PATHOLOGY & STAGING OF GYNAECOLOGICAL CANCERS

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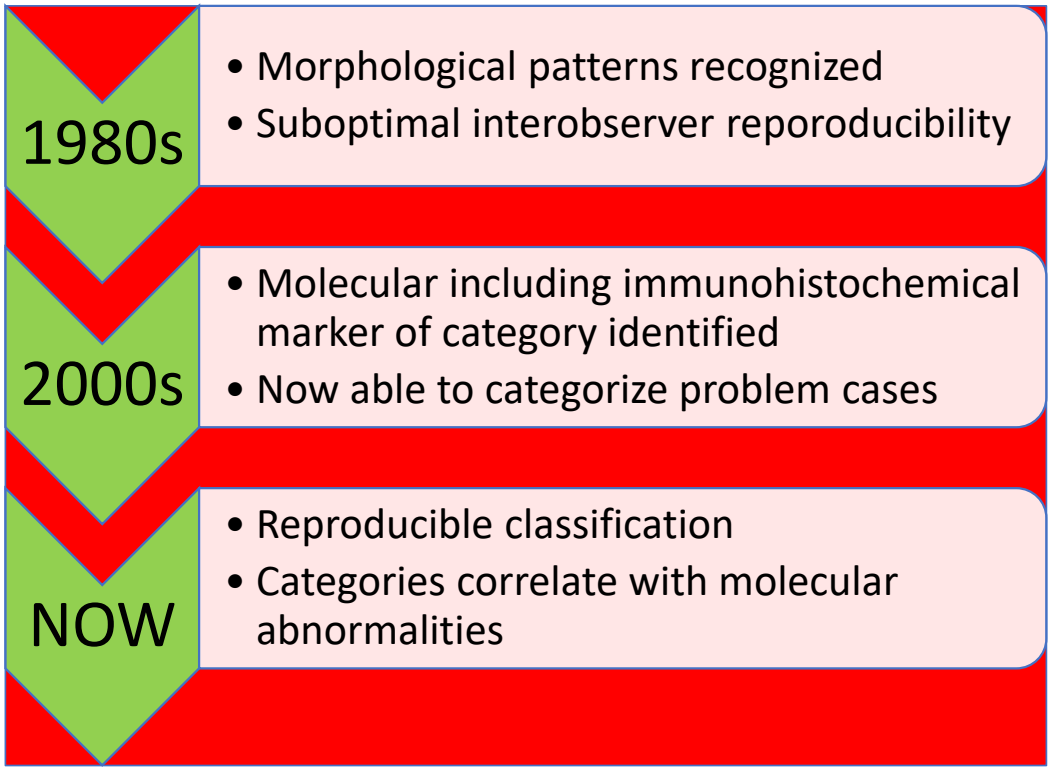
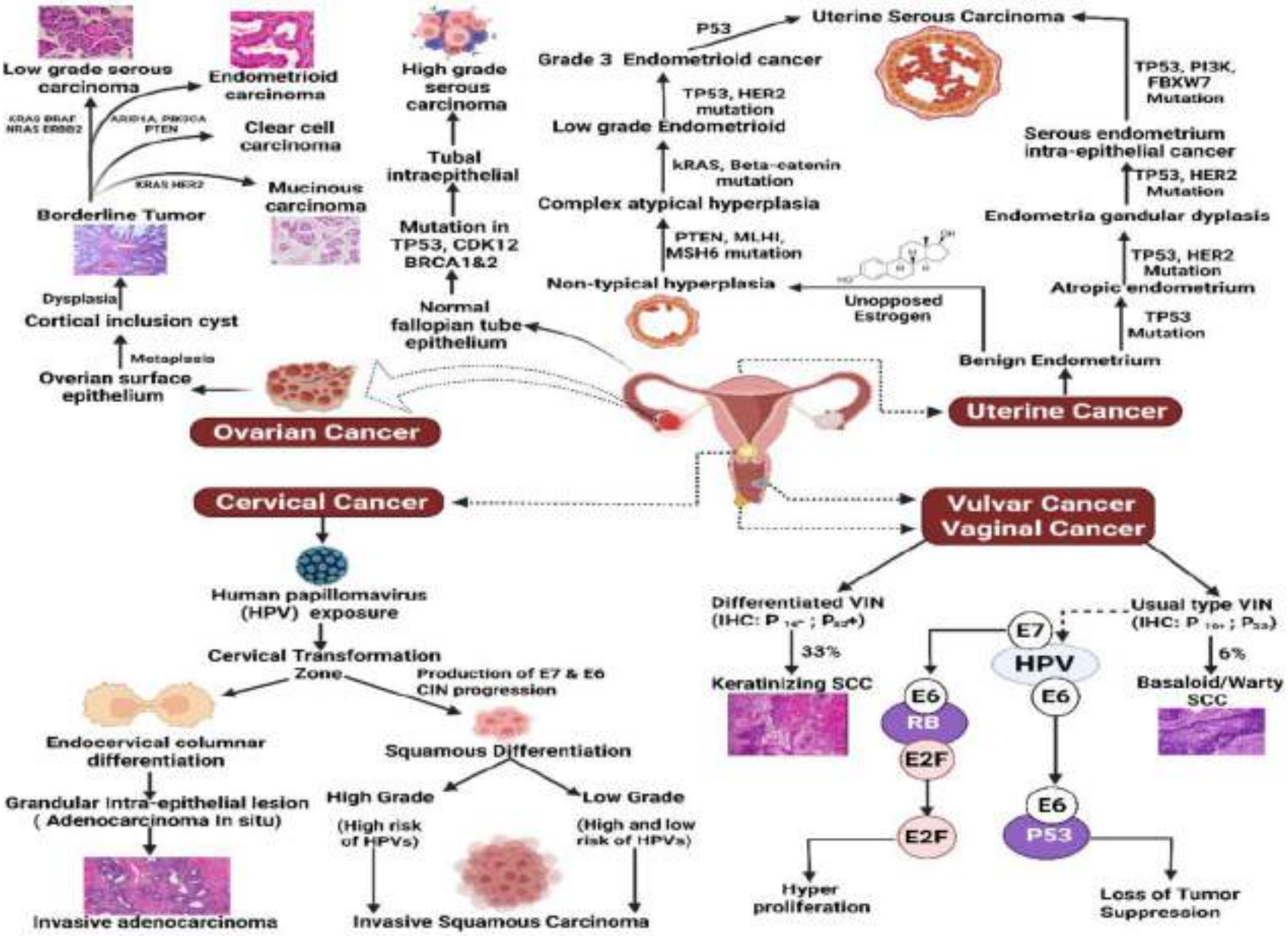
- Classification of Female Genital Tract tumors has evolved significantly over the past decade in light of new and often key molecular discoveries that have influenced the categorization of a number of these neoplasms
- Standard aspects of conventional pathology remain the bedrock of the interpretation and classification of FGT neoplasms in routine practice



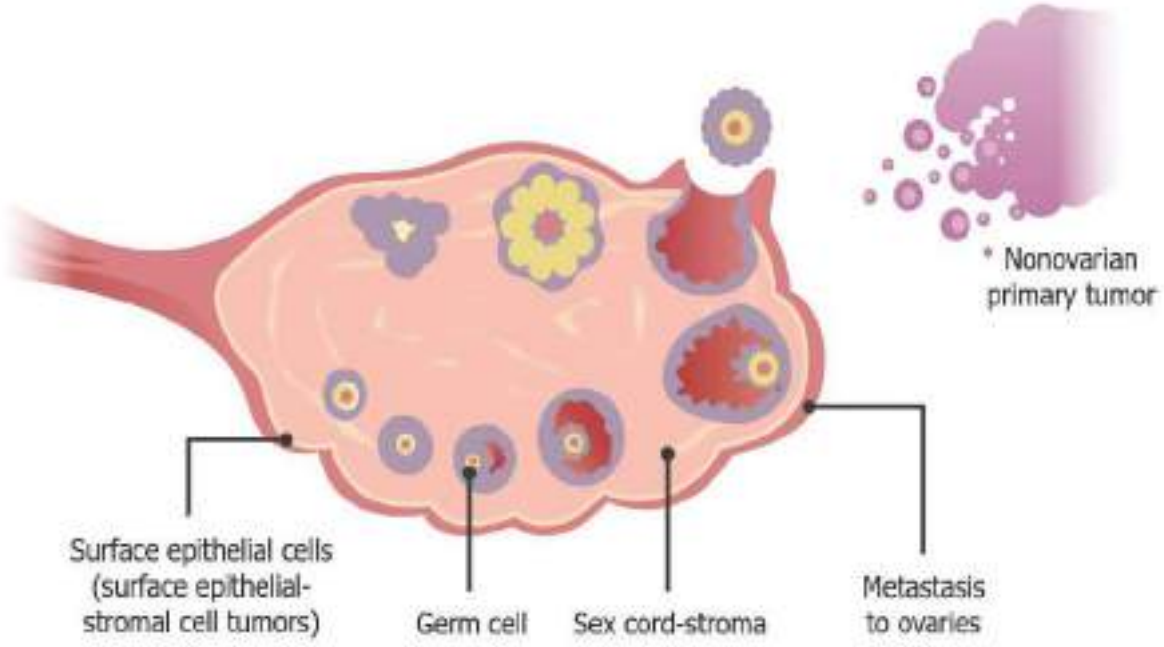


Pathogenesis of gynecological cancers

OVARIAN CANCERS

CLASSIFICATION

- CARCINOMAS
- MESENCHYMAL TUMORS
- MIXED EPITHELIAL MESENCHYMAL TUMORS
- GERM CELL TUMORS
- SEX CORD STROMAL TUMORS
- GERM CELL-SEX CORD STROMAL TUMORS
- MISCELLANEOUS TUMORS
- METASTASES



CARCINOMAS

- Carcinoma of the ovary, considered formerly to be a single disease with a common origin from the ovarian surface epithelium and considerable morphological variability, is now recognized to be five distinct ‘histotypes’:

✓High-grade serous carcinoma(HGSC)

✓Endometrioid carcinoma (EC)

✓Clear cell carcinoma (CCC)

✓Low-grade serous carcinoma (LGSC) and

✓Mucinous carcinoma (MC)

- These differ with respect to precursor lesions, patterns of spread, biomarker expression, survival and association with hereditary cancer syndromes
- They also have very distinct underlying molecular abnormalities, and the ovarian carcinoma histotype diagnosis reflects those potentially targetable molecular changes

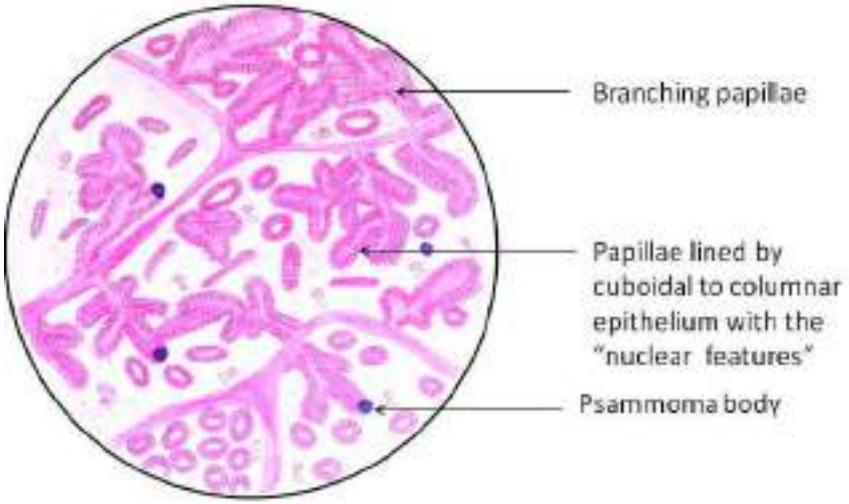
Features of the five major histologic types of ovarian carcinoma.

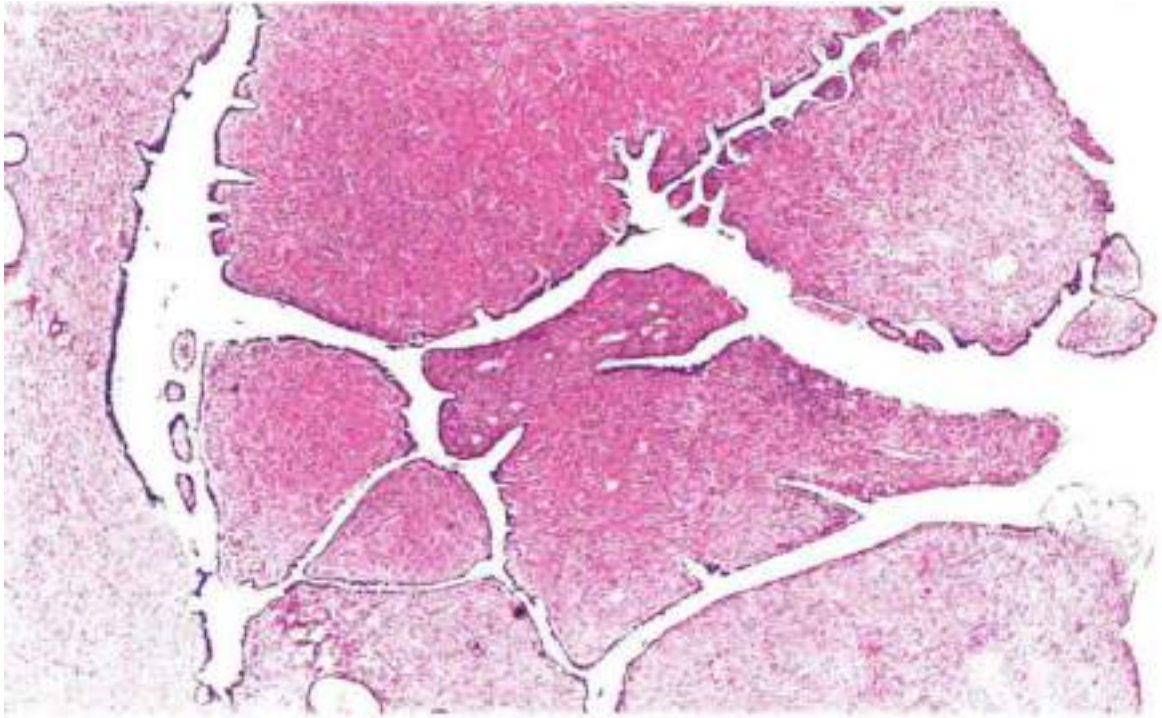
	HGSC	CCC	EC	LGSC	MC
Mean age	63	55	58	53	45
5-Year survival (stage III only)	40	23	66	71	NA
Origin	Fallopian tube	Endometriosis	Endometriosis	Cystadenoma	Germ cell, transitional epithelium
Molecular abnormalities	Genomic instability; TP53 mutation; homologous recombination DNA damage repair defects; CCNE1, NOTCH3 activation; Rb, NF1 inactivation	Wnt-catenin activation; ARID1A-chromatin remodeling complex inactivation; PI3K activation; PTEN inactivation, MMR abnormalities		KRAS/BRAF/MEK pathway activation	ERBB2/KRAS/ BRAF/MEK pathway activation
Inherited syndromes	HBOC	LS	LS	?LS	?LS
Sensitivity to platinum-based chemotherapy	Sensitive	Relatively resistant	Relatively resistant	Relatively resistant	Relatively resistant
Adjuvant/targeted therapies licensed or in trial	PARPi; immune checkpoint inhibitors	Radiotherapy; Sunitinib	mTOR inhibitors	Selumetinib (MEK1/2 inhibitors)	Trastuzumab

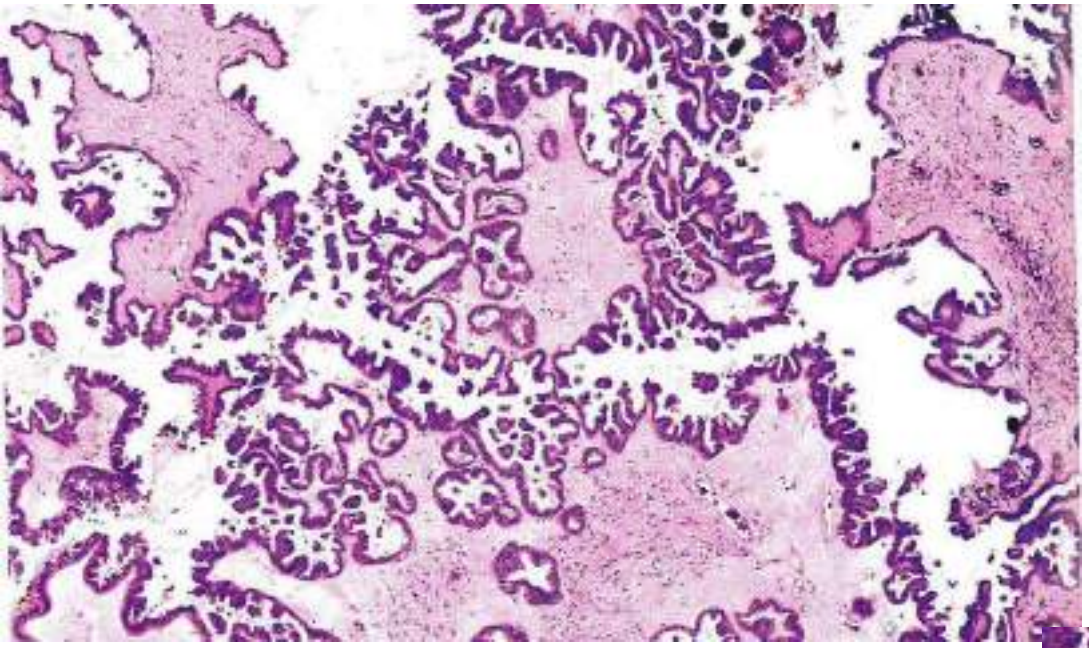
CCC, Clear cell carcinoma; *EC*, endometrioid carcinoma; *HBOC*, hereditary breast and ovarian cancer syndrome; *HGSC*, high-grade serous carcinoma; *LGSC*, low-grade serous carcinoma; *MC*, mucinous carcinoma; *LS*, Lynch syndrome; *NA*, not applicable.

From Singh N, Gilks CB. The changing landscape of gynaecological cancer diagnosis: implications for histopathological practice in the 21st century. *Histopathology*. 2017;70:56–69.

SEROUS CYSTADENOMA



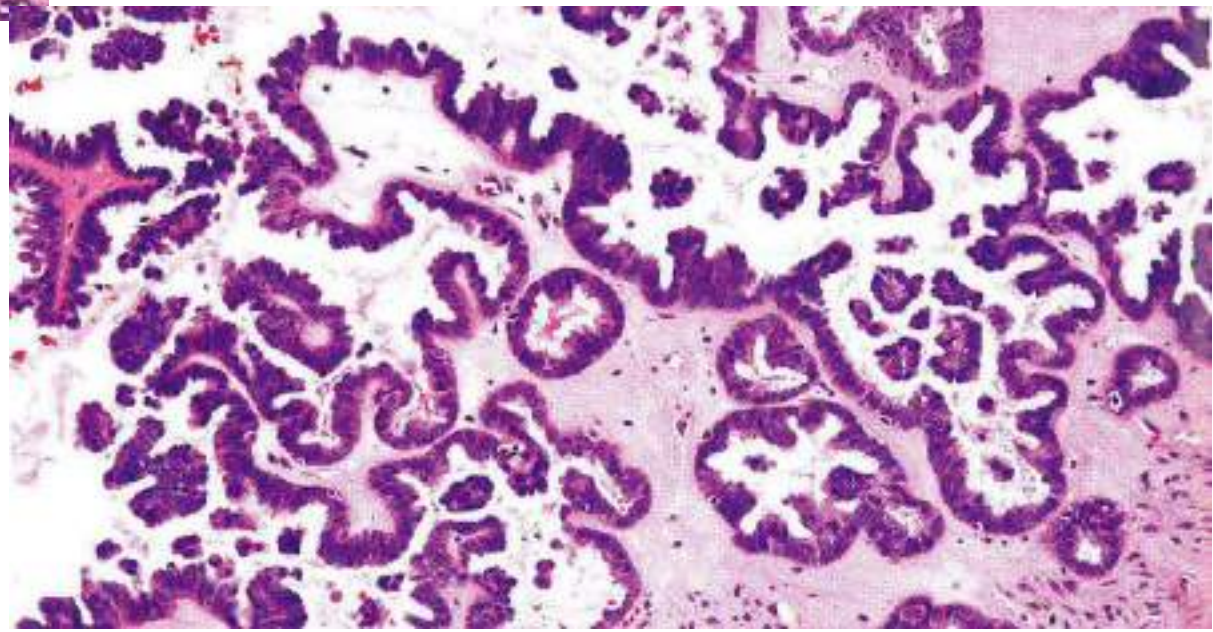




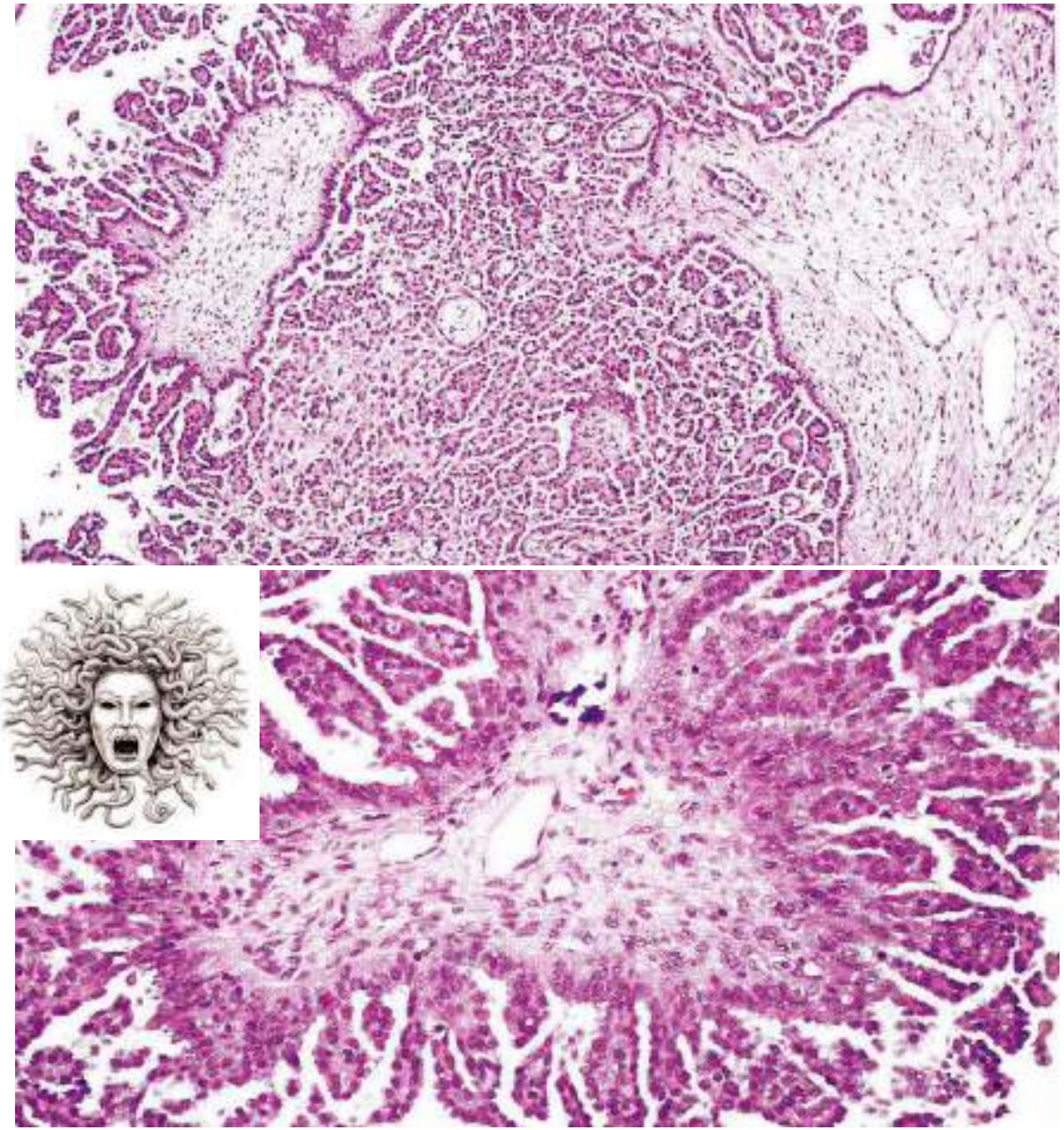
SEROUS BORDERLINE TUMOR

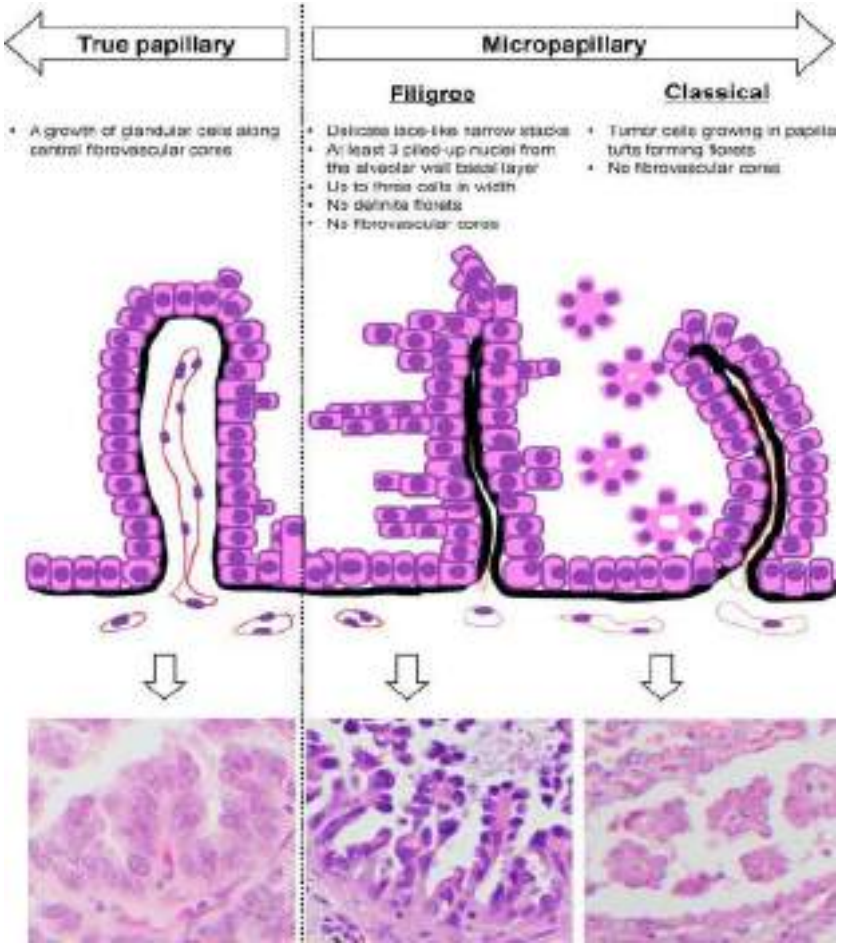
Non-invasive low grade proliferative serous epithelial neoplasm

- Numerous slender to bulbous, irregularly contoured papillae with fibrous, hyaline or myxoid cores
- Hierarchical branching pattern - larger papillae arborize to sequentially smaller papillae terminating in epithelial clusters or single cells
- Pseudostratified, crowded lining with hobnailing or epithelial tufting, which exfoliate from papillae



- ✓ Heterogenous cellular population - cuboidal to columnar ciliated, secretory or eosinophilic cells
- ✓ Up to moderate atypia - mild cellular enlargement, chromatin coarsening, small nucleoli
- ✓ Minimal, nonatypical mitotic activity
- ✓ Psammomatous (concentrically lamellated) or dystrophic calcifications
- ✓ If this intracystic proliferation < 10% of the tumor, the neoplasm should be classified as serous cystadenoma with focal epithelial proliferation



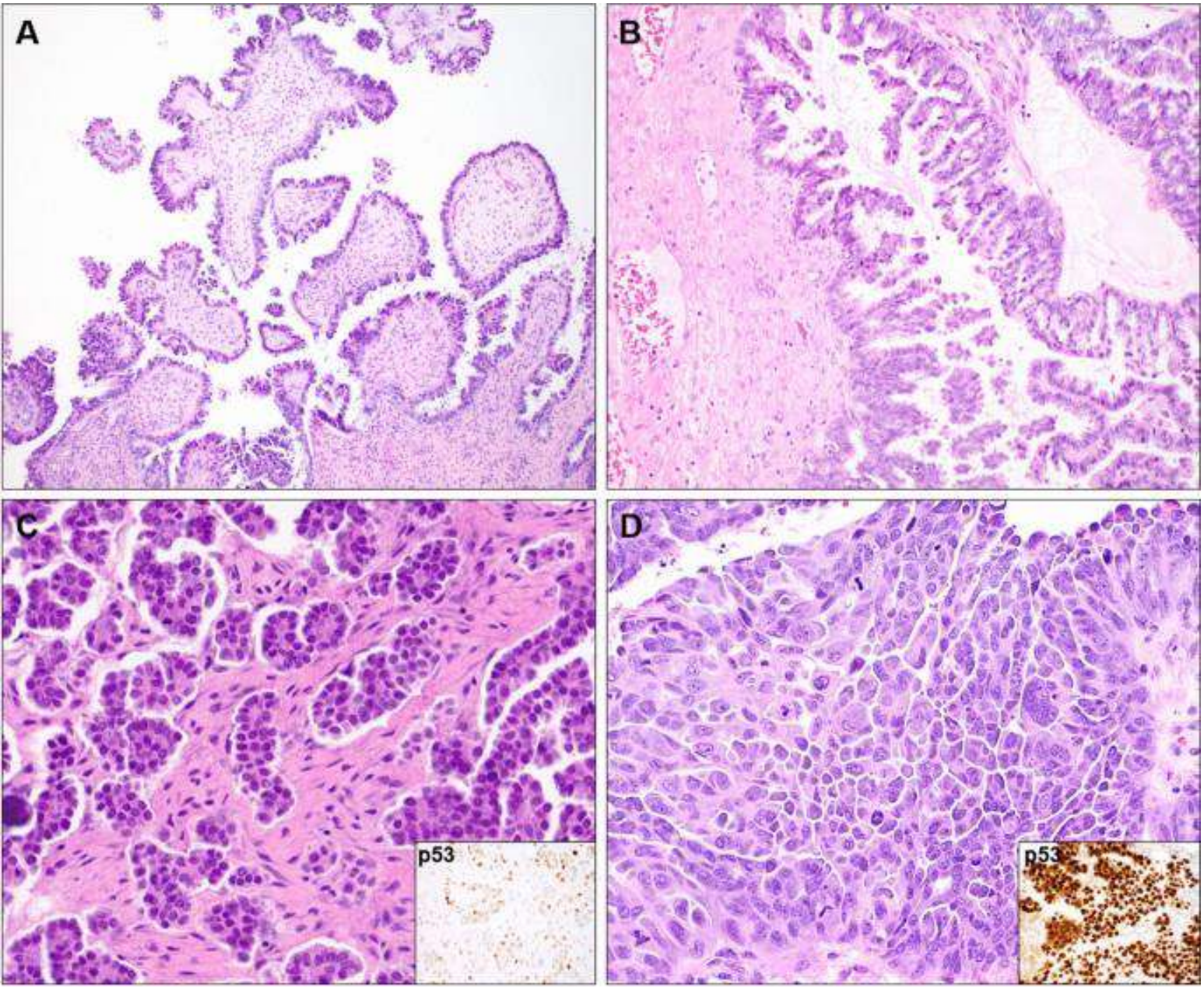


MICROPAPILLARY SBT

Micropapillary / cribriform subtype defined as SBT harboring a focus of ≥ 5 mm (confluent linear extent) of pure micropapillary/cribriform growth

LOW GRADE SEROUS CARCINOMA

- Epithelial carcinoma of serous cell lineage, usually with distinctive patterns of invasion and low grade malignant cytologic atypia
- Often bilateral ovarian masses that are solid or solid and cystic with calcifications
- Presents ~10 years earlier than patients with high grade serous carcinoma
- Precursor lesion is often a borderline serous tumor
- Fine papillary, nodular growth
- Little to no necrosis
- Calcification in the ovary and extraovarian lesions can be extensive



Uniform/homogeneous population of small cells with scant cytoplasm

Mild to moderate nuclear atypia at most (grade 1 or 2)

No nuclear pleomorphism (< 3x variation in size)

May have a conspicuous nucleolus

Low mitotic index: < 12 mitotic figures per 10 high power fields

Little to no necrosis

Psammoma bodies are frequent

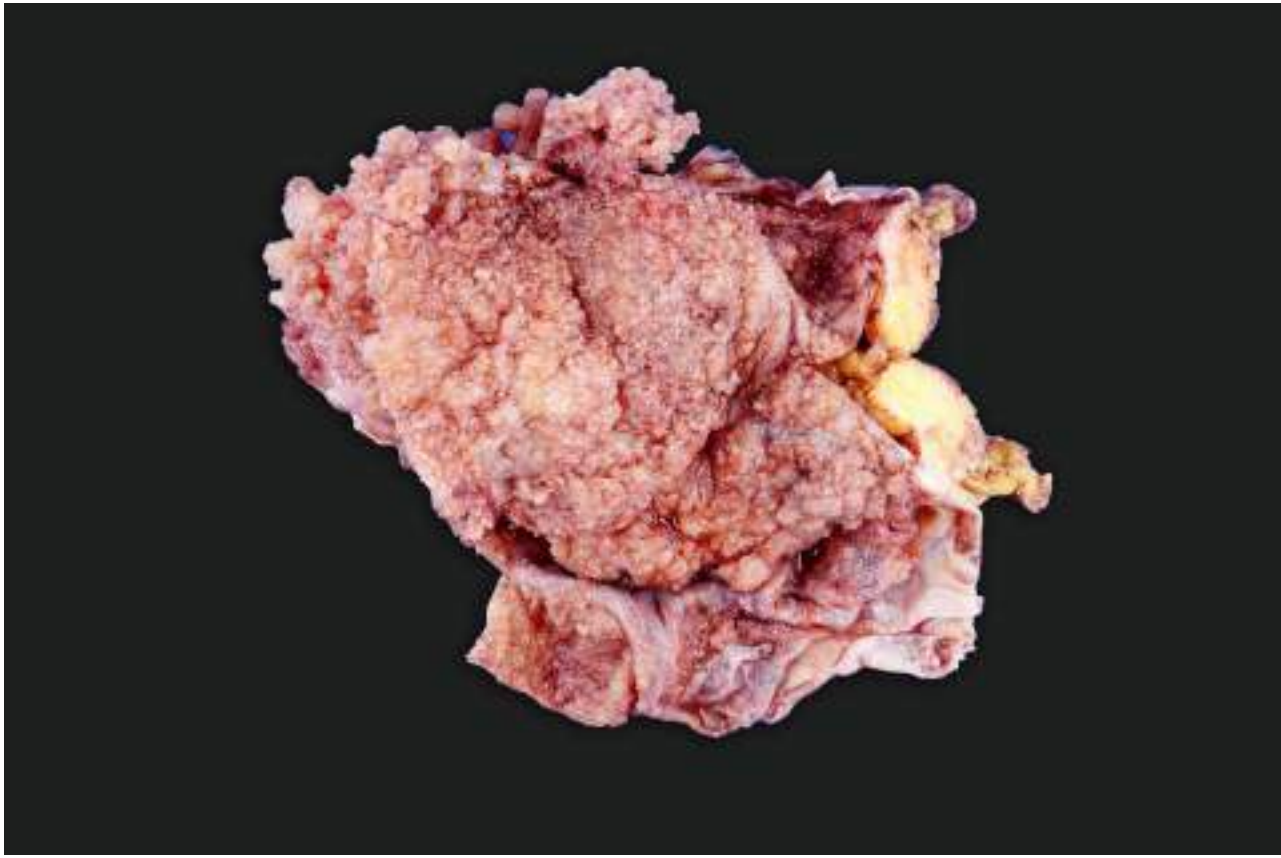
CK7, PAX8, WT1, ER (95%), PR (50 %)
Low Ki67 proliferation index

HIGH GRADE SEROUS CARCINOMA

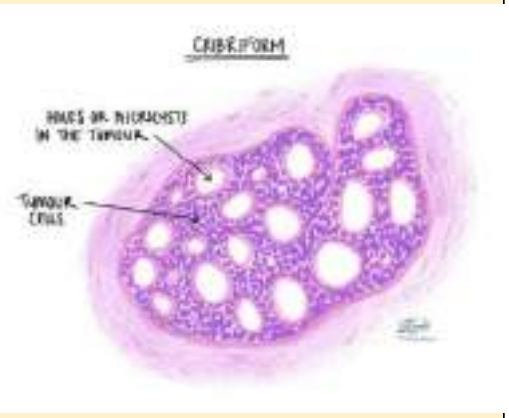
Epithelial carcinoma of serous cell lineage with papillary, glandular and solid growth patterns and high grade cytologic atypia

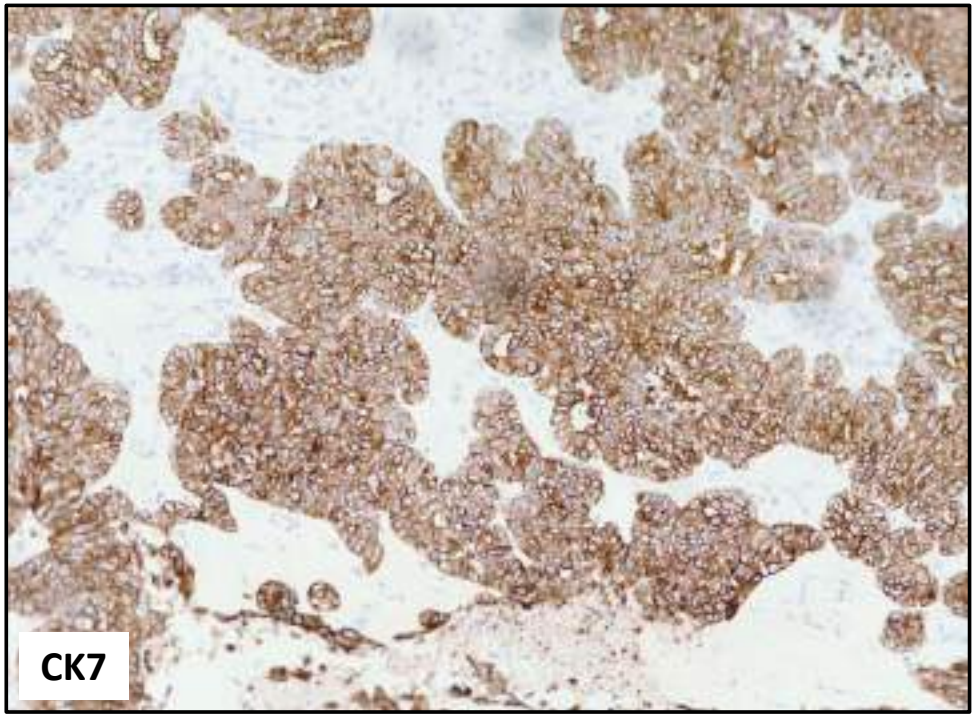
MACROSCOPIC APPEARANCE

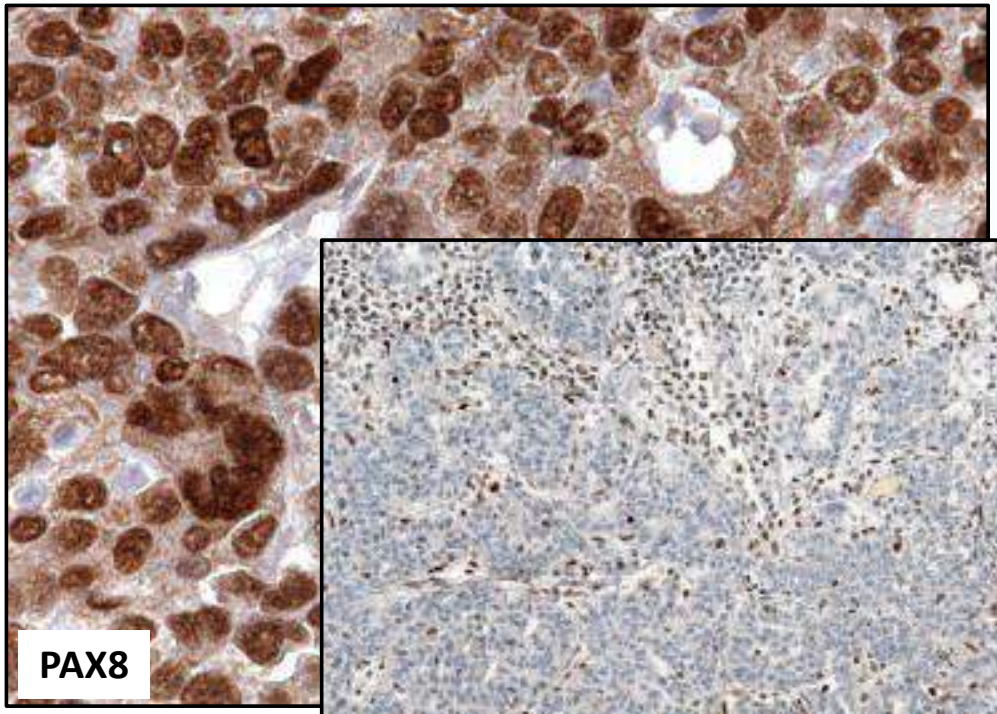
- Often bilateral
- Variable in size; often large
- Exophytic with solid or papillary growth
- Solid areas tan to white with necrosis and hemorrhage
- Serous / bloody fluid filled cysts
- Fallopian tube can be grossly involved at fimbriated end

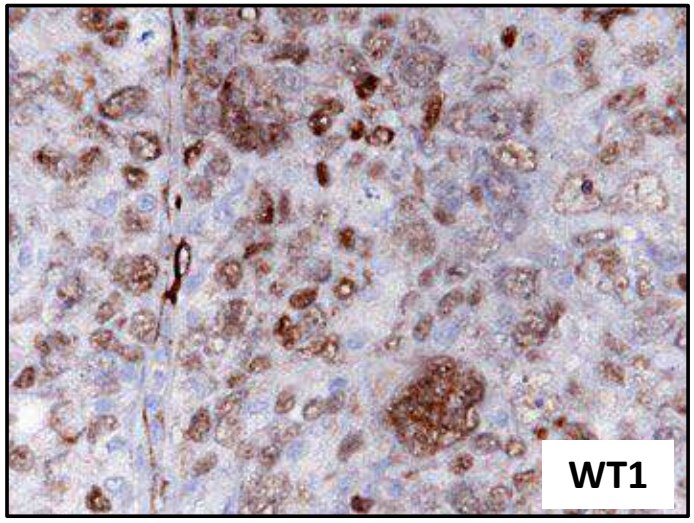


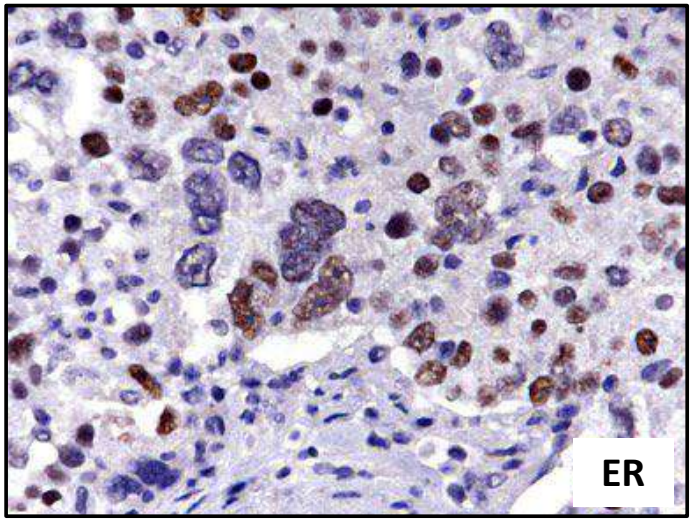
- Solid masses of columnar to cuboidal cells with eosinophilic cytoplasm and slit-like spaces (fusion of papillae)
- Solid, pseudoendometrioid, transitional cell carcinoma-like (SET) appearance
- Hierarchical papillary branching, glandular and cribriform patterns common
- Significant nuclear atypia
- Significant nuclear pleomorphism (> 3x variation in size) with large, bizarre and multinucleated forms
- Prominent nucleolus, often large and eosinophilic
- High mitotic index: ≥ 12 mitotic figures per 10 high power fields, often atypical
- Necrosis is frequent

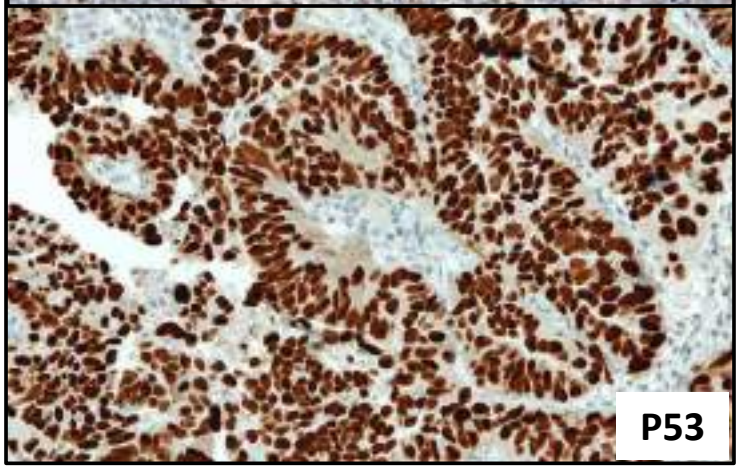


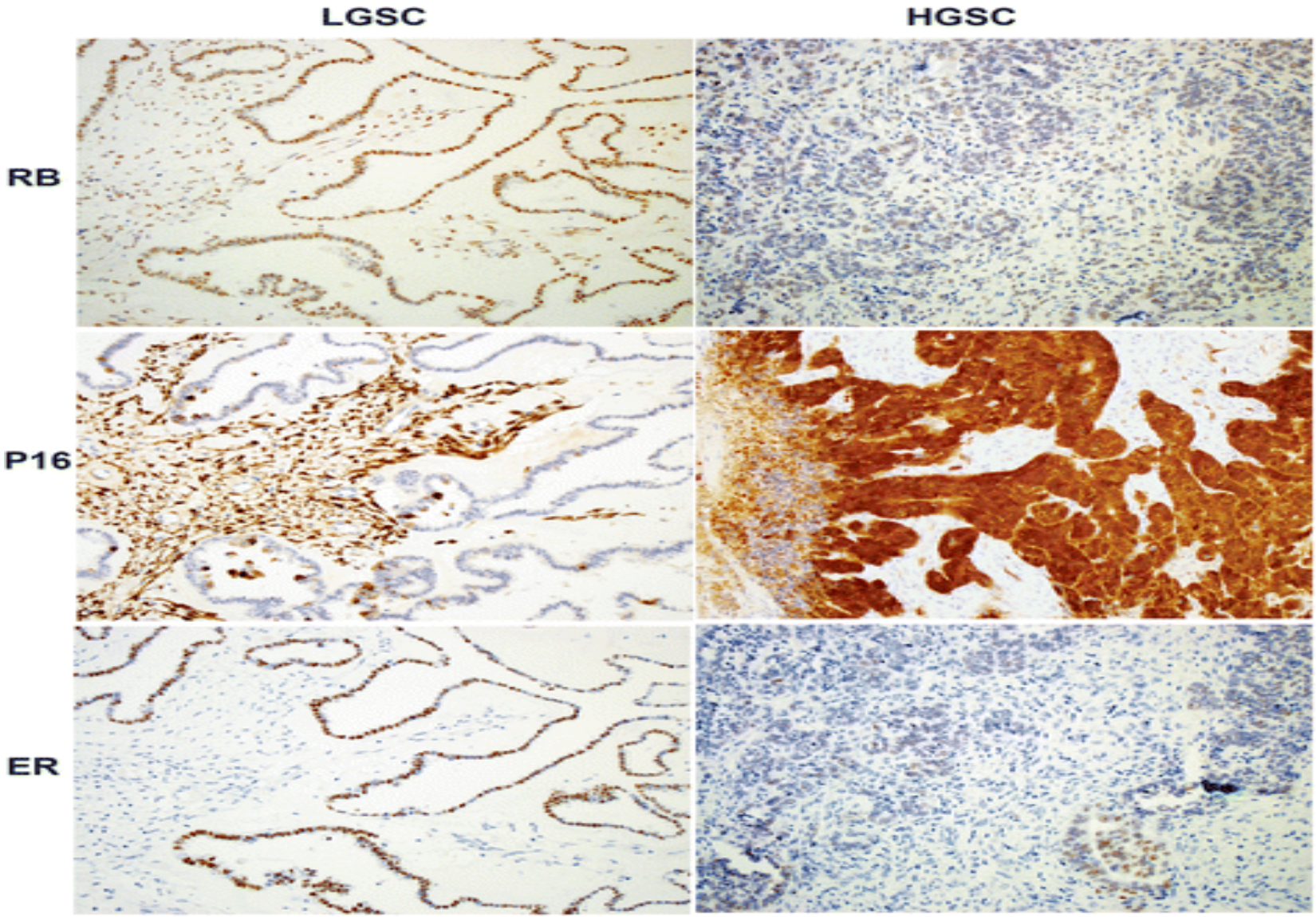

CK7


PAX8


WT1

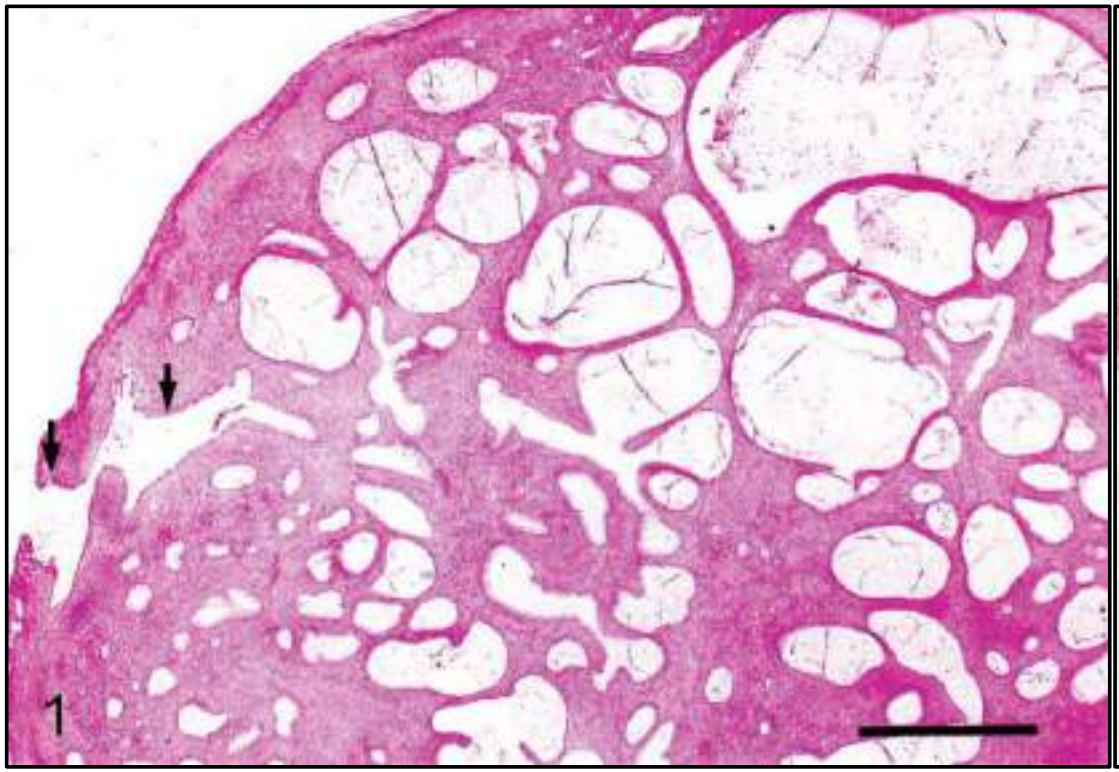

ER

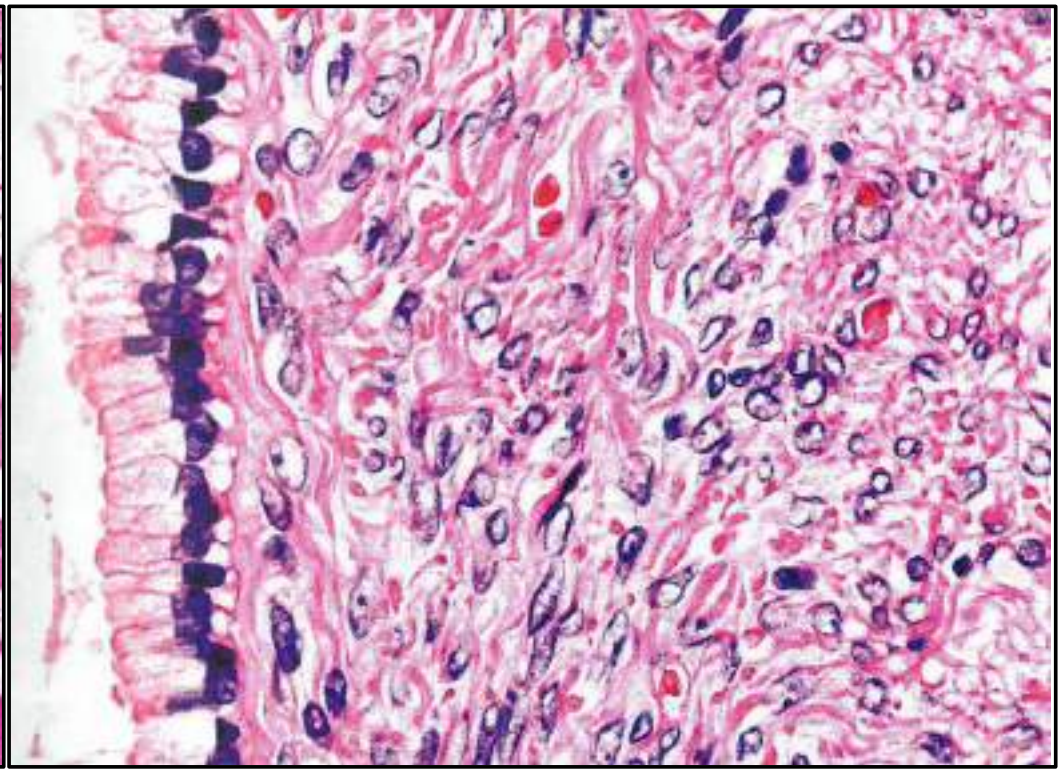

P53


LGSC
HGSC
RB
P16
ER

MUCINOUS CYSTADENOMA

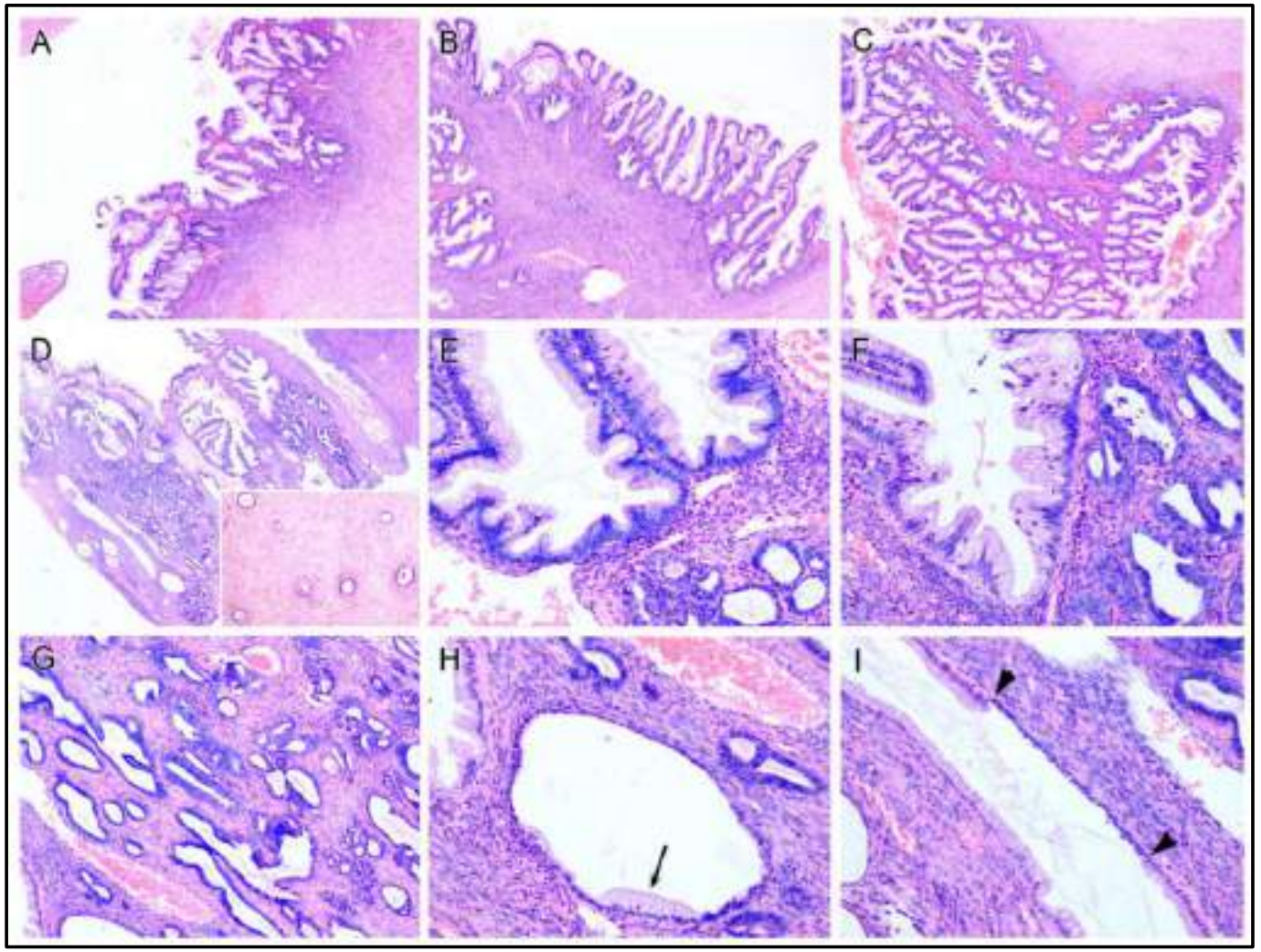
Benign mucinous neoplasm composed of cysts and glands lined by gastrointestinal or Müllerian type mucinous epithelium lacking architectural complexity or cytologic atypia





