Female genital tract

Endometrial Hyperplasia

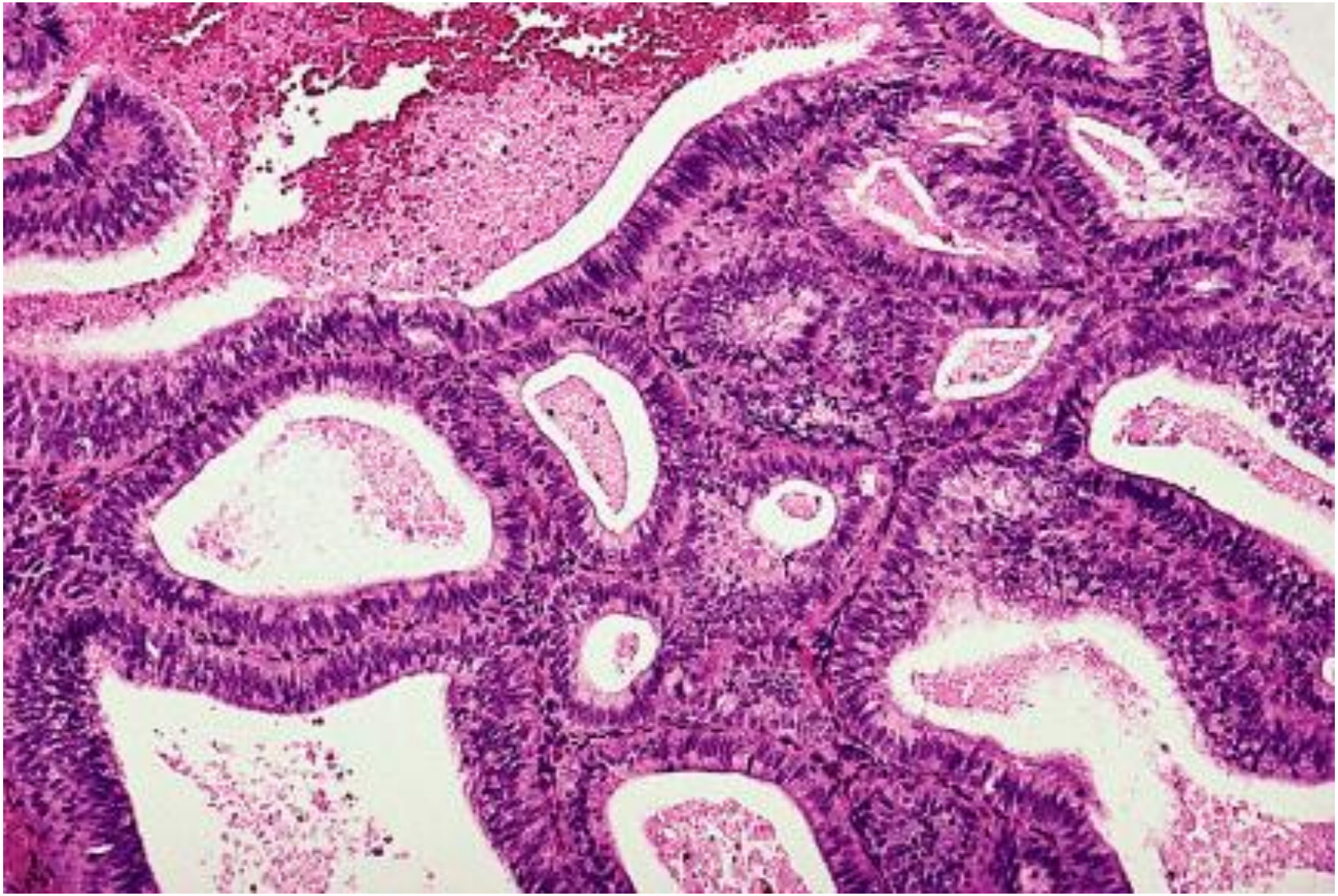
" An exaggerated endometrial proliferation"

- A preneoplastic condition
- **WHO classification**
- Based on architectural crowding:
  - Simple or Complex
- Based on cytological atypia
  - Without or with atypia
- Complex hyperplasia with atypia may progress to CA in 20-30% of cases

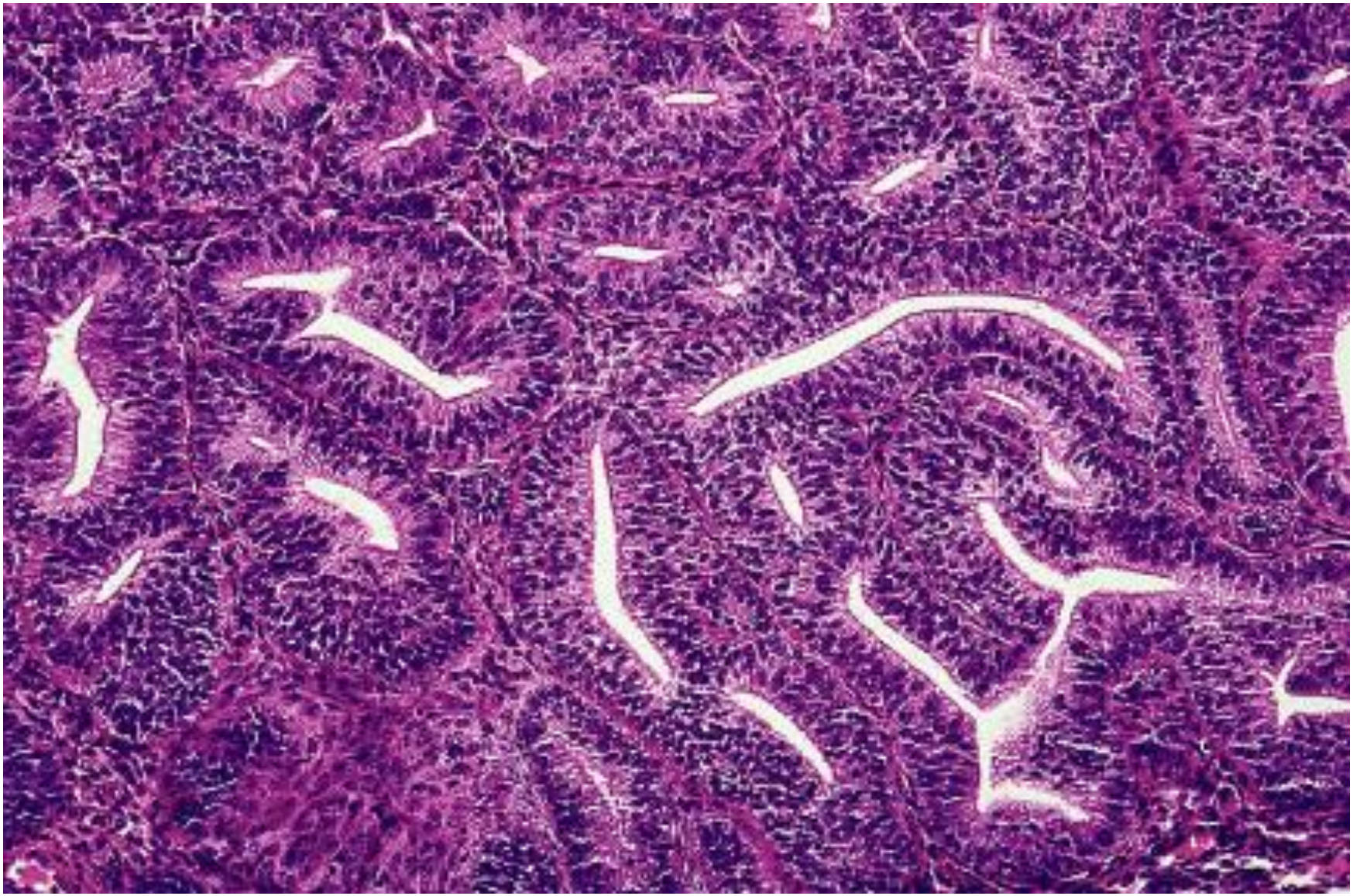
Causes

- **Excess estrogen relative to progestin**:
- Failure of ovulation; around the menopause
- Prolonged administration of estrogen alone
- Polycystic ovaries
- Cortical stromal hyperplasia
- Granulosa–theca cell tumors of the ovary
- Obesity, because adipose tissue processes steroid precursors into estrogens

Simple hyperplasia



Complex hyperplasia



Endometrial Polyps

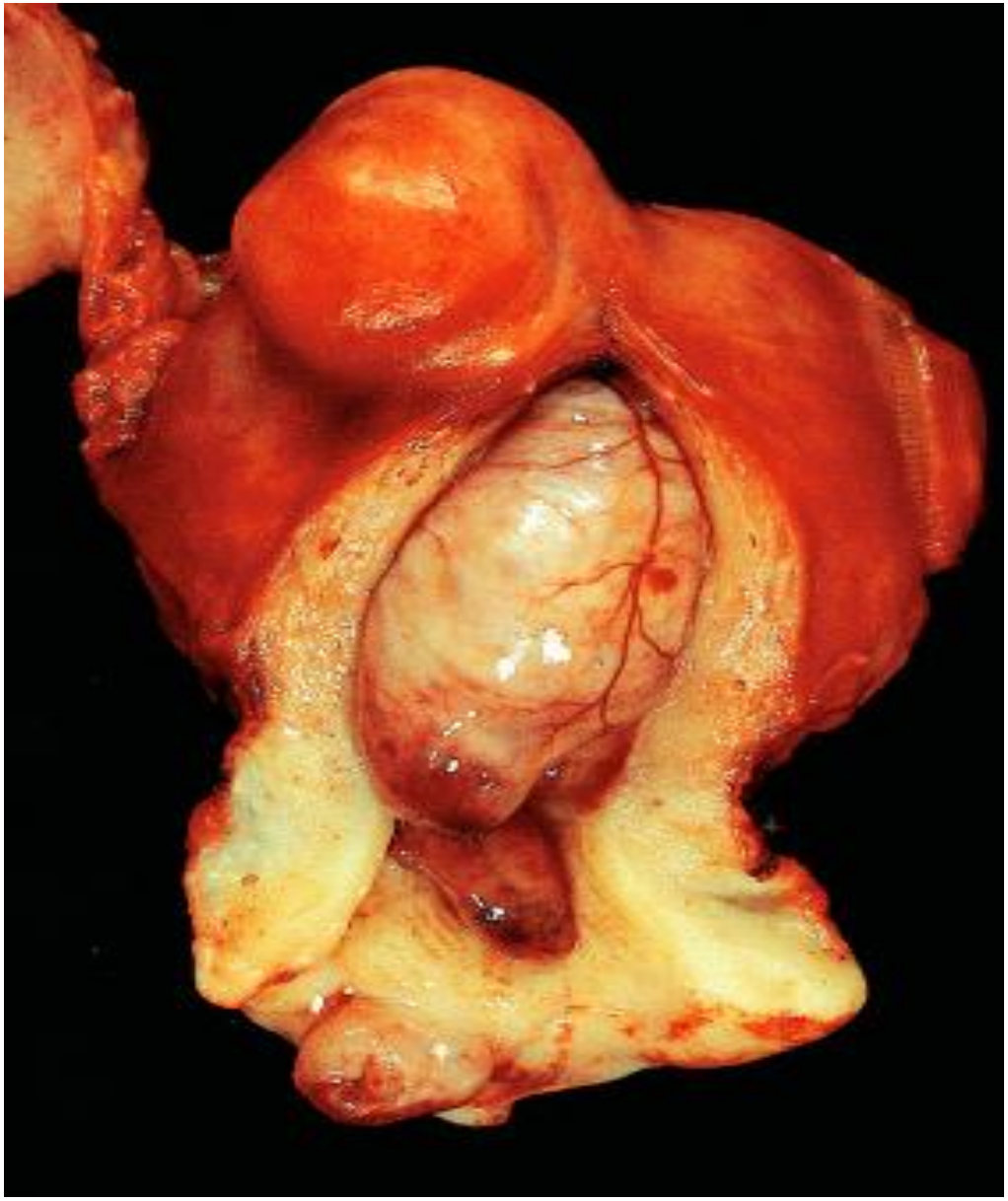
- The stromal cells are monoclonal and have a cytogenetic rearrangement at 6p21

- **Clinical picture**:
- Any age, more common at menopause
- Abnormal uterine bleeding
- Small risk of malignant transformation

