OVARIAN CANCER

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Ovarian cancer

- Three theories as to origins:
- (1) Extra-uterine Müllerian epithelium of the fallopian tube as well as from endometriosis
- Coelomic epithelium and Müllerian epithelium arise from proximally situated epithelial anlage near the mesonephros.
- Metaplasia may be the precursor lesion to primary peritoneal carcinomas.
- (2) Germ cells, which migrate to the ovary from the yolk sac, and are pluripotent

Ovarian cancer

- (3) Stromal cells, including the sex cords, which are forerunners of the endocrine apparatus of the postnatal ovary

Ovarian cancer

- Risk increases with age and positive family history (first degree relatives).
- Hereditary breast (BRCA1mutation) and ovarian cancer syndromes (BRCA2 mutation) as well as hereditary nonpolyposis cancer syndrome (Lynch, MLH mutation) pose high risk.
- Bilaterality common in malignant serous carcinomas, endometrioid carcinomas, and clear cell carcinomas.

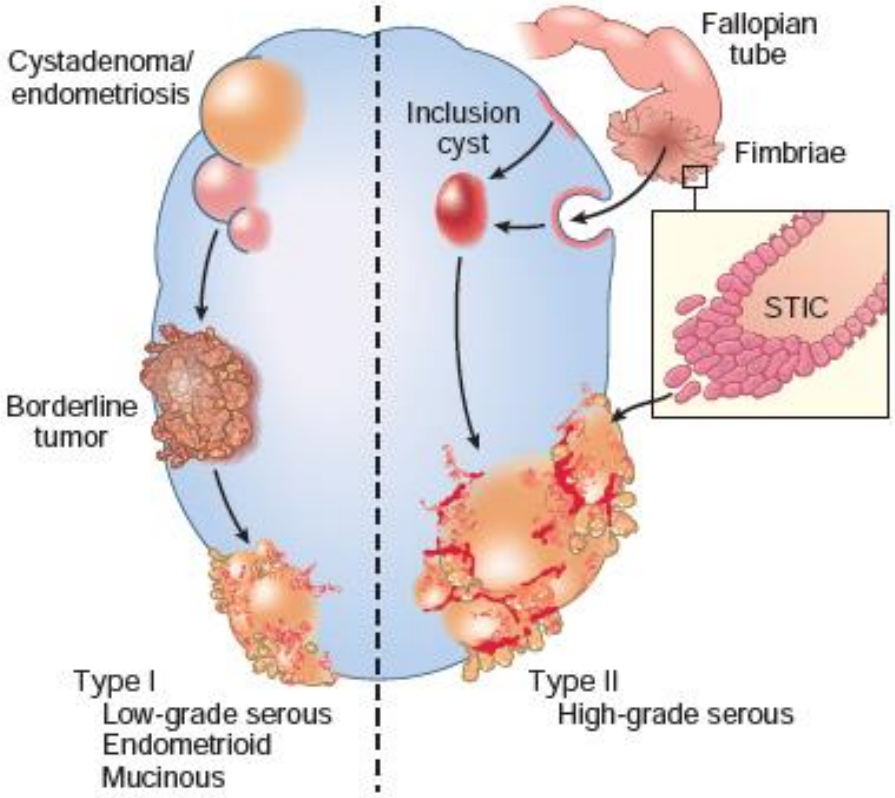
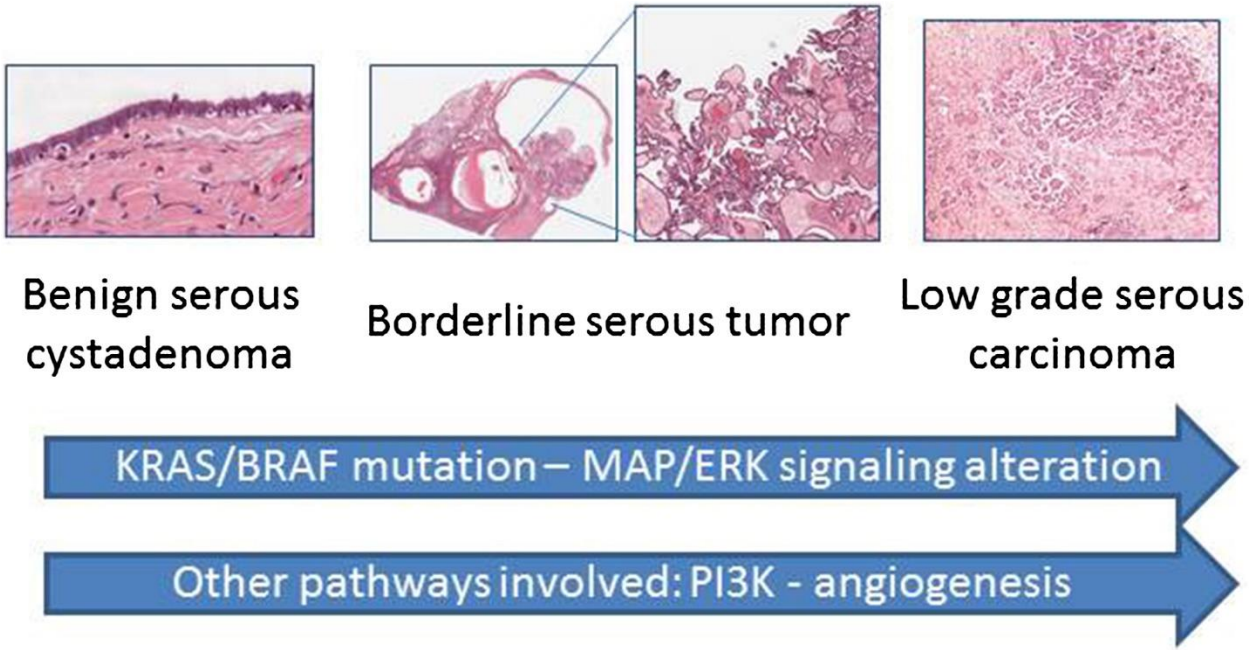


Figure 22-30 Schematic diagram of the pathogenesis of ovarian epithelial tumors. Type I tumors progress from benign tumors through borderline tumors that may give rise to a low-grade carcinoma. These include low-grade serous, endometrioid and mucinous carcinomas. Type II tumors arise from inclusions cysts/fallopian tube epithelium via intraepithelial precursors that are often not identified. They demonstrate high-grade features and are most commonly of serous histology. STIC, serous tubal intraepithelial carcinoma.



https://ascopubs.org/doi/full/10.1200/EDBK_158675

Ovarian cancer

- CA125 is not a good screening tool.
- Produced in a number of tissues
- Predictive value is low
- Best used in conjunction with HE4 (human epidydimis protein) as HE4 not generally expressed by benign conditions
- Used for triage in women with pelvic mass
- Negative predictive value >99%
- May eliminate need for second surgery and debulking by separating high and low risk disease
- CA125 is surrogate marker for epithelial tumor response.

Classification of Tumours of the Ovary
Epithelial tumours (ET)
Sex cord–stromal tumours (SCST)
Germ cell tumours (GCT)
Monodermal teratoma and somatic type tumours arising from dermoid cyst
Germ cell–sex cord stromal tumours
Mesenchymal and mixed epithelial and mesenchymal tumours
Other rare tumours, tumour-like conditions
Lymphoid and myeloid tumours
Secondary tumours

WHO, 2014

Carcinomas, accounting for over 80% of cancers, peak at the 6th decade; SCSTs peak in the perimenopausal period; GCTs peak in the first three decades.

Table 22-5 WHO Classification of Ovarian Neoplasms

Surface Epithelial-Stromal Tumors
Serous tumors
Benign (cystadenoma, cystadenofibroma)
Borderline (serous borderline tumor)
Malignant (low- and high-grade serous adenocarcinoma)
Mucinous tumors, endocervical-like and intestinal type
Benign (cystadenoma, cystadenofibroma)
Borderline (mucinous borderline tumor)
Malignant (mucinous adenocarcinoma)
Endometrioid tumors
Benign (cystadenoma, cystadenofibroma)
Borderline (endometrioid borderline tumor)
Malignant (endometrioid adenocarcinoma)
Clear cell tumors
Benign
Borderline
Malignant (clear cell adenocarcinoma)
Transitional cell tumors
Benign Brenner tumor
Brenner tumor of borderline malignancy
Malignant Brenner tumor
Epithelial-stromal
Adenosarcoma
Malignant mixed müllerian tumor
Sex Cord-Stromal Tumors
Granulosa tumors
Fibromas
Fibrothecomas
Thecomas
Sertoli-Leydig cell tumors
Steroid (lipid) cell tumors
Germ Cell Tumors
Teratoma
Immature
Mature
Solid
Cystic (dermoid cyst)
Monodermal (e.g., struma ovarii, carcinoid)
Dysgerminoma
Yolk sac tumor
Mixed germ cell tumors
Metastatic Cancer From Non-ovarian Primary
Colonic, appendiceal
Gastric
Pancreaticobiliary
Breast

Table 22-6 Frequency of Major Ovarian Tumors

Type	Percentage of Malignant Ovarian Tumors	Percentage That Are Bilateral
Serous		
Benign (60%)		25
Borderline (15%)	47	30
Malignant (25%)		65
Mucinous		
Benign (80%)		5
Borderline (10%)	3	10
Malignant (10%)		<5
Endometrioid carcinoma	20	40
Undifferentiated carcinoma	10	—
Clear cell carcinoma	6	40
Granulosa cell tumor	5	5
Teratoma		15
Benign (96%)	1	Rare
Malignant (4%)		
Metastatic	5	>50
Others	3	—

Ovarian cancer

- Six distinct subtypes have been identified with molecular screening:
- Low malignant potential serous carcinoma (C3 subtype)
- Low expression of proliferation markers (MKI67, TOP2A, CCNB1, CDC2, KIF11)
- Overexpression of MAPK pathway genes (DUSP4, DUSP6, SERPIN5A, MAP3K5, SPRY2), likely associated with mutations in MAPK pathway members KRAS and BRAF
- Overexpression of axonemal dyneins (associated with enrichment of ciliated cells)

Ovarian cancer

- Low malignant potential endometrioid carcinoma (C6 subtype)
- Low expression of proliferation markers (MKI67, TOP2A, CCNB1, CDC2, KIF11)
- Overexpression of transcriptional targets of the β-catenin/LEF/TCF complex

Ovarian cancer

- High stroma (C1 subtype)
- Low numbers of intratumoral CD3+ T-cell numbers
- Early relapse
- An enhanced stromal response has a significant negative effect on tumor behavior and clinical outcome across many cancer types

Ovarian cancer

- Mesenchymal (C5 subtype)
- Characterized by overexpression of genes associated with WNT signaling, developmental transcription factors in combination with reduced membranous E-cadherin staining is strongly suggestive of epithelial-mesenchymal transition (EMT).
- Overexpress homeobox genes.
- Low expression of CA-125 and MUC1 cancer markers
- Low numbers of intratumoral CD3+ T-cells

Ovarian cancer

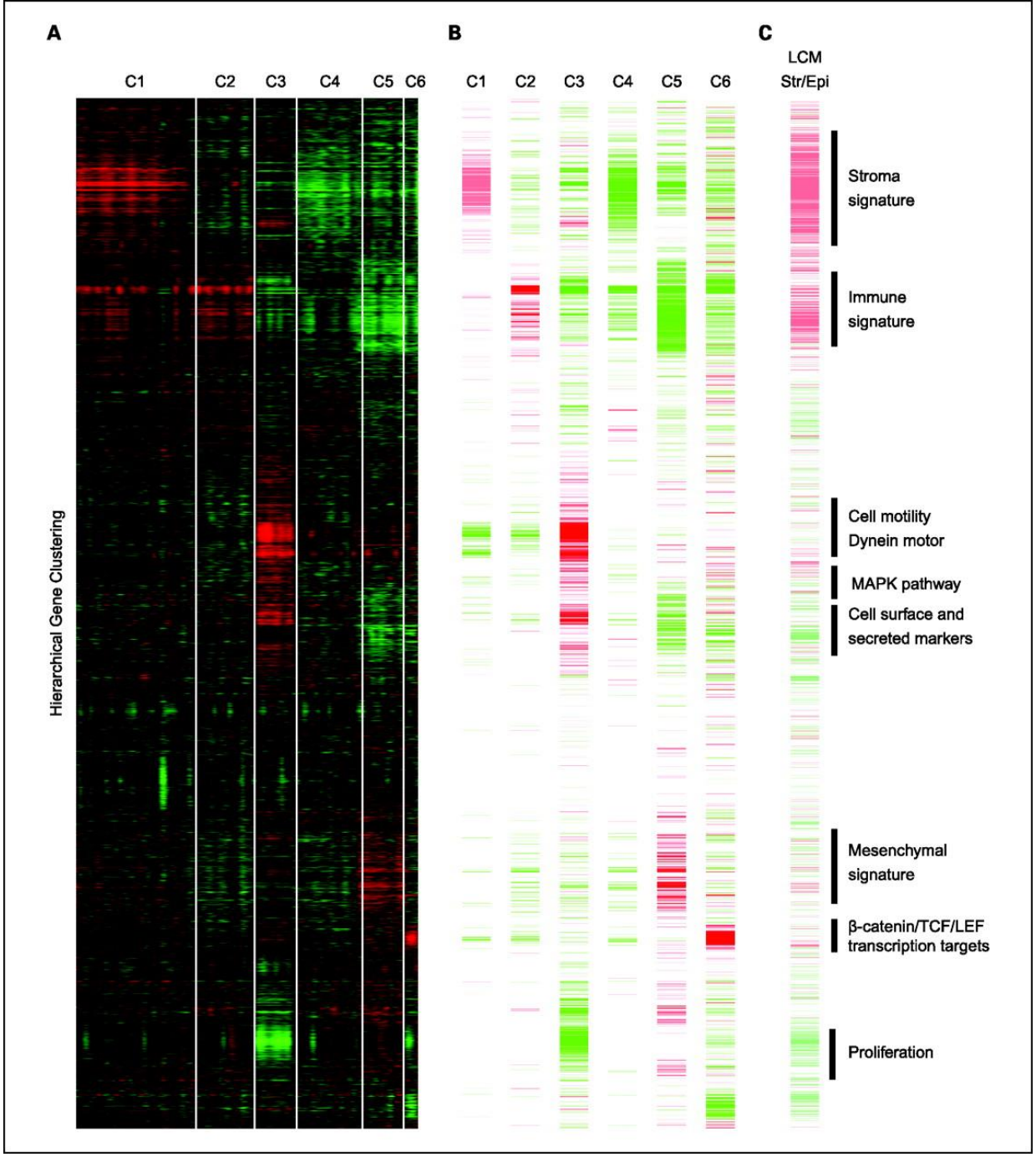
- Immune (C2 subtype)
- Increased numbers of CD3+ intratumoral T-cells
- Differentiated (C4 subtype)
- Little stromal reaction

Ovarian cancer

- High-grade endometrioid and serous tumors are molecularly similar
- The sine qua non of high-grade serous cancers is the dysregulation of p53 and associated effects on DNA repair, leading to genomic instability and the characteristic of high copy number variability. These tumors are also characterized by expression of WT-1, ERα, and PAX8.
- Invasive serous cancers are composed exclusively of the secretory cell, not ciliated cell, type

