PATHOLOGY OF THE FEMALE GENITAL TRACT

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Exam questions

C/71. Diseases of vulva and vagina
C/72. Pathology of cervix
C/73. Endometritis, endometrial hyperplasia, endometriosis
C/74. Tumors of the endometrium and myometrium
C/75. Non-neoplastic diseases of the ovary and fallopian tubes
C/76. Ovarian tumors

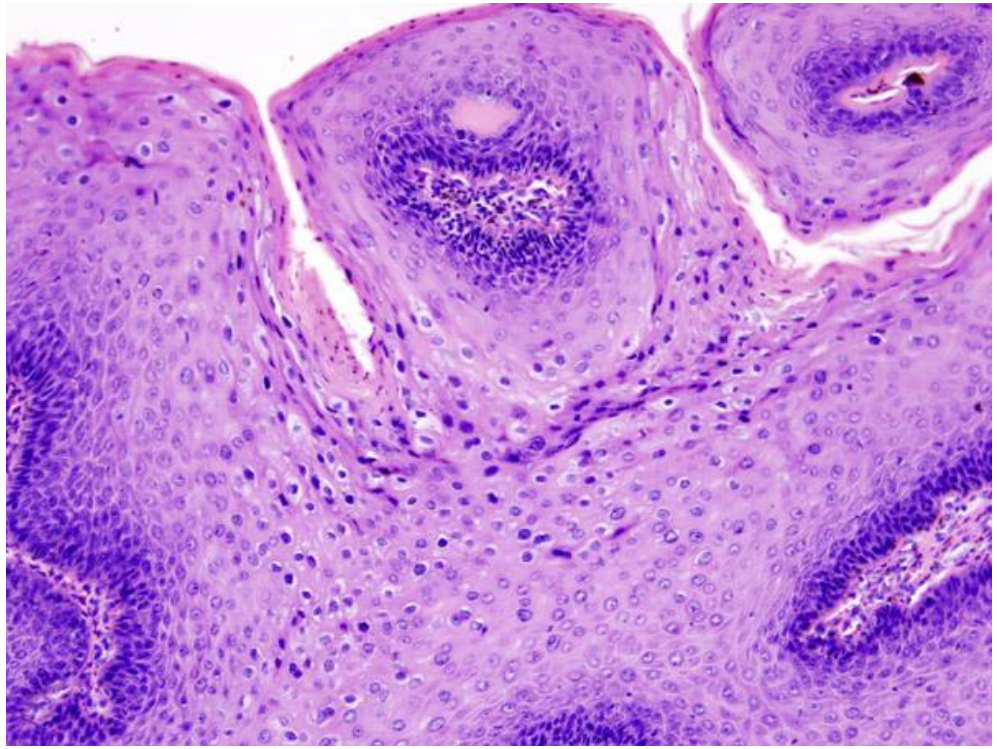
Vulva – Infectious conditions

- Bacterial
  - Syphilis (Treponema pallidum)
  - Gonorrhea (Neisseria gonorrhoeae)
  - TBC
- Viral
  - Condyloma acuminatum (HPV)
  - Herpes (HSV-1, HSV-2)
  - Molluscum contagiosum
- Fungal
  - Candidiasis

- Complication: Bartholin gland cyst, abscess (can mimic tumor)

Condyloma acuminatum (genital wart)

- Exophytic, warty lesion
- Can affect vulva, vagina, cervix, urethra, anal canal
- Cause: low-risk HPV infection (mainly HPV-6, -11)
  - →affected patients can have HPV-associated lesions elsewhere, e. g. cervix
- Often multiple lesions, can be widespread in immunosupressed patients
- Size: few mm-few cm
- Can enlarge during pregnancy
- Histology: branching fibrovascular cores, hiperkeratosis, koilocytes
- May regress, but usually slowly grows
- Doesn’t progress to HSIL or carcinoma



Inflammatory dermatoses of vulva

- Contact dermatitis
- Lichen simplex chronicus
  - Consequence of chronic irritation (scratching), epithelial thickening
- Lichen sclerosus
  - Former name: lichen sclerosus et atrophicus
  - Smooth white plaques, often starts in the clitoral area, can affect the entire vulva
  - Most common in premenarchal and postmenopausal years
  - Histology: Epithelial thinning, loss of rete ridges, dermal homogenization
  - Complications:
    - Scarring, can cause stenosis of introitus
    - Squamous cell carcinoma can arise (through dVIN – differentiated vulvar intraepithelial neoplasia)! →follow-up of patients is mandatory
- Other dermatoses can also cause white plaques (psoriasis, lichen planus, etc.) → role of biopsy!

Neoplastic diseases of vulva

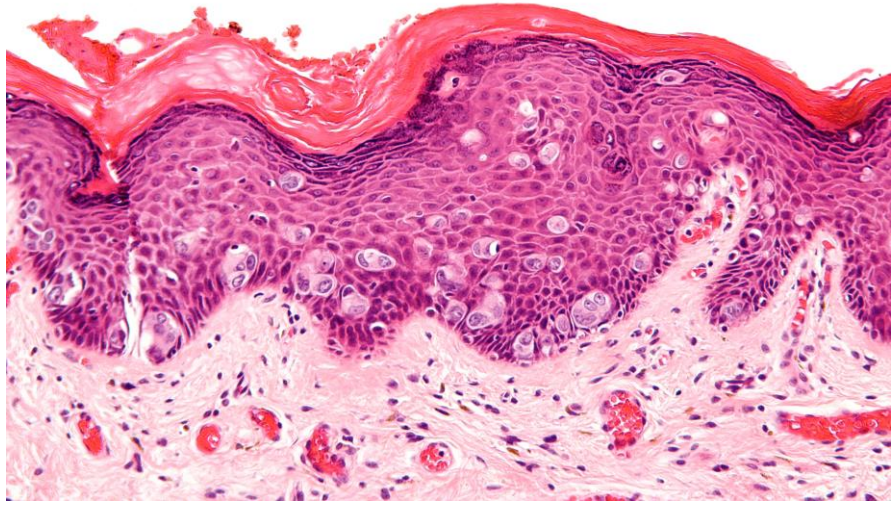
- Tumors can arise from the skin, Bartholin gland, adnexal structures, mammary-type glands, soft tissues
- Most common malignancy (~75%): squamous cell carcinoma of the skin, second most common: melanoma (8-10%)

Squamous cell carcinoma of vulva

- Two distinct pathways: HPV-related, non-HPV related
- HPV-related squamous cell carcinoma
  - Middle-aged women
  - Precursor lesion: HSIL (VIN II-III) – high risk HPV types (HPV-16)
  - HSIL slowly progresses, only a few percents will progress to carcinoma
  - Better prognosis (lower stage, less likely to have lymph node metastasis)
- Non-HPV related squamous cell carcinoma
  - Chronic irritation, inflammation predisposes – especially lichen sclerosus
  - Older age
  - Precursor lesion: differentiated vulvar intraepithelial neoplasia (dVIN)
  - dVIN has a high risk for developing into squamous cell cc., usually progresses fastly
  - TP53 mutation
  - Poor prognosis
- Regional lymph node metastases: inguinal lymph nodes

Extramammary Paget disease

- Intraepidermal proliferation of neoplastic glandular (mucinous cells)
- Can be primary or secondary
- Primary: cutaneous origin can have associated invasive component
- Secondary: origin is an underlying anal, rectal or bladder carcinoma
- Complete resection can be very challenging (usually macroscopically the borders are not distinct), recurrences are frequent
- Invasive neoplasm can develop from longstanding primary Paget disease

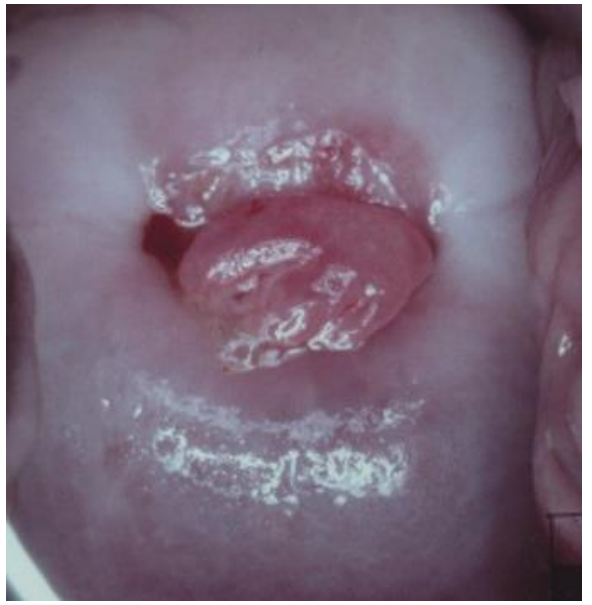


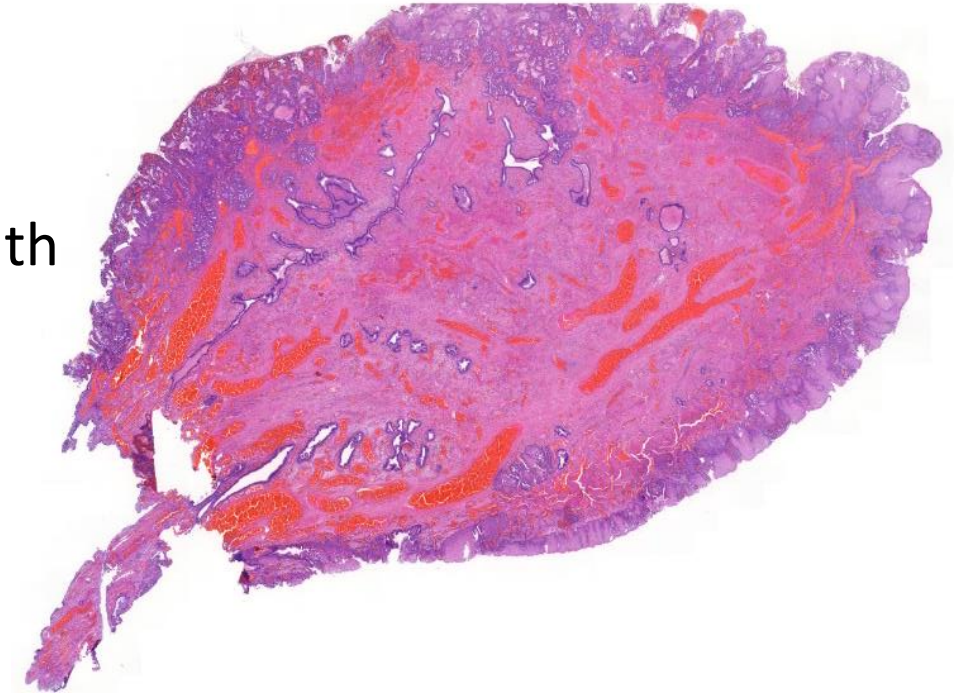
Vagina

- Vaginitis
  - Common, causes vaginal discharge
  - Frequent causes: Candida albicans, Trichomonas vaginalis
- Malignant neoplasms
  - Squamous cell carcinoma (80%)
    - Primary vaginal squamous cell carcinoma is uncommon
    - Vast majority is HPV-associated
    - Precursor lesion: HSIL/VaIN II-III – caused by high risk HPV types
  - Clear cell adenocarcinoma
    - Very rare, has historic significance
    - In utero DES (diethylstilbestrol) exposure increased the risk (DES is not used in pregnancy since 1971)
    - DES-associated tumors form in young girls and women
  - Embryonal rhabdomyosarcoma
    - Polypoid tumor, in young children (sarcoma botryoides)
    - Most common malignant neoplasm of vagina in young children (90% of cases: below 5 years of age)