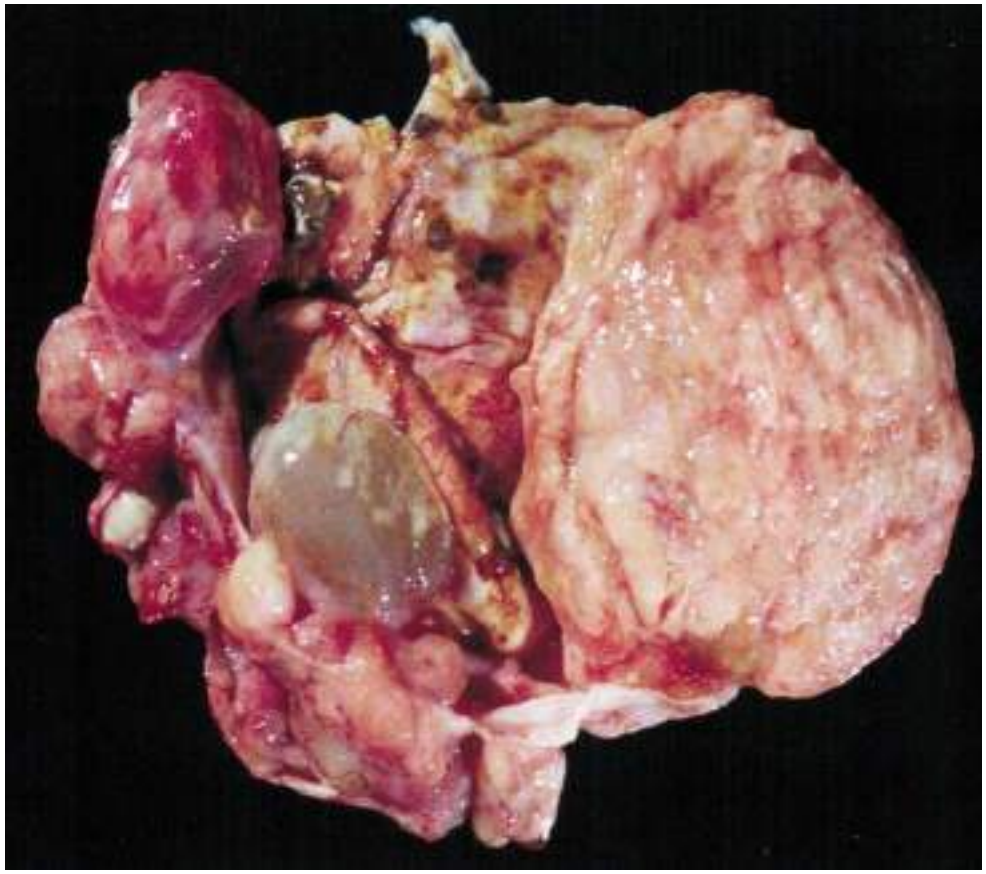
MUCINOUS BORDERLINE TUMOR

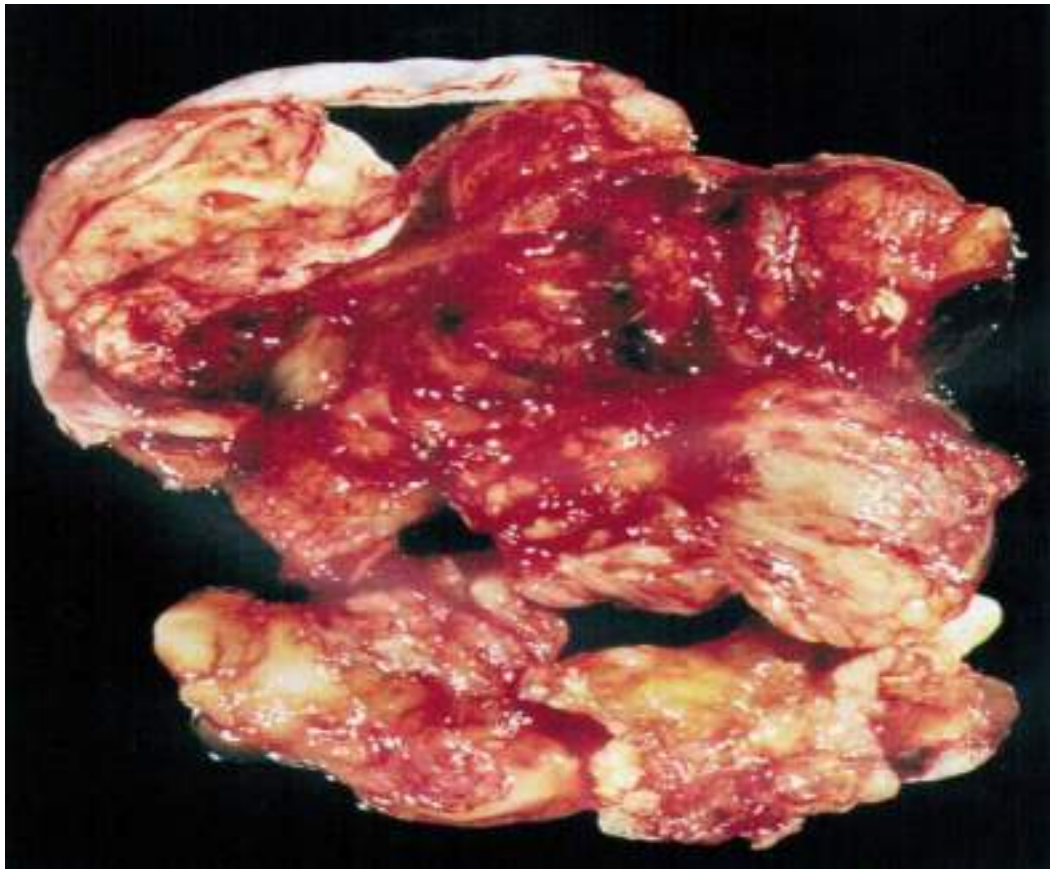
Noninvasive mucinous neoplasm with complex architecture and gastrointestinal type differentiation

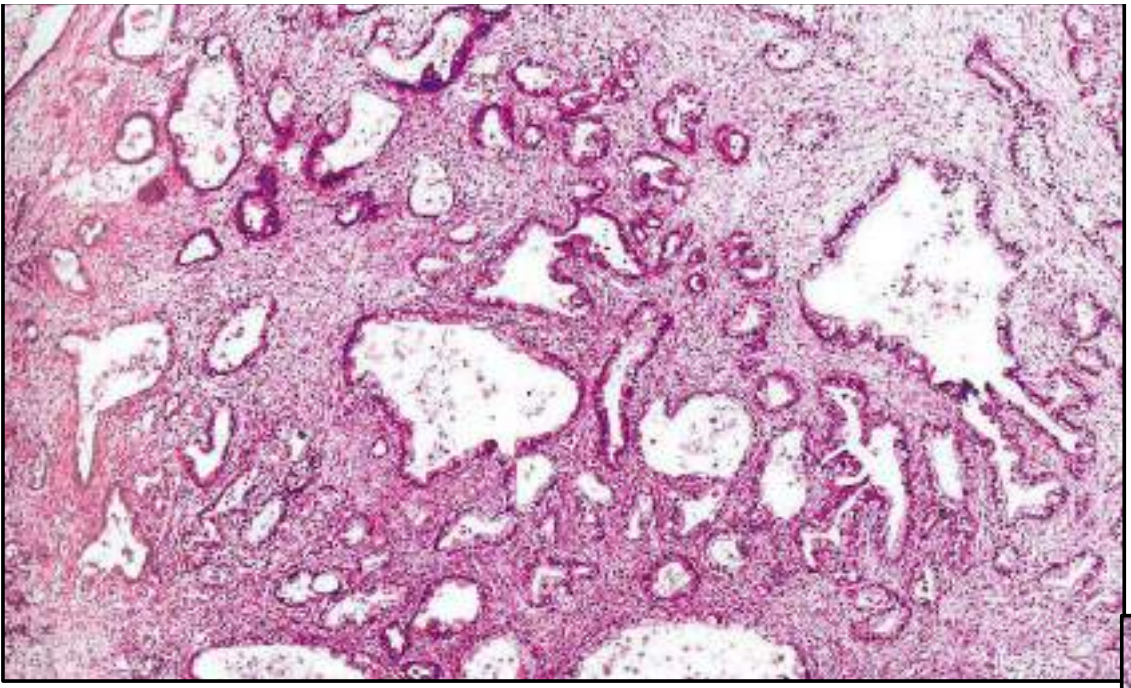


MUCINOUS CARCINOMA

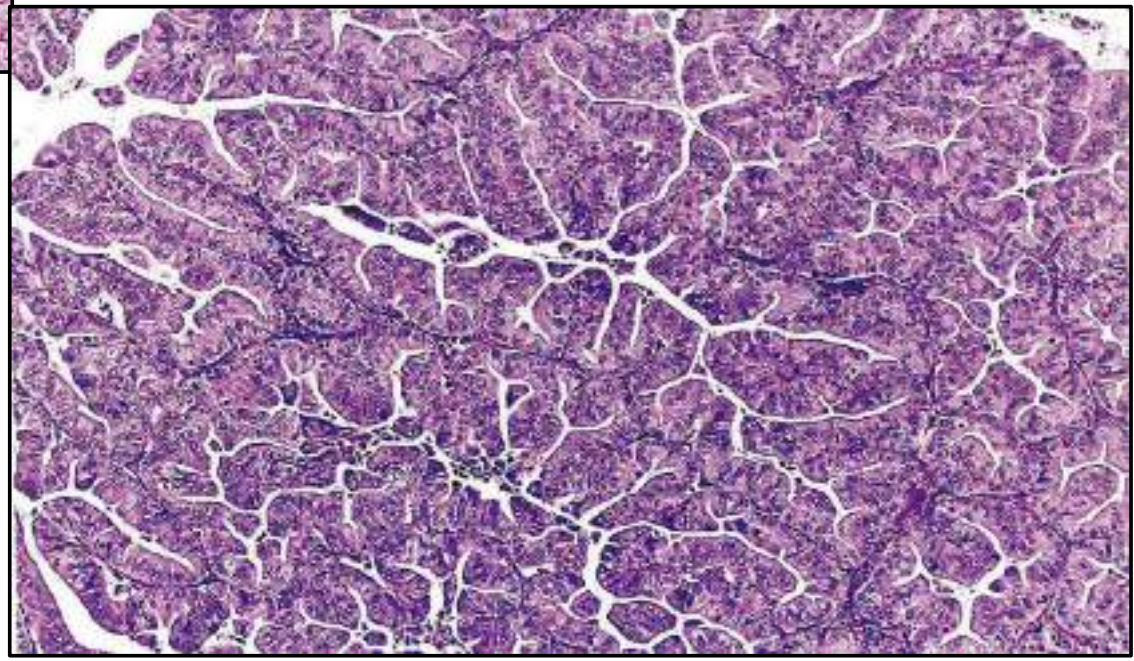
- Invasive mucinous neoplasm composed of gastrointestinal type-cells
- 77% of ovarian mucinous carcinomas are metastases, 23% are ovarian primaries







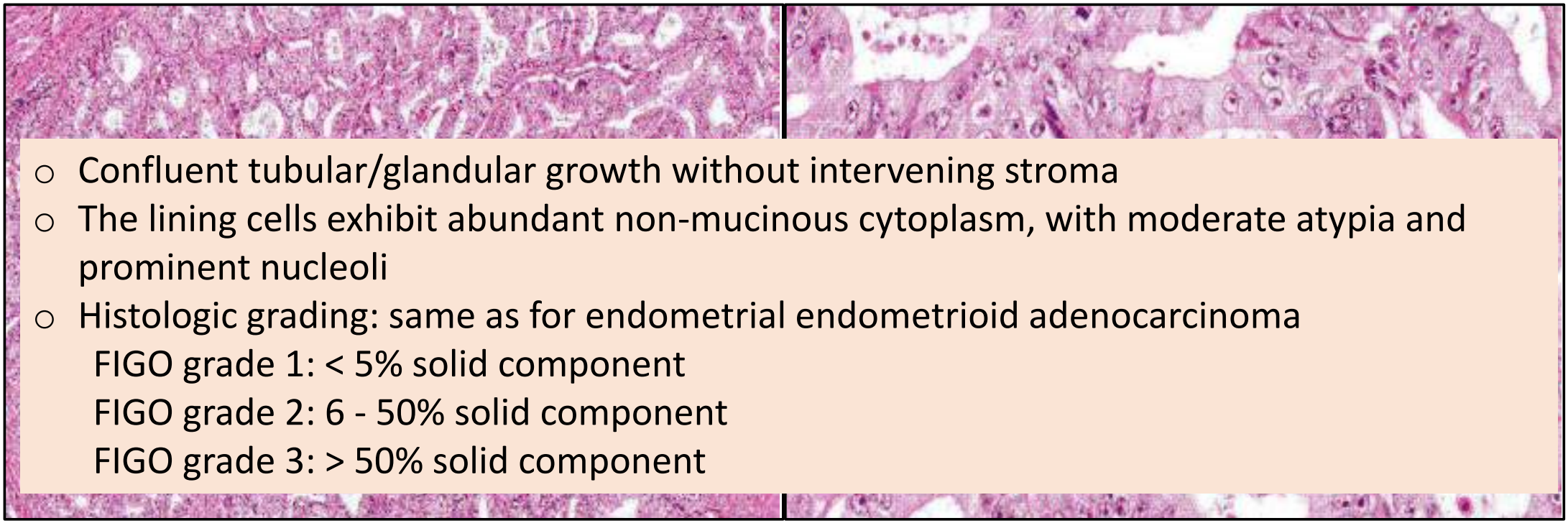
Stromal invasion may be ***<u>infiltrative</u>*** with disorderly penetration of stroma by neoplastic glands, single cells or cell clusters, may have desmoplastic response or ***<u>expansile (confluent)</u>*** with complex arrangement of glands, cysts or papillae lined by malignant epithelium with minimal or no intervening stroma with a broad, sharply defined border



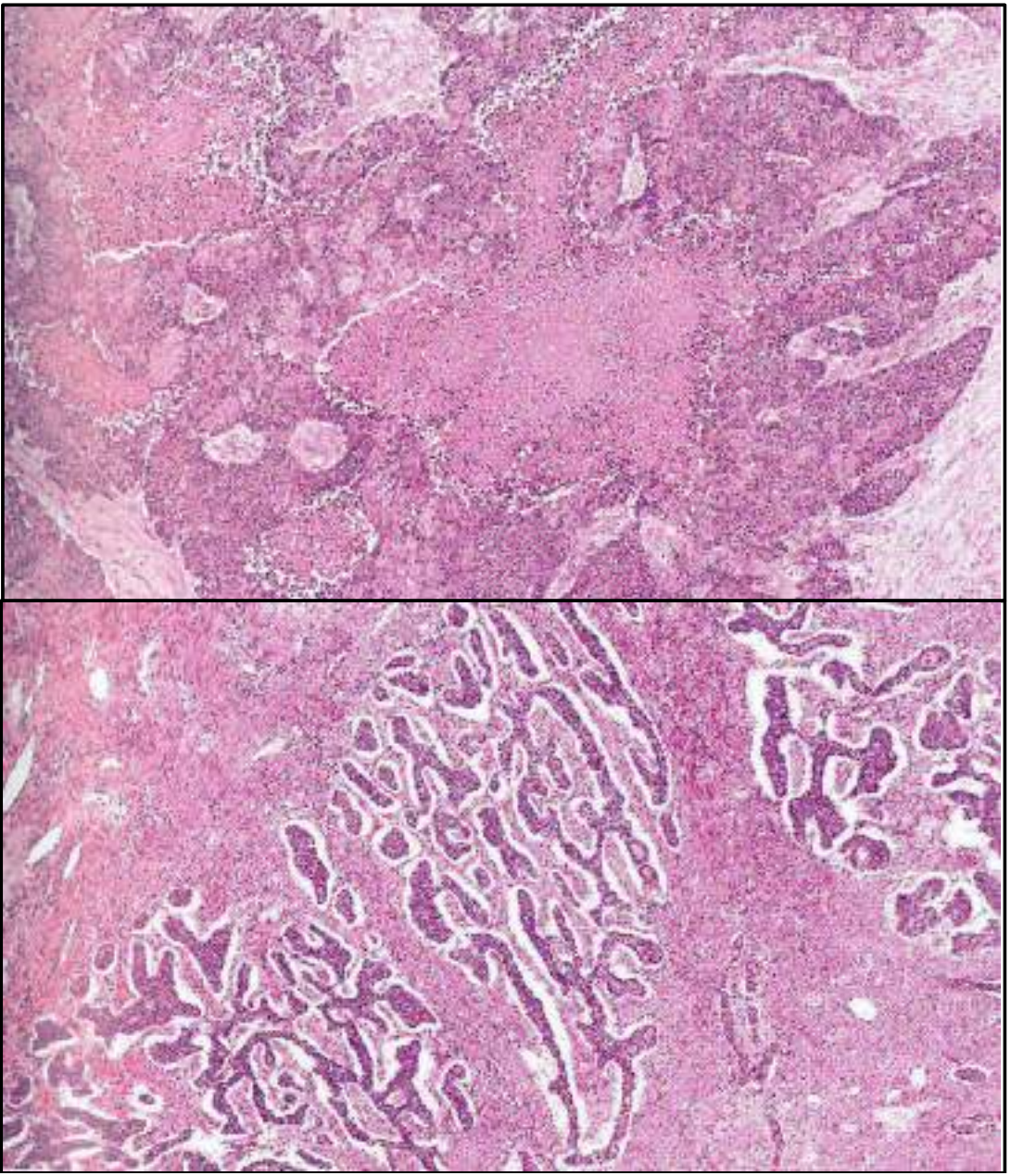
- ✓ Diffusely positive for CK7 and variably positive for CK20, CDX2 and CEA
- ✓ Usually negative for WT1, vimentin, NapsinA, ER and PR
- ✓ PAX8 usually focal and weak is positive in a subet of tumors
- ✓ P53 may show a wild type or mutation type of staining pattern
- ✓ P16 is usually negative or focally positive

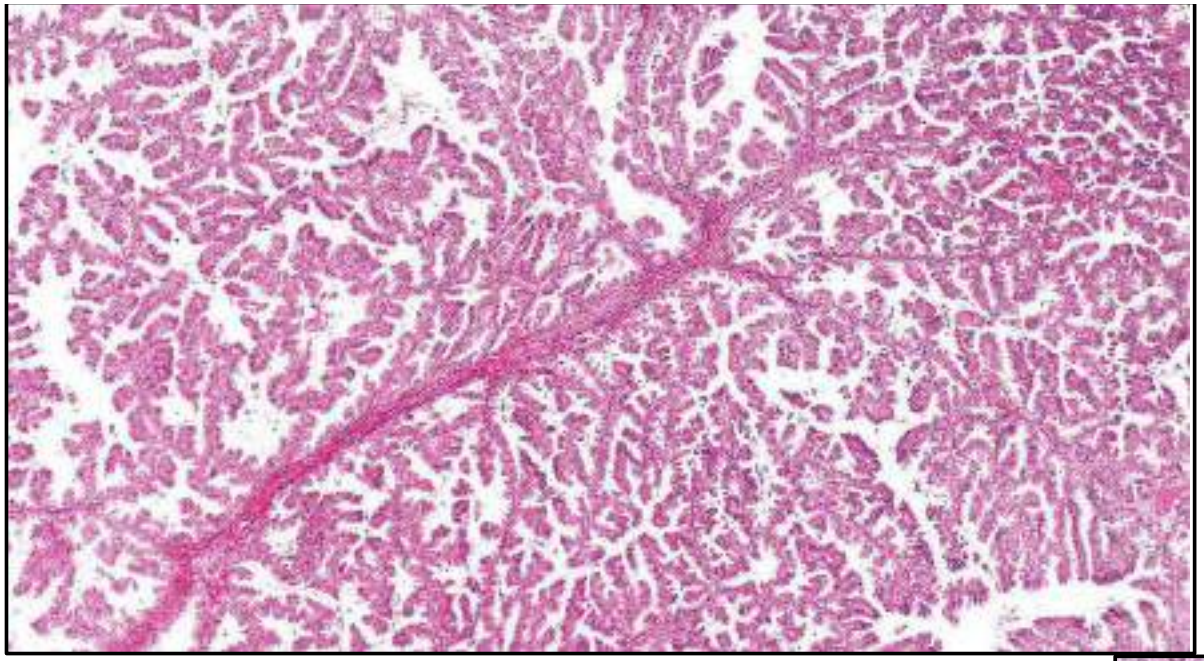
ENDOMETRIOID CARCINOMA

- 10% of primary ovarian carcinomas
- Associated with endometriosis / endometriotic cyst (15%), endometrioid adenofibroma, synchronous endometrial endometrioid adenocarcinoma or endometrial hyperplasia (15 - 30%)



- Confluent tubular/glandular growth without intervening stroma
- The lining cells exhibit abundant non-mucinous cytoplasm, with moderate atypia and prominent nucleoli
- Histologic grading: same as for endometrial endometrioid adenocarcinoma
  FIGO grade 1: < 5% solid component
  FIGO grade 2: 6 - 50% solid component
  FIGO grade 3: > 50% solid component





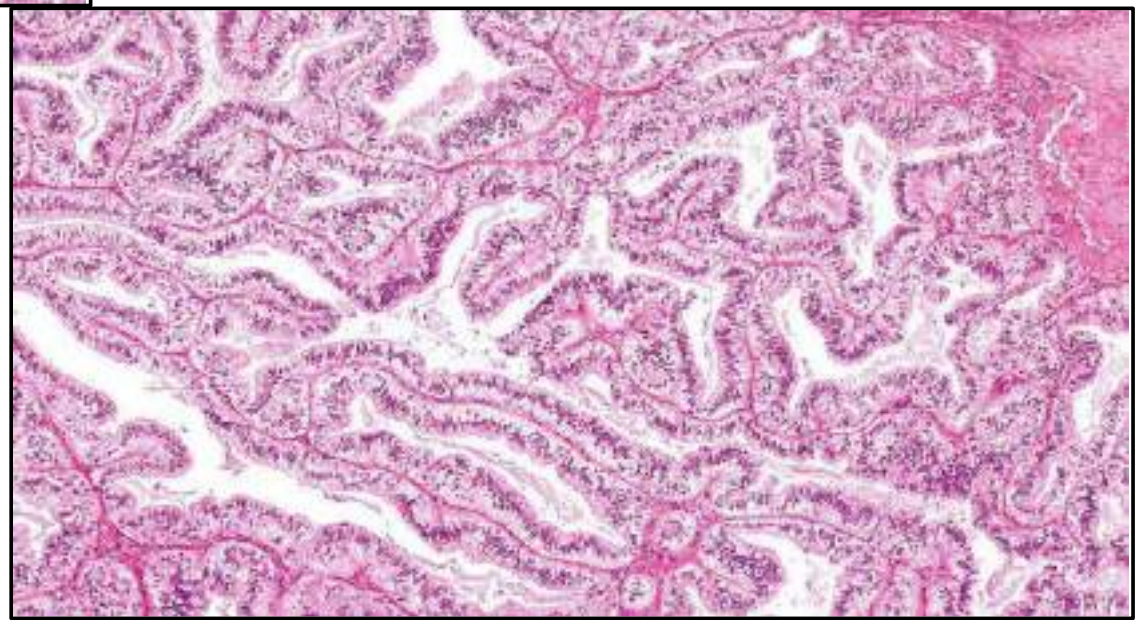
Squamous metaplasia (morules or keratin pearls), cytoplasmic mucin, intracytoplasmic vacuoles, oncocytic changes, clear cell changes and cilia and sex cord-like elements (sertoliform) can be observed

None of these morphologic features affect the histologic grade

- **CK7**, **PAX8** (15% negative), **ER** (81-85%) and **PR**
- **p53**: wild / normal type expression (most tumors)

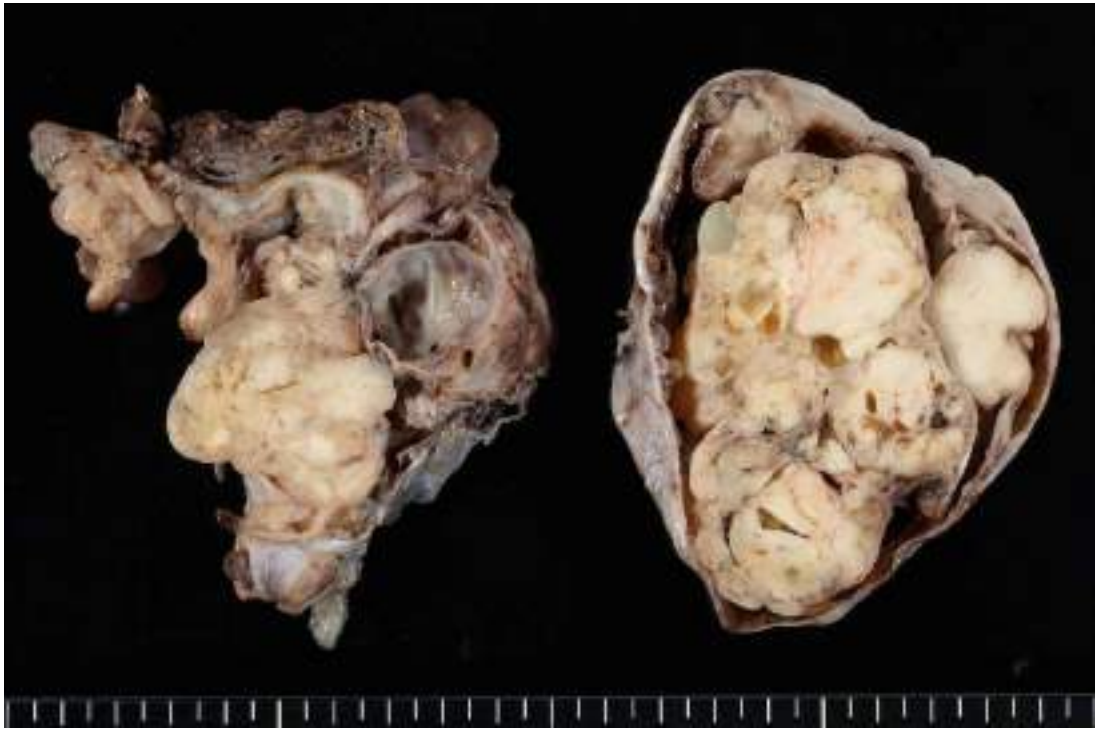
High grade endometrioid cancers might demonstrate mutational pattern (nuclear staining in > 80% of cells, complete absence of staining, diffuse cytoplasmic staining)

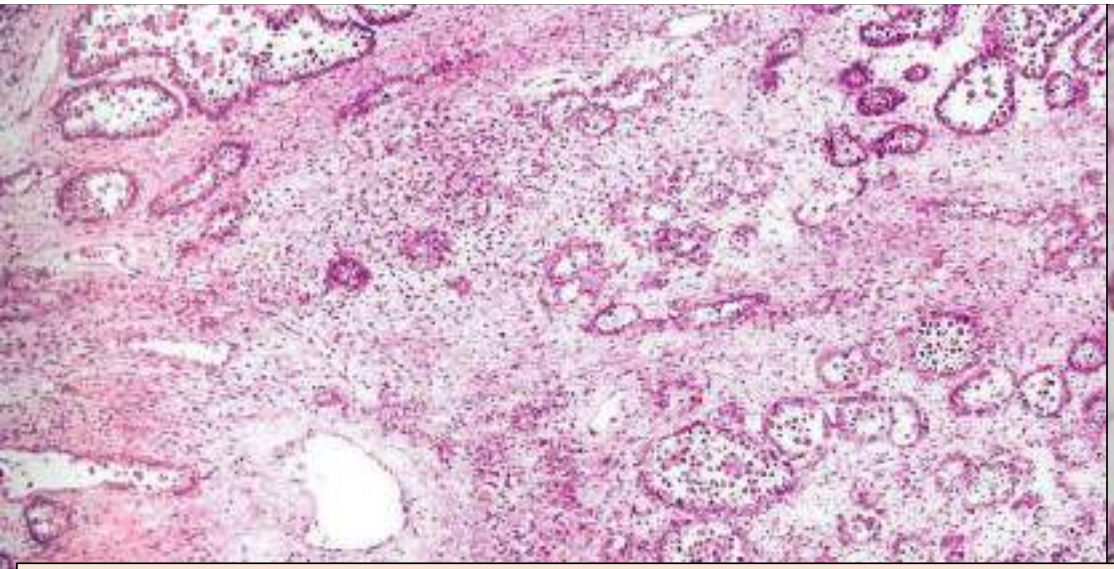
- **WT1** (10 - 14% can express)
- **Napsin A** (3-8% can express, usually in areas with secretory changes)
- **CDX2**
- **SATB2** (15% positive in squamous morules)

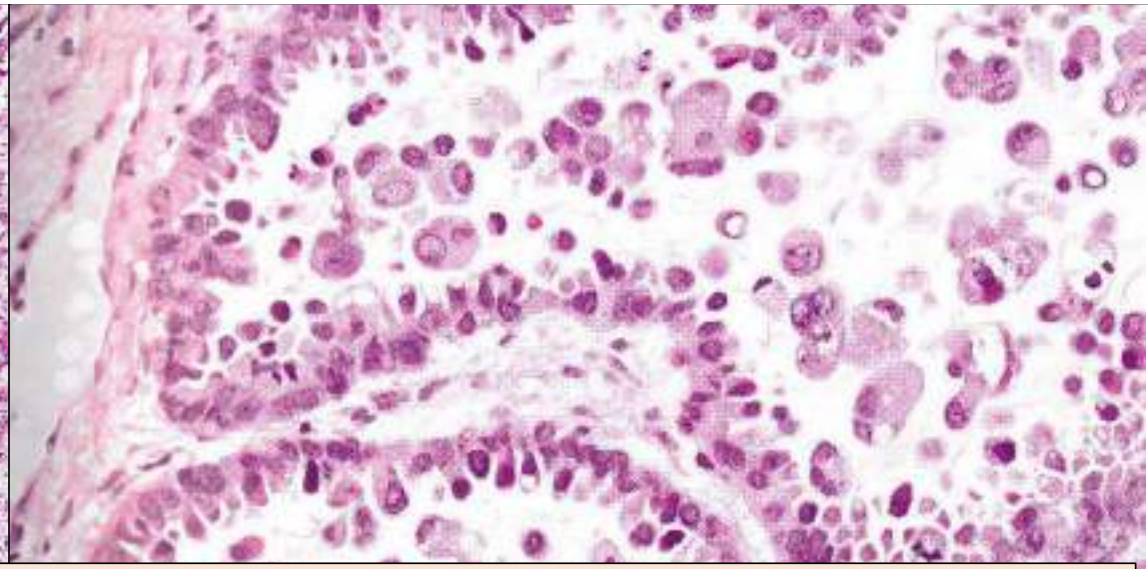


CLEAR CELL CARCINOMA

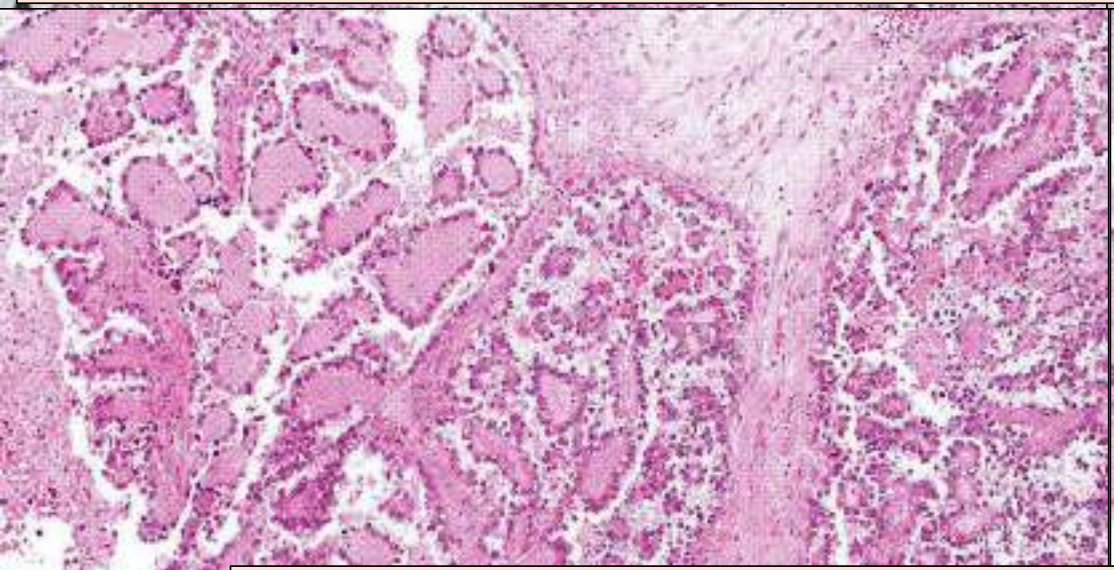
- Malignant epithelial tumor composed of clear, eosinophilic or hobnail cells with, papillary, tubulocystic & solid growth patterns
- Increased risk associated with Endometriosis, including endometriotic cysts (50 - 74%)
- M.C. ovarian epithelial neoplasm associated with paraneoplastic syndromes, such as hypercalcemia, thromboembolism, subacute cerebellar degeneration or bilateral diffuse uveal melanocytic proliferation

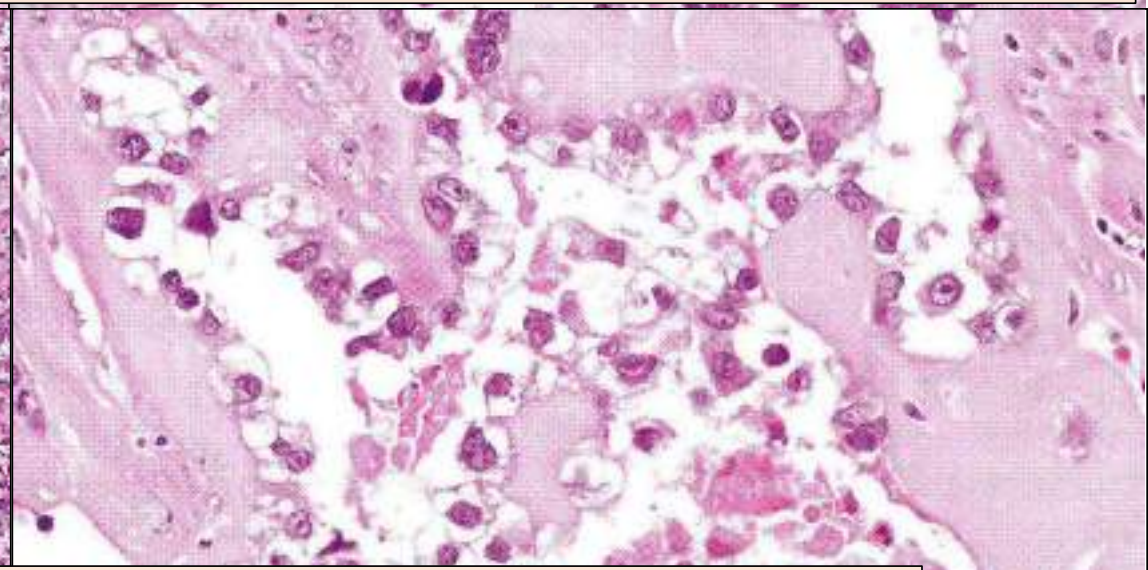




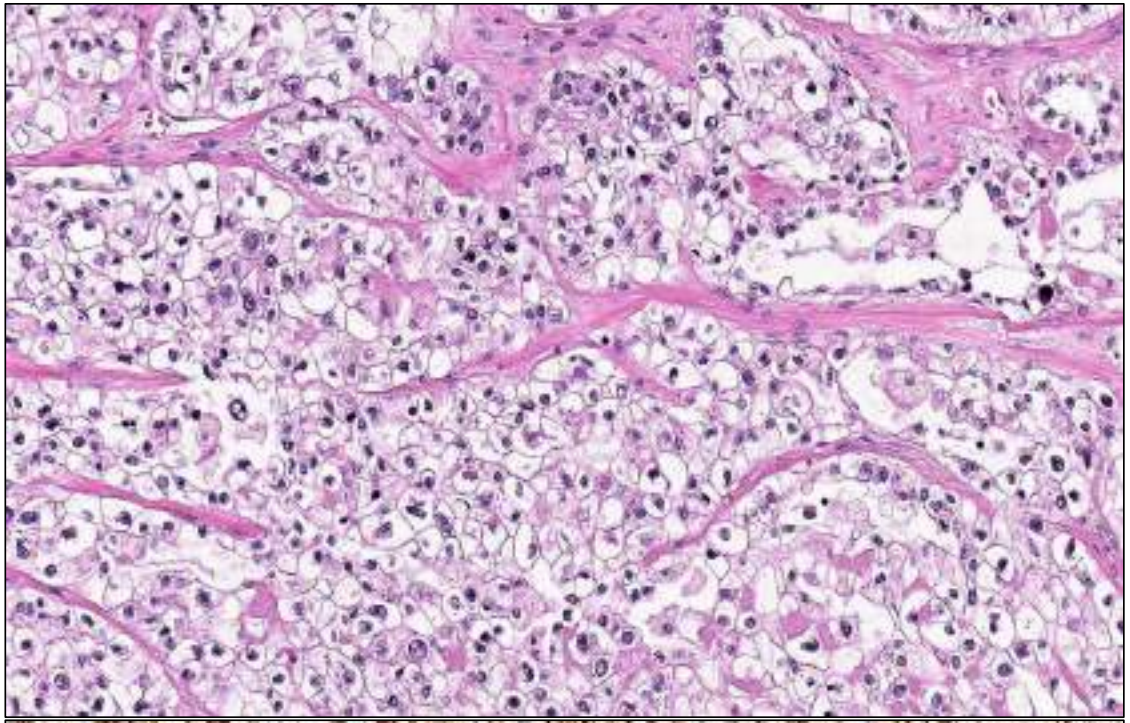


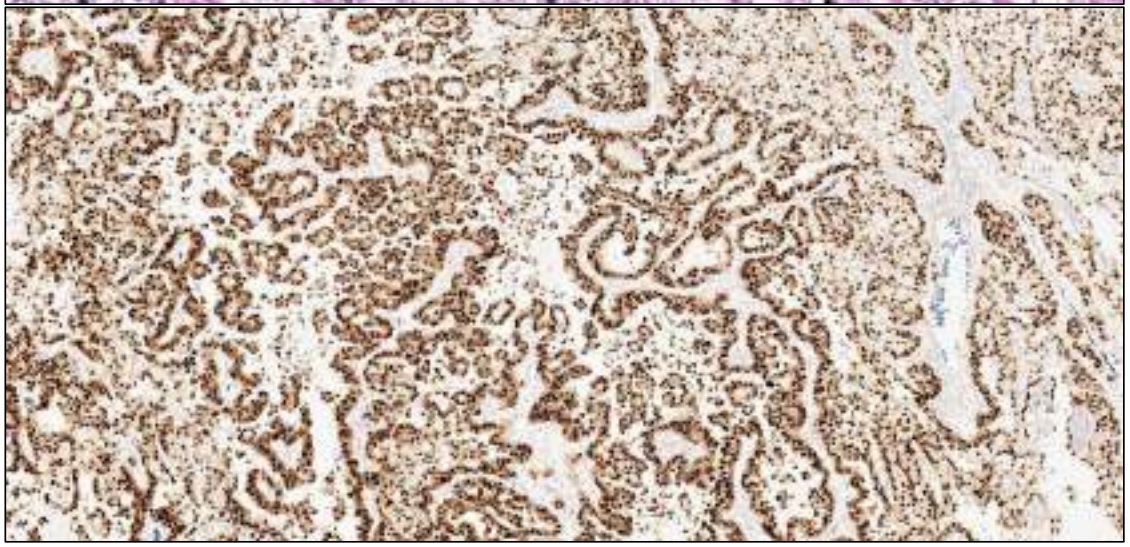
Neoplastic glands infiltrating the fibromatous stroma. Tubules lined by a single layer of hobnail cells with eosinophilic cytoplasm

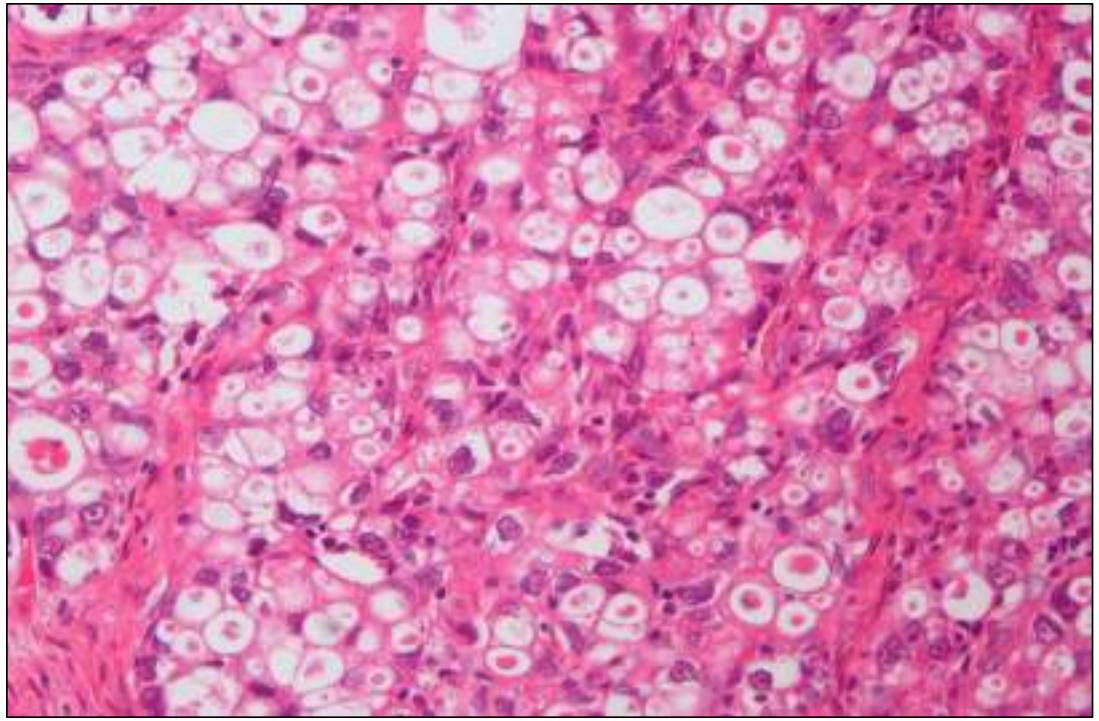




Papillary architecture with simple papillae lined by a single layer of cuboidal cells with clear cytoplasm







- Not graded (high grade by definition)
- Multinucleated cells (rarely)
- Psammoma bodies (rarely)
- Diastase resistant intracytoplasmic material imparting a signet ring appearance (so called targetoid cells)
- Intraglandular cellular sloughing mimicking high grade serous CA
- Typically positive for PAX8, napsinA and HNF-1β
- Negative for WT1, ER & PR
- WT1, napsinA and ER together recommended for distinction from High grade serous CA
- NapsinA and PR for distinction from Endometroid CA

Table Markers of value in histotype diagnosis of ovarian carcinoma

	HGSC	LGSC	ENDOMETRIOID	CLEAR CELL	MUCINOUS
WT1	Diffuse positive	Diffuse positive	Negative	Negative	Negative
p53	Mutation type	Wild type	Wild type or mutation type	Wild type	Wild type or mutation type
p16	Diffuse positive	Focal positive	Focal positive	Variable	Variable
ER	Diffuse or focal positive or negative	Diffuse positive	Diffuse positive	Negative	Negative or focal positive
HNF-1β	Negative	Negative	Negative	Diffuse or focal positive	Variable
Napsin A	Negative	Negative	Negative	Diffuse or focal positive	Negative

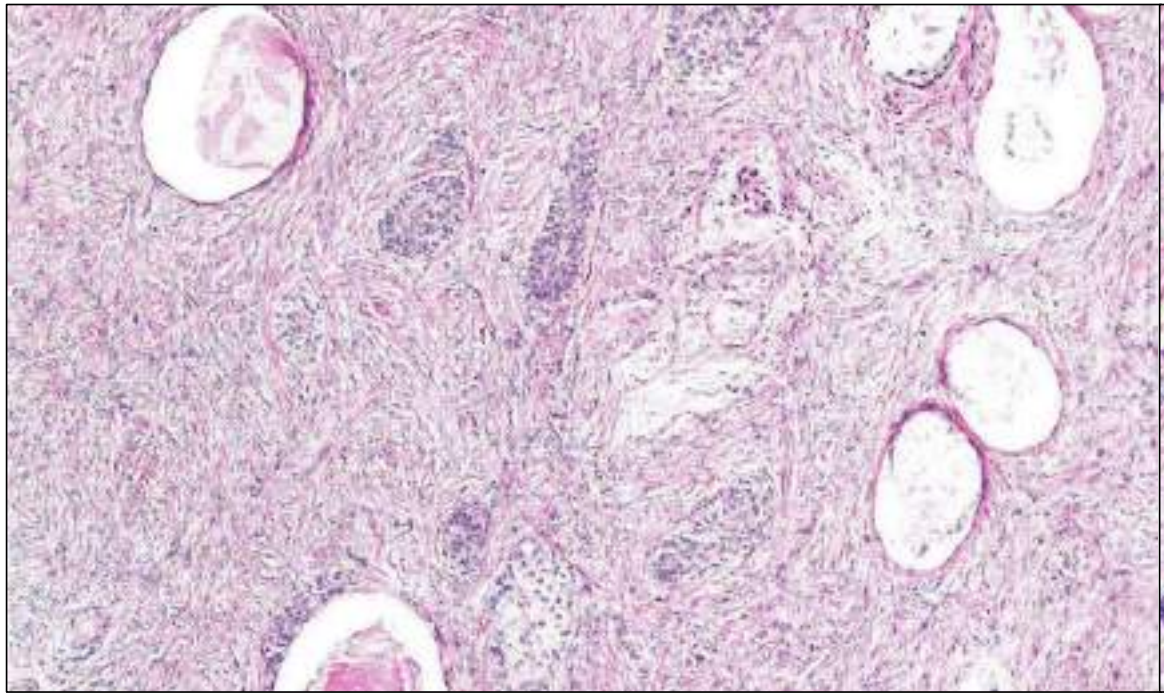
From Singh N, McCluggage WG, Gilks CB. High-grade serous carcinoma of tubo-ovarian origin: recent developments. *Histopathology*. 2017 May 6. [Epub ahead of print]

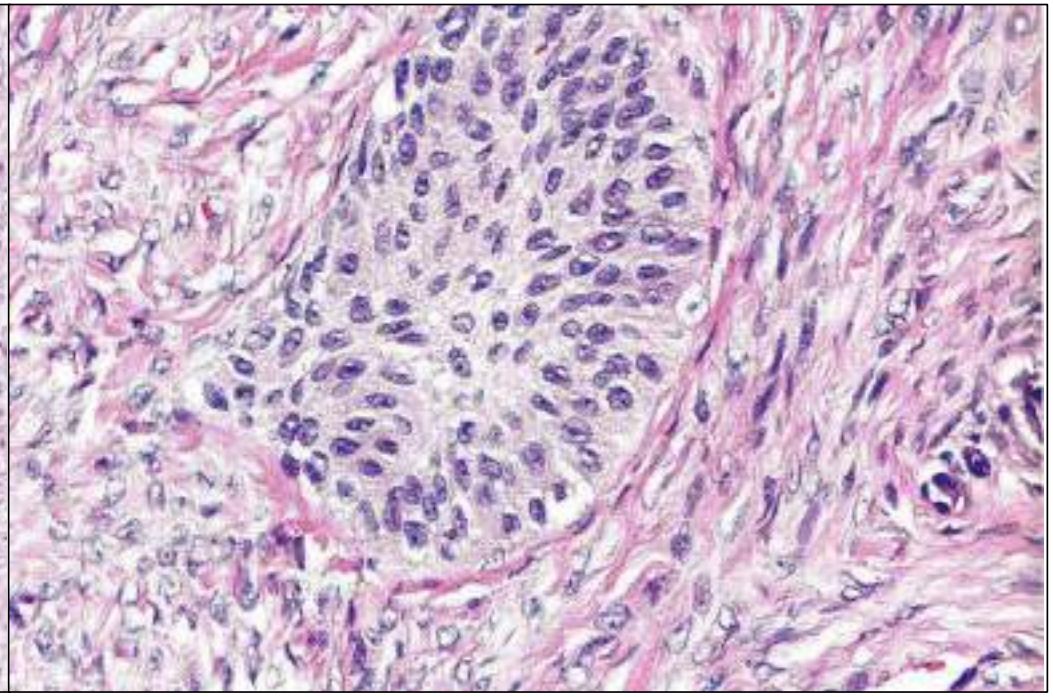
Note: These are the most common staining patterns, but exceptions may occur with all of the markers.

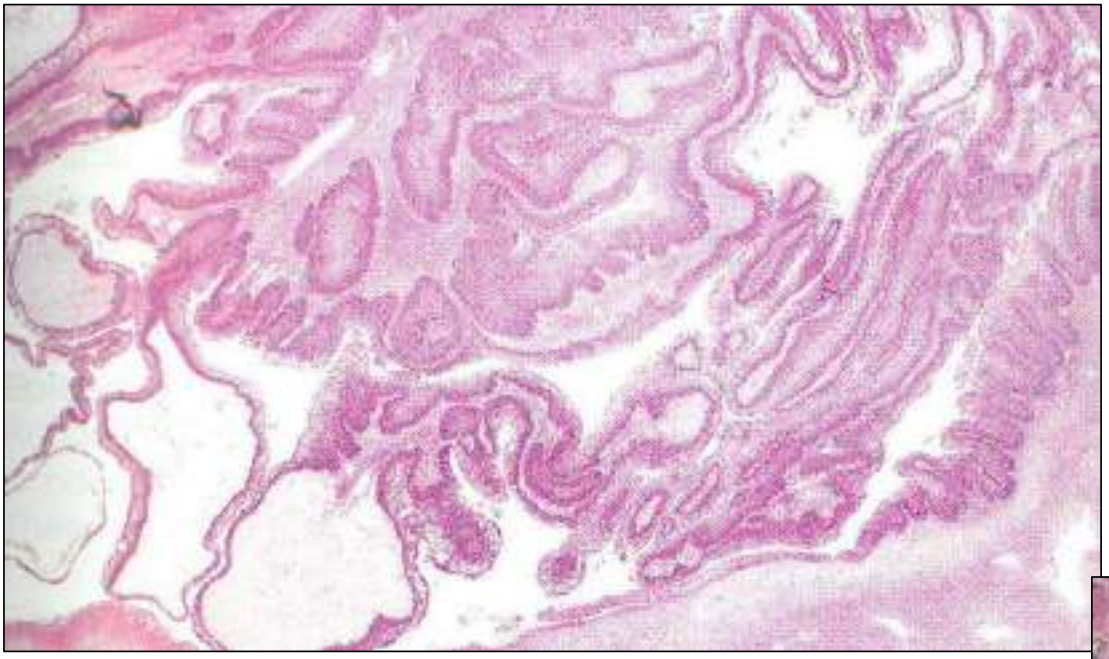
ER, Estrogen receptor; *HGSC*, high-grade serous carcinoma; *HNF-1β*, hepatocyte nuclear factor-1β; *LGSC*, low-grade serous carcinoma

BRENNER TUMOR

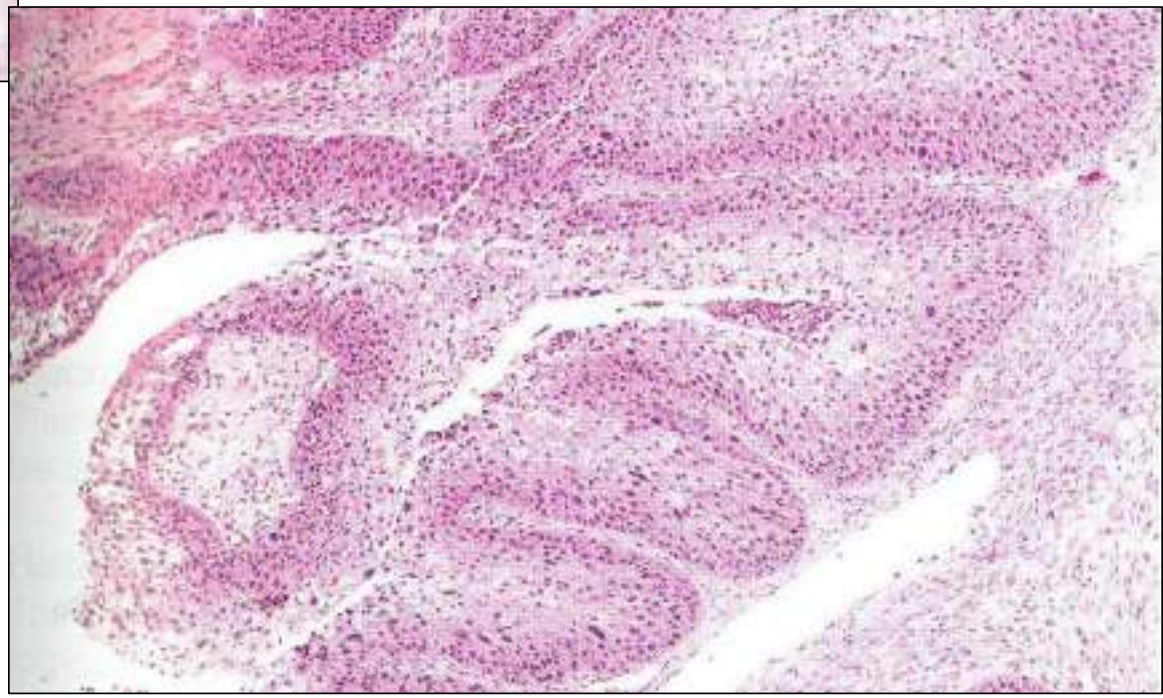
- Tumor composed of transitional / urothelial-like epithelium, typically embedded in fibromatous stroma
- Benign, borderline and malignant variants are recognized, based on the growth pattern and cytological features of the epithelial cells



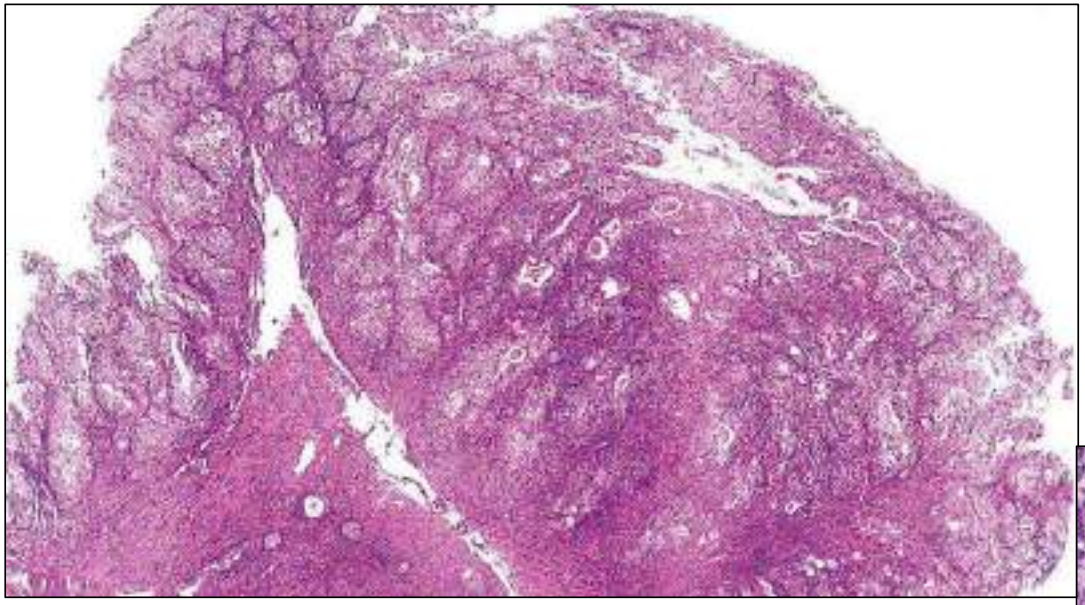




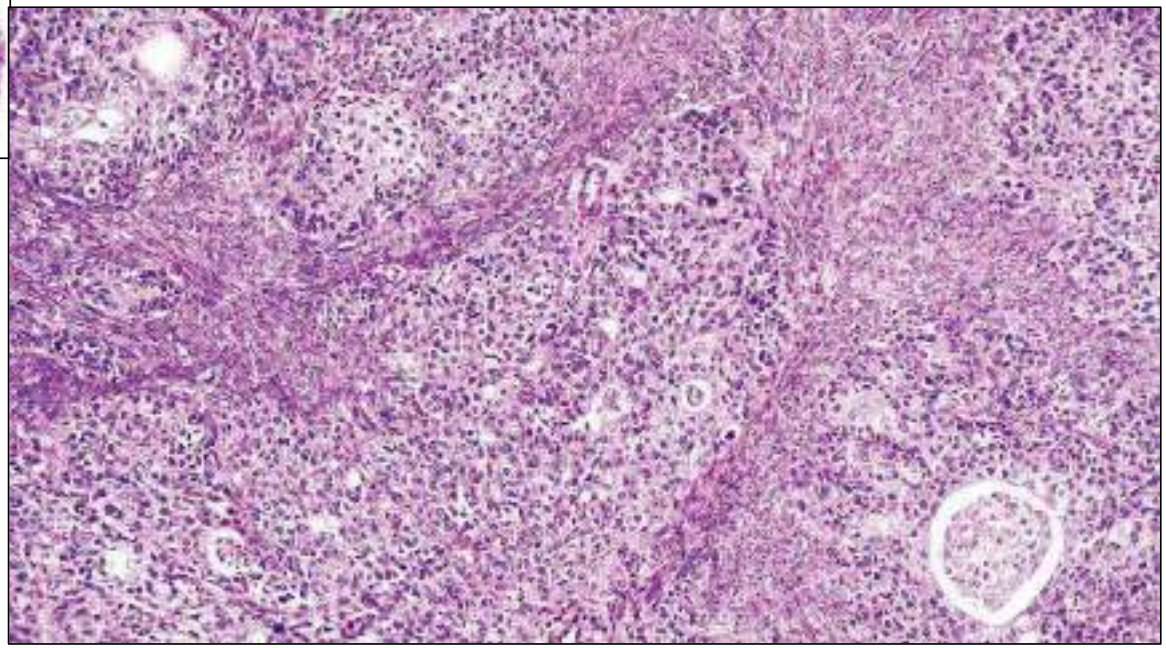
BORDERLINE BRENNER TUMOR



MALIGNANT BRENNER TUMOR

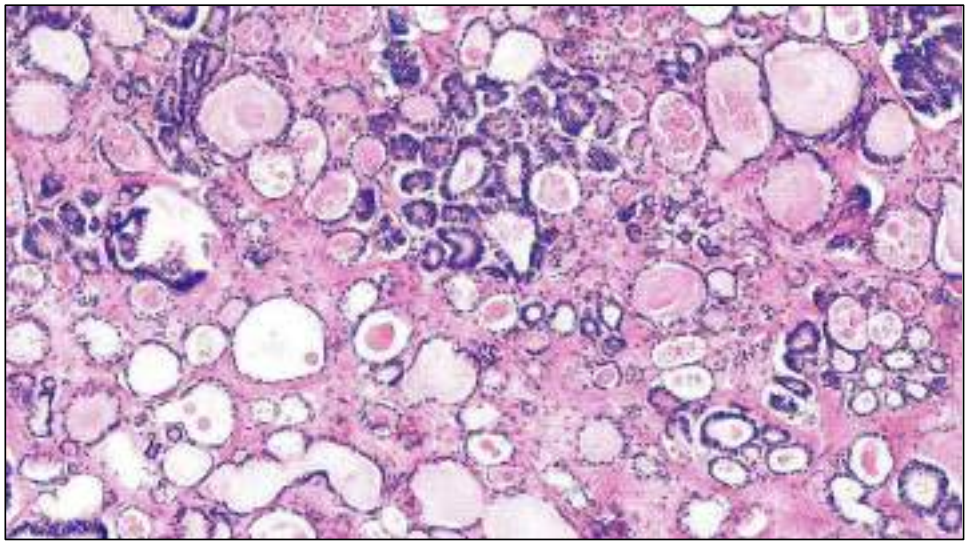


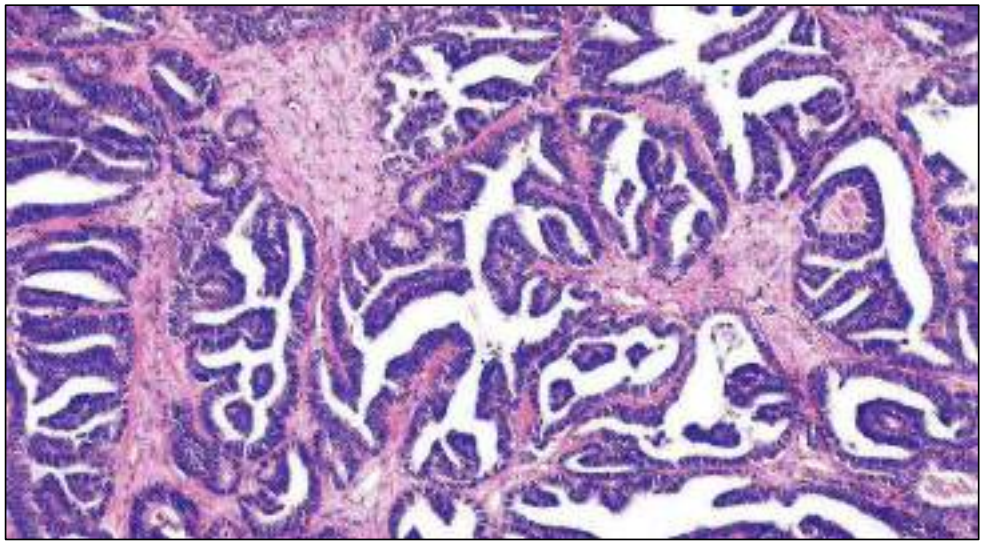
- ✓ Stromal invasion by carcinoma with transitional cell features, with irregular nests of cells and single cells in an infiltrative pattern
- ✓ Squamous or mucinous differentiation may be present
- ✓ Benign or borderline Brenner tumor component is present

