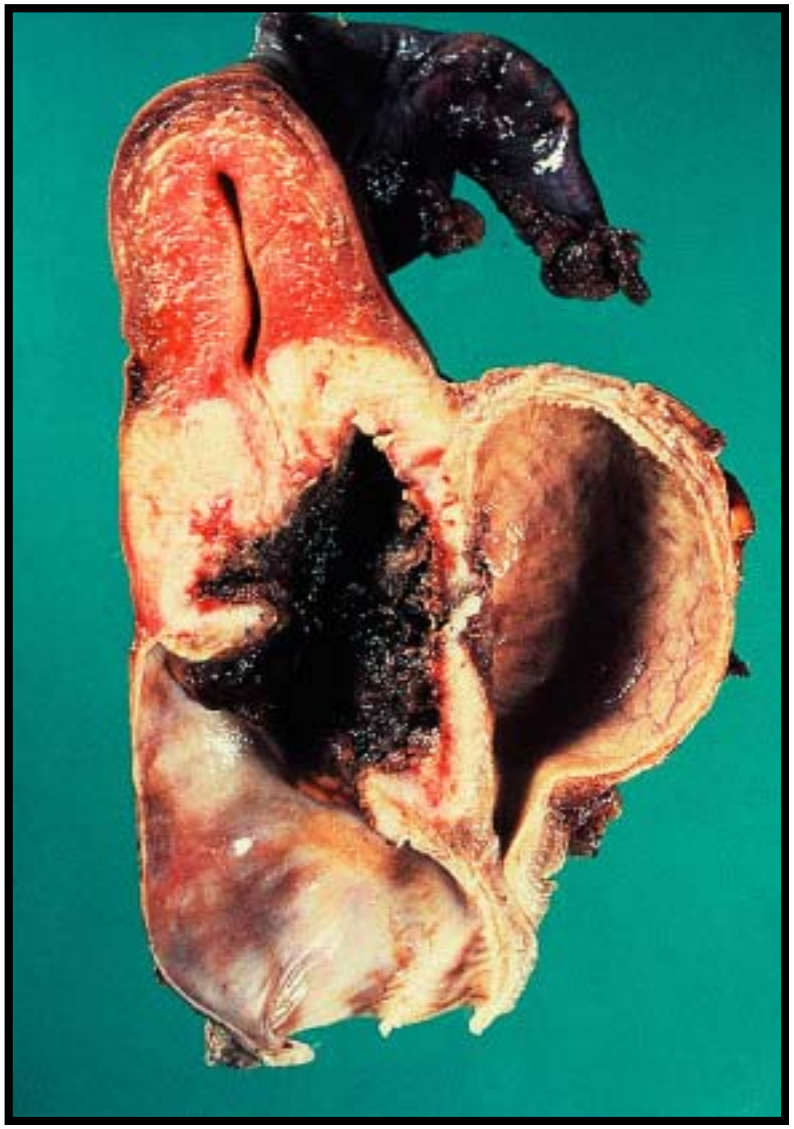
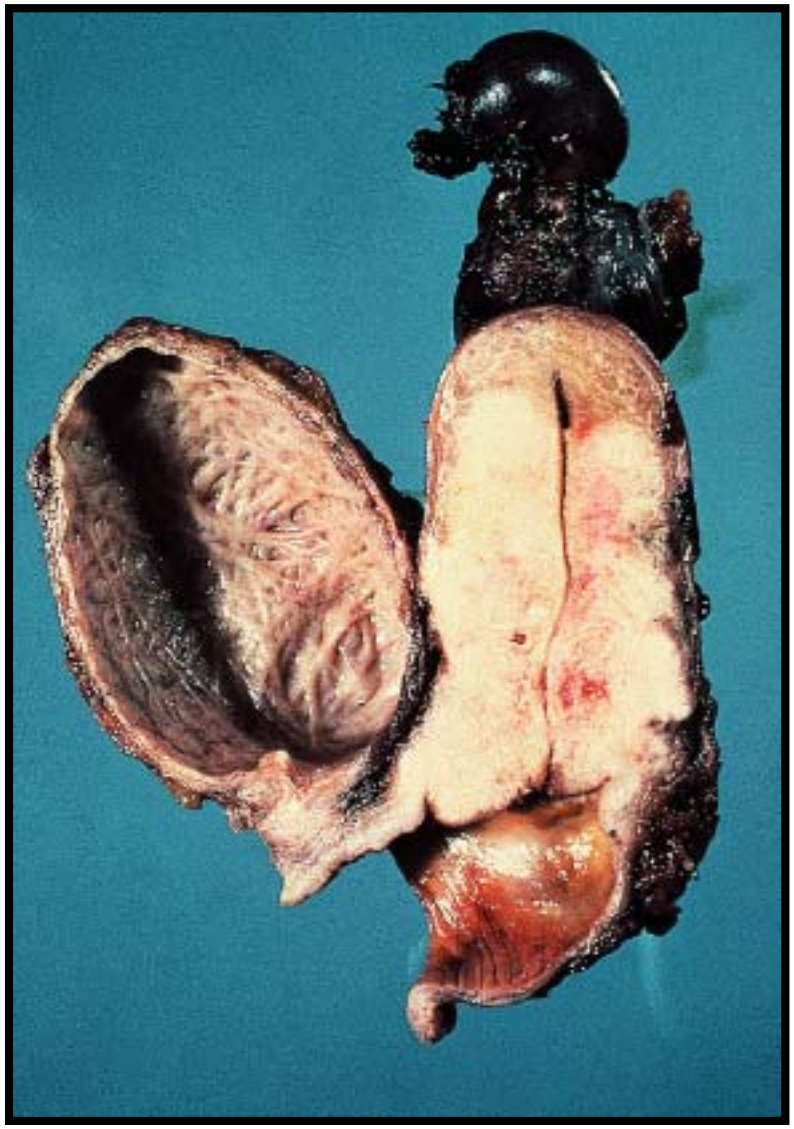
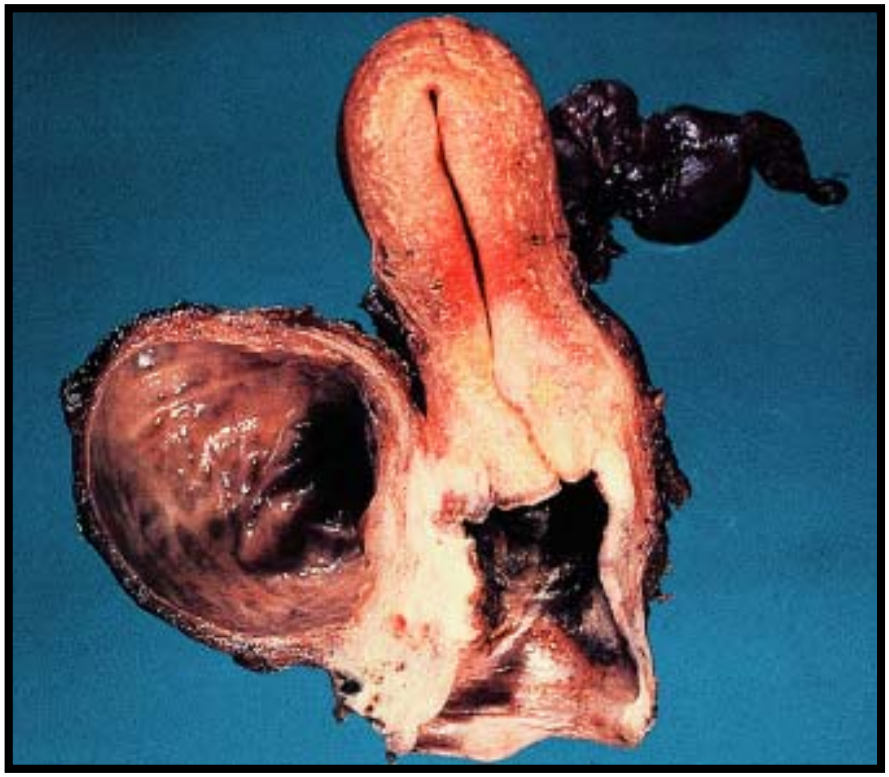