Endometrial Polyps

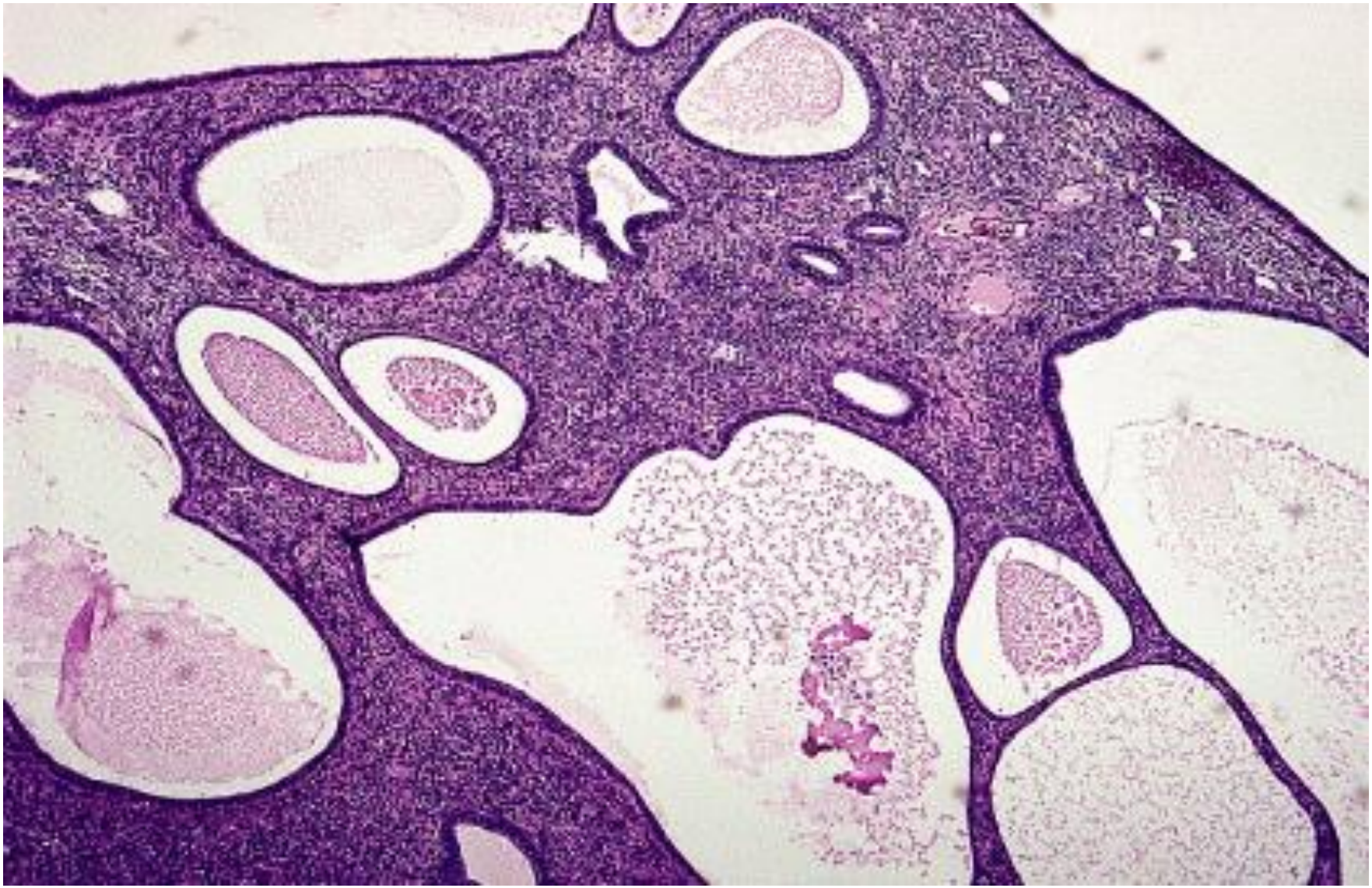
- Sessile (rarely pedunculated) lesions

- **Microscopically:**
- Endometrium resembling the stratum basalis
- Small muscular arteries
- Cystically dilated glands
- Spindled stroma



Endometrial polyp, small cervical polyp, and subserosal leiomyoma

Endometrial Polyp



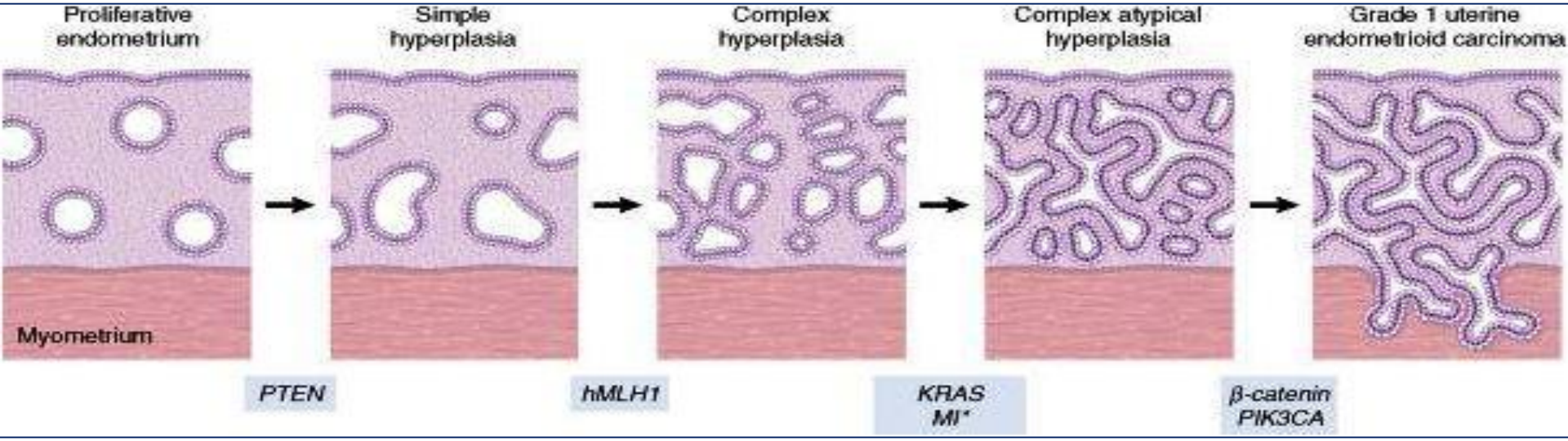
Endometrial Carcinoma

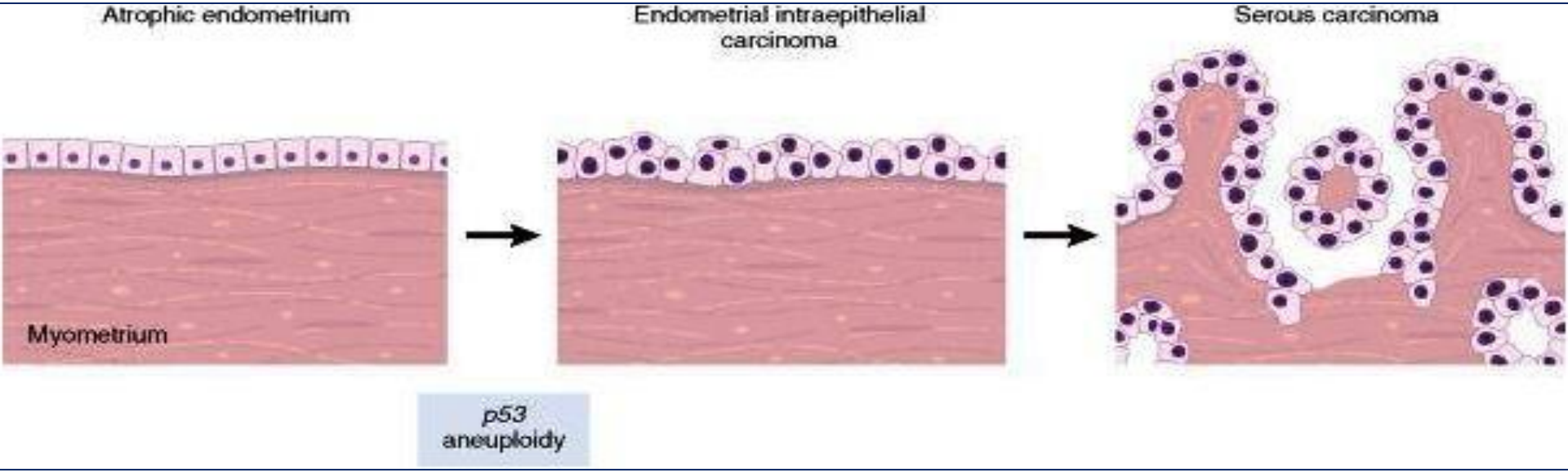
- The most frequent cancer of the female genital tract in US and the west
- Age: most frequent between 55 and 65 y
- Postmenopausal bleeding

Types of endometrial cancer

Endometrioid carcinoma Type I	Serous carcinoma Type II
Perimenopausal women with estrogen excess In a background of hyperplasia **Risk factors** ▪Obesity , DM, HTN ▪Infertility (nulliparous) ▪Nonovulatory cycles ▪Prolonged ERT ▪Functioning ovarian tumors	Older women Unrelated to estrogen In a background of endometrial atrophy Sometimes in a polyp
Familia cancer: ▪HNPCC .. Missmatch repair genes ▪Cowden syndrome … PTEN mutation **Sporadic cancer**: MSI and PTEN mutation	P53 mutation

Pathogenesis





Endometrioid carcinomas

- **Gross appearance:**
- Exophytic or infiltrative

- **Microscopic appearance:**
- Back to back malignant glands ± solid areas
- Shows a range of patterns, including:

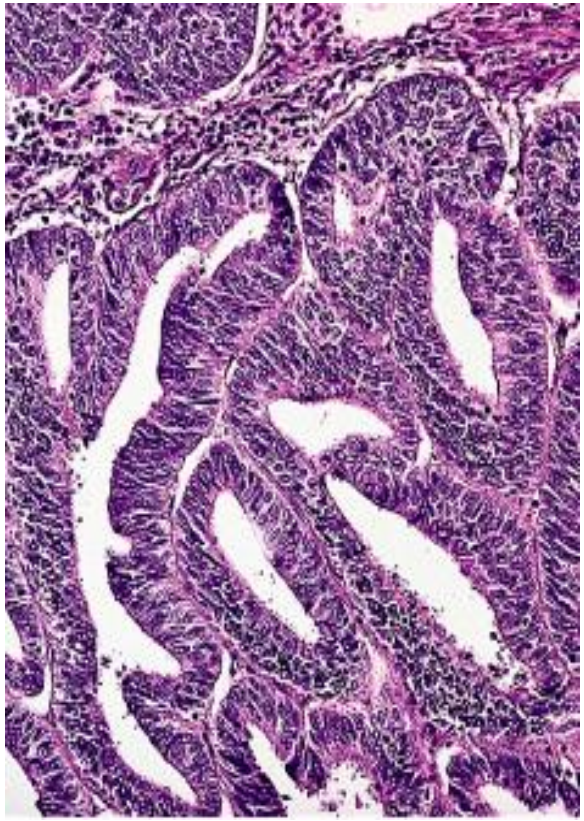
  Villoglandular, tubal (ciliated), squamous and adenosquamous differentiation

Endometrioid adenocarcinoma

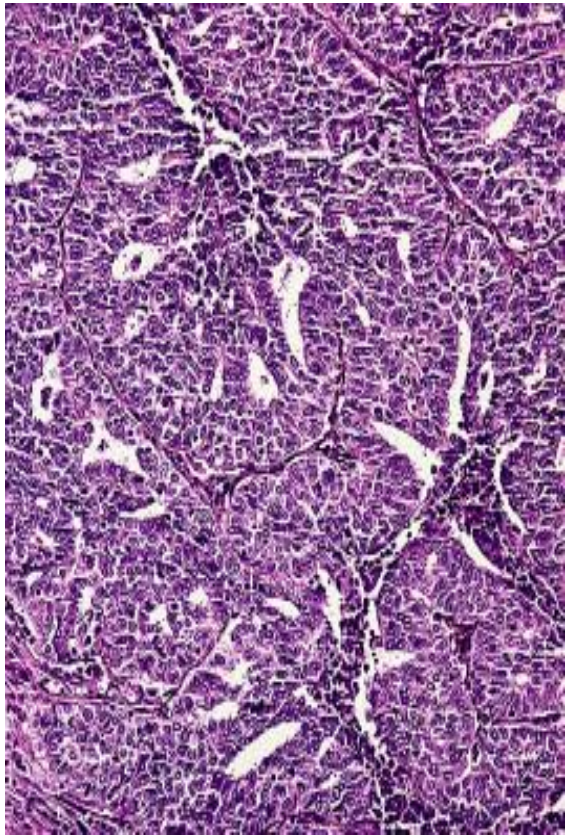
Endometrioid carcinomas

- **FIGO grading:**
- Grade 1 $\leq$ 5% solid growth pattern
- Grade 2 6% – 50% solid growth pattern
- Grade 3 $>$ 50% solid growth pattern
- Severe nuclear atypia raises the grade