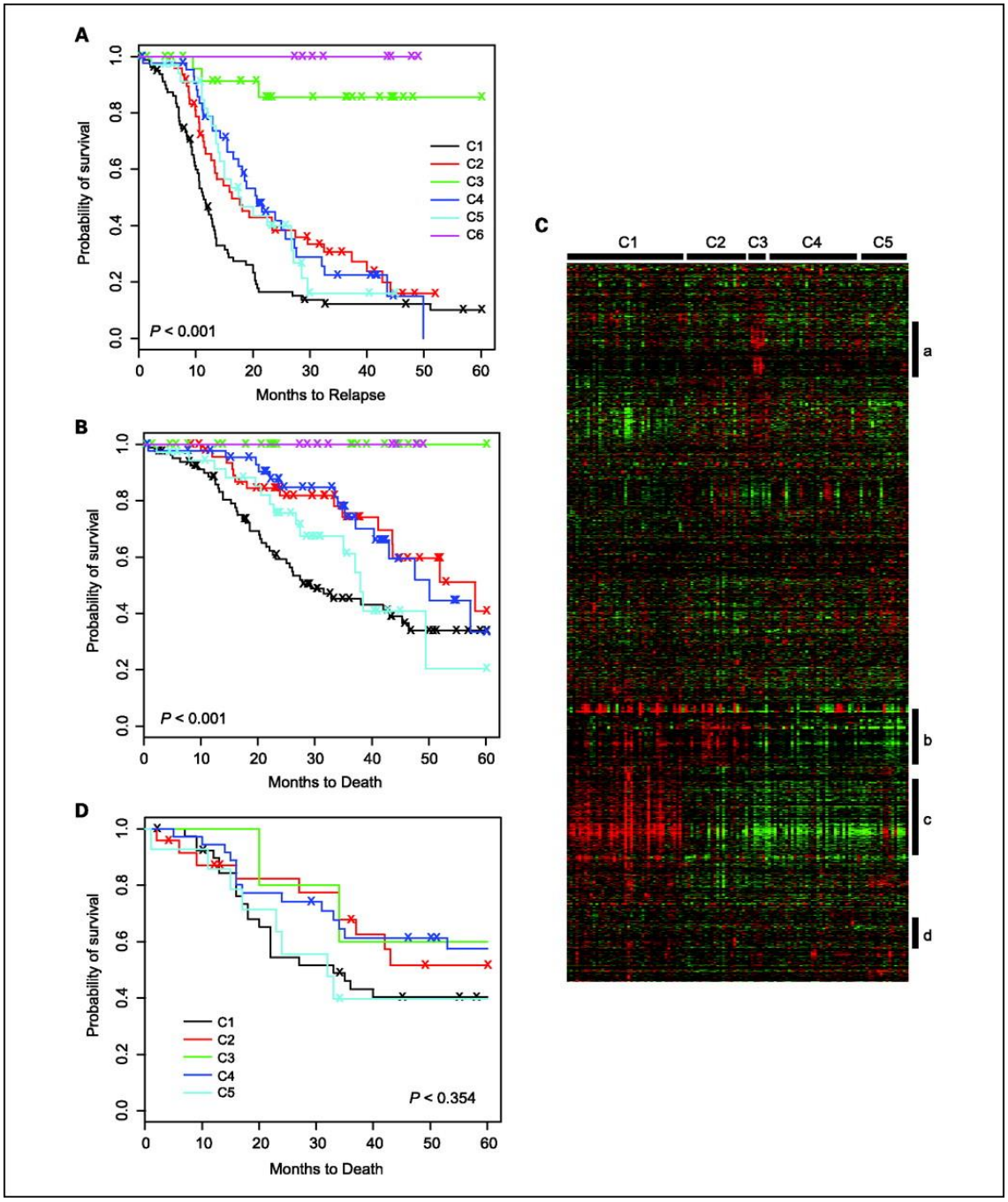
Ovarian cancer

- The most validated prognostic and predictive biomarker within high-grade serous cancers is germline deleterious mutation in either BRCA1 or BRCA2 (noted in 14%).
- Loss of function of these genes requires loss normal p53 regulation for cellular viability
- 33% have either germline or biallelic mutations
- Germline BRCA mutation is prognostic of generally good outcomes, and is predictive of platinum sensitivity and PARP inhibitor sensitivity



Red, overexpressed in stroma; green, overexpressed in the tumor.

https://clincancerres.aacrjournals.org/content/14/16/5198.long



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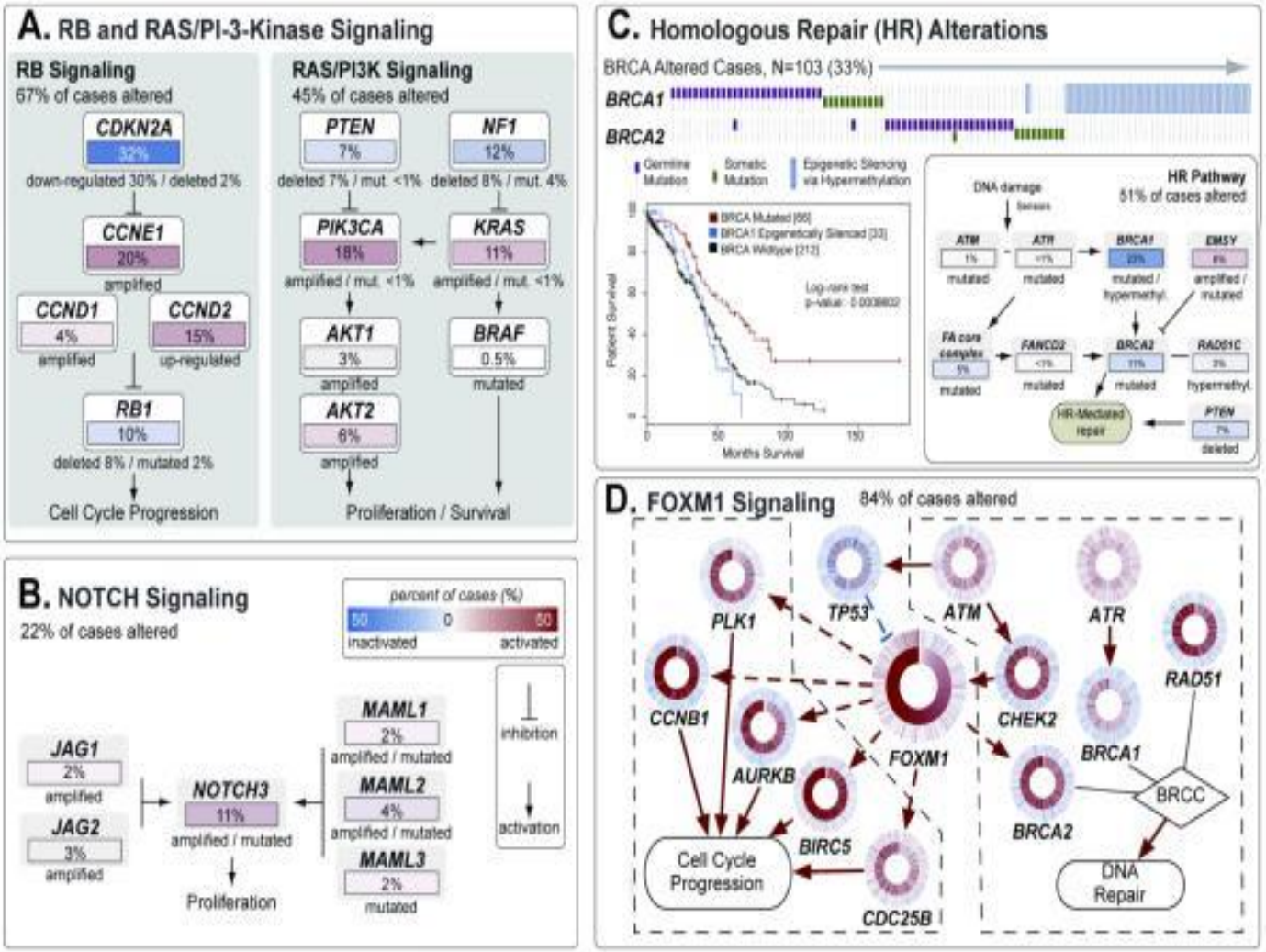
Ovarian cancer

- Disruption of the G1/S cell-cycle transition by CCNE1 amplification (20%), by overexpression or amplification of CCND1 or CCND2 (19%), or loss of regulation of the G1/S checkpoint by loss of function of pRB (10%) will account for nearly one-third to one-half of cases.
- Disruption of normal G1/S transitions also leads to poor DNA repair, also contributing to the classic genomic instability phenotype of ovarian cancers that overexpress Cyclin E.



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3163504/

Ovarian cancer

- More than 90% of ovarian tumors have an epithelial origin:
- High risk:
- Serous (high grade), 70% of ovarian tumors;
- Clear cell, 10% of ovarian tumors;
- Malignant Brenner tumor (transitional cell)
- Intermediate risk:
- Mucinous, 4% of ovarian tumors
- Low risk**:**
- Endometrioid, 10% of ovarian tumors
- Serous (low grade), 3% of ovarian tumors
- Transitional cell (low grade)

Site of origin (+ immunohistochemical markers) and histological type (+ *genetic association*) of ovarian carcinomas

Fallopian tube (PAX8, WT1)
High-grade serous (*p53, BRCA1, BRCA2*)

Endosalpingiosis, serous borderline tumours (PAX8, WT1)
Low-grade serous (*BRAF, Kras, PIK3CA, MSI*)

Endometriosis (PAX8, ER, PR)
Clear cell (*ARID1a*)
Endometrioid (*ARID1a, β-catenin, PTEN, MSI*)

Not known, tubal peritoneal-junction? (-)
Mucinous (*Kras, HER2*)
Brenner

Stage I: Tumour confined to ovaries or Fallopian tube(s)

IA: Tumour limited to 1 ovary (capsule intact) or Fallopian tube; no tumour on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings

IB: Tumour limited to both ovaries (capsules intact) or Fallopian tubes; no tumour on ovarian or Fallopian tube surface; no malignant cells in the ascites or peritoneal washings

IC: Tumour limited to 1 or both ovaries or Fallopian tubes, with any of the following:

- **IC1:** Surgical spill
- **IC2:** Capsule ruptured before surgery or tumour on ovarian or Fallopian tube surface
- **IC3:** Malignant cells in the ascites or peritoneal washings

Stage II: Tumour involves 1 or both ovaries or Fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer

IIA: Extension and/or implants on uterus and/or Fallopian tubes and/or ovaries

IIB: Extension to other pelvic intraperitoneal tissues

FIGO, 2013

Stage III: Tumour involves 1 or both ovaries or Fallopian tubes, or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes

IIIA1: Positive retroperitoneal lymph nodes only
- IIIA1(i) Metastasis up to 10 mm
- IIIA1(ii) Metastasis more than 10 mm

IIIA2: Microscopic extrapelvic peritoneal involvement with or without positive lymph nodes

IIIB: Macroscopic extrapelvic peritoneal metastasis up to 2 cm, with or without metastasis to the retroperitoneal lymph nodes

IIIC: Extrapelvic peritoneal metastasis more than 2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes

Stage IV: Distant metastasis excluding peritoneal metastases

IVA: Pleural effusion with positive cytology

IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

FIGO, 2013

Serous carcinoma

- The histologic distinction is made based on the degree of nuclear atypia:
- Low-grade (well-differentiated) carcinoma
- Low-grade carcinomas may arise in association with serous borderline tumors
- Can develop from inclusion cysts
- Low-grade tumors arising in serous borderline tumors have mutations in the KRAS, BRAF, or ERBB2 oncogenes
- Usually have wild type TP53 genes

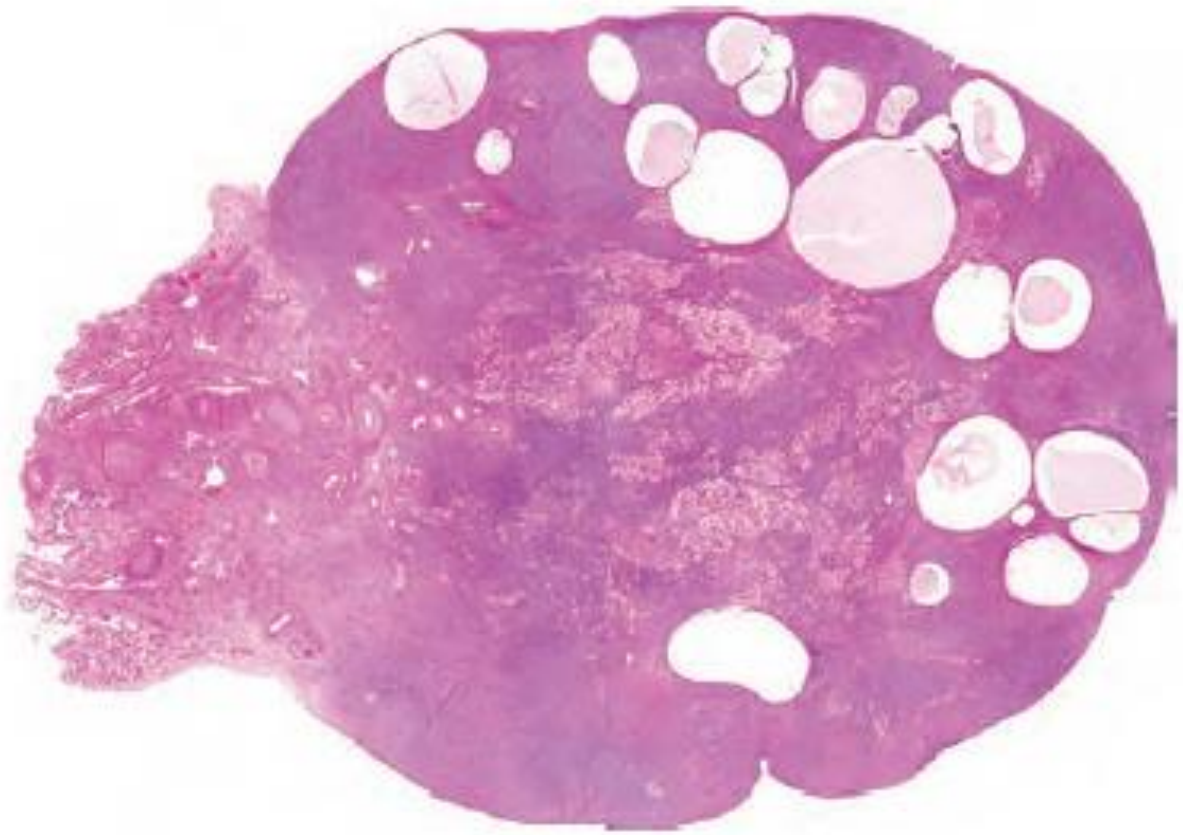
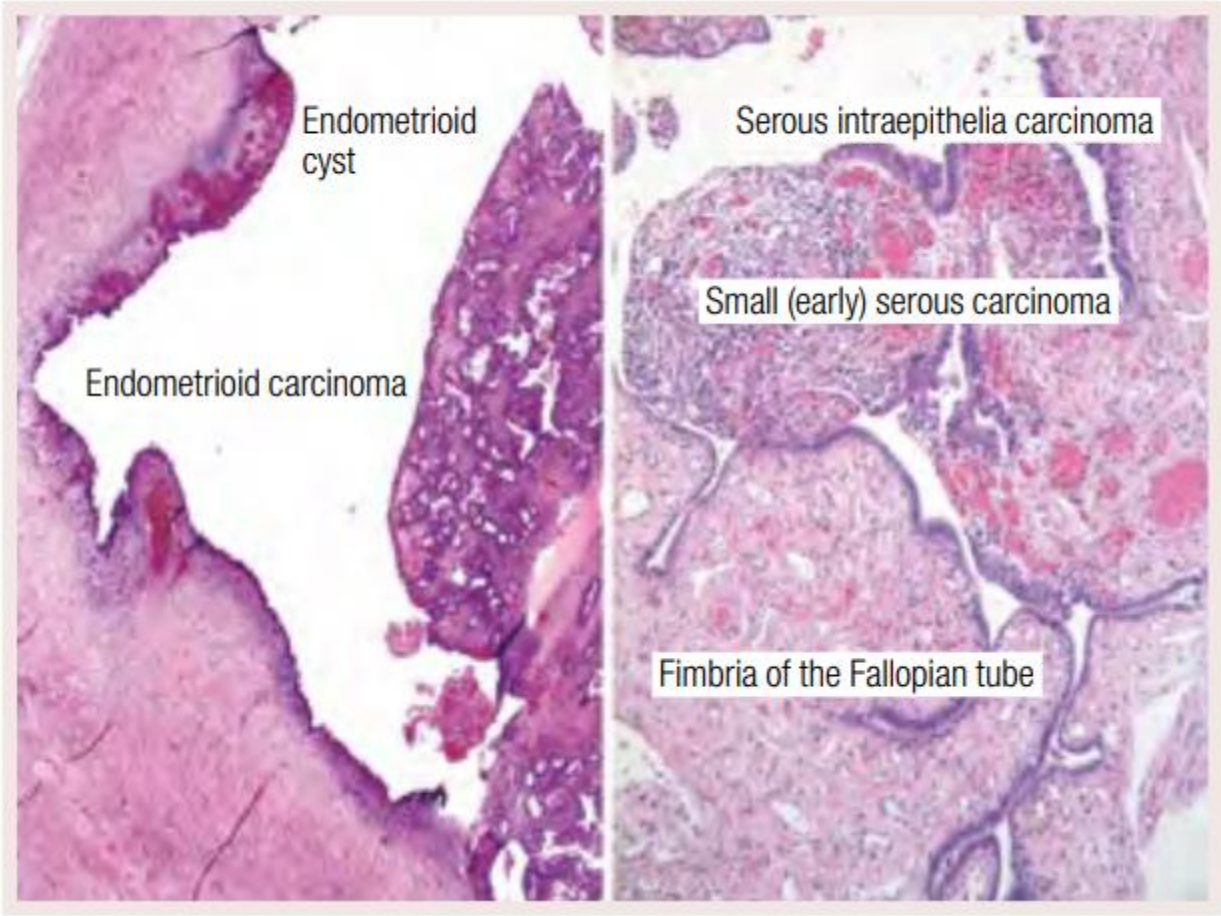


Figure 22-31 Cortical inclusion cysts of the ovary.