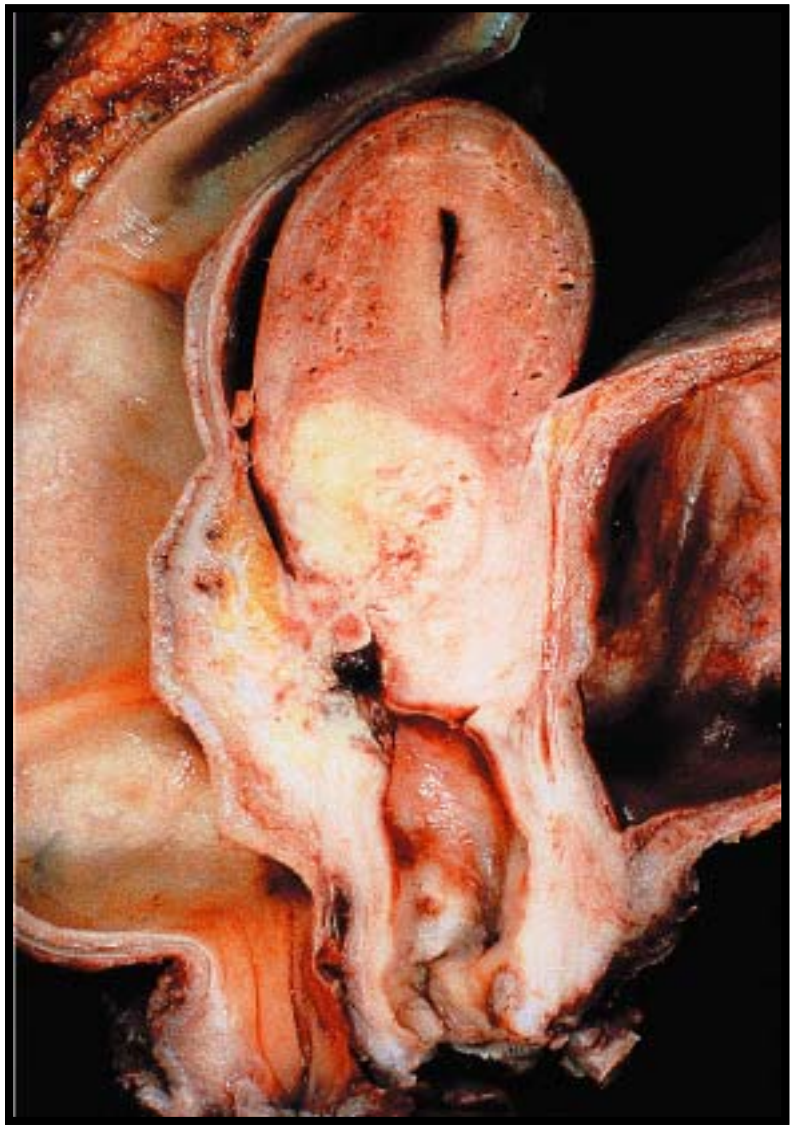
Large ulcerated tumor involving uterine isthmus and vagina