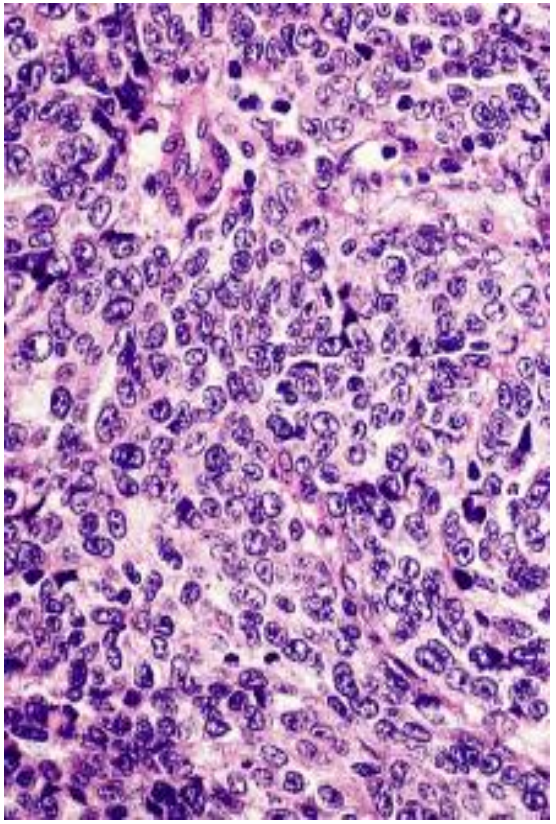
FIGO grade



Grade I



Grade II



Grade III

Endometrioid carcinomas

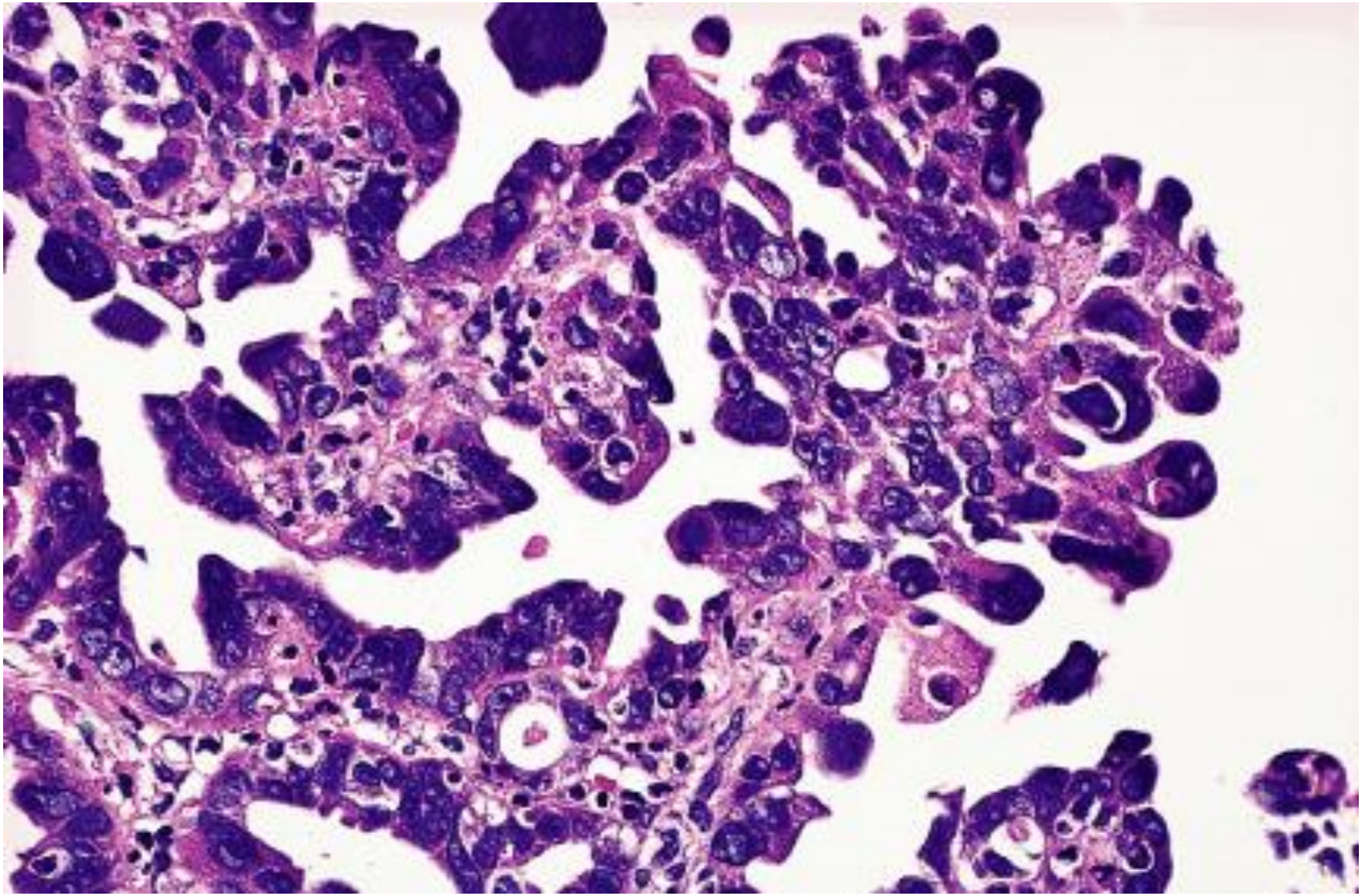
- Tumors originate in the mucosa
- It may infiltrate the myometrium
- May metastasize to regional lymph nodes
- Synchronous endometrioid tumors may arise in the uterus and ovary
  - Usually two separate primary neoplasms
  - Has a favorable prognosis

Serous carcinoma

- Highly aggressive neoplasm
- Small or superficial serous tumors may spread via the fallopian tube to peritoneal cavity

- Resembles ovarian papillary serous carcinoma:
- Complex papillary pattern
- High nuclear grade
- Psammoma bodies in 30%

Papillary serous carcinoma



Smooth muscle tumors

- Tumors arise from smooth muscle cells of myometrium:

- Benign:Leiomyoma
- Smooth muscle tumor of uncertain malignant potential (STUMP)
- Malignant: leiomyosarcoma

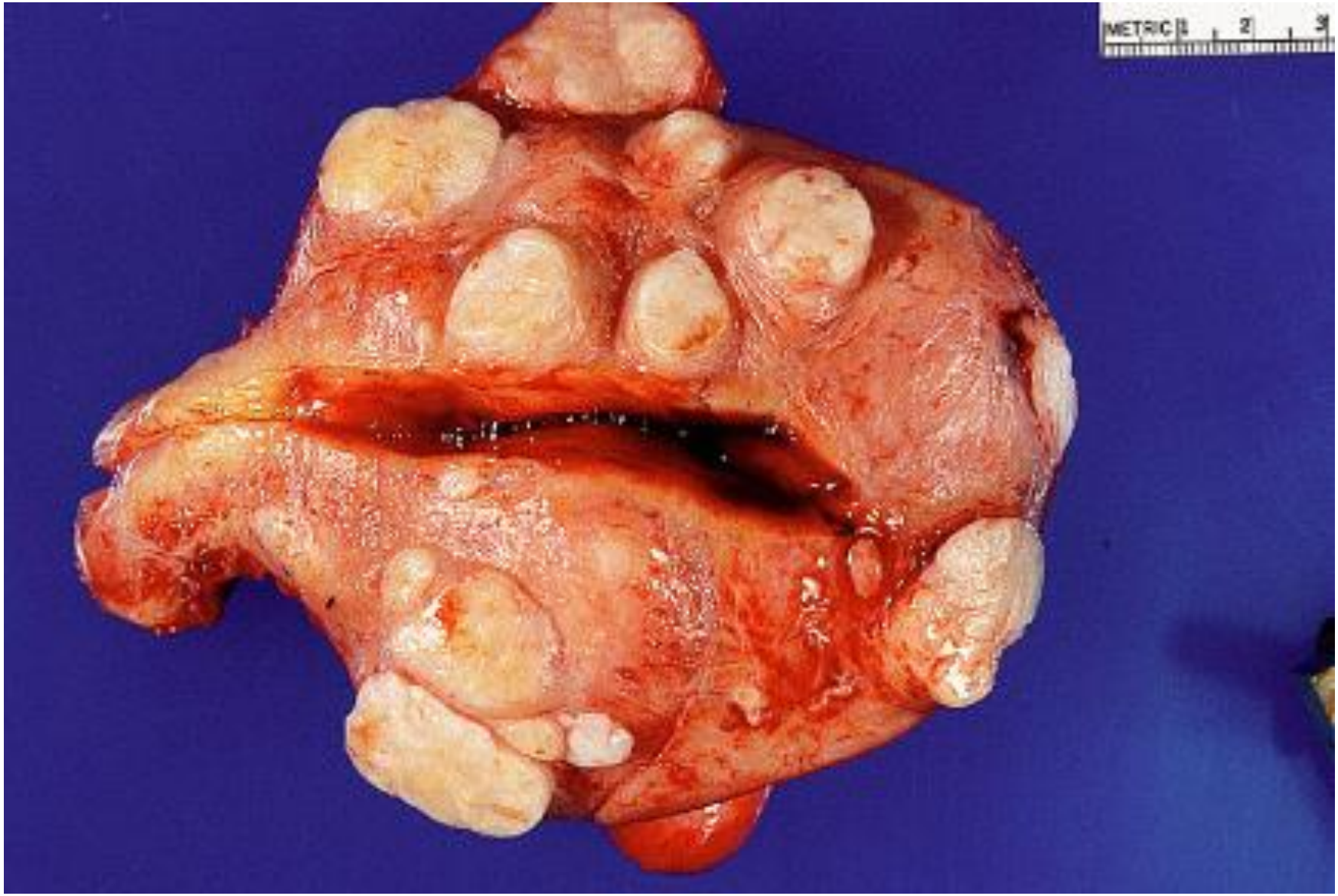
Leiomyoma (fibroid)

- The most common benign tumor in females, found in 30% to 50% of women
- In blacks more than in whites
- Estrogens and OCPs stimulate their growth
- They shrink postmenopausally
- Usually multiple

Morphology

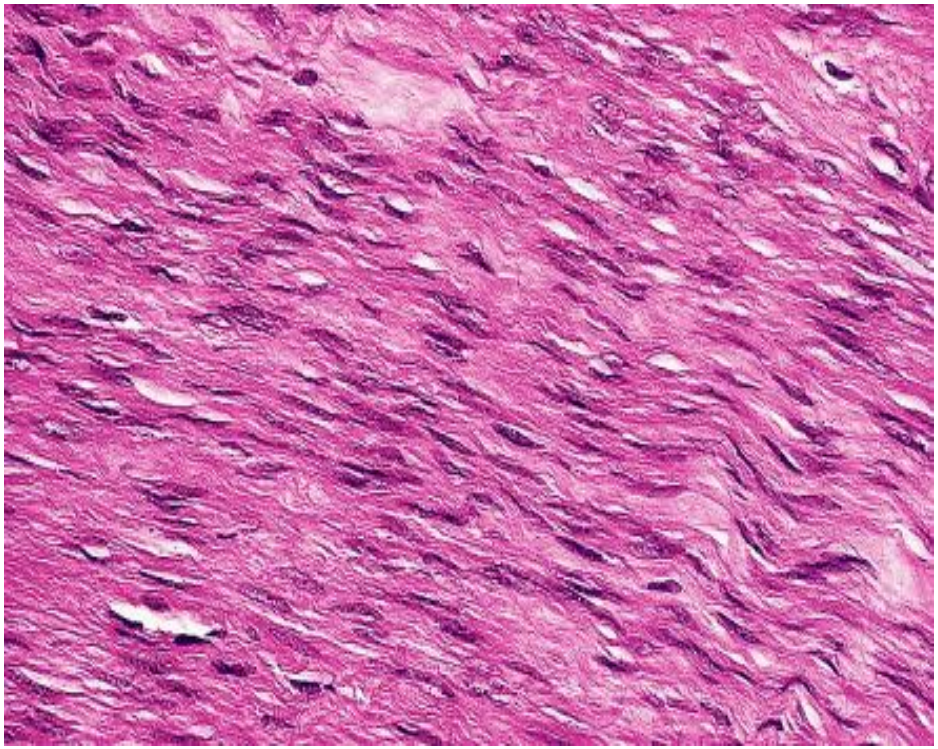
- **Gross appearance:**
- Well-circumscribed, firm gray-white masses with a characteristic whorled cut surface
- **Site:**
- Intramural .. embedded within myometrium
- Submucosal .. Beneath endometrium
- Subserosal .. Beneath serosa