Endometrioid cyst
Endometrioid carcinoma
Serous intraepithelia carcinoma
Small (early) serous carcinoma
Fimbria of the Fallopian tube

Serous carcinoma

- Present as either a multicystic lesion in which papillary epithelium is contained within a few fibrous walled cysts (intracystic) or as a mass projecting from the ovarian surface.
- Benign tumors typically have a smooth glistening cyst wall with no epithelial thickening or with small papillary projections.
- Borderline tumors contain an increased number of papillary projections

Serous carcinoma

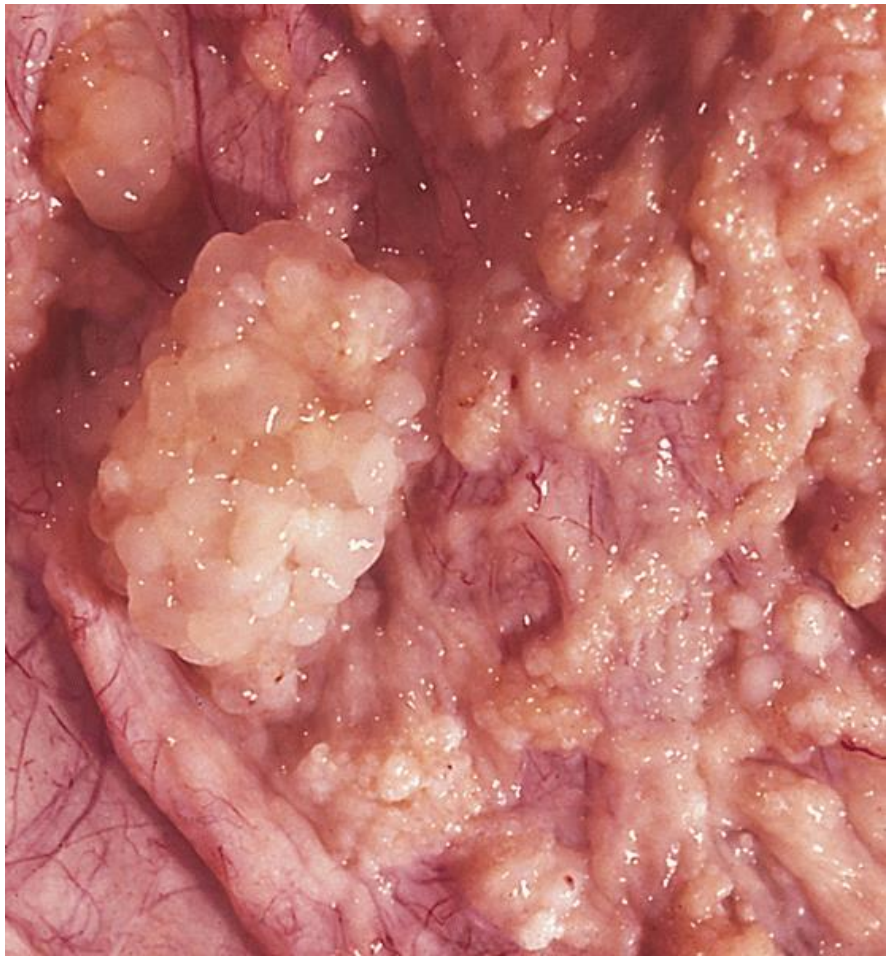
- High-grade (moderately to poorly differentiated) carcinoma.
- High-grade carcinomas arise from in situ lesions in the fallopian tube fimbriae (in BRCA patients) or from serous inclusion cysts within the ovary (serous tubal intraepithelial carcinoma, STIC)
- Cortical cysts arise from implantation of detached fallopian tube epithelium at sites where ovulation has disrupted the surface of the ovary
- High-grade tumors have a high frequency of TP53 mutations and lack mutations in either KRAS or BRAF.
- Familial BRCA1/2 mutations

Serous carcinoma

- Individual tumor cells display marked nuclear atypia, including pleomorphism, atypical mitotic figures, and multinucleation.
- The serous tubal intraepithelial carcinomas consist of cells morphologically identical to high-grade serous carcinomas but are distinguished by the lack of invasion.
- Psammoma bodies
- Spread to peritoneum

Ovarian Carcinomas			
Type	**%**	**Stage 1 %**	**Survival %**
Type 1			
Endometrioid	10	>60	78
Clear cell	10	>60	80
Mucinous	3	80	80
Low-grade serous	<5		>85
Type 2			
High-grade serous	70	<5	40

Serous cystadenoma

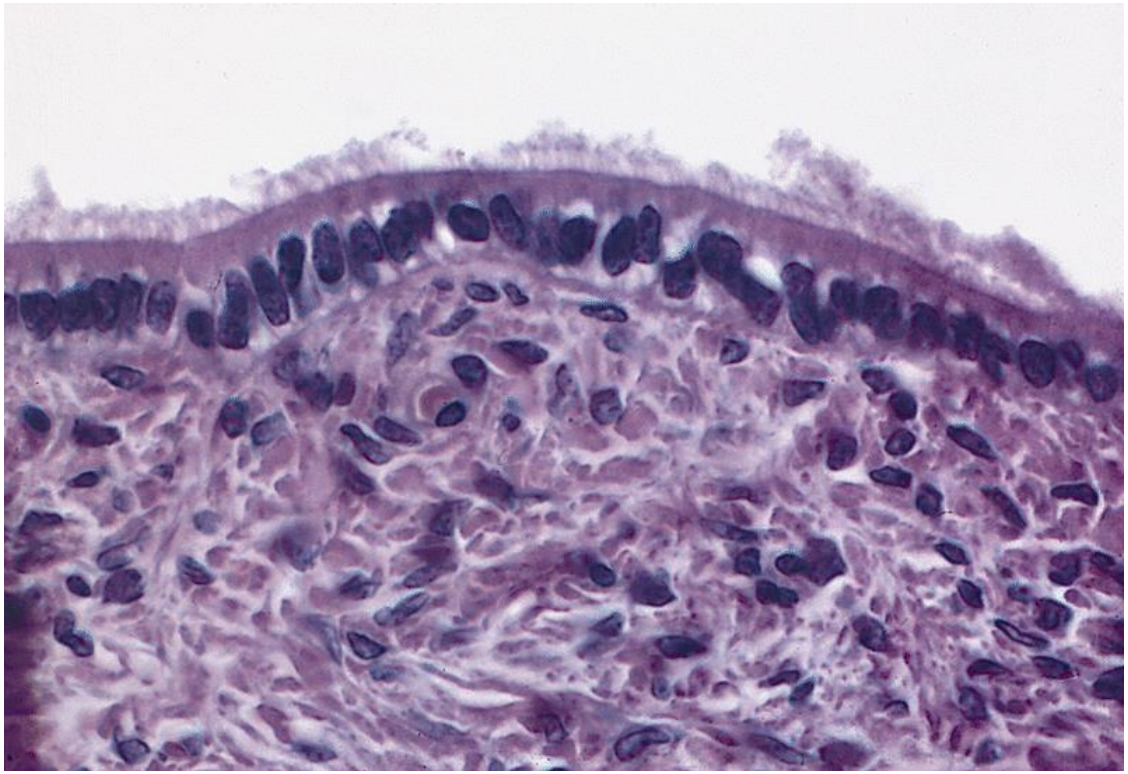


Serous cystadenoma is composed of one or more thin-walled cysts filled with watery fluid.The cyst lining may bear polypoid excrescences composed almost entirely of stroma and characterized by a firm consistency if the stroma is dense and fibrous, or a soft consistency if it is edematous.

Fig. 3-2R

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology .Washington, D.C, 1998.

Serous cystadenoma

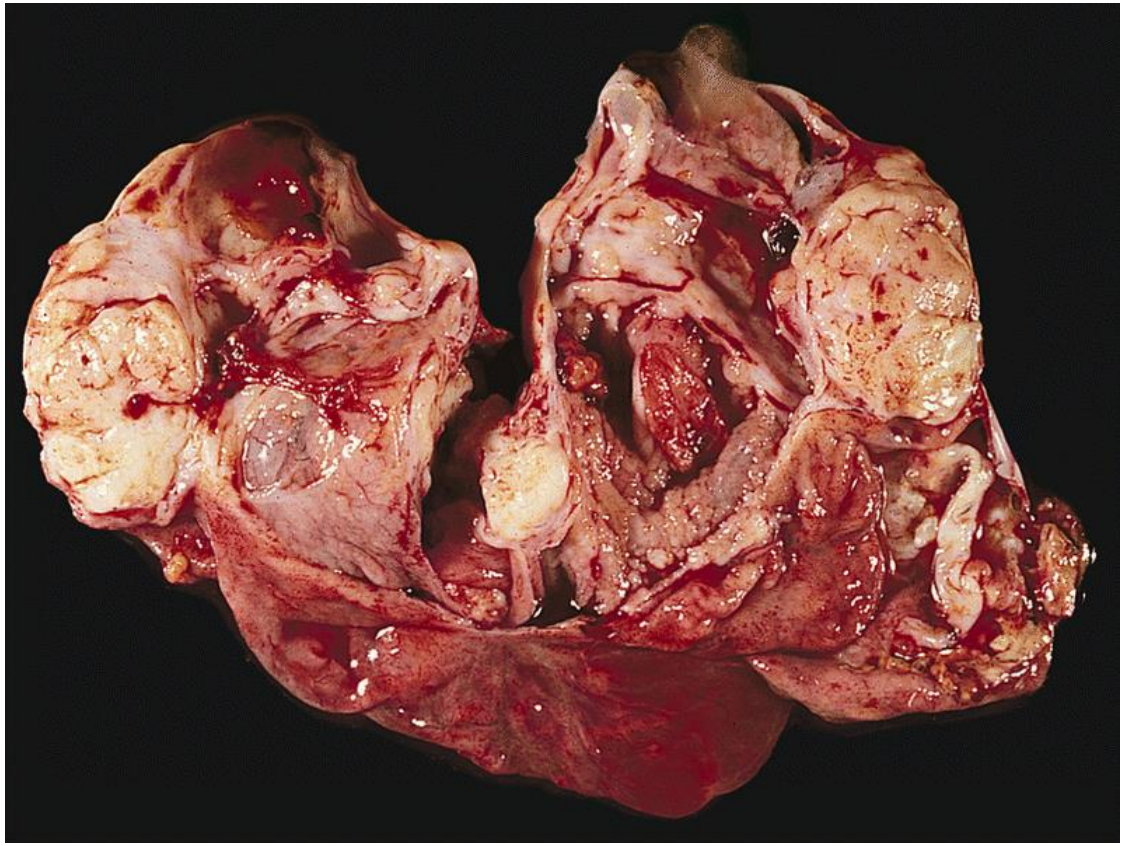


The cyst is lined by ciliated epithelium without significant nuclear atypia.

Fig. 3-9

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology .Washington, D.C, 1998.

Serous adenocarcinoma



The tumors are partly solid and partly cystic. The rough- surfaced polypoid tumor has extended through the capsule.

Fig. 3-7

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology .Washington, D.C, 1998.

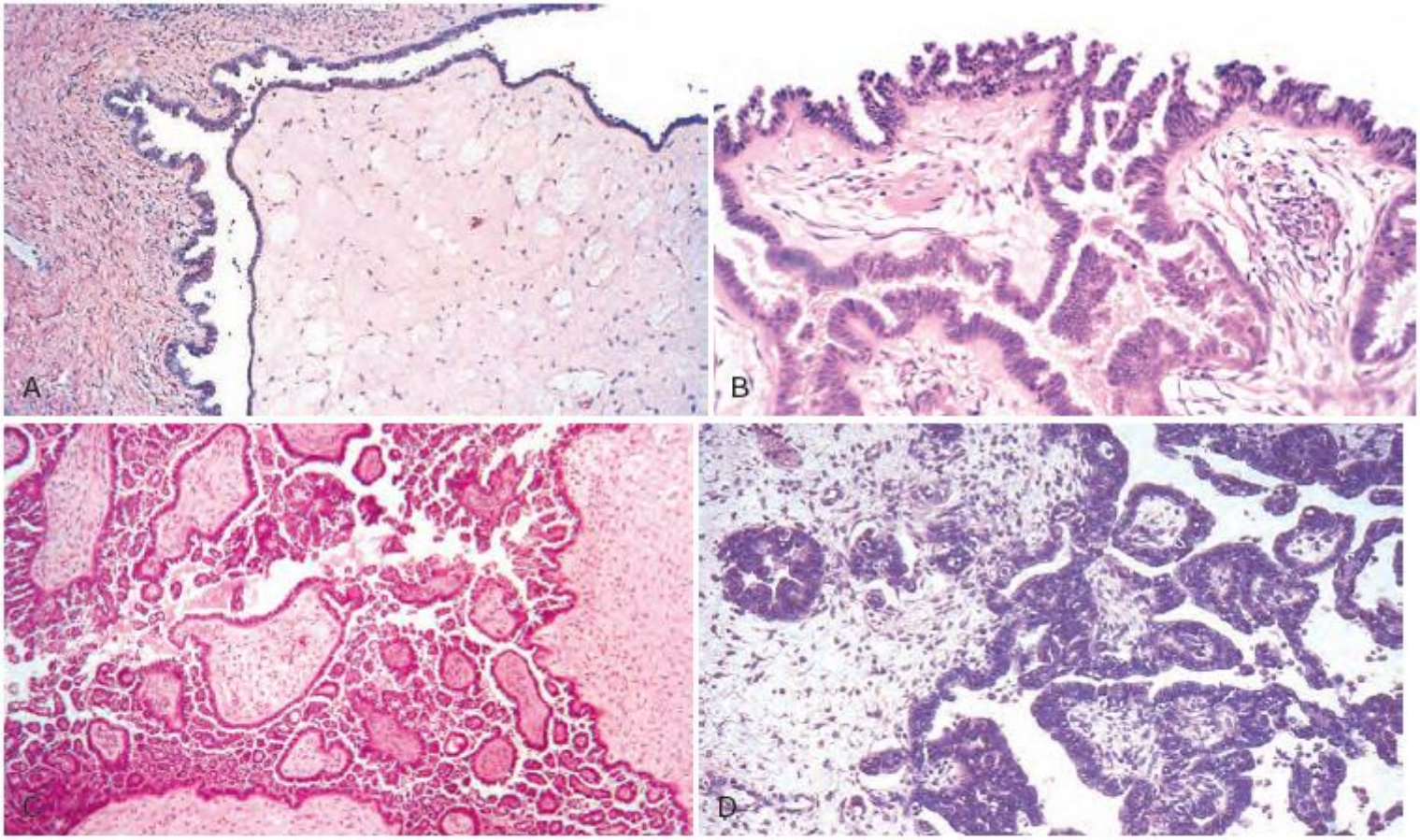
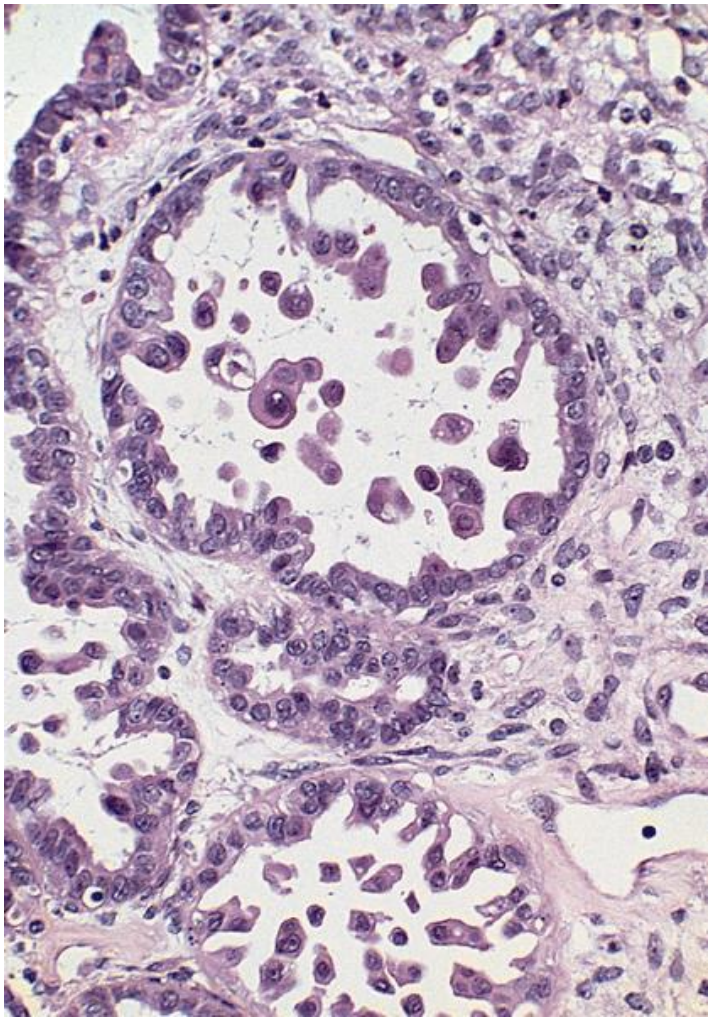


Figure 22-33 Microscopic appearances of serous tumors of the ovary. **A,** Serous cystadenoma revealing stromal papillae with a columnar epithelium. **B,** Borderline serous tumor showing increased architectural complexity and epithelial cell stratification. **C,** Complex micropapillary growth defines a low-grade "micropapillary" serous carcinoma. **D,** High-grade serous carcinoma of the ovary with invasion of underlying stroma.