Cervical carcinoma extending into uterine corpus

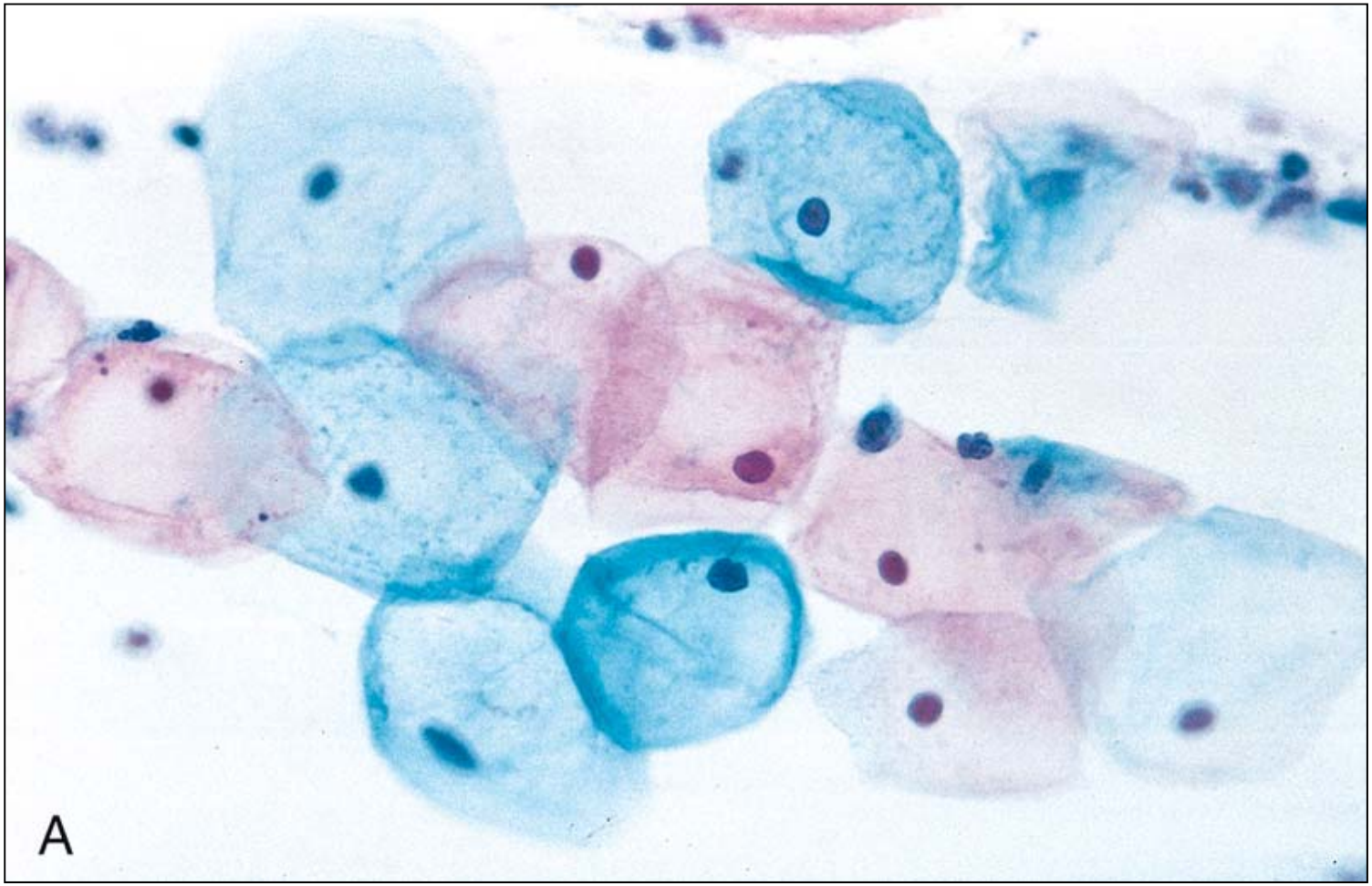


Cervical carcinoma extending into bladder

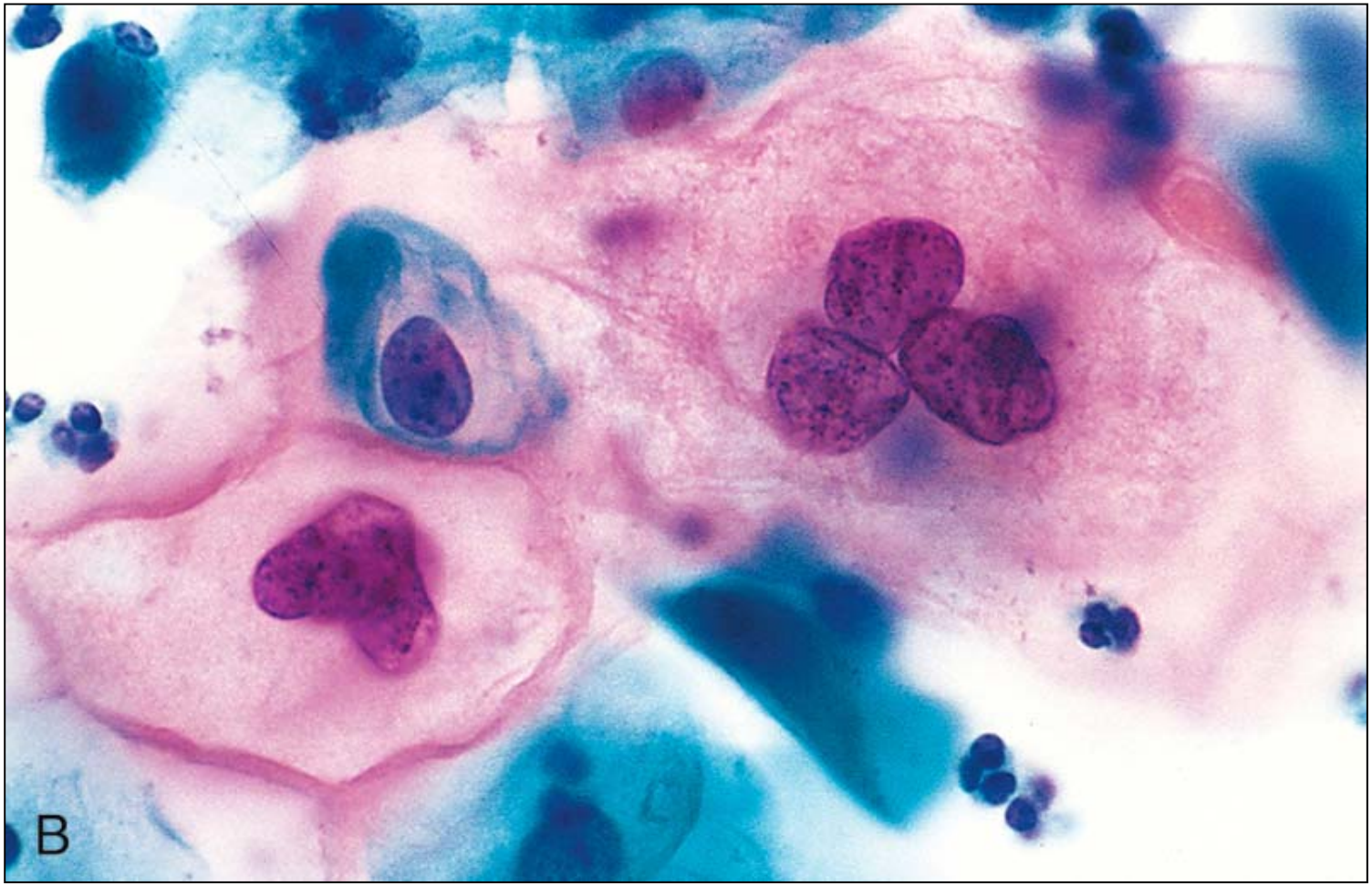