Cervix

- Cervicitis
  - Extremely common
  - Infectious (Chlamydia trachomatis, N. gonorrhoeae, Trichomonas vaginalis) or non-infectious (chemical, mechanical) cause
  - Chronic or acute – acute cervicitis can result in purulent discharge
- Endocervical polyp
  - Common, usually small, but can reach large size
  - Histology: endocervical glands, endocervical stroma with thick-walled vessels





Neoplastic diseases of the cervix

- Most tumors are of epithelial origin and caused by HPV
- HPV associated lesions:
  - HPV has a tropism for the immature squamous cells in the transfomation zone
  - Majority of HPV infections are only transient
  - A minority can persist and progress to squamous cell carcinoma
  - The term Cervical Intraepithelial Neoplasia (CIN) is used for the spectrum of HPV-associated squamous lesions (similar to other regions – vulva: VIN, vagina: Vain, penis: PeIN, anus: AIN)
  - Modern terminology: LSIL (low-grade squamous intraepithelial lesion), HSIL (high-grade squamous intraepithelial lesion)
  - Low-risk (6, 11) and high-risk (16, 18) HPV-types
  - Infections with high-risk types are more likely to persist →can integrate into the host cell genom (E6 and E7 oncoproteins inhibit Rb1 and p53 → increases cell proliferation)
  - Low-risk types don’t integrate to the host cell genom

Neoplastic diseases of the cervix

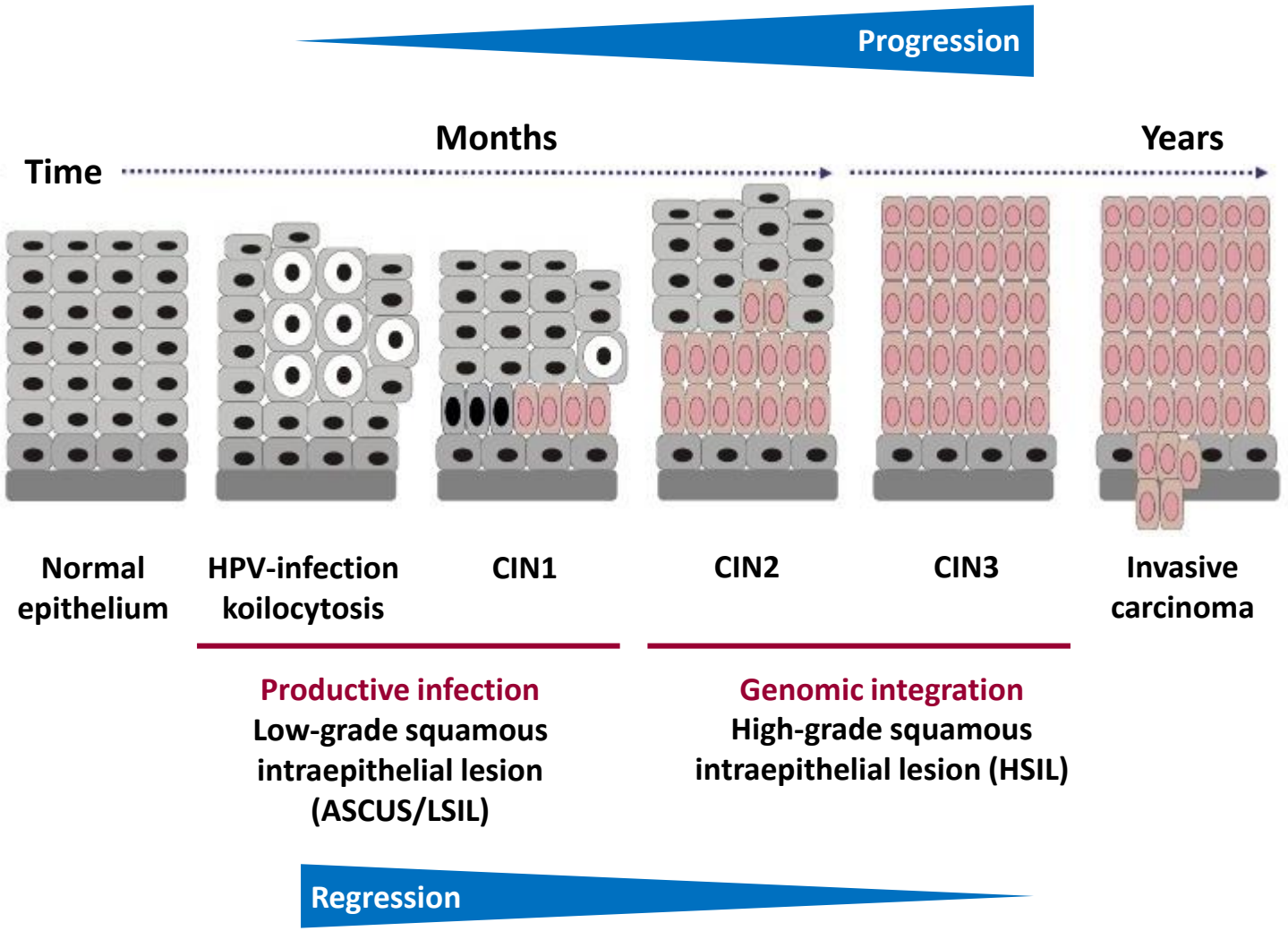
Risk factors for cervical cancer

- Early sexual activity
- High number of sexual partners
- HPV-infected partner
- Immunosuppression
- Smoking
- Other sexually transmitted diseases

- HPV can induce malignant neoplasms, mainly squamous cell carcinomas in other regions: vulva, vagina, penis, anus, oral cavity, sinonasal tract, larynx

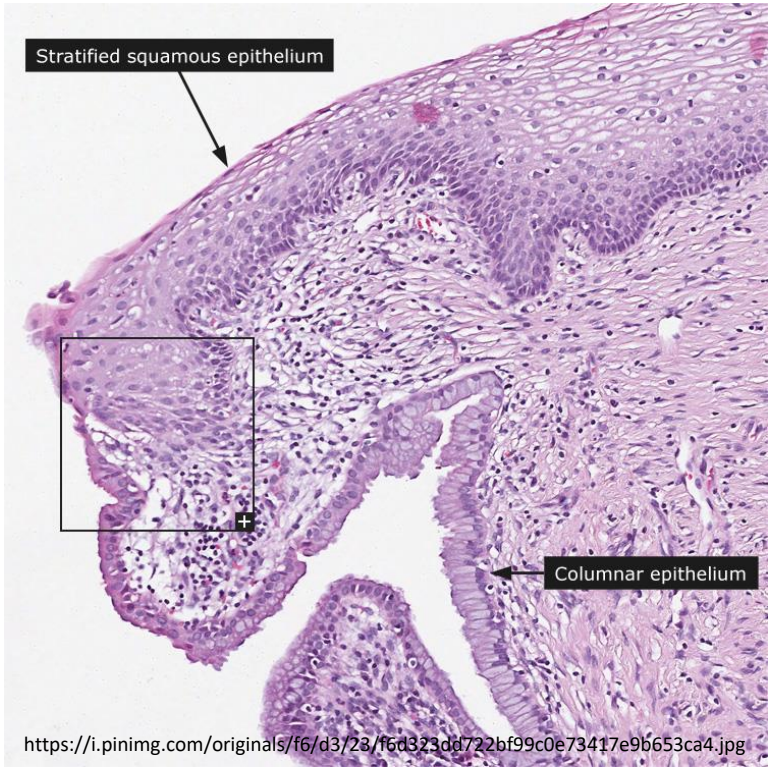
- Screening!! Papanicolau (Pap) smear
- Prevention: Vaccination

Neoplastic diseases of the cervix



Older classification	CIN Classifiaction	Bethesda classification
Mild dysplasia	CIN1	LSIL
Moderate dysplasia	CIN2	HSIL
Severe dysplasia	CIN3	
Carcinoma in situ		