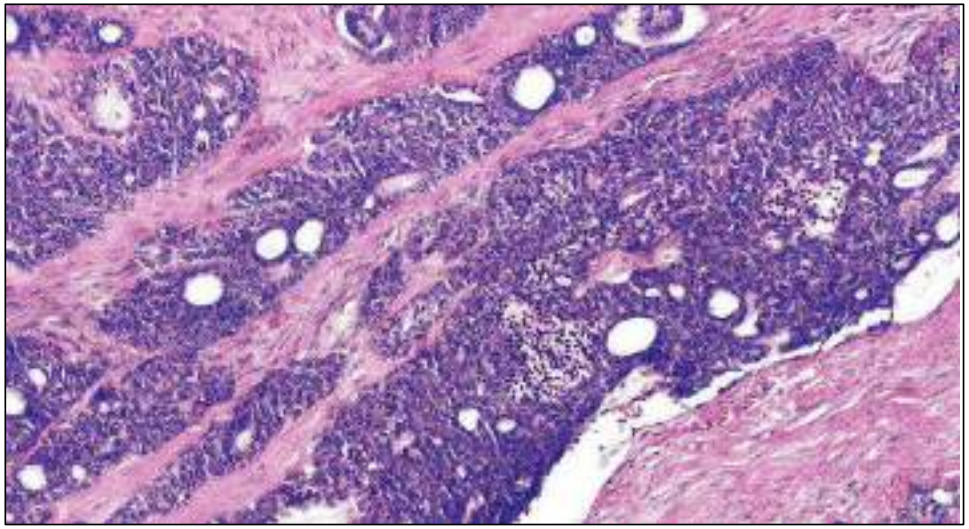


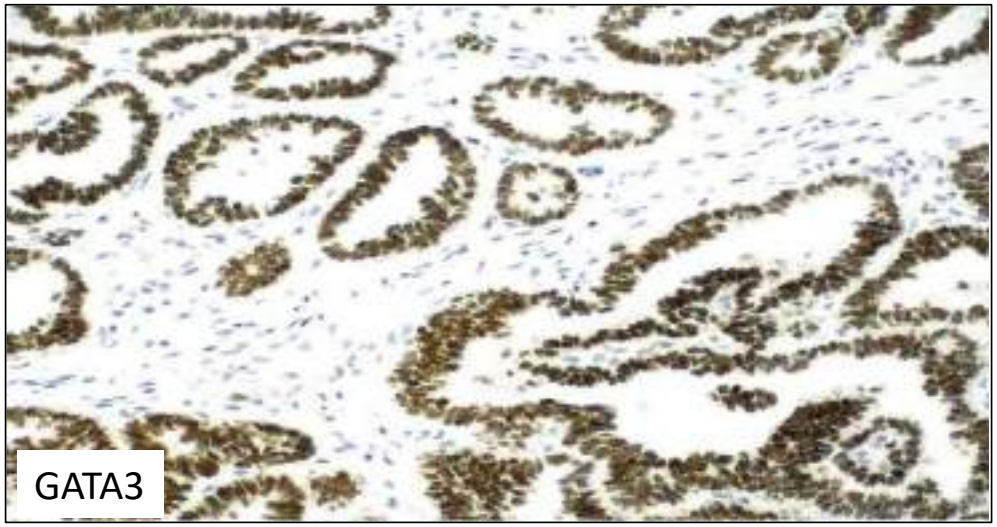
- ✓ **p63**, **GATA3**
- ✓ **ER**, **PR**, **WT1** (weak / focal positivity may be seen)
- ✓ Wild type **p53** staining in benign and borderline Brenner tumors
- ✓ Malignant Brenner tumors may show mutant pattern staining

MESONEPHRIC-LIKE ADENOCARCINOMA

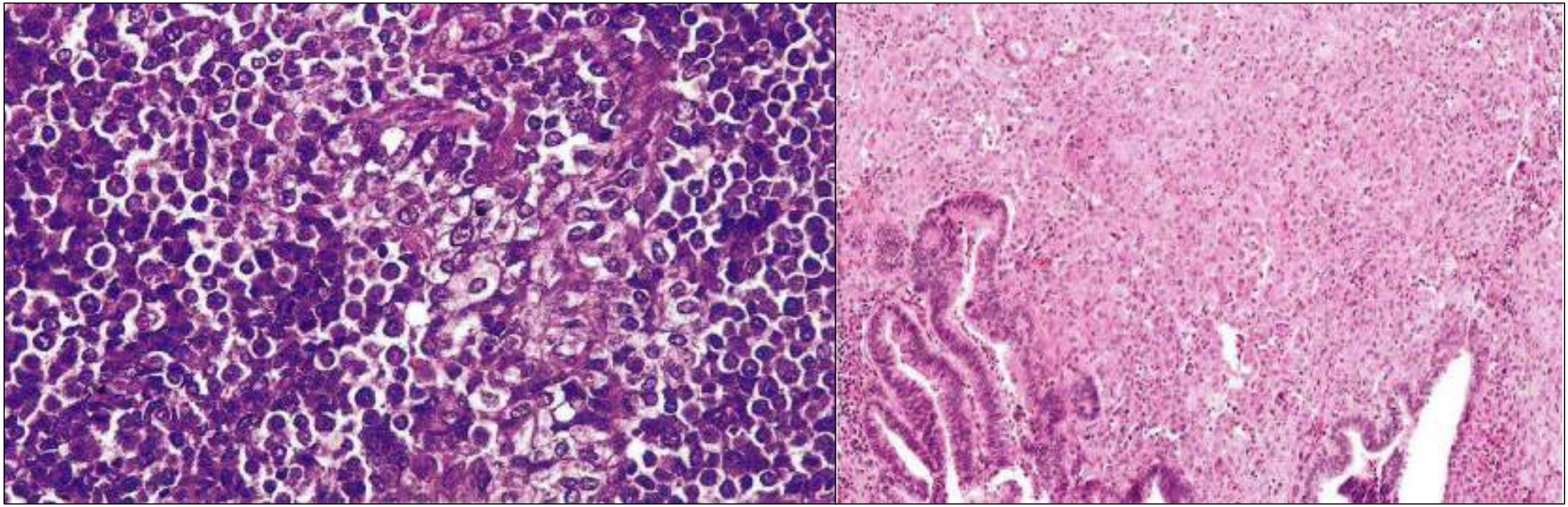




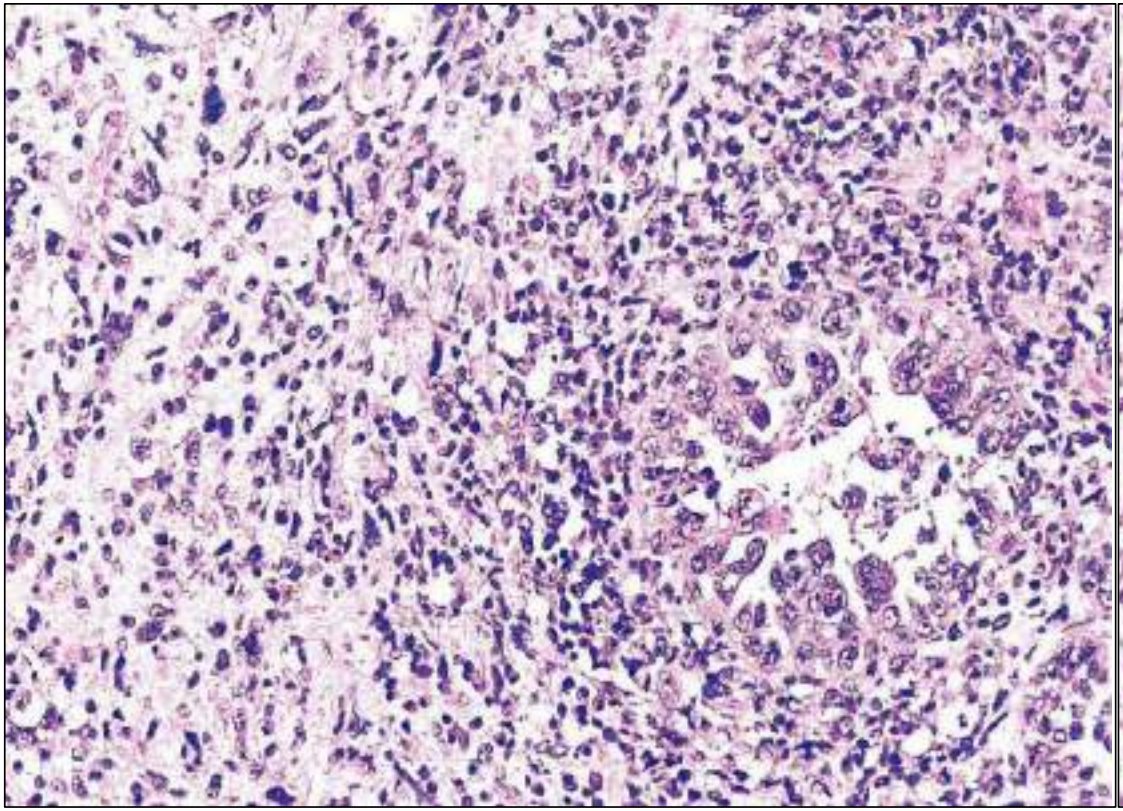


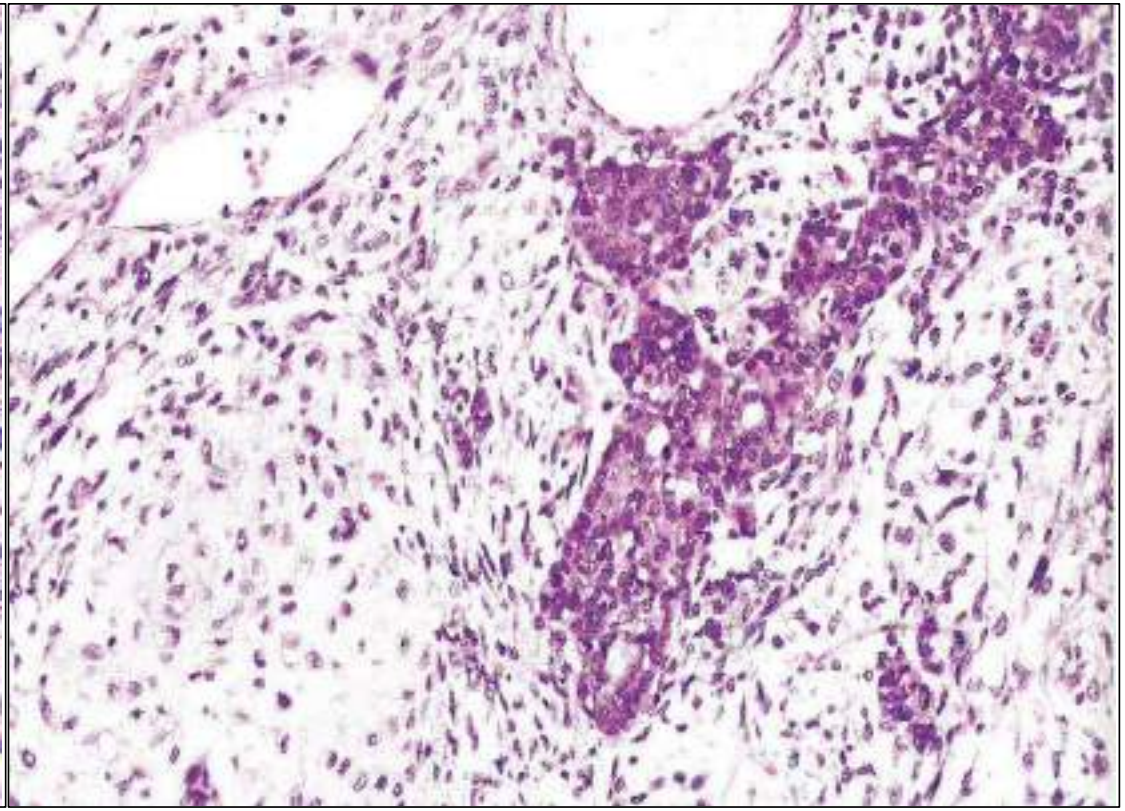


UNDIFFERENTIATED AND DEDIFFERENTIATED CARCINOMAS



CARCINOSARCOMA



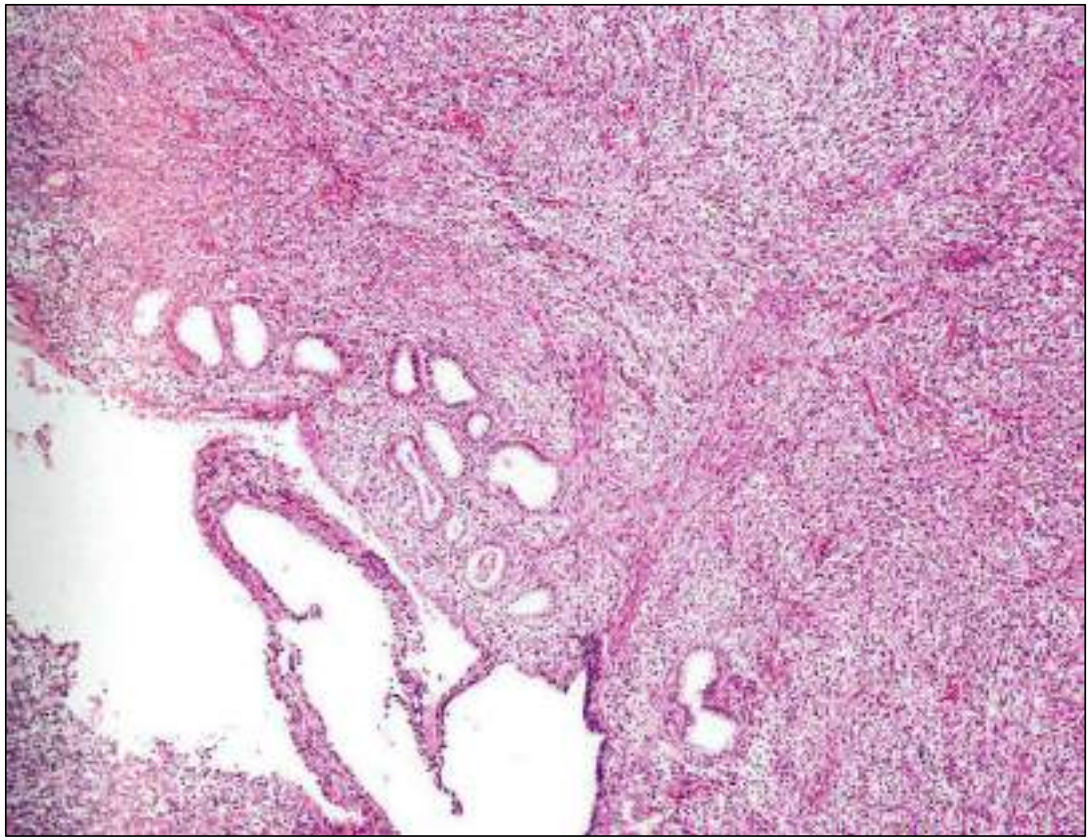


MESENCHYMAL TUMORS

- **ENDOMETRIAL STROMAL SARCOMA**
- **SMOOTH MUSCLE TUMORS**
- **OVARIAN MYXOMA**
- **OTHER OVARIAN MESENCHYMAL TUMORS**

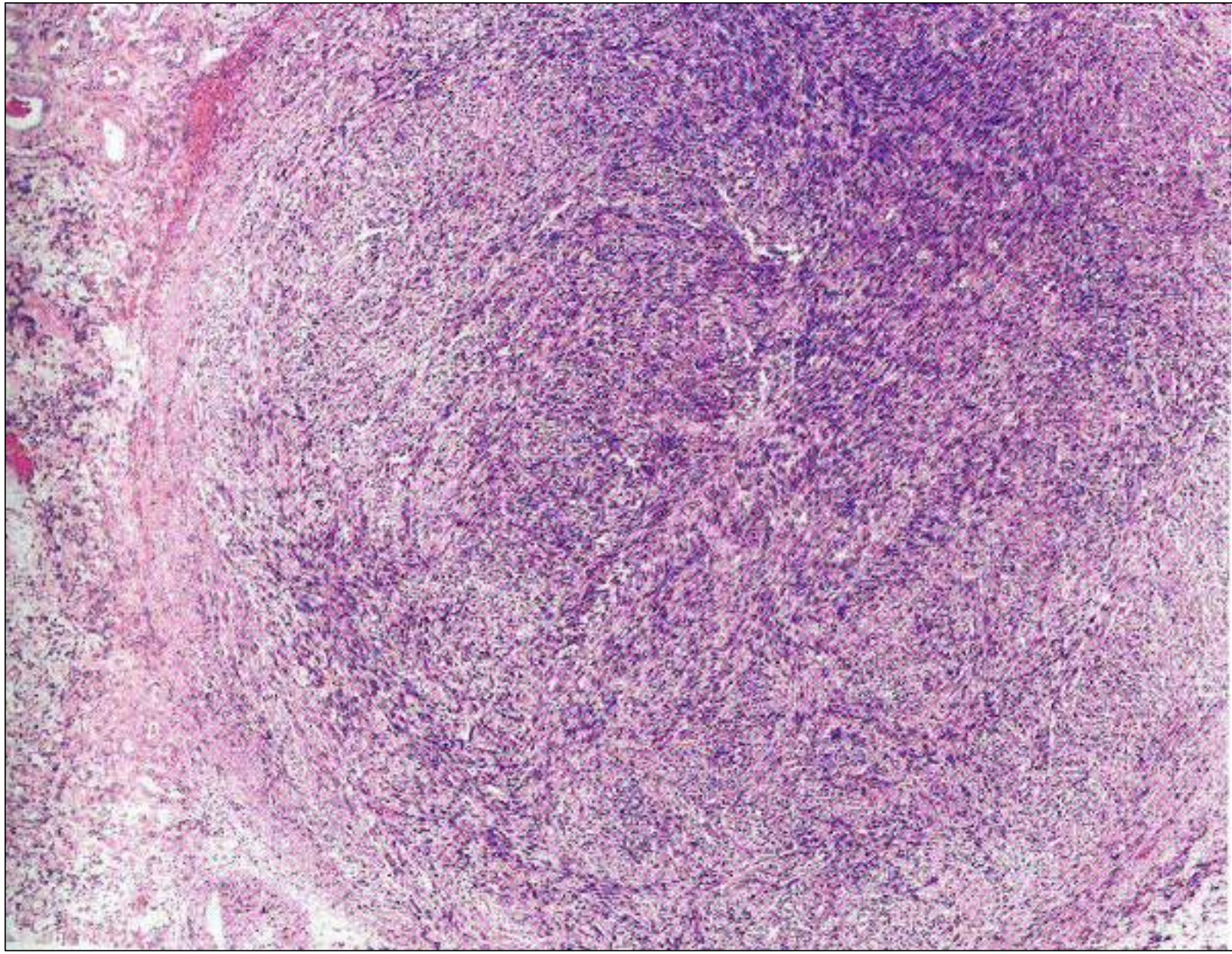
ENDOMETRIAL STROMAL SARCOMA

- Low grade mesenchymal neoplasm with a morphology resembling that of proliferative-type endometrial stroma
- Arise from endometriosis
- Diffuse growth of uniform small cells sometimes with whorling around arteriole-like vessels, resembling proliferative-type endometrial stroma
- Exclusion of uterine tumor
- Express CD10, ER and PR
- Variable expression of keratin, WT1 and actins



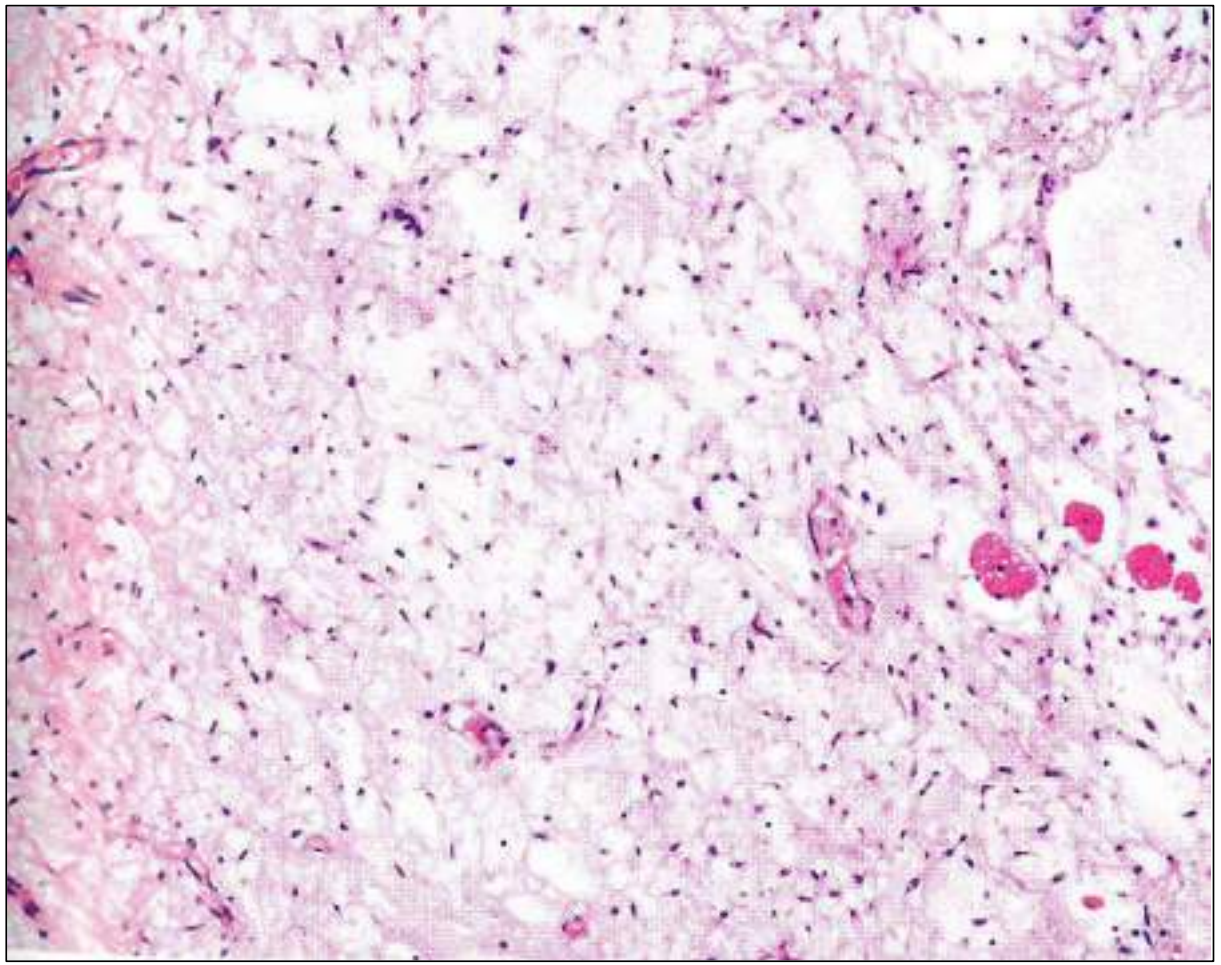
SMOOTH MUSCLE TUMORS

- Include benign (leiomyoma), low-malignant potential and malignant mesenchymal tumors (leiomyosarcoma) exhibiting smooth muscle differentiation
- Positive for SMA, ER & PR



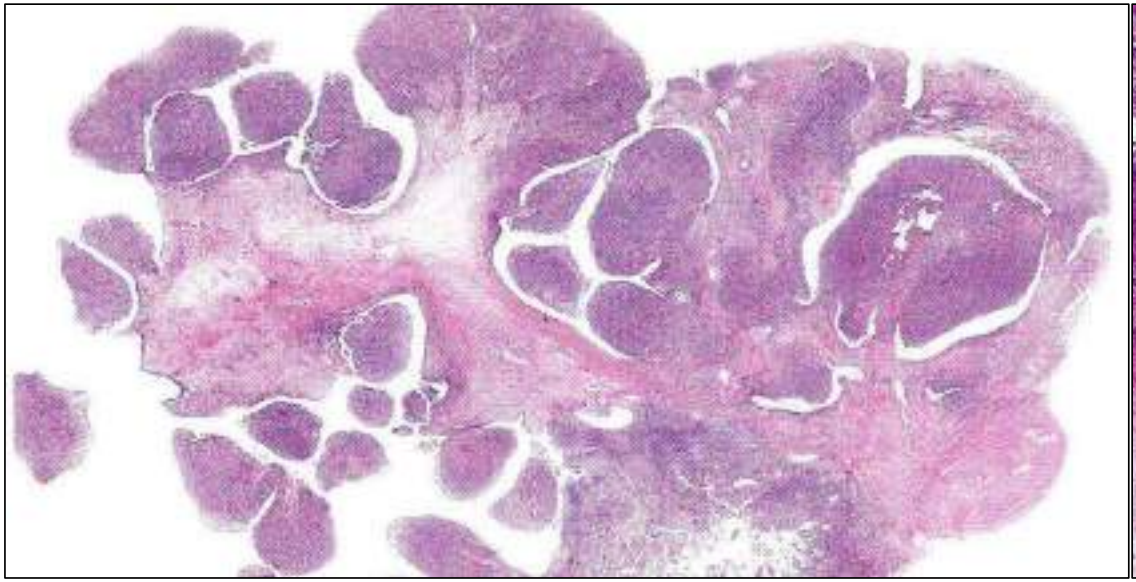
OVARIAN MYXOMA

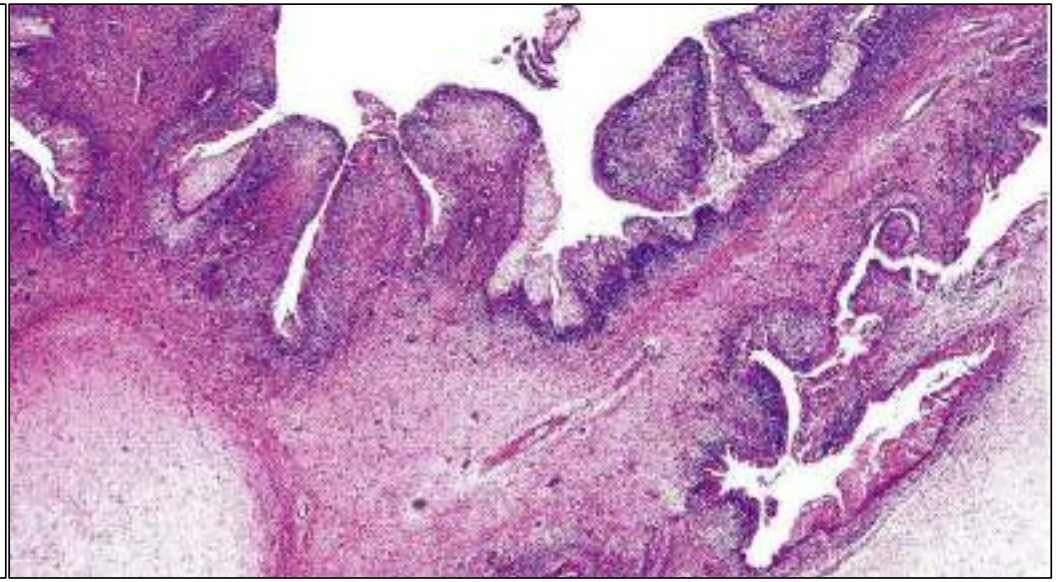
- Benign tumor with abundant myxoid matrix, resembling its soft tissue counterpart
- Paucicellular tumor composed of oval to spindle cells with bland cytological features
- Abundant capillaries
- Absent to minimal mitotic activity



MIXED MALIGNANT EPITHELIAL AND MESENCHYMAL TUMORS

ADENOSARCOMA



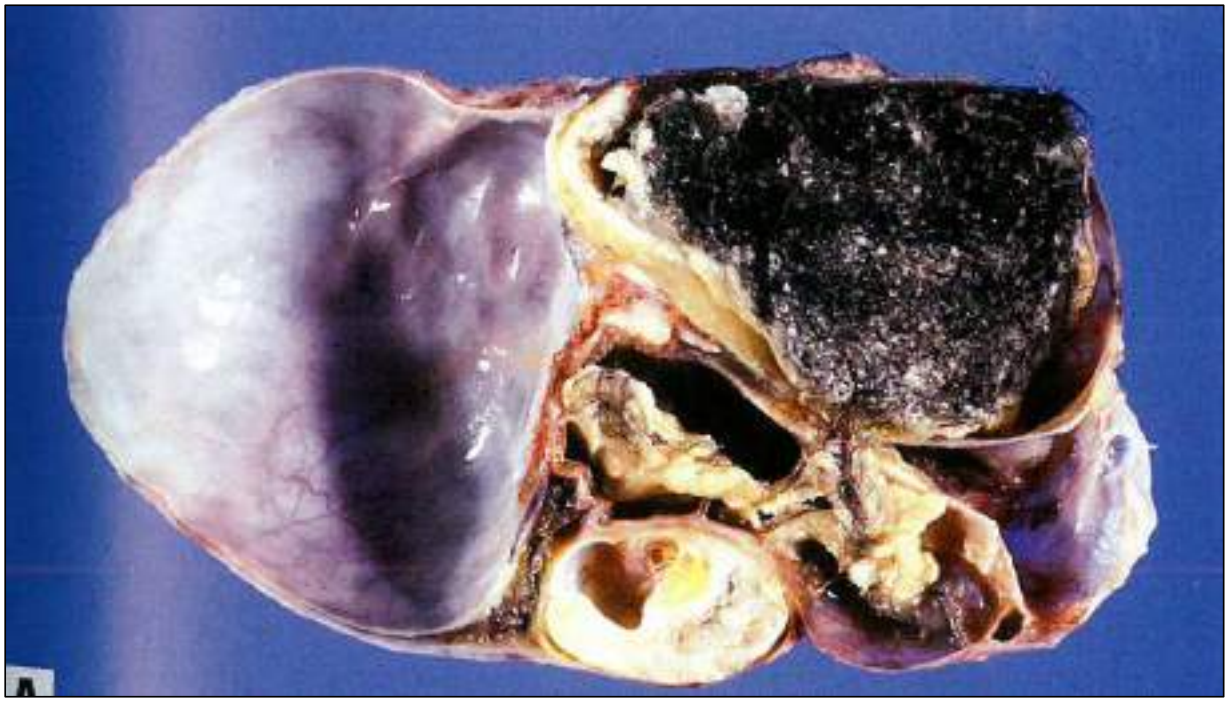


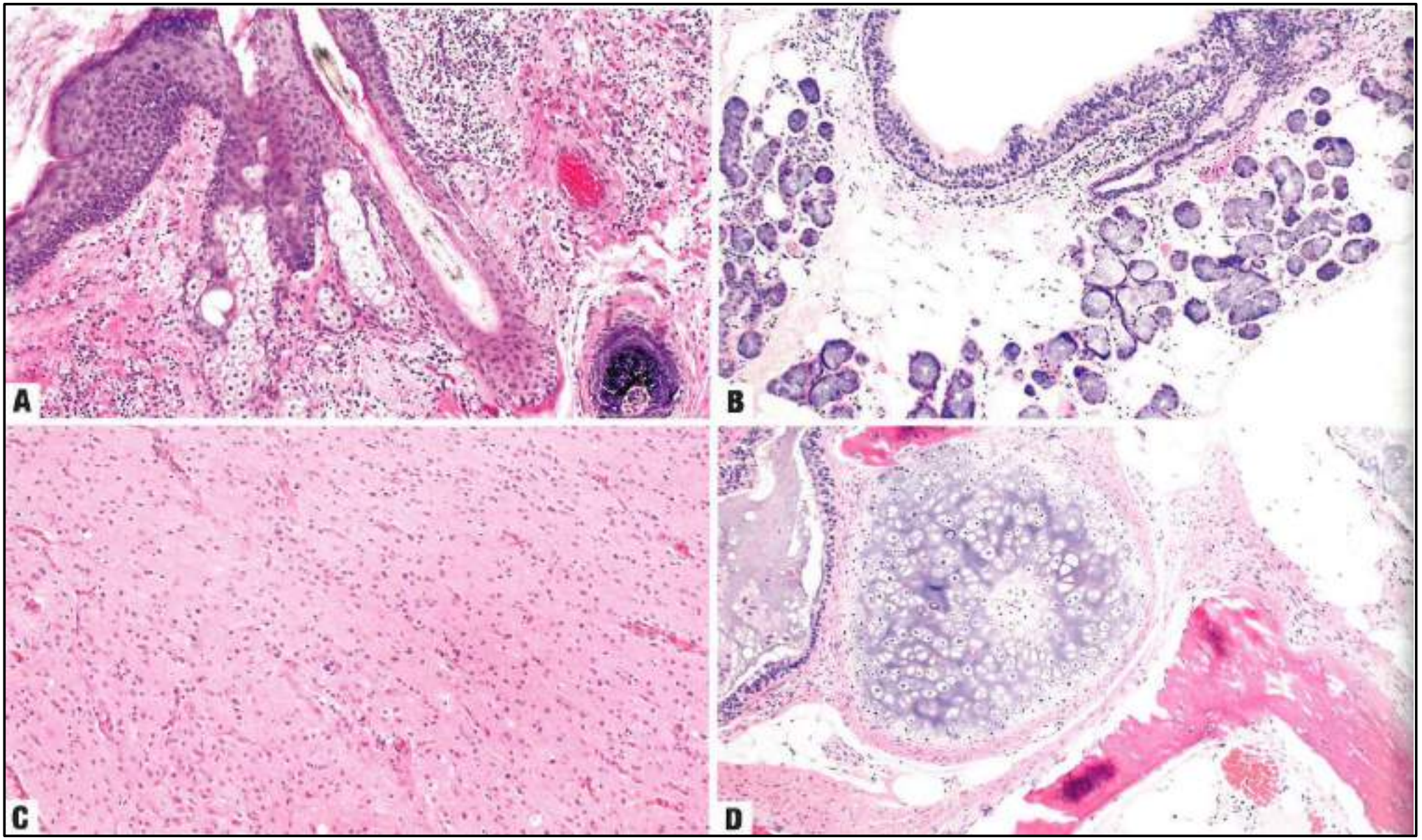
GERM CELL TUMORS

- MATURE TERATOMA
- IMMATURE TERATOMA
- DYSGERMINOMA
- YOLK SAC TUMOR
- EMBRYONAL CARCINOMA
- NON-GESTATIONAL CHORIOCARCINOMA
- MIXED GERM CELL TUMOR
- MONODERMAL TERATOMAS AND SOMATIC TYPE TUMORS ARISING FROM A DERMOID CYST --- STRUMA OVARII & CARCINOID

MATURE TERATOMA

- Benign tumor of the ovary composed of mature tissue representing at least 2 embryonic layers (ectoderm, mesoderm or endoderm)
- Most common ovarian tumor (20% of all ovarian tumors, 95% of all ovarian germ cell tumors)
- Slow growing, often incidental finding
- Smooth cyst that may contain hair, teeth, cartilage, bone or sebaceous material
- Raised protuberance in cyst wall (Rokitansky nodule)




A
B
C
D

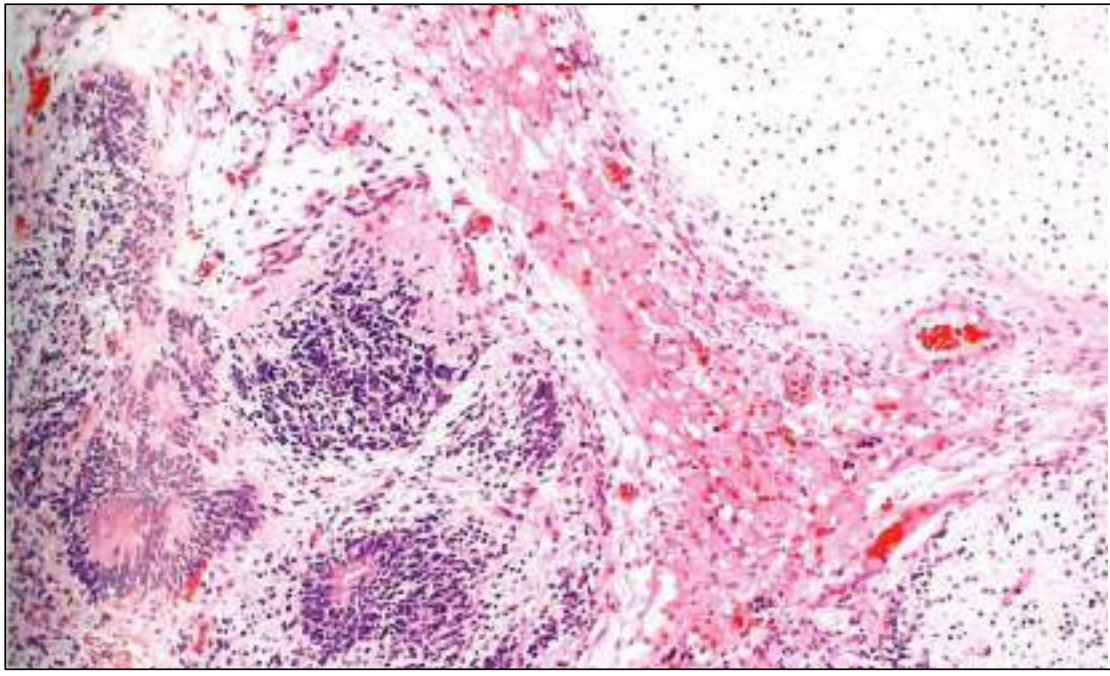
IMMATURE TERATOMA

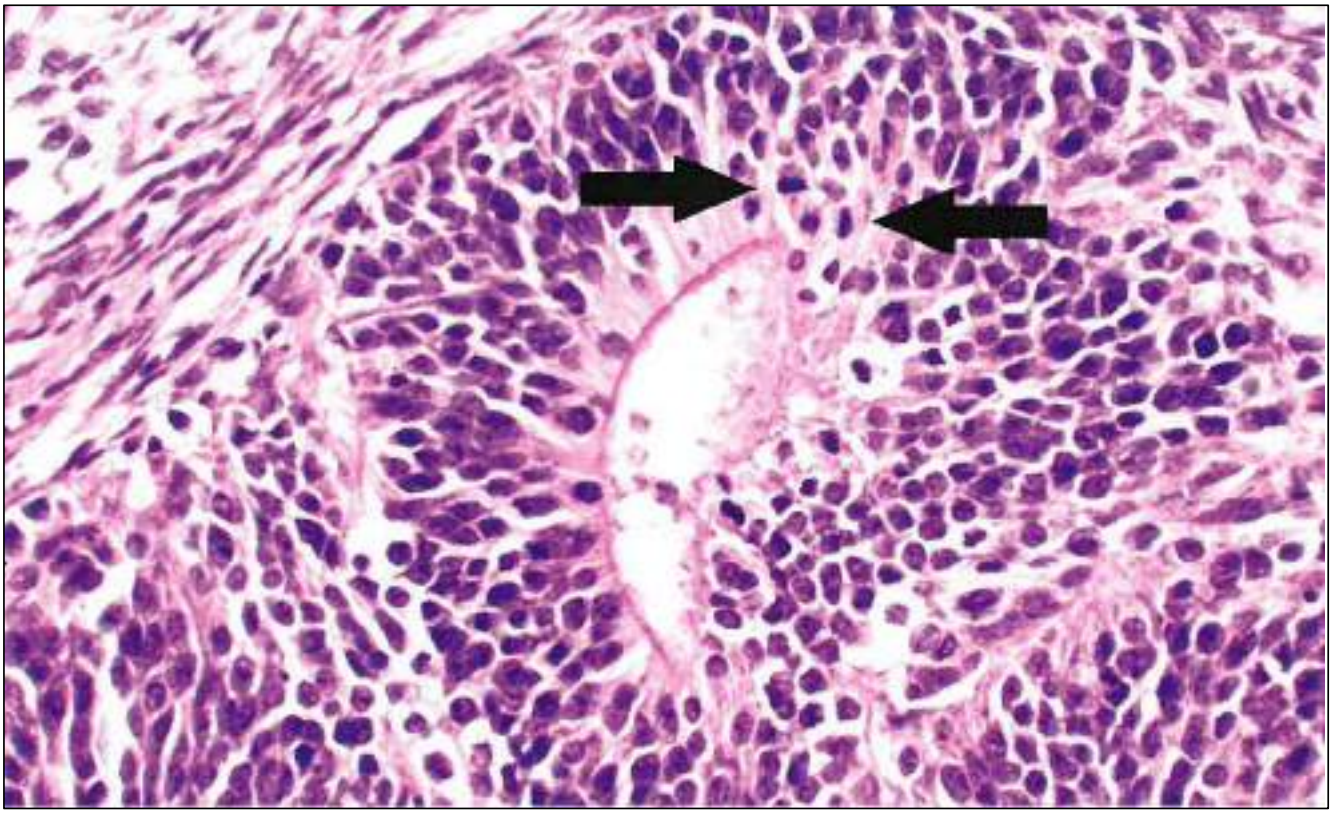
- Malignant germ cell tumor of the ovary composed of cells from the three germ layers, containing variable amounts of mature and immature tissue (typically primitive neuroectodermal)
- A third of malignant germ cell tumors
- Affects mostly young females

  < 20 years old
- Grossly solid ovarian tumor mass

  with necrosis and hemorrhage on

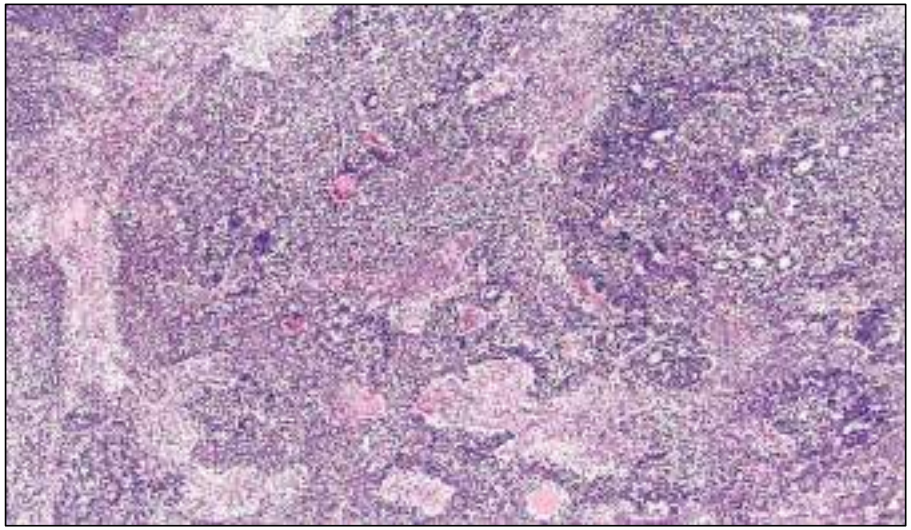
  cut sections





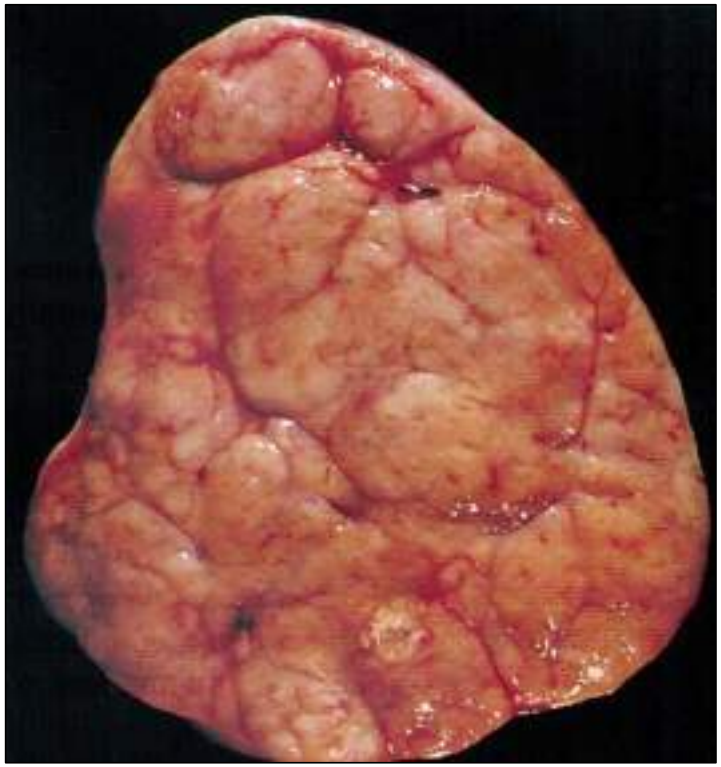
- ✓ Immature neuroepithelium can be spindled (sarcomatoid) or with rosette, pseudorosette and primitive tubule formation
- ✓ Cells appear primitive, with scant cytoplasm, hyperchromatic nuclei and frequent mitoses, which helps differentiate the immature elements from mature brain tissue
- ✓ Only immature neuroepithelium used for grading, so important to recognize as such on histological slides
- ✓ Peritoneal and nodal gliomatosis nodules consist of mature glial tissue, considered grade 0 for grading purposes; thorough sampling is required to identify immature tissue (metastatic immature teratoma component), which has a worse prognosis

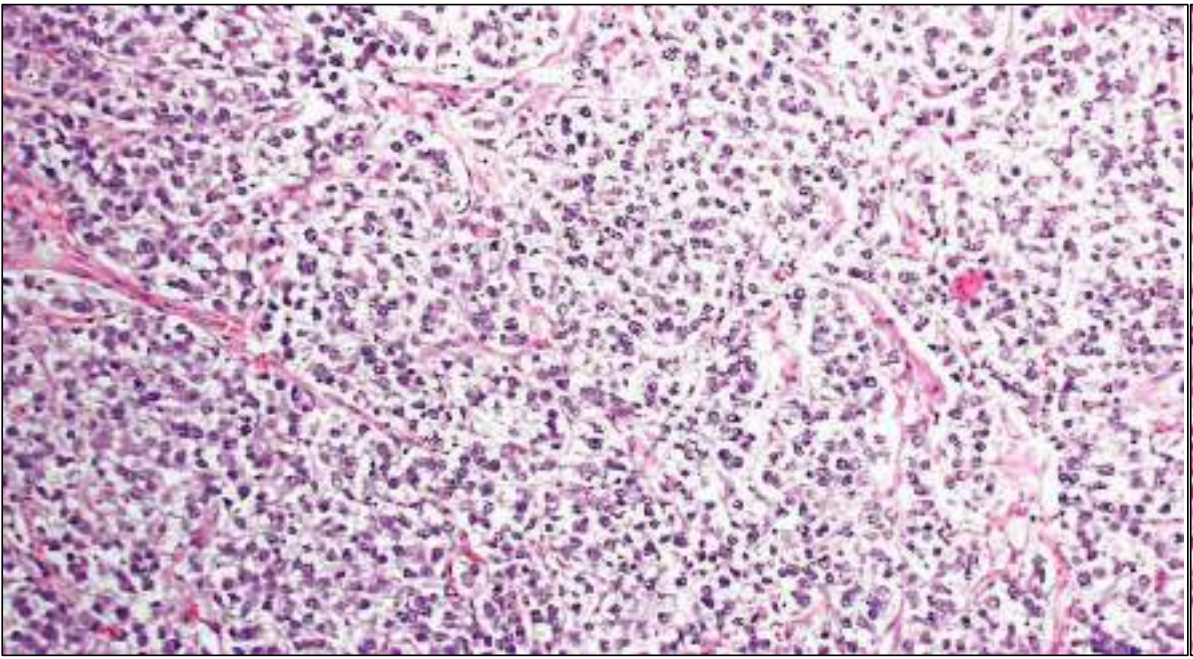
Number of fields	Grade (3-tiered system) (1983)	Grade (2-tiered system) (2008)
≤ 1	Grade 1	Low grade
> 1 to ≤ 3	Grade 2	High grade
> 3	Grade 3	High grade

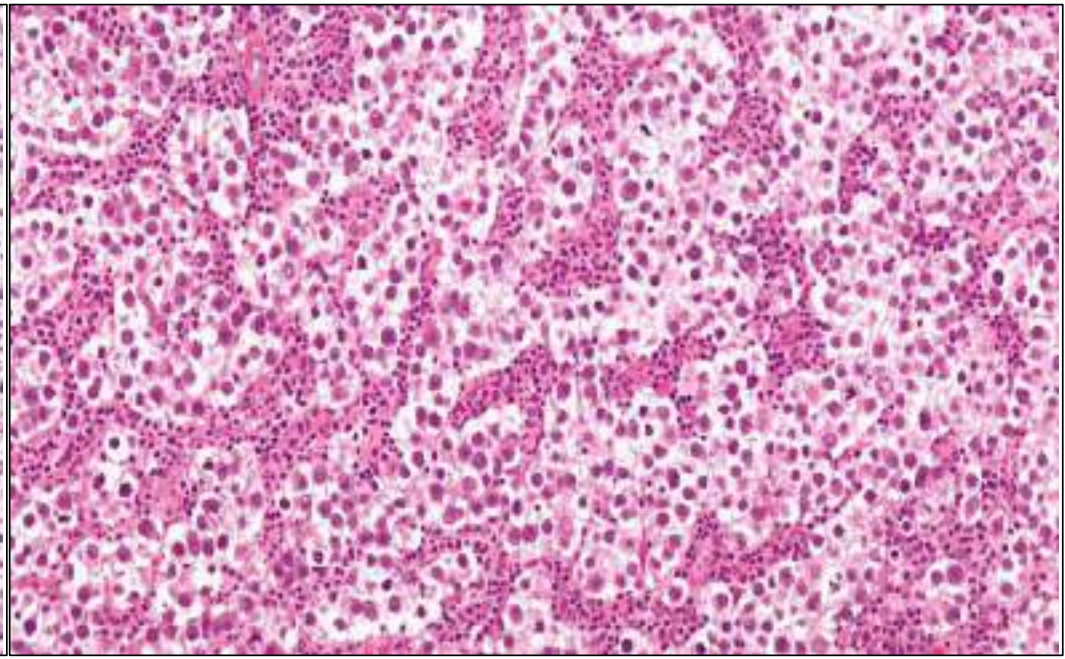


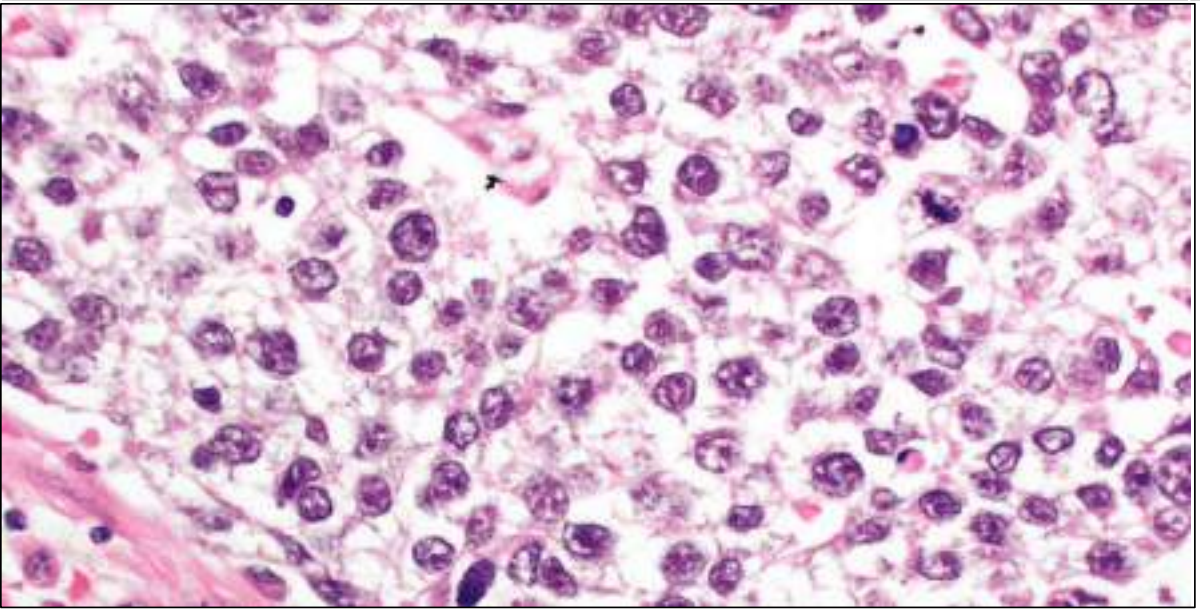
DYSGERMINOMA

- Malignant primitive germ cell tumor with no specific type of differentiation
- Most common malignant ovarian germ cell tumor; female counterpart to testicular seminoma
- Most common in children and young women
- Excellent prognosis with chemotherapy
- Solid and lobulated with fleshy tan-white cut surface
- Hemorrhage and necrosis with cystic degeneration may be present

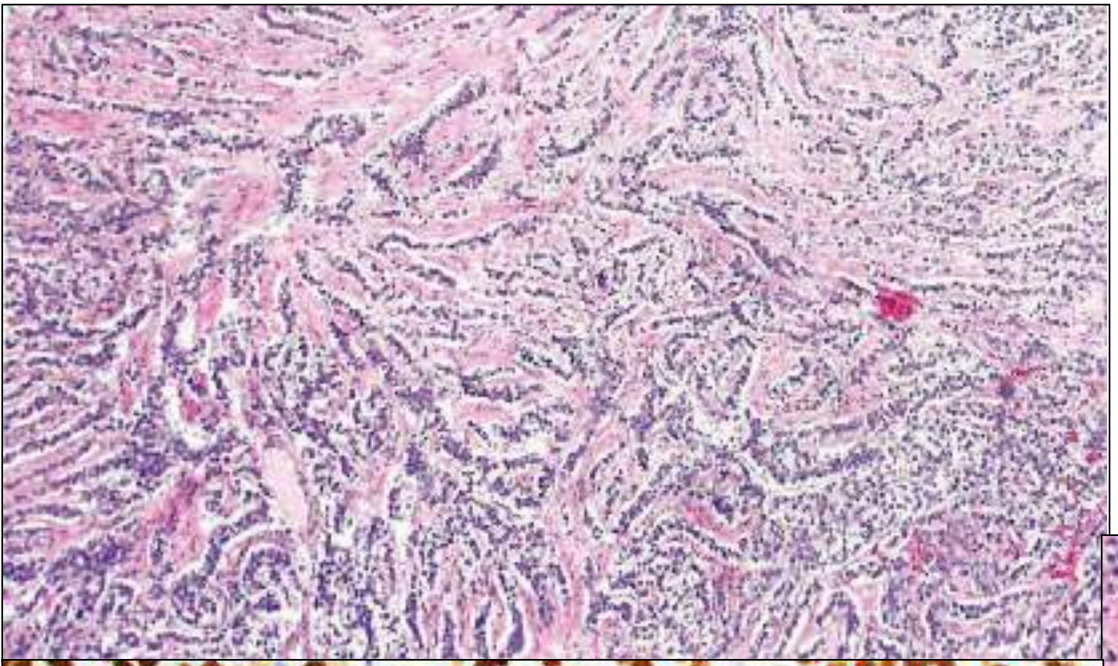




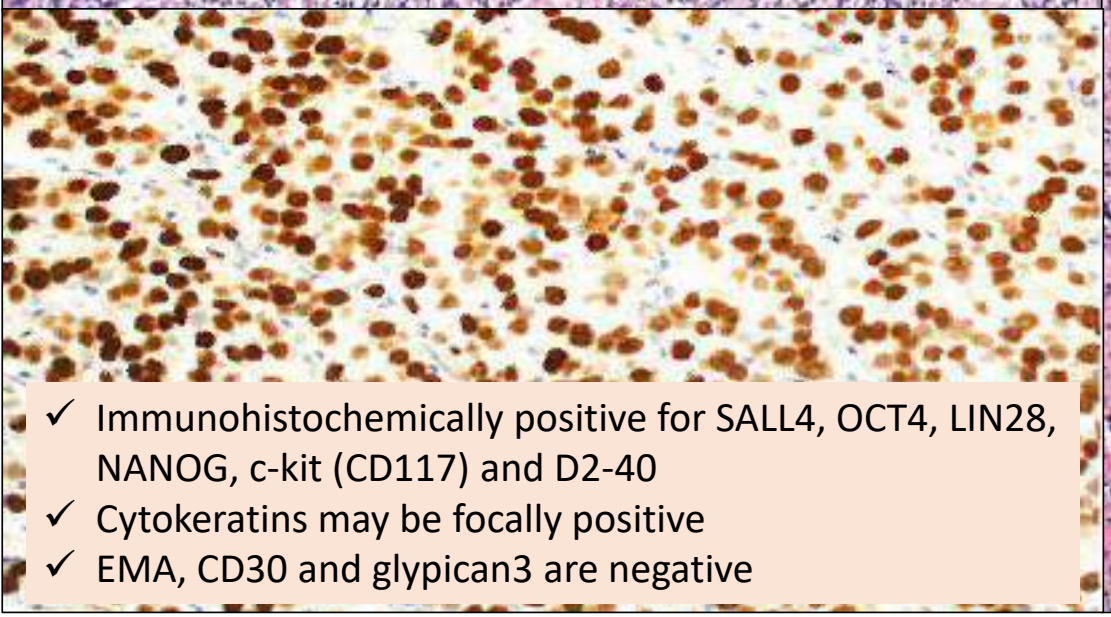




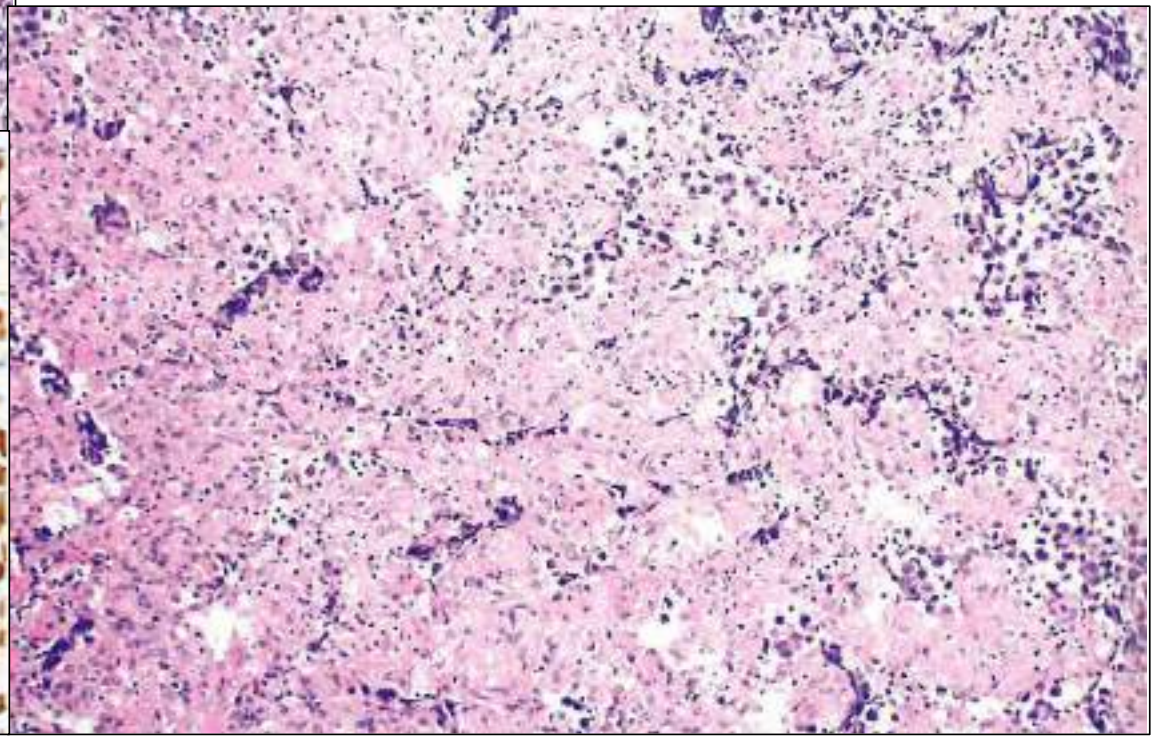
- ✓ Characteristic appearance of nests of large, uniform polygonal cells with clear or eosinophilic cytoplasm and distinct cell membranes separated by thin fibrous septa (alveolar pattern)
- ✓ Fibrous septa contain variable numbers of lymphocytes and plasma cells
- ✓ Stroma usually loose and delicate but in some cases may be hyalinized, myxoid or luteinized
- ✓ Numerous mitotic figures