Multiple leiomyomas



Morphology

- **Microscopic appearance:**
- Whorling bundles of smooth muscle cells



Leiomyosarcoma

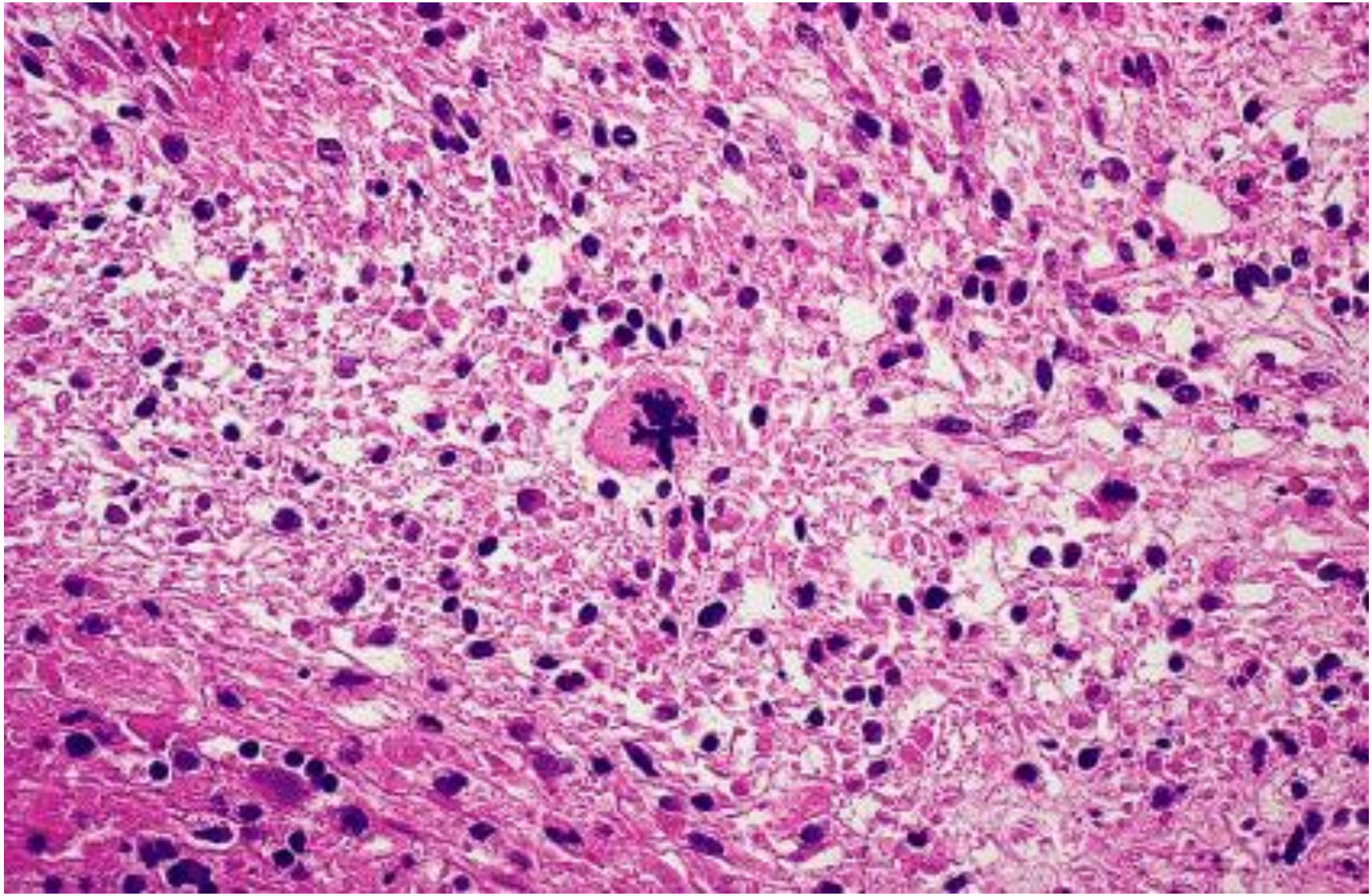
- Usually arises de novo, not from preexisting leiomyoma
- Usually solitary tumors
- 5-year survival rate is about 40%

- **Gross appearance:**
- Bulky infiltrative masses &/or
- Polypoid lesions projecting into the cavity
- Soft, hemorrhagic, and necrotic

Morphology

- A wide range of differentiation from those resemble leiomyoma to anaplastic tumors
- **The diagnostic features:**
  - Tumor necrosis
  - Cytologic atypia
  - Mitotic activity
  - Infiltrative borders
- Recurrence after removal is common
- Tend to metastasize, typically to the lungs

leiomyosarcoma



FALLOPIAN TUBES

- Salpingitis
- Ectopic (tubal) pregnancy
- Endometriosis
- Rare primary tumors
  - Primary adenocarcinoma

Salpingitis

- Inflammations of the tube
- The most common disease of fallopian tubes

- Most commonly a component of PID
- Gonococcal & nongonococcal infections as *Chlamydia, Mycoplasma and* coliforms.
- Postpartum:streptococci and staphylococci
- Tuberculous salpingitis is less common

Primary tumors of fallopian tubes

- Primary adenocarcinoma
  - Endometrioid or papillary serous
  - ↑ risk in BRCA mutation
  - Frequently involve omentum and peritoneal cavity at presentation

Luteal cyst

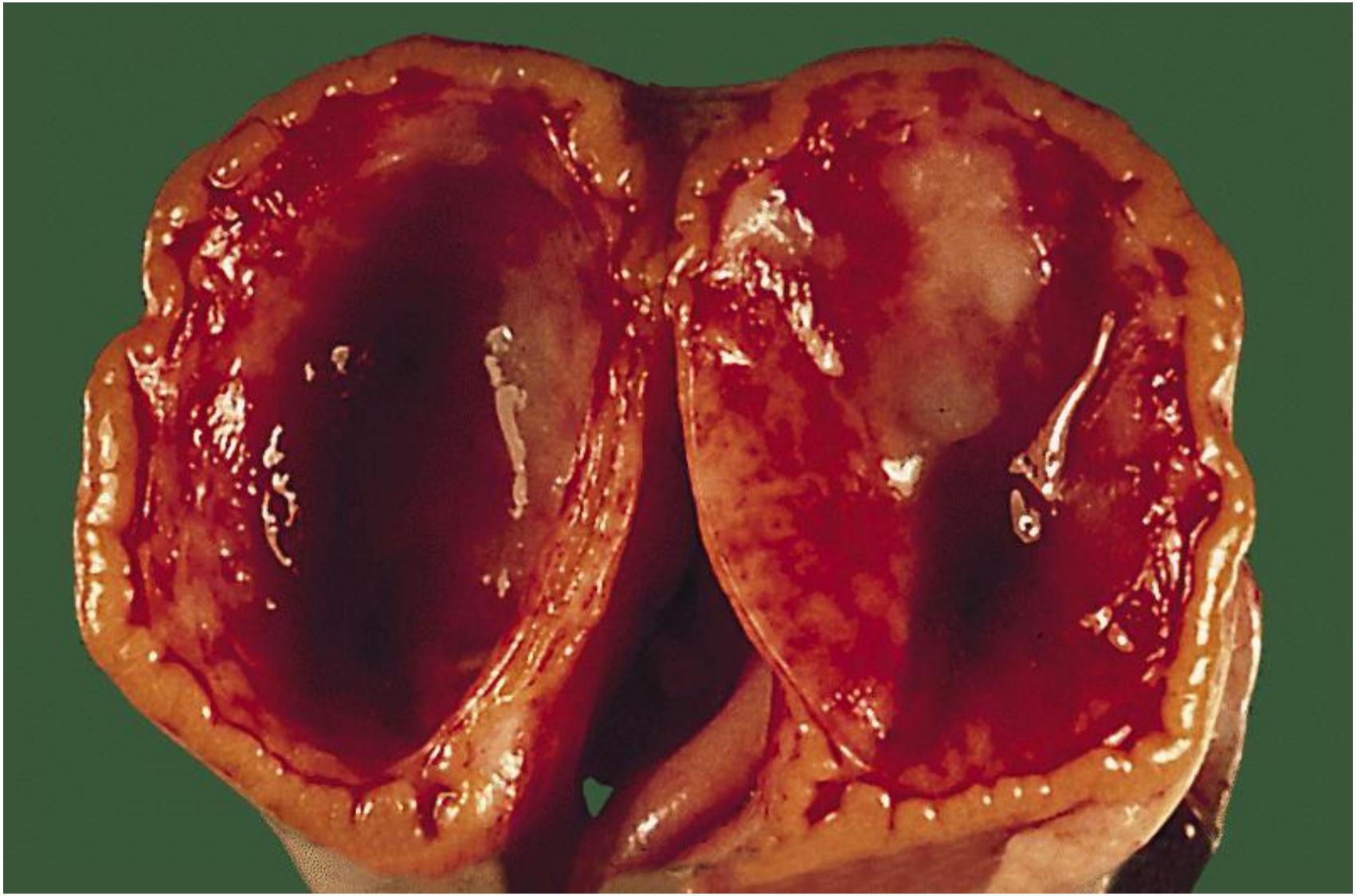
- Originate in corpus luteum
- At end of menstrual cycle or in pregnancy

- > 2.5 cm
- Lined by lutenized granulosa and theca cells

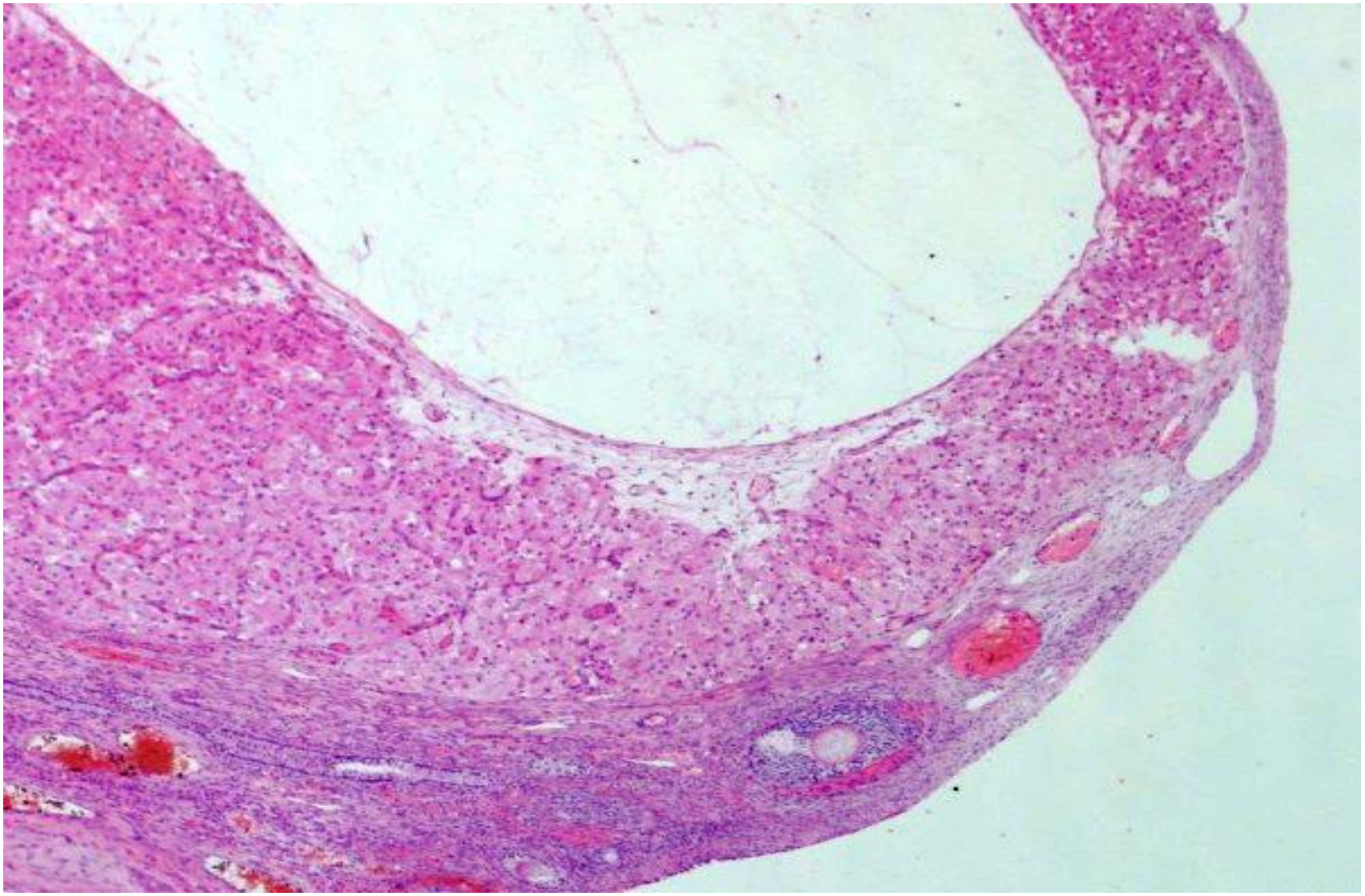
- May rupture producing intraperitoneal bleeding and acute abdomen