Serous cystic tumor of borderline malignancy

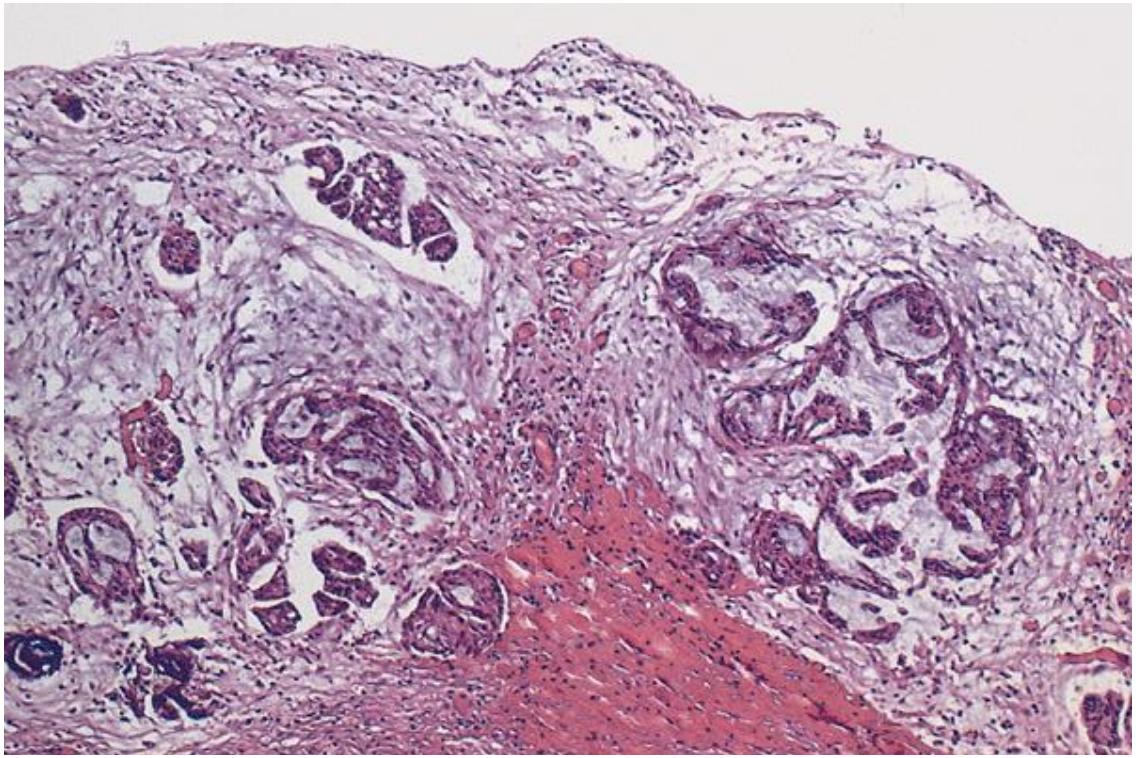


The lining cells are stratified with cellular budding. The nuclei are moderately atypical
and the cytoplasm is moderately abundant.

Fig. 3-14

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Serosal implant

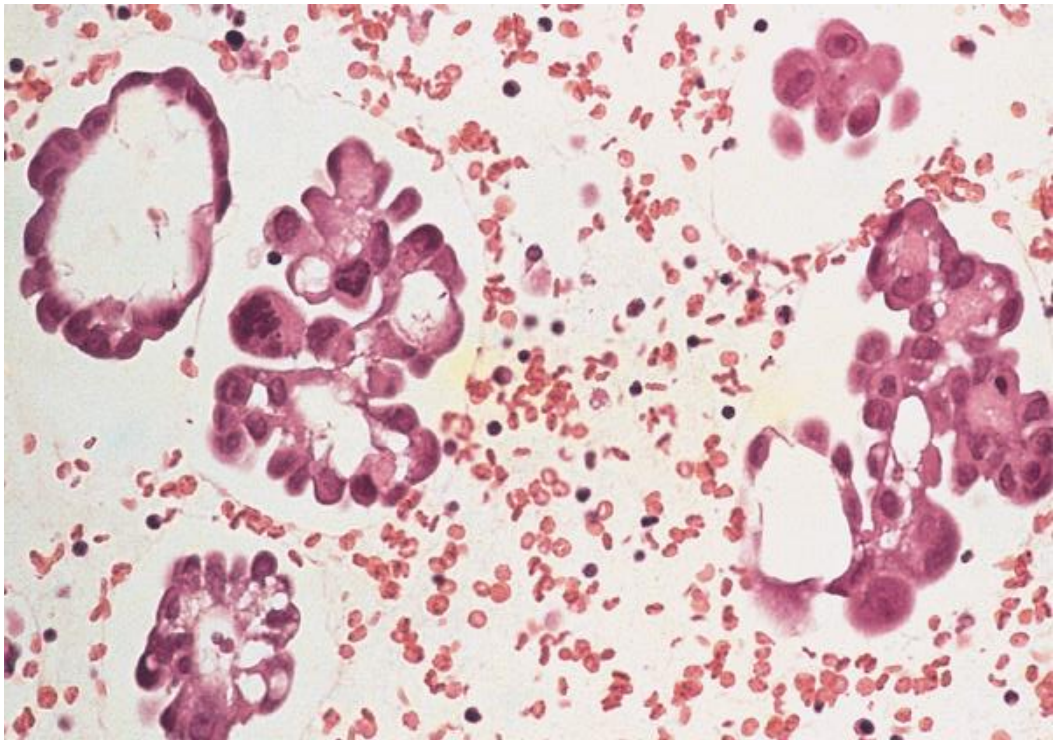


Large numbers of epithelial cell islands are present.

Fig. 3-31L

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Serous adenocarcinoma

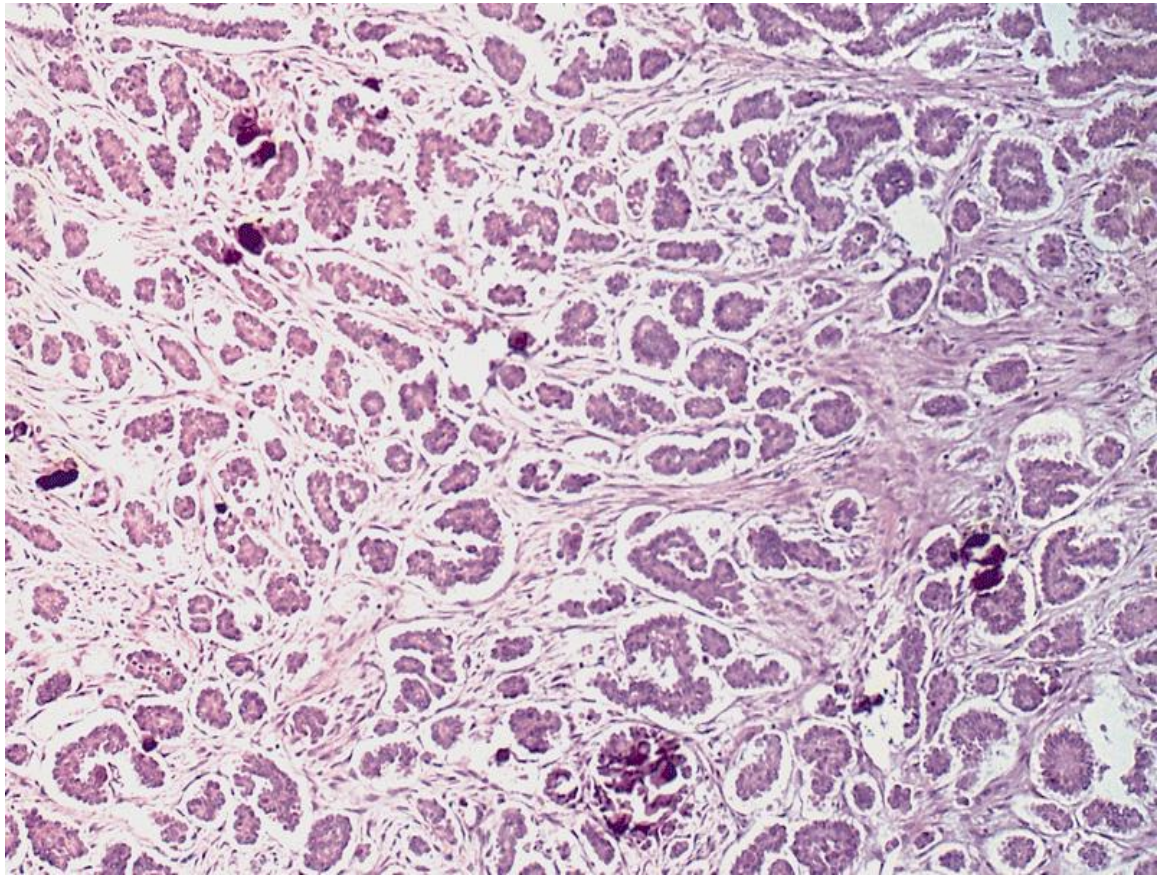


Papillary clusters of vacuolated carcinoma cells in cell block.

Fig. 2-17

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology .Washington, D.C, 1998.

Serous adenocarcinoma



The tumor is composed of small nests of well-differentiated epithelial cells lying in a fibrous stroma, with occasional psammoma body formation.

Fig. 3-37

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Mucinous cancer

- Ovarian surface rarely involved
- Multi-loculated, filled with gelatinous glycoprotein rich fluid
- The vast majority demonstrate gastric or intestinal type differentiation
- Uncommonly, tumors may show endocervical type mucinous differentiation
- Usually develop within borderline tumors.

Mucinous cancer

- Mucinous borderline tumors are distinguished from cystadenomas by epithelial stratification, tufting, and/or papillary intraglandular growth
- Mucinous carcinomas characteristically demonstrate confluent glandular growth (“expansile” invasion).
- KRAS mutation common
- Bilateral presentation requires exclusion of non-ovarian origin
- Pseudomyomatous peritoneii usual from appendiceal carcinoma

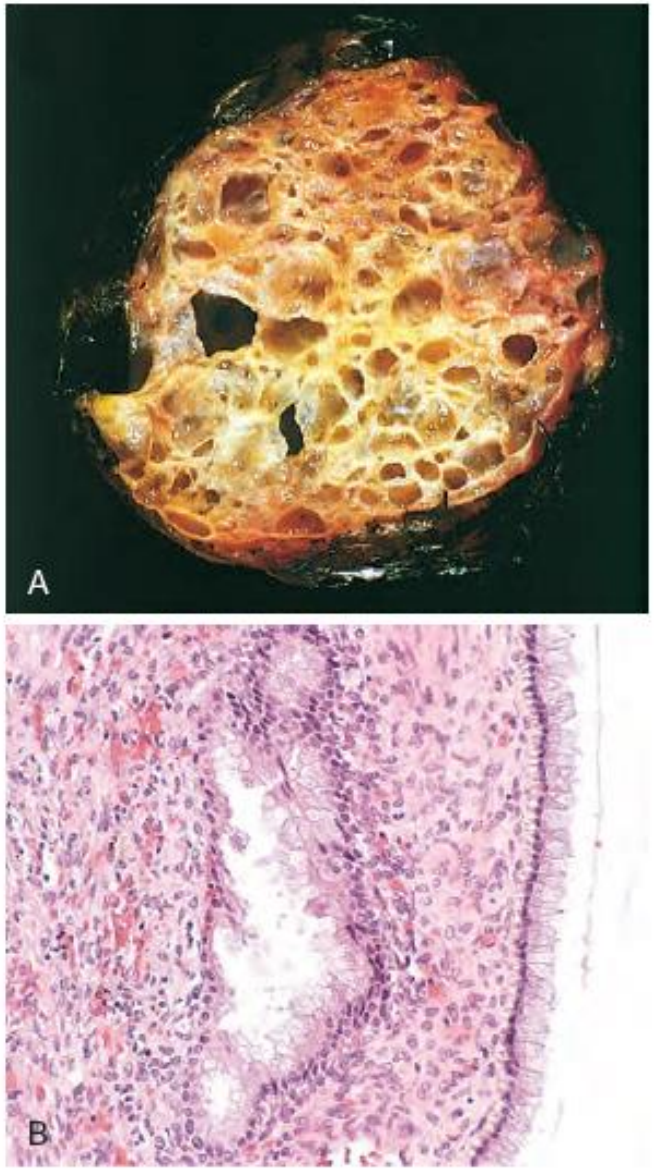
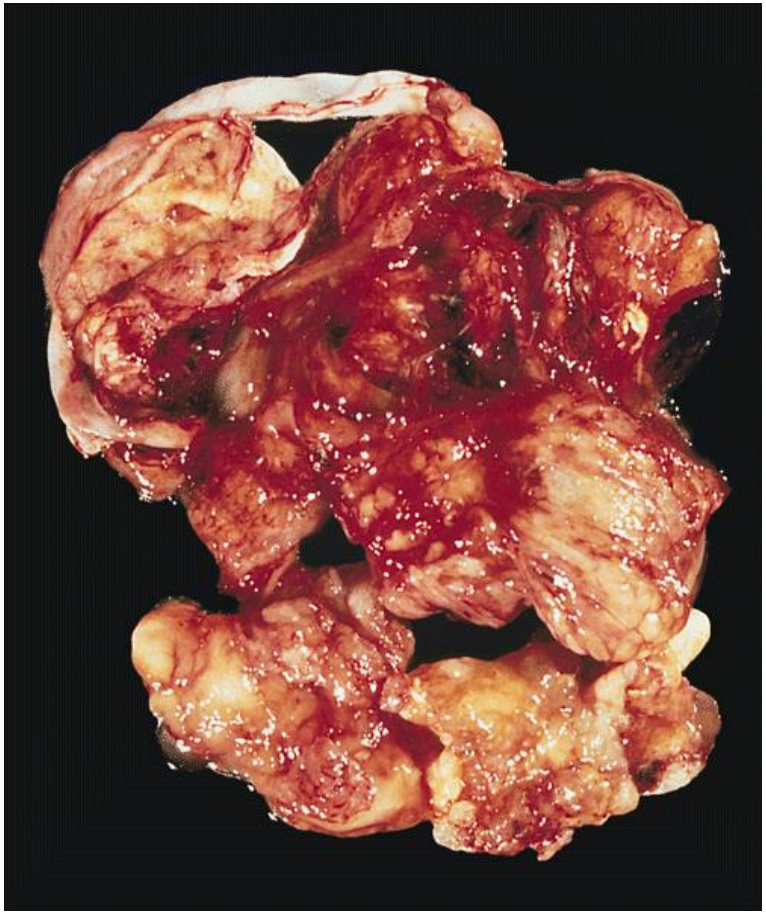


Figure 22-34 Mucinous cystadenoma **A,** Note the multicystic appearance, delicate septa, and the presence of glistening mucin within the cysts. **B,** Columnar cells lining the cysts.