- ✓ May also show sheets, cords, macronodules, insular growth, microcysts, tubules, pseudoglandular spaces or trabeculae
- ✓ Langhans type giant cells, syncytiotrophoblasts, noncaseating granulomas or lymphoid follicles with germinal centers may be present and sometimes extensive
- ✓ Rare cases show syncytiotrophoblastic cells, singly or in clusters, without cytotrophoblastic cells; sample tumor thoroughly to exclude choriocarcinoma
- ✓ Extensive hemorrhage and necrosis may be present with dystrophic calcification

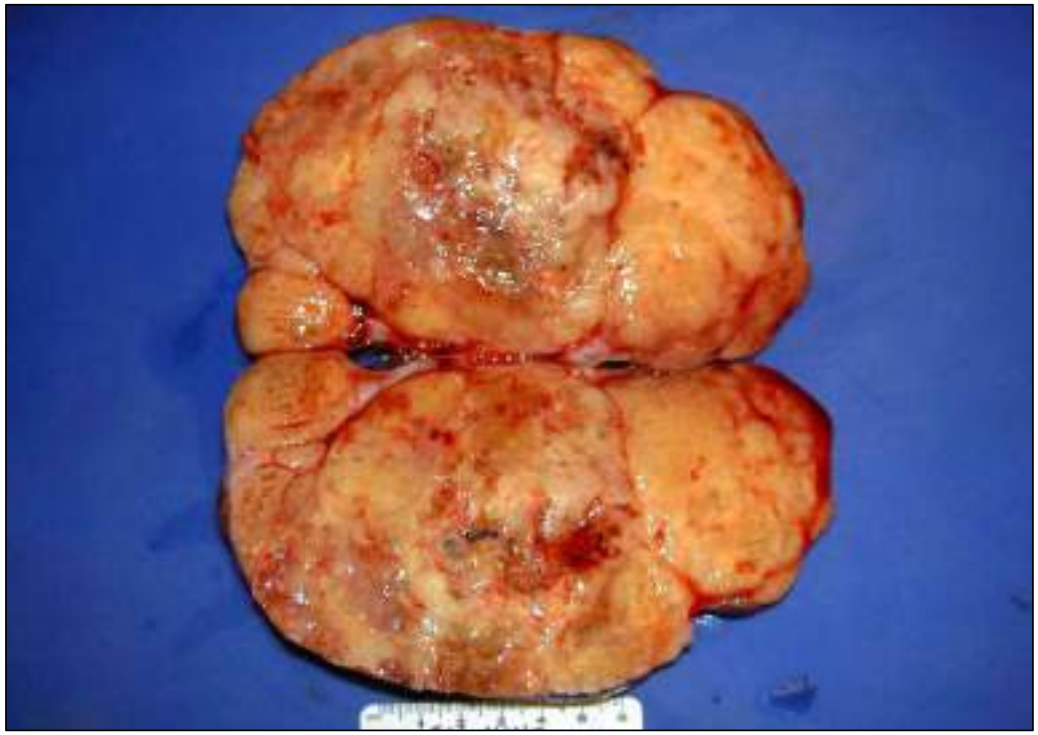


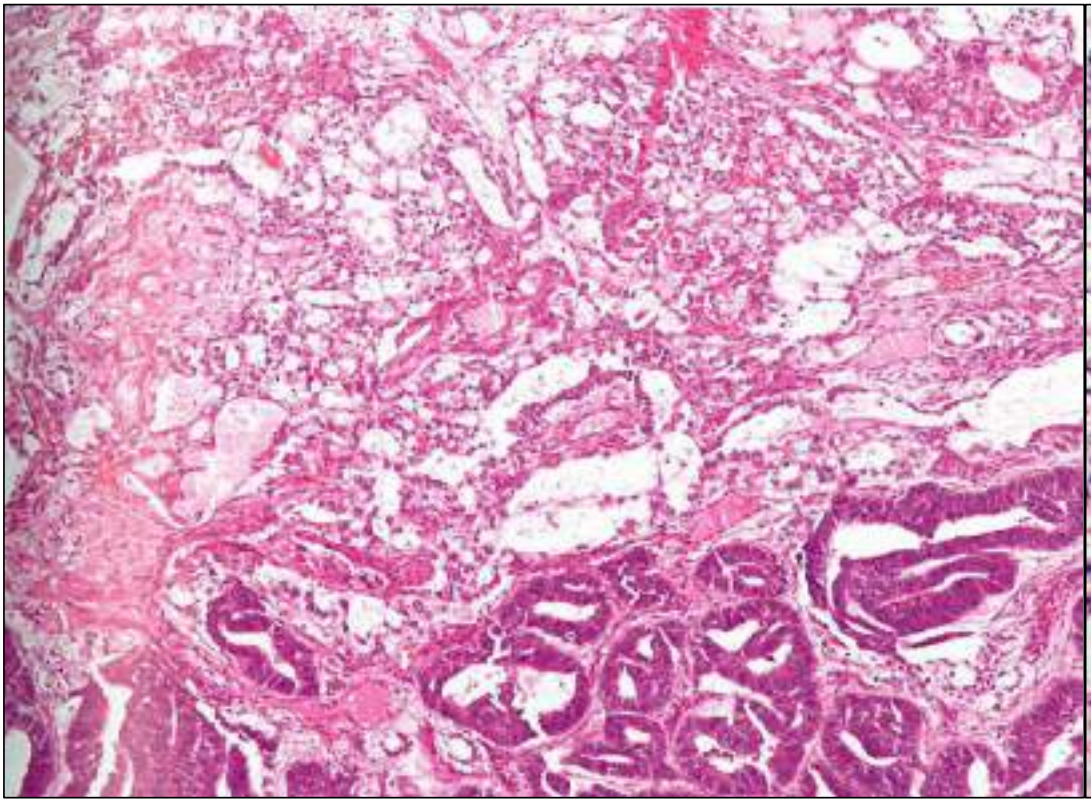
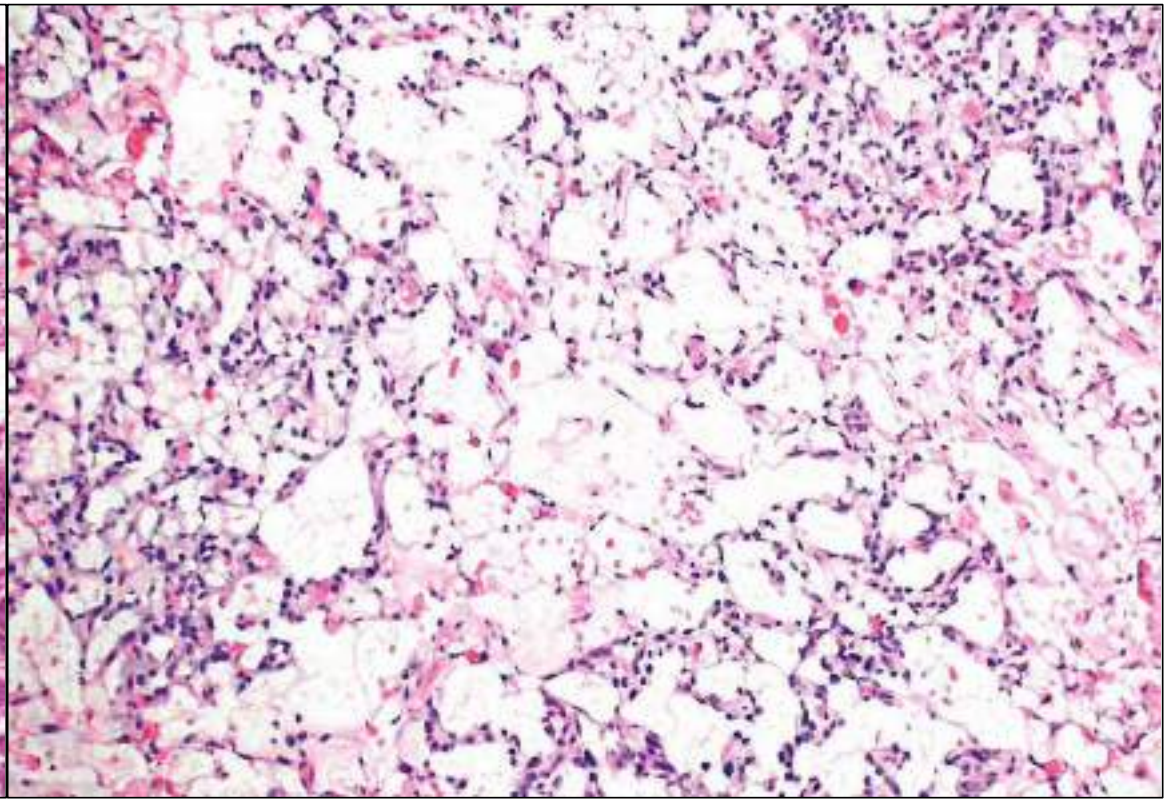
- ✓ Immunohistochemically positive for SALL4, OCT4, LIN28, NANOG, c-kit (CD117) and D2-40
- ✓ Cytokeratins may be focally positive
- ✓ EMA, CD30 and glypican3 are negative



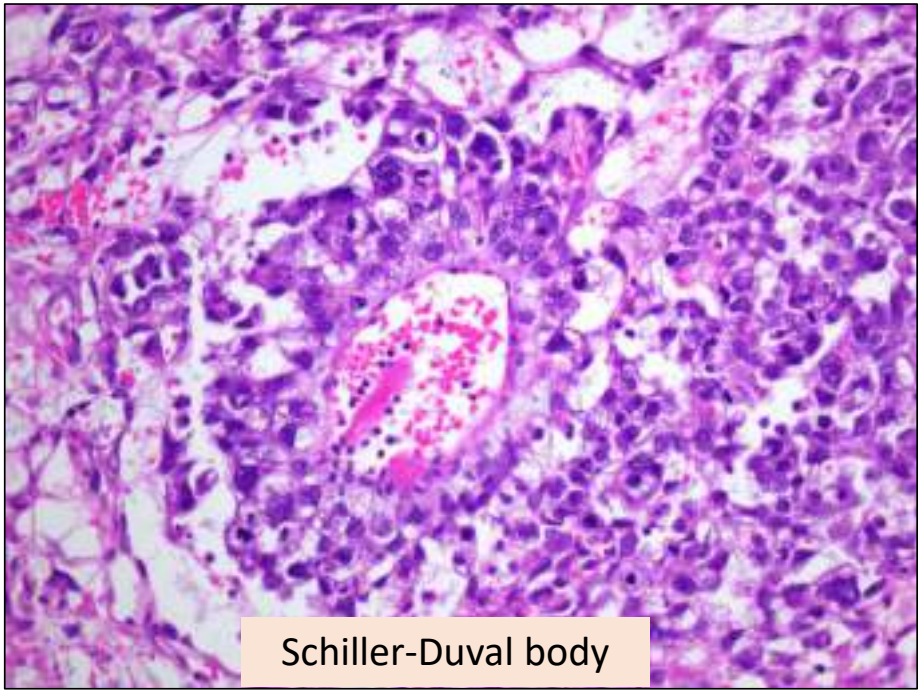
YOLK SAC TUMOR

- Primitive germ cell tumor with a variety of morphologic patterns, ranging from endodermal extraembryonic structures (secondary yolk sac, allantois) to, less commonly, endodermal somatic tissues (intestine, liver, mesenchyme)
- Second most common malignant ovarian germ cell tumor after dysgerminoma
- Most common before the age of 30
- Often associated with elevated serum **alpha fetoprotein (AFP)**

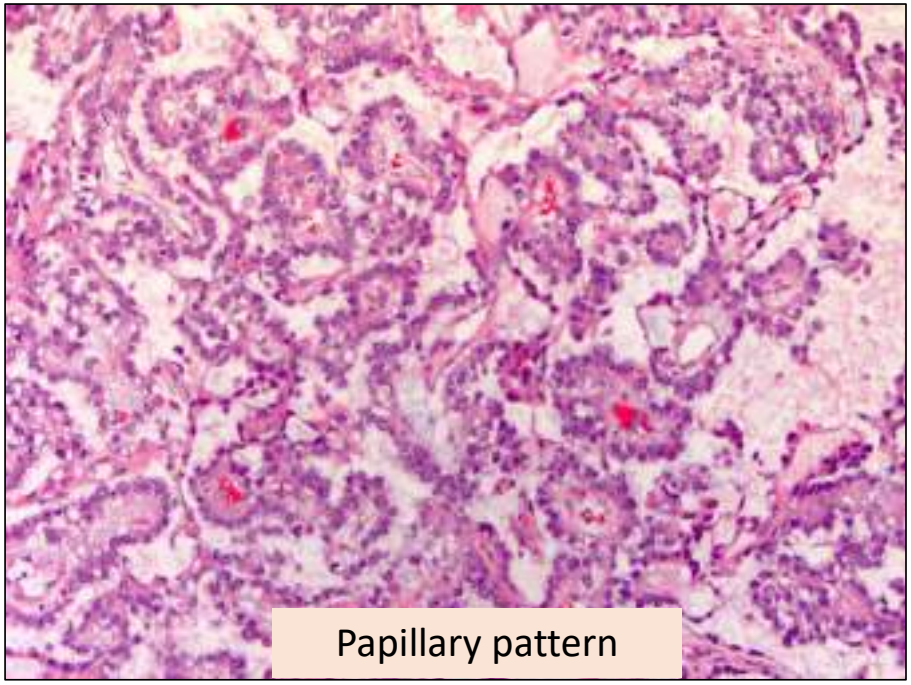


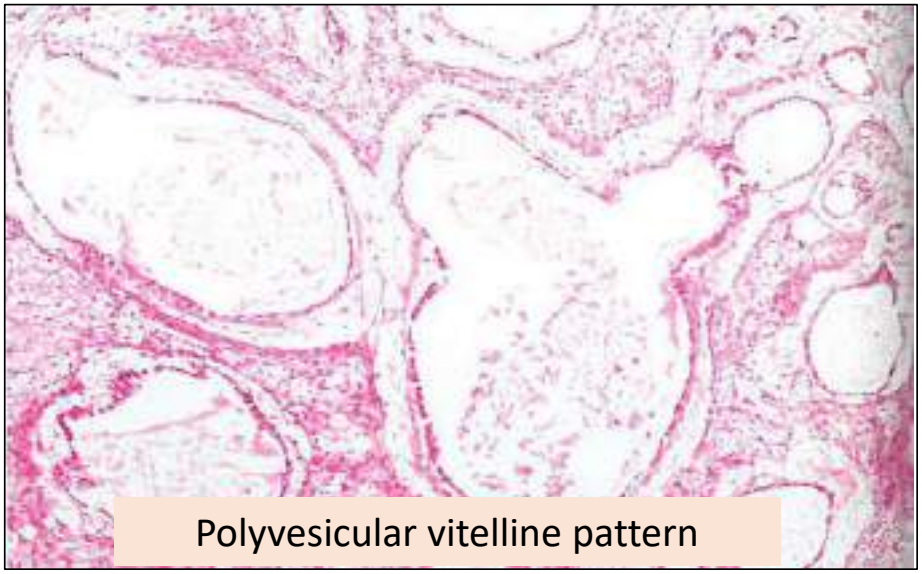
- Multiple histologic patterns with predominance of 1 or 2 patterns
- Reticular / microcystic pattern: Most common pattern. Loose meshwork of anastomosing channels and variably sized cysts (macro or microcysts) lined by primitive tumor cells with varying amounts of clear to eosinophilic cytoplasm
- Loose, hypocellular or myxoid stroma
- Endodermal sinus pattern: Anastomosing network of labyrinthine-like spaces lined by tumor cells. Formation of vaguely glomeruloid perivascular structures (Schiller-Duval bodies). Hallmark of yolk sac tumor but their absence does not rule out the diagnosis
- Glandular pattern (forming endodermal somatic derivatives): Endometrioid type areas with glandular or villoglandular structures lined by single or multiple layers of tall columnar cells containing subnuclear or supranuclear vacuoles resembling secretory endometrium



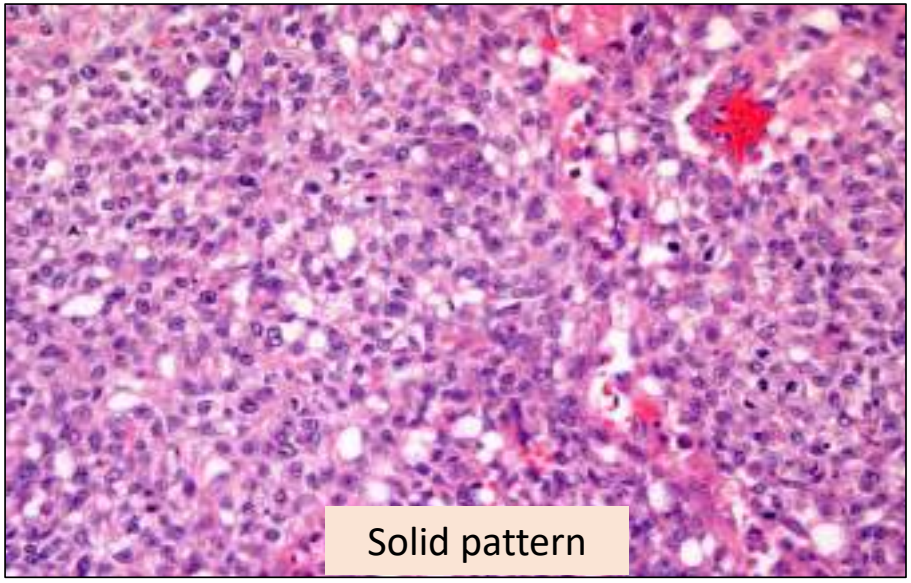
Schiller-Duval body



Papillary pattern

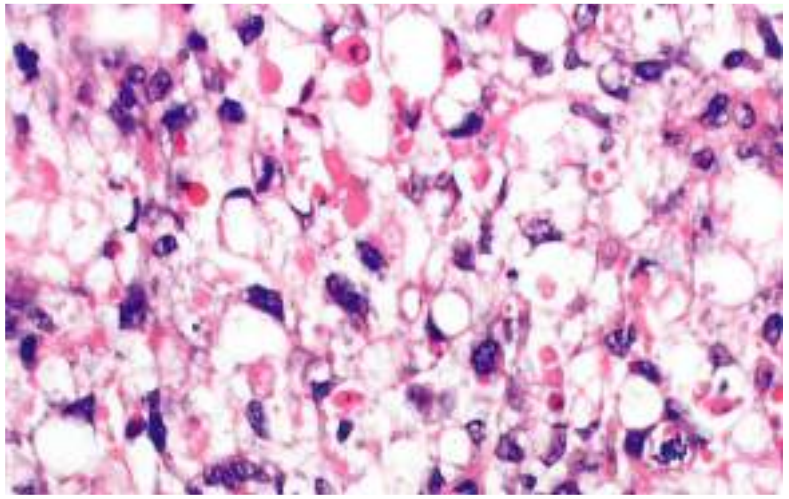


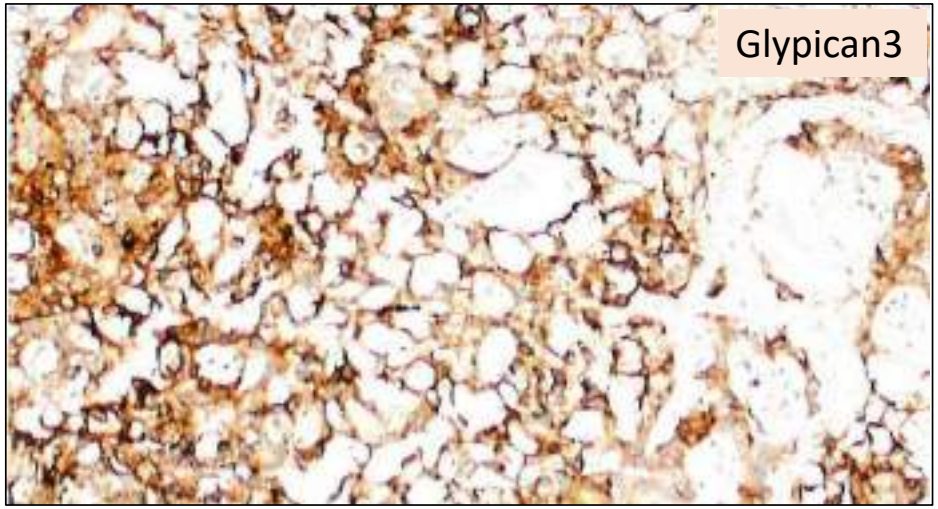
Polyvesicular vitelline pattern



Solid pattern

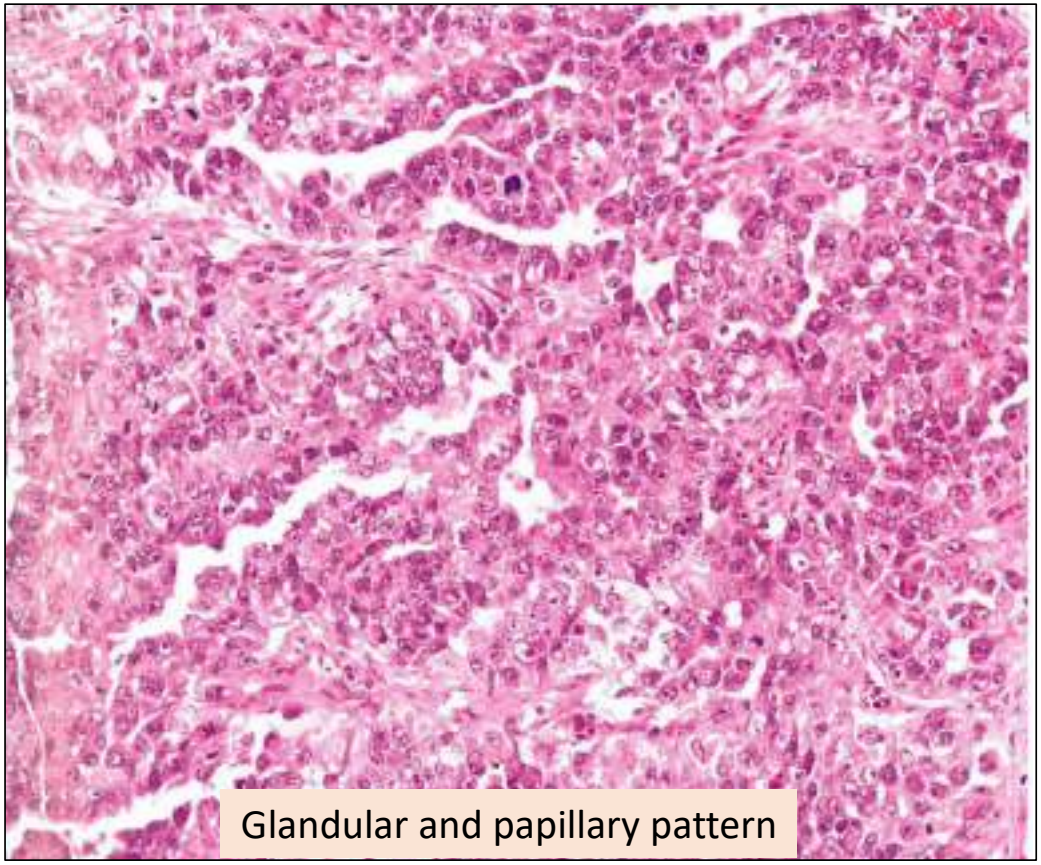
- General features:
  - Variable cytologic atypia and mitotic activity
  - Pale eosinophilic to clear cytoplasm
  - Prominent nucleoli
  - Intracellular hyaline globules
  - Tumor cells lining cystic structures can be deceptively bland
  - May be admixed with other malignant germ cell tumor, usually with dysgerminoma or gonadoblastoma in patients with gonadal dysgenesis
  - May be associated with synchronous or metachronous ipsilateral or contralateral mature cystic teratoma
  - Positive IHC markers include SALL4 (marker of primitive germ cell differentiation), glypican3, LIN28 and AFP
  - CDX2 can be positive in the intestinal pattern,
  - HepPar1 in the hepatoid pattern
  - TTF1 in the foregut/respiratory pattern



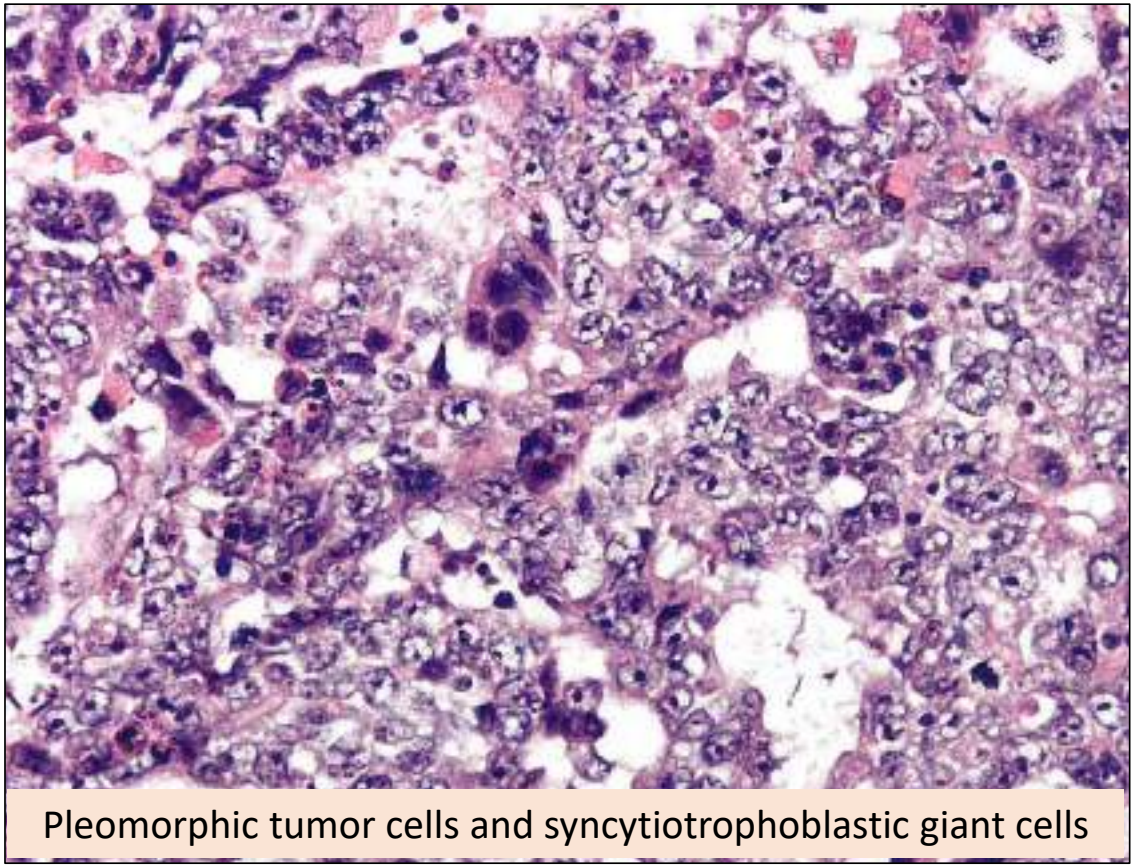


EMBRYONAL CARCINOMA

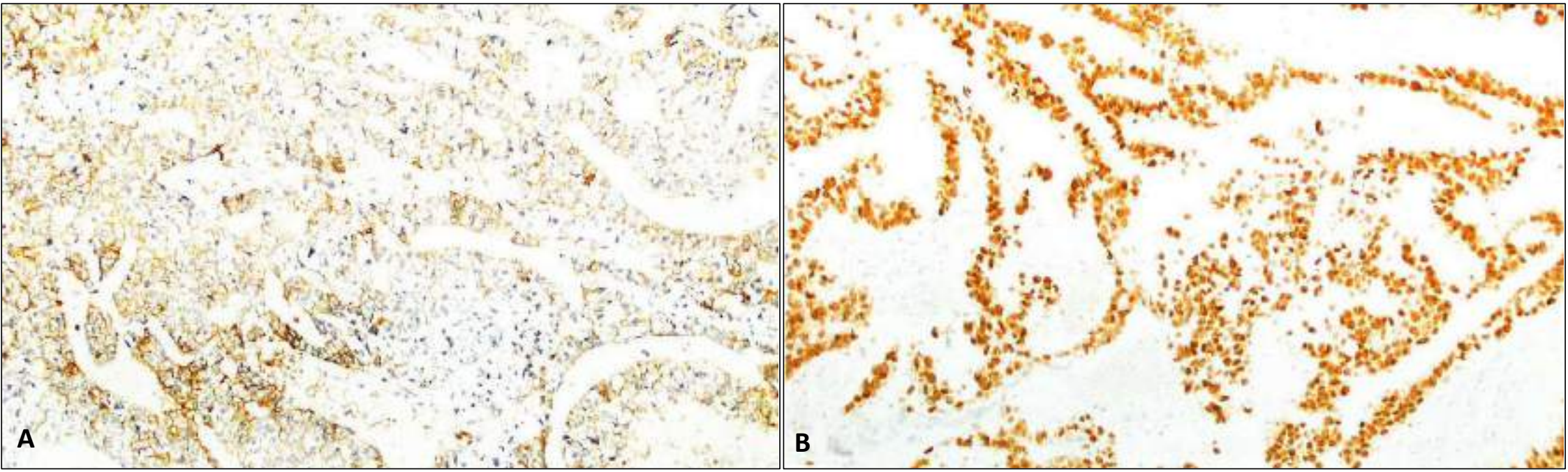
- Primitive malignant germ cell tumor that may exhibit somatic or extraembryonal differentiation



Glandular and papillary pattern



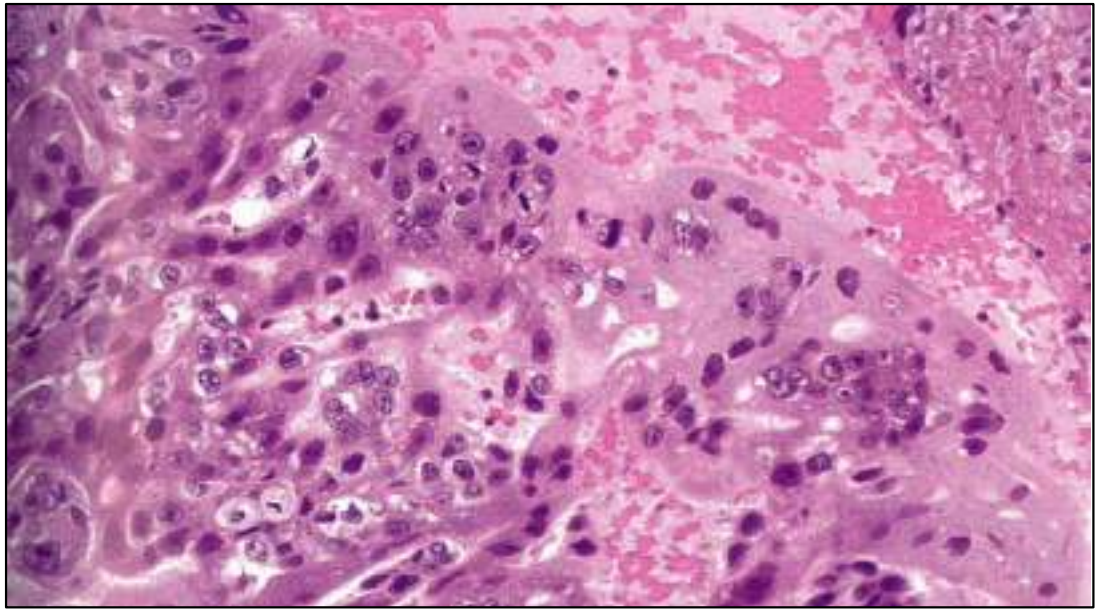
Pleomorphic tumor cells and syncytiotrophoblastic giant cells

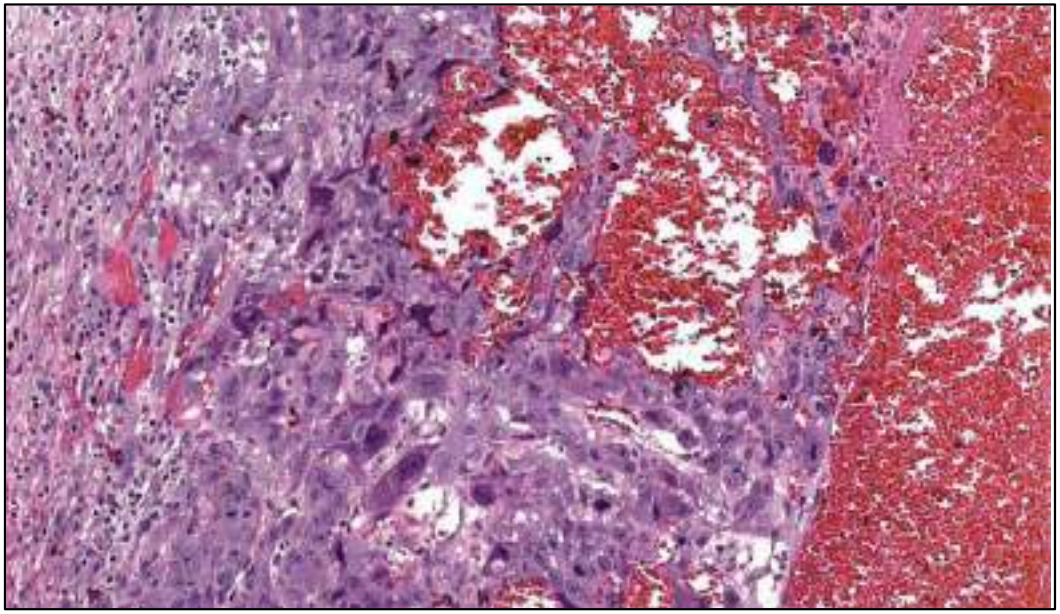


Embryonal carcinoma. **A** CD30 stains embryonal carcinoma in a membranous pattern. **B** SOX2 stains embryonal carcinoma in a nuclear pattern.

NON-GESTATIONAL CHORIOCARCINOMA

- Malignant tumor composed of cytotrophoblasts and syncytiotrophoblasts that is not of gestational origin

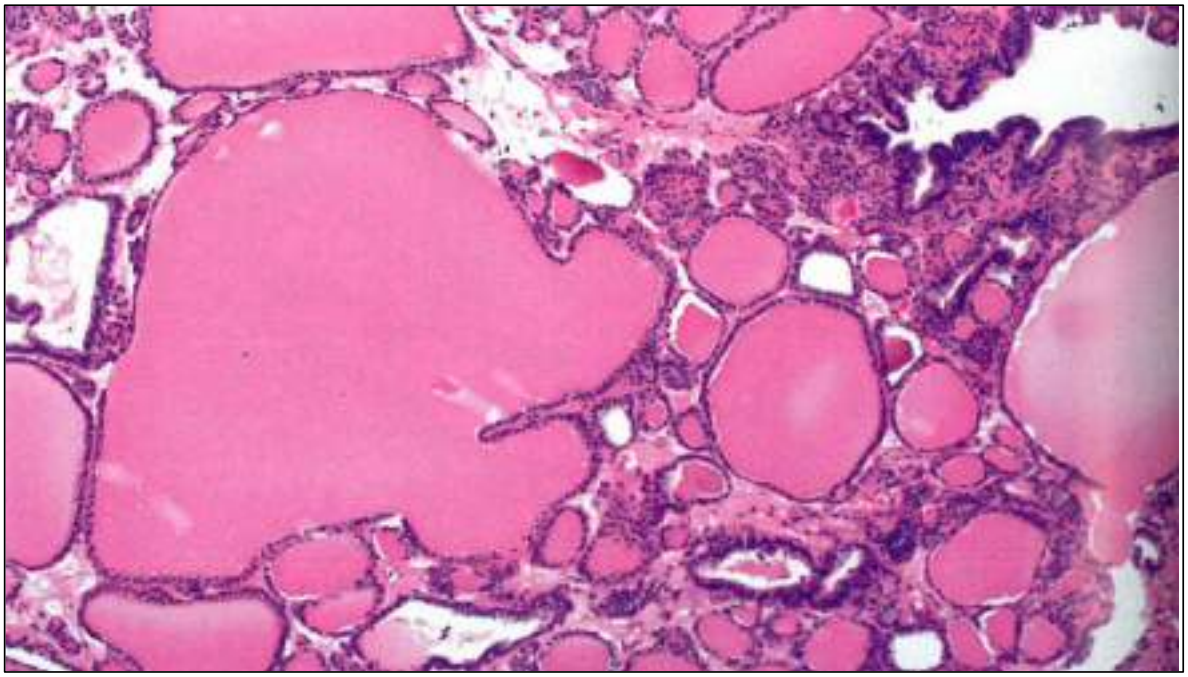




- Composed of mononucleated cytotrophoblast, intermediate trophopblast and multinucleated syncytiotrophoblast often accompanied by extensive hemorrhage and necrosis
- Tumor cells are positive for hCG by immunohistochemistry

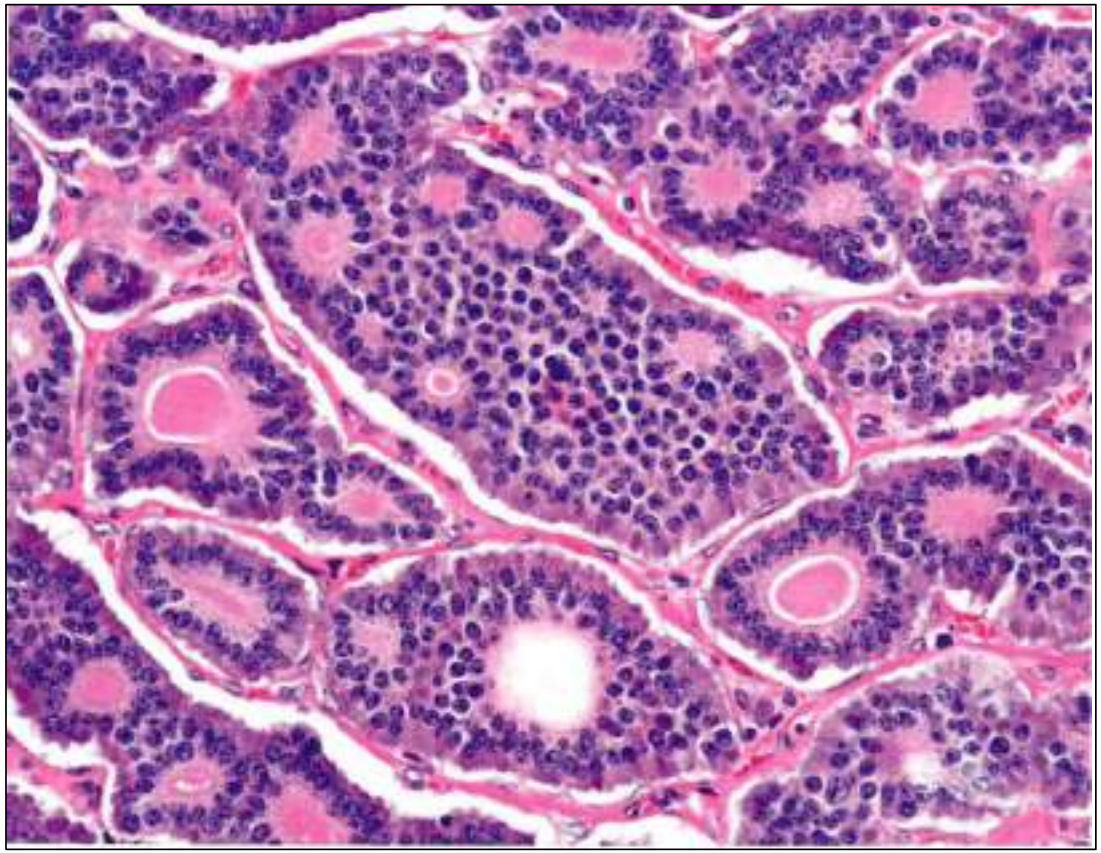
STRUMA OVARII

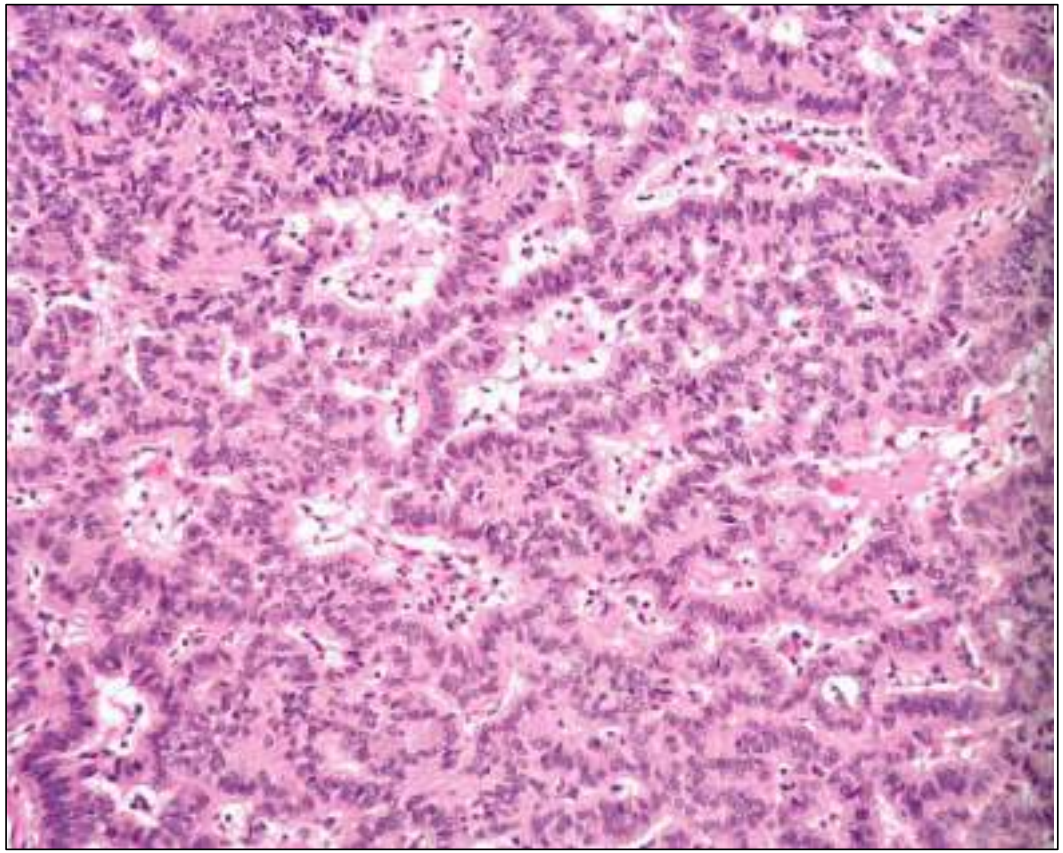
- Monodermal ovarian teratoma primarily (> 50%) or exclusively composed of benign thyroid tissue
- Multicystic, filled with colloid/mucoid material
- Variably sized thyroid follicles filled with colloid and hyperplastic papillae



OVARIAN CARCINOID

- Well differentiated neuroendocrine tumor resembling those arising in the gastrointestinal tract



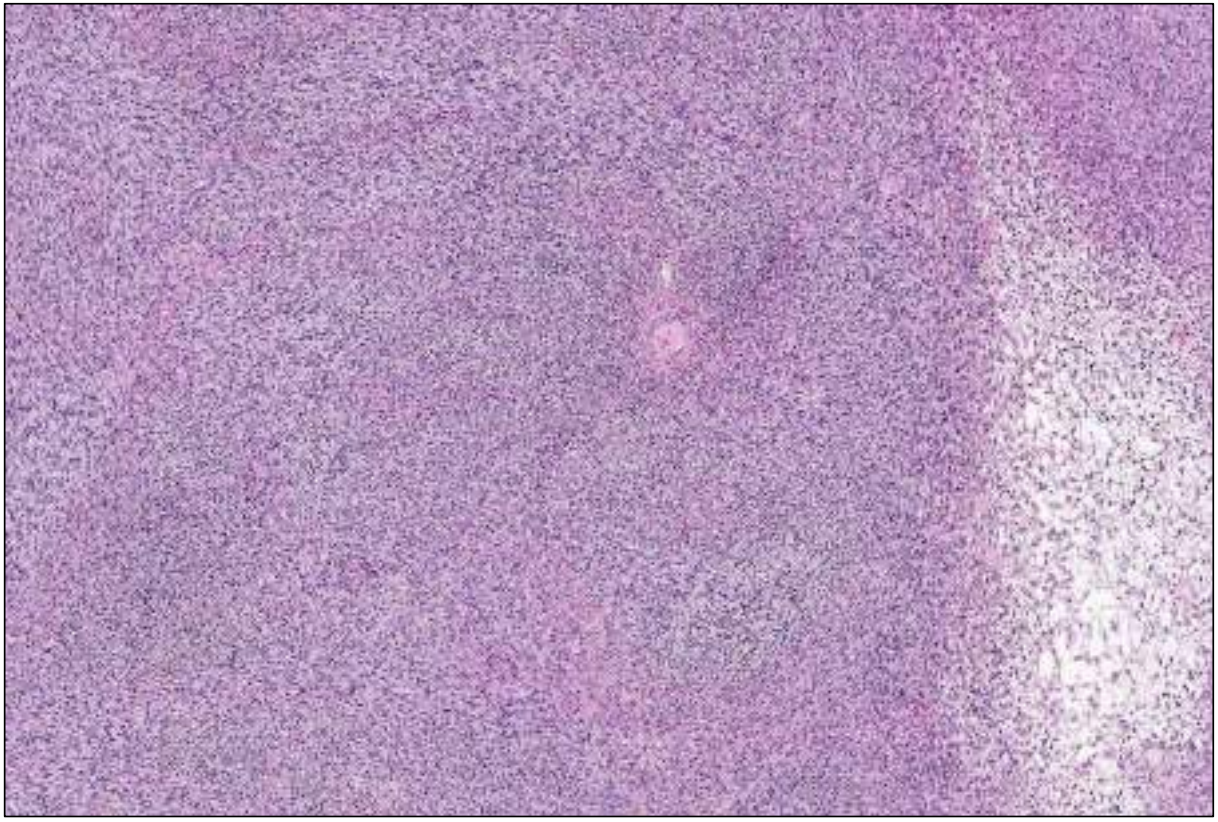


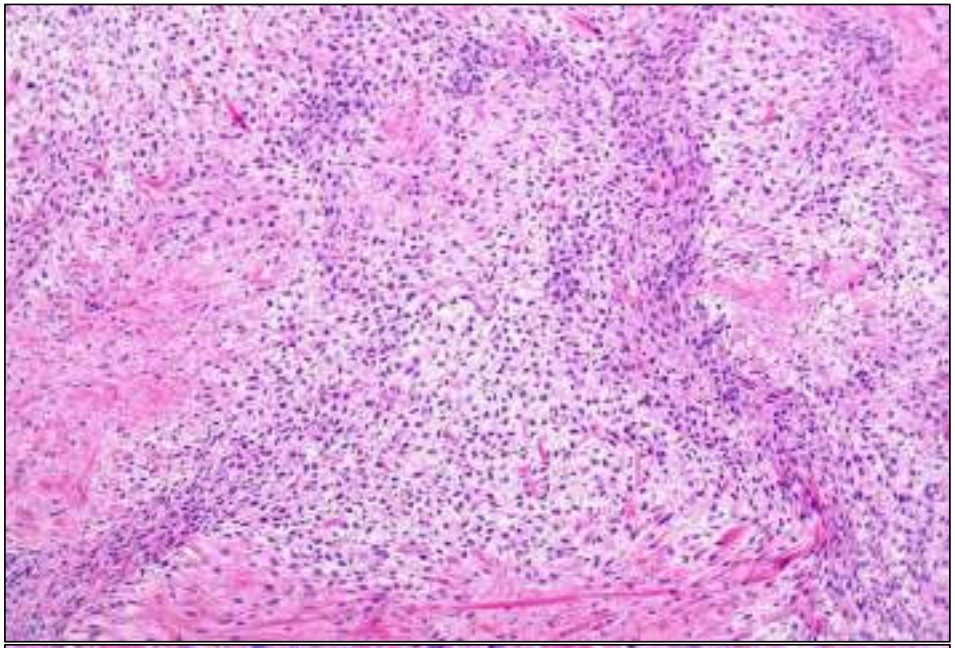
SEX CORD-STROMAL TUMORS

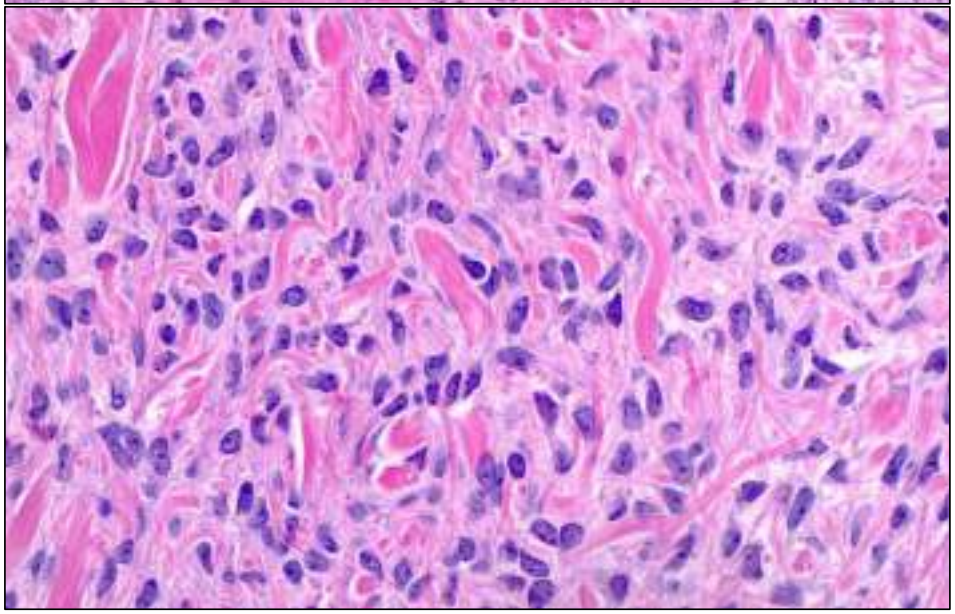
- Sex cord–stromal tumours
  - Pure stromal tumours
    - Ovarian fibroma
    - Thecoma
    - Luteinized thecoma associated with sclerosing peritonitis
    - Sclerosing stromal tumour
    - Microcystic stromal tumour
    - Signet-ring stromal tumour
    - Leydig cell tumour
    - Steroid cell tumour
    - Ovarian fibrosarcoma
  - Pure sex cord tumours
    - Adult granulosa cell tumour
    - Juvenile granulosa cell tumour
    - Sertoli cell tumour
    - Sex cord tumour with annular tubules
  - Mixed sex cord–stromal tumours
    - Sertoli–Leydig cell tumour
    - Sex cord–stromal tumour NOS
    - Gynandroblastoma

OVARIAN FIBROMA

- Benign stromal tumor composed of fibroblastic cells within a variably collagenous stroma

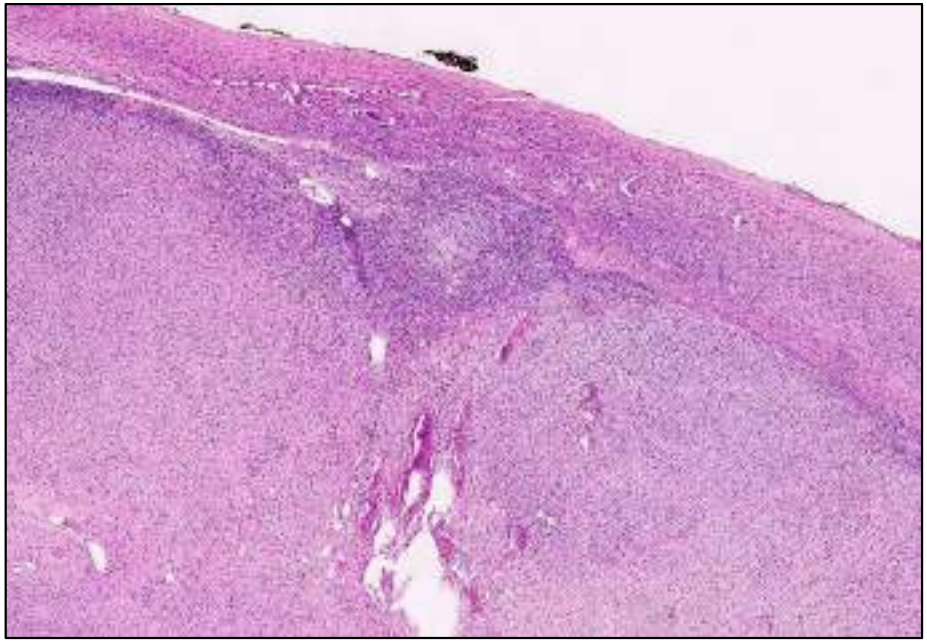


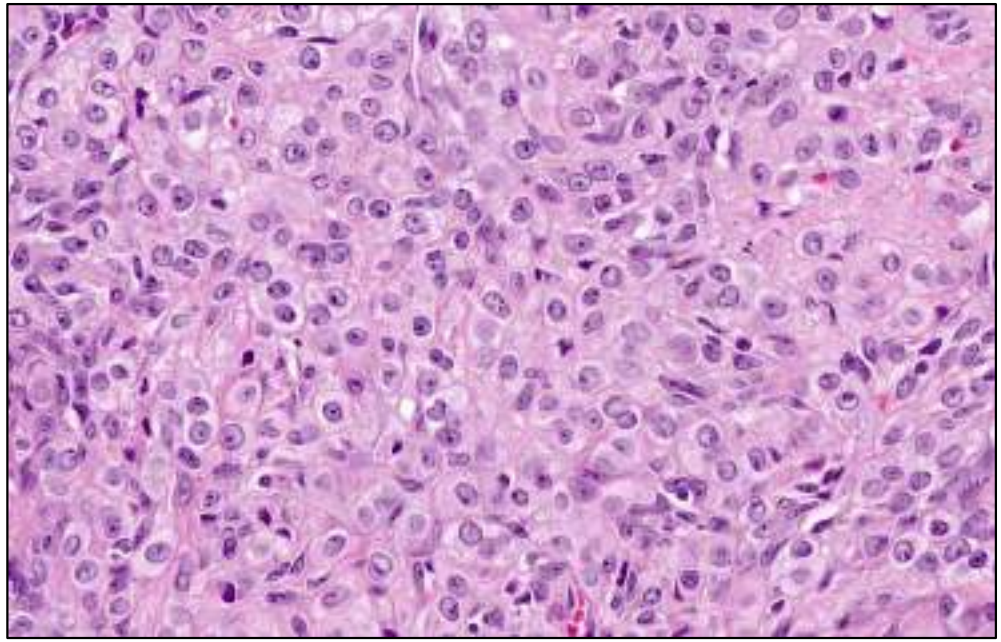




THECOMA

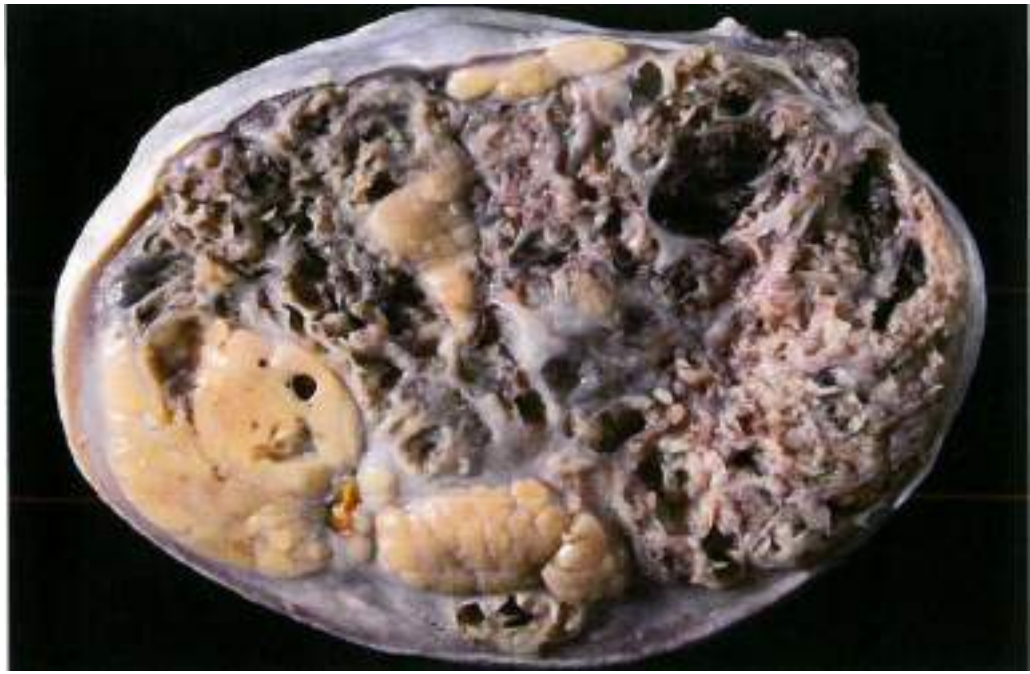
- Ovarian stromal neoplasm, almost always benign, composed of cells resembling theca cells
- Predominant population of cells showing ovoid to round nuclei and pale gray cytoplasm, which can be abundant
- Minor component of the tumor may have spindled nuclei, reflecting overlap between fibroma and thecoma
- Indistinct cell membranes impart a syncytial appearance
- Diffuse or nodular growth pattern
- Absent or minimal nuclear atypia