Normal cervix



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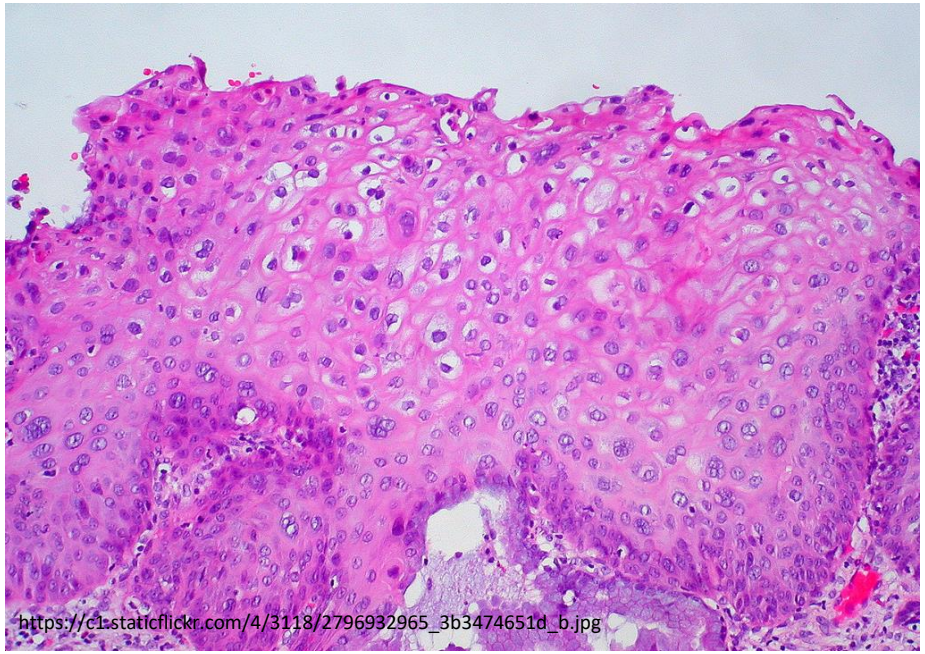
Low-grade SIL (LSIL)
CIN-1; koilocytosis!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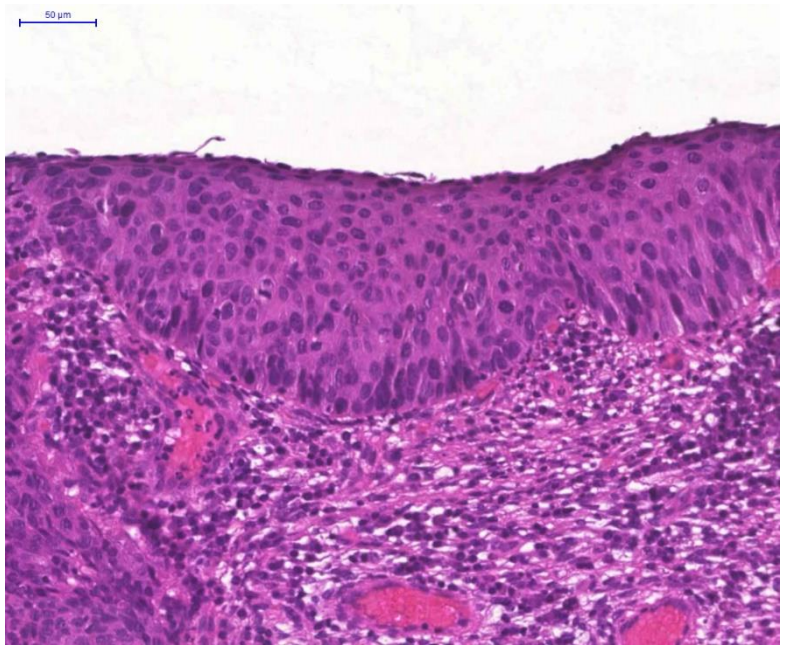
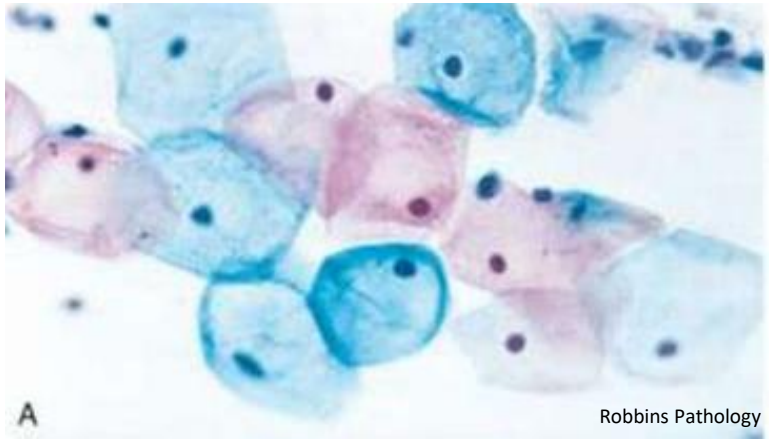
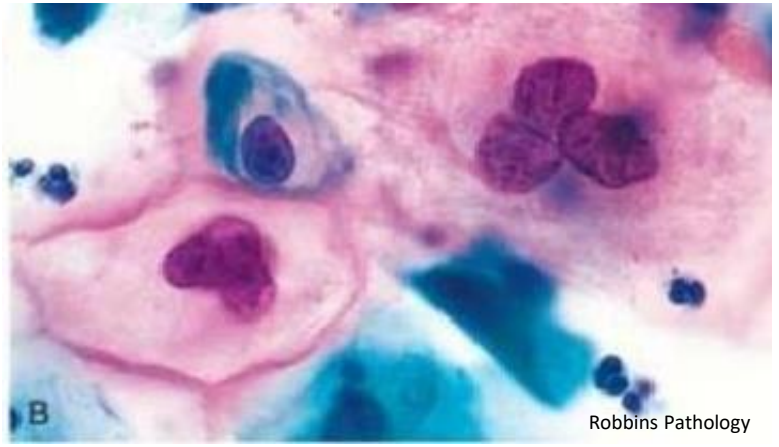
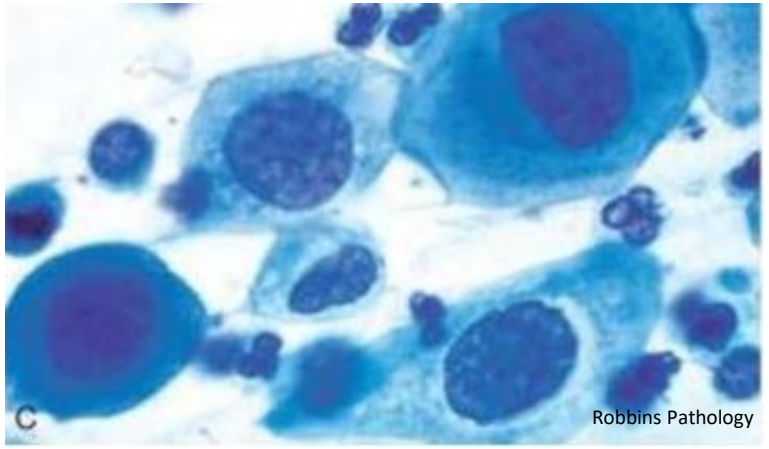
High-grade SIL (HSIL)
CIN-2, CIN-3; (in situ cc.)







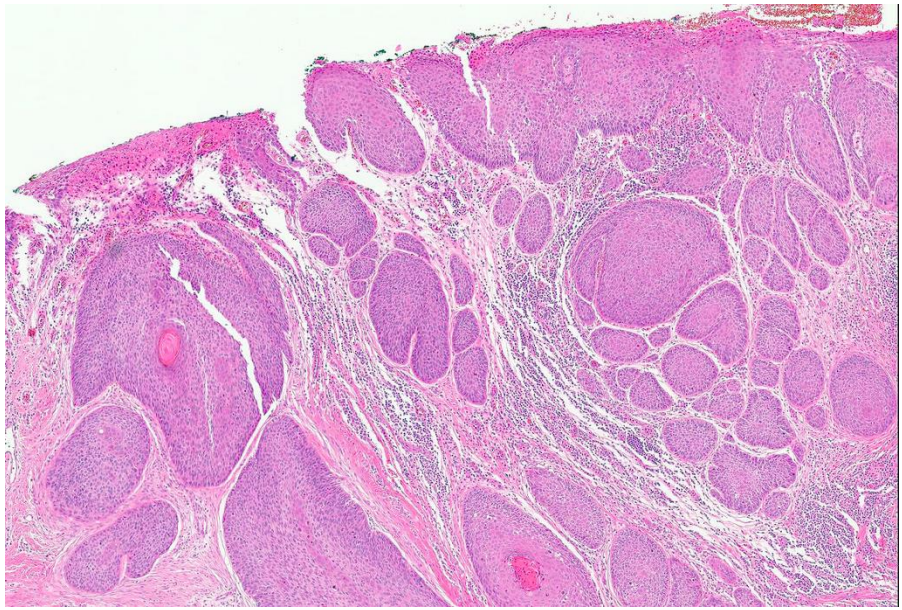


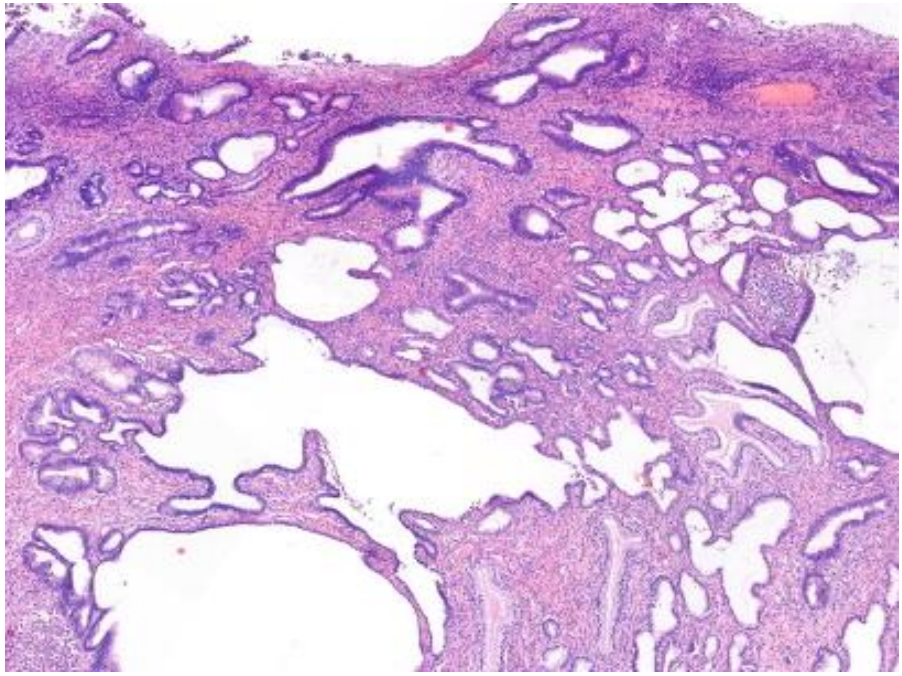
Papanicolaou smear

Neoplastic diseases of the cervix

Invasive carcinoma of cervix

- Squamous cell carcinoma (75%)
  - Virtually every case is HPV-associated, arises from HSIL
  - Peak incidence: 45 years
  - Cytologic diagnosis of HSIL → cone biopsy!
  - Advanced tumors can cause pain, bleeding, painful intercourse
  - Important risk factor: depth of invasion
- Adenocarcinoma (20%)
  - Majority is HPV-associated – precursor: in situ adenocarcinoma
  - Non HPV-related adenocarcinomas (clear cell, mesonpehri, gastric-type) are agressive
- Neuroendocrine carcinoma (5%)
  - Caused by high-risk HPV-types





Uterine corpus

- Abnormal uterine bleeding
- Diseases of endometrium:
  - Endometritis
  - Endometrial polyp
  - Endometrial hyperplasia
  - Endometrial carcinoma
- Adenomyosis
- Tumors of myometrium

Uterine corpus

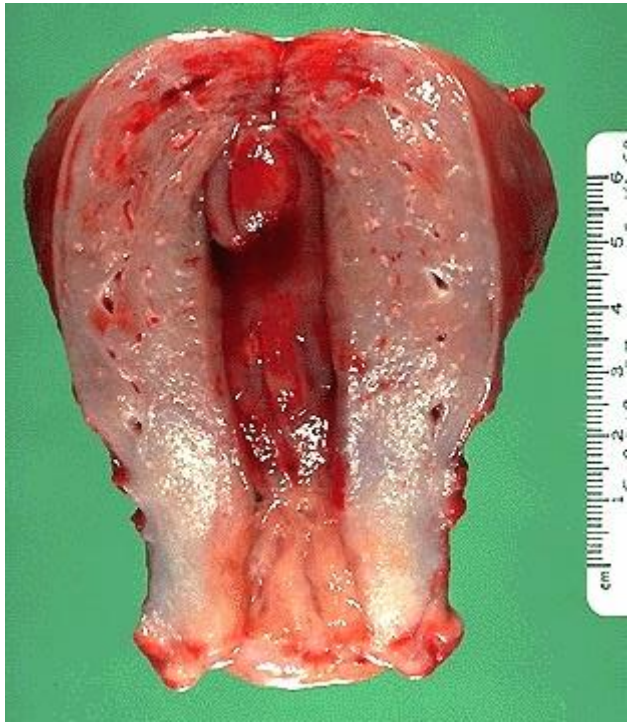
- Abnormal uterine bleeding
  - Menorrhagia – heavy menstrual bleeding
  - Metrorrhagia – abnormal bleeding independent of menstruation
  - Postmenopausal bleeding
- Causes of abnormal uterine bleeding:
  - Specific causes: Leiomyoma, endometrial polyp, adenomyosis, endometritis, endometrial hyperplasia, carcinoma
  - If no specific cause: dysfunctional uterine bleeding
    - Reason is usually endogenous hormonal imbalance (anovulatory cycle or inadequate luteal phase)
- Abnormal uterine bleeding is an indication for histological sampling (curettage)