Corpus luteum

Corpus luteum cyst



Corpus luteum cyst



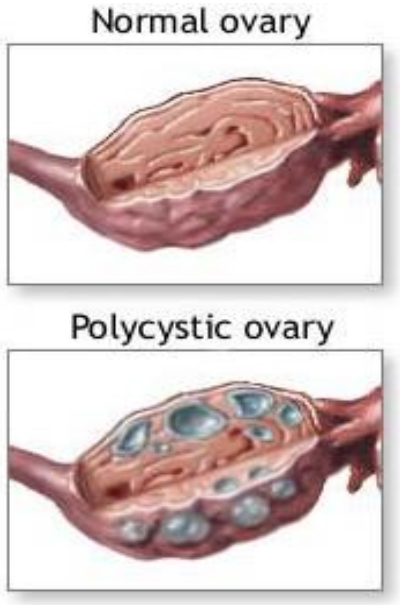
POLYCYSTIC OVARIES
Stein-Leventhal syndrome

- Multiple ovarian cystic follicles with excess production of androgen and estrone
- Anovulatory cycles

- **Clinical picture:**
- Usually obese young girls
- Oligomenorrhea, hirsutism and infertility

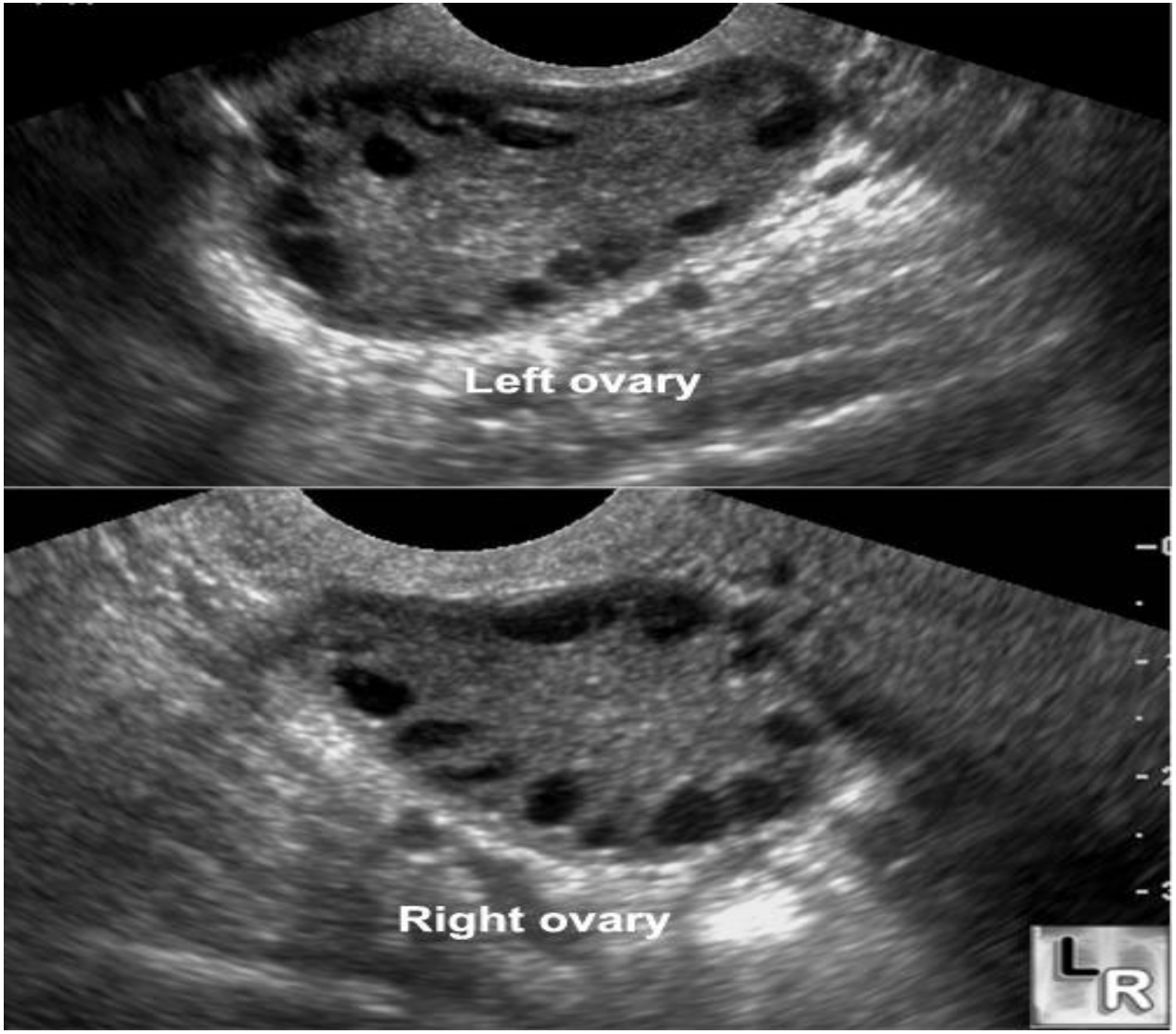
Morphology

- **Gross appearance:**
- large ovaries twice the normal size
- Gray-white with a smooth outer cortex
- Studded with subcortical follicles < 1cm



PCO

PCO



Morphology

- **Microscopic examination:**
- Thick fibrotic outer tunica
- Multiple cystic follicles lined by granulosa cells with enlarged hyperplastic luteinized theca interna
- Absence of corpora lutea.

Pathogenesis

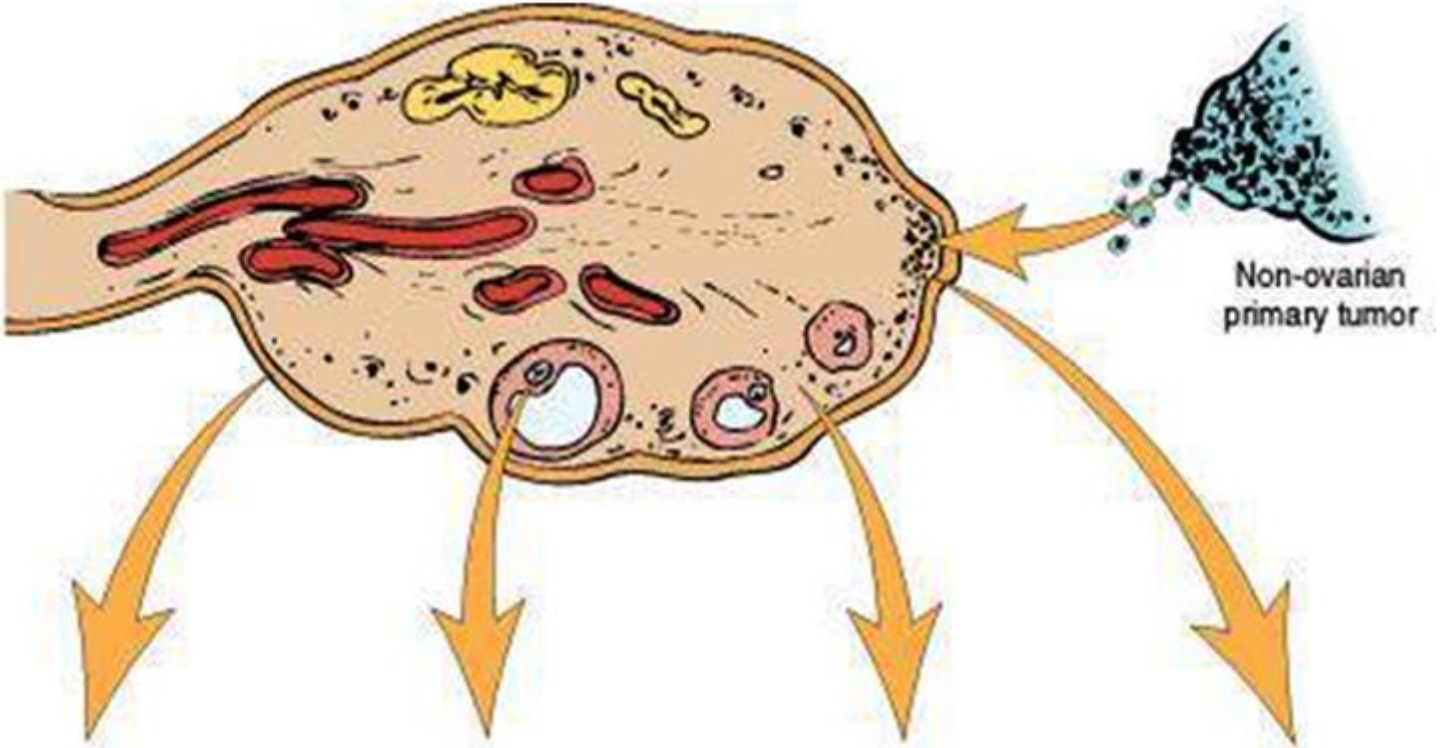
- Ovaries elaborate excess androgens, which are converted in peripheral fat to estrone
- Estrone inhibit the secretion of FSH

- **Biochemical abnormalities:**
- Excessive production of androgens
- High concentrations of LH
- Low concentrations of FSH

Ovarian neoplasms

- The 5th most common cancer and the 5th cause of cancer related deathes in US women
- **Classification:**
- Primarily **morphologic** but reflect the embryogenesis and histogenesis of ovary:
  - Surface epithelial tumors
  - Germ cell tumors
  - Sex cord-stromal tumors
  - Metastatic tumors

Incidence



ORIGIN	SURFACE EPITHELIAL CELLS (Surface epithelial–stromal cell tumors)	GERM CELL	SEX CORD–STROMA	METASTASIS TO OVARIES
Overall frequency	65–70%	15–20%	5–10%	5%
Proportion of malignant ovarian tumors	90%	3–5%	2–3%	5%
Age group affected	20+ years	0–25+ years	All ages	Variable
Types	• Serous tumor • Mucinous tumor • Endometrioid tumor • Clear cell tumor • Brenner tumor	• Teratoma • Dysgerminoma • Endodermal sinus tumor • Choriocarcinoma	• Fibroma • Granulosa cell tumor • Sertoli–Leydig cell tumor	

Surface epithelial tumors

Parameter	Nomenclature
Cell type	Serous, mucinous, endometrioid, clear cell, Brenner
Atypia and invasiveness	Benign Borderline Tumors of low malignant potential Malignant
Growth pattern Cystic or solid	Benign usually cystic (cystadenoma) Malignant Usually solid (carcinoma) May be cystic (cystadenocarcinoma)
Amount of fibrous stroma	Benign Adenofibroma or Cystadenofibroma

Pathogenesis

- **Risk factors of epithelial tumors:**
- Nulliparity and low parity
- Prolonged use of OCPs ↓ the risk
- Family history

- Hereditary ovarian cancer (5% to 10%)
- BRCA1 and BRCA2 mutations

- Sporadic ovarian cancer
- BRCA in 8-10%, K-RAS (mostly mucinous), p53, her2/neu (poor prognosis)

Serous Tumors

- The most frequent of the ovarian tumors

Type	Bilateral	Age & genetics
Benign (60%)	25%	Age 30–40 *BRAF* and *K-RAS*
Borderline (15%)	30%	
Malignant (25%)	65%	Age 45–60 P53 and BRCA

Gross morphology

- The better differentiated tumors are cystic
- Small or large, usually unilocular
- Containing serous fluid
- Papillary formation
- Malignant: more solid components
  more complex papillae