Mucinous cystadenocarcinoma

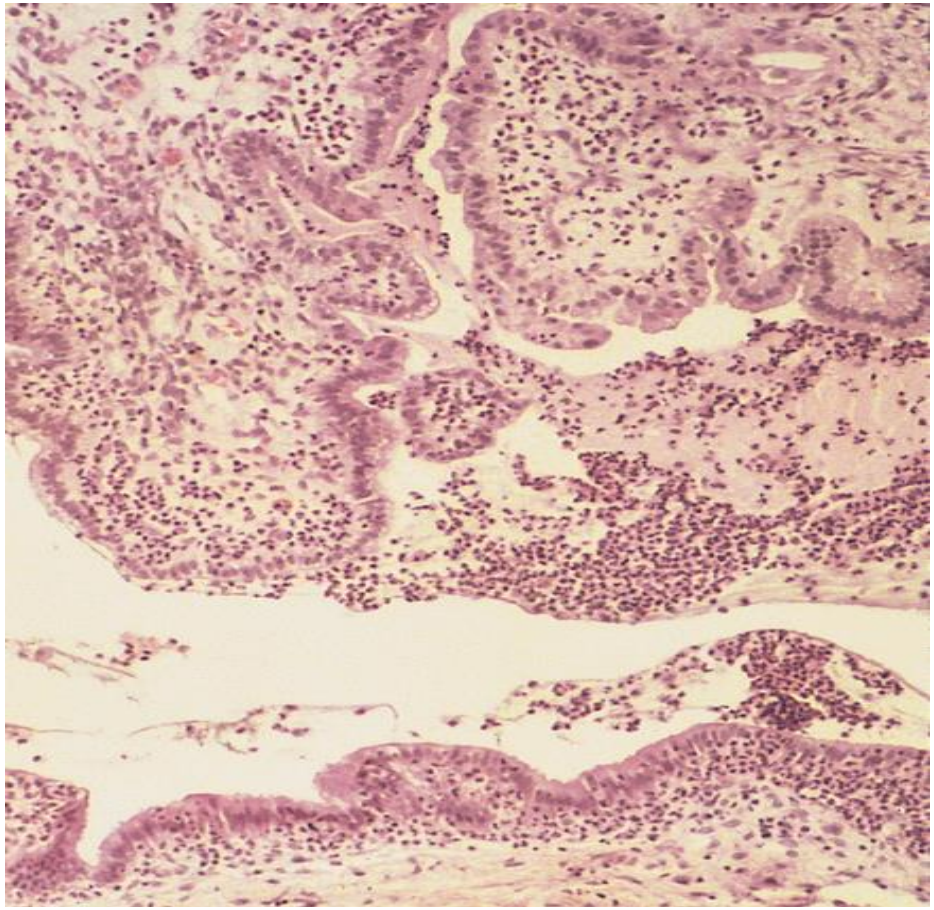


The sectioned surface appears gelatinous, with extensive hemorrhage and necrosis.

Fig. 4-8

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Mucinous cystadenocarcinoma

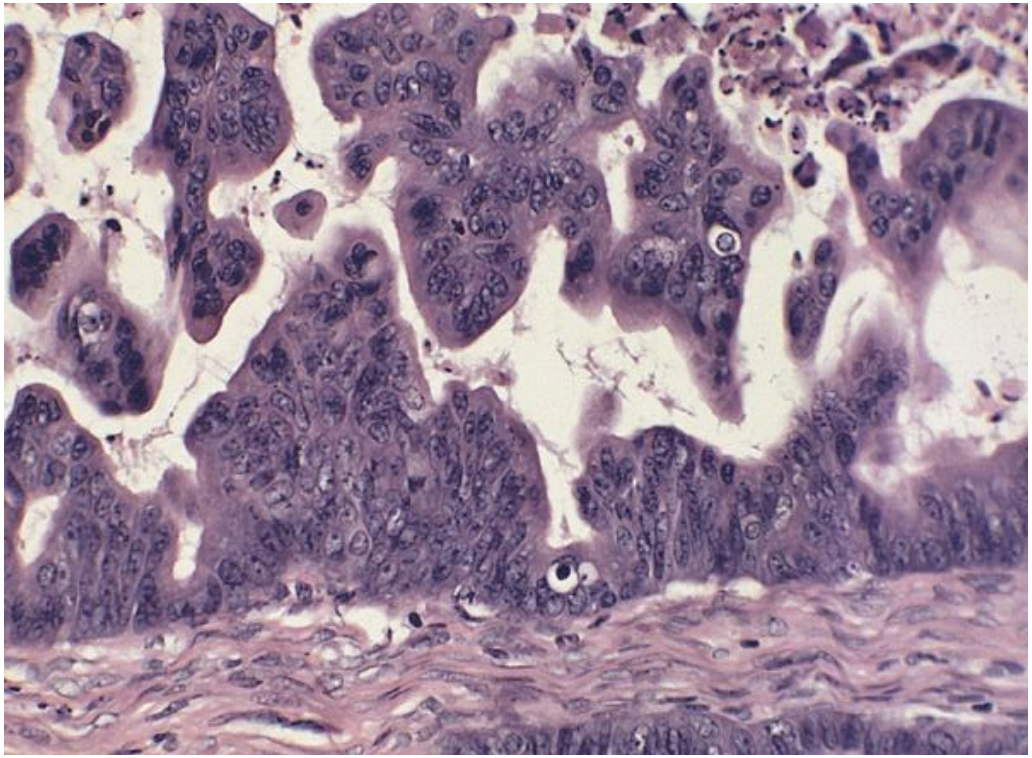


The tumor resembles endocervical tissue.

Fig. 4-18

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Mucinous cystadenocarcinoma



The tumor is well differentiated and characterized by stroma- free cellular papillae and marked nuclear atypia.

Fig. 4-20

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

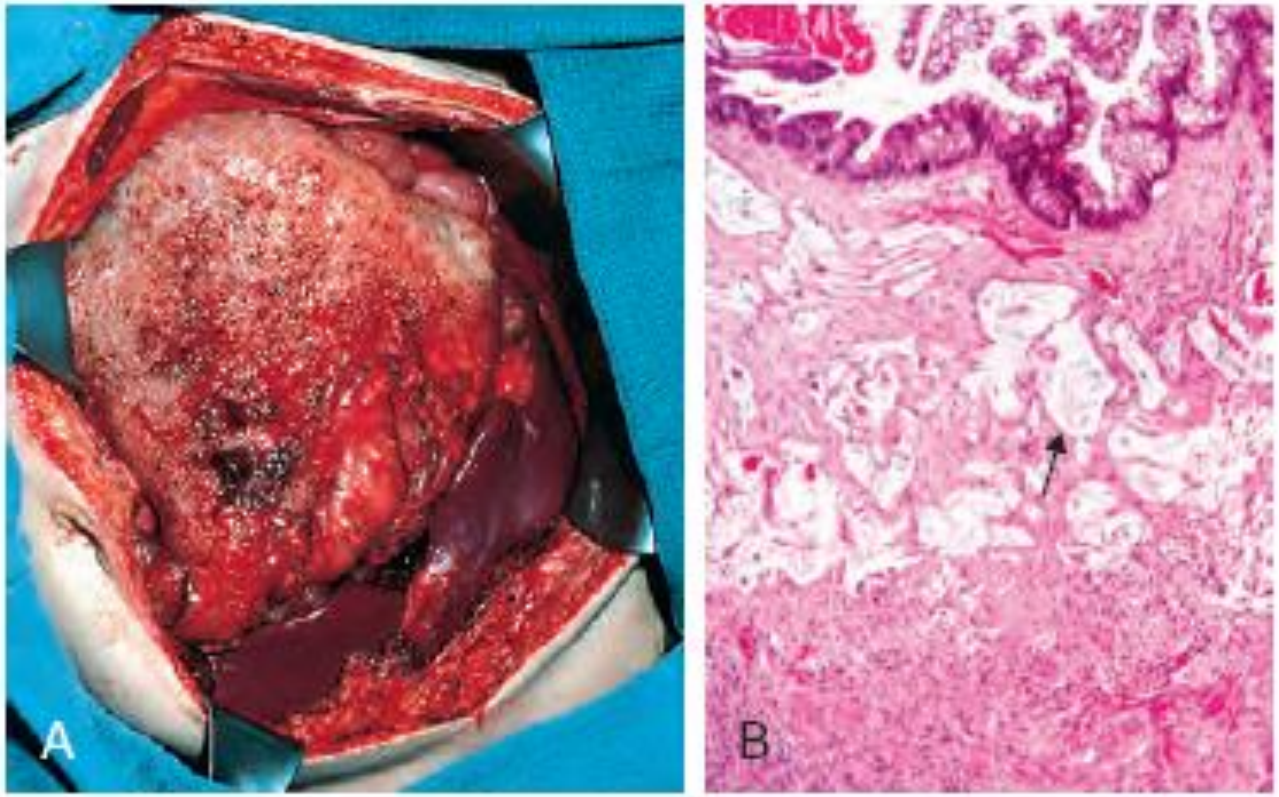


Figure 22-35 Pseudomyxoma peritonei. **A,** View at laparotomy revealing massive overgrowth of a gelatinous metastatic tumor. **B,** Histology of peritoneal implants from an appendiceal tumor, showing mucin-producing epithelium and free mucin *(arrow)*. (**A,** Courtesy Dr. Paul H. Sugarbaker, Washington Hospital Cancer Center, Washington, D.C.)

Endometrioid carcinoma

- Endometriotic cyst origin (ARID1A mutation)
- Stepwise progression to adenocarcinoma
- 15-30% associated with endometrial carcinoma (independent origin)
- 15-20% co-exist with endometriosis
- Both solid and cystic growth

Clear cell carcinoma

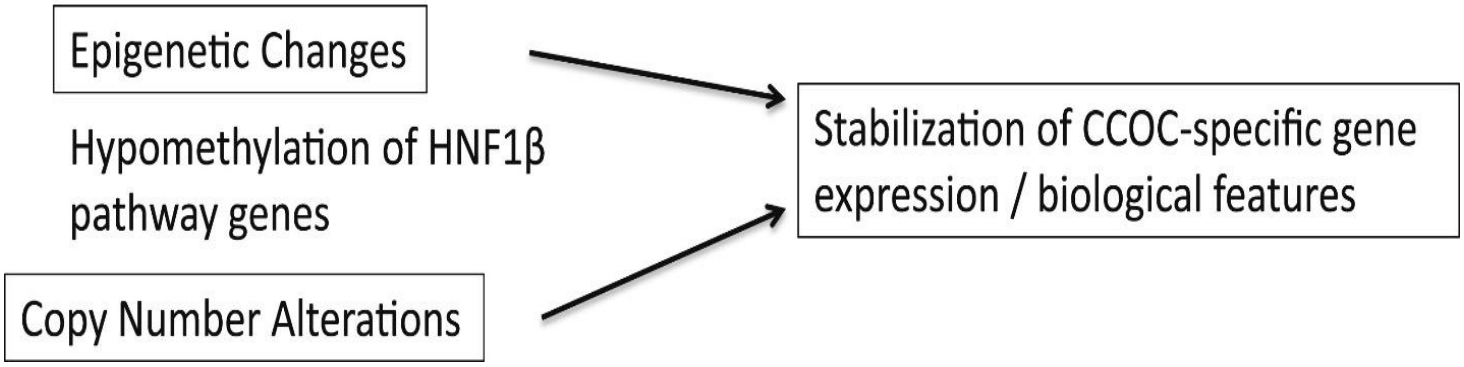
- Variant of endometrioid carcinoma
- Progresses from endometriosis
- HNF-1β mutation
- PIK3CA, ARID1A, KRAS, PTEN, TP53 mutations also identified
- Ki 67 (proliferation index) low
- High risk of extra-uterine metastases.
- Intermediate prognosis although poorly responsive to chemotherapy

Clear cell carcinoma

Progression from endometriosis:

Fe-induced oxidative stress → DNA damage
→ PIK3CA mutation and ARID1A mutation
→ Carcinogenesis of CCOC ; HNF1β↑ & IL6/STAT3↑

HNF1β ; Warburg effect / Resistance to Oxidative Stress
→ Progression in stressful condition of endometiotic cyst / Platinum resistance



Clear cell carcinoma

- Composed of large epithelial cells with abundant clear cytoplasm, an appearance that resembles hypersecretory gestational endometrium.
- In the solid variety, the clear cells are arranged in sheets or tubules
- In the cystic variety, the neoplastic cells line the spaces.
- Copy number is distinct between histologic subtypes.

Ovarian fibroma

- Develop from mature fibroblasts.
- May present with ascites (and/or Meig's syndrome of fibroma, ascites, and right hydrothorax).
- Total hysterectomy with bilateral salpingo-oöphorectomy as primary therapy.

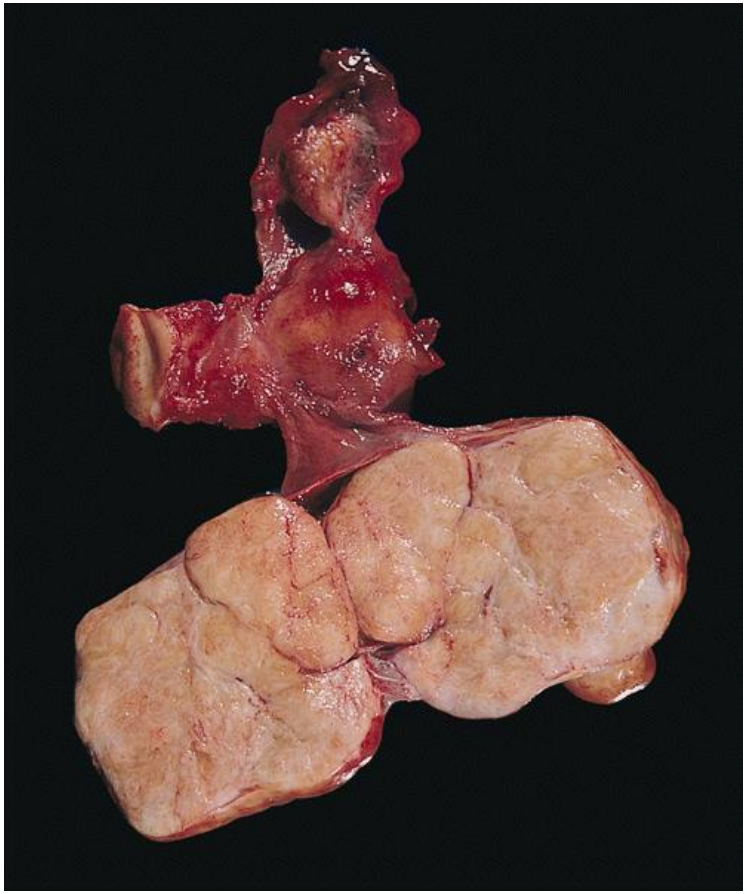
Brenner tumor

- Transitional cell
- 10% of epithelial tumors
- 90% unilateral
- The fibrous stroma resembles that of the normal ovary
- It is marked by sharply demarcated nests of of epithelial cells resembling urothelium
- Mucinous glands may be found in the nests.
- Infrequently, the stroma is composed of somewhat plump fibroblasts resembling theca cells
- Hormonally active
- Generally benign tumors

Brenner Tumor

- Malignant Brenner tumor is often a variant of high-grade serous adenocarcinoma.
- WT1 positive.
- Poor prognosis although responsive to chemotherapy.