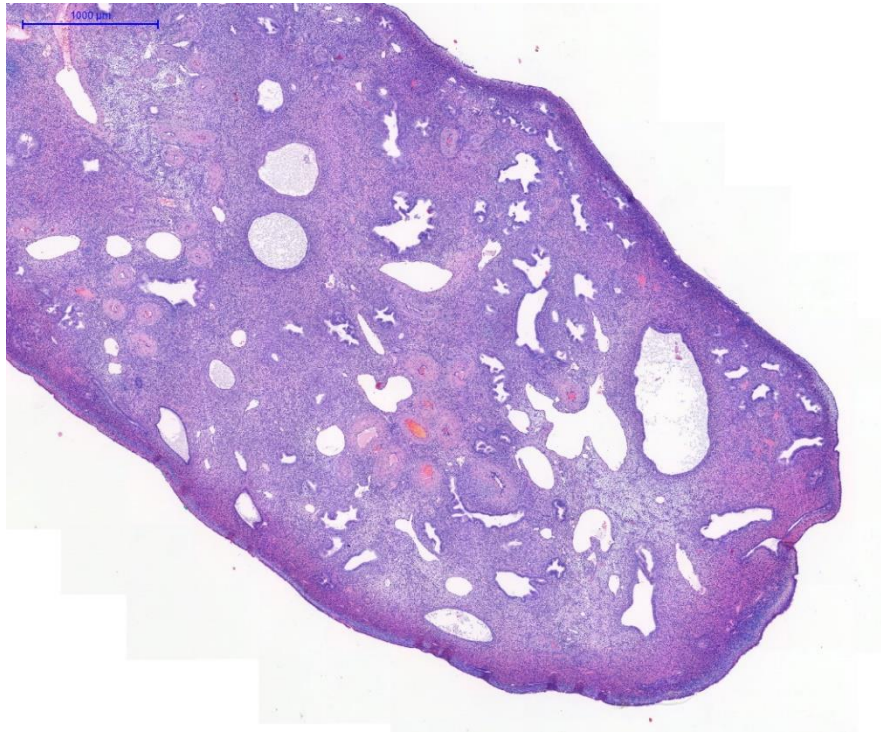
Uterine corpus

- Endometritis
  - Can be acute or chronic (presence of plasma cells)
  - Acute endometritis can be the compliation of pelvic inflammatory disease (N. gonorrhoeae, C. trachomatis)
  - Long-standing IUD use predisposes to Actinomyces endometritis
  - Retained products of conception also predispose to acute endometritis
  - Complications: acute endometritis - fever, sepsis (rare)
    chronic endometritis – scarring, infertility

Proliferative lesions of the endometrium

- Endometrial polyp
  - Usually sessile, can be large
  - Most common in perimenopausal years, can cause bleeding
  - Rarely atypical hyperplasia or carcinoma can develop in the polyp



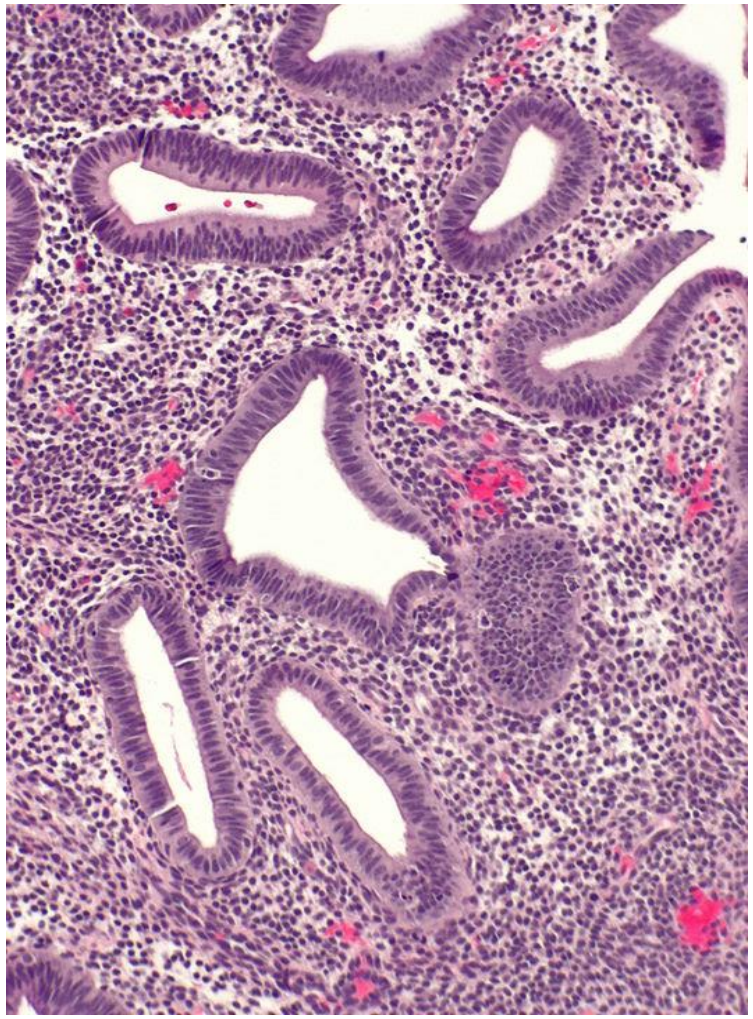


Proliferative lesions of the endometrium

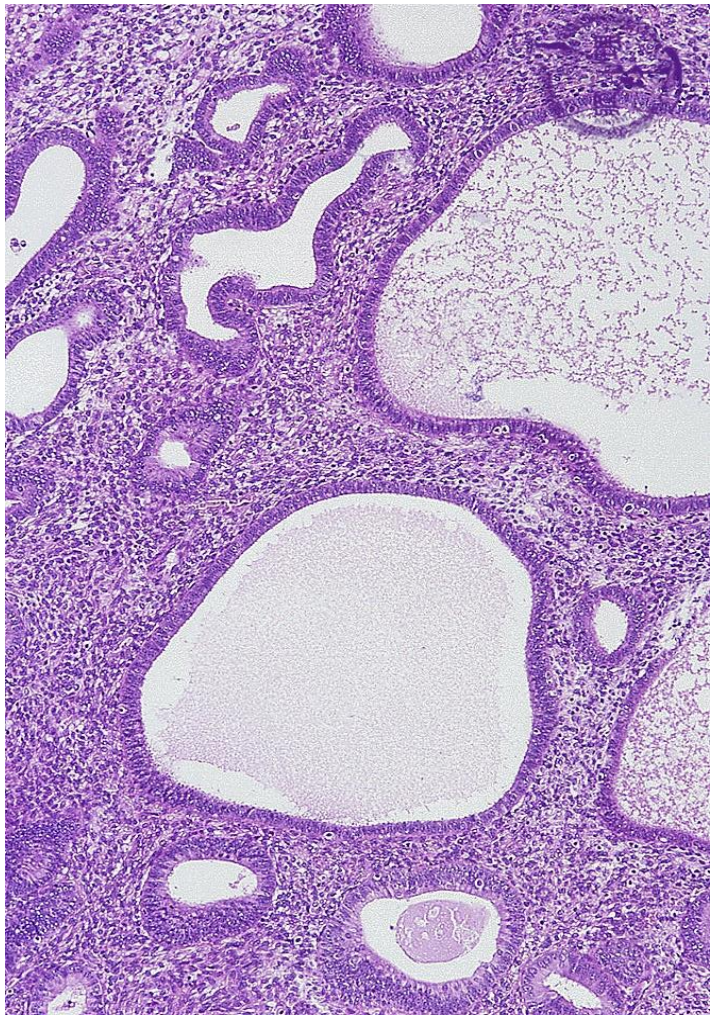
- Endometrial hyperplasia
  - Background: prolonged relative excess of estrogen to progestin
  - Normal endometrium →disordered proliferation → endometrial hyperplasia
  - Causes: obesity, anovulatory cycles, exogenous estrogen administration, estrogen-producing ovarian lesions (polycystic ovary, granulosa cell tumor)
  - Can cause bleeding
  - Important histological distinction: Hyperplasia **without** atypia, hyperplasia **with** atypia
  - Hyperplasia without atypia: low risk (1-3%) of progression to carcinoma
  - Hyperplasia with atypia = EIN (endometrioid intraepithelial neoplasia)
    - Risk of malignant transformation (endometrioid adenocarcinoma): 20-50%
    - Indicates hysterectomy (or high-dose progestin therapy in young patients)

Proliferative lesions of the endometrium

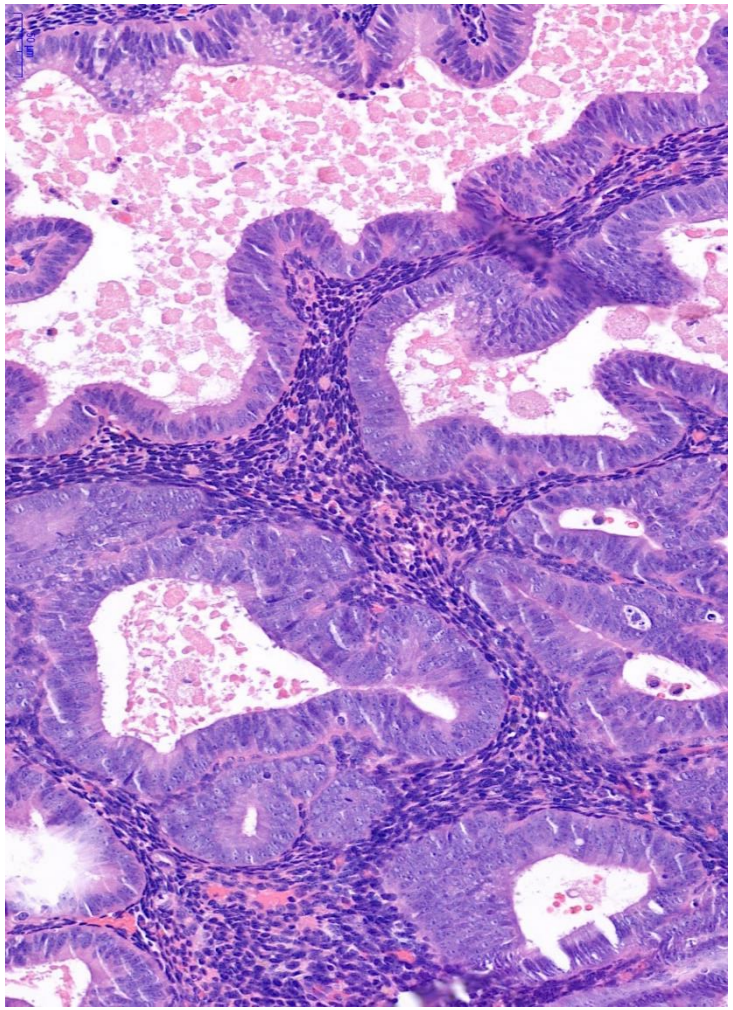
Disordered proliferation



Hyperplasia without atypia



Hyperplasia with atypia/Endometrioid Intraepithelial Neoplasia (EIN)