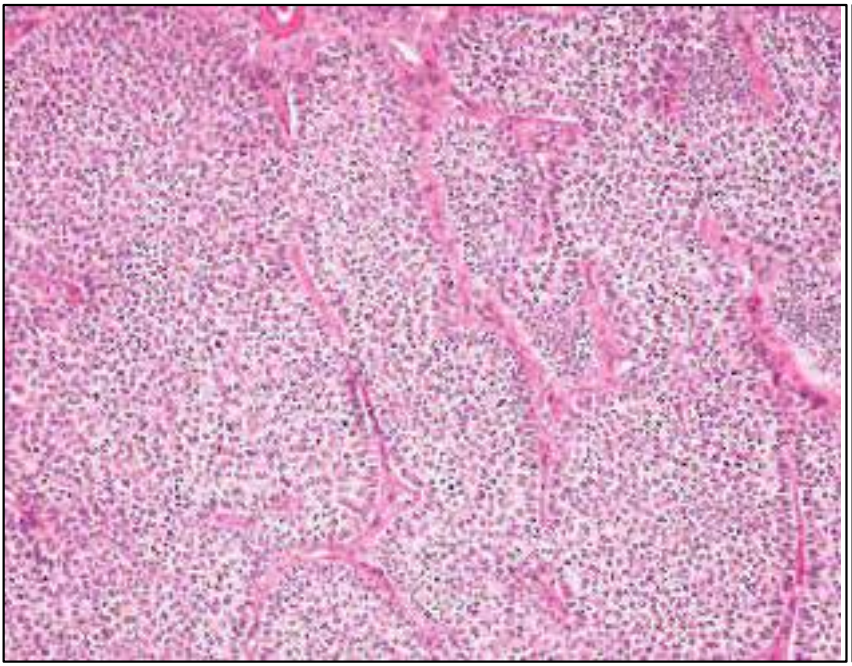


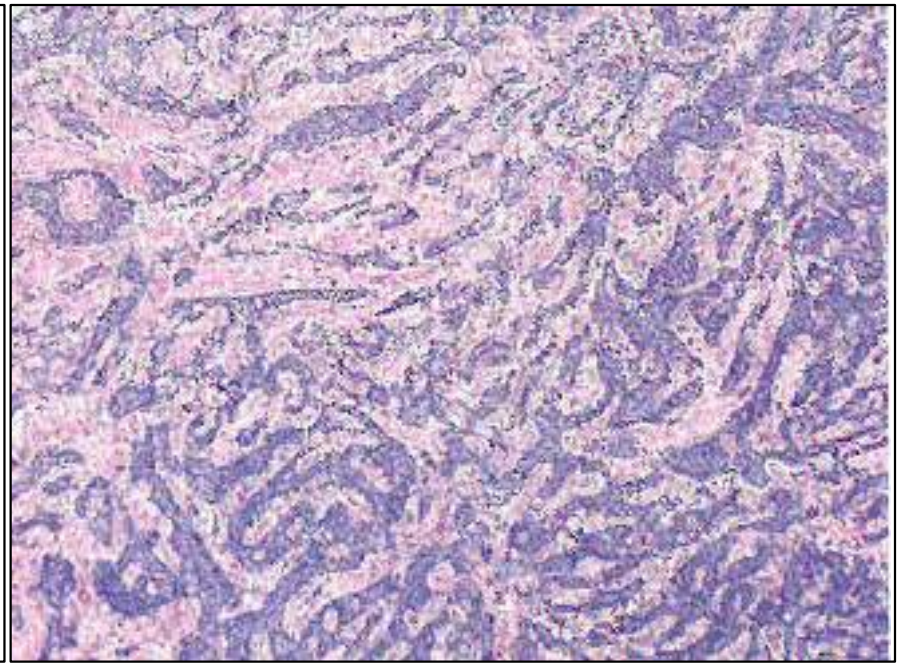


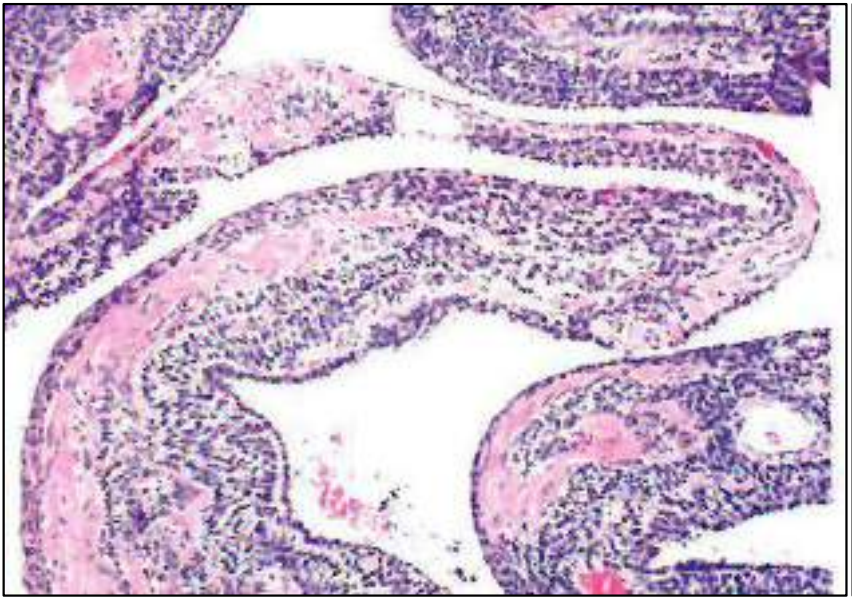
ADULT GRANULOSA CELL TUMOR

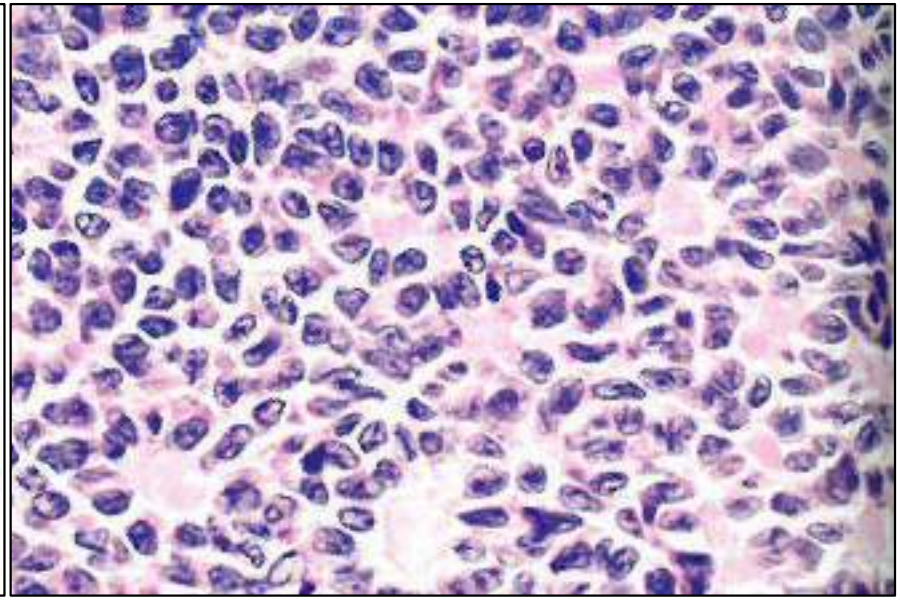
- Low grade malignant neoplasm composed of granulosa cells growing in a variety of patterns, admixed with a variable population of fibroblasts or theca cells
- 10% of all sex cord stromal tumors of the ovary
- Should be considered in the differential diagnosis of solid / cystic and hemorrhagic ovarian mass in postmenopausal patients
- Nearly all tumors harbour a recurrent somatic FOXL2 missense mutation
- Encapsulated with smooth lobulated surface, tan or yellow, soft to firm, usually solid and cystic with straw colored or mucoid fluid, can have areas of necrosis and hemorrhage



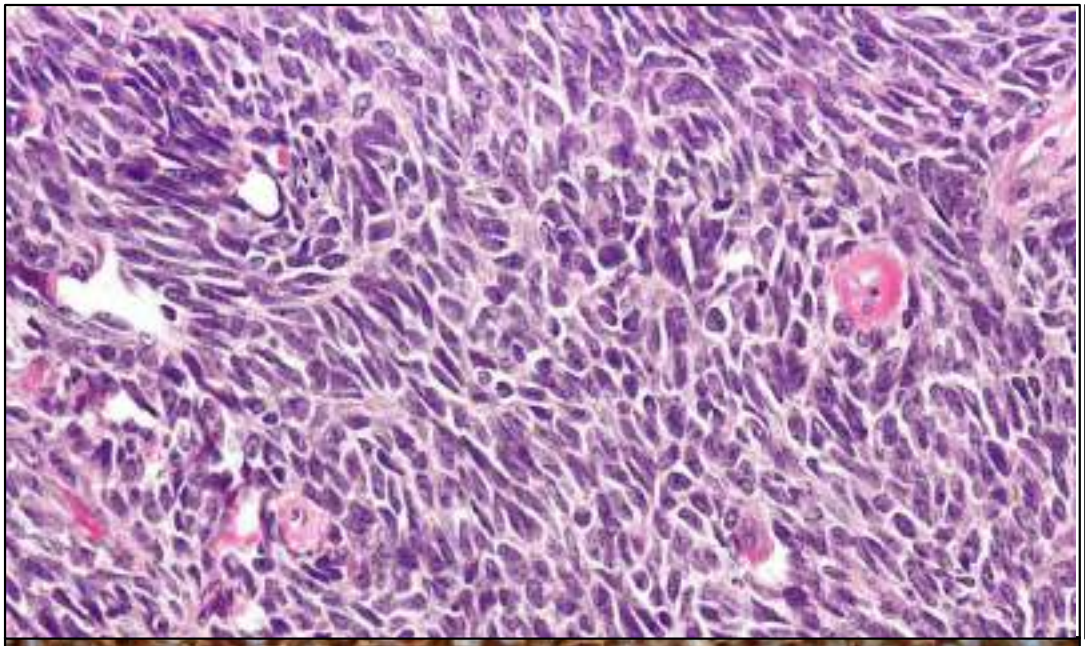


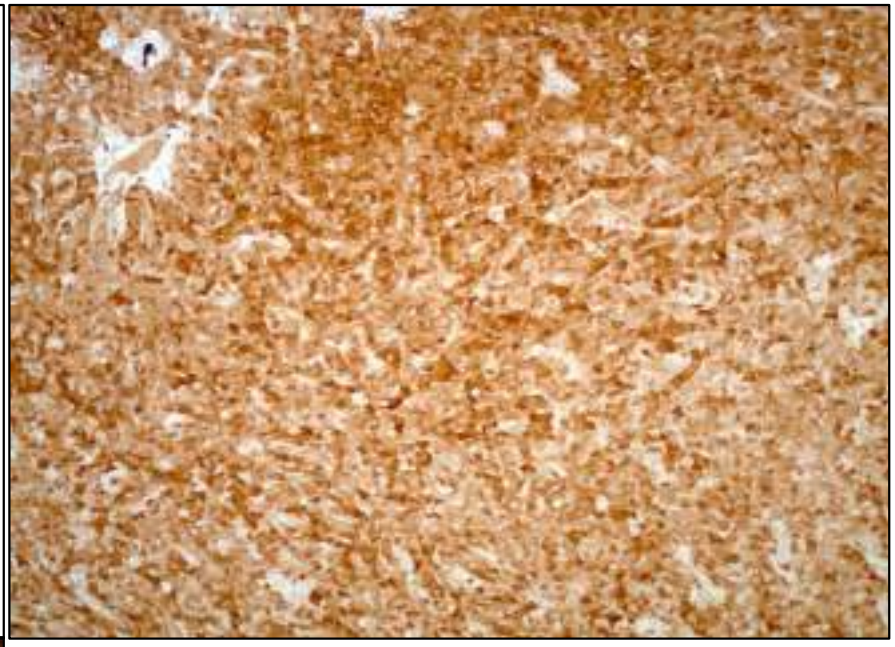


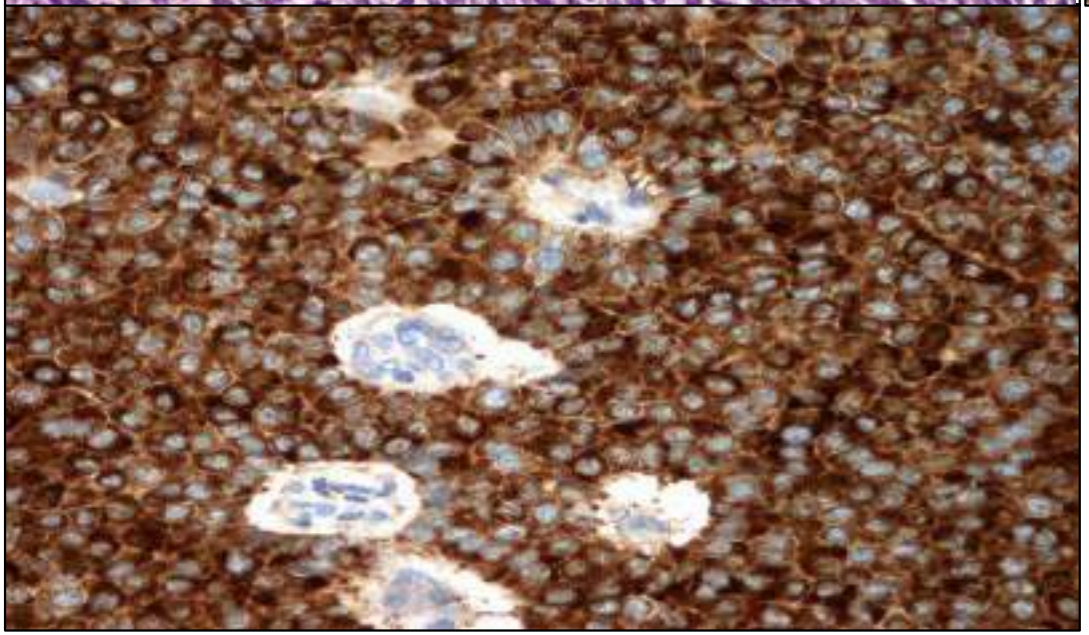




- ✓ Various patterns, including diffuse (M.C.), trabecular and corded, insular, microfollicular (resembling Call-Exner bodies of the Graafian follicles: small follicle-like structures filled with eosinophilic material) and macrofollicular
- ✓ Small, bland, cuboidal to polygonal cells with scant cytoplasm and pale, uniform angulated and usually grooved nuclei (coffee bean)
- ✓ Mitotic activity is usually not brisk
- ✓ High grade transformation can occur characterized by marked nuclear atypia and high mitotic count



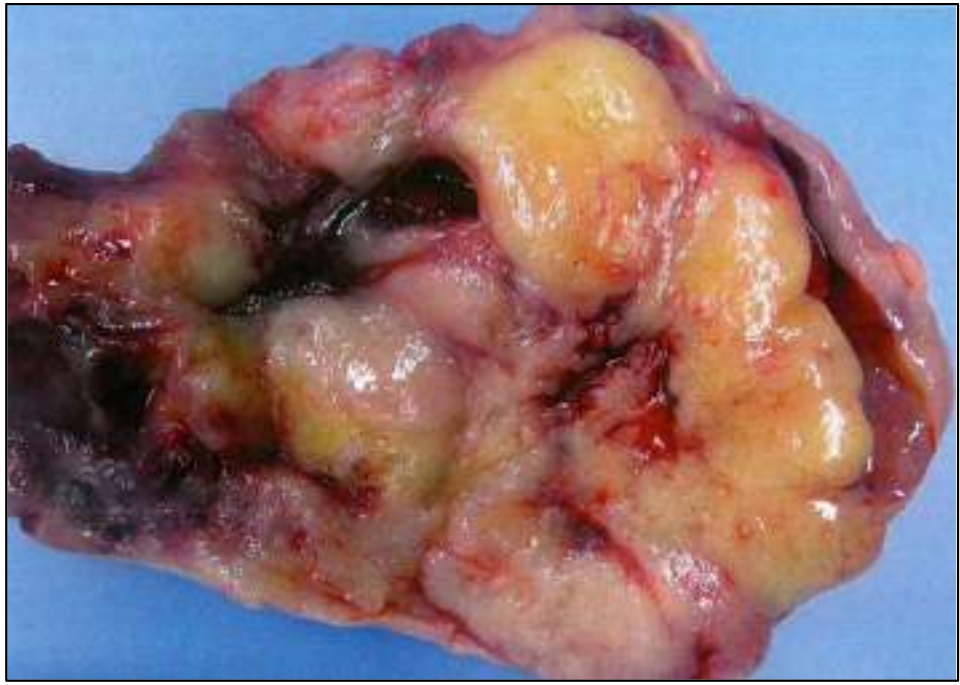


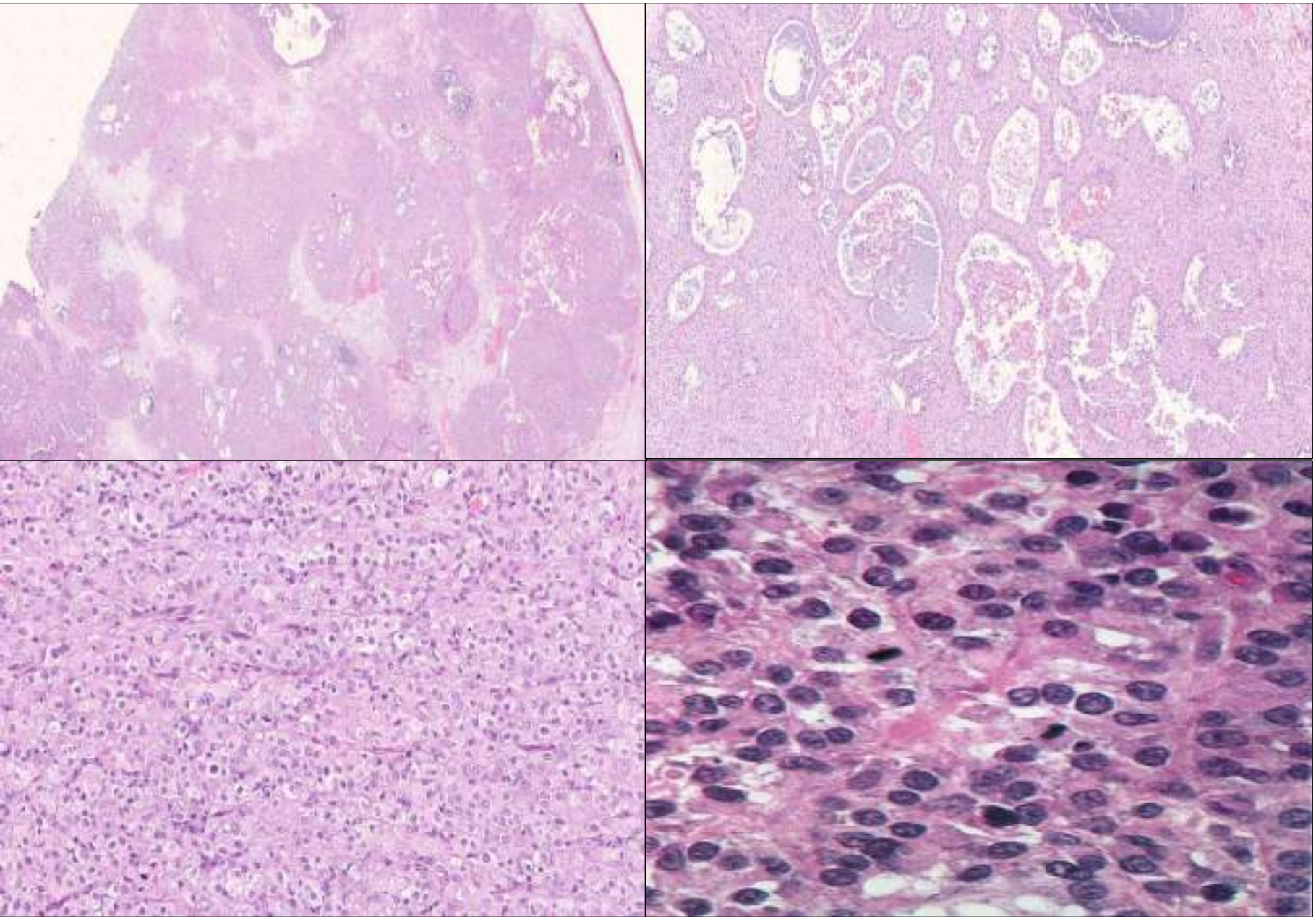


- Tumors are typically positive for FOXL2, calretinin, inhibin and SF1 (most sensitive marker)
- ER, pancytokeratin, CD99 and WT1 are frequently positive
- Can be positive for SMA, desmin, and CD10
- Pax8, CK7 and EMA are typically negative
- Propensity for late recurrence
- Patients may be followed for recurrence by monitoring of serum β-inhibin levels

JUVENILE GRANULOSA CELL TUMOR

- Sex cord stromal tumor composed of primitive appearing granulosa cells with follicular and solid growth patterns
- Almost always occurs in patients younger than 30 years
- Lacks the *FOXL2* somatic mutation seen in adult granulosa cell tumor
- Possibility of juvenile granulosa cell tumor may be suspected if there are estrogenic manifestations in a prepubertal patient
- Multiloculated, cystic and solid tumor with yellow-white solid areas

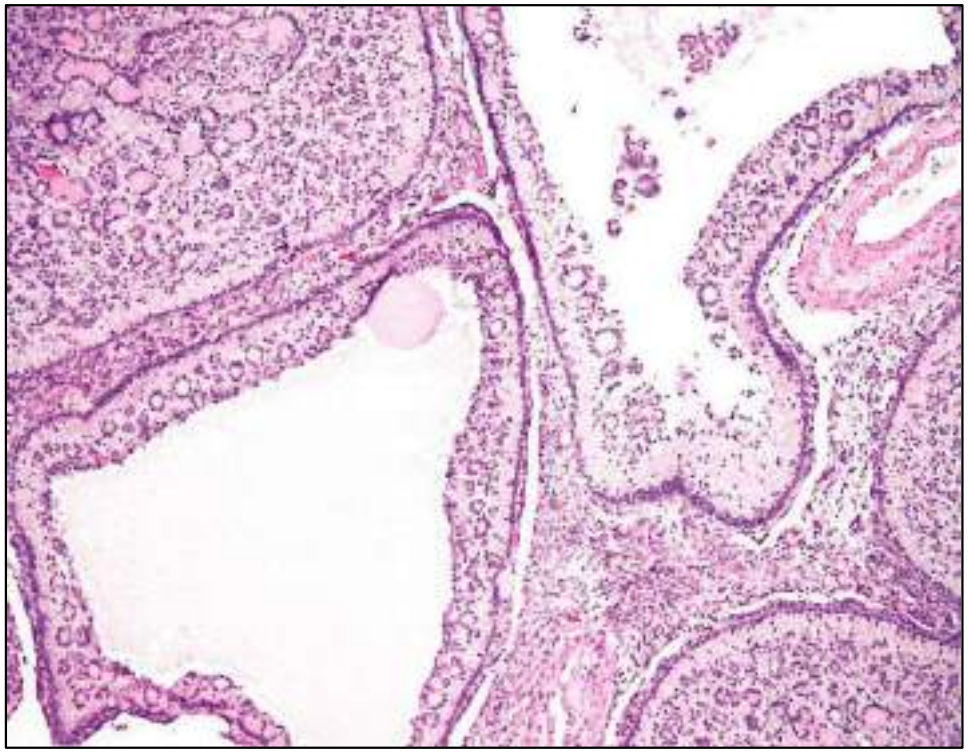


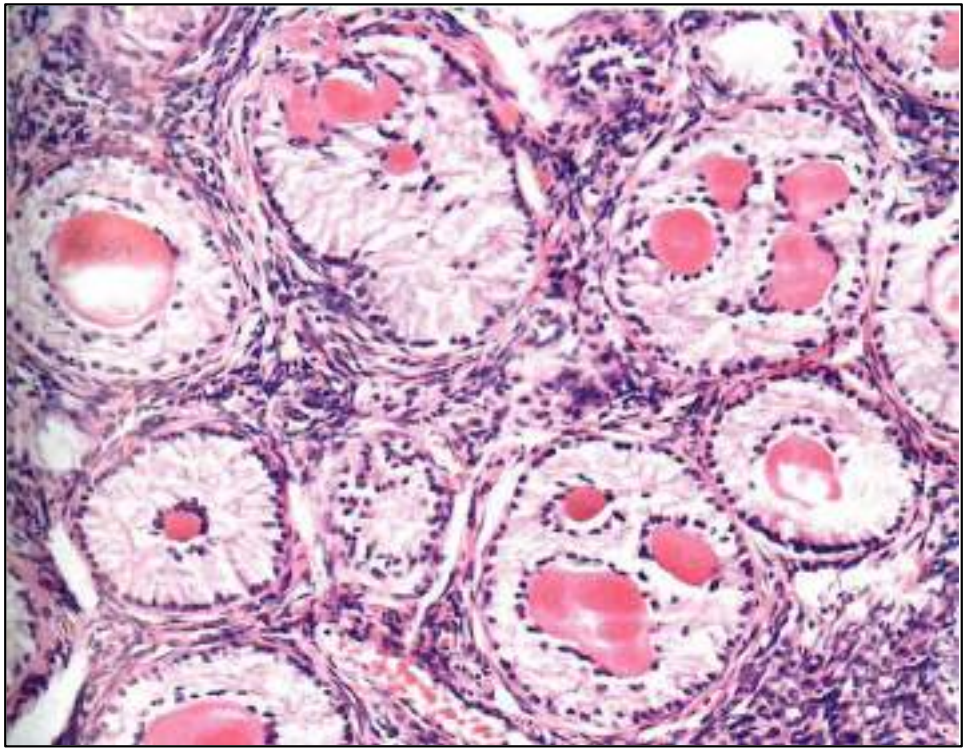


- Diffuse or nodular appearance at low power
- Macrofollicle and microfollicle formation containing eosinophilic secretions
- Round / oval hyperchromatic nuclei with small nucleoli, irregular nuclear contours
- No / rare nuclear grooves
- Mitotic activity can be brisk in 10% cases
- Usually express SF1, inhibin, calretinin, WT1, CD99 and CD56, sometimes FOXL2 and EMA

SEX CORD TUMOR WITH ANNULAR TUBULES

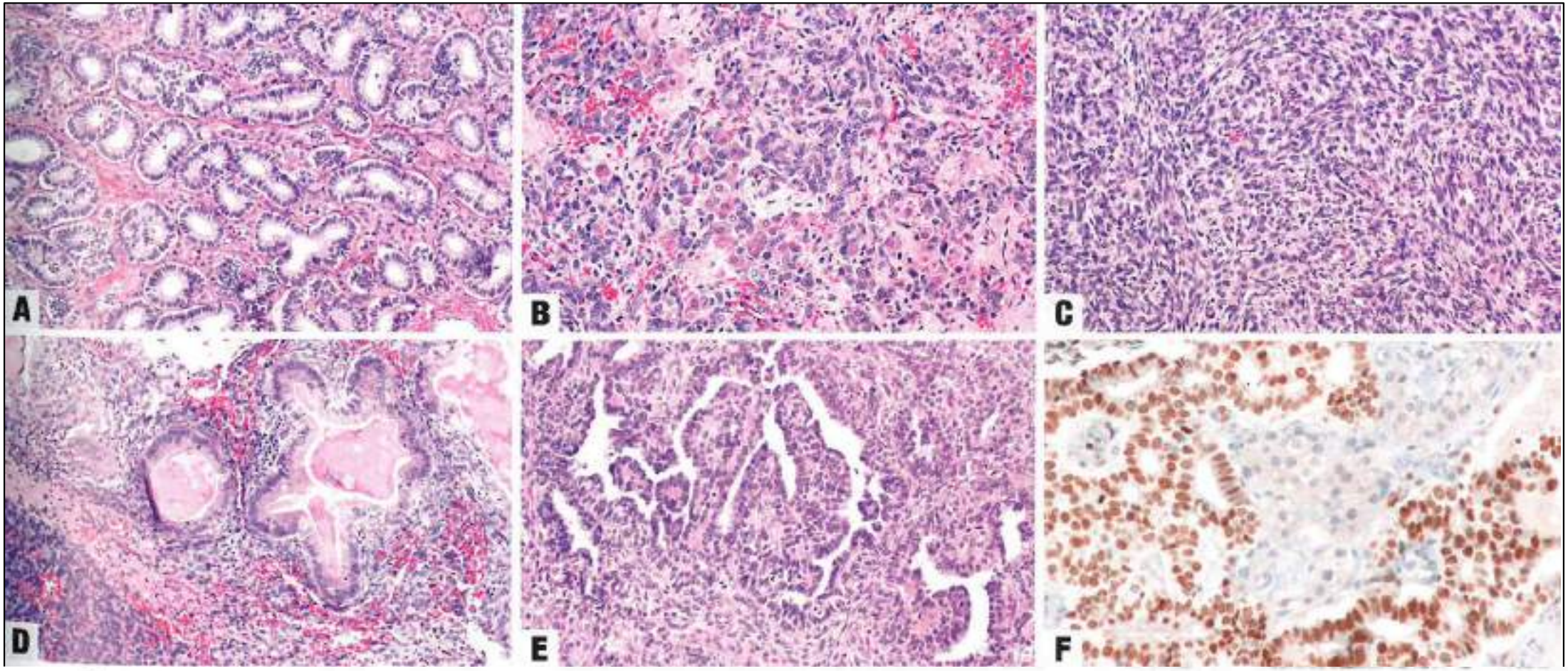
- Sex cord tumor with sharply circumscribed nests composed of ring-like tubules that encircle basement membrane-like material
- Distinctive ovarian tumor associated with hyperestrinism (50%)
- 1/3 with tumor have Peutz-Jegher syndrome





SERTOLI LEYDIG CELL TUMOR

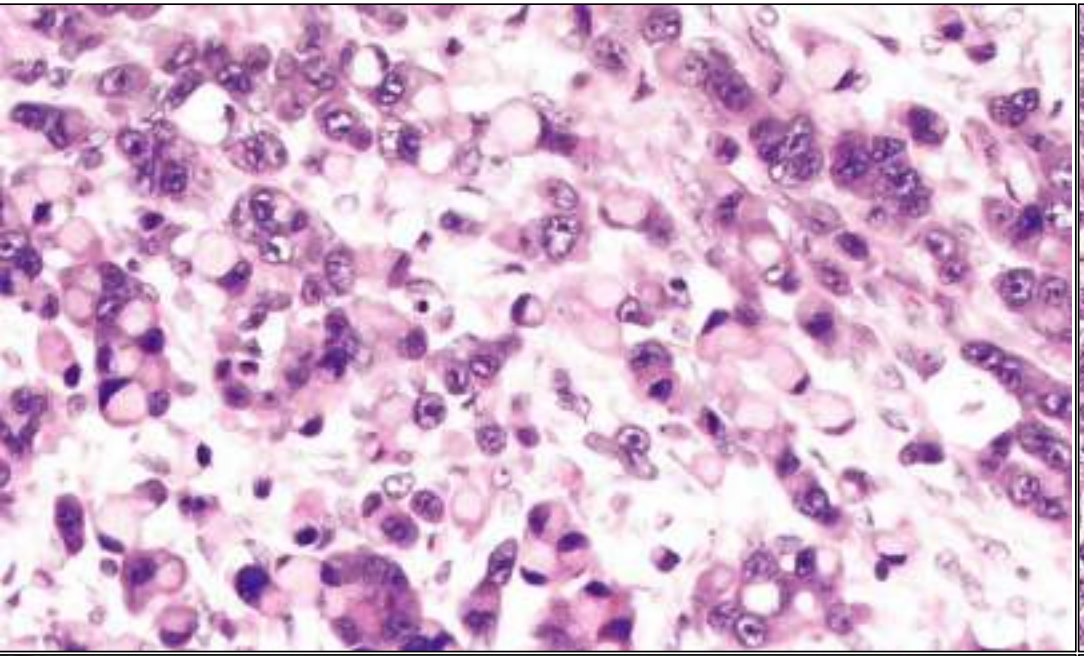
- Rare ovarian tumor composed of sex cord (Sertoli cells) and stromal (Leydig cells) elements, accounting for < 0.5% of all ovarian neoplasms
- May occur sporadically or in patients with DICER1 syndrome
- 3 molecular subtypes:
  - DICER1 mutant: younger age, moderately / poorly differentiated, retiform or heterologous elements
  - FOXL2 c.402C>G (p.Cys134Trp) mutant: postmenopausal patients, moderately / poorly differentiated, no retiform or heterologous elements
  - DICER1 / FOXL2 wildtype: intermediate age, no retiform or heterologous elements, including all well differentiated tumors
- May be suspected clinically in a young patient presenting with a combination of virilization, elevated testosterone levels and ovarian / pelvic mass on imaging studies

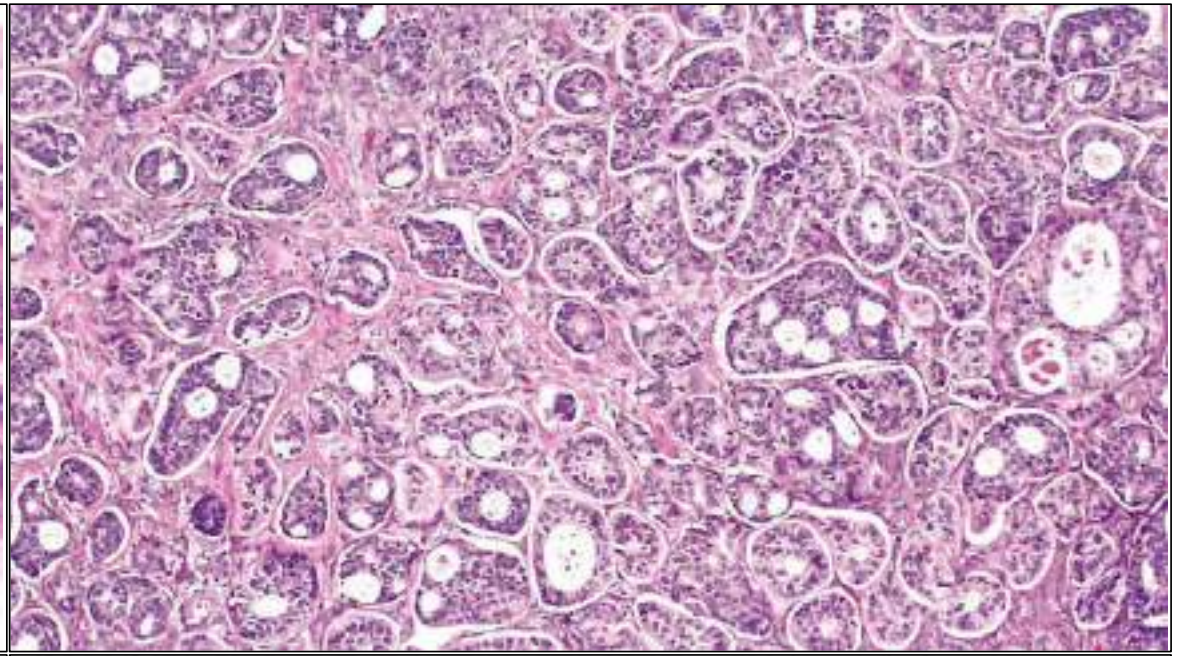


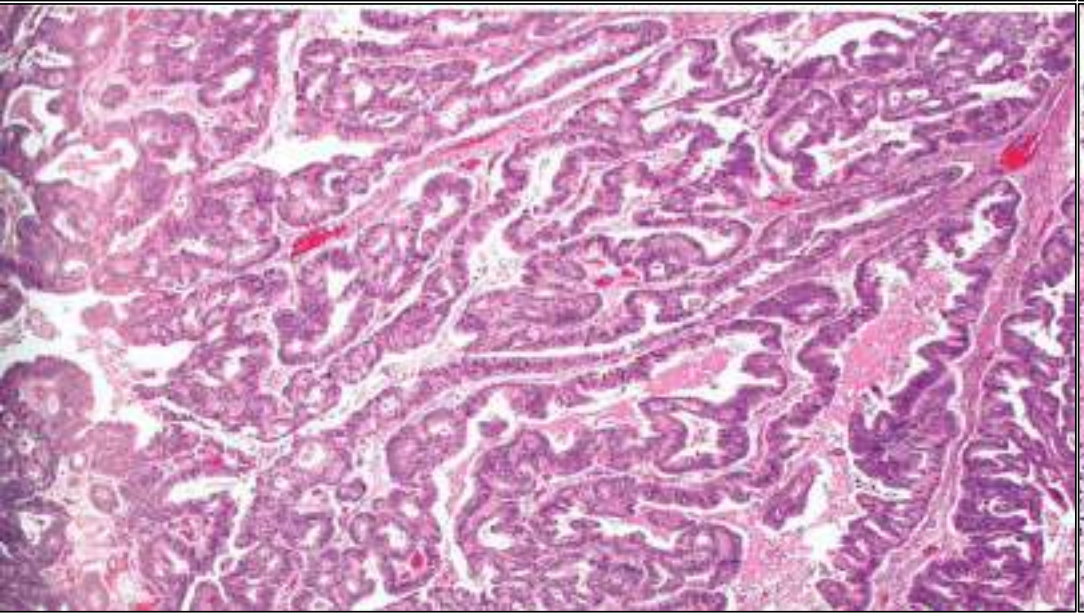
Sertoli–Leydig cell tumour (SLCT). **A** Well-differentiated SLCT, with open sertoliform tubules and Leydig cell clusters between tubules. **B** Moderately differentiated SLCT, with irregular anastomosing cords and closed sertoliform tubules admixed with plump eosinophilic Leydig cells. **C** Poorly differentiated SLCT, with storiform arrangement of primitive gonadal stromal cells and rare individual Leydig cells. Other areas of this tumour showed closed sertoliform tubules and Leydig cells. **D** Heterologous intestinal mucinous differentiation in a moderately differentiated tumour. **E** Retiform differentiation in a moderately differentiated tumour. Panels B–E show tumours harbouring hotspot mutations in the RNase IIIb domain of *DICER1*. **F** FOXL2 immunohistochemistry showing staining of the sertoliform component and no staining of the Leydig cells, in a well-differentiated SLCT.

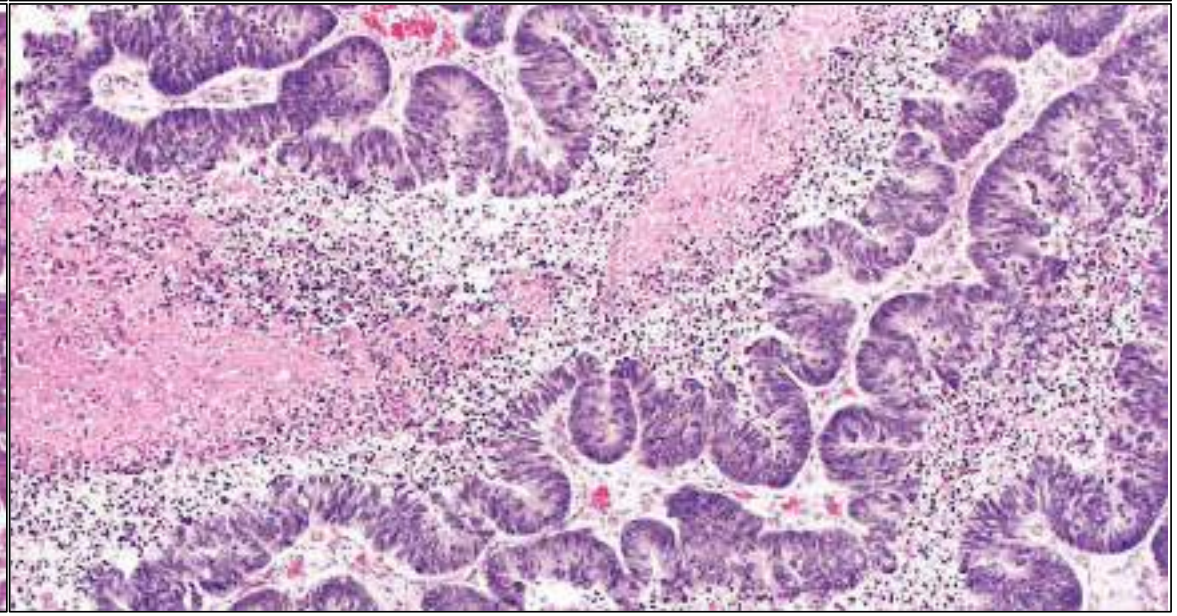
METASTASES TO THE OVARY

- Common site for metastases
- 5-10% of ovarian tumors are metastases
- Usually are bilateral, small, multinodular surface tumors with extensive extraovarian spread
- Most common metastases are from endometrium, appendix, breast, colon, carcinoid, pancreas and stomach
- Metastatic mucinous carcinomas are most difficult to distinguish from primary mucinous ovarian neoplasm
- Histological features favouring metastasis – infiltrative growth pattern with stromal desmoplasia, a nodular growth pattern, involvement of the ovarian surface and superficial cortex, and hilar and lymphovascular space involvement
- In contrast, primary ovarian tumors lack these features and have a confluent growth pattern









Which STAGING system to use for gynaecological cancers?

J Clin Pathol. 2010 Sep;63(9):768-70. doi: 10.1136/jcp.2010.080978. Epub 2010 Aug 5.

Which staging system to use for gynaecological cancers: a survey with recommendations for practice in the UK

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Affiliations + expand

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Abstract

Aims: There are two commonly used staging systems for gynaecological cancers, namely Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and TNM. The authors wished to ascertain which staging system is most commonly used in dealing with gynaecological cancers in the UK.

Methods: The authors undertook a survey among participants in the National Gynaecological Pathology EQA scheme to investigate whether gynaecological pathologists in the UK use FIGO or TNM staging in their routine reporting of gynaecological cancers.

Results: There were 105 respondents out of 278 participants (38%). Of the analysed results, a majority of respondents (64%) use FIGO staging, while 32% use both FIGO and TNM. 80% of respondents stated that their multidisciplinary team meeting uses FIGO staging, while 18% use both FIGO and TNM. Only an extremely small minority of pathologists and multidisciplinary team meetings use TNM alone. A survey of members of the British Gynaecological Cancer Society revealed similar findings.

Conclusions: Since FIGO and TNM are not always equivalent, and there may be confusion when more than one staging system is used, it is recommended that FIGO staging be used for gynaecological cancers. The survey revealed support for the use of TNM, as well as FIGO, only for cervical cancer, since FIGO does not take the lymph node status into account. Given the prevalent practice in the UK, the British Association of Gynaecological Pathologists, British Gynaecological Cancer Society and gynaecological clinical reference group of the National Cancer Intelligence Network recommend that FIGO staging be used for gynaecological cancers with recording of the lymph node status for cervical cancer. This may be done by providing a TNM stage for this cancer type only or by recording the lymph-node status at the multidisciplinary team meeting.

Take-home messages

- There are two staging systems in widespread use for gynaecological cancers, namely FIGO and TNM, and there is controversy and confusion among specialists dealing with gynaecological cancers as to what staging system to use.
- FIGO and TNM are not always directly comparable, particularly in the recording of lymph-node involvement.
- The results of our survey show that most gynaecological pathologists in the UK exclusively report gynaecological cancers using FIGO staging systems. A significant minority use FIGO and TNM, while very few use TNM alone.
- The BAGP, BGCS and gynaecological clinical reference group of the NCIN recommend that FIGO staging be used for gynaecological cancers. The TNM-style recording of lymph-node status for cervical cancer is also recommended, since this is not included in FIGO staging.

Procedure	Description
Resection	Includes oophorectomy, salpingo-oophorectomy, salpingectomy, subtotal resection, or removal of tumor in fragments
Tumor Type	**Description**
Primary malignant tumors of ovary, fallopian tube or peritoneum	Includes all primary epithelial borderline tumors and carcinomas, carcinosarcoma, malignant germ cell tumors, malignant sex cord-stromal tumors, and ovarian sarcomas.

FIGO STAGE

+FIGO Stage (2018 FIGO Cancer Report)

___ I: Tumor limited to ovaries (one or both) or fallopian tube(s)
___ IA: Tumor limited to one ovary (capsule intact) or fallopian tube; no tumor on ovarian or fallopian tube surface; no malignant cells in ascites or peritoneal washings
___ IB: Tumor limited to both ovaries (capsules intact) or fallopian tubes; no tumor on ovarian or fallopian tube surface; no malignant cells in the ascites or peritoneal washings
___ IC: Tumor limited to one or both ovaries or fallopian tube(s), with any of the following subcategories below
___ IC1: Surgical spill
___ IC2: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface
___ IC3: Malignant cells present in the ascites or peritoneal washings
___ II: Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer
___ IIA: Extension and / or implants on the uterus and / or fallopian tube(s) and / or ovaries
___ IIB: Extension to and / or implants in other pelvic tissues
___ III: Tumor involves one or both ovaries or fallopian tubes, or primary peritoneal cancer, with microscopically confirmed peritoneal metastasis outside the pelvis and / or retroperitoneal lymph node involvement
___ IIIA: Metastasis to the retroperitoneal lymph nodes with or without microscopic peritoneal involvement beyond the pelvis
___ IIIA1: Positive (microscopically confirmed) retroperitoneal lymph nodes only
 # This is tumor dimension and not lymph node dimension.
___ IIIA1(i): Metastasis less than or equal to 10 mm in greatest dimension#
___ IIIA1(ii): Metastasis greater than 10 mm in greatest dimension#
___ IIIA2: Microscopic peritoneal metastasis beyond the pelvis with or without positive retroperitoneal lymph nodes
Includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ.

___ IIIB: Macroscopic peritoneal metastases beyond the pelvic brim less than or equal to 2 cm in greatest dimension with or without positive retroperitoneal lymph nodes##
___ IIIC: Macroscopic peritoneal metastases beyond the pelvic brim greater than 2 cm in greatest dimension including extension to liver capsule or spleen without parenchymal involvement of those organs and with or without positive retroperitoneal lymph nodes##
Stage IV distant metastasis excludes peritoneal metastases if that is the only finding.
___ IV: Distant metastasis including cytology-positive pleural effusion; liver or splenic parenchymal involvement; extra-abdominal organ involvement excluding inguinal lymph nodes; transmural intestinal involvement###
___ IVA: Pleural effusion with positive cytology
Parenchymal metastases are stage IVB. Disease invading through the bowel wall and into the mucosa increases the stage to IVB, and transmural involvement of a visceral structure also represents stage IVB disease.
___ IVB: Liver or splenic parenchymal metastasis; metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside the abdominal cavity); transmural involvement of intestine####

UTERINE CORPUS

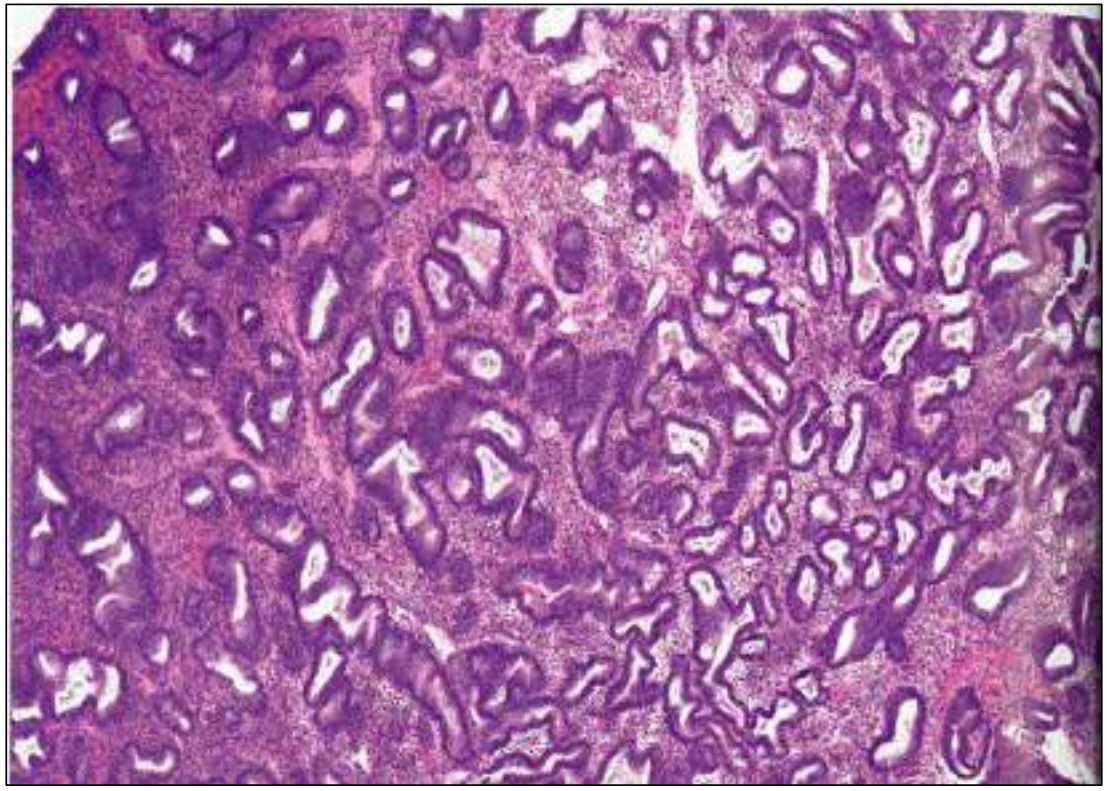
Tumours of the uterine corpus

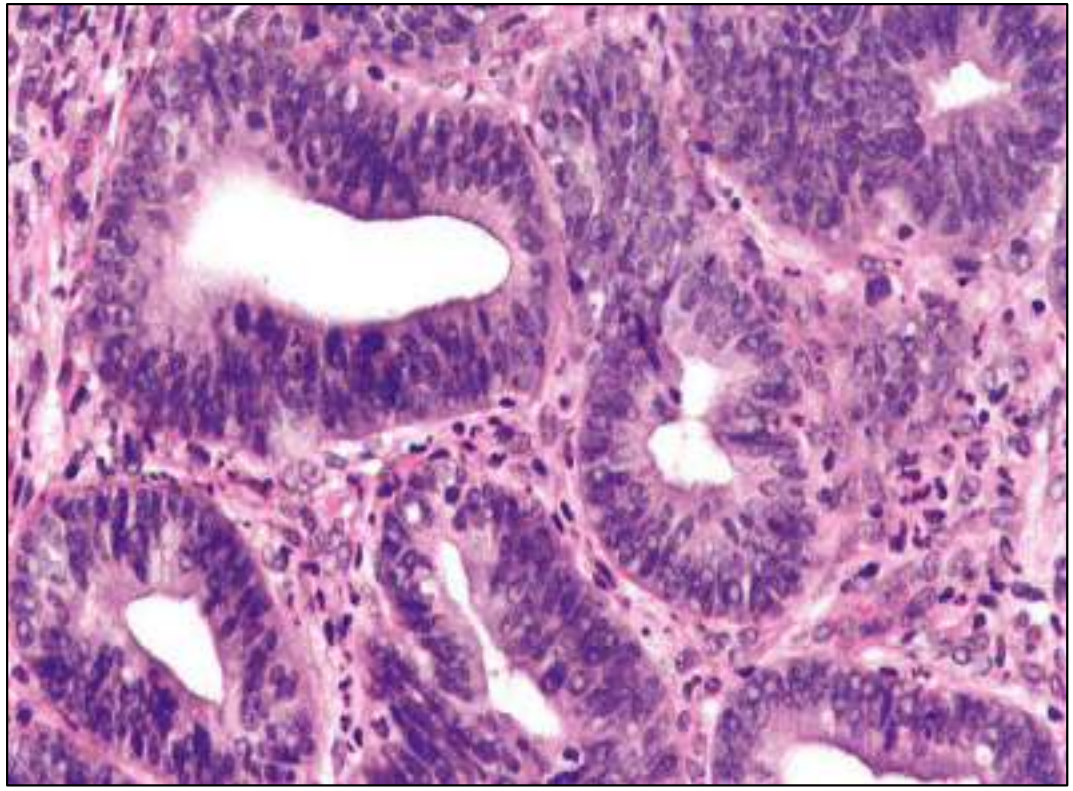
- Introduction
- Endometrial epithelial tumours and precursors
  - Precursor lesions
    - Endometrial hyperplasia without atypia
    - Endometrial atypical hyperplasia / endometrioid intraepithelial neoplasia
  - Endometrial carcinomas
    - Endometrioid carcinoma
    - Serous carcinoma
    - Clear cell carcinoma
    - Undifferentiated and dedifferentiated carcinomas
    - Mixed carcinoma
    - Other endometrial carcinomas
    - Carcinosarcoma
- Tumour-like lesions
  - Endometrial polyp
  - Endometrial metaplasia
  - Arias-Stella reaction
- Mesenchymal tumours of the uterus
  - Smooth muscle tumours
    - Uterine leiomyoma
    - Intravenous leiomyomatosis
    - Smooth muscle tumour of uncertain malignant potential
    - Metastasizing leiomyoma
    - Uterine leiomyosarcoma
  - Endometrial stromal and related tumours
    - Endometrial stromal nodule
    - Low-grade endometrial stromal sarcoma
    - High-grade endometrial stromal sarcoma
    - Undifferentiated uterine sarcoma
  - Miscellaneous mesenchymal tumours
    - Uterine tumour resembling ovarian sex cord tumour
    - Perivascular epithelioid cell tumour (PEComa)
    - Inflammatory myofibroblastic tumour
    - Other mesenchymal tumours of the uterus
- Mixed epithelial and mesenchymal tumours
  - Adenomyoma
  - Atypical polypoid adenomyoma
  - Adenosarcoma
- Miscellaneous tumours
  - Central primitive neuroectodermal tumour / CNS embryonal tumour
  - Germ cell tumours

EPITHELIAL TUMORS

ENDOMETRIAL HYPERPLASIA

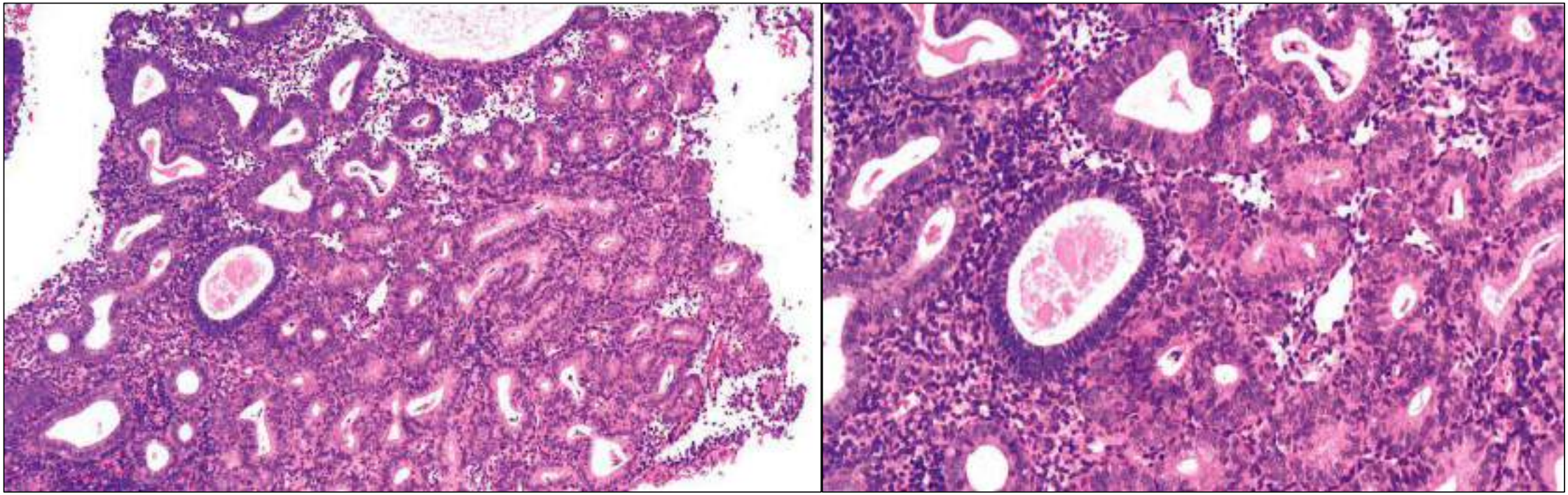
- Proliferation of endometrial glands of irregular size and shape without cytological atypia





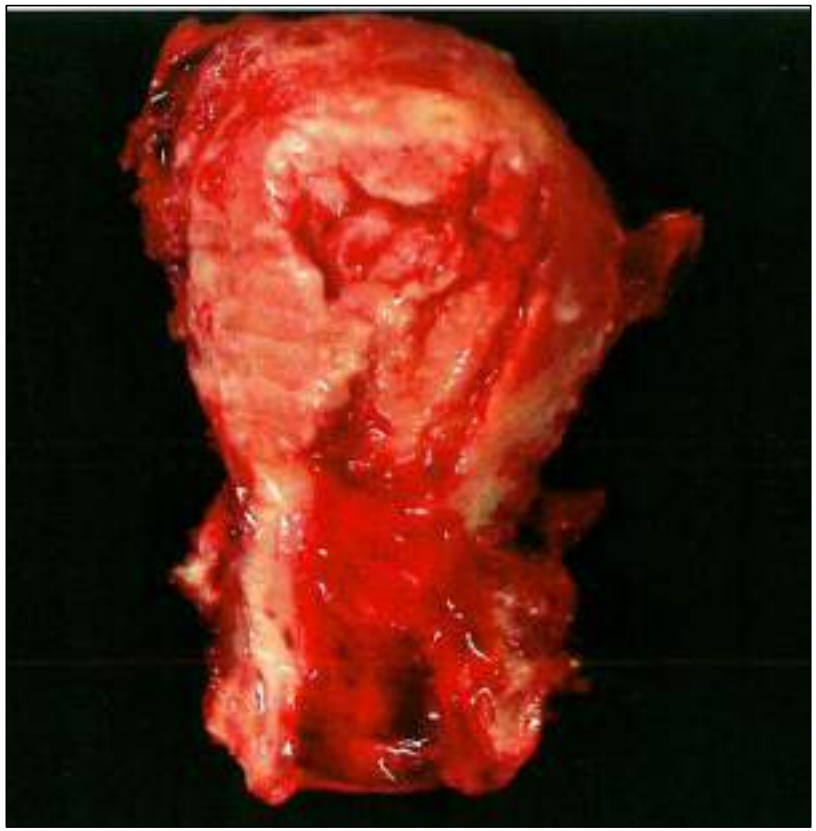
ENDOMETRIAL ATYPICAL HYPERPLASIA/ENDOMETRIOID INTRAEPITHELIAL NEOPLASIA

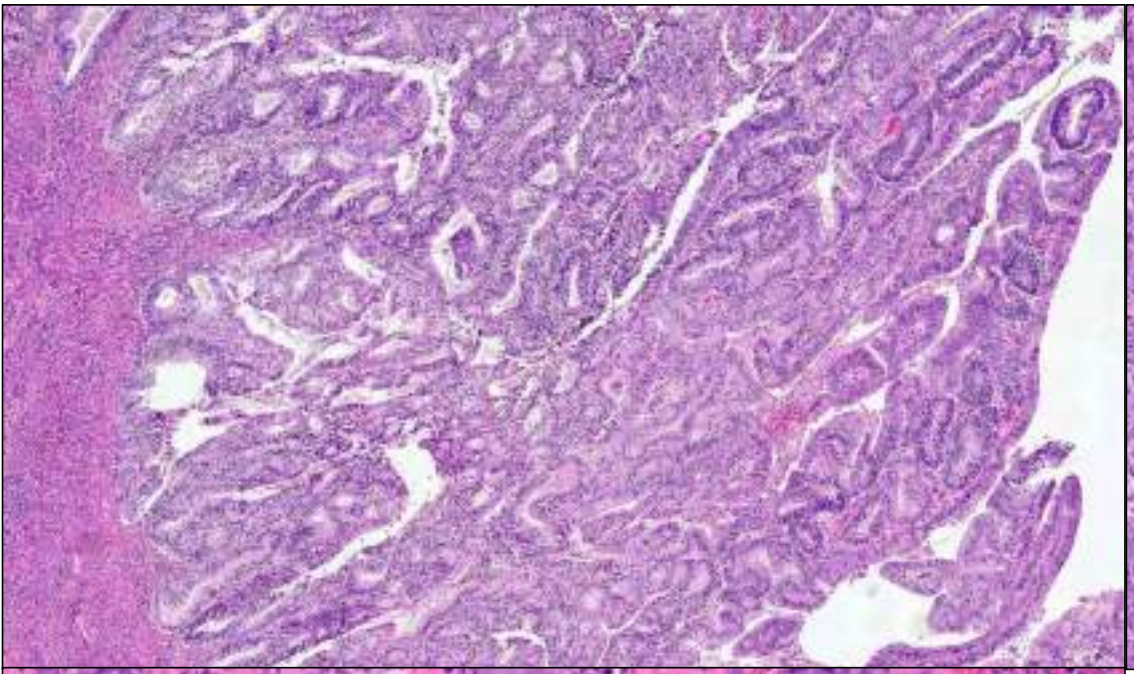
- Simulataneous change of epithelial cytology and an increased number of endometrial glands in comparison with the stroma (crowded gland architecture) within a morphologically defined region, distinct from the surrounding endometrium or from entrapped normal glands