Brenner tumor



There is a solid fibrous tissue component as well as two cysts (lined by transitional epithelium).

Fig. 7-2

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

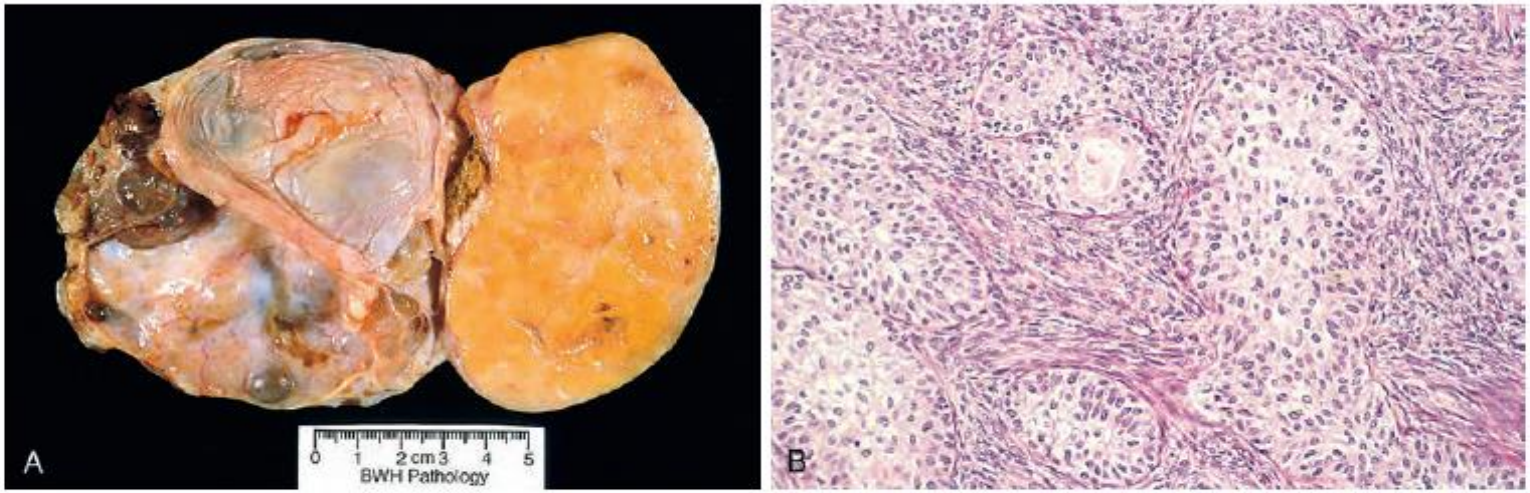
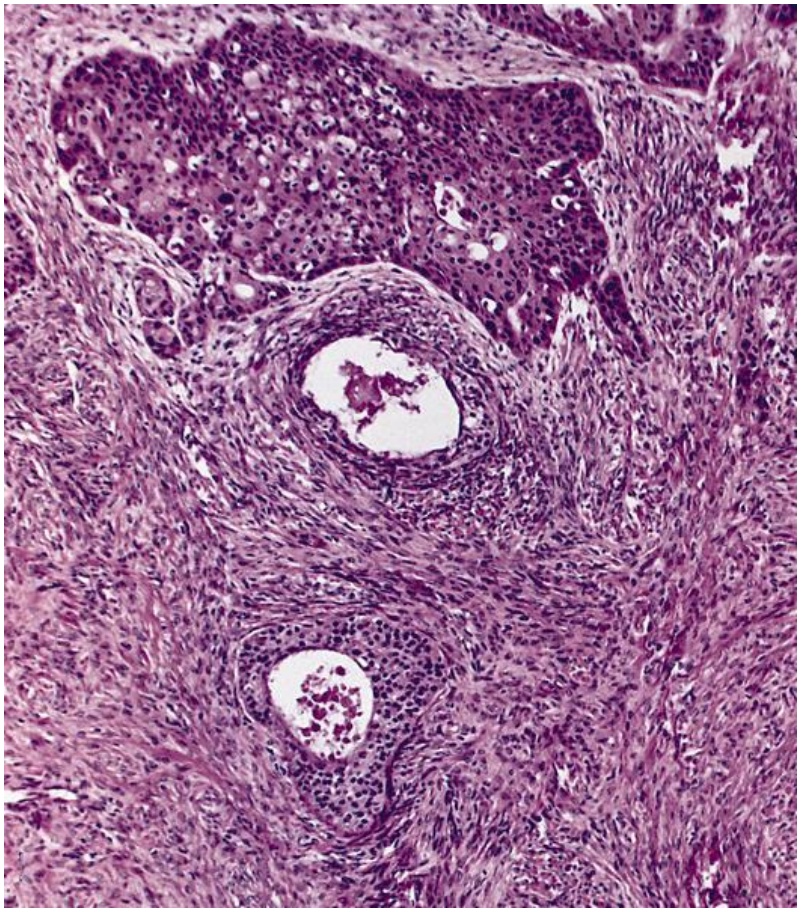


Figure 22-36 Brenner tumor **A,** Brenner tumor *(right)* associated with a benign cystic teratoma *(left)*. **B,** Histologic detail of characteristic epithelial nests within the ovarian stroma. (Courtesy Dr. M. Nucci, Brigham and Women's Hospital, Boston, Mass.)

Malignant Brenner tumor

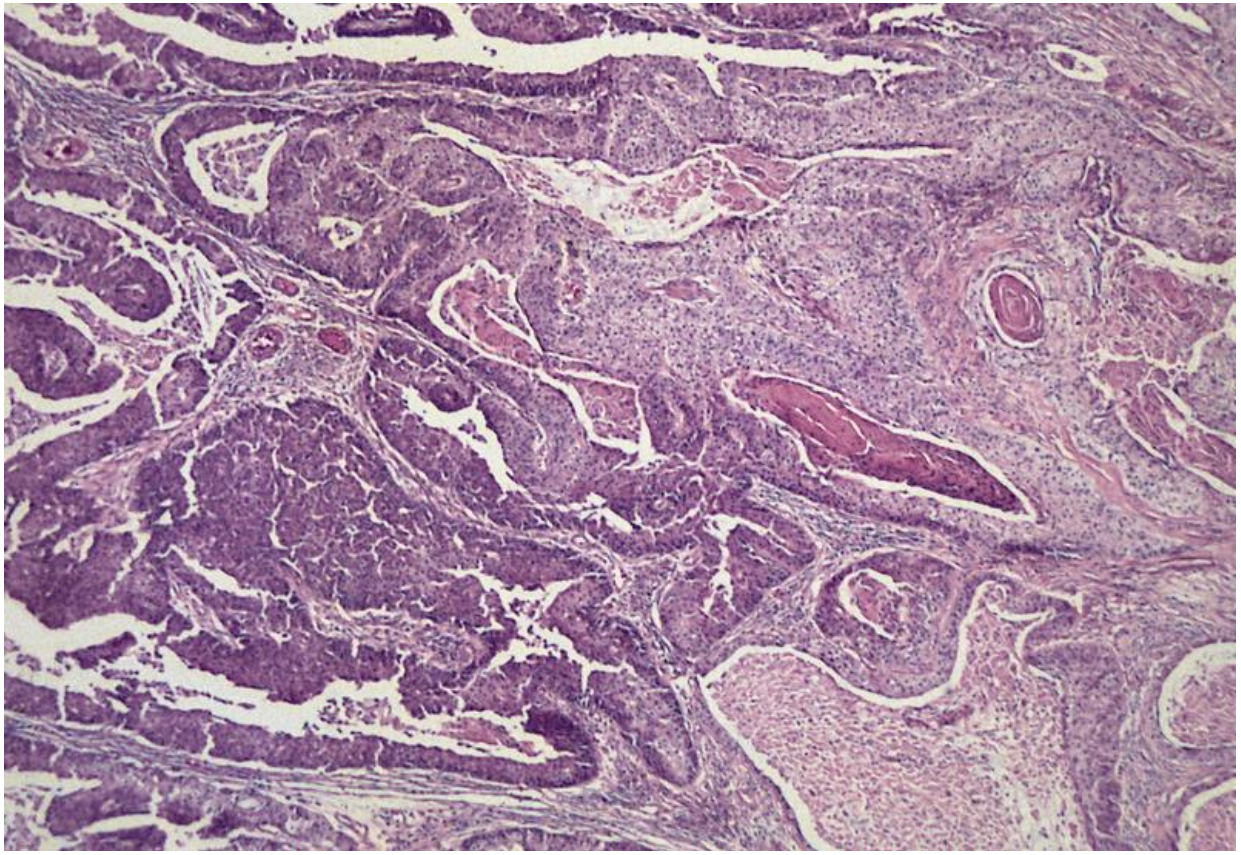


A large irregular nest of malignant transitional cells with jagged margins lies above two benign Brenner nests with central cavities.

Fig. 7-16

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Adenosquamous carcinoma

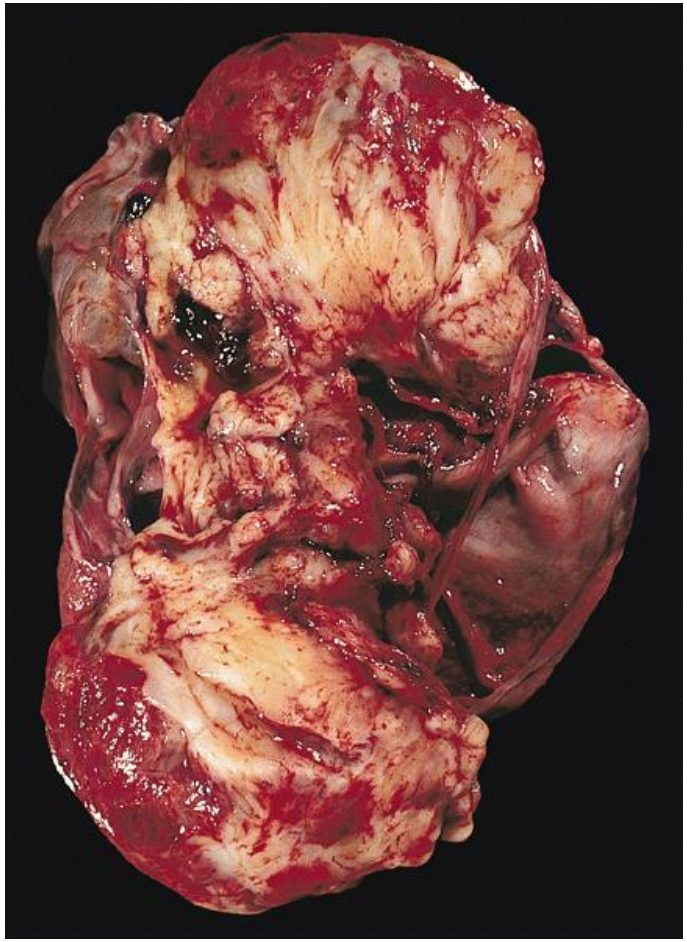


Keratinizing squamous cell carcinoma (right) merges with adenocarcinoma (left).

Fig. 5-30

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Mixed mesodermal tumor

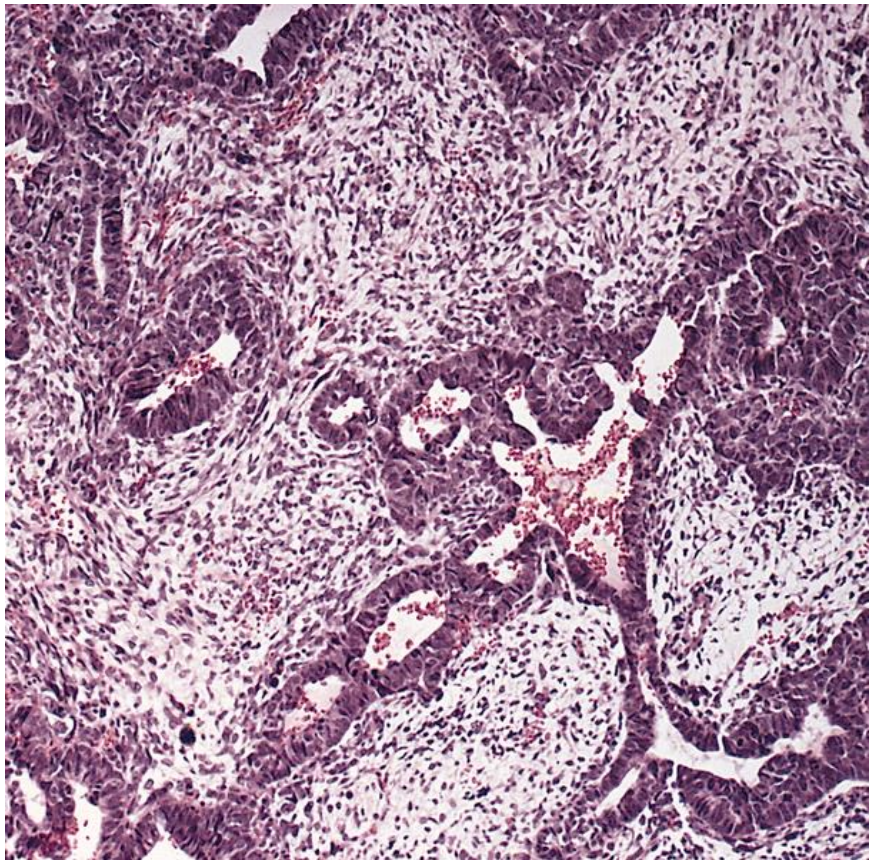


The sectioned surface is composed of solid tissue with areas of necrosis and hemorrhage.

Fig. 5-41

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Mixed mesodermal tumor

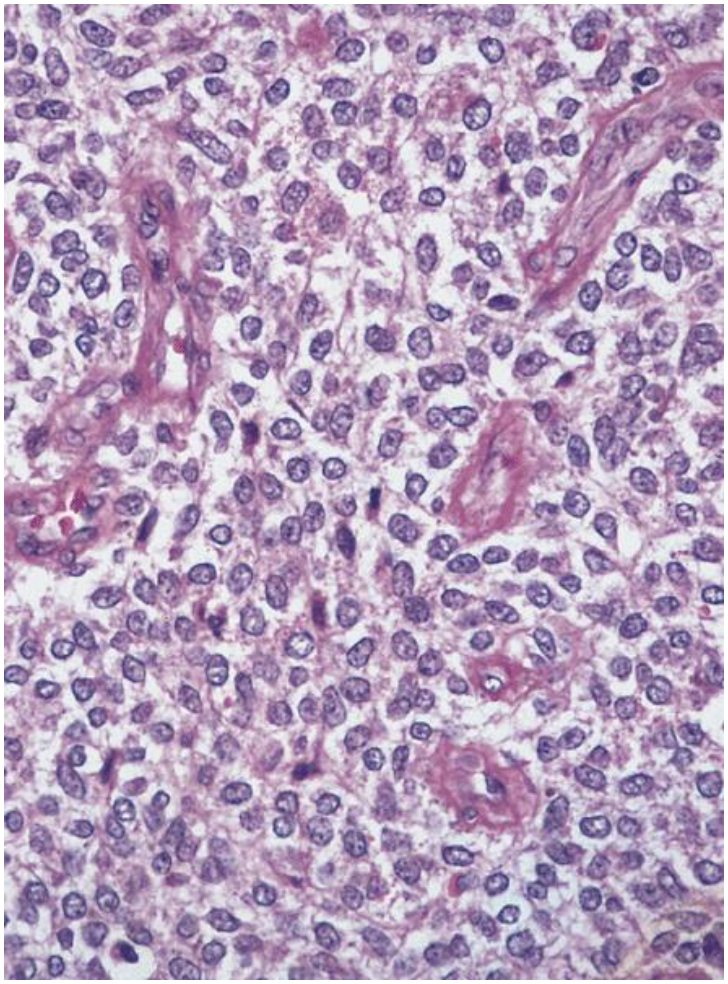


Glands and solid aggregates of carcinoma cells are separated by a fibrosarcomatous component.

Fig. 5-42

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Endometrioid stroma sarcoma



This well-differentiated tumor is composed of cells with small rounded nuclei. Numerous arterioles resembling the spiral arteries of the late secretory endometrium are a characteristic feature.