Proliferative lesions of the endometrium

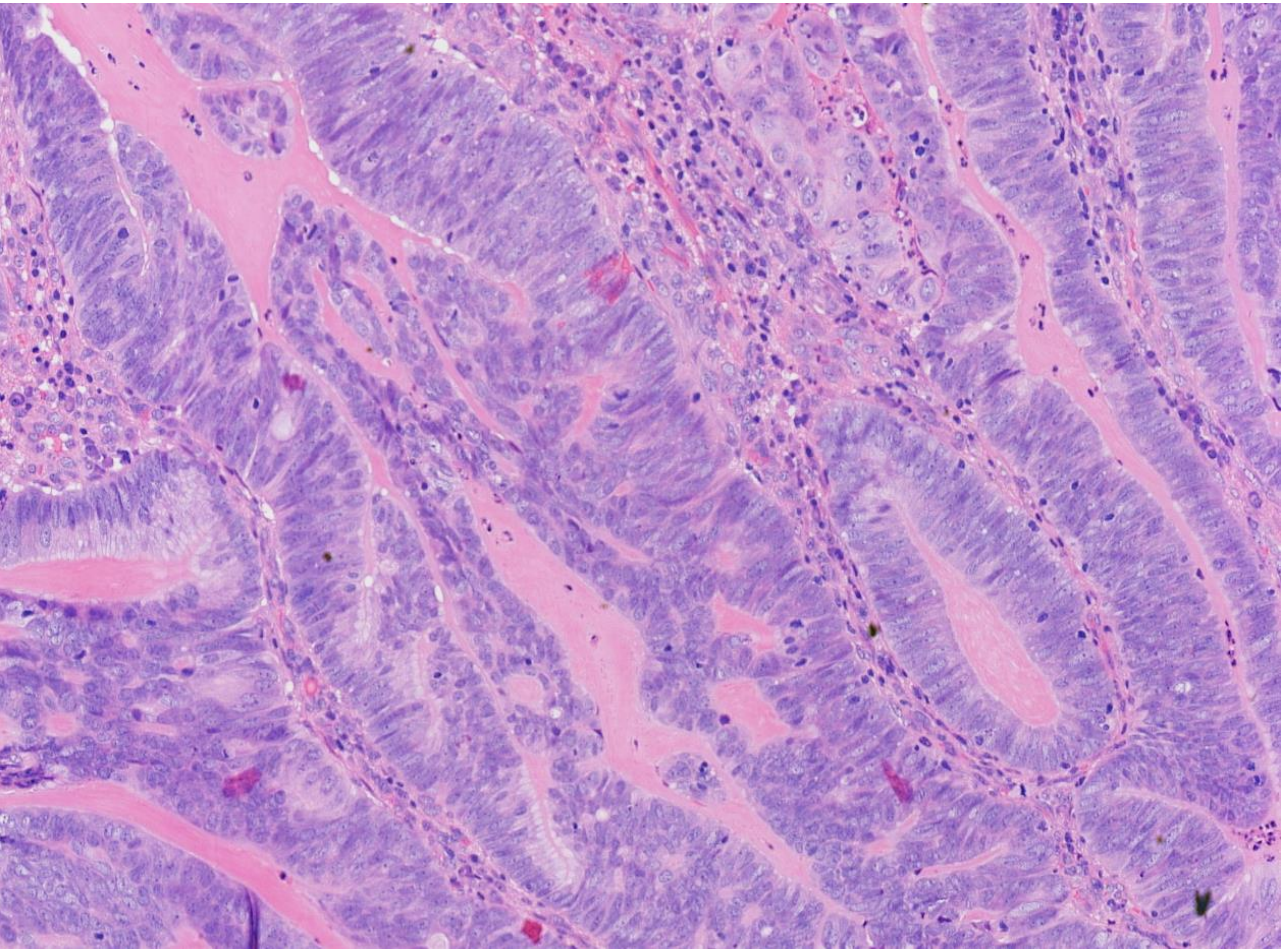
- Endometrial carcinoma
  - Most frequent malignancy of gynaecologic tract

  - Endometrioid carcinoma
    - Most frequent type (80%), middle-aged women
    - Gland forming tumor, glands resemble endometrial glands
    - Background: exposure to unopposed estrogen – endometrial hyperplasia (risk factors: obesity, diabetes, hypertension)
    - Can be graded (Grade I-III)
    - PTEN mutations are common
    - Can be part of Lynch-syndrome! (microsatellite instability testing)
    - Early stage tumors have a good prognosis

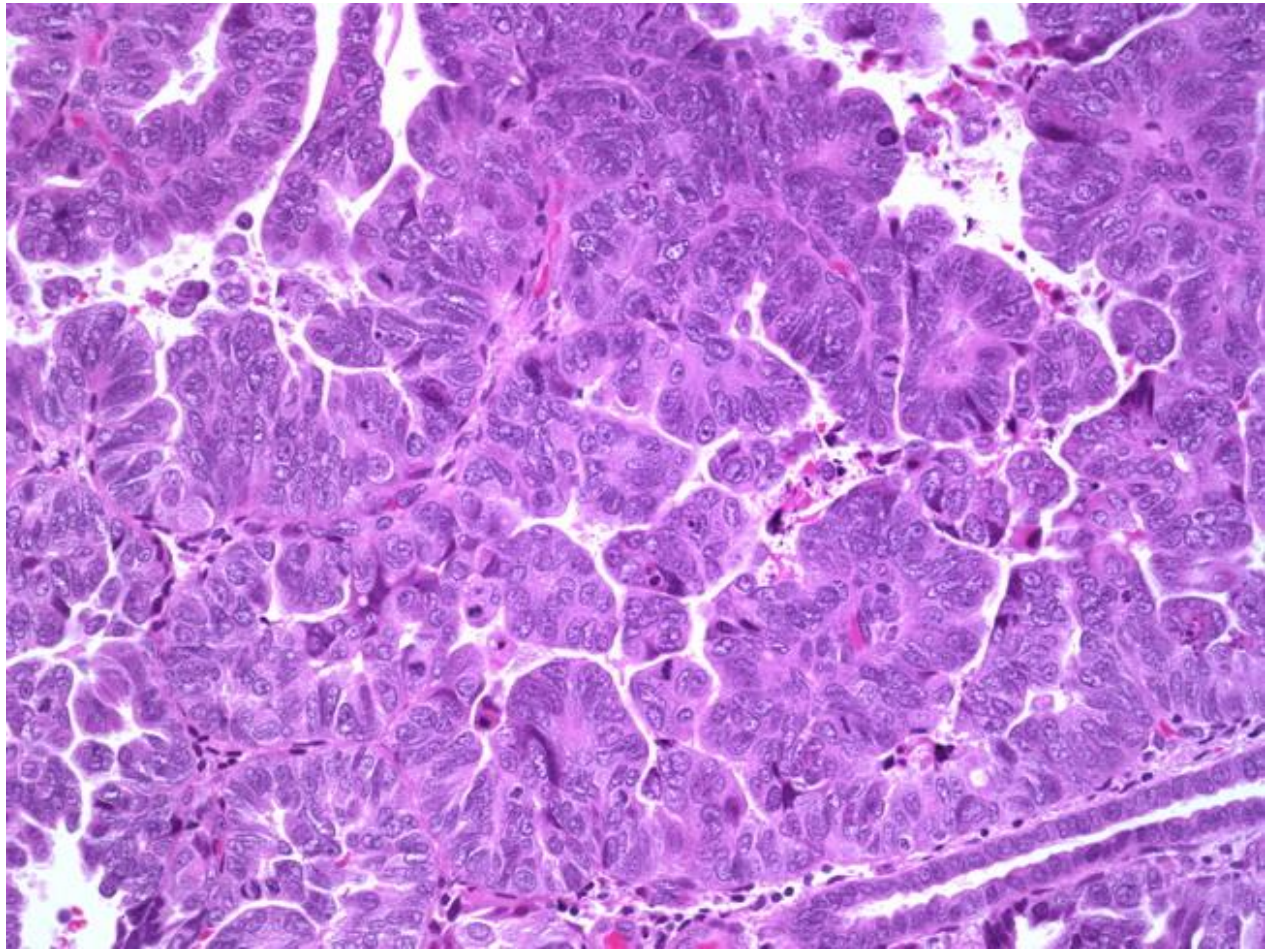
Proliferative lesions of the endometrium

- Endometrial carcinoma
  - Serous carcinoma (15%)
    - Not associated with estrogen excess or endometrial hyperplasia
    - Precursor: serous endometrial intraepithelial carcinoma (SEIC)
    - High-grade by definition
    - In older women
    - TP53 mutations
    - Usually papillary, but can form glands!
  - Other rare, high-grade types (5%)
    - Clear cell carcinoma, carcinosarcoma
  - Prognosis:
    - Low-grade endometrioid carcinomas are usually confined to the uterus – hysterectomy can be sufficient, good prognosis
    - Tumors with advanced stage show adnexal or peritoneal involvement, can have distant metastases – chemotherapy, radiotherapy, poor prognosis

Proliferative lesions of the endometrium



Endometrioid endometrial carcinoma,
Grade I



Serous endometrial carcinoma

Proliferative lesions of the endometrium

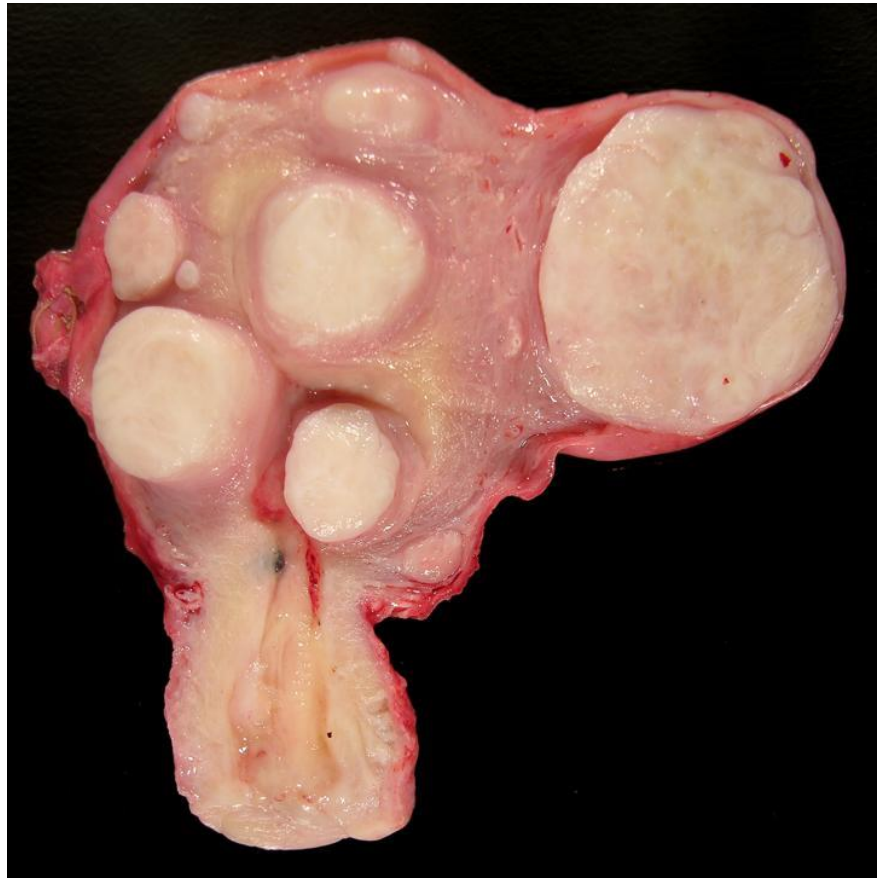
- Endometrial stromal sarcoma
  - Malignant mesenchymal neoplasm arising from endometrial stroma
  - Very rare, has low-grade and high-grade subtypes