Benign serous cystadenoma

Smooth inner and outer surface

Papillary projections

Borderline serous neoplasm

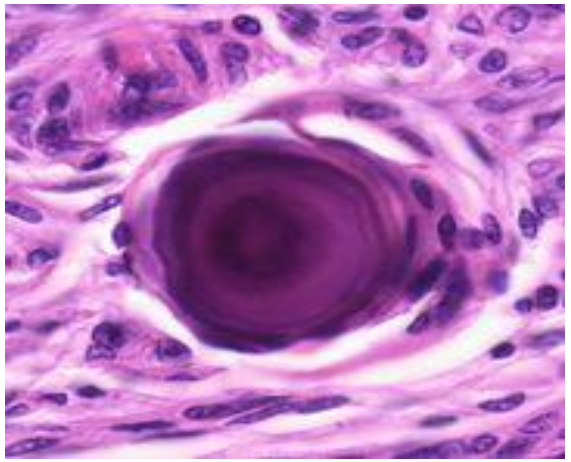
More complex papillary structures protruding in the surface

Serous cystadenocarcinoma

The tumor is predominantly solid with areas of hemorrhage and necrosis

Microscopic appearance

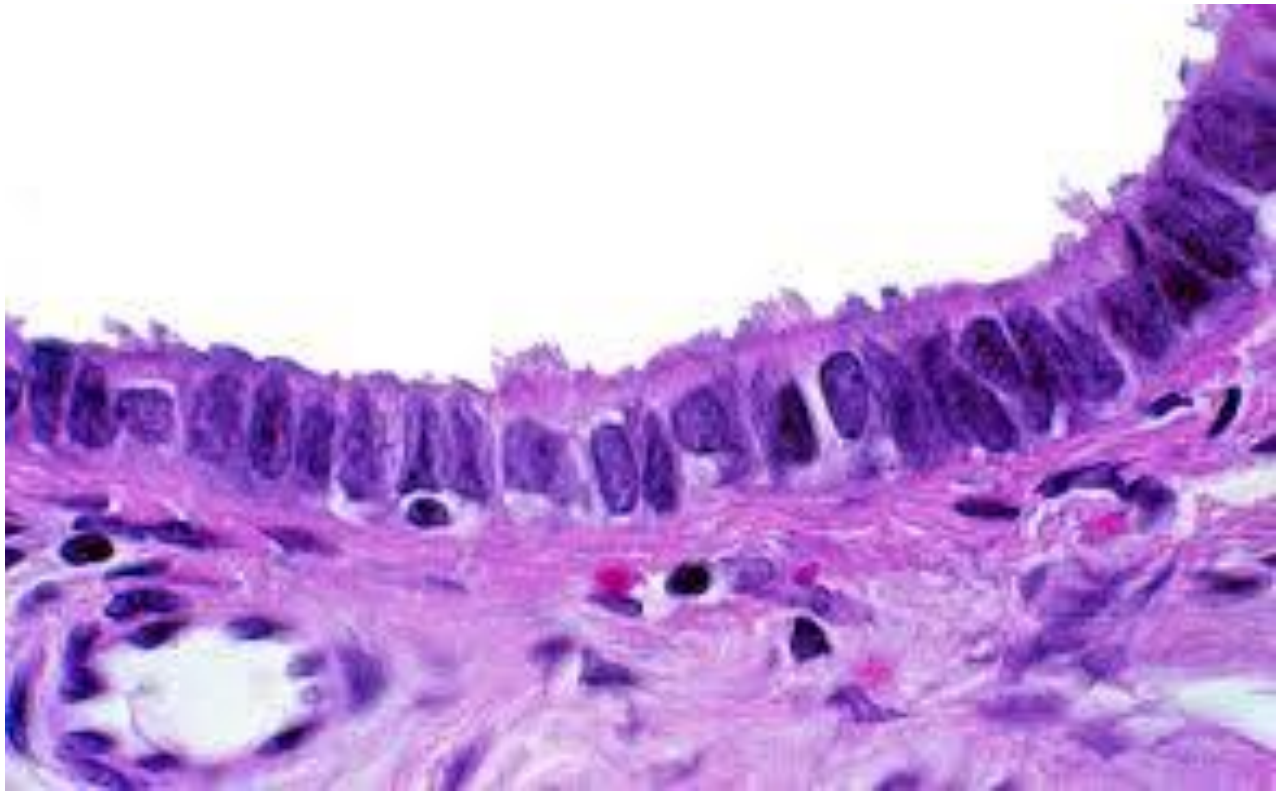
- The cyst is lined **tall columnar epithelium** resembles tubal epithelium
- Papillary formation
- **Psammoma bodies** (concentrically laminated calcified concretions) in 30%



Benign tumors

- **Serous cystadenoma**
- A single layer of cells without atypia, architectural complexity or invasion

Benign tumors

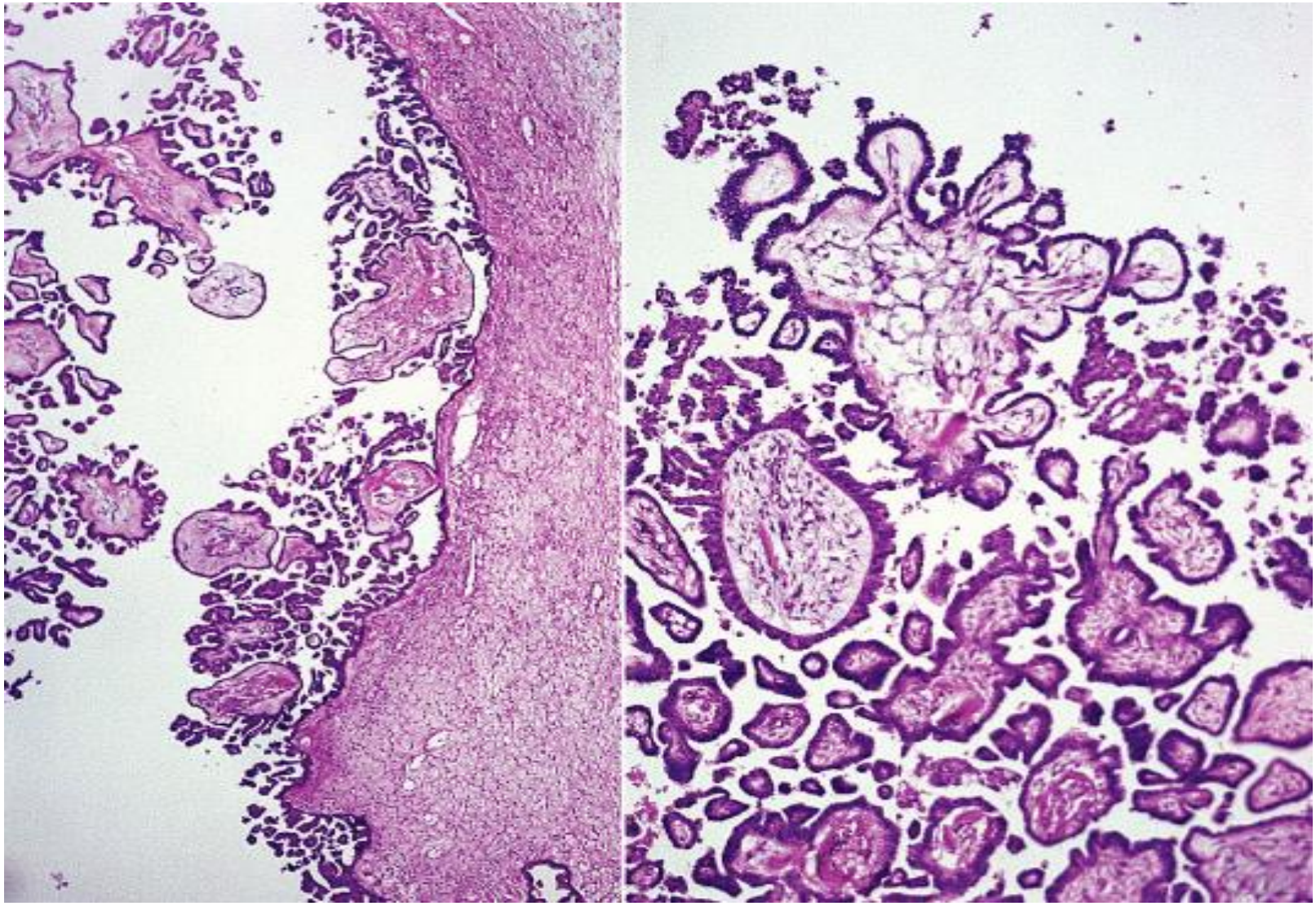


Serous cystadenoma

Borderline serous neoplasms

- Architectural complexity:
- Stratification of cells and branching papillae
- Nuclear atypia
- No stromal invasion

Borderline serous neoplasm

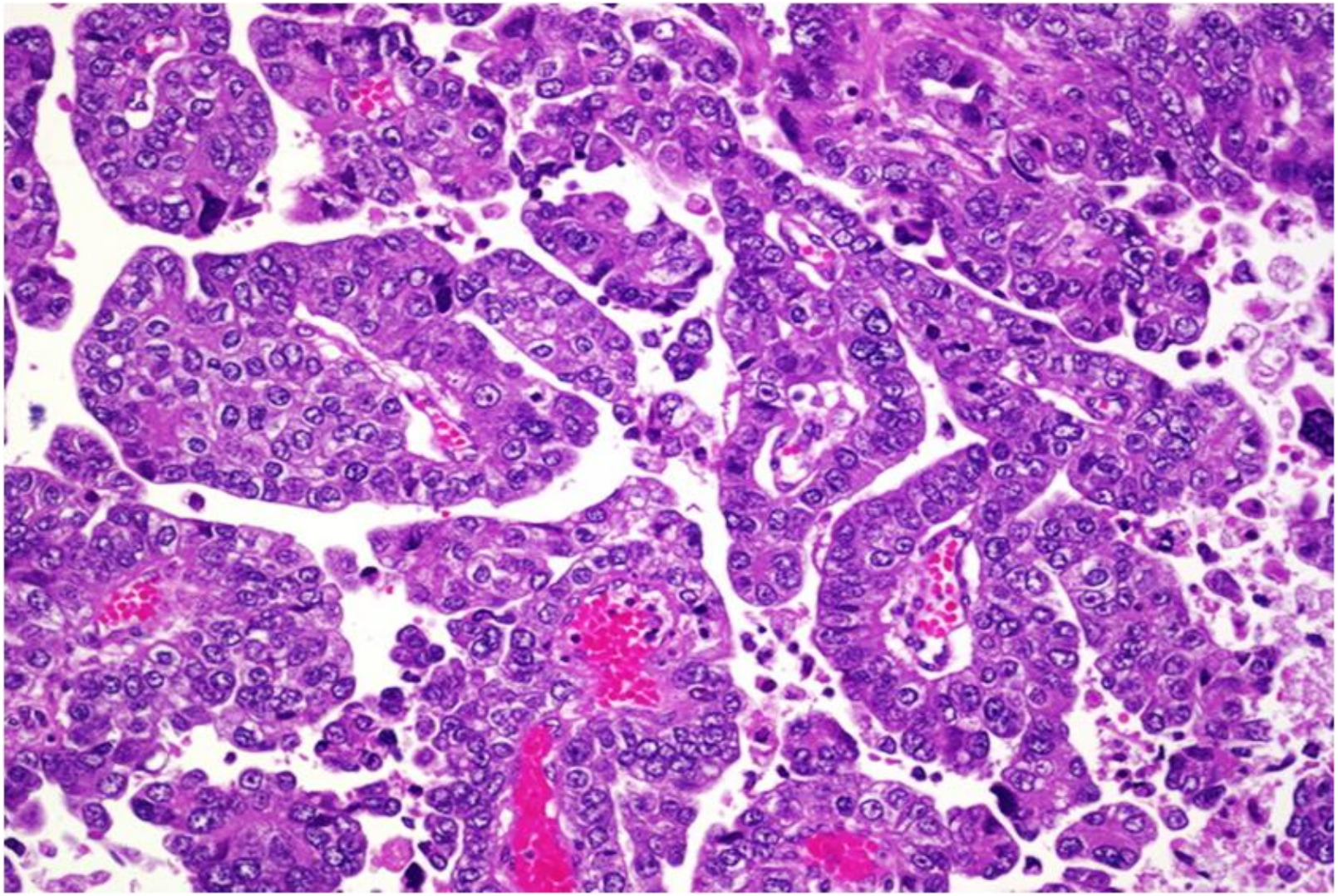


Serous cystadenocarcinoma

- Architectural complexity
- Severe atypia (anaplasia)
- Frank stromal invasion

- Spread to peritoneal cavity and LNs
- Distant metastasis is rare
- Poor prognosis, depends on the stage

Serous cystadenocarcinoma



Mucinous Tumors

- Lined by mucin-secreting epithelial cells
- Less likely to be malignant or bilateral than serous neoplasms
- The prognosis of mucinous cystadenocarcinoma is better than serous.