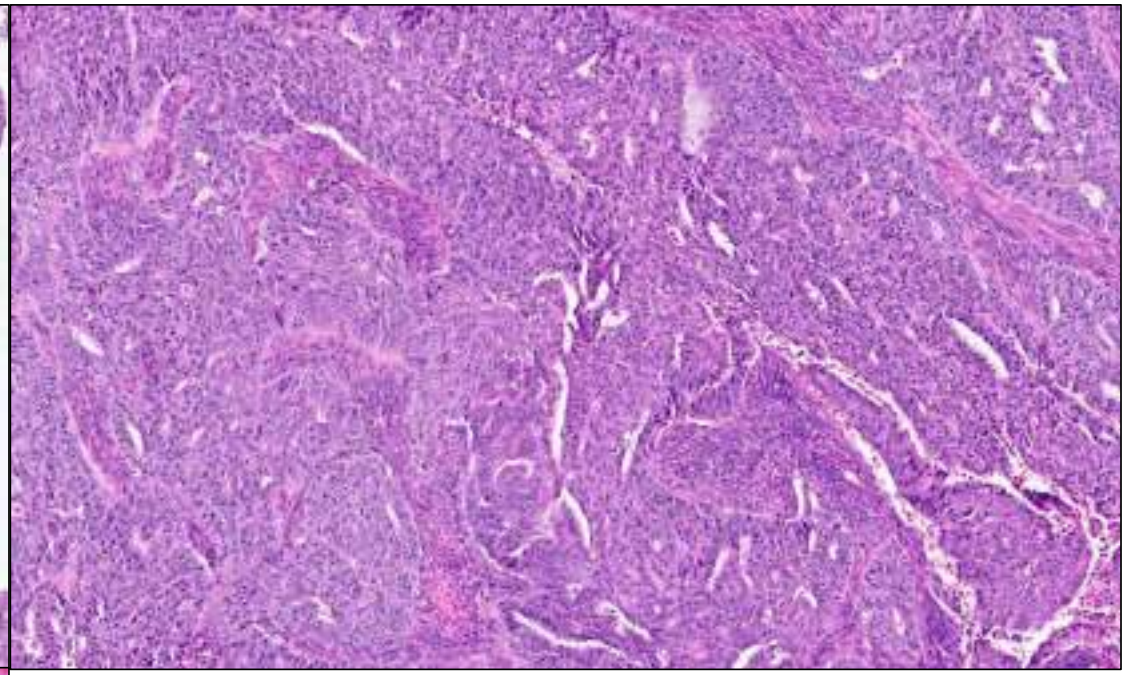


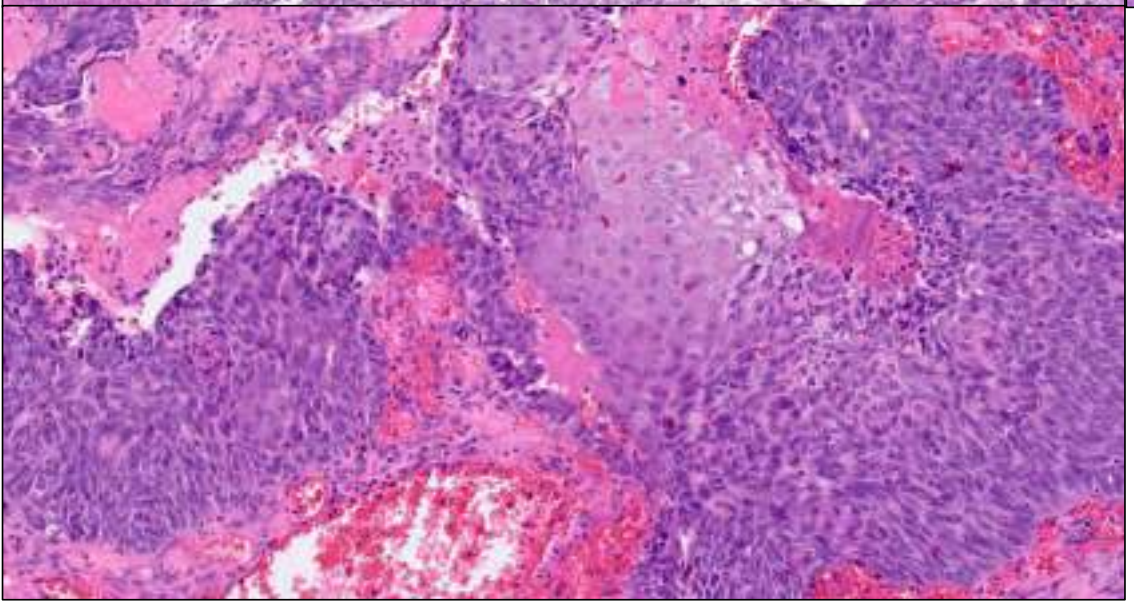
ENDOMETRIOID CARCINOMA

- Malignant epithelial neoplasm displaying varying proportions of glandular, papillary and solid architecture with the neoplastic cells showing endometrioid differentiation
- Mean age is sixth decade, with a range from the third to ninth decades
- Increased endogenous or exogenous estrogen unopposed by progesterone
- Abnormal, dysfunctional or postmenopausal uterine bleeding
- Mass arising from endometrial surface with varied appearances / sizes but usually exophytic and friable in texture









- EEC typically displays villoglandular architecture composed of cells that are usually columnar with pseudostratified nuclei
- Nuclear atypia mild to moderate except in high grade EEC
- Mitotic count highly variable
- Squamous differentiation frequent
- Secretory patterns, papillary, spindle cell pattern, sertoliform pattern, sex cord like formations, mucinous pattern

❖**FIGO grading system** (based primarily on architecture)

✓Grade 1: 5% or less nonsquamous solid growth pattern

✓Grade 2: 6 - 50% nonsquamous solid growth pattern

✓Grade 3: > 50% nonsquamous solid growth pattern

- Nuclear atypia exceeding that expected for the architectural grade increases FIGO grade by 1

❑Low grade EEC shows diffuse strong immunoreactivty for ER/PR and patchy positivity for p16

❑Abnormal p53 expression reported in 2-5% of low-grade and 20% of high-grade EECs

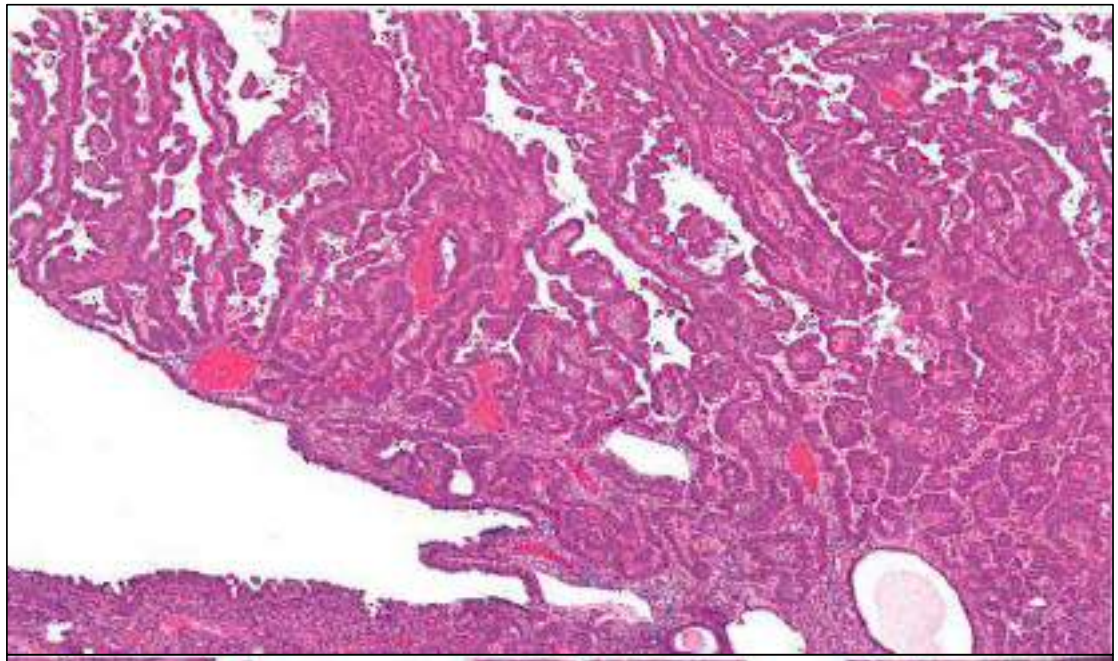
❑High grade EECs may be difficult to distinguish from serous efdometrial carcinoma, but shows less pronounced nuclear pleomorphism

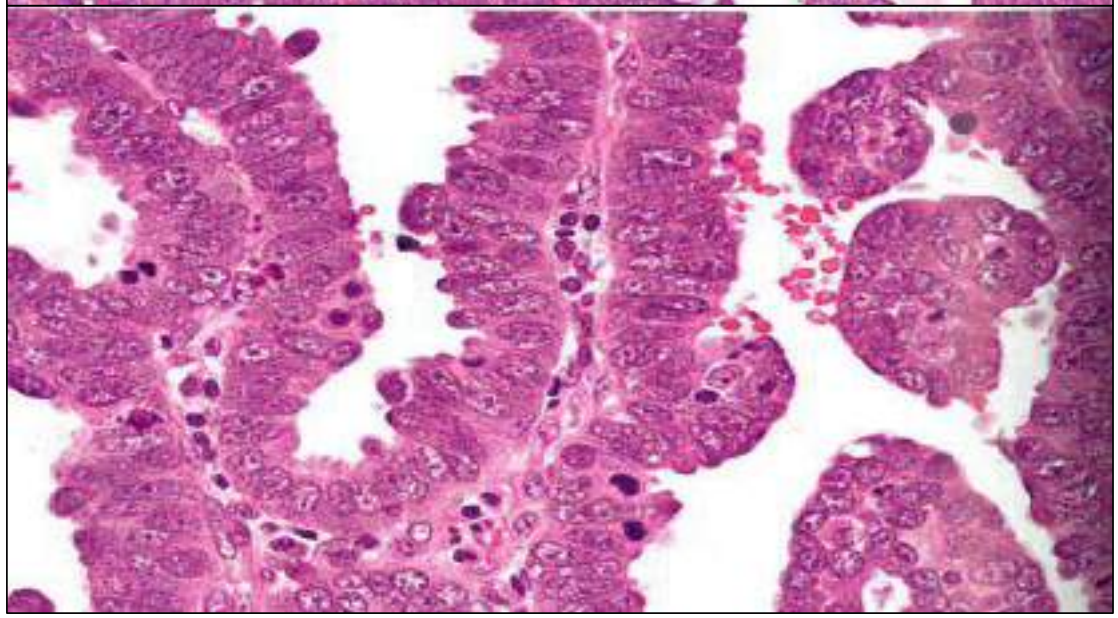
Molecular classification of endometrioid carcinoma (EC) and its typical features

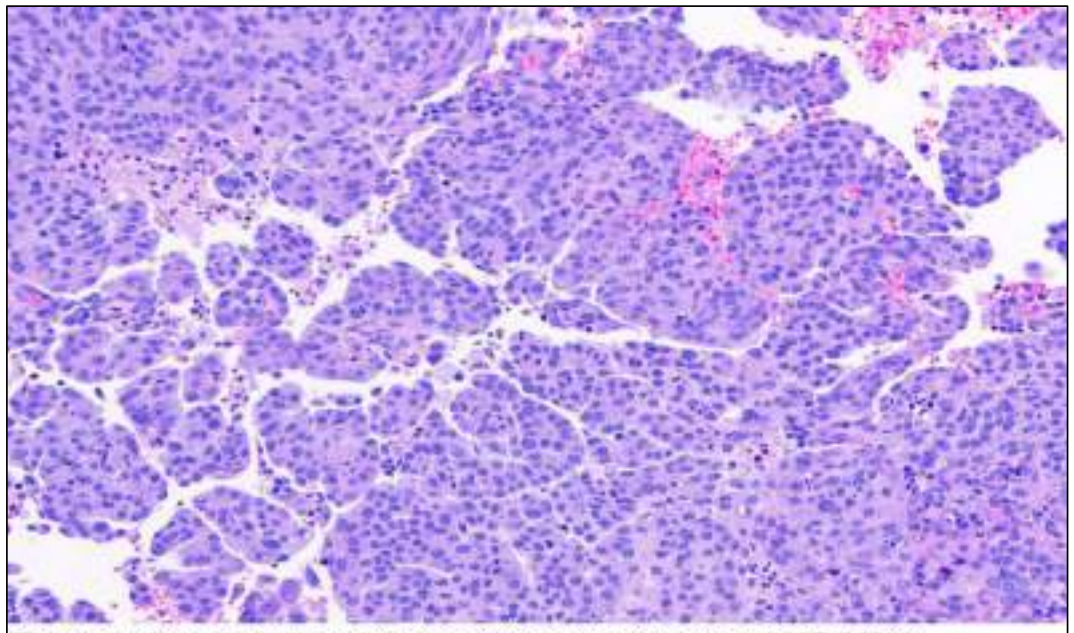
	POLE-ultramutated EC	MMR-deficient EC	p53-mutant EC	NSMP EC
Associated molecular features	> 100 mutations/Mb, SCNA very low, MSS	10–100 mutations/Mb, SCNA low, MSI	< 10 mutations/Mb, SCNA high, MSS	< 10 mutations/Mb, SCNA low, MSS, 30–40% with *CTNNB1* mutations
Associated histological features	Often high-grade, ambiguous morphology with scattered tumour giant cells, prominent TILs	Often high-grade, prominent TILs, mucinous differentiation, MELF-type invasion, LVSI	Mostly high-grade with diffuse cytonuclear atypia; glandular and solid forms exist	Mostly low-grade with frequent squamous differentiation or morule, absence of TILs
Diagnostic tests	NGS / Sanger sequencing / hotspot analysis includes p.Pro286Arg, p.Val411Leu, p.Ser297Phe, p.Ala456Pro, and p.Ser459Phe	MMR-IHC: MLH1, MSH2, MSH6, and PMS2; MSI assay; NGS	p53-IHC: mutant-like staining[a]	MMR-proficient, p53-wildtype, and pathogenic *POLE* variant absent
Associated clinical features	Younger age at presentation	May be associated with Lynch syndrome	Advanced stage at presentation	Higher body mass index
Prognosis	Excellent	Intermediate	Poor	Intermediate to excellent

SEROUS CARCINOMA OF THE UTERINE CORPUS

- High grade estrogen independent carcinoma of the endometrium showing marked cytologic atypia
- Complex papillary, solid or glandular architecture; similar to ovarian / tubal high grade serous carcinoma
- Accounts for approximately 5 - 10% of endometrial carcinomas
- Typically postmenopausal, nonobese women
- Regarded as an aggressive subtype of endometrial cancer
- More likely to present at high stage (disease outside uterus) than endometrioid carcinomas, even when confined to a polyp or without evidence of invasive disease
- Mutations in *TP53* (80 - 90%) and *PIK3CA* (24 - 40%) common
- Mutations in *PTEN* and *ARIDA1A* uncommon
- Serous carcinomas show high somatic copy number abnormalities





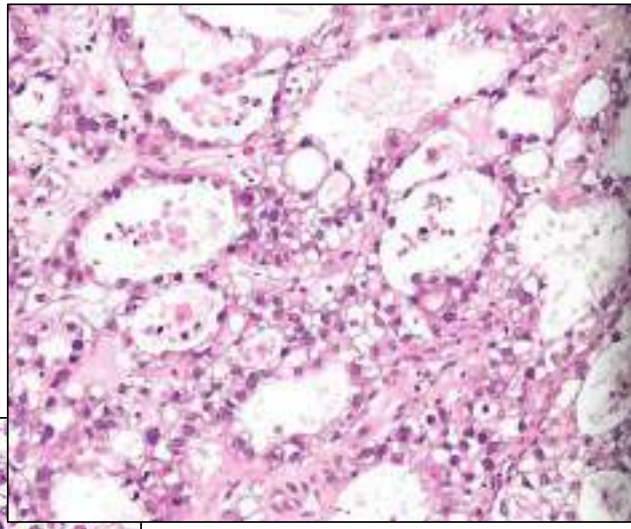


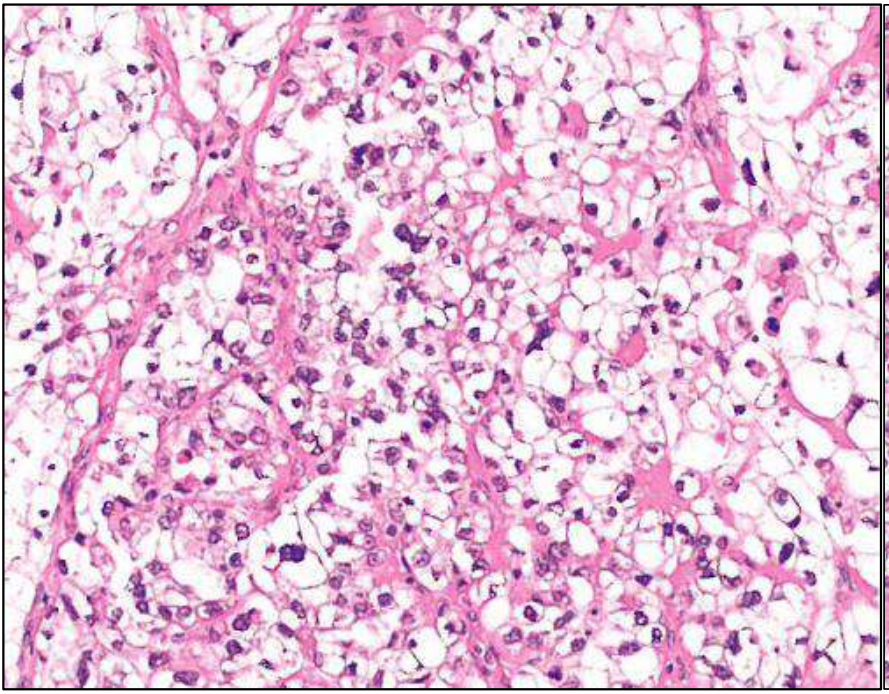
Sheets and small papillae of endometrial serous carcinoma (H&E 200X)

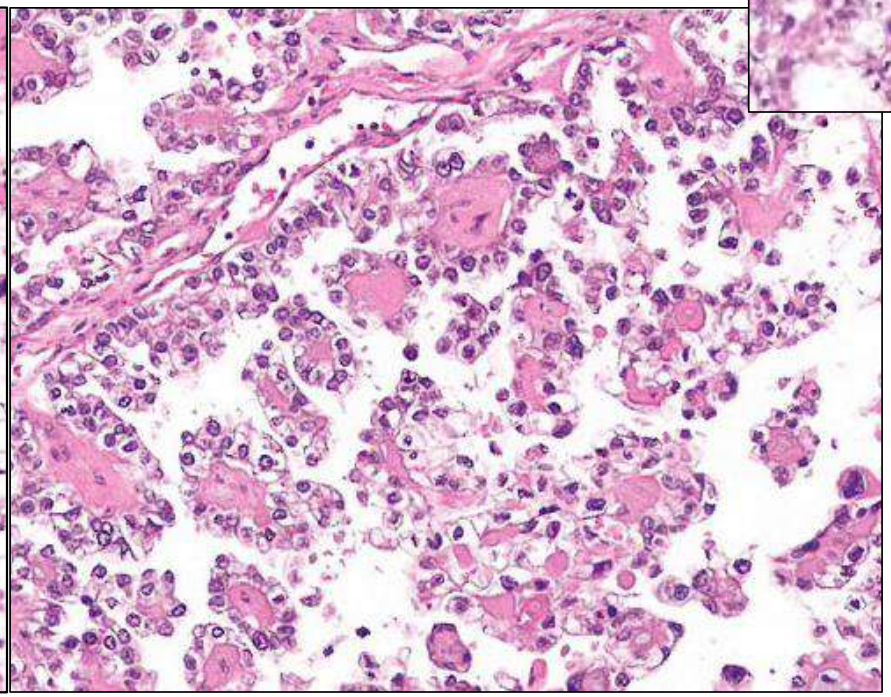
- ✓ **p53**: mutation type staining either strong and diffuse, complete absence of staining (“null type” pattern) or abnormal cytoplasmic localization
- ✓ **p16**: often strong and diffuse (not related to HPV infection)
- ✓ **PanCK** and **CK7**: strong membranous staining
- ✓ **PAX8**: strong nuclear staining
- ✓ **MLH1**, **MSH1**, **MSH2** and **MSH6** [mismatch repair proteins]: typically retained

CLEAR CELL CARCINOMA OF THE UTERINE CORPUS

- Tumor of postmenopausal patients that histologically resembles ovarian clear cell carcinoma with clear, oxyphil or hobnail cells
- < 5% of all endometrial carcinomas

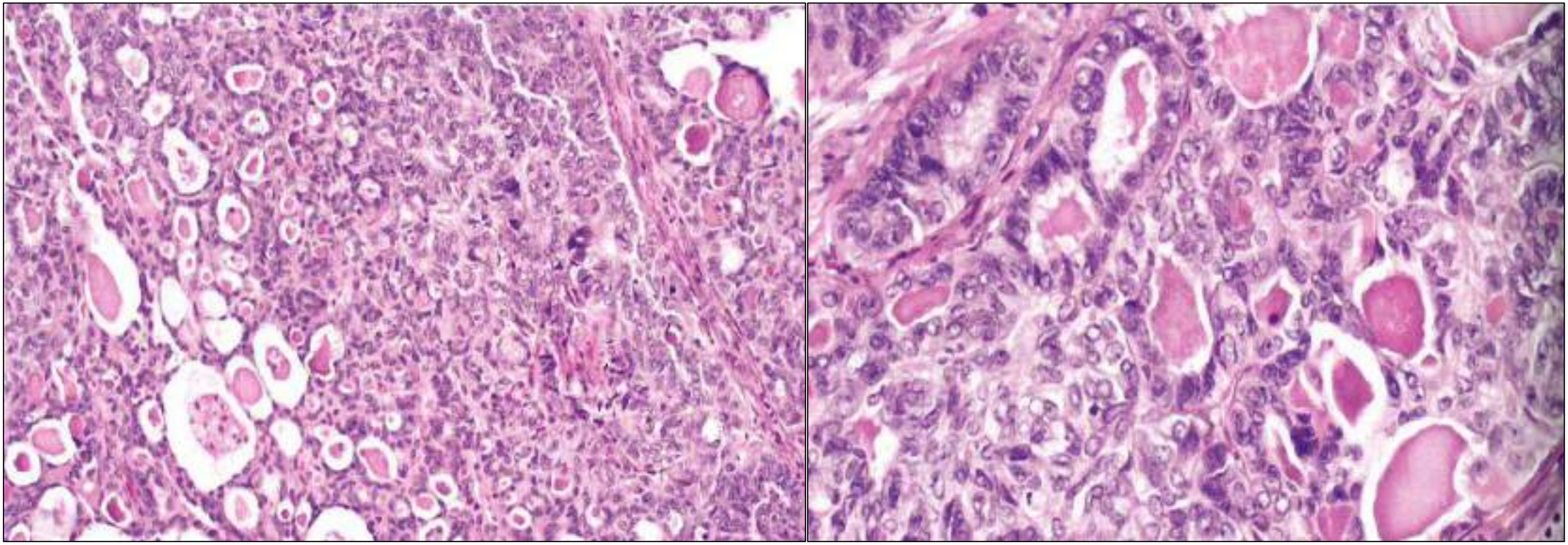




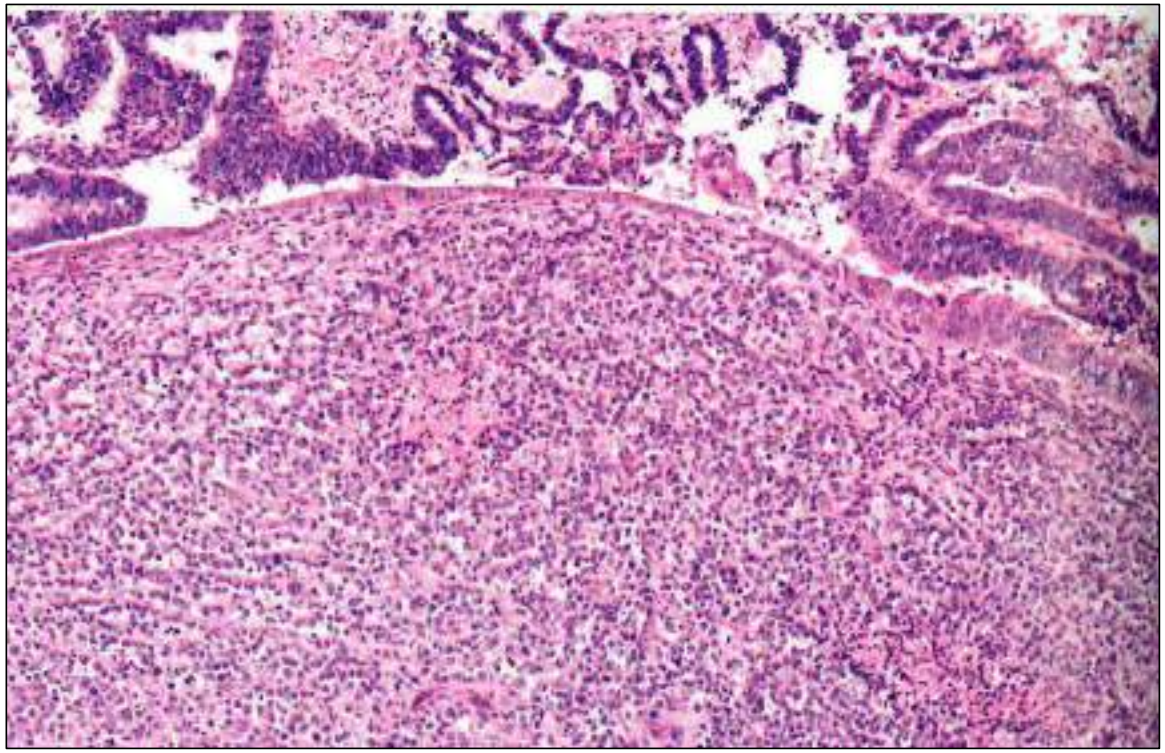


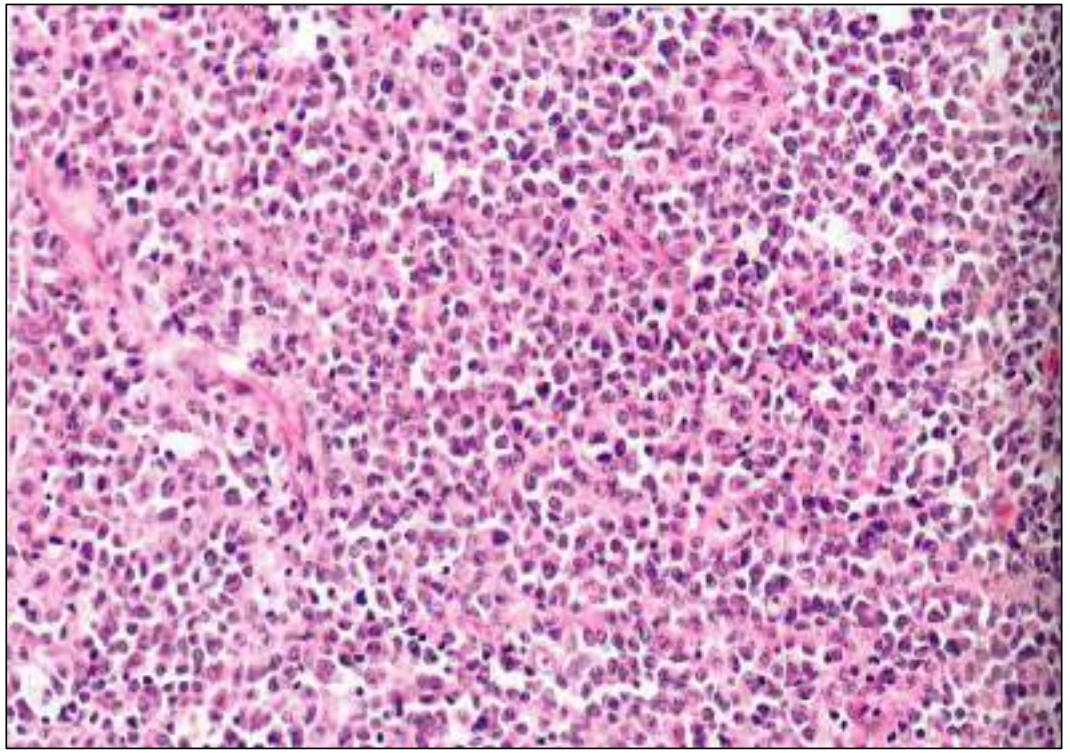
- Tumors are positive for HNF1ß, napsinA and AMACR, usually in the majority of cells
- ER and PR are usually negative or only focally positive
- 22-72% of cases display mutation-pattern p53 staining

MESONEPHRIC ADENOCARCINOMA

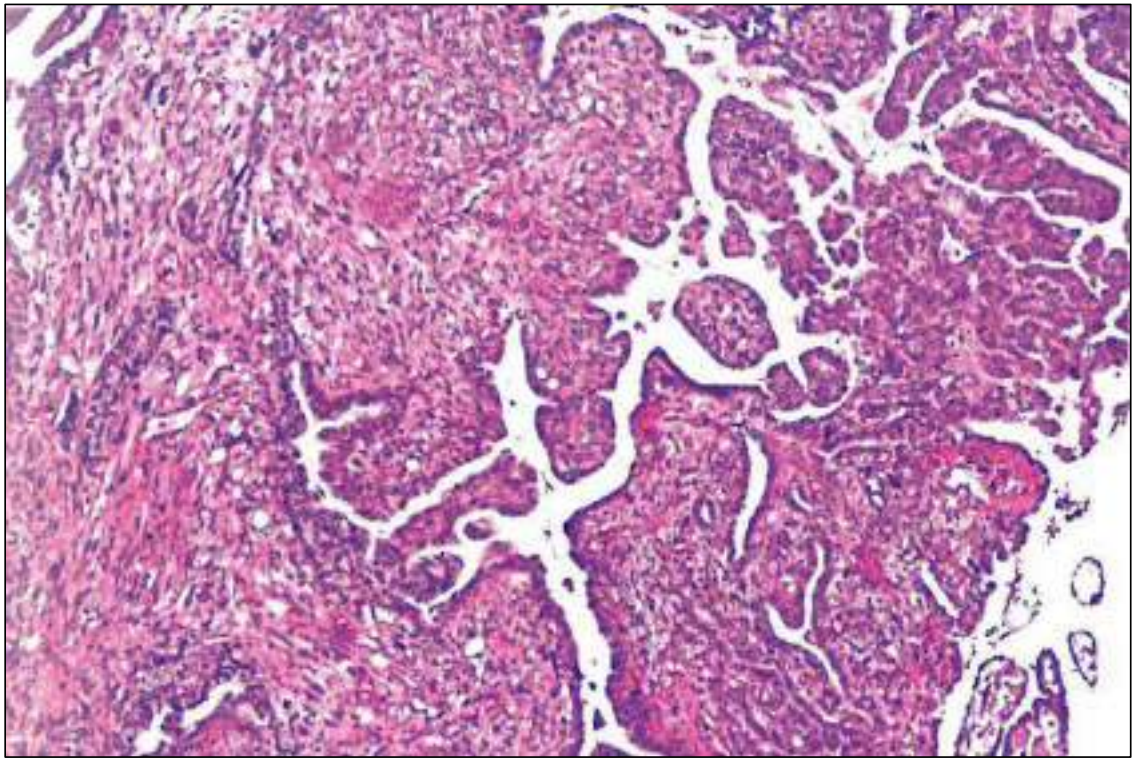


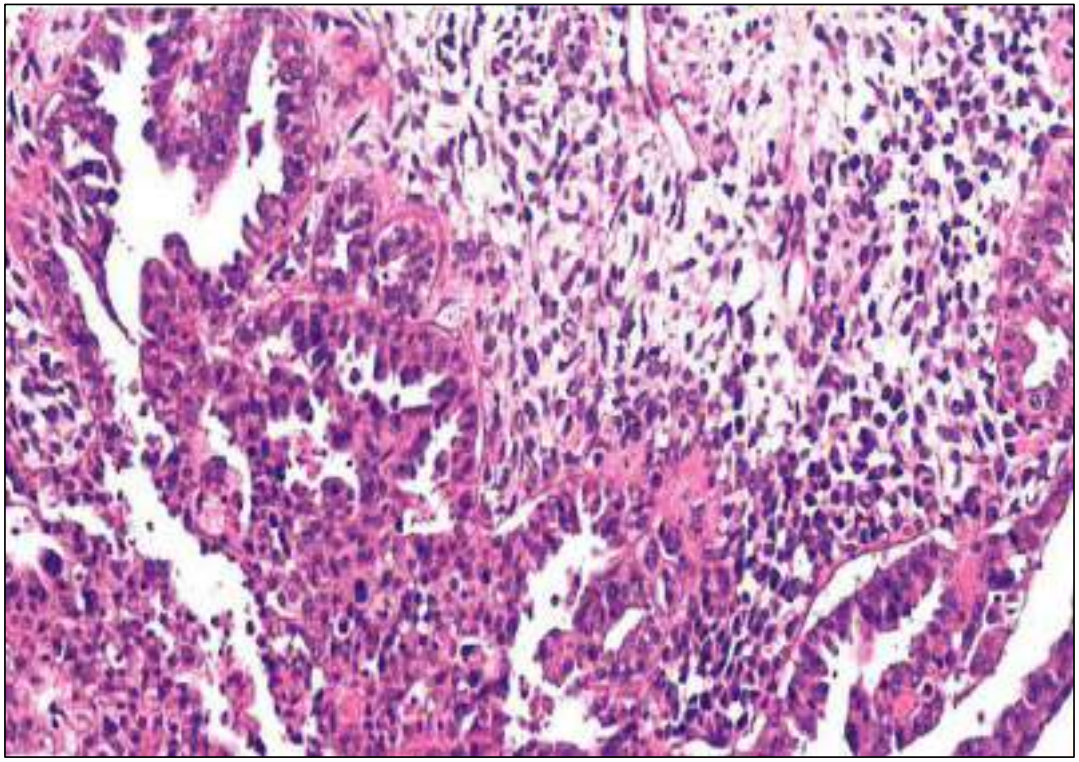
UNDIFFERENTIATED AND DEDIFFERENTIATED CRACINOMAS OF THE UTERINE CORPUS





CARCINOSARCOMA OF THE UTERINE CORPUS





STAGING

Procedure	Description
Hysterectomy	
Tumor Type	**Description**
Carcinoma	Includes carcinomas, carcinosarcomas (malignant mixed Müllerian tumor) and neuroendocrine carcinomas arising in the endometrium

FIGO STAGE

+FIGO Stage (2018 FIGO Cancer Report)

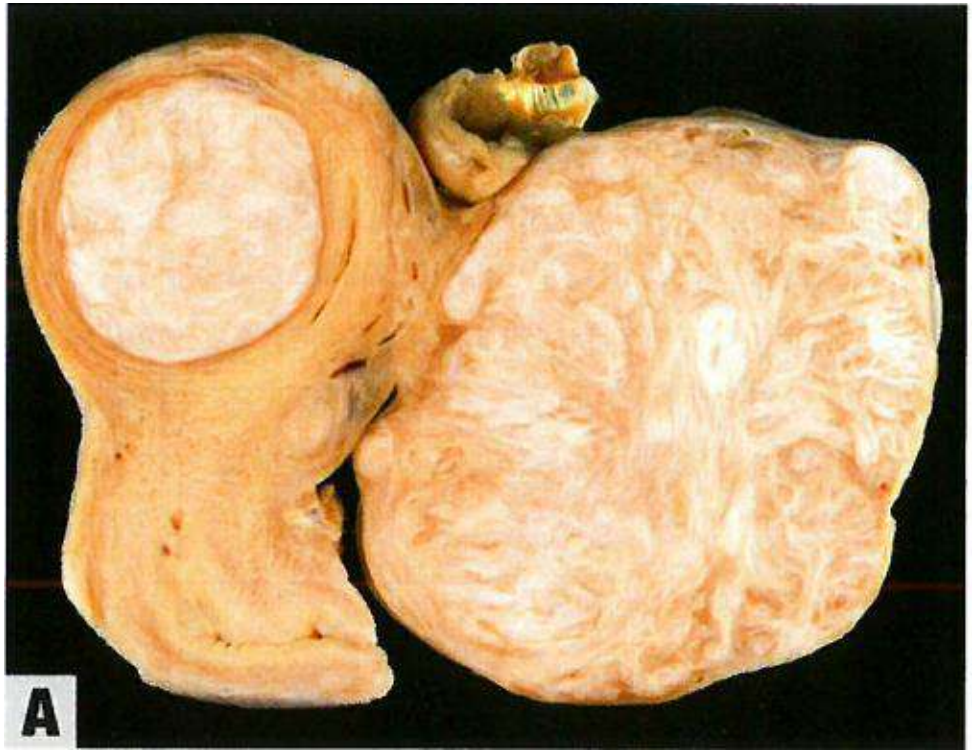
___ I: Tumor confined to the corpus uteri
___ IA: No or less than half myometrial invasion
___ IB: Invasion equal to or more than half of the myometrium
___ II: Tumor invades cervical stroma, but does not extend beyond the uterus
___ III: Local and / or regional spread of the tumor
___ IIIA: Tumor invades the serosa of the corpus uteri and / or adnexae
___ IIIB: Vaginal and / or parametrial involvement
___ IIIC: Metastases to pelvic and / or para-aortic lymph nodes
___ IIIC1: Positive pelvic nodes
___ IIIC2: Positive para-aortic nodes with or without positive pelvic lymph nodes
___ IV: Tumor invades bladder and / or bowel mucosa, and / or distant metastases
___ IVA: Tumor invasion of bladder and / or bowel mucosa
___ IVB: Distant metastasis, including intra-abdominal metastases and / or inguinal nodes

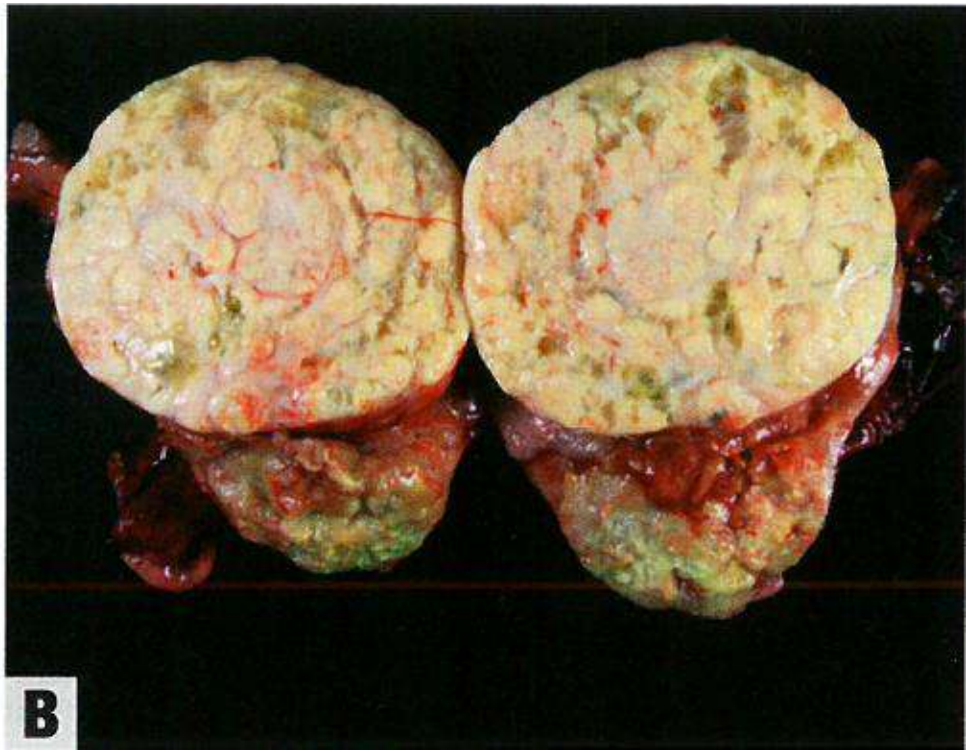
MESENCHYMAL TUMORS

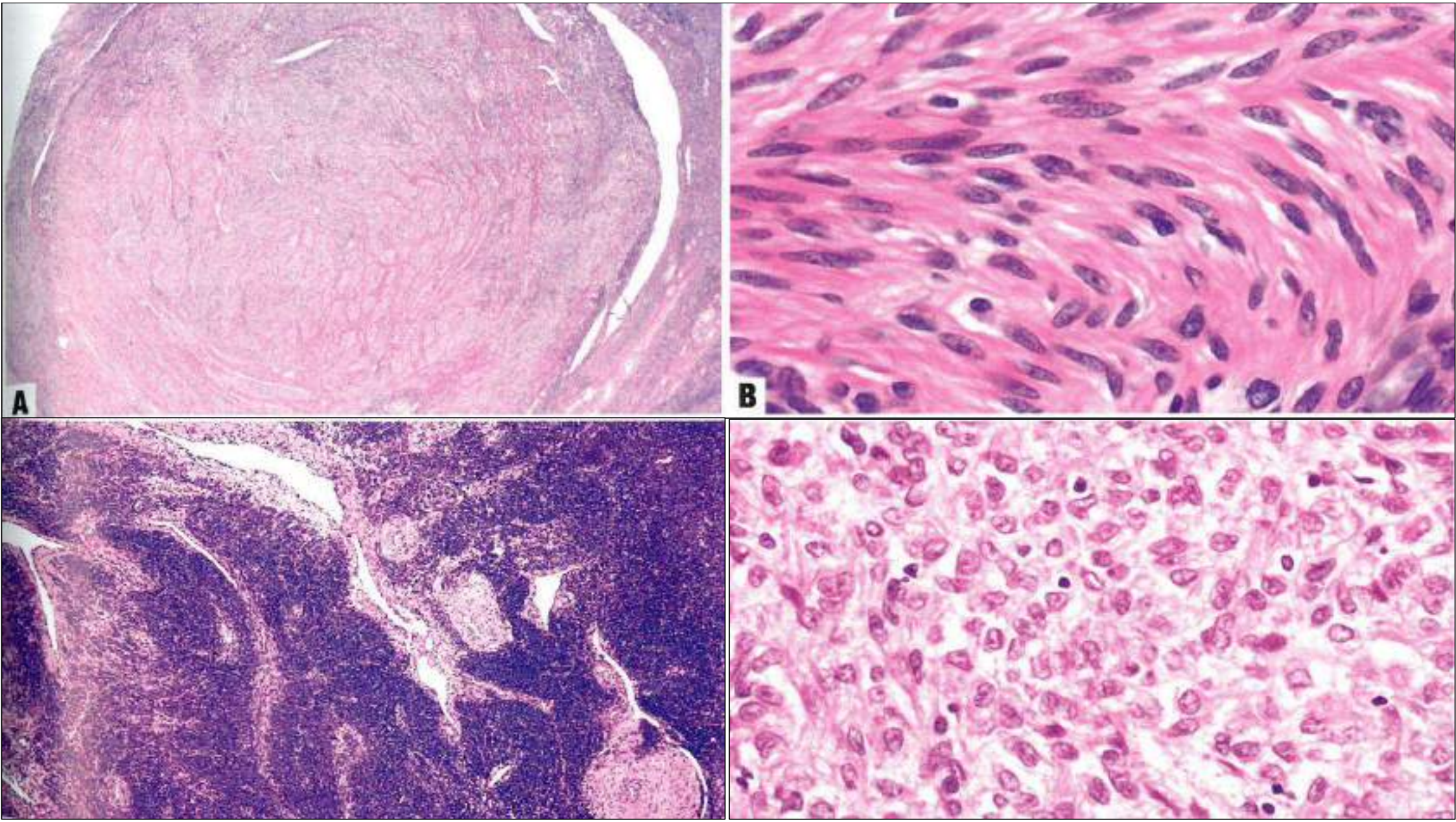
- Mesenchymal tumours of the uterus
  - Smooth muscle tumours
    - Uterine leiomyoma
    - Intravenous leiomyomatosis
    - Smooth muscle tumour of uncertain malignant potential
    - Metastasizing leiomyoma
    - Uterine leiomyosarcoma
  - Endometrial stromal and related tumours
    - Endometrial stromal nodule
    - Low-grade endometrial stromal sarcoma
    - High-grade endometrial stromal sarcoma
    - Undifferentiated uterine sarcoma
- Miscellaneous mesenchymal tumours
  - Uterine tumour resembling ovarian sex cord tumour
  - Perivascular epithelioid cell tumour (PEComa)
  - Inflammatory myofibroblastic tumour
  - Other mesenchymal tumours of the uterus

SMOOTH MUSCLE TUMORS
LEIOMYOMA

- M.C. uterine tumor
- May be intramural, submucosal or subserosal



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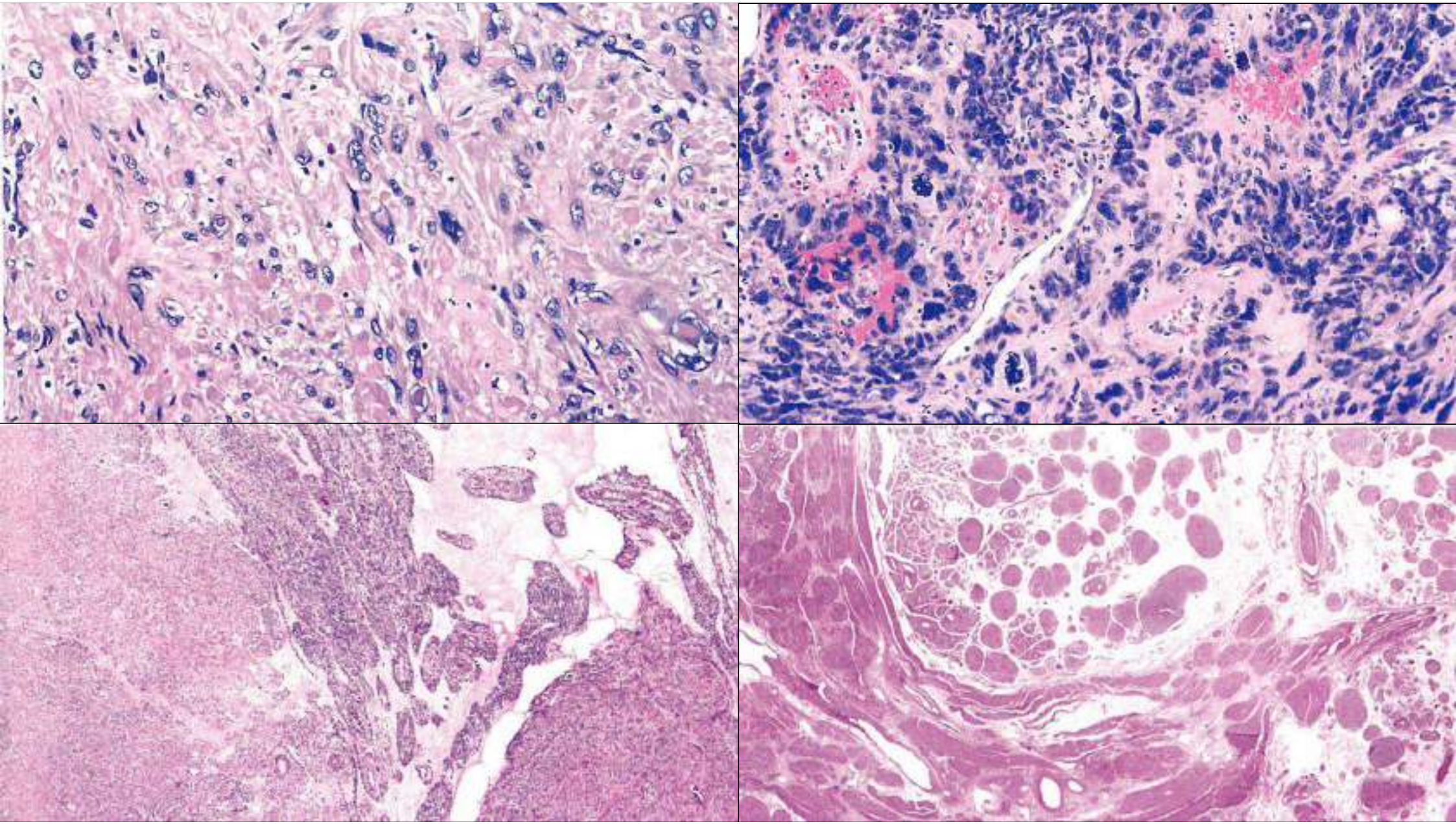
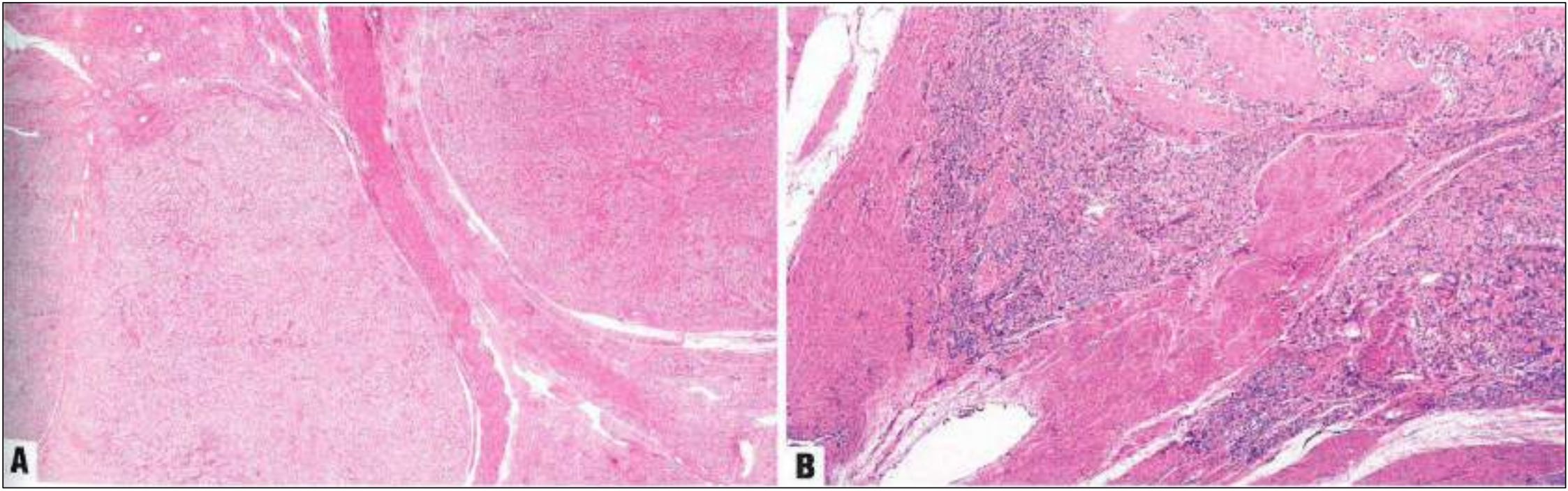


SMOOTH MUSCLE TUMORS OF UNCERTAIN MALIGNANT POTENTIAL (STUMPs)

- Morphological features that exceed criteria for leiomyoma or its subtypes, yet are insufficient for a diagnosis of leiomyosarcoma
- Behave in a malignant fashion in only a minority of cases



Tumour cell necrosis	Moderate to severe atypia	Mitotic count[a]		Frequency of recurrence
		Mitoses/mm^2 (mitoses/10 HPF)	Mean mitoses/mm^2 (mitoses/10 HPF) in tumours with a recurrence	
Absent	Focal/multifocal	< 4 (< 10)	1.4 (3.2)	17% (6 of 35 cases)
Absent	Diffuse	< 4 (< 10)	1.5 (3.5)	12% (10 of 81 cases)
Present	None (or mild atypia)	< 4 (< 10)	1.1 (2.6)	28% (5 of 18 cases)
Absent	None	> 6.3 (> 15)	Not applicable	0% (0 of 42 cases)

- ✓Morphologically heterogeneous
- ✓Should have one of the criteria used for the diagnosis of leiomyosarcoma
- ✓Other parameters that may be useful are the findings of atypical mitosis, vascular involvement and infiltrative/irregular margins

UTERINE LEIOMYOSARCOMA

- Malignant mesenchymal tumor of myometrial smooth muscle derivation exhibiting spindle cell, epithelioid or myxoid morphology
- M.C. uterine sarcoma
- Patients typically aged > 50 yrs
- Intramural, submucosal or subserosal

Conventional (spindle cell) uterine leiomyosarcoma

Two or more of the following:

- Marked cytological atypia (2+/3+ nuclear atypia)
- Tumour cell necrosis
- ≥ 4 mitoses/mm^2 (equating to ≥ 10 mitoses/10 HPF of 0.55 mm in diameter and 0.24 mm^2 in area)

Epithelioid uterine leiomyosarcoma

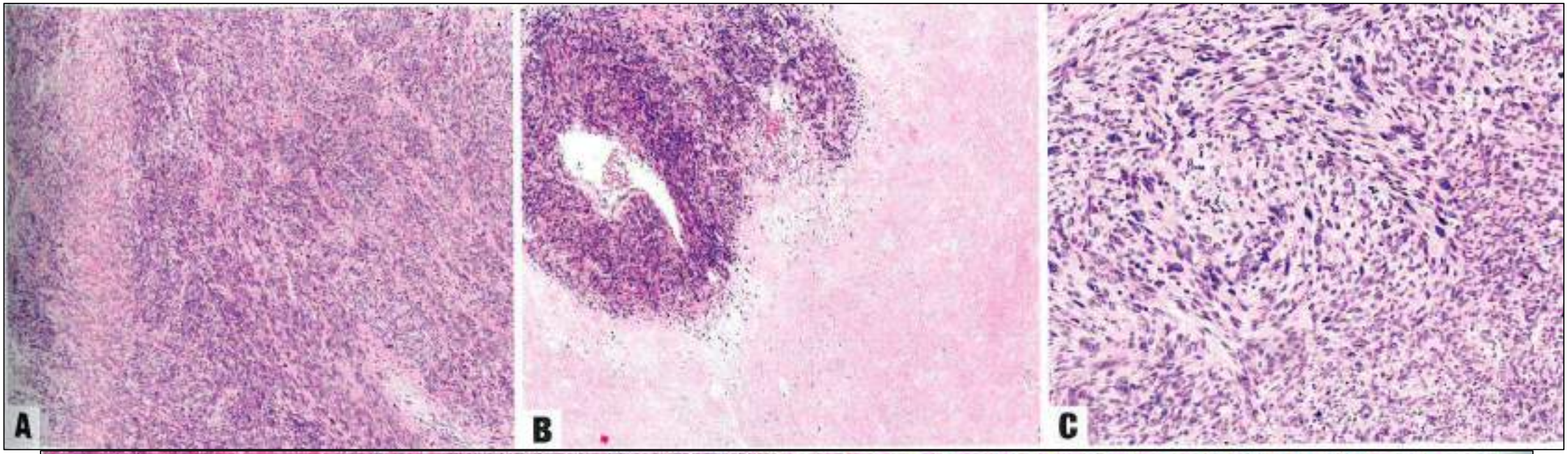
One or more of the following:

- Moderate to severe cytological atypia (2+/3+ atypia)
- Tumour cell necrosis
- ≥ 1.6 mitoses/mm^2 (equating to ≥ 4 mitoses/10 HPF of 0.55 mm in diameter and 0.24 mm^2 in area)

Myxoid uterine leiomyosarcoma

One or more of the following:

- Moderate to severe cytological atypia (2+/3+ atypia)
- Tumour cell necrosis
- > 0.4 mitoses/mm^2 (equating to > 1 mitosis/10 HPF of 0.55 mm in diameter and 0.24 mm^2 in area)
- Infiltrative borders / irregular margins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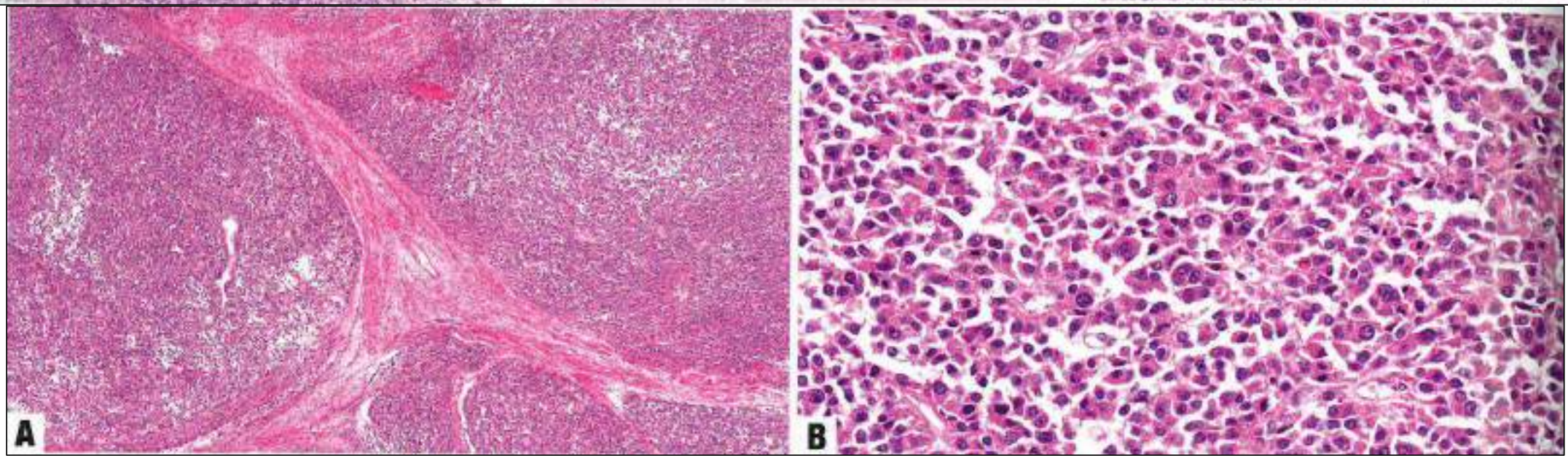
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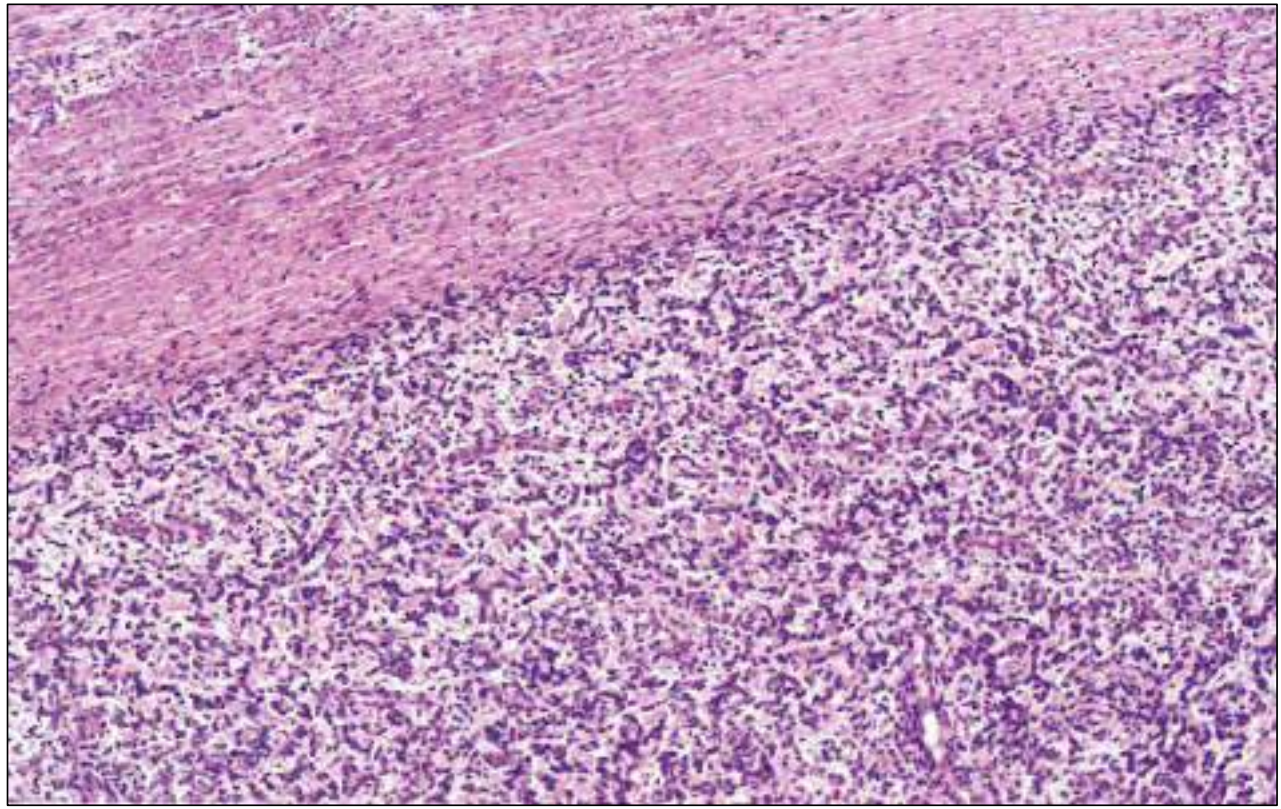
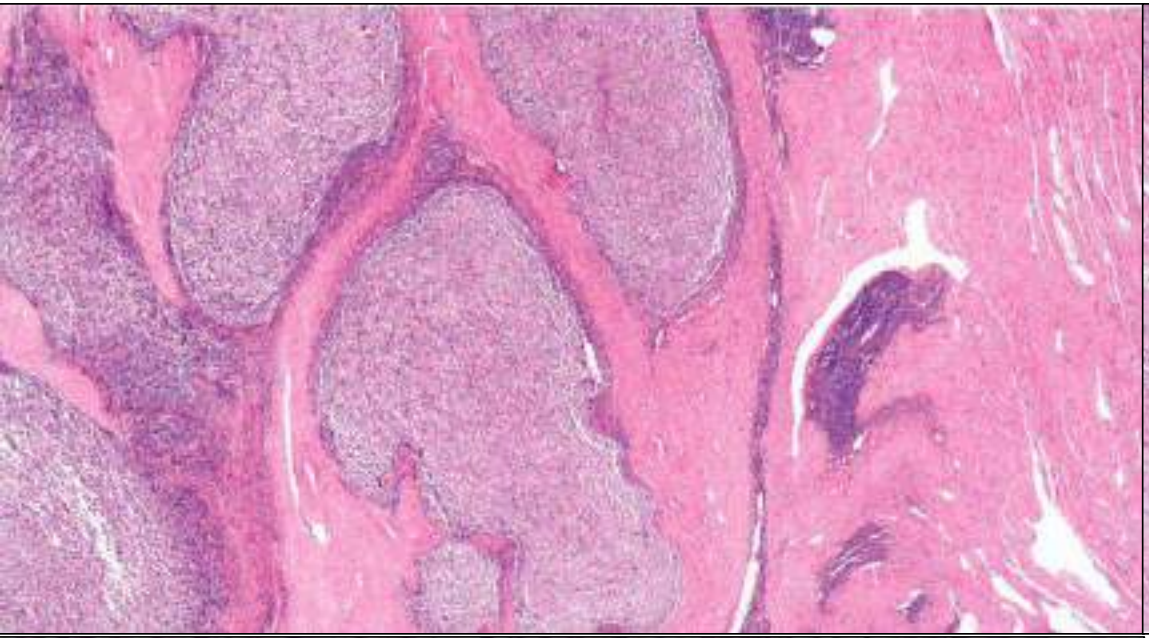
ENDOMETRIAL STROMAL AND RELATED TUMORS: ENDOMETRIAL SROMAL NODULE (ESN)