Fig. 5-53

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998.

Treatment

- Surgery is primary staging tool.
- Tumor confined to one or both ovaries without tumor on external surface can be treated by bilateral salpingo-oöphorectomy alone.
- Omentectomy, and bilateral pelvic and peri-aortic lymphadenectomy are important for surgical staging and may improve overall survival.

Treatment

- If fertility sparing surgery is desired, the affected fallopian tube and ovary alone can be removed but only in combination with complete surgical staging.
- Relapse in the affected ovary may occur.
- Only for young woman with a low grade lesion involving one ovary and with no tumor on ovarian surface

Treatment

- Surgical debulking (cytoreduction) is critical to response.
- If residual tumor <1cm extension (peritoneal seeding), may follow surgery with intraperitoneal hyperthermia-chemotherapy (cisplatin, paclitaxel) and systemic chemotherapy (paclitaxel).
- Surgical debulking may follow neo-adjuvant chemotherapy (carboplatin and paclitaxel). It is associated with lesser surgical morbidity than with intraperitoneal hyperthermia-chemotherapy.
- 12 months of chemotherapy is recommended.

Treatment

- The addition of pazopanib, a PARP inhibitor, to those with advanced lesions (and BRCA 1 mutation) is beneficial in platinum sensitive disease as well as PI3KCA mutation
- The addition of bevacizumab to paclitaxel chemotherapy is recommended for Stage IV disease in patients who have relapsed >3months after platinum therapy.
- Single agent chemotherapy for recurrent disease.
- Hypomagnesemia is a poor prognostic sign.

Other ovarian cancers

- Germ cell tumors are dysgerminoma, endodermal sinus tumor, malighant teratoma, embryonal carcinoma, or primary choriocarcinoma.
- Stromal cell tumors are granulosa cell (estrogen) or Sertoli-Leydig cell (androgen) tumors and are mesenchymal in origin.

Germ cell tumors

- 15-20% of ovarian tumors
- Arise from totipotent germ cells.
- Occurs in adolescents and young women. Rapidly enlarging adnexal mass with abdominal pain.
- 95% benign.
- AFP elevated in embryonal and endodermal sinus carcinomas
- HCG elevated in primary choriocarcinoma.

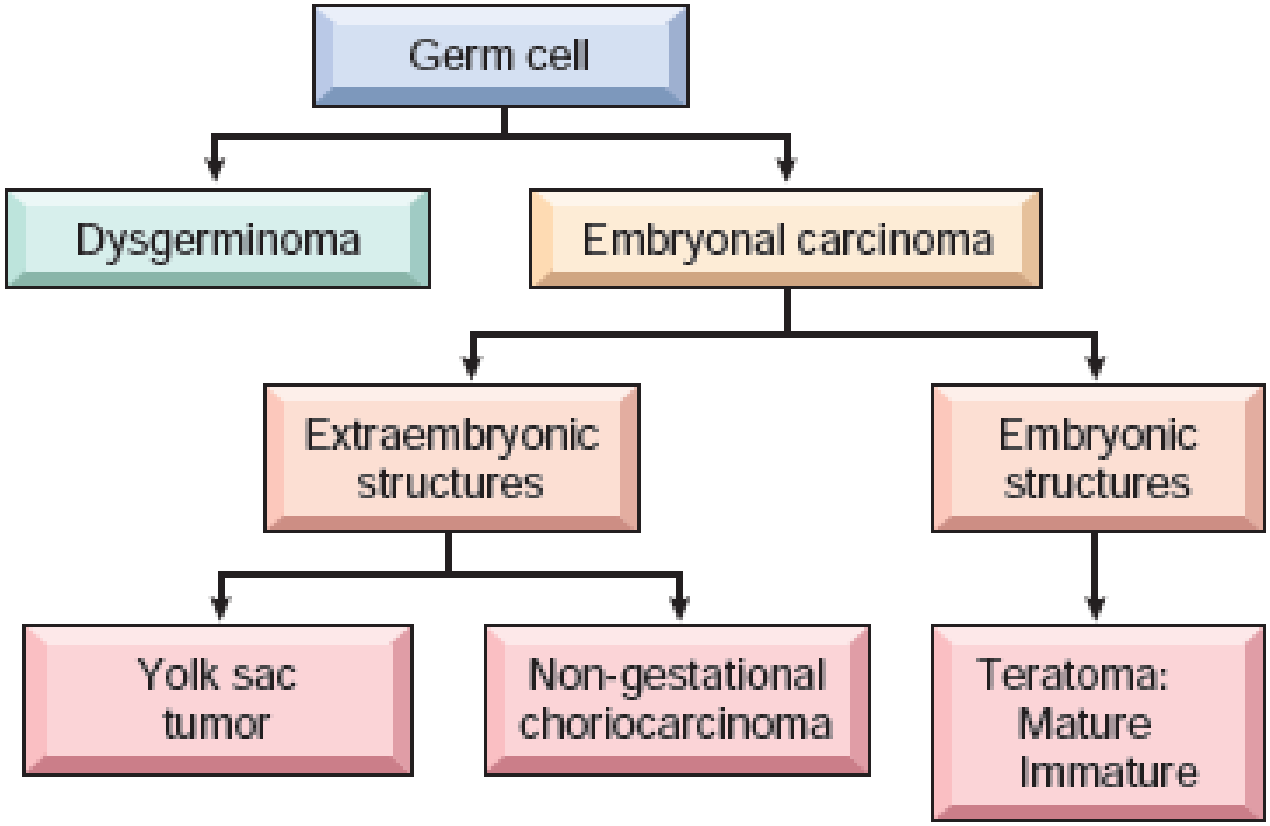


Figure 22-37 Histogenesis and interrelationships of tumors of germ cell origin.

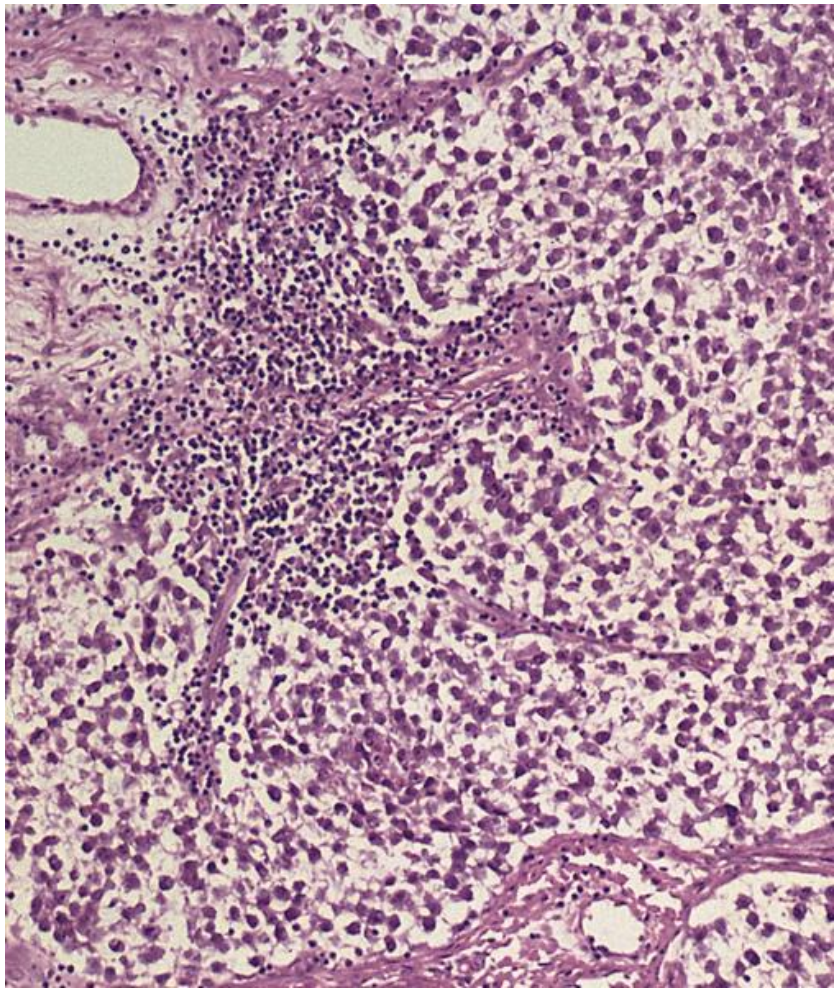
Dysgerminoma

- 50% of malignant ovarian tumors
- 75% occur in teens and twenties
- 90% unilateral
- Counterpart of seminoma in the male
- OCT3/4 and NANOG expressed (reflecting pluripotency)
- 33% have activating C-KIT mutation

Dysgerminoma

- Solid yellow-white to gray-pink appearance
- Composed of large vesicular cells having a clear cytoplasm, well-defined cell boundaries, and centrally placed regular nuclei.
- The tumor cells grow in sheets or cords separated by scant fibrous stroma, which is infiltrated by mature lymphocytes.
- May produce HCG if syncytiotrophoblasts present

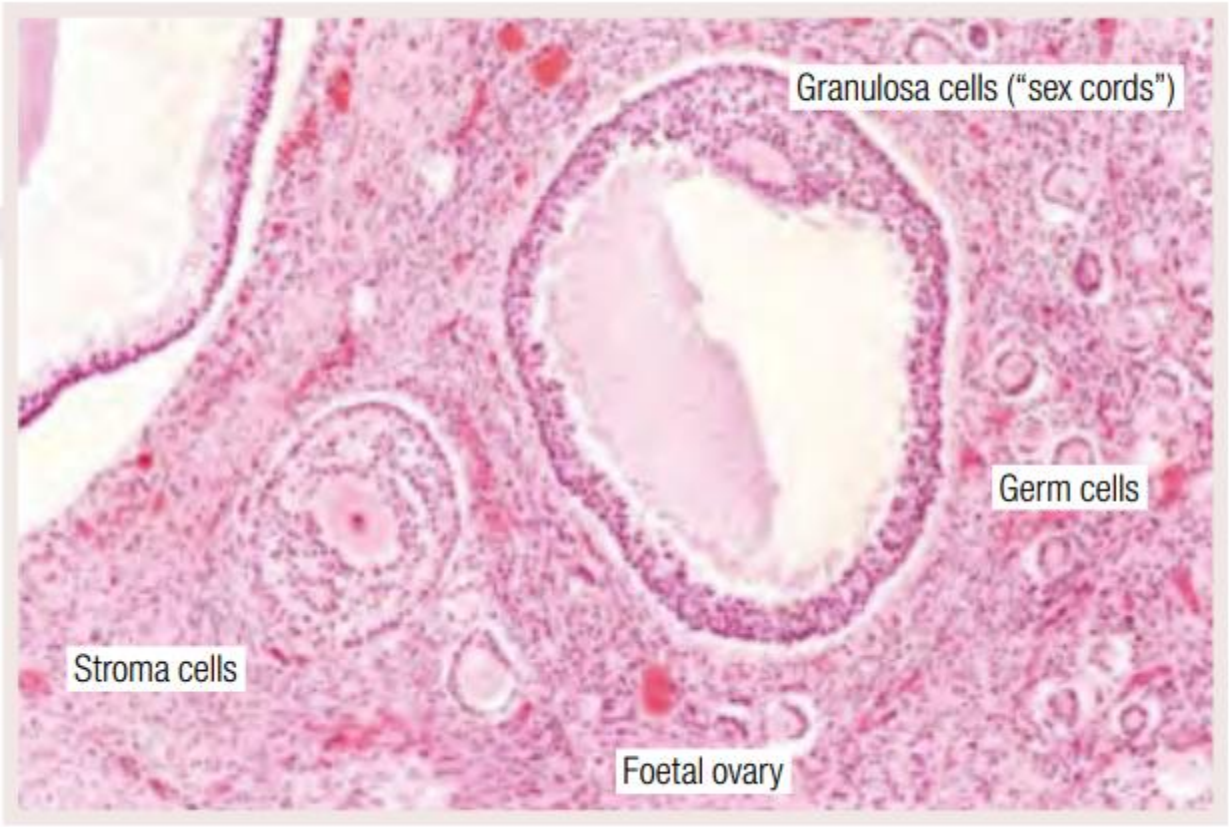
Dysgerminoma



The tumor is composed of uniform cells resembling primordial germ cells in diffuse, insular, trabecular, and cord-like patterns. Rarely, the tumor cells line irregular or rounded gland-like spaces or form solid tubular structures.

Fig. 13-4

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

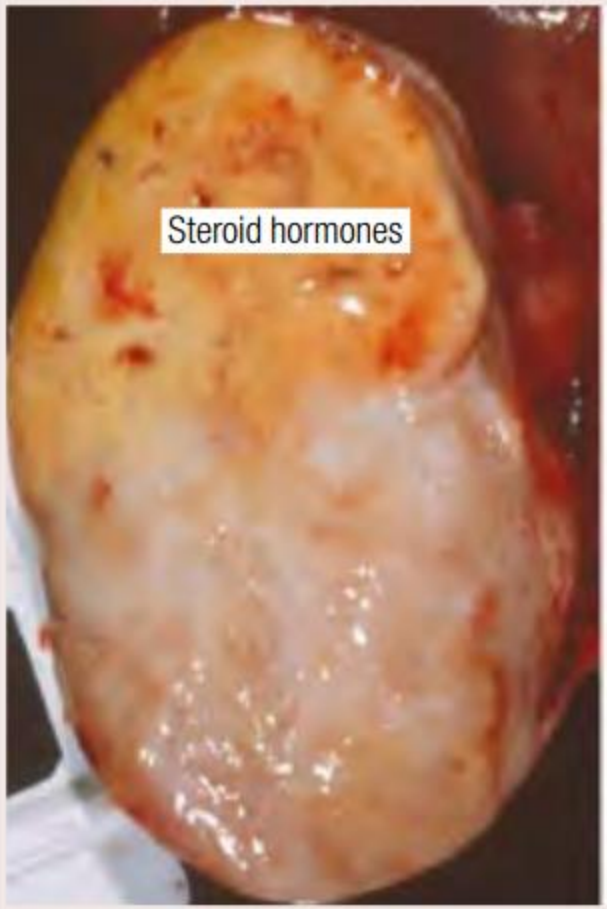

Granulosa cells ("sex cords")
Germ cells
Stroma cells
Foetal ovary

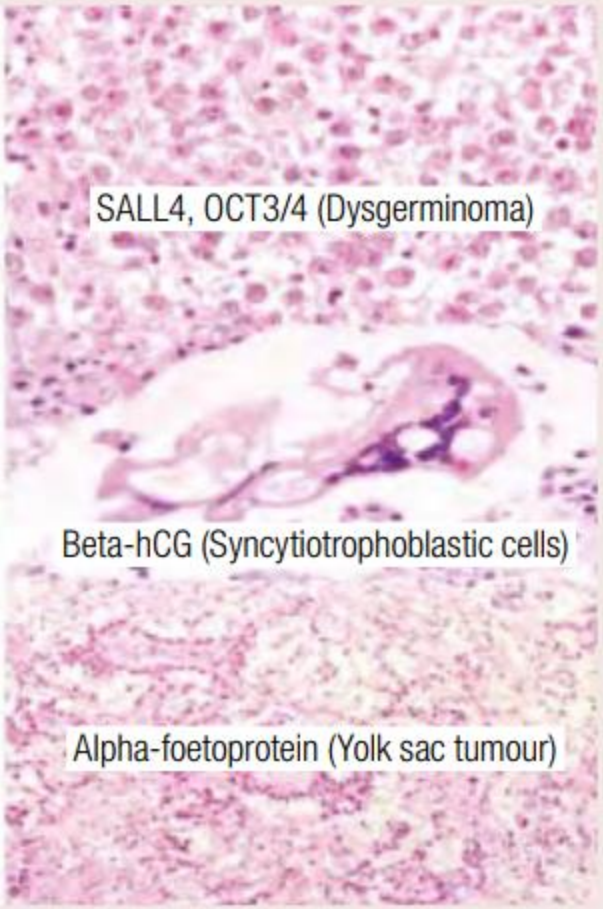
Germ cell tumors

- Most GCTs are benign mature teratomas (dermoid cysts)
- Only rarely may a malignant tumor arise from somatic-type teratomatous tissues.
- Primitive (malignant) GCTs are similar to those occurring in males;
- Include dysgerminoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma alone or in combination (10%).
- Immature (embryonal) teratomas also are in this group.