Cervical carcinoma extending into rectal wall

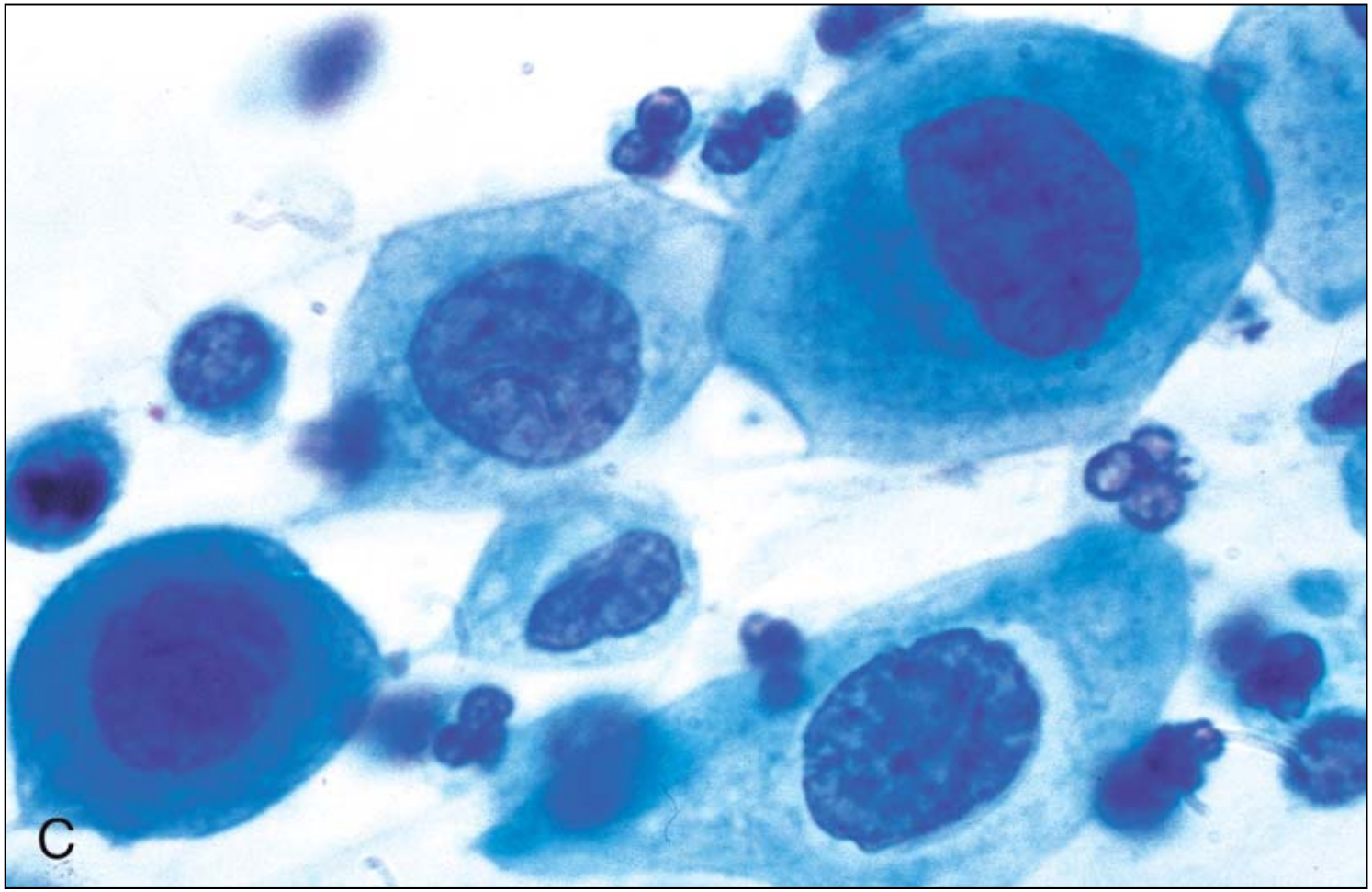
PAP SMEAR – Cervical cancer screening programme