Type	Bilateral
Mucinous cystadenoma 80%	5%
Borderline mucinous neoplasm10%	10%
Mucinous cystadenocarcinomas 10%	20%

Gross morphology

- Usually large & multilocular, containing mucin
- Malignant tumors have more solid component
- May rupture with spillage of mucin
- **Pseudomyxoma peritoneii**
  - Mucin and epithelial cells in peritoneal cavity
  - Primary GI neoplasm metastasize to ovary, mostly originate in the appendix

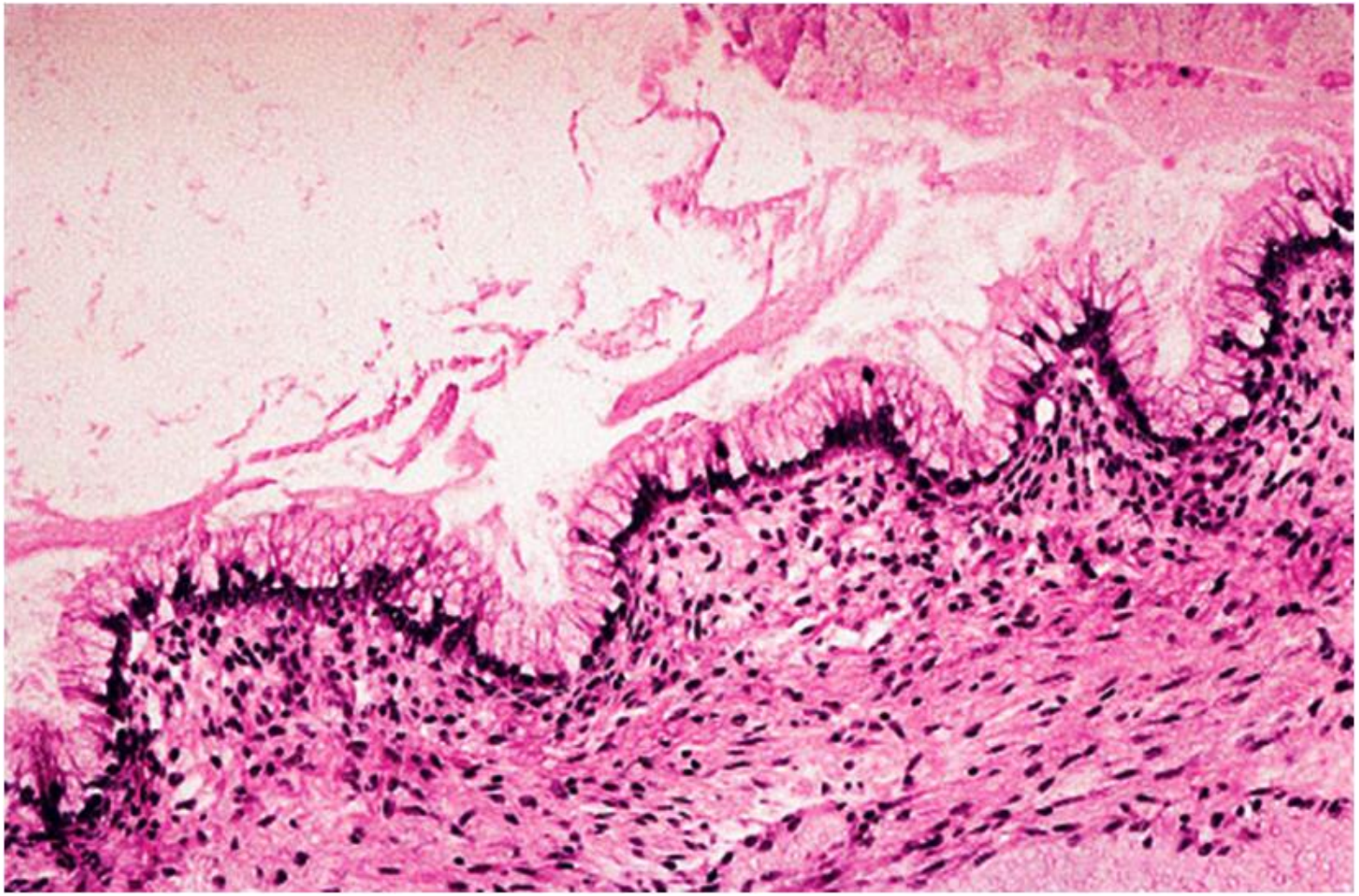
Borderline mucinous neoplasm

Microscopic appearance

- The cyst is lined by mucin secreting cells
- Papillae are not common & No psammomma

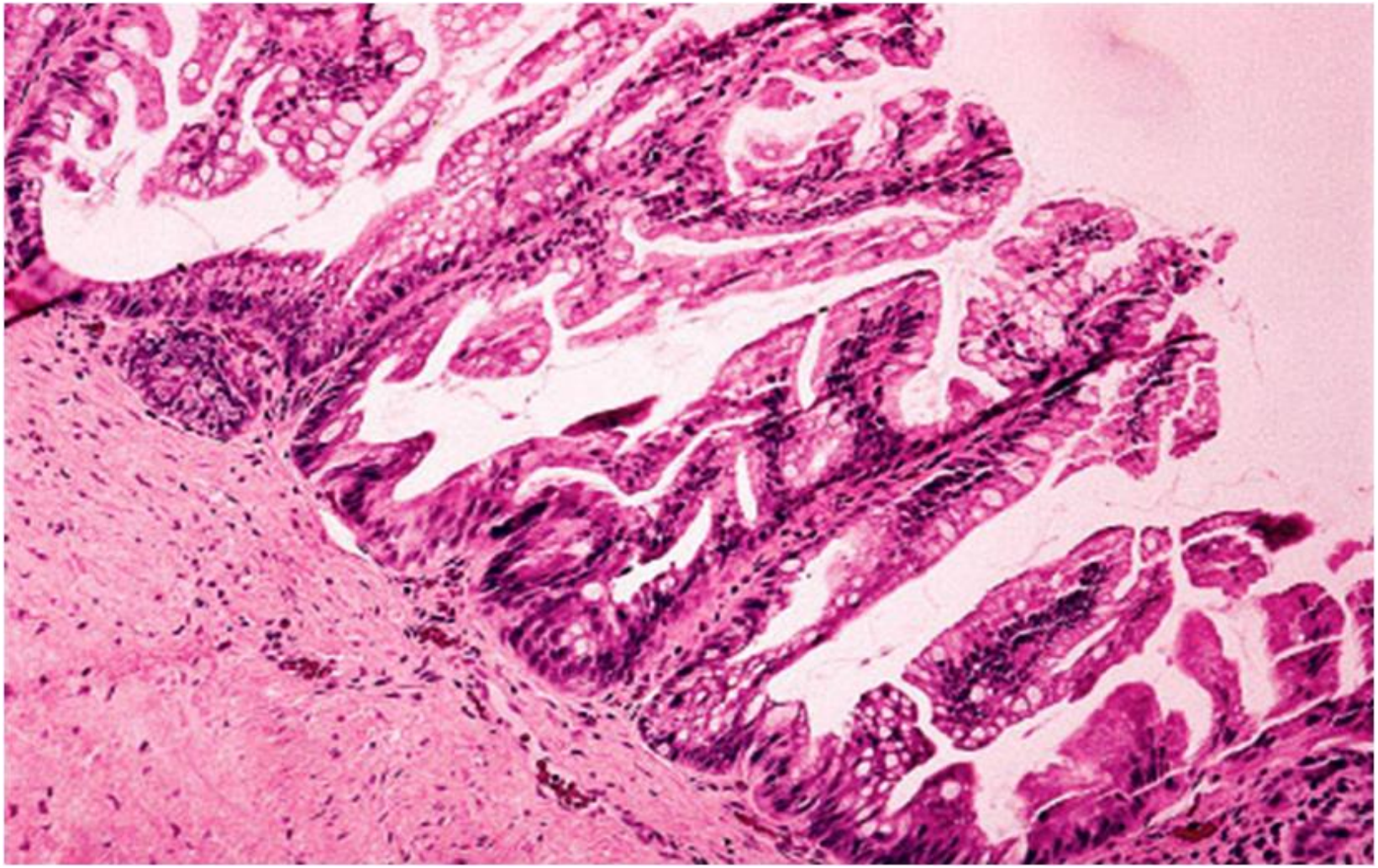
- Two histologic types:
- Endocervical type
- Intestinal type type
  - More in borderline & malignant tumors

Mucinous cystadenoma



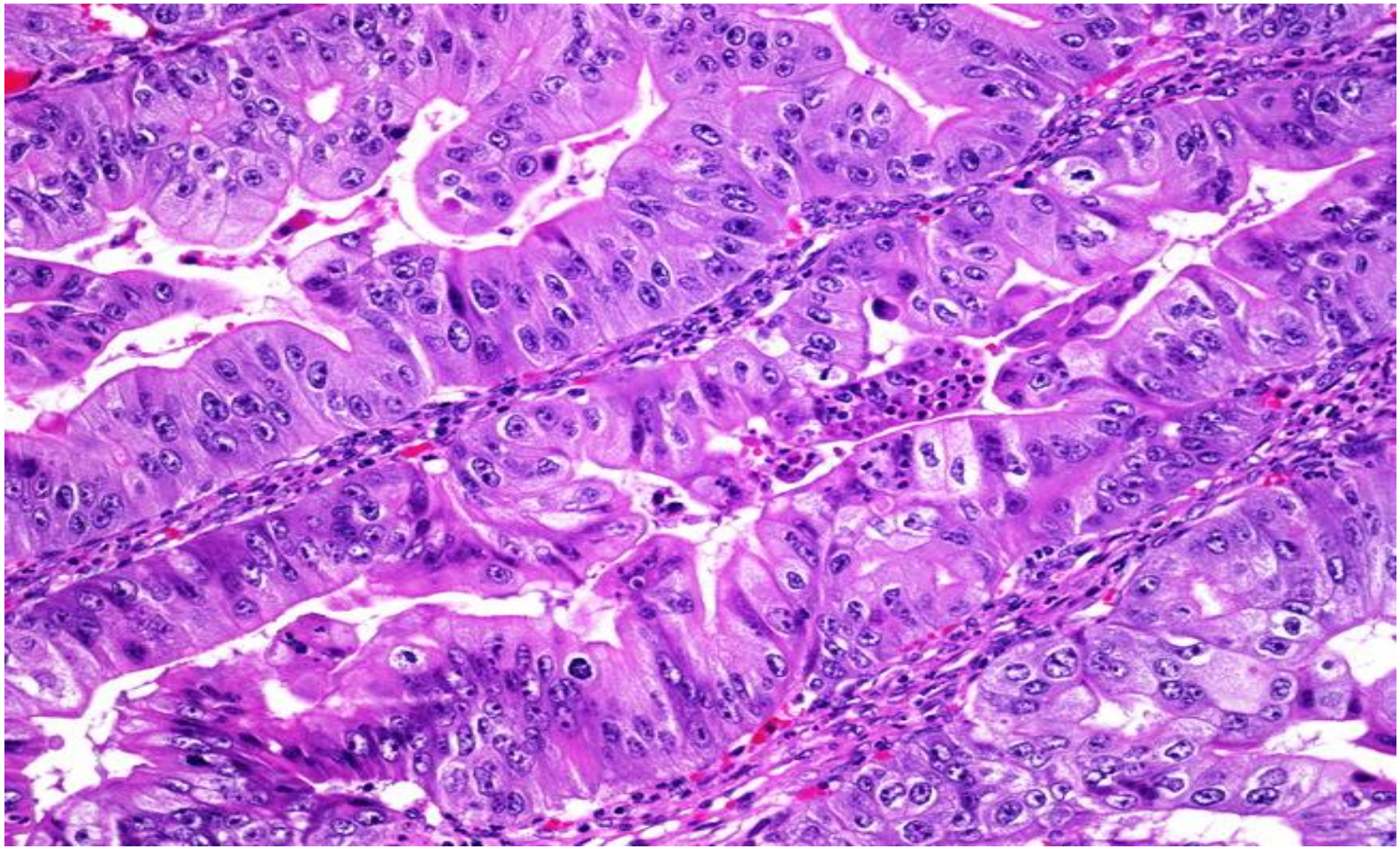
A single layer of mucin secreting cells without atypia