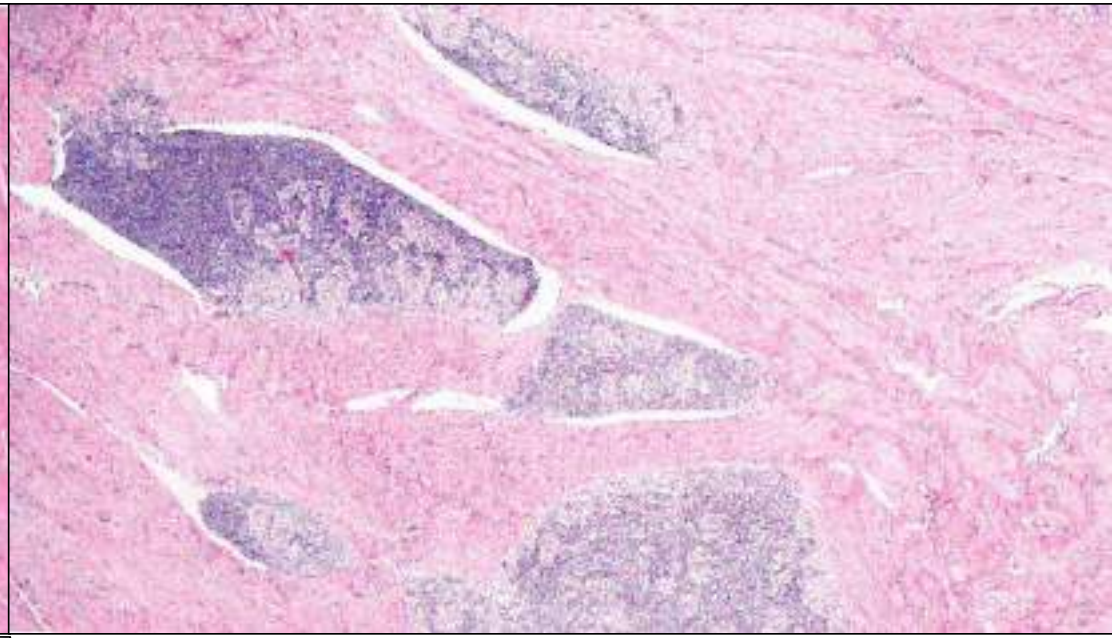
- ESN is a well-circumscribed endometrial stromal tumor resembling proliferative-phase endometrial stroma and lacking lymphovascular invasion
- More often in perimenopausal women
- 70% of tumors harbour t(7;17)(p21;q15) resulting in JAZF1-SUZ12 fusion

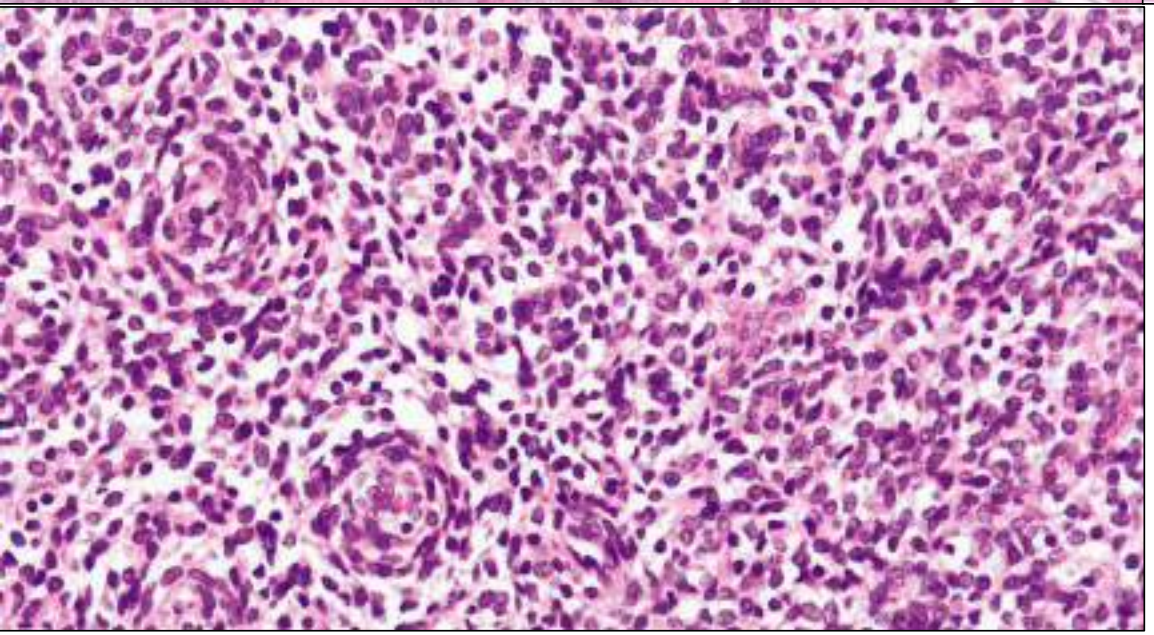


LOW GRADE ENDOMETRIAL STROMAL SARCOMA

- 2nd M.C. uterine sarcoma composed of cells resembling proliferative phase endometrial stroma with infiltrative growth or lymphovascular invasion
- Histologic features include permeative tongue-like islands of tumor cells composed of monotonous oval to spindle cells with minimal cytologic atypia, often demonstrating whorling around blood vessels
- Smooth muscle and sex cord-like differentiation are common
- Recurrent rearrangements involving *JAZF1* and *PHF1* are common, though absence does not preclude the diagnosis
- Poorly circumscribed soft yellow-tan to white nodules extending from the endometrium and invading into the myometrium
- Worm-like plugs of tumor may be seen in the myometrium or lymphovascular channels





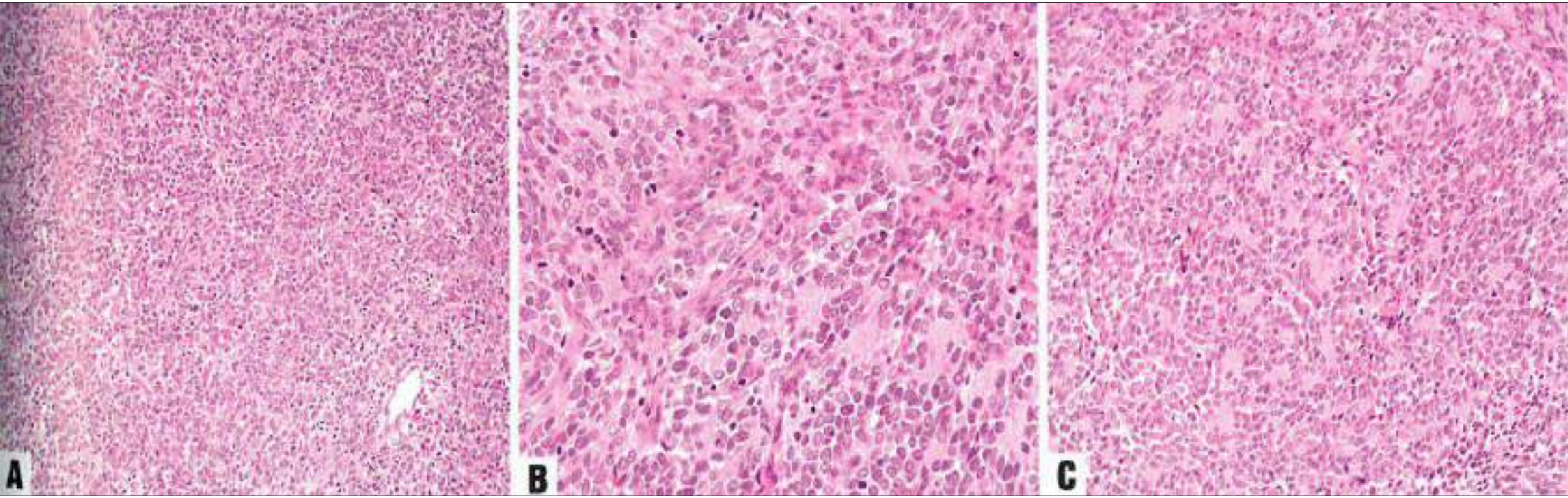


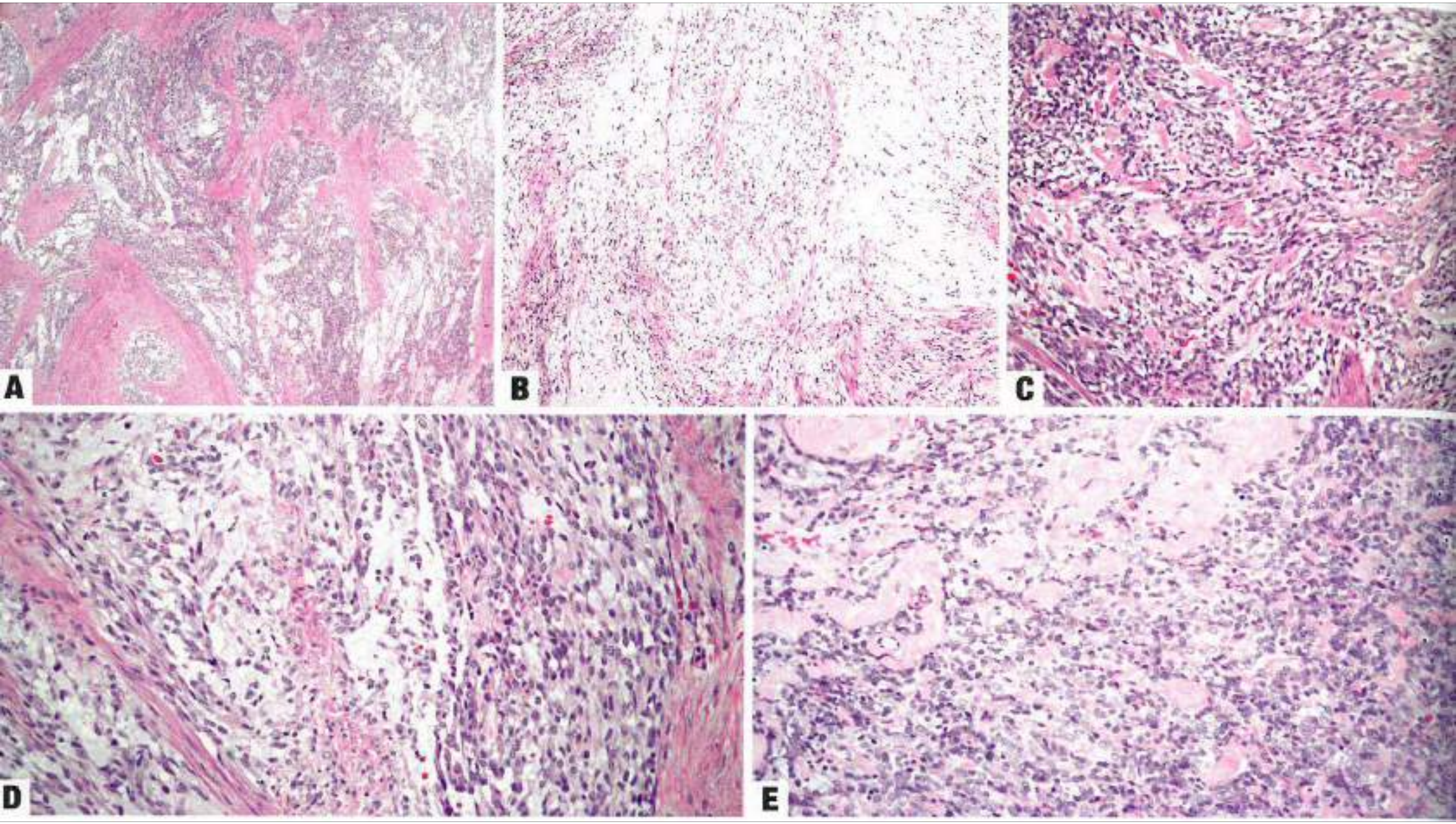
Positive IHC stains:

- **CD10**: sensitivity 91%, specificity 45%
- **IFITM1**: sensitivity 83%, specificity 70%
- **ER** (40 - 100%), **PR** (69 - 100%)
- **CyclinD1** focal
- **Keratins**: **AE1 / AE3**, **CAM5.2**
- Smooth muscle markers (**SMA**, **desmin**, **caldesmon**) often positive in areas of smooth muscle differentiation
- Sex cord markers (**inhibin**, **calretinin**, **CD99**, **MelanA**, **WT1**) may be positive in areas of sex cord differentiation

HIGH GRADE ENDOMETRIAL STROMAL SARCOMA

- Malignant endometrial stromal tumor composed of uniform high-grade round and/or spindle morphology, sometimes with a low-grade component
- Tumours harbour YWHAE-NUTM2A/B, ZC3H7B-BCOR fusions or BCOR-ITD

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Immunophenotype of endometrial stromal tumours

Tumour type	CD10	ER	PR	Cyclin D1	BCOR	Desmin	SMA	Caldesmon
ESN	+ (D)	+ (D)	+ (D)	−/+ (F)[a]	−/+ (F)[a]	−/+ (F/D)[b]	+ (D)	+ (F/D)[b]
LGESS	+ (D)	+ (D)	+ (D)	−/+ (F)[a]	−/+ (F)[a]	−/+ (F/D)[b]	+ (D)	+ (F/D)[b]
YWHAE-NUTM2A/B HGESS low-grade component	+ (D)	+ (D)	+ (D)	−/+ (F)[a]	−/+ (F)[a]	−	−	−
YWHAE-NUTM2A/B HGESS high-grade component	−	−	−	+ (D)[a]	+ (D)[a]	−	−	−
ZC3H7B-BCOR HGESS	+ (D)	−/+ (F)	−/+ (F)	+ (D)[a]	−/+ (F/D)[a,c]	−	−/+ (F)	−/+ (F)
BCOR ITD HGESS	+ (F/D)	−	−	+ (D)[a]	+ (F/D)[a]	−/+ (F)	−	−

D, diffuse; ESN, endometrial stromal nodule; F, focal; HGESS, high-grade endometrial stromal sarcoma; ITD, internal tandem duplication; LGESS, low-grade endometrial stromal sarcoma.

[a] "F" (focal) indicates nuclear staining in < 50% of tumour cells; "D" (diffuse), in ≥ 70% of tumour cells.

[b] Desmin and caldesmon are diffuse only in the setting of variant smooth muscle differentiation.

[c] Diffuse staining with variable intensity in 50% of lesions.

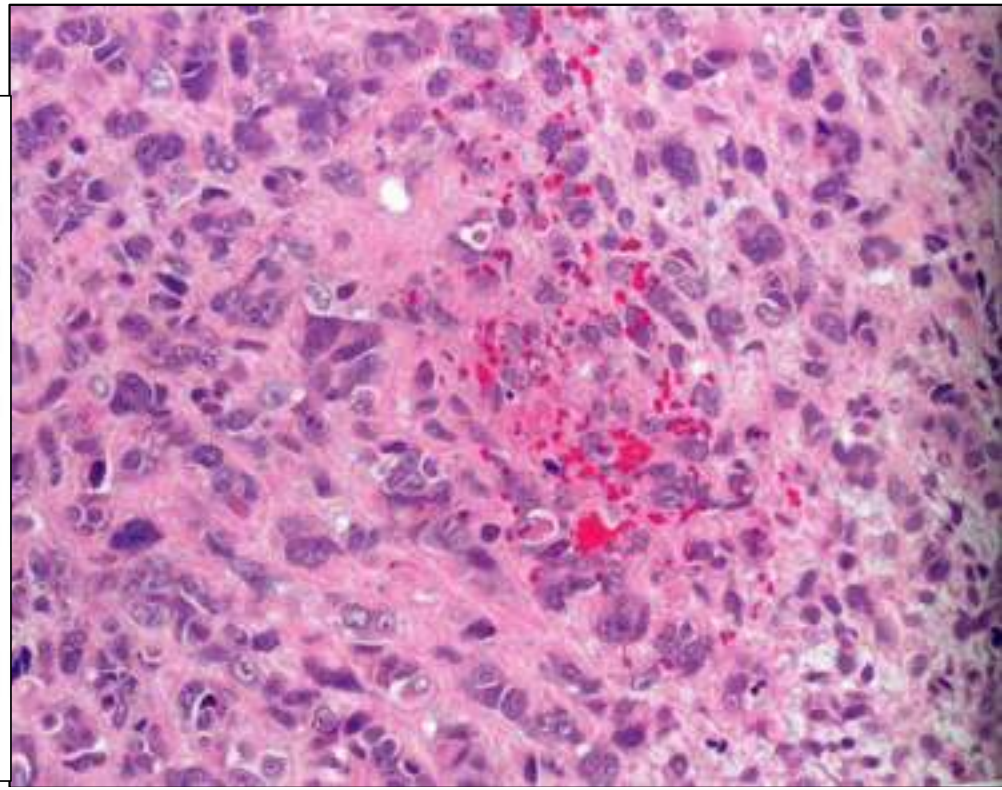
UNDIFFERENTIATED UTERINE SARCOMA

- Malignant mesenchymal tumor lacking evidence of specific lines of differentiation
- Diagnosis of exclusion

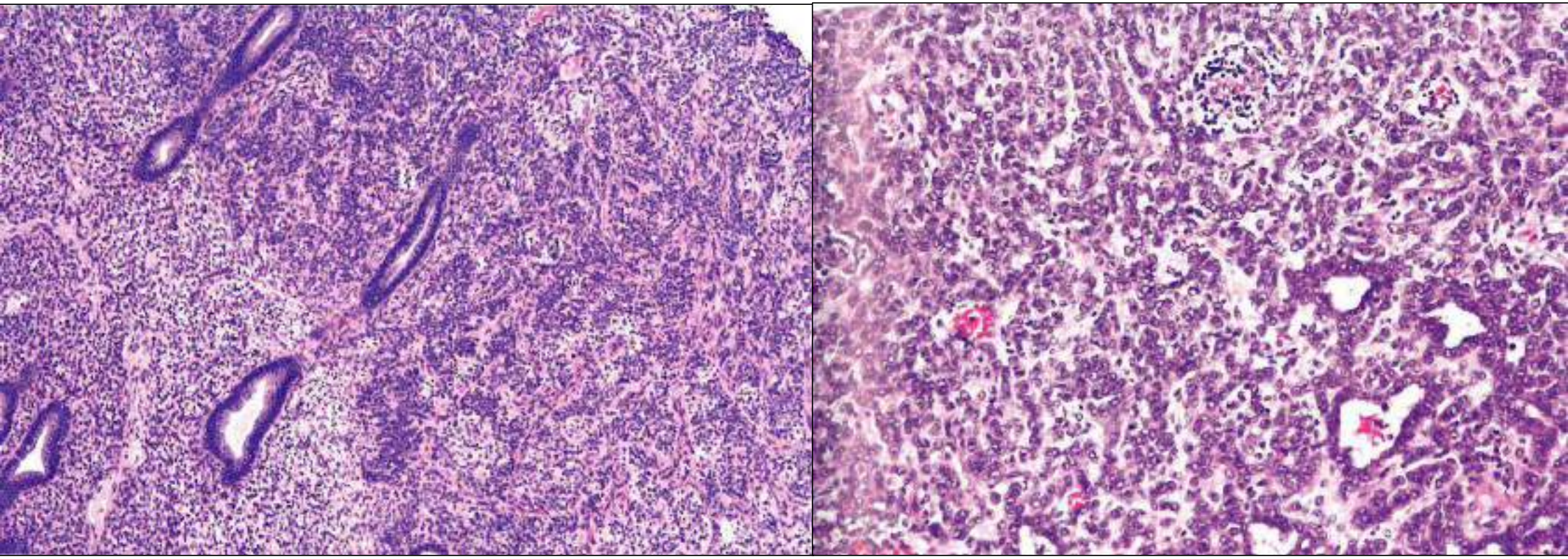
Essential and desirable diagnostic criteria

Essential: uniform or pleomorphic high-grade mesenchymal cells with brisk mitotic activity; exclusion of other high-grade tumours by extensive sampling (poorly differentiated carcinoma, carcinosarcoma, sarcomatous overgrowth in adenosarcoma) and immunohistochemistry for *ZC3H7B-BCOR*, *YWHAE-NUTM2* (*FAM22*), and *BCOR* ITD high-grade endometrial stromal sarcomas and NTRK sarcomas.

Desirable: exclusion of the presence of fusion genes associated with other sarcoma types may be required.

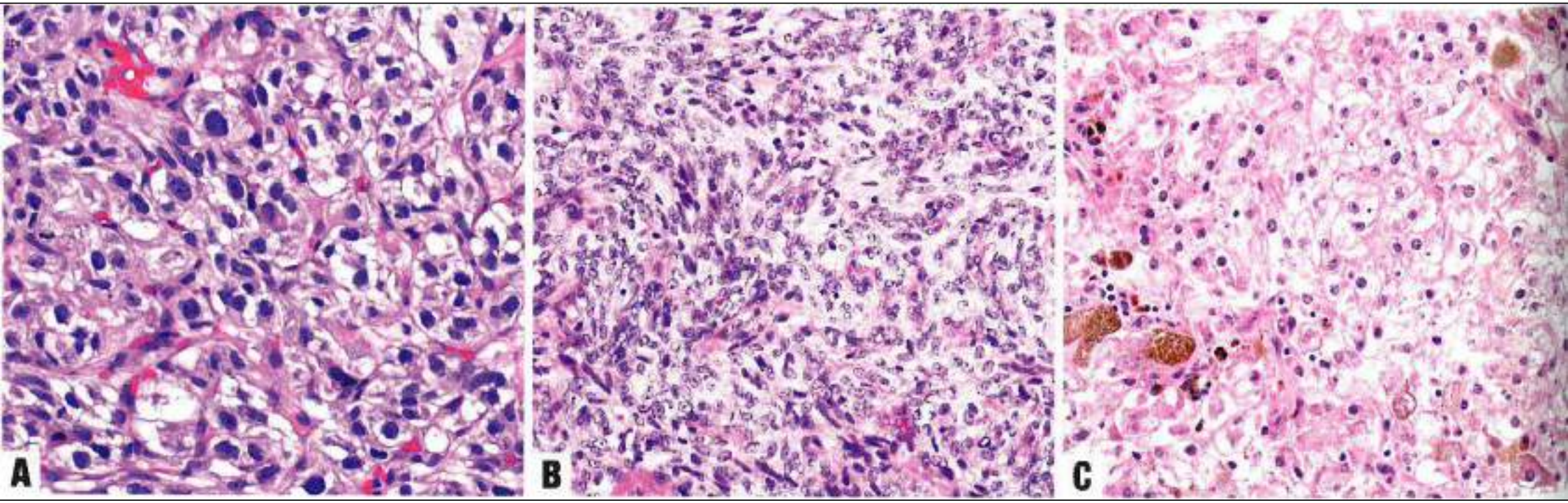


UTERINE TUMOR RESEMBLING OVARIAN SEX CORD TUMOR



PERIVASCULAR EPITHELIOID CELL TUMOR (PEComa)

- Member of a family of mesenchymal neoplasms composed of perivascular epithelioid cells (PECs) that express melanocytic (HMB45, MelanA) and smooth muscle markers (SMA, desmin and h-caldesmon)



STAGING

Procedure	Description
Resection	Includes total hysterectomy and supracervical hysterectomy
Tumor Type	**Description**
Sarcoma	Includes leiomyosarcoma, adenosarcoma, endometrial stromal sarcoma, and undifferentiated uterine/endometrial sarcoma

FIGO STAGE

+FIGO Stage (2018 FIGO Cancer Report) for All Sarcomas Except Adenosarcoma#

 # Including leiomyosarcoma, endometrial stromal sarcoma, and undifferentiated endometrial sarcoma / uterine sarcoma

___ I: Tumor limited to uterus
___ IA: Less than or equal to 5 cm
___ IB: More than 5 cm
___ II: Tumor extends beyond the uterus, within the pelvis
___ IIA: Adnexal involvement
___ IIB: Involvement of other pelvic tissues
___ III: Tumor invades abdominal tissues (not just protruding into the abdomen)
___ IIIA: One site
___ IIIB: More than one site
___ IIIC: Metastasis to pelvic and / or para-aortic lymph nodes
___ IV: Tumor invades bladder and / or rectum and / or distant metastasis
___ IVA: Tumor invades bladder and / or rectal mucosa
___ IVB: Distant metastasis

+FIGO Stage (2018 FIGO Cancer Report) for Adenosarcoma

___ I: Tumor limited to uterus
___ IA: Tumor limited to endometrium / endocervix with no myometrial invasion
___ IB: Less than or equal to half myometrial invasion
___ IC: More than half myometrial invasion
___ II: Tumor extends beyond the uterus, within the pelvis
___ IIA: Adnexal involvement
___ IIB: Tumor extends to extrauterine pelvic tissue
___ III: Tumor invades abdominal tissues (not just protruding into the abdomen)
___ IIIA: One site
___ IIIB: More than one site
___ IIIC: Metastasis to pelvic and / or para-aortic lymph nodes
___ IV: Tumor invades bladder and / or rectum and / or distant metastasis
___ IVA: Tumor invades bladder and / or rectal mucosa
___ IVB: Distant metastasis

CERVICAL CANCERS

Tumours of the uterine cervix

- Introduction
- Squamous epithelial tumours
  - Mimics of squamous precursor lesions
    - Squamous metaplasia
    - Atrophy
  - Squamous cell tumours and precursors
    - Condyloma acuminatum (see Ch. 10)
    - Squamous intraepithelial lesions
    - Squamous cell carcinoma, HPV-associated
    - Squamous cell carcinoma, HPV-independent
    - Squamous cell carcinoma NOS
- Glandular tumours and precursors
  - Benign glandular lesions
    - Endocervical polyp
    - Müllerian papilloma
    - Nabothian cyst
    - Tunnel clusters
    - Microglandular hyperplasia
    - Lobular endocervical glandular hyperplasia
    - Diffuse laminar endocervical hyperplasia
    - Mesonephric remnants and hyperplasia
    - Arias-Stella reaction
    - Endocervicosis
    - Tuboendometrioid metaplasia
    - Ectopic prostate tissue
  - Adenocarcinomas
    - Adenocarcinoma in situ, HPV-associated
    - Adenocarcinoma, HPV-associated
    - Adenocarcinoma in situ, HPV-independent
    - Adenocarcinoma, HPV-independent, gastric type
    - Adenocarcinoma, HPV-independent, clear cell type
    - Adenocarcinoma, HPV-independent, mesonephric type
    - Other adenocarcinomas
  - Other epithelial tumours
    - Carcinosarcoma

SQUAMOUS CELL TUMORS

SQUAMOUS INTRAEPITHELIAL LESIONS (SILs)

- Aka Cervical Intraepithelial Neoplasia (CIN), are proliferations of squamous cells driven by HPV infection, showing maturation abnormalities and/or viral cytopathic changes that do not extend beyind the basement membrane
- Divided into low grade SILs and high grade SILs

Essential and desirable diagnostic criteria

LSIL (condyloma / CIN 1)

Essential: full-thickness atypia with moderate to abundant cytoplasm in cells within the upper two thirds of the epithelium; basaloid morphology and significant mitotic activity should be restricted to the lower epithelial third.

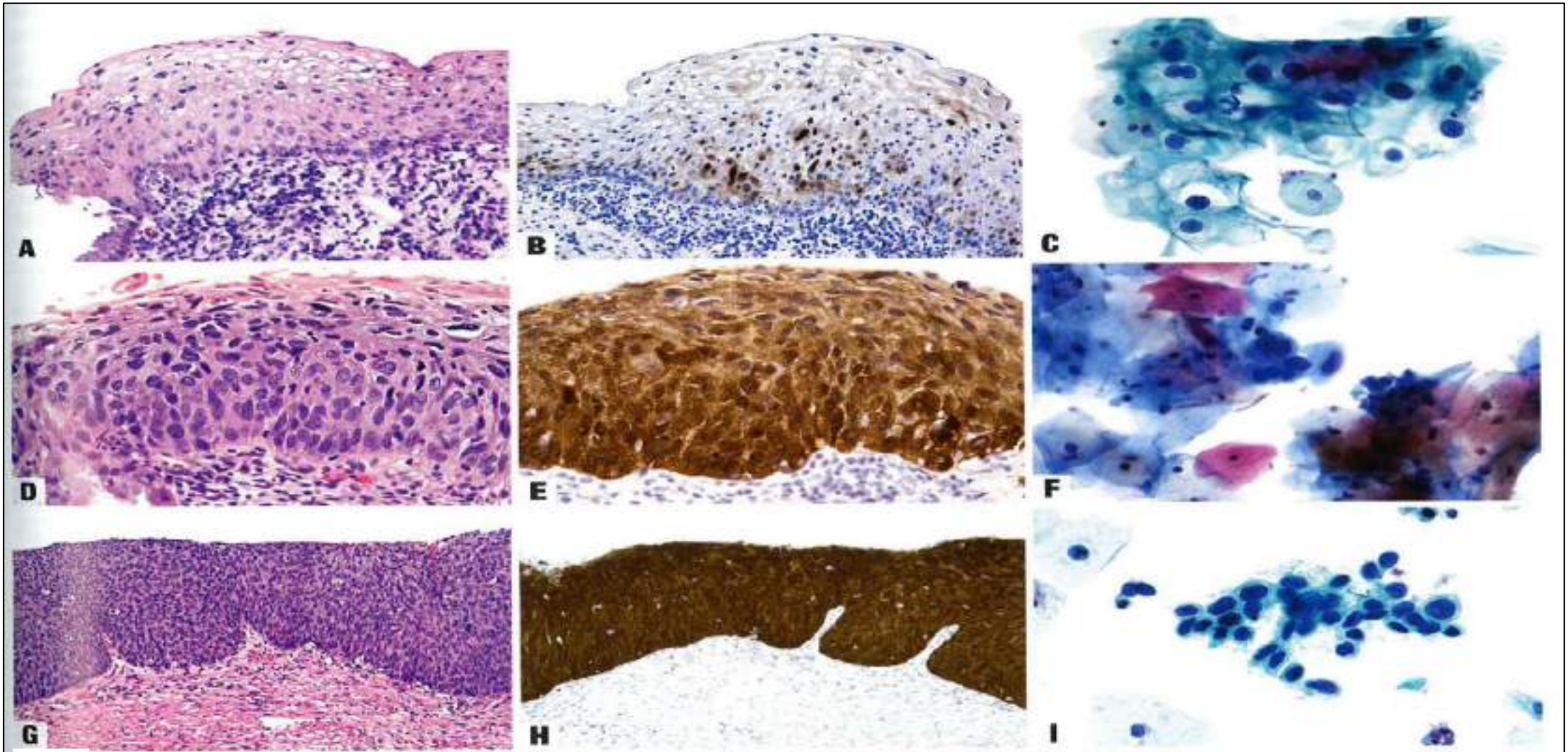
Desirable: koilocytic atypia within the middle and surface cells (highly desirable).

HSIL (CIN 2)

Essential: full-thickness atypia characterized by basaloid cells and mitotic activity extending into the upper half to upper two thirds of the epithelium, but with retained koilocytic change on the surface.

HSIL (CIN 3)

Essential: full-thickness atypia wherein the base of the lesion is often indistinguishable from the surface; mitotic activity may be identified throughout the epithelium; the upper portions of the epithelium show a significantly higher N:C ratio than in LSIL and HSIL (CIN 2).



Top row: Low-grade SIL (CIN 1). **A** The mucosal surface is notable for koilocytes with enlarged, irregular nuclei and perinuclear haloes. **B** p16 staining can be negative (with patchy nuclear and cytoplasmic staining only) or block-positive. **C** Koilocytes with enlarged, hyperchromatic nuclei and sharply punched-out perinuclear haloes (ThinPrep). **Middle row:** High-grade SIL (CIN 2). Abnormal cells with a high N:C ratio extend above the lower third of the mucosa (**D**) and exhibit block-positive p16 reactivity (**E**). **F** The dysplastic cells have a moderately increased N:C ratio (1:1) and nuclei with irregular nuclear contours (ThinPrep Pap). **Bottom row:** High-grade SIL (CIN 3). Abnormal cells with a high N:C ratio involve more than two thirds of the mucosal thickness (**G**) and exhibit block-positive p16 reactivity (**H**). **I** Dysplastic cells with a high N:C ratio and irregular, hyperchromatic nuclei (ThinPrep).

SQUAMOUS CELL CARCINOMA (SCC), HPV-ASSOCIATED OF THE UTERINE CERVIX

- HPV-associated squamous tumor with stromal invasion and/or exophytic-type invasion

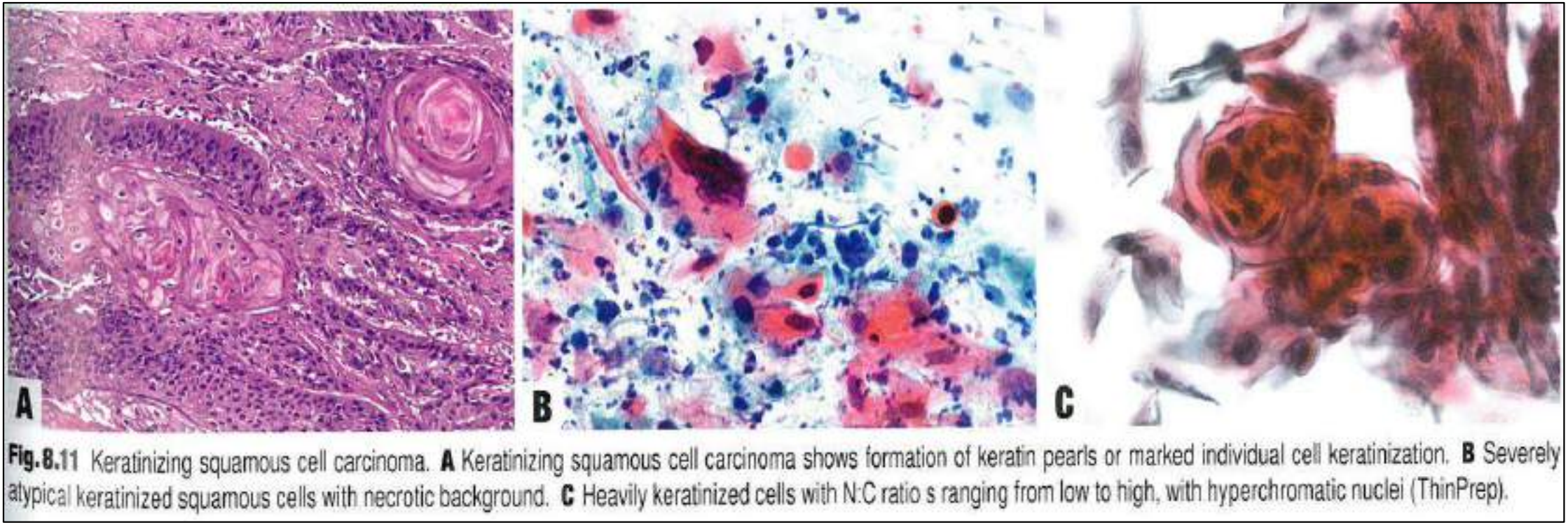
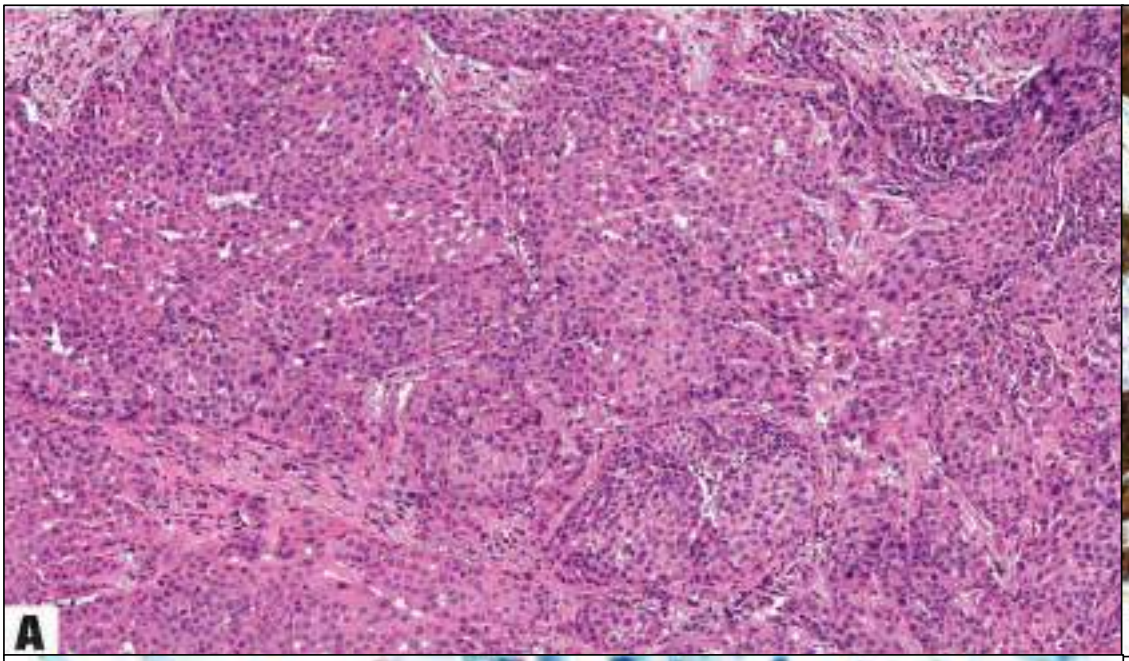
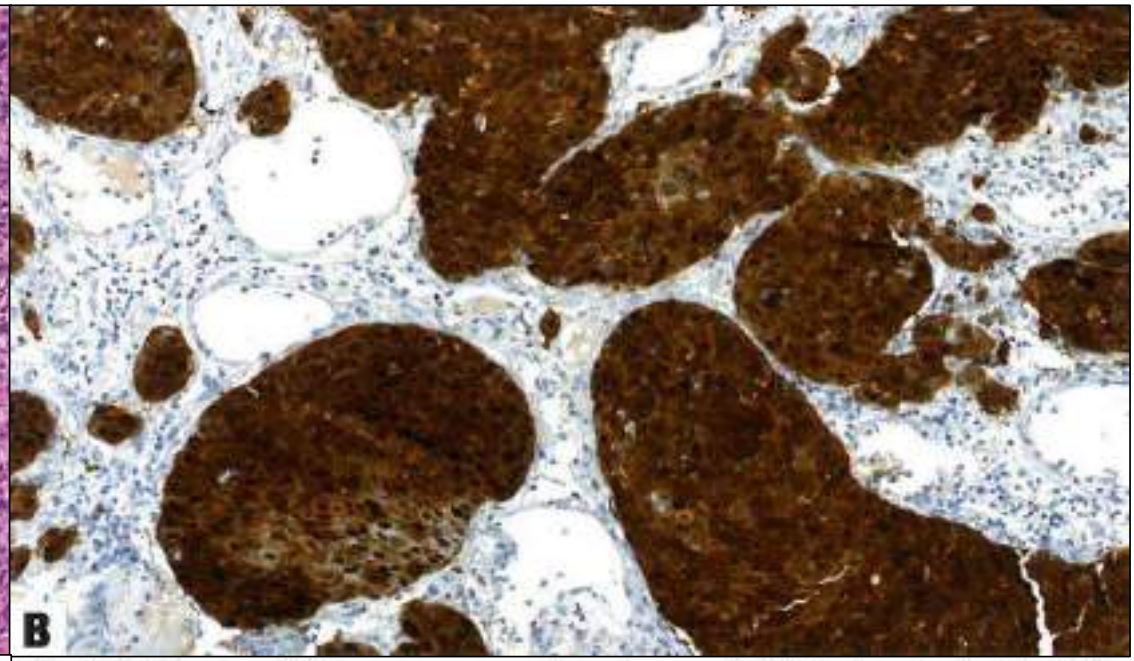
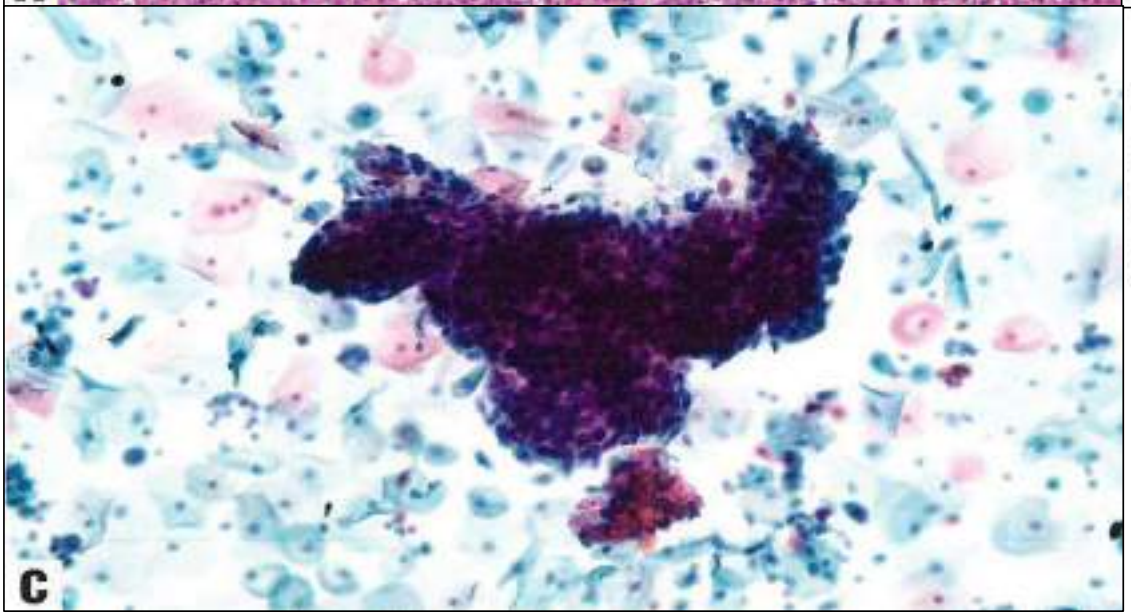


Fig. 8.11 Keratinizing squamous cell carcinoma. **A** Keratinizing squamous cell carcinoma shows formation of keratin pearls or marked individual cell keratinization. **B** Severely atypical keratinized squamous cells with necrotic background. **C** Heavily keratinized cells with N:C ratio s ranging from low to high, with hyperchromatic nuclei (ThinPrep).







Non-keratinizing squamous cell carcinoma. **A** This is characterized by infiltrative nests of squamous cells without keratinization. **B** Strong and diffuse p16 overexpression is present in almost all HPV-associated squamous cell carcinomas. **C** Cytology: large syncytial aggregates of tumour cells with karrhyorectic debris along the edges (SurePath).

- High-risk HPV genotypes cause the vast majority (> 90-95%) of SCCs
- 12 HPV types classified by WHO as oncogenic: 16, 18, 31, 33. 35, 39, 45, 51, 52, 56, 58 and 59
- 2 types (16 and 18) responsible for 70% of all SCCs

SQUAMOUS CELL CARCINOMA (SCC), HPV-INDEPENDENT OF THE UTERINE CERVIX

- Frequently of keratinizing type
- No morphological criteria can reliably differentiate between HPV-associated and HPV-independent SCCs
- Negative p16 immunostaining
- Molecular testing for HPV DNA or mRNA is negative

ADENOCARCINOMAS:
ADENOCARCINOMA IN SITU, HPV ASSOCIATED & HPV INDEPENDENT

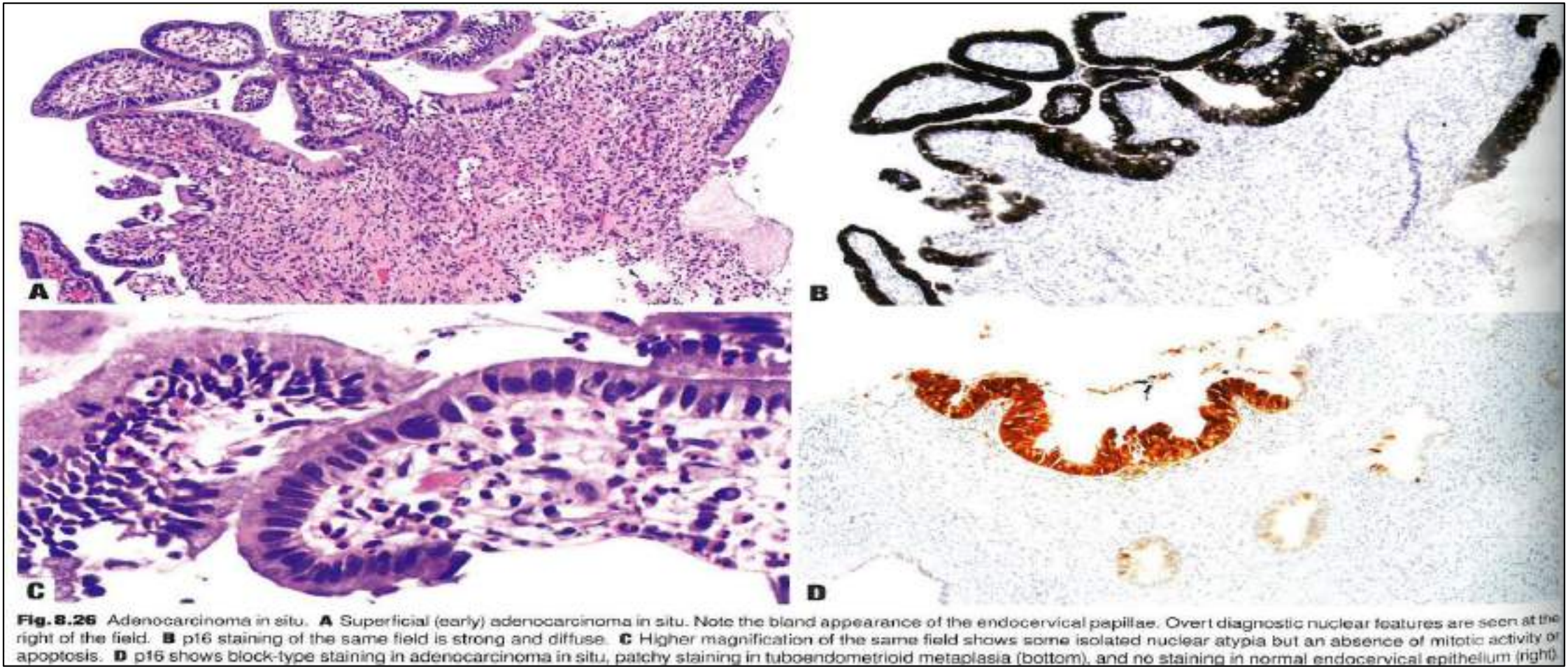
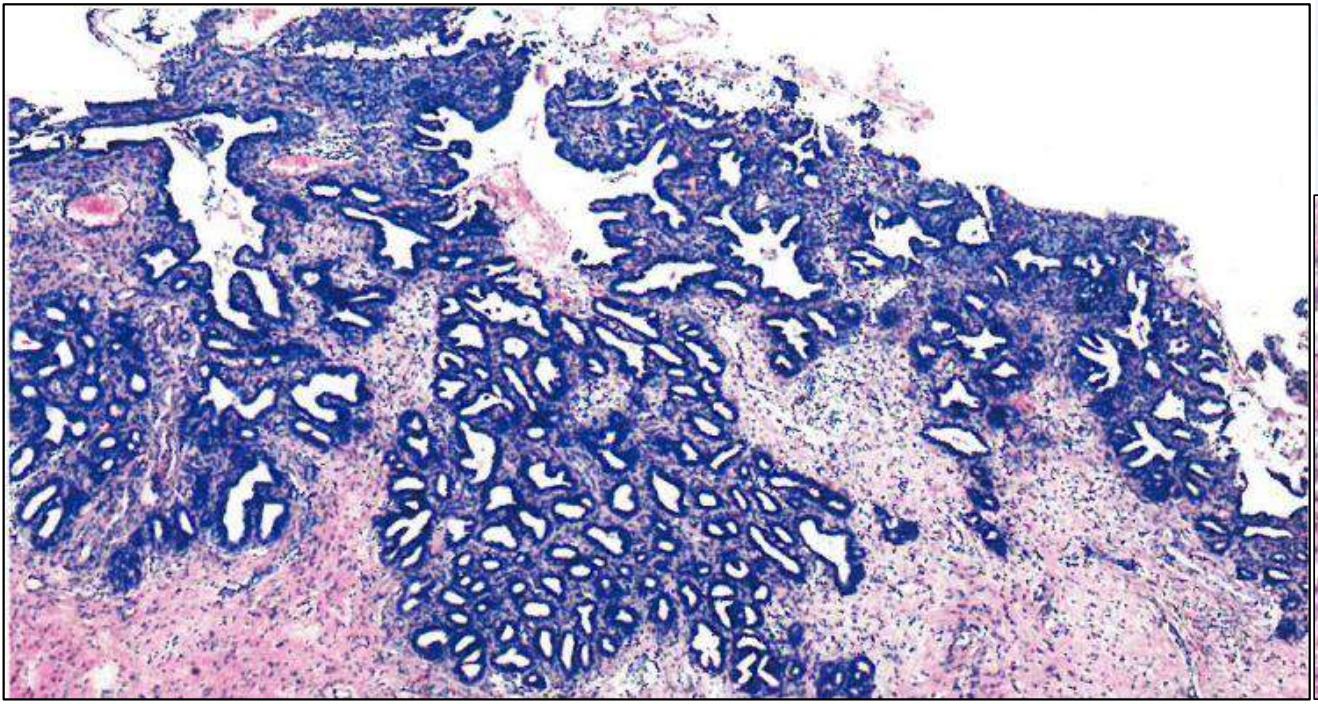


Fig. 8.26 Adenocarcinoma in situ. **A** Superficial (early) adenocarcinoma in situ. Note the bland appearance of the endocervical papillae. Overt diagnostic nuclear features are seen at the right of the field. **B** p16 staining of the same field is strong and diffuse. **C** Higher magnification of the same field shows some isolated nuclear atypia but an absence of mitotic activity or apoptosis. **D** p16 shows block-type staining in adenocarcinoma in situ, patchy staining in tuboendometrioid metaplasia (bottom), and no staining in normal endocervical epithelium (right).

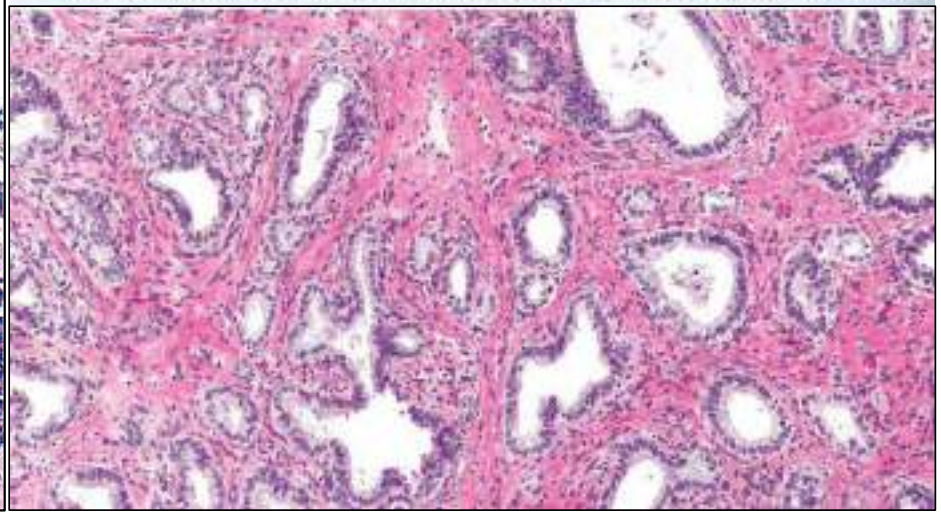
ADENOCARCINOMA, HPV ASSOCIATED

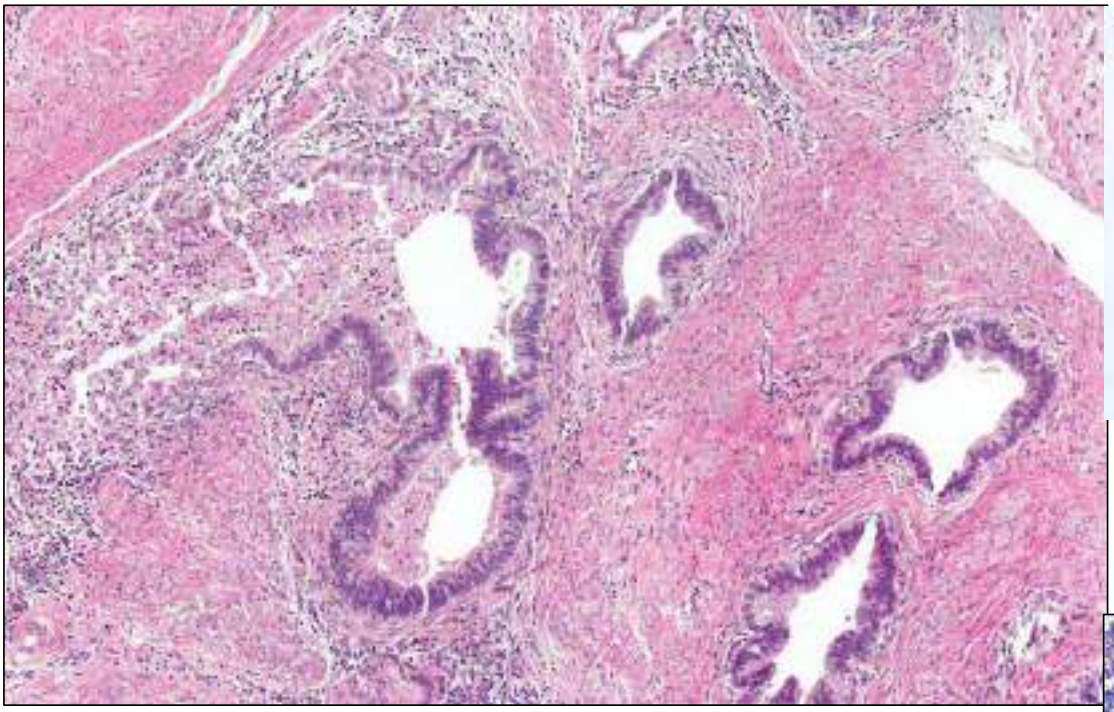
- Glandular tumor with stromal invasion and/or exophytic expansile-type invasion, associated with high-risk HPV (HR-HPV) infection
- M.C. HPV types are 18, 16 and 45 (~ 95% cases)



Pattern A (non-destructive invasion)

- Well-demarcated glands with rounded contours
- No lymphovascular invasion
- Complex intraglandular growth acceptable (i.e. cribriform growth, papillae)
- Lack of solid growth (i.e. architecturally well to moderately differentiated)



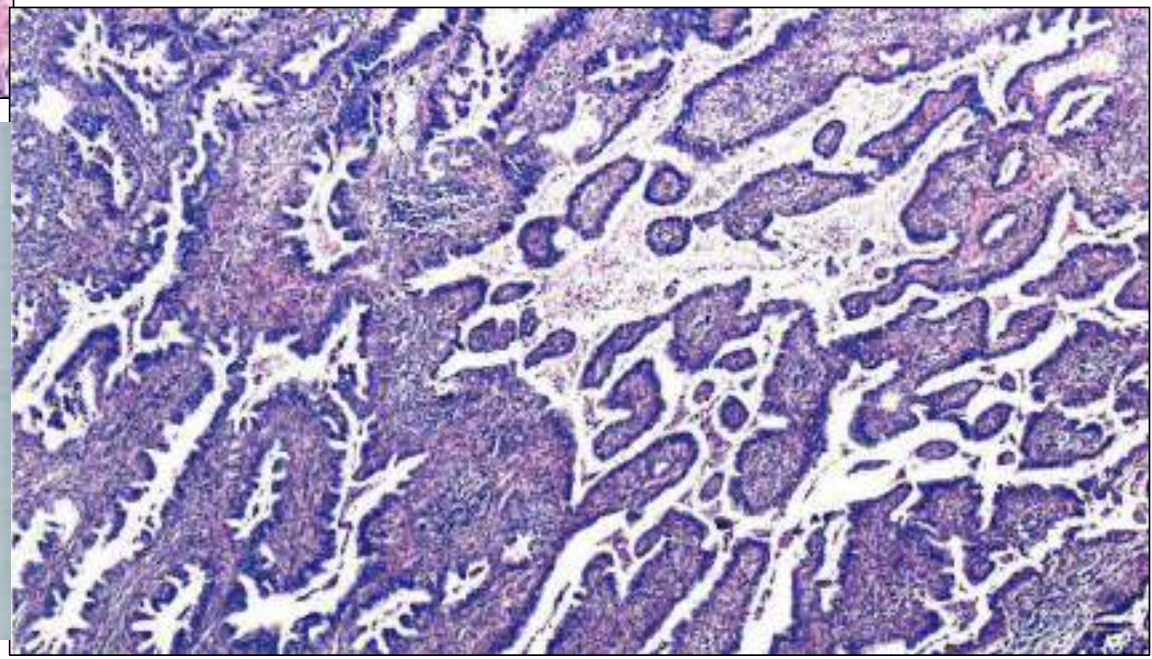


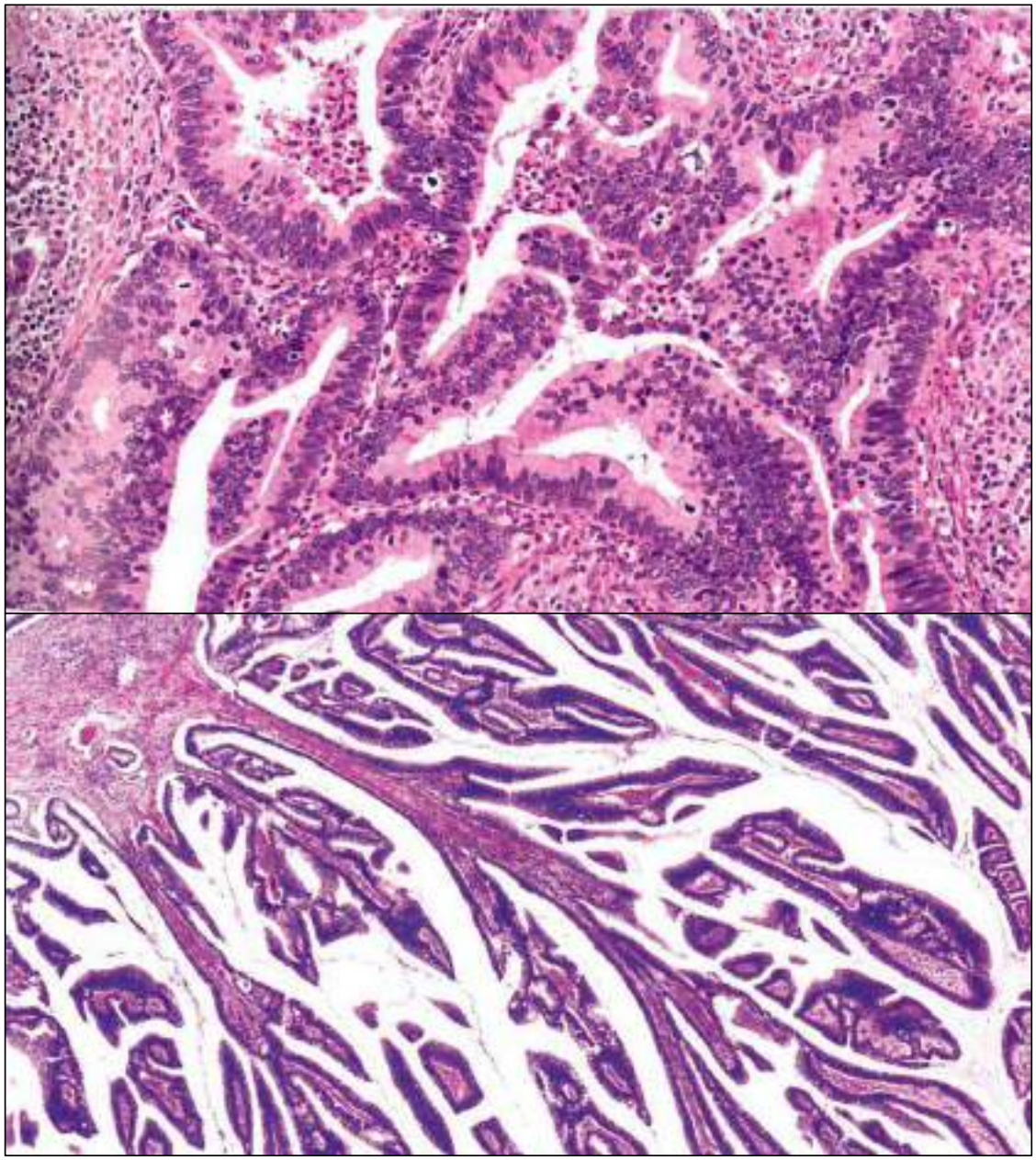
Pattern B (early / focally destructive invasion)

- Individual or small groups of tumour cells, separated from the rounded glands; focally desmoplastic or inflamed stroma
- Foci may be single, multiple, or linear at base of tumour
- Lymphovascular invasion +/–
- Lack of solid growth (i.e. architecturally well to moderately differentiated)

Pattern C (diffusely destructive invasion)

- Diffusely infiltrative glands with associated extensive desmoplastic response
- Glands often angulated or with canalicular pattern, with interspersed open glands
- Confluent growth filling a 4× field (5 mm): glands, papillae (stroma only within papillae), or mucin lakes
- Solid, poorly differentiated component (architecturally high-grade); nuclear grade is disregarded
- Lymphovascular invasion +/–





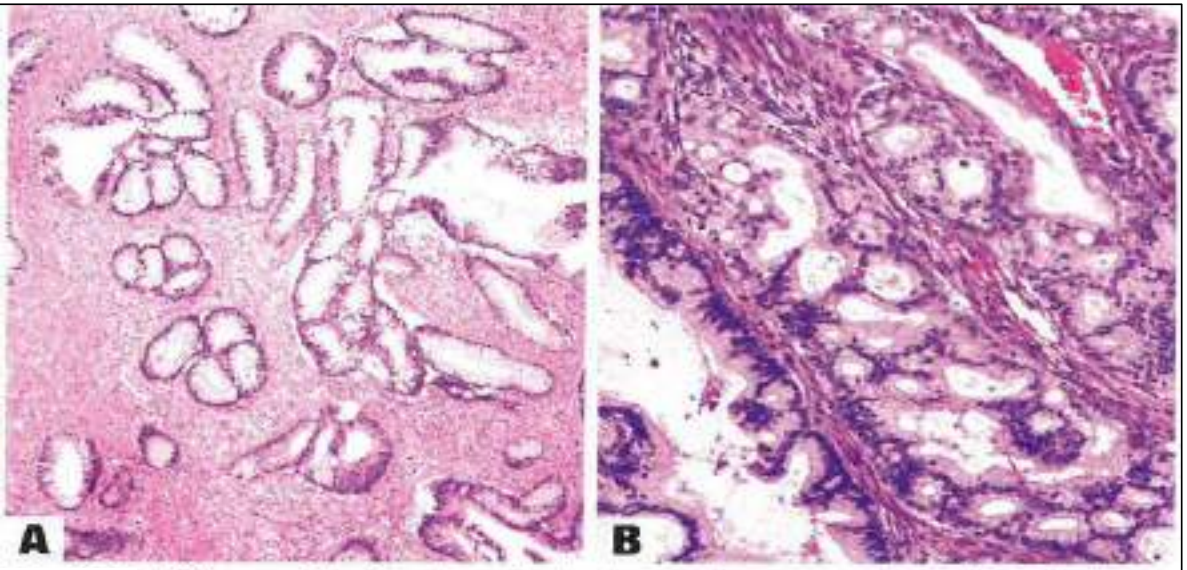
- Hallmark of HPV-associated endocervical adenocarcinoma – apical mitoses and karyorrhexis, conspicuous and identifiable at low-power magnification
- Nuclei are enlarged, elongated and hyperchromatic

Usual type:
This type accounts for ~75% of all endocervical adenocarcinomas {2636,3043}. Cells with mucinous cytoplasm constitute only 0–50% of the tumour. Papillary (including villoglandular) and micropapillary growth can be observed, mimicking serous carcinoma architecturally but not cytologically.