Adenomyosis

- Presence of endometrial tissue deep in the myometrium (at least 2,5 mm below the endometrium-myometrium border)
- Common, present in 15-30% of hysterectomy specimens
- Frequent cause of abnormal uterine bleeding

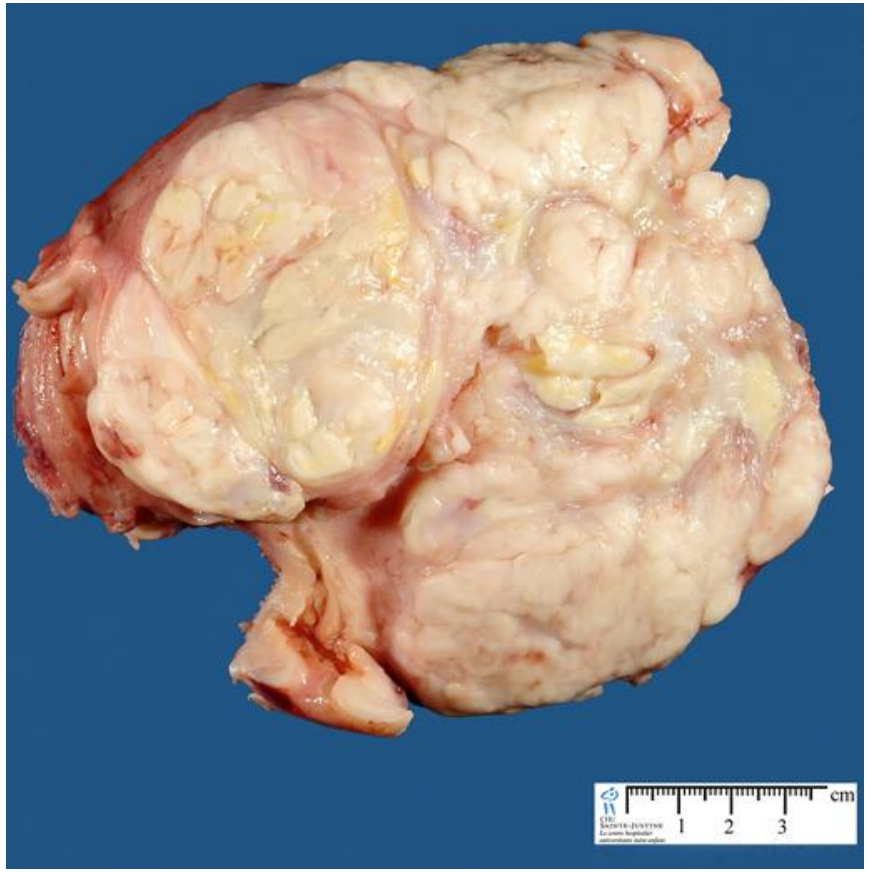
Tumors of myometrium

- Leiomyoma
  - By far the most common benign tumor in females, affects 30-50% of women in reproductive age
  - Can be single or multiple (uterus leiomyomatosus)
  - Submucosal, subserosal or intramural
  - Frequent cause of abnormal uterine bleeding
  - Can cause infertility
  - Does not transform into leiomyosarcoma
  - Histology: Fascicles of typical smooth muscle cells
  - Can have degenerative changes (calcification, edema)



Tumors of myometrium

- Leiomyosarcoma
  - Malignant neoplasm of smooth muscle origin
  - Does not arise from leiomyoma
  - Usually in older women
  - Recurrences and lung metastases are frequent, 5-year survival is only 40%.

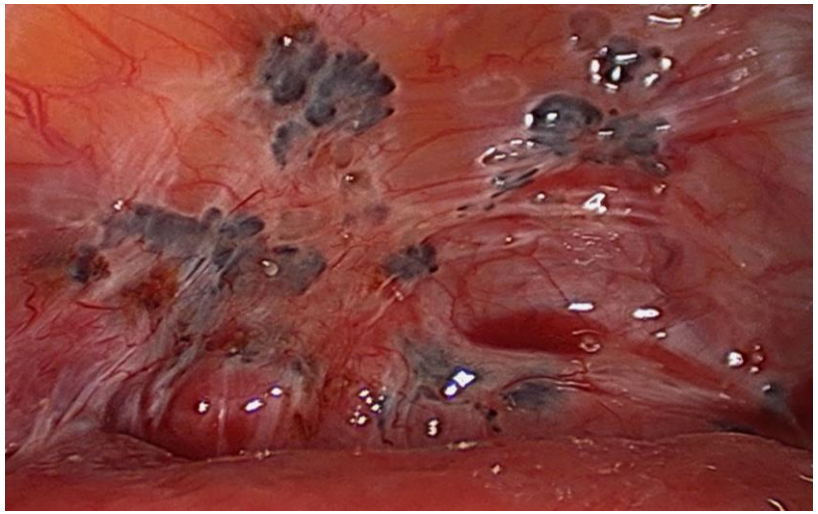


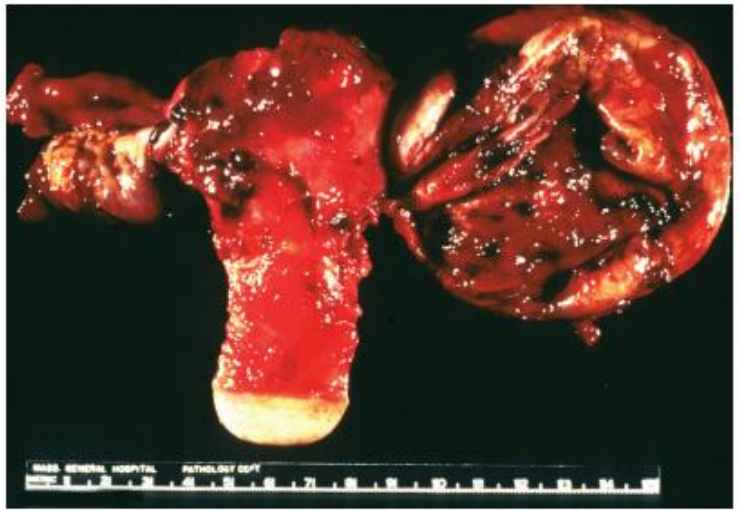
Endometriosis

- Definition: Presence of endometrial glands and/or stroma (typically both) outside of the uterine corpus
- Can affect: cervix, ovaries, fallopian tubes, uterine ligaments, peritoneal surfaces, intestines, lymph nodes, skin, rarely distant organs
- Frequent disease (10% of women in reproductive age), very common in infertile women!
- Hypotheses for formation of endometriosis:
  - Regurgitation theory: Menstrual backflow through the fallopian tubes → implantation
  - Metastatic theory: Endometrial tissue spreads via blood vessels and lymphatics
  - Metaplastic theory: endometriosis form in situ from coelomic epithelium
  - Stem cell theory: Circulating stem cells differentiate intp endometrial tissue

Endometriosis

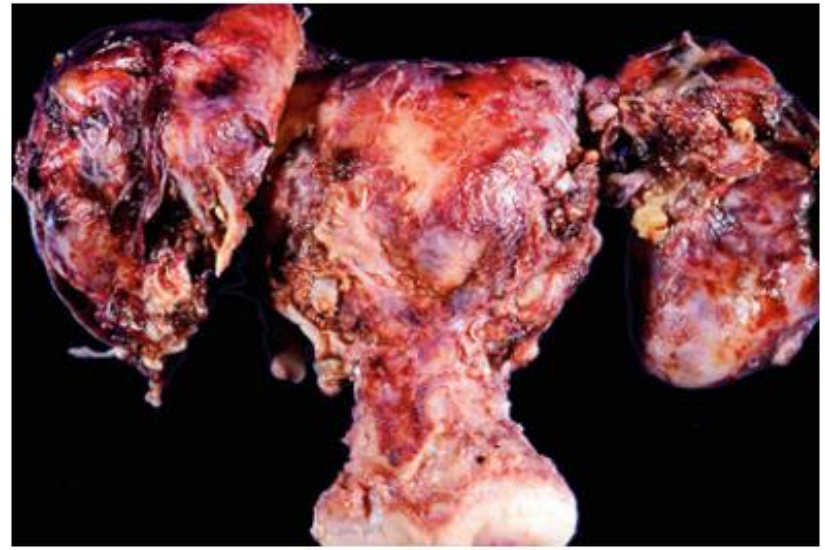
- Endometriosis can be functional (react to hormonal cycle) →bleeding
  - Macroscopic appearance: red-brown nodules
  - Ovaries: often cystic endometriosis (chocolate cyst)
- Surface lesions can be vaporised, symptomatic deep lesions require surgical removal
- Complications:
  - Scarring, adhesions →infertility
  - Can indicate extensive surgery (e. g. intestinal resections)
  - Pain
  - Tumors can arise from endometriosis (e. g. endometrioid carcinoma of ovary)

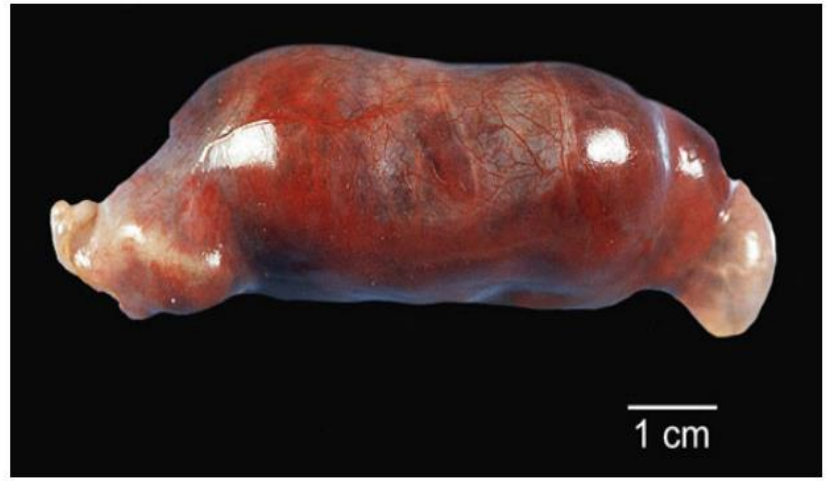




Fallopian tubes

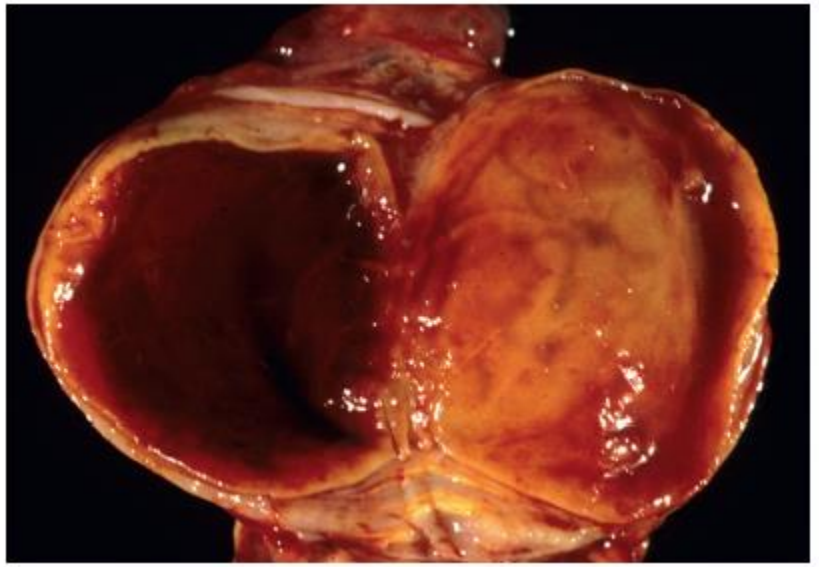
- Most common disease: inflamation (salpingitis)
  - Usually part of pelvic inflammatory disease
  - Tubo-ovarial abscess can form
  - Complication: scarring → can predispose to tubal pregnancy
- Tubal pregnancy
  - Most common site of extrauterine gravidity
  - 50% of cases have chronic salpingitis in the anamnesis
  - Complications: hematoma, rupture can cause hypovolaemic shock
- Malignant neoplasms:
  - Majority of ovarian high-grade serous carcinomas arise in the fallopian tubes!
  - Precursor: serous tubal intraepithelial carcinoma (STIC)
  - STIC is common in women with BRCA1, BRCA2 mutations →prophylactic salpingectomy