Mucinous borderline neoplasm



Architectural complexity and atypia without invasion

Mucinous cystadenocarcinoma



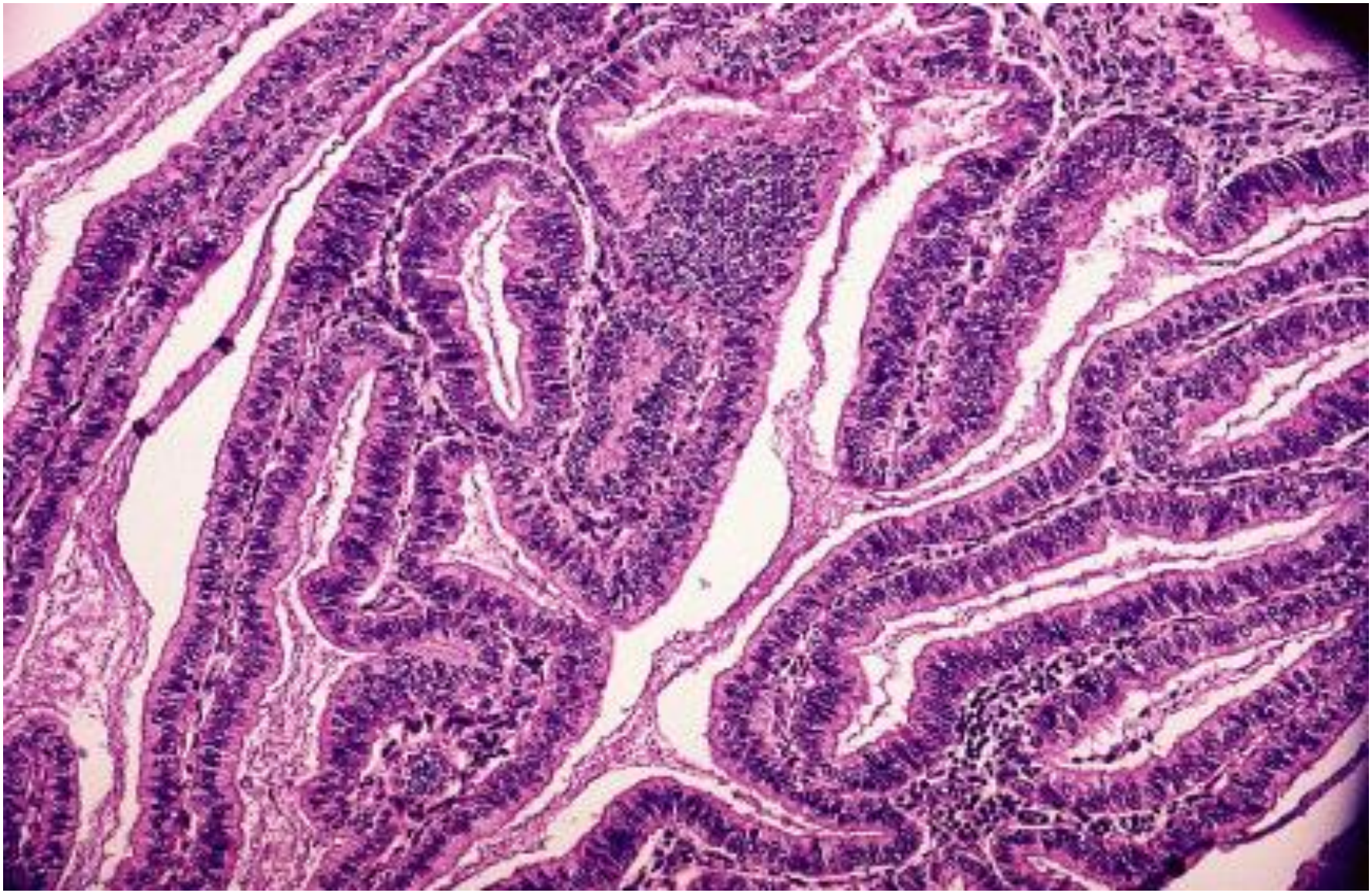
The cyst wall in this case showed papillae & cribriform glands lined by highly atypical cells with frequent mitoses. The underlying stroma was penetrated by nests of malignant cells with desmoplastic response

Endometrioid Tumors

- Arise in a background of endometriosis
- May be solid or cystic
- Usually malignant, bilateral in 30%
- Benign and borderline may exist

- **Endometrioid carcinoma**
- Microscopically resemblse endometrioid adenocarcinoma of endometrium.
- 15-30% have endometrial carcinoma
- PTEN mutation

Endometrioid carcinoma of ovary



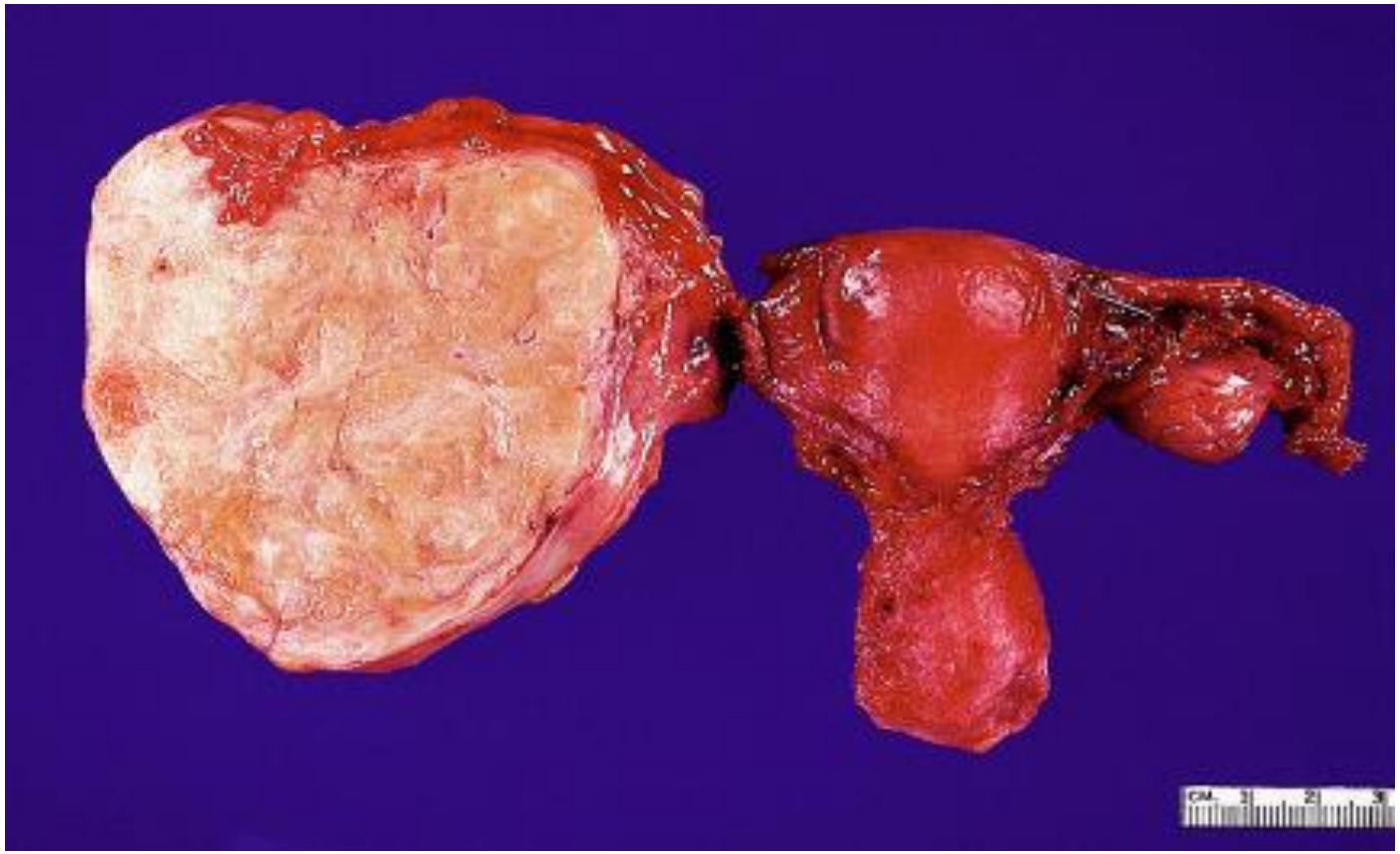
Brenner Tumor

- An uncommon tumor
- Most are benign and unilateral
- May be malignant or borderline

- Rarely, found as nodules within the wall of a mucinous cystadenoma

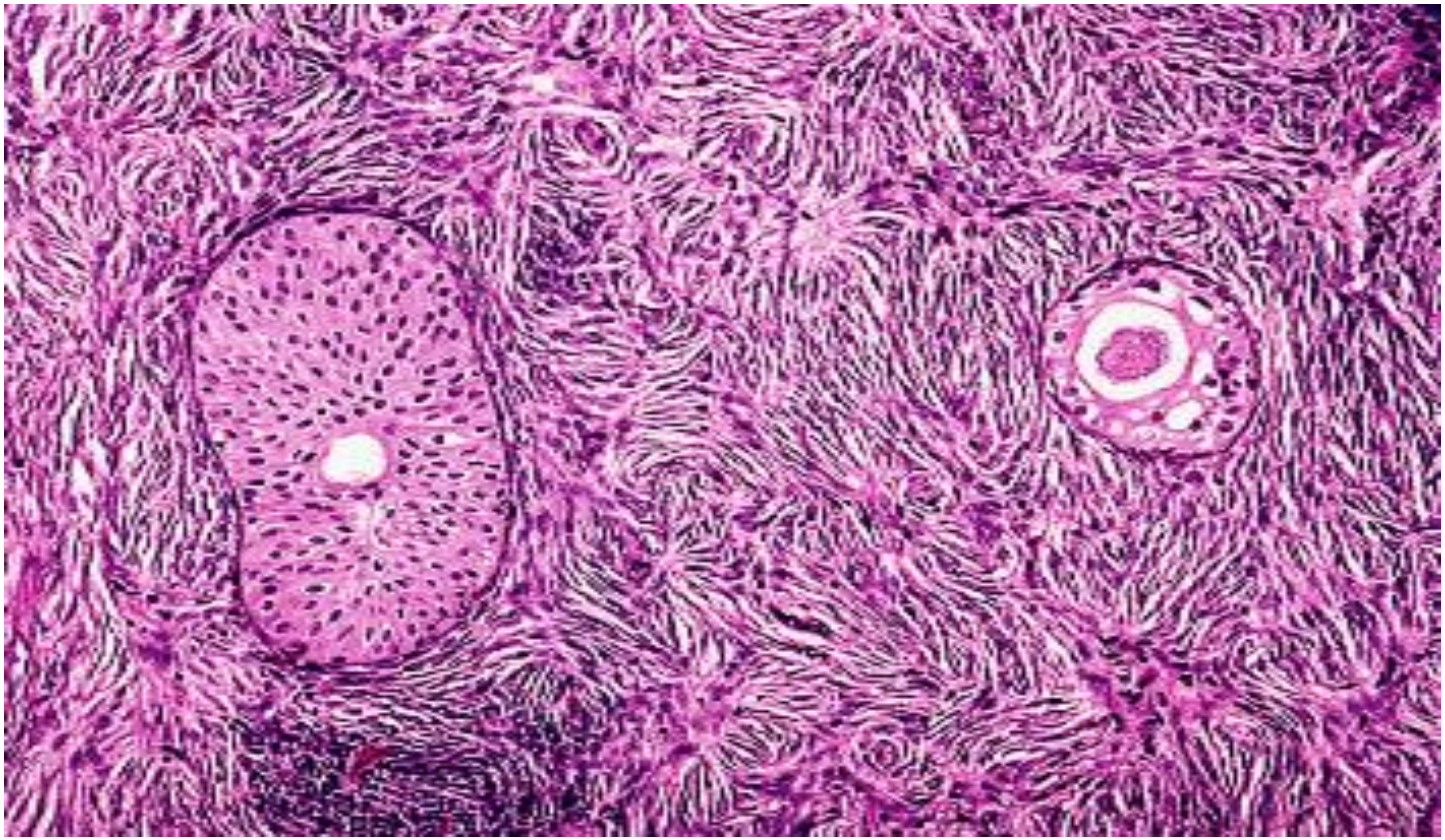
Gross appearance

- Encapsulated
- Usually solid with gray-white cut surfaces



Microscopic appearance

- Abundant stroma containing nests of transitional-like epithelium



Features of surface epithelial tumors

- Usually asymptomatic until advanced
- Local pressure symptoms (e.g., pain, GI upset, urinary frequency, ↑ abdominal girth)
- Metastatic seeding of peritoneal cavity produce malignant ascites

- CA125 tumor marker
- Elevated in 75-90%
- Used in screening, diagnosis, follow up