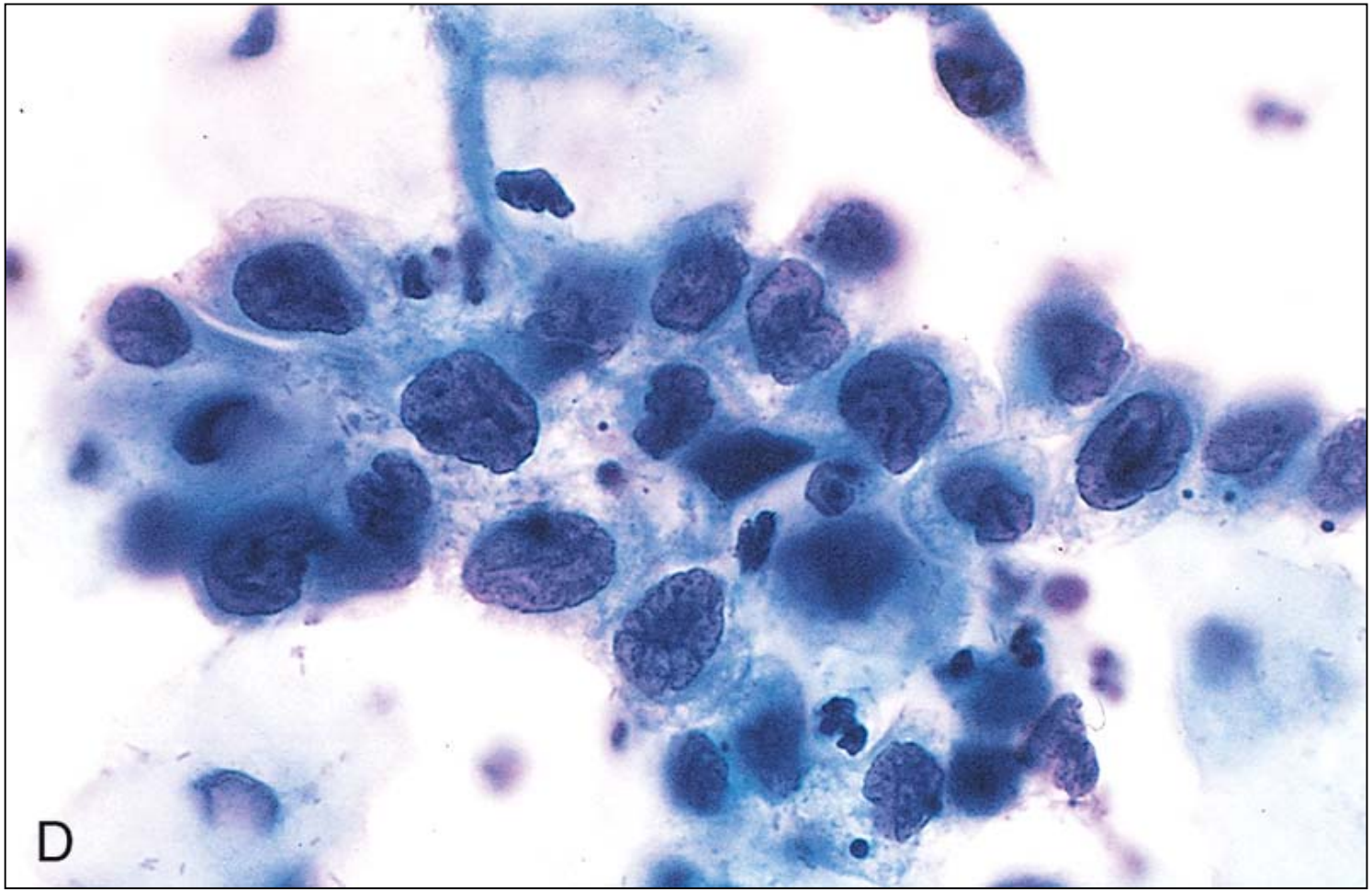
Koilocytotic atypia



HSIL



HSIL

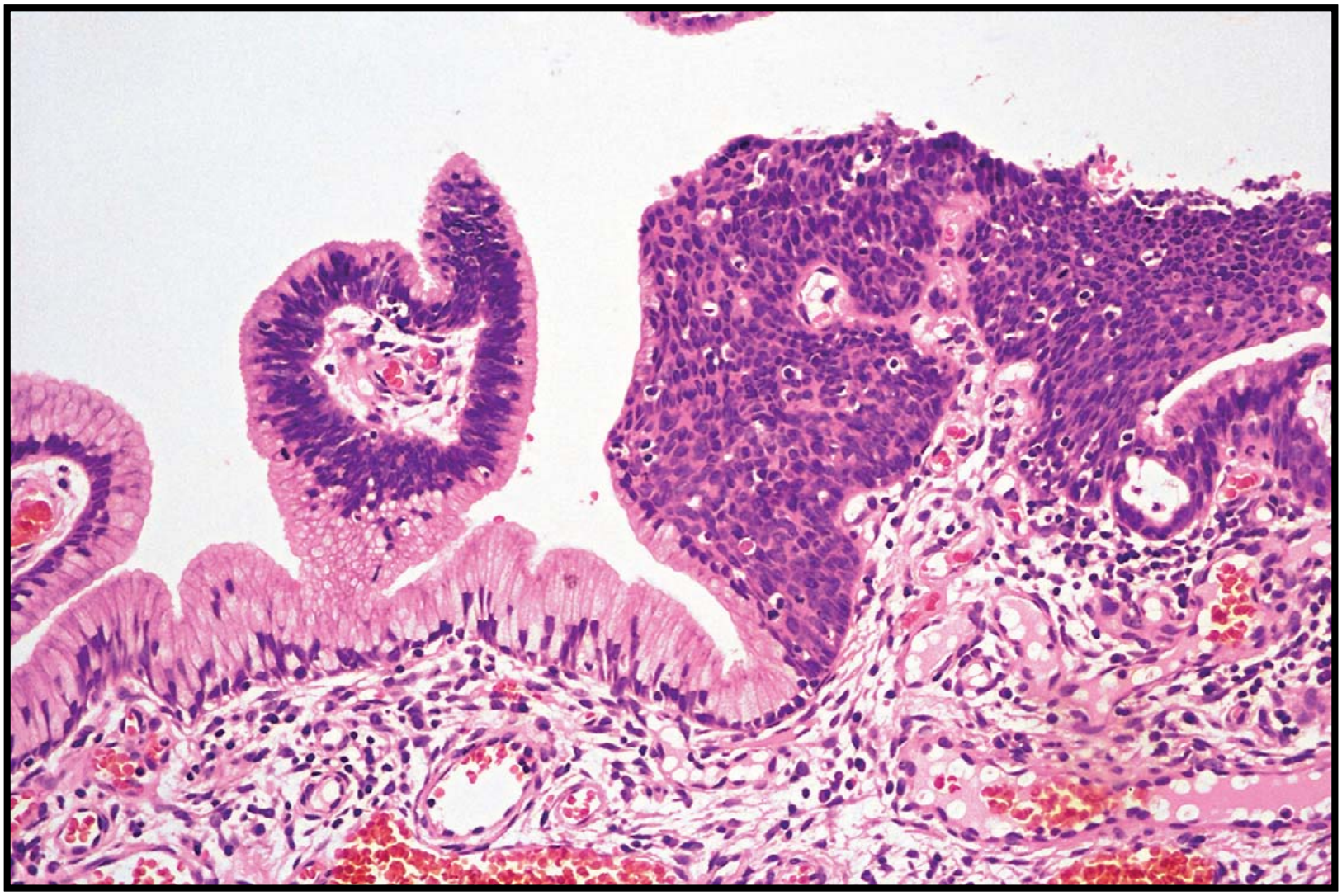


TREATMENT

- Cone biopsy for selected stage IA tumors.
- Radiotherapy or surgery (Radical Wertheim's hysterectomy) for early invasive tumors. (IB to IIA)
- Combined radiation and chemotherapy for advanced tumors.
- Tumor stage is the single most important determinant of outcome.

ADENOCARCINOMA IN SITU

- Precursor to most invasive cervical adenocarcinomas.