- *Villoglandular variant:* a rare lesion characterized by exophytic papillary growth {1212}. Papillae are lined by columnar epithelium of usual type (most often) with mild atypia. Luminal borders are smooth. Invasion of the underlying cervical stroma is absent or minimal.

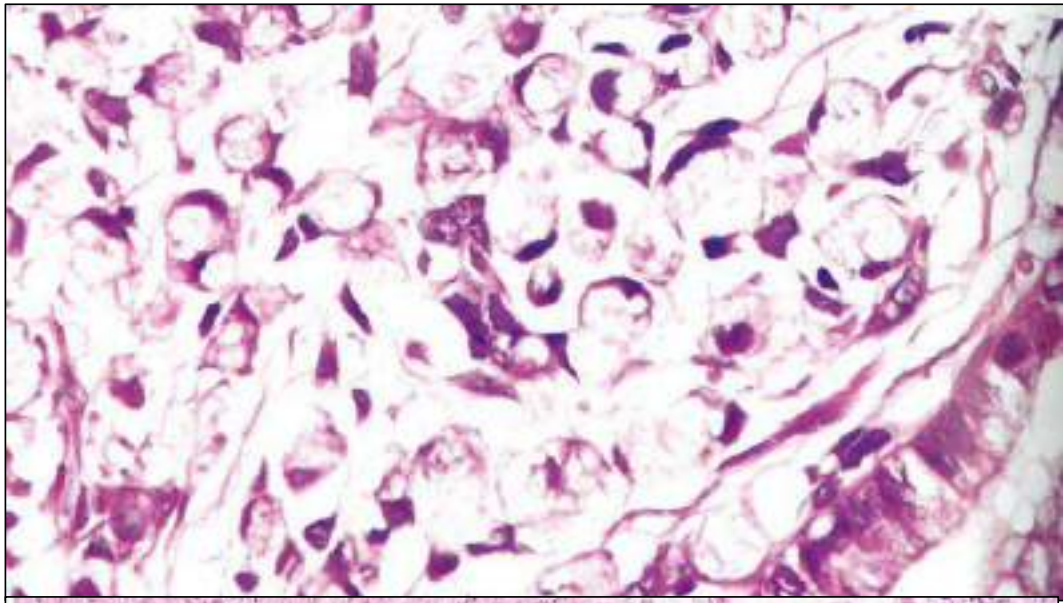
Mucinous type:
This type accounts for ~10% of all endocervical adenocarcinomas {2636,1073}. There is intracytoplasmic mucin in ≥ 50% of cells, typically with a minor component of usual adenocarcinoma. This type is subdivided into the following variants:

- *Mucinous NOS adenocarcinoma:* mucinous cytoplasm resembling normal endocervix with pale-purple staining on H&E {1073}
- *Intestinal adenocarcinoma:* goblet cell and/or enteroendocrine cell differentiation representing ≥ 50% of the tumour {1720}
- *Signet-ring cell adenocarcinoma:* loose non-cohesive round cells with a mucinous vacuole displacing the nucleus, representing ≥ 50% of the tumour
- *Stratified mucin-producing carcinoma:* often associated with adjacent stratified mucin-producing intraepithelial lesion, composed of invasive nests of stratified epithelium with intracytoplasmic mucin; most are moderately or poorly differentiated {1461,2037}



HPV-associated endocervical adenocarcinoma, mucinous NOS (endocervical) type. **A** Irregular glands lined by columnar mucinous epithelium displaying evident nuclear hyperchromasia, mitoses, and apoptoses. **B** Cribriform proliferation composed of columnar mucinous epithelium displaying evident nuclear hyperchromasia.

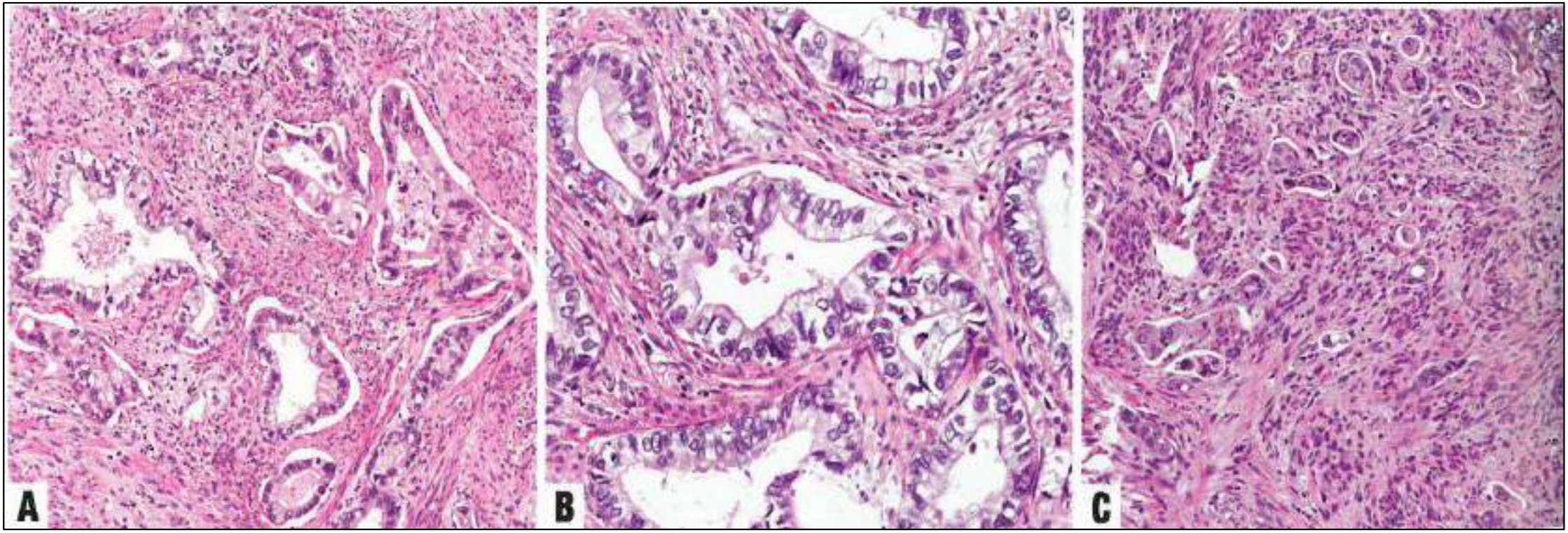
- **p16**: overexpressed in > 95% of cases (diffuse, strong nuclear and cytoplasmic staining)
- **mCEA**: 100% (any degree of staining)
- Other positive markers include CK7 and PAX8 (~ 75% cases)
- Most cases have normal p53 staining
- Negative for ER, PR, vimentin, CK20 and SATB2



HPV-associated adenocarcinoma, mucinous intestinal type. Goblet cell intestinal mucinous differentiation is noted in an otherwise usual-type adenocarcinoma.

ADENOCARCINOMA, HPV INDEPENDENT, GASTRIC TYPE

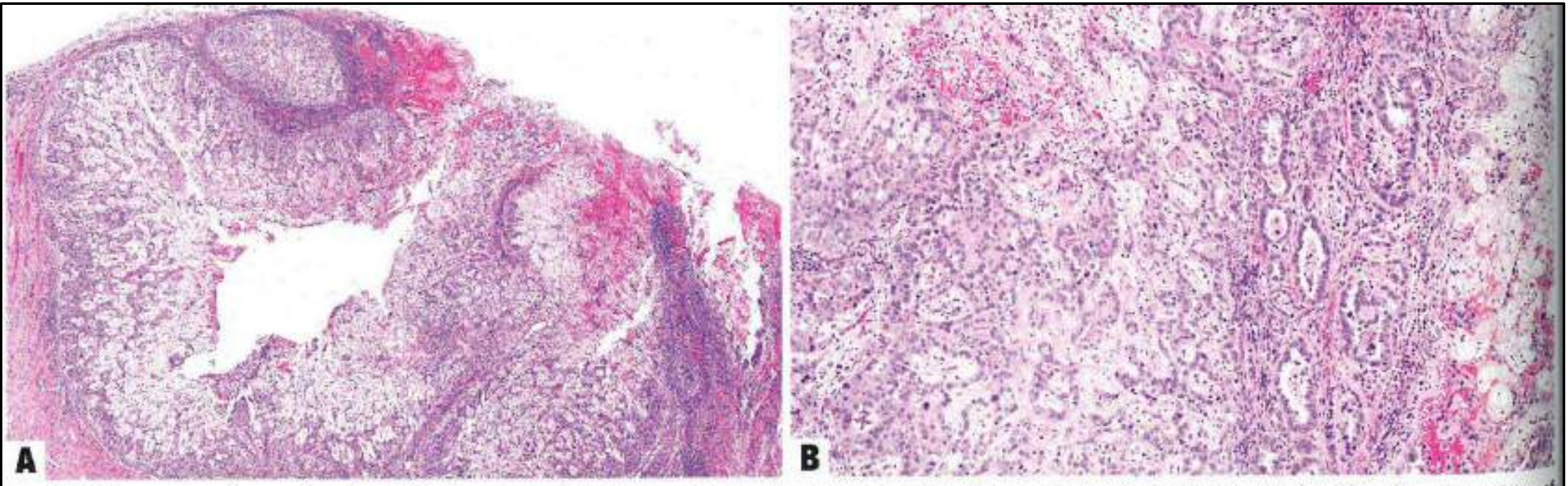
- Most common subtype of non HPV associated endocervical adenocarcinoma
- Usually sporadic but can be associated with germline *STK11* mutations (Peutz-Jeghers syndrome)
- Gastric type adenocarcinomas are best regarded as inherently high grade
- Aggressive, chemorefractory tumor with a propensity for peritoneal and abdominal spread
- Most patients present at advanced stage (II to IV) at diagnosis
- By immunohistochemistry, the gastric (pyloric) markers HIK1083 and MUC6 are frequently positive
- PAX8, CEA and CK7 usually positive
- ER and PR usually negative
- p16 usually negative or focally positive, although up to 8 - 9% of cases have diffuse strong expression typical of HPV associated tumors



Gastric-type endocervical adenocarcinoma. **A** Irregularly shaped, infiltrative mucinous glands and tumour clusters with evident nuclear atypia. **B** Tumoural glan are composed of mucinous cells with ample granular to foamy cytoplasm and distinct cell borders. **C** Poorly differentiated areas display frank infiltration and severe atypi Notice the relatively abundant eosinophilic to vacuolated cytoplasm.

ADENOCARCINOMA, HPV INDEPENDENT, CLEAR CELL TYPE

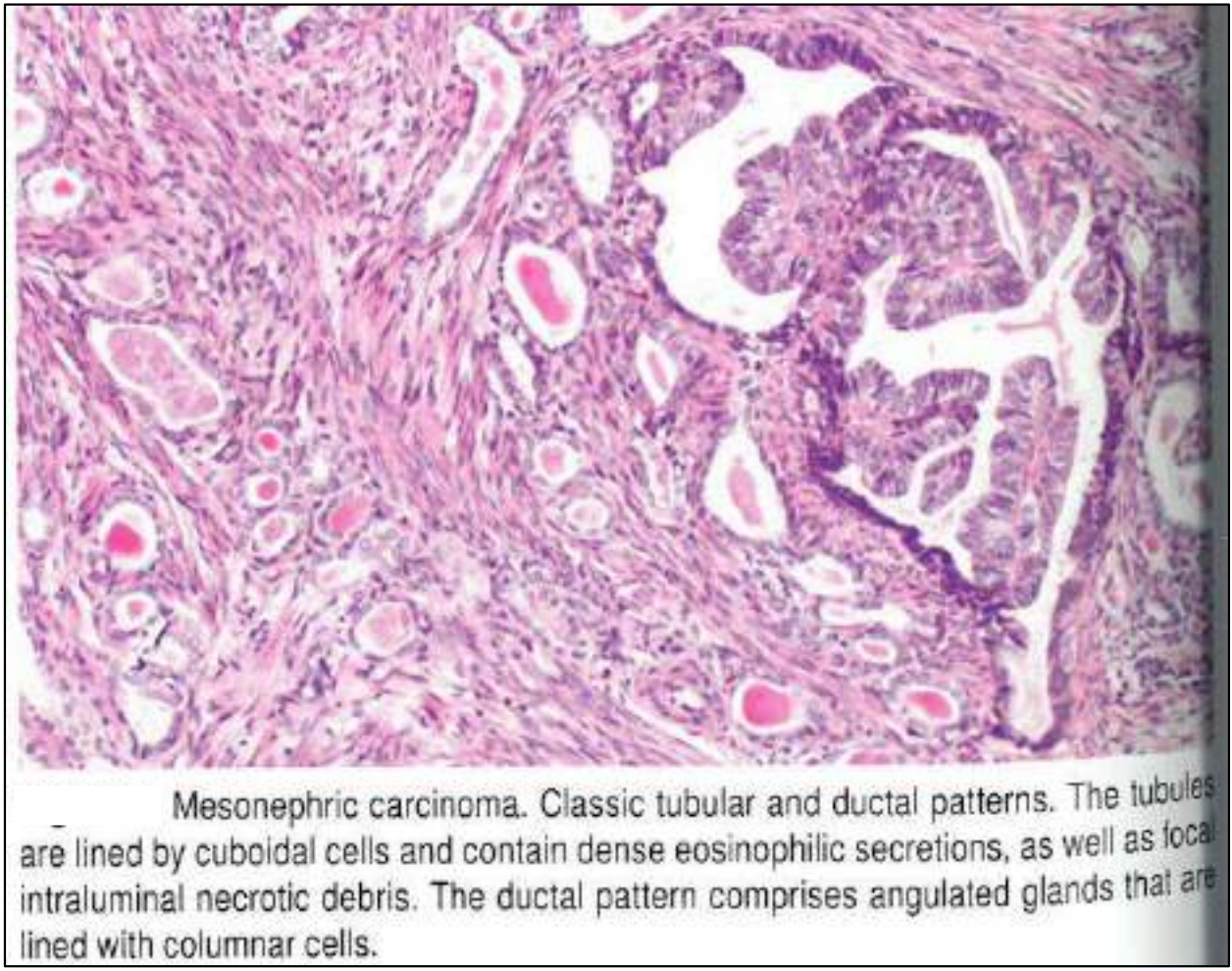
- Malignant glandular neoplasm composed of uniform, clear or eosinophilic, flat or cuboidal cells arranged in one or more patterns: tubulocystic, papillary, solid



Clear cell carcinoma of cervix, HPV-independent. **A** The tumour invades into the inner portion of the cervical wall. **B** Tubules and glands lined by a monolayer of cuboidal cells with uniform nuclei are present in myxohyaline stroma.

ADENOCARCINOMA, HPV INDEPENDENT, MESONEPHRIC TYPE

- Malignant neoplasm with mesonephric (Wolffian) differentiation
- Tumors are positive for GATA3, PAX8 and CD10
- Negative for ER and napsinA
- Can be positive for TTF1 rarely
- P53 is wildtype
- P16 is not diffuse and HPV is not detected
- Tumor recurrences can occur over long periods



Mesonephric carcinoma. Classic tubular and ductal patterns. The tubules are lined by cuboidal cells and contain dense eosinophilic secretions, as well as focal intraluminal necrotic debris. The ductal pattern comprises angulated glands that are lined with columnar cells.

STAGING

Procedure	Description
Resection	Includes radical trachelectomy, radical hysterectomy, or pelvic exenteration
Tumor Type	**Description**
Carcinoma	
Carcinosarcoma	

+FIGO Stage (2018 FIGO Cancer Report)#

 # Please note that this section includes the Corrigendum to Revised FIGO staging for carcinoma of the cervix uteri. See the appropriate reference in Note G.

___ I: Carcinoma is strictly confined to the cervix (extension to the uterine corpus should be disregarded)

 # For FIGO IA cancers, the depth of invasion should not be more than 5.0 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space invasion does not alter the staging.

___ IA: Invasive cancer identified only microscopically (All gross lesions even with superficial invasion are stage IB cancers) Invasion is limited to measured stromal invasion with a maximum depth of 5.0 mm#

The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to FIGO IA1.

___ IA1: Measured stromal invasion of 3.0 mm or less in depth##

___ IA2: Measured stromal invasion of more than 3.0 mm and not more than 5.0 mm

Lymphatic and / or vascular space invasion does not alter the staging.

___ IB: Invasive carcinoma with measured stromal invasion greater than 5.0 mm (greater than stage IA) and limited to the uterus###

___ IB1: Invasive carcinoma with measured stromal invasion greater than 5.0 mm and 2 cm or less in greatest dimension

___ IB2: Invasive carcinoma greater than 2 cm but 4 cm or less in greatest dimension

___ IB3: Invasive carcinoma greater than 4 cm in greatest dimension

___ II: Carcinoma extends beyond the uterus but has not extended onto the pelvic sidewall or to the lower third of vagina

___ IIA: Carcinoma involves the upper two-thirds of the vagina without parametrial invasion

___ IIA1: Invasive carcinoma 4 cm or less in greatest dimension

___ IIA2: Invasive carcinoma greater than 4 cm in greatest dimension

___ IIB: Parametrial involvement but not involving the pelvic sidewall

___ III: Carcinoma involves the lower third of the vagina and / or extends to the pelvic sidewall and / or causes hydronephrosis or nonfunctioning kidney and / or involves pelvic and / or para-aortic lymph nodes

___ IIIA: Involvement of the lower third of the vagina but no extension onto pelvic sidewall

___ IIIB: Extension onto the pelvic sidewall, and / or causing hydronephrosis / nonfunctioning kidney (unless known to be due to another cause)

___ IIIC: Involvement of pelvic and / or para-aortic lymph nodes (including micrometastases), irrespective of tumor size and extent (with r and p notations)####

___ IIIC1: Pelvic lymph node metastasis only

___ IIIC2: Para- aortic lymph node metastasis

Involvement of the uterine or pelvic serosa and / or fallopian tubes alone does not constitute FIGO Stage IV disease, but is considered M1 disease in the AJCC / UICC system.

___ IV: Carcinoma extends beyond the true pelvis or involves (biopsy proven) the mucosa of the bladder and / or rectum (bullous edema is not sufficient) or spread to distant organs#####

___ IVA: Spread to adjacent organs, i.e., tumor invading the mucosa of the bladder and / or rectum (biopsy proven) and / or extending beyond the true pelvis (bullous edema is not sufficient)

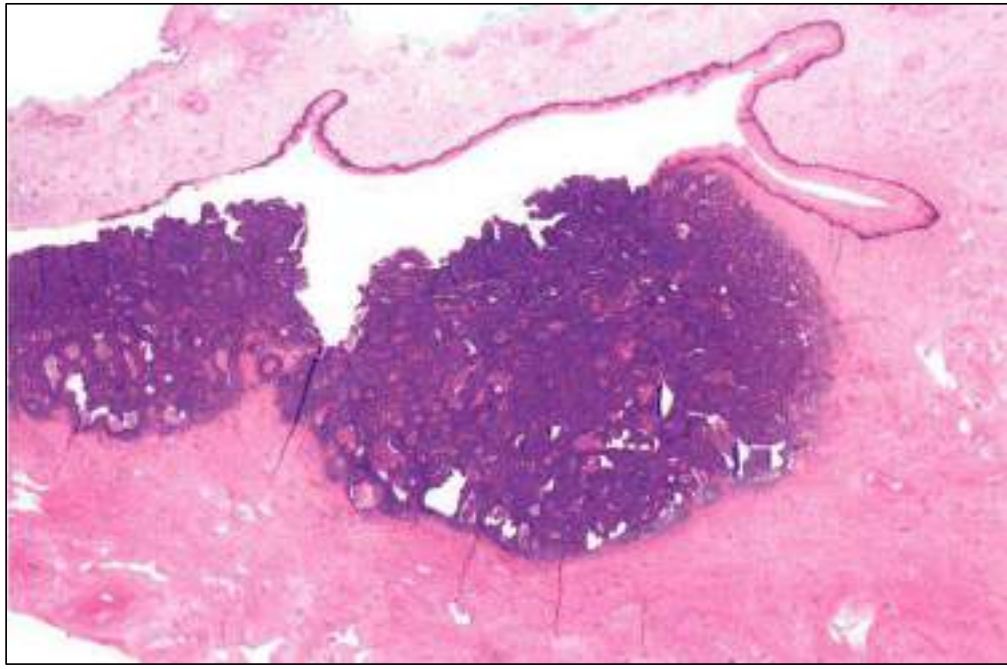
___ IVB: Spread to distant organs

TUMORS OF THE VAGINA

Tumours of the vagina
- Introduction
- Epithelial tumours
  - Benign squamous lesions
    - Condyloma acuminatum (see Ch. 10)
    - Squamous papilloma
    - Atrophy
    - Tubulosquamous polyp
  - Squamous cell tumours and precursors
    - Squamous intraepithelial lesions
    - Squamous cell carcinoma, HPV-associated
    - Squamous cell carcinoma, HPV-independent
    - Squamous cell carcinoma NOS
  - Benign glandular lesions
    - Villous adenoma
    - Müllerian papilloma
    - Vaginal adenosis
    - Endocervicosis
    - Cysts
  - Glandular tumours
    - Adenocarcinoma, HPV-associated
    - Endometrioid carcinoma
    - Clear cell carcinoma
    - Mucinous carcinoma, gastric type
    - Mucinous carcinoma, intestinal type
    - Mesonephric adenocarcinoma
    - Carcinosarcoma
  - Other epithelial tumours
    - Mixed tumour of the vagina
    - Adenocarcinoma of Skene gland origin
    - Adenosquamous carcinoma
    - Adenoid basal carcinoma
- Mixed epithelial and mesenchymal tumours
  - Adenosarcoma
- Miscellaneous tumours
  - Germ cell tumours

SQUAMOUS CELL CARCINOMA, HPV ASSOCIATED

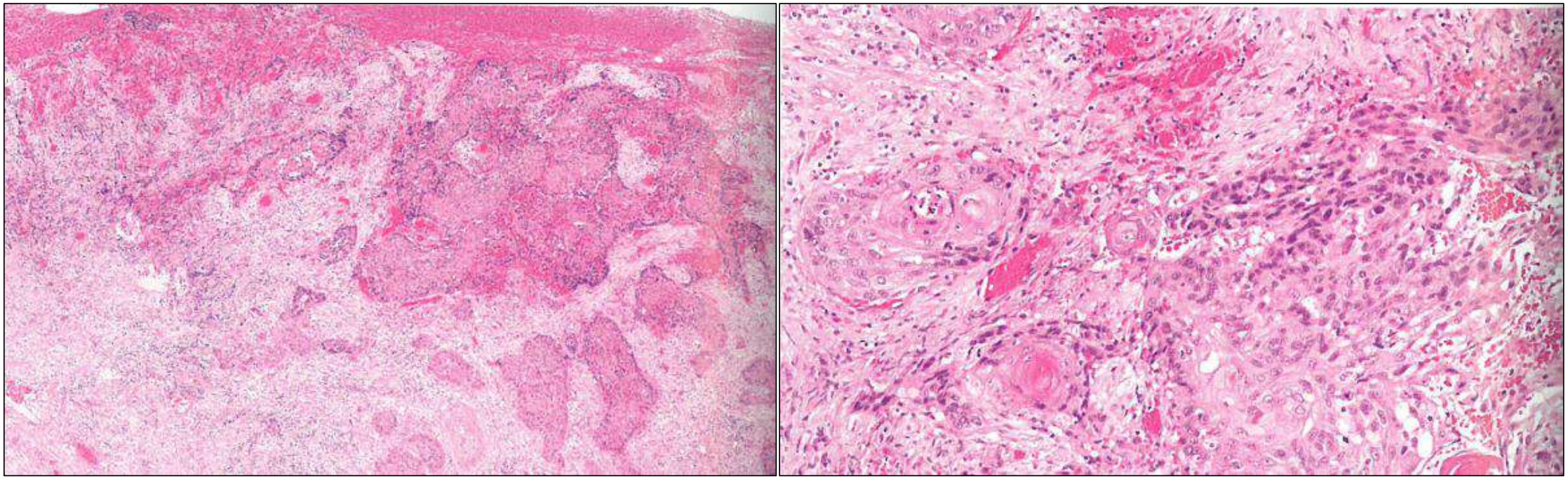
- Predominantly in the upper third of the vagina
- More common in the posterior wall
- HPV16 M.C. type
- Coincident cervical or vulval carcinoma, or a prior history of these tumors within 5 years must be excluded



- Histological patterns similar to those of cervical SCC: keratinizing, non-keratinizing, warty, basaloid and papillary
- Overexpression of p16 as an acceptable surrogate marker of HPV association

SQUAMOUS CELL CARCINOMA, HPV INDEPENDENT

- Histopathology similar to that of HPV-associated vaginal SCC
- Majority of cases keratinizing type
- P16 negativity and p53 immunopositivity common



STAGING

Procedure	Description
Resection	Includes vaginectomy
Tumor Type	**Description**
Carcinoma	Includes squamous cell carcinoma, adenocarcinoma and variants, carcinosarcoma, adenosarcoma, neuroendocrine carcinoma, mixed epithelial – neuroendocrine tumors, and germ cell tumors

+FIGO Stage (2018 FIGO Cancer Report)

___ I: Tumor of any size confined to the vagina

___ II: Tumor of any size that invades paravaginal tissue but not the pelvic sidewall

___ III: Tumor extends to the pelvic sidewall and / or involves the lower third of the vagina and / or causes hydronephrosis or nonfunctioning kidney or T1-T3 tumor involving pelvic or inguinal lymph nodes (N1) but not distant sites

___ IV: Tumor extends beyond the true pelvis or involves the bladder and / rectal mucosa (bullous edema alone does not constitute stage IV)

___ IVA: Tumor invades bladder and / or rectal mucosa and / or extends beyond the true pelvis, regardless of lymph node involvement (any N)

___ IVB: Tumor of any size with spread to distant sites (M1), with or without involvement of adjacent structures (any T) or lymph nodes (any N)

TUMORS OF THE VULVA

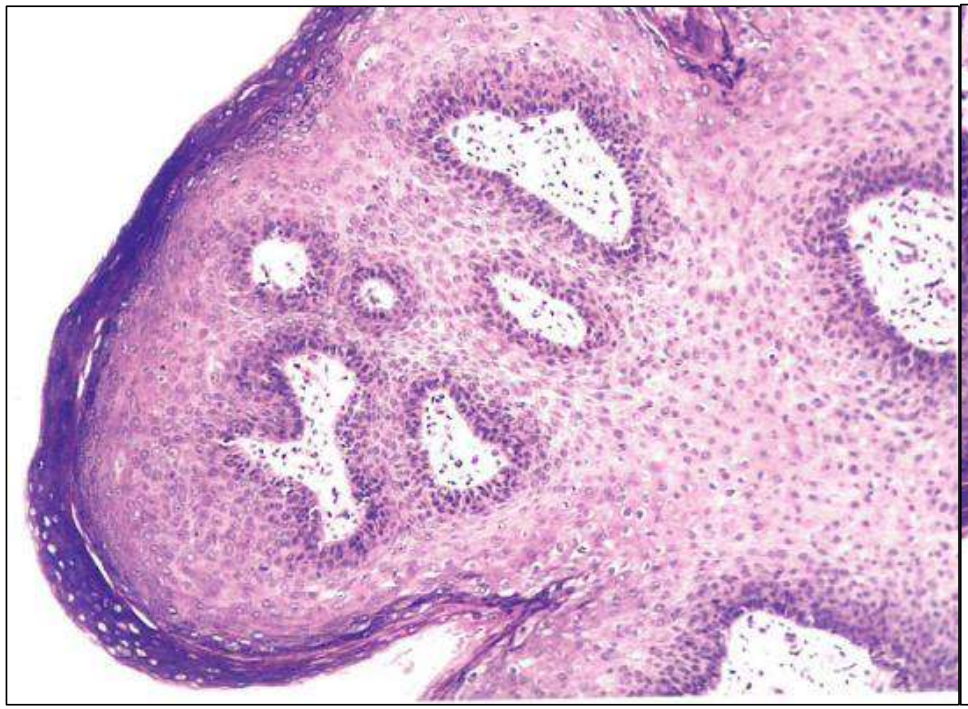
Tumours of the vulva
- Introduction
- Epithelial tumours
  - Benign squamous lesions
    - Seborrhoeic keratosis
    - Condyloma acuminatum
  - Squamous cell tumours and precursors
    - Squamous intraepithelial lesions, HPV-associated
    - Vulvar intraepithelial neoplasia, HPV-independent
    - Squamous cell carcinoma, HPV-associated
    - Squamous cell carcinoma, HPV-independent
    - Squamous cell carcinoma NOS
    - Basal cell carcinoma
  - Glandular tumours and cysts
    - Mammary-type glandular lesions
      - Papillary hidradenoma
      - Chondroid syringoma
      - Fibroadenoma
      - Phyllodes tumour
      - Adenocarcinoma of mammary gland type
    - Bartholin gland lesions
      - Bartholin gland cyst
      - Hyperplasia, adenoma, and adenomyoma
      - Bartholin gland carcinomas
    - Other cysts
  - Adenocarcinomas of other types
    - Paget disease
    - Carcinomas of sweat gland origin
    - Adenocarcinoma of intestinal type
- Germ cell tumours

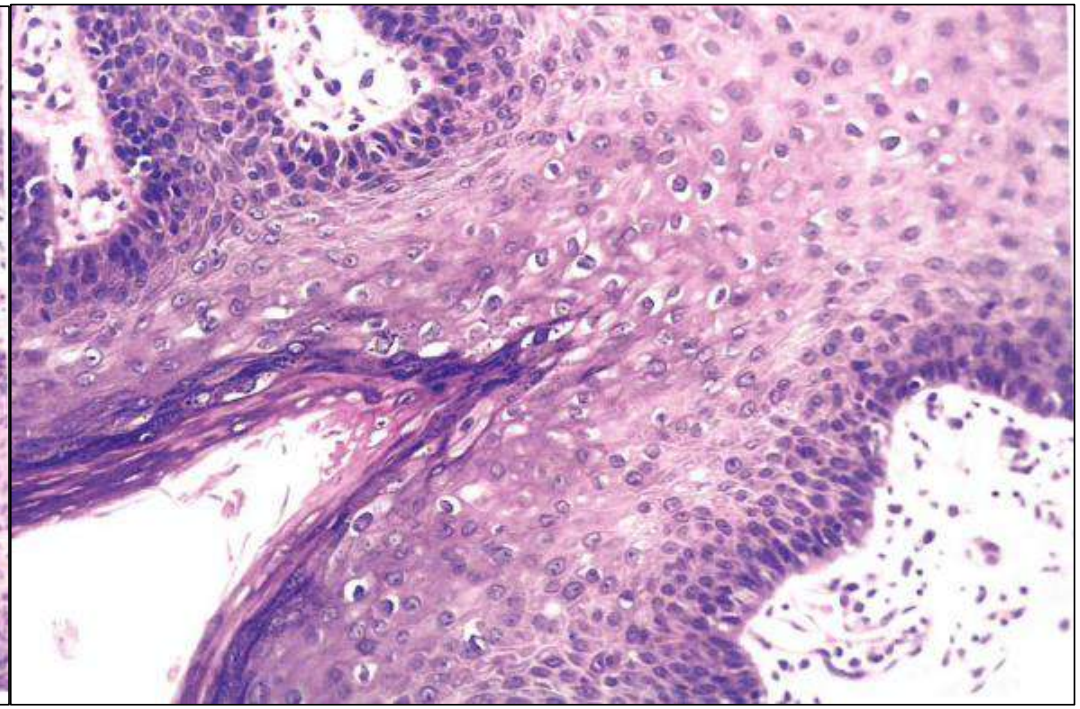
CONDYLOMA ACUMINATUM (GENITAL WART)

- Benign verrucous papillary lesion caused by HPV
- May occur singly, but more often found in clusters
- Young women
- Low-risk HPV types, M.C. HPV16 and HPV11

Essential and desirable diagnostic criteria

Essential: acanthosis and papillomatosis, with formation of papillary structures and thickened rete ridges; parakeratosis, hyperkeratosis, and variable degrees of koilocytic atypia.





GLANDULAR TUMOURS
MAMMARY TYPE GLANDULAR LESIONS
ADENOCARCINOMA OF MAMMARY GLAND TYPE

- Group of primary vulval tumours showing histopathological features identical to those of breast carcinomas
- Thought to arise from anogenital mammary-like glands
- M.C. location – labia majora

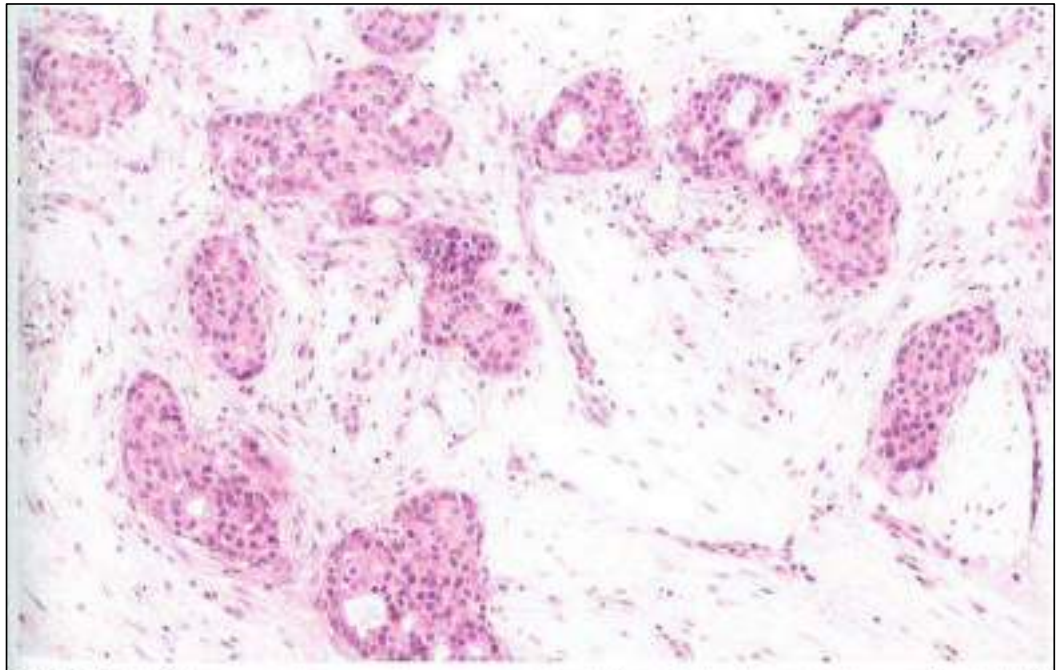
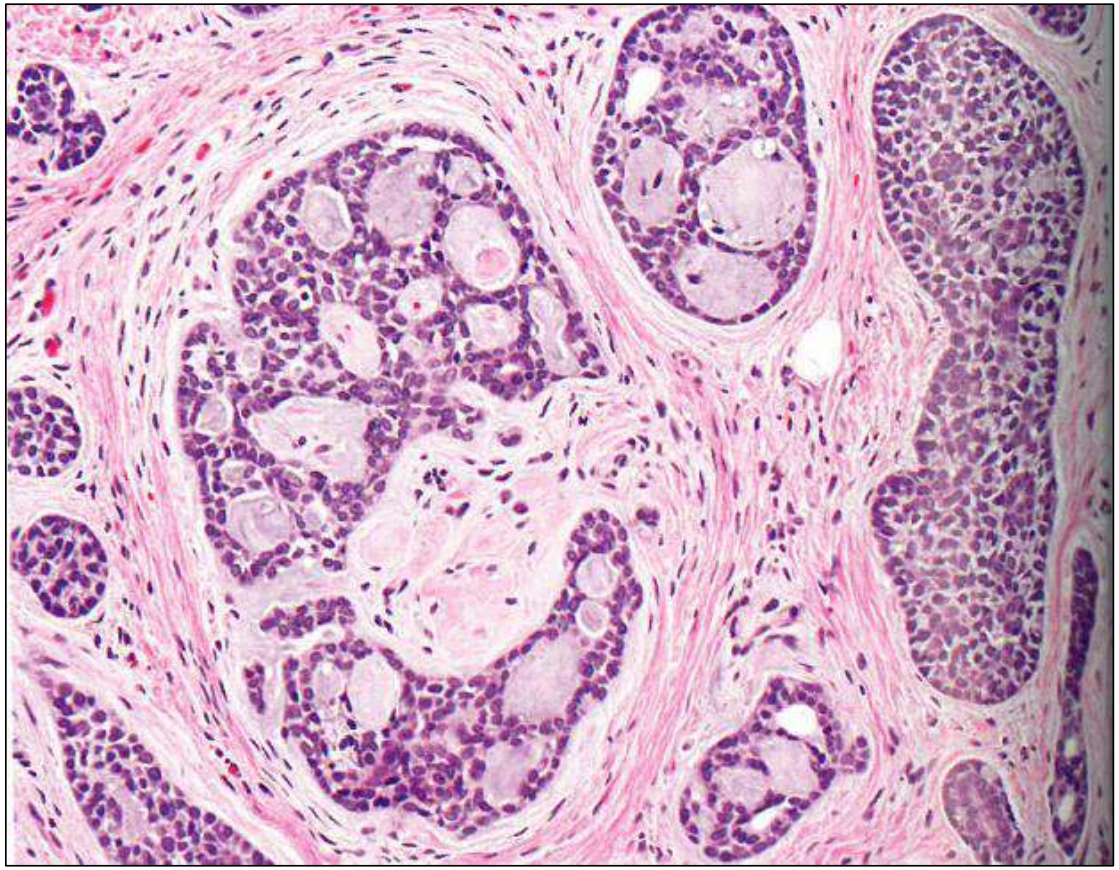


Fig. 10.20 Adenocarcinoma of mammary gland type. The tumour shows ductal differentiation, similar to breast carcinoma of invasive ductal type.

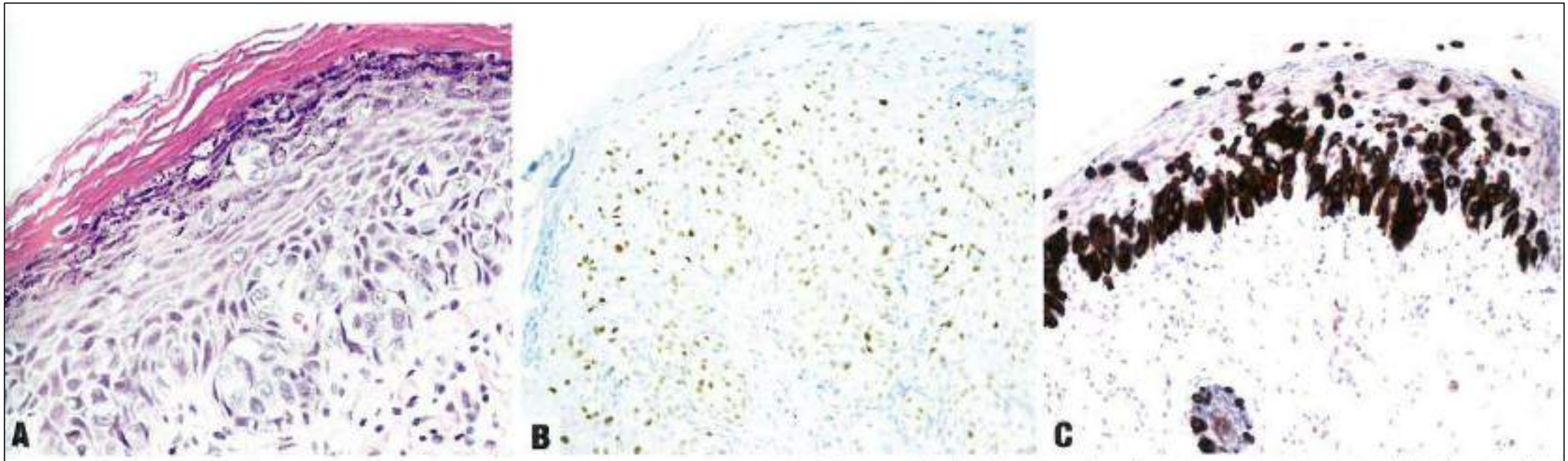
BARTHOLIN GLAND CARCINOMAS

Squamous cell carcinoma NOS
Adenoid cystic carcinoma
Carcinoma, poorly differentiated, NOS
Adenosquamous carcinoma
Neuroendocrine tumour NOS
Myoepithelial carcinoma
Epithelial–myoepithelial carcinoma
Squamous cell carcinoma, HPV-positive



PAGET DISEASE OF THE VULVA

- In-situ adenocarcinoma of the vulvar skin, with/without underlying invasive adenocarcinoma
- Secondary involvement of vulvar skin by carcinoma of rectal, bladder or cervical origin --- Secondary Paget disease



Vulvar Paget disease. **A** Clusters of atypical vacuolated cells are present in the basal layer, with individual cells and smaller clusters extending upwards into the superficial epidermis. **B** Diffuse nuclear staining for ER in Paget cells. **C** The cells of vulvar Paget disease strongly express CK7.

STAGING

Procedure	Description
Resection	Includes vulvectomy (with or without removal of other organs and tissues)
Tumor Type	**Description**
Carcinoma	Includes squamous cell carcinoma, adenocarcinoma and variants, carcinosarcoma, neuroendocrine carcinoma, and mixed epithelial – neuroendocrine tumors

+FIGO Stage (2018 FIGO Cancer Report)

___ I: Tumor confined to the vulva and / or peritoneum, without lymph node metastasis

[#] *The LAST definition of superficial invasive squamous cell carcinoma (SISCCA) conforms to AJCC pT1a/FIGO IA.*

___ IA: Tumor less than or equal to 2 cm in size, confined to the vulva and / or perineum and with stromal invasion less than or equal to 1.0 mm, no nodal metastasis[#]

___ IB: Tumor greater than 2 cm in size or with stromal invasion greater than 1.0 mm, confined to the vulva and / or perineum

___ II: Tumor of any size with extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) without lymph node metastasis

___ III: Tumor of any size with or without extension to adjacent perineal structures (lower third of urethra, lower third of vagina, anus) with metastasis to inguinofemoral lymph nodes

___ IIIA: With 1 lymph node metastasis (greater than or equal to 5 mm)

___ IIIA: With 1 to 2 lymph node metastasis(es) (less than 5 mm)

___ IIIB: With 2 or more lymph node metastases (greater than or equal to 5 mm)

___ IIIB: With 3 or more lymph node metastases (less than 5 mm)

___ IIIC: With positive nodes with extranodal extension

___ IV: Tumor invades other regional (upper two-thirds urethra, upper two-thirds vagina), or distant structures

___ IVA: Tumor invades any of the following: upper urethral and / or vaginal mucosa, bladder mucosa, rectal mucosa, or fixed to pelvic bone, or fixed or ulcerated inguinofemoral lymph nodes

___ IVB: Any distant metastasis including pelvic lymph nodes

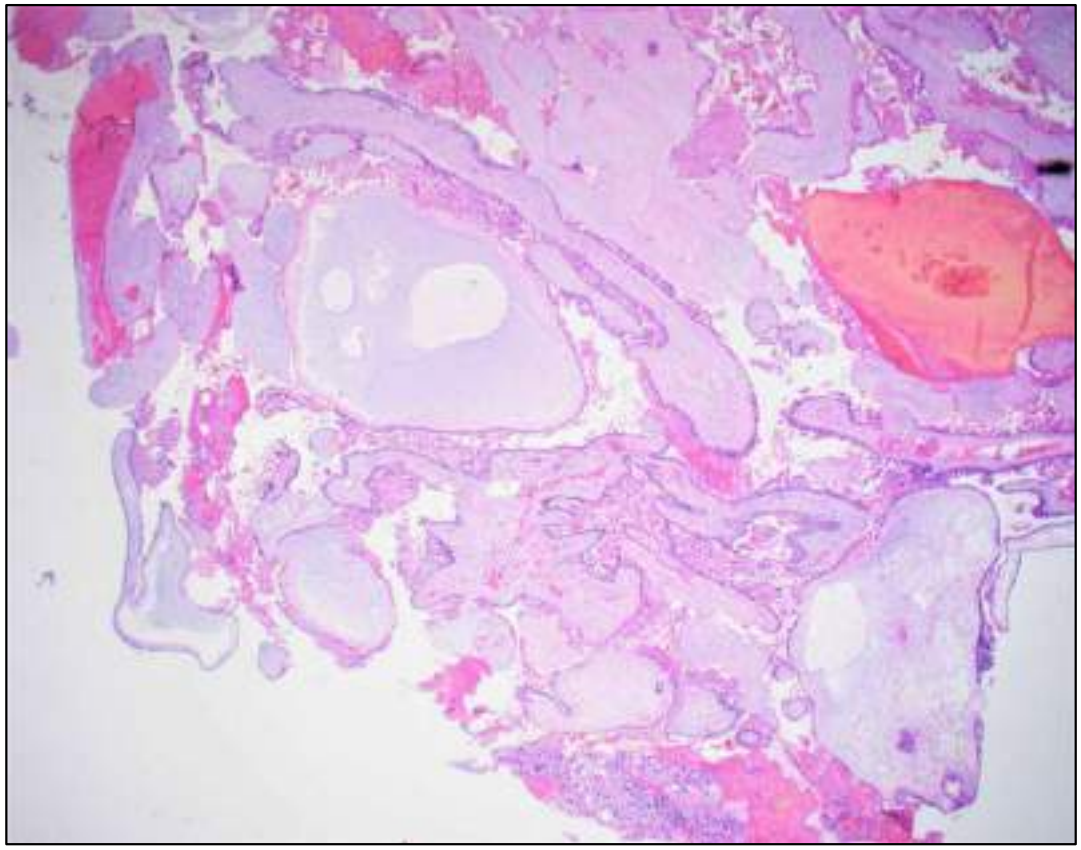
GESTATIONAL TROPHOBLASTIC DISEASE

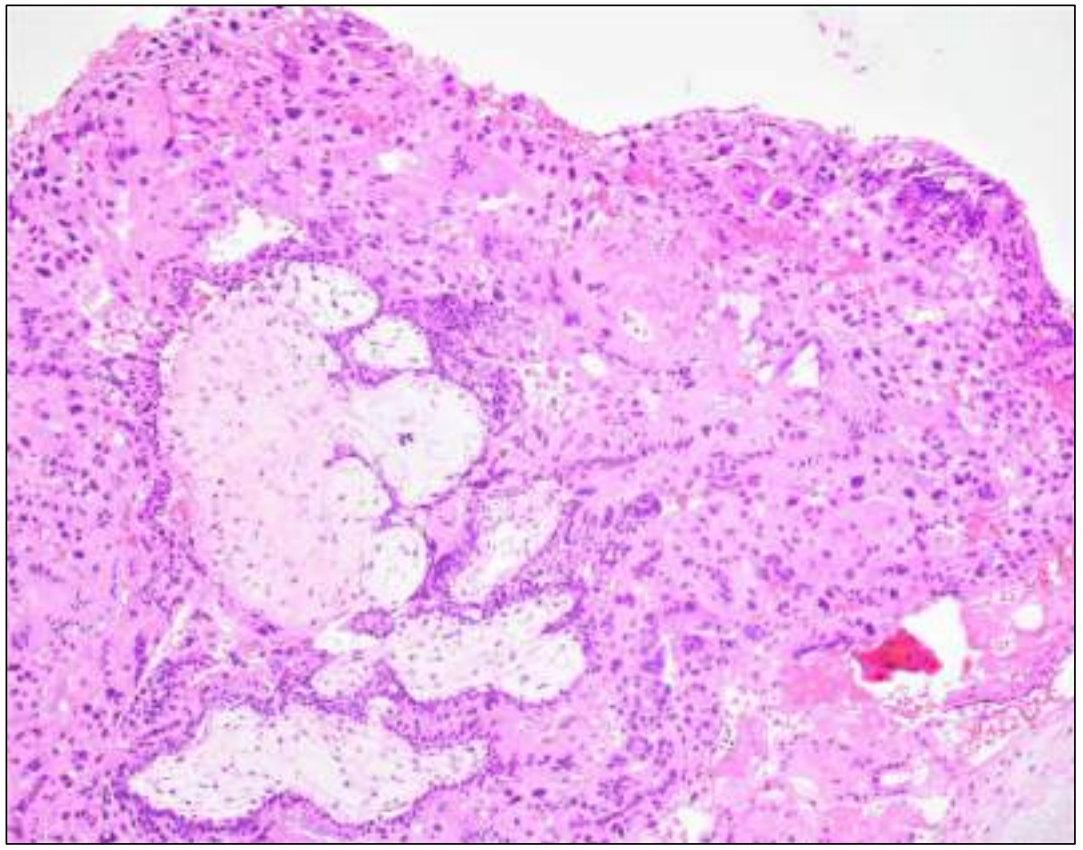
Gestational trophoblastic disease

- Introduction
- Tumour-like lesions
  - Non-neoplastic lesions
    - Exaggerated placental site reaction
    - Placental site nodule and plaque
- Abnormal (non-molar) villous lesions
- Molar pregnancies
  - Partial hydatidiform mole
  - Complete hydatidiform mole
  - Invasive and metastatic hydatidiform moles
- Gestational trophoblastic neoplasms
  - Epithelioid trophoblastic tumour
  - Placental site trophoblastic tumour
  - Gestational choriocarcinoma
  - Mixed trophoblastic tumour

HYDATIDIFORM MOLE

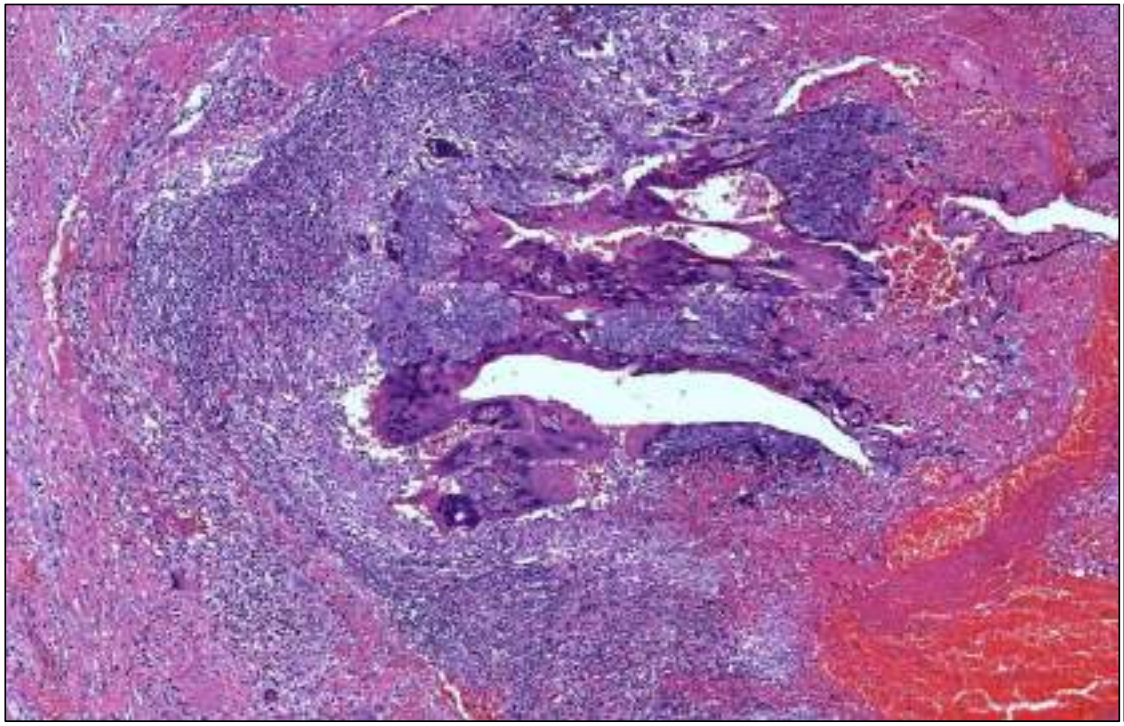
- characterized by diffuse hydropic enlargement and trophoblastic proliferation of the chorionic villi without embryonic development

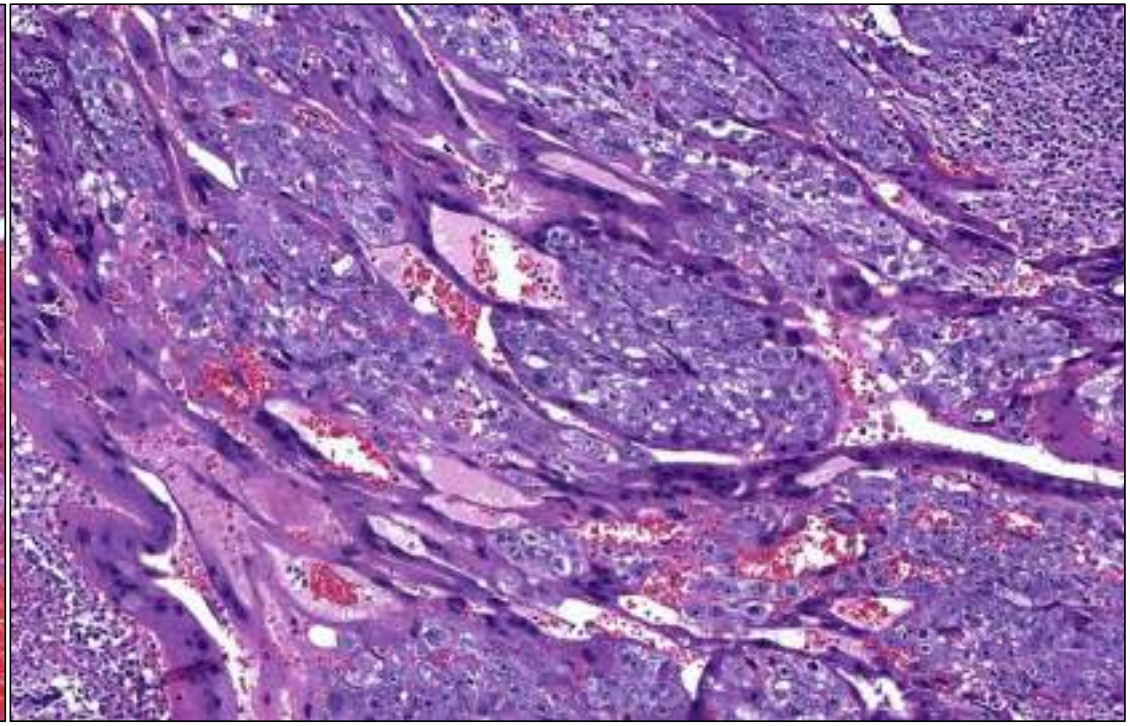




GESTATIONAL CHORIOCARCINOMA

- Aggressive form of gestational trophoblastic neoplasia composed of syncytiotrophoblast, cytotrophoblast and intermediate trophoblast
- Absence of chorionic villi, infiltrative and destructive pattern
- High mitotic activity





STAGING

Procedure	Description
Resection	Includes hysterectomy with or without oophorectomy and/or salpingectomy
Tumor Type	**Description**
Malignant gestational trophoblastic tumor	Includes invasive hydatidiform mole, choriocarcinoma, placental site trophoblastic tumor, epithelioid trophoblastic tumor

+FIGO Stage (2018 FIGO Cancer Report)

___ I: Disease confined to the uterus

___ II: Gestational trophoblastic tumor extends outside of the uterus, but limited to the genital structures (adnexa, vagina, broad ligament)

___ III: Gestational trophoblastic tumor extends to the lungs, with or without known genital tract involvement

___ IV: All other metastatic sites

THANK YOU