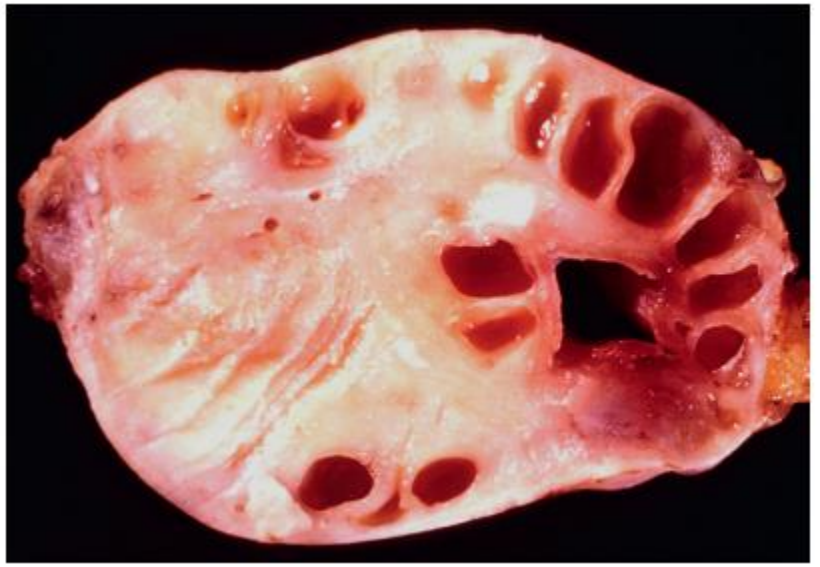




Ovaries, non-neoplastic diseases

- Follicular cysts
  - Very common, arise from unruptured follicles
  - Can be multiple, can reach large sizes (above 10 cm), but usually small
  - Lining resembles normal follicle (granulosa and theca cell layer)
- Corpus luteum cyst
  - Cystically dilated corpus luteum, above 2 cm in diameter
- Polycystic ovary syndrome (Stein-Leventhal syndrome)
  - Complex endocrine disorder
  - Hyperandrogenism, chronic anovulation, infertility
  - Patients may suffer from obesity, diabetes
  - Etiology unknown (low FSH, high LH)
  - Histology: Subcortical follicular cyst, fibrotic capsule
- Endometriosis
- Tubo-ovarial abscess





Tumors of the ovary

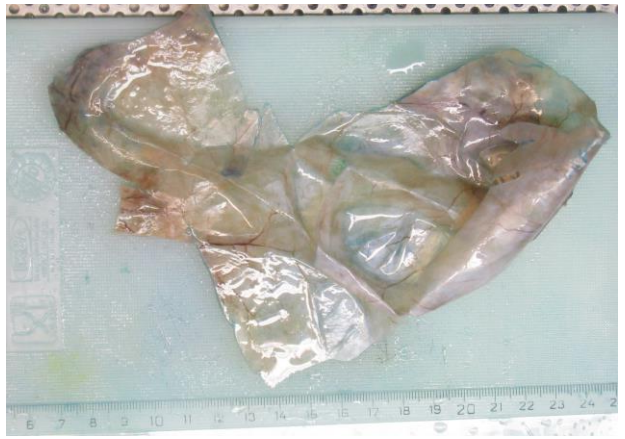
- Very diverse group of tumors
- Ovarian malignancies have the highest mortality rate among gynecologic malignancies
- Three main categories:
  - Surface epithelial tumors (benign, borderline, malignant)
  - Sex cord-stromal tumors
  - Germ cell tumors
- Symptoms:
  - Often vague or nonspecific symptoms
  - Abdominal mass
  - Abdominal or pelvic pain, abdominal complaints
  - Abdominal distension (ascites!)
  - Symptoms of estrogen or androgen production (amenorrhea, virilization, precocity, abnormal uterine bleeding)
  - Lymphadenopathy
  - Weight loss
- Tumor markers: CA-125, HE-4 (ROMA-index)

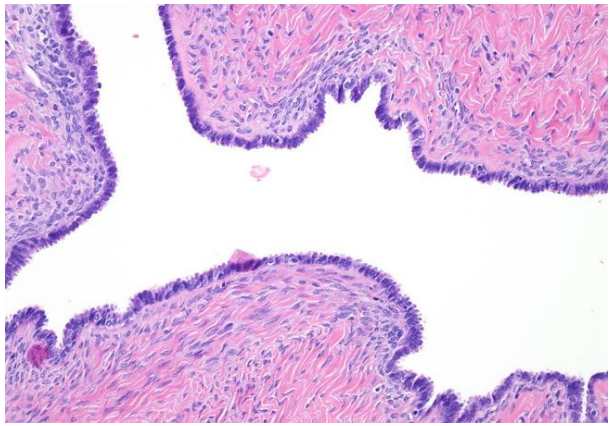
Tumors of the ovary

- Surface epithelial tumors
  - Serous tumors
    - Two different pathways:
    - 1. Serous cystadenoma, cystadenofibroma →borderline serous tumor →low-grade serous carcinoma
    - 2. Serous tubal intraepithelial carcinoma → high-grade serous carcinoma
    - →low-grade and high-grade serous carcinoma are not two grades of the same tumor!!

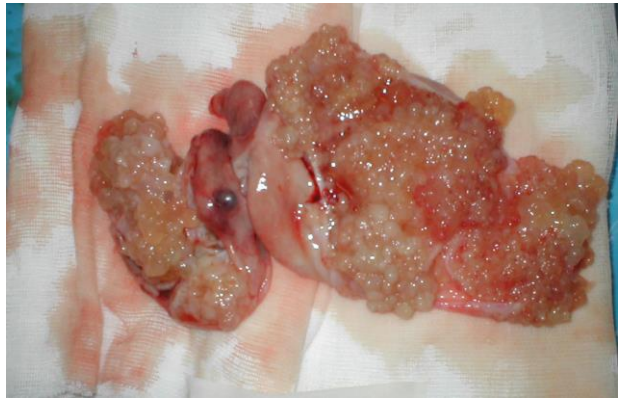
SEROUS TUMORS – 1.

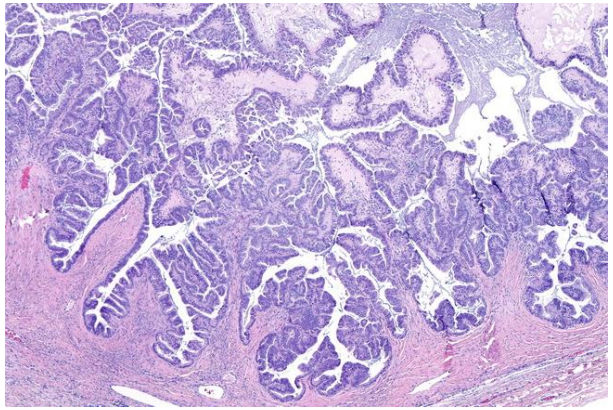
Benign (60%)
Serous cystadenoma
(or cystadenofibroma)





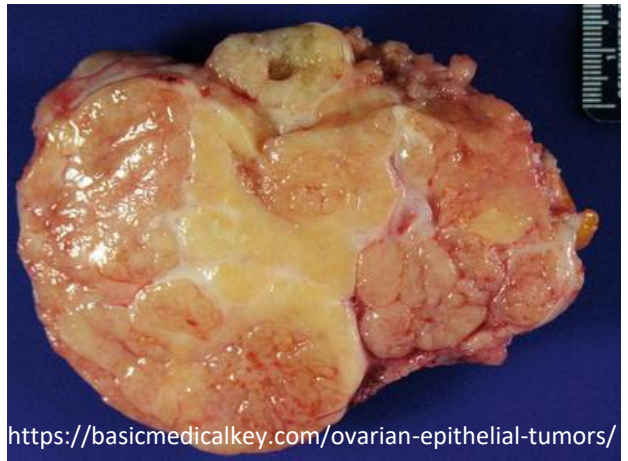
Borderline (15%)
Serous borderline tumor