- Mostly occurs in young females.
- Commonly asymptomatic, may present with abnormal vaginal bleeding.
- Almost always arises at the squamo-columnar junction.
- ***In comparison to SIL's, PAP smear examination has a lower sensitivity for detecting both adenocarcinoma in situ and invasive adenocarcinoma.***



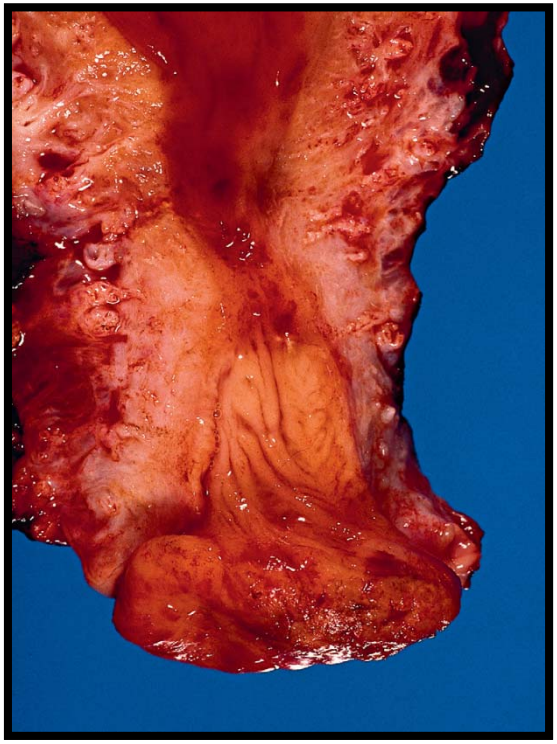
Adenocarcinoma in situ. A segment of normal glandular epithelium separates AIS (left) and HGSIL (right) involving the surface epithelium.