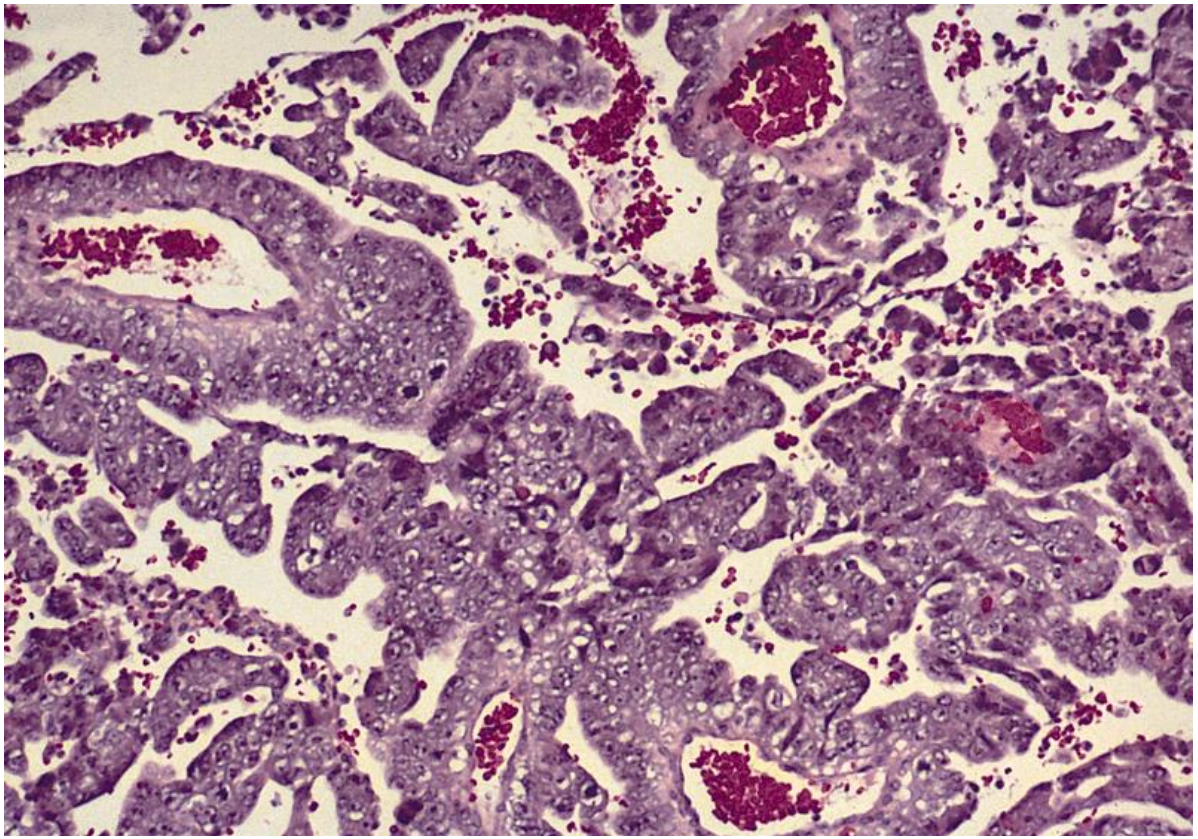
Germ cell tumors

- A few occur in subjects with disorders of sexual development (most phenotypically females with Y chromosome) from a mixed germ cell–sex cord stromal tumor (gonadoblastoma).
- Steroid cell tumors can be malignant.


Steroid hormones


SALL4, OCT3/4 (Dysgerminoma)
Beta-hCG (Syncytiotrophoblastic cells)
Alpha-foetoprotein (Yolk sac tumour)

Embryonal carcinoma



Solid sheets and nests of cells, often with central necrosis, gland-like spaces, and papillae composed of or lined by large primitive cells or atypical forms, are usually numerous. Syncytiotrophoblast giant cells are generally found.

Fig. 13-32

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

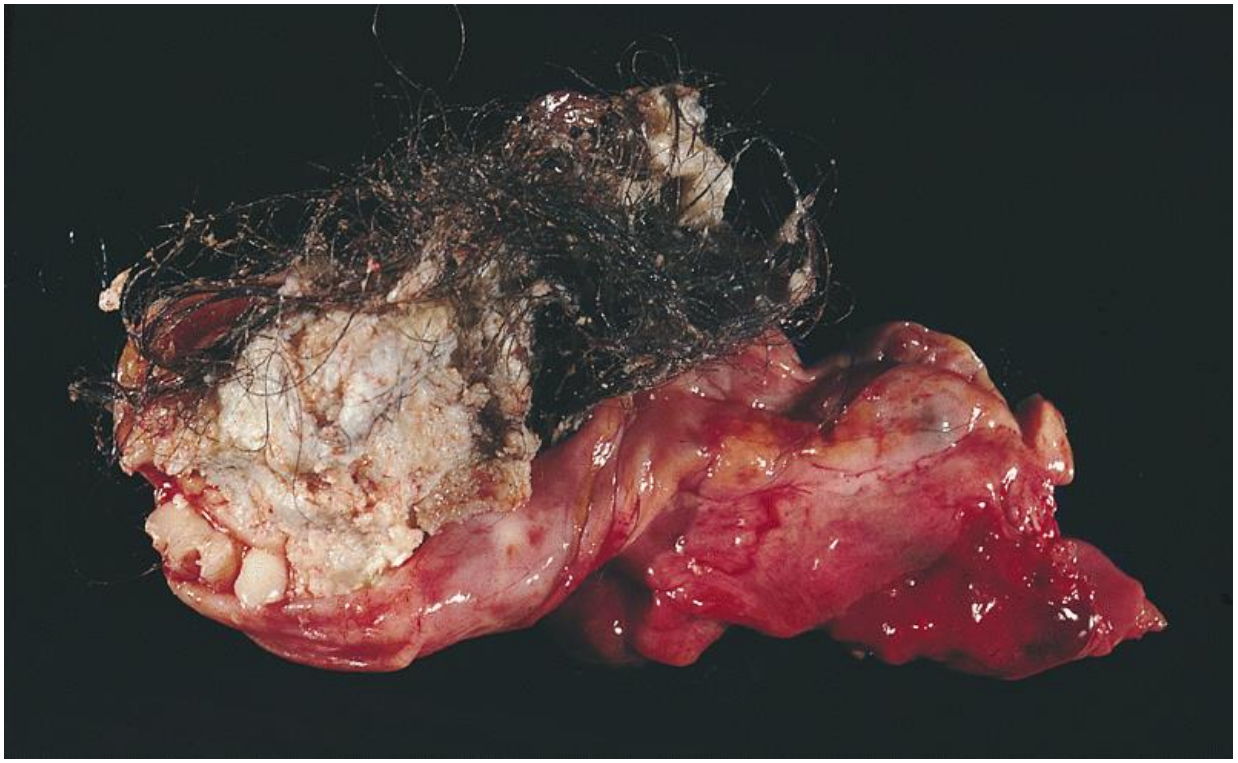
Mature teratoma

- Benign
- Bilateral in 10% to 15% of cases.
- Unilocular cysts containing hair and sebaceous material
- The cyst wall is thin and lined by an opaque, gray-white, wrinkled epidermis, frequently with protruding hair shafts.
- It is common to find grossly evident tooth structures and areas of calcification.

Mature teratoma

- Microscopically, the cyst wall is composed of stratified squamous epithelium with underlying sebaceous glands, hair shafts, and other skin adnexal structures
- Tissues from other germ layers can be identified
- The karyotype of almost all benign ovarian teratomas is 46,XX.
- The majority of teratomas arise from an ovum after the first meiotic division, while a minority arise before the first division.

Mature teratoma (dermoid cyst)



The cyst is filled with hair and sebaceous material. Several teeth are visible.

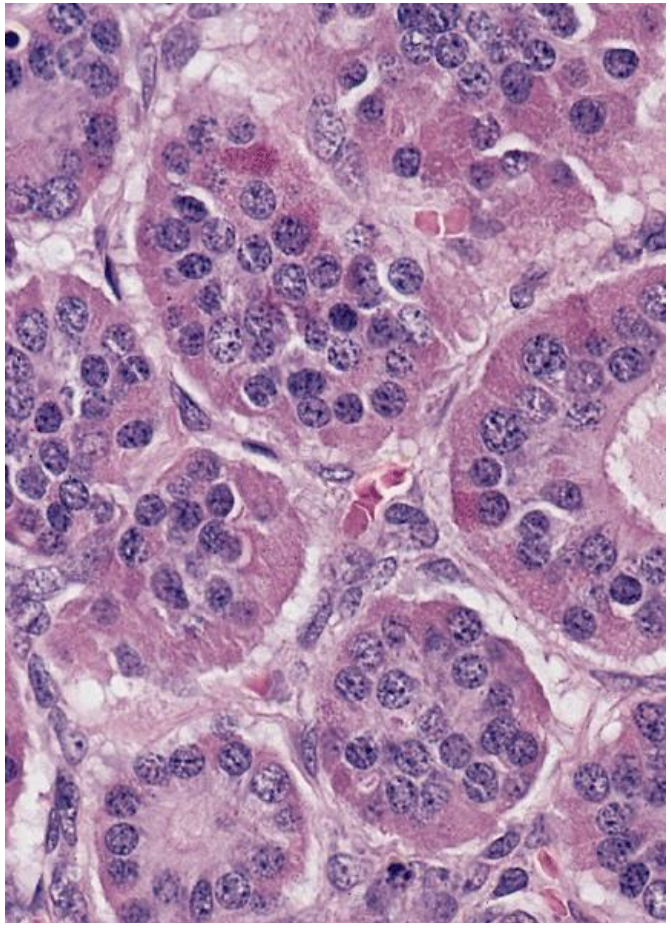
Fig. 14-14

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Specialized teratoma

- Usually unilateral
- Struma ovarii
- Comprised of mature thyroid tissue
- Carcinoid
- May be functional
- Symptomatic as ovarian veins drain into vena cava
- If bilateral, probably metastasis
- Both struma ovarii and carcinoid may be found in rare tumors

Struma ovarii



The struma may resemble normal thyroid tissue; a thyroid adenoma, with patterns including macrofollicular, microfollicular, pseudotubular, trabecular, and solid (nests or sheets), alone or in combination as demonstrated here; or a thyroid carcinoma. The neoplastic cells typically have bland or minimally atypical. Mitotic activity may be low. Colloid within the follicles often contains birefringent calcium oxalate crystals.

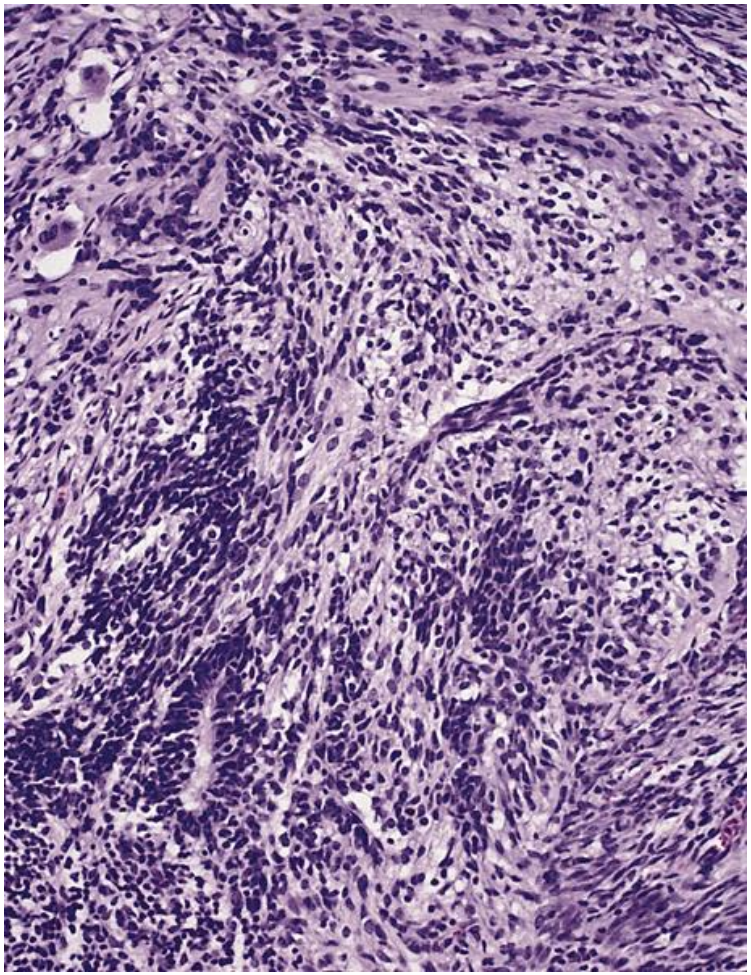
Fig. 15-5

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Immature teratoma

- Prepubertal adolescents and young women
- Unilateral
- Differ from mature teratoma in that there are varying amounts of immature neuroepithelium, cartilage, bone, muscle, and other elements.
- The extent of immature neural tissue determines the grade (and risk)
- Frequently penetrate the capsule and spread locally (initially)

Immature teratoma



This peritoneal implant is composed exclusively of Immature neuroectodermal tissue.

May be associated with anti-NDMA receptor encephalitis.

Fig. 14-10

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Yolk sac tumors

- Second most common malignant germ cell tumor
- Reticular pattern
- A loose meshwork of communicating spaces lined by primitive tumor cells with clear cytoplasm, containing glycogen
- Reticular areas frequently merge with microcystic or macrocystic areas.
- Eosinophilic AFP-positive and α_1-antitrypsin hyaline globules present within and outside cytoplasm.

Yolk sac tumors

- Endodermal sinus pattern
- The presence of single papillae superficially resembling a glomerulus, are characteristic of yolk sac tumor
- They are lined by primitive epithelium, with fibrovascular cores containing single vessels and occupying spaces lined by hobnail cells (Schiller-Duval bodies)
-

Yolk sac tumors

- Polyvesicular vitelline
- Prominent cysts lined by flattened to columnar cells within a variably cellular stroma, occasionally with eccentric constriction
- Resembles the division of the primary yolk sac vesicle
- Other patterns are possible
- A malignant primitive germ cell tumor that shows various patterns of endodermal differentiation (primitive gut, mesenchyme, secondary yolk sac), including their derivatives (intestine, liver, lung)

Yolk sac tumor

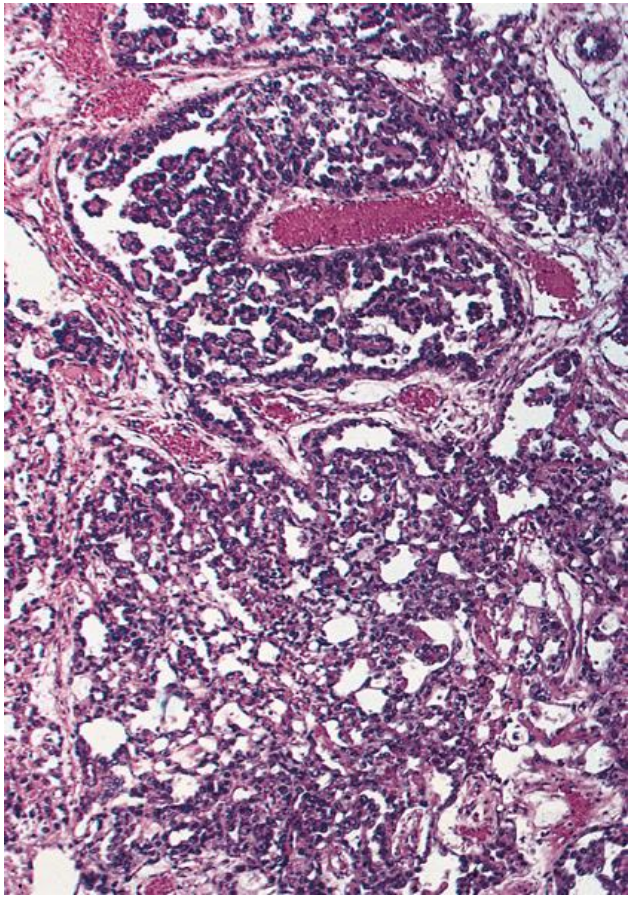