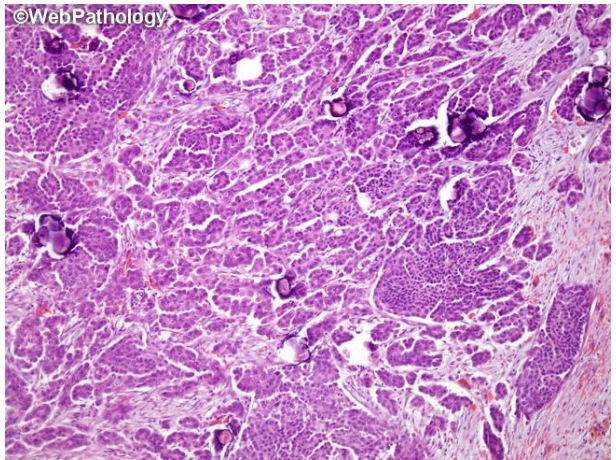




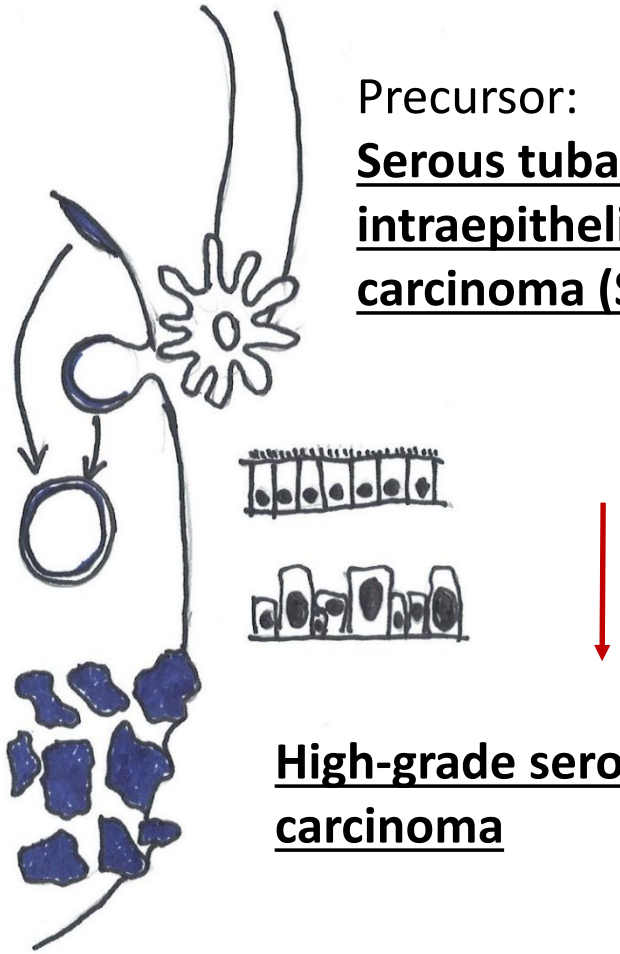
KRAS, BRAF mutations

Malignant (Type I) 1-2%
Low-grade serous carcinoma





SEROUS TUMORS – High-grade serous carcinoma

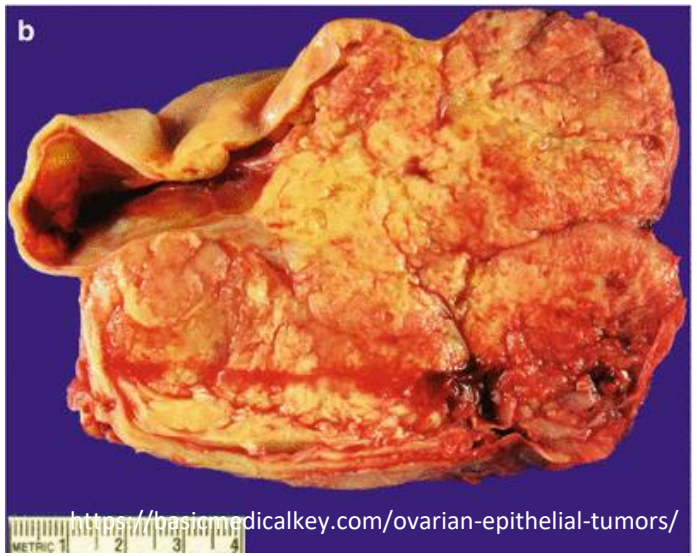


Precursor:
Serous tubal intraepithelial carcinoma (STIC)

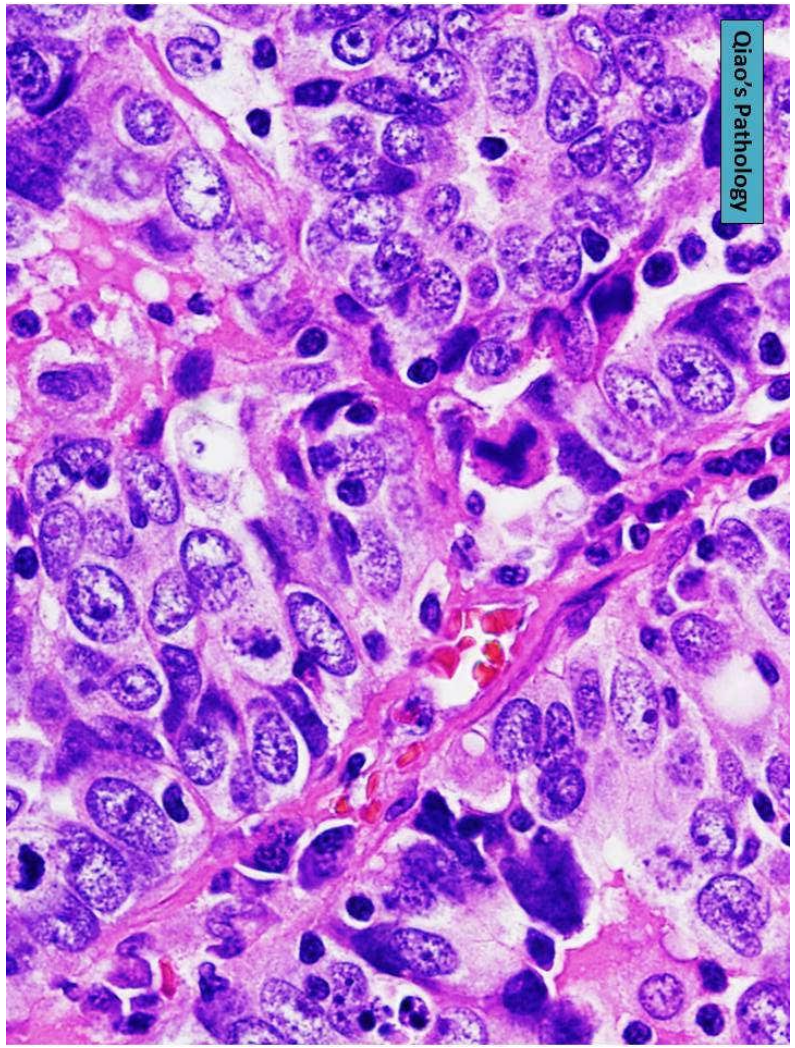
High-grade serous carcinoma

ovary
Fallopian tube
peritoneum

Almost half of ovarian malignant tumors
Often bilateral



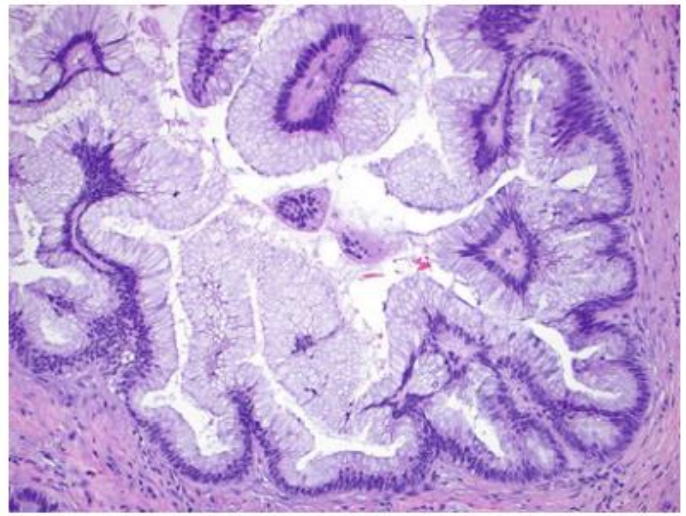
TP53 mutations
chromosomal instability



Tumors of the ovary

- Surface epithelial tumors
  - High-grade serous carcinoma
    - Most common malignant ovarian neoplasm
    - Often bilateral
    - Nearly every case is associated with TP53 mutations
    - 5-10% associated with germline BRCA1, 2 mutations (hereditary breast-ovarian cancer syndrome)
    - BRCA mutated cases have better prgnosis (reaction to PARP-inhibitors)

Tumors of the ovary



- Surface epithelial tumors
  - Mucinous tumors
    - 80% benign, 10% borderline, 10% malignant
    - Can reach huge size
    - Ruptured tumor → pseudomyxoma peritonei
    - In case of a mucinous ovarian tumor, always have to rule out metastasis!!
    - Metastases can mimic borderline and benign tumors!
    - Metastatic signet ring cell carcinoma to the ovary: Krukenberg-tumor
    - Origin of metastatic mucinous carcinoma to the ovary: colon, rectum, appendix, pancreas, bile ducts
  - Endometrioid tumors
    - Majority is malignant, morphology identical to endometrioid endometrium carcinomas
    - Can develop in endometriotic cyst
    - Must rule out endometrial primary!
    - Borderline tumors are rare

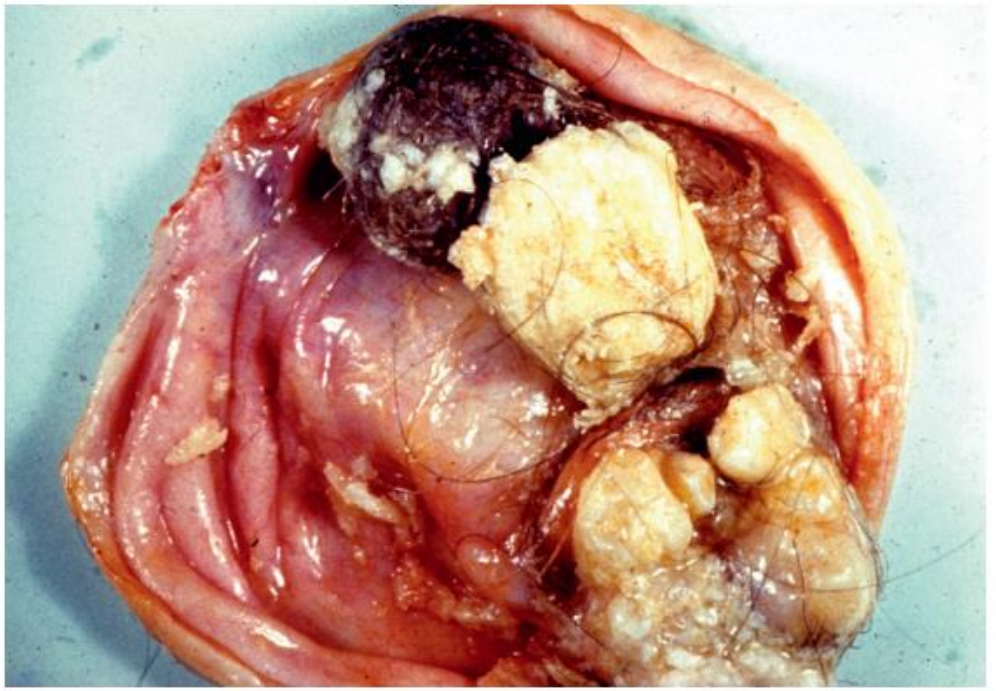
Tumors of the ovary

- Surface epithelial tumors
  - Clear cells tumors
    - Majority is malignant, borderline and benign forms are very rare
    - Can develop in endometriotic cyst
    - Clear cell carcinoma is a high-grade tumor, advanced stages have poor prognosis
  - Brenner tumors
    - Most are benign, borderline and malignant forms are rare
    - Urothelial epithelial islands in fibrotic stroma

Tumors of the ovary

- Sex cord-stromal tumors
  - Pure stromal tumors:
    - Fibroma: most common sex cord-stroma tumor, benign, can cause ascites and hydrothorax (Meigs syndrome)
    - Thecoma: benign, in older women, can cause endometrial hyperplasia, carcinoma (estrogen production)
  - Pure Sex cord tumors:
    - Granulosa cell tumor: Malignant behaviour, late recurrence, can cause endometrial hyperplasia, carcinoma (estrogen production)
    - Sertoli-cell tumor: rare inthe ovary, more common in testis, benign
  - Mixed sex cord-stromal tumors
    - Sertoli-Leydig cell tumor: in young women, poorly differentiated form has a bad prognosis

Tumors of the ovary



- Germ cell tumors
  - Teratomas: consist of tissues derived from all three germ cell layers
    - Majority is mature (contains mature tissues)
    - Mature cystic teratoma is usually unilateral, usually discovered in young age, benign
      - Synonym: Dermoid cyst (epidermal lining with skin appendages)
      - Macroscopy: Cyst filled with hair and sebaceous material
      - Common tissues: Tooth-like structures, bone, cartilage, thyroid, neural
    - Immature teratoma is rare, behaves in malignant fashion, forms in first 2 decades
      - Solid neoplasm containing immature elements
    - Monodermal teratomas exist: struma ovarii, ovarian carcinoid
  - Other germ cell tumors (dysgerminoma, yolk sac tumor, embrional carcinoma, choriocarcinoma) are rare, malignant, usually present in young age

THANK YOU FOR YOUR ATTENTION!