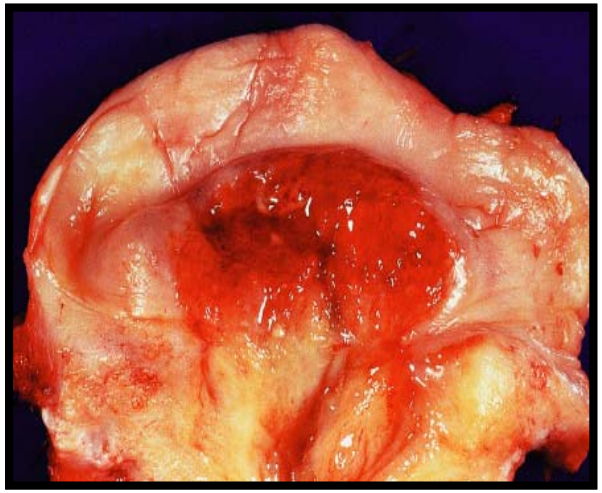
INVASIVE ADENOCARCINOMA

- Approximately 25% of all cervical carcinomas.
- ***Endocervical adenocarcinoma is the most common type. (80%)***
- Occurs in transformation zone.
- Most commonly present from 45 to 55 years.
- Clinically present with vaginal bleeding/discharge.
- Similar to slightly worse prognosis than squamous cell carcinoma.

GROSS FEATURES

- Exophytic, polypoid, or fungating mass in half of the cases
- Nodular or diffuse enlargement (barrel cervix) less frequent
- Occasionally, not grossly apparent

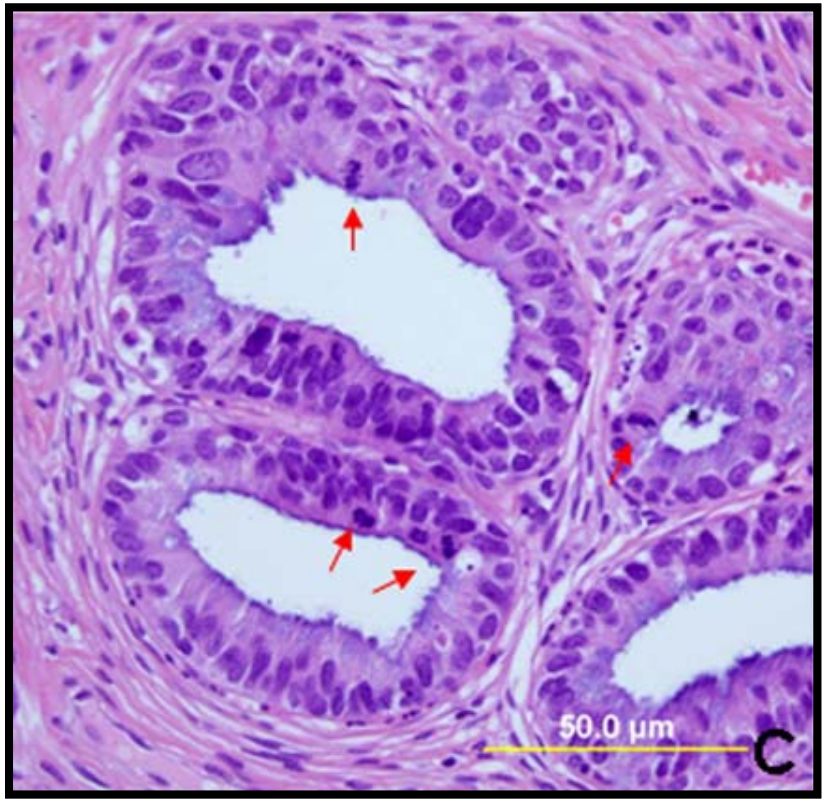




Mucinous adenocarcinoma

MICROSCOPIC FEATURES

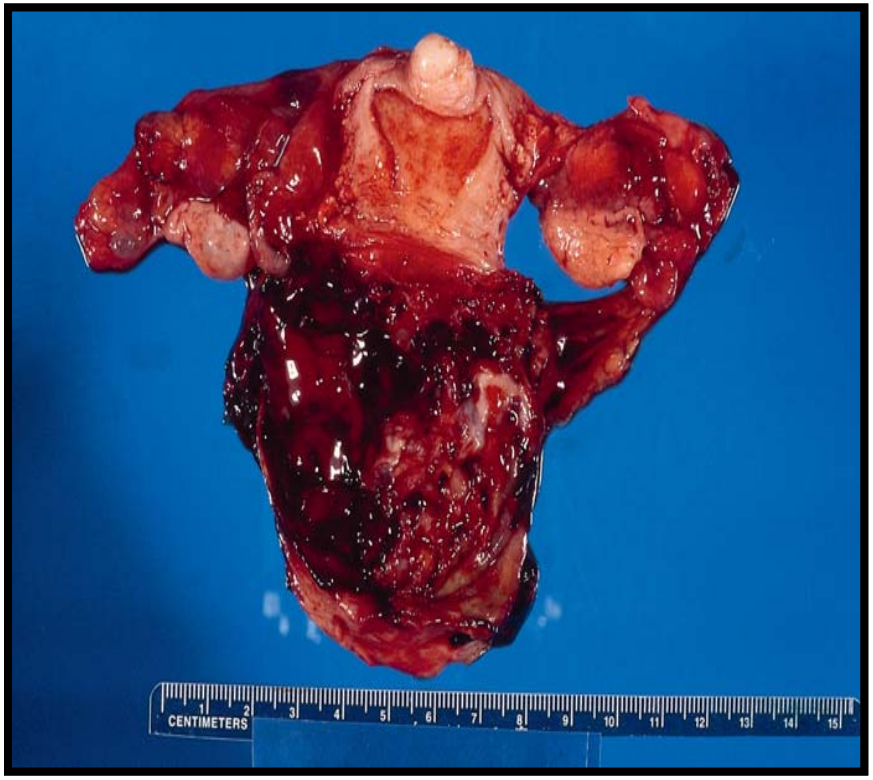
- Complex architecture with cribriform and papillary growth
- Neoplastic cells simulate endocervical epithelium
- Columnar cells with variable amount of mucinous/eosinophilic cytoplasm
- Pseudostratified, basally located atypical, enlarged nuclei
- Frequent mitoses and apoptotic bodies
- Desmoplastic stroma with occasional pools of mucin



Mucinous adenocarcinoma, endocervical type. The neoplastic glands are lined by cells with abundant mucinous cytoplasm. Mitotic figures seen.

ADENOSQUAMOUS CARCINOMA

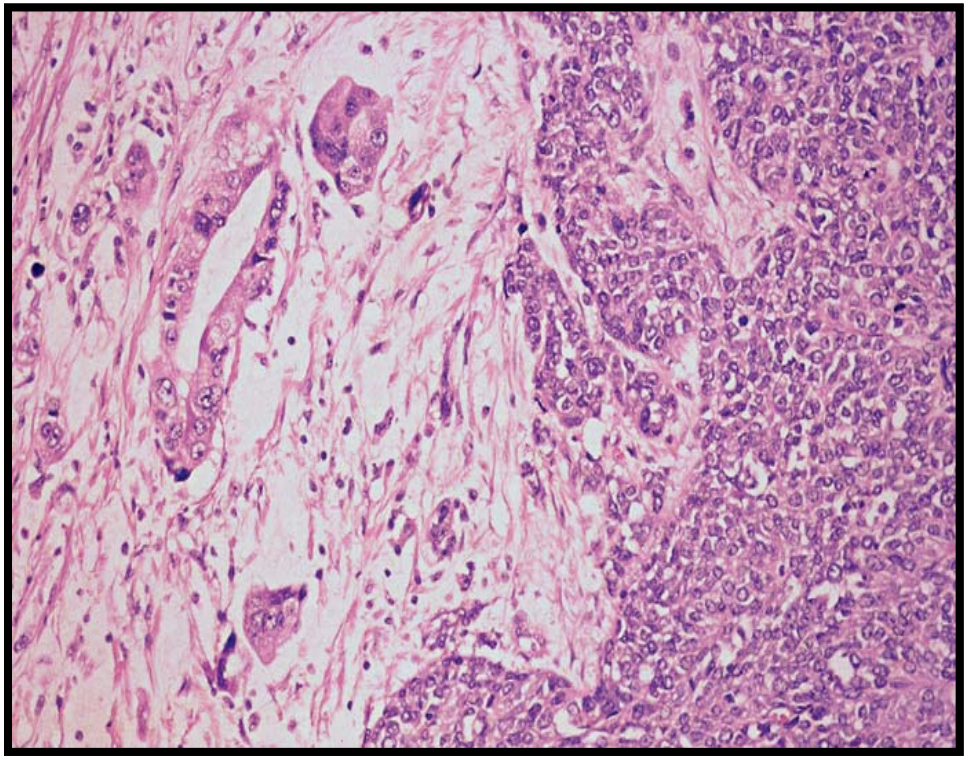
- Grossly, exophytic/ulcerating mass or nodular enlargement.
- Two histological variants :
  - Glassy cell carcinoma
  - Clear cell adenosquamous carcinoma



Adenosquamous carcinoma. A large, fungating, hemorrhagic mass occupies the cervix and extends into the lower uterine segment

MICROSCOPIC FEATURES

- Coexistence of malignant squamous and glandular elements
- Well-differentiated tumors : keratin pearls, intercellular bridges, glands showing complex patterns



Adenosquamous carcinoma. Distinct squamous (right) and glandular (left) components are seen.

SMALL CELL NEUROENDOCRINE CARCINOMA

- Poorly differentiated neuroendocrine tumor histologically similar to its pulmonary counterpart.
- Vaginal bleeding or, less frequently, paraneoplastic syndrome.
- Association with high-risk HPV, most frequently type 18.
- Poor outcome even in patients diagnosed at early stages.
- ***Highest rate of recurrence among all cervical carcinomas.***

THANK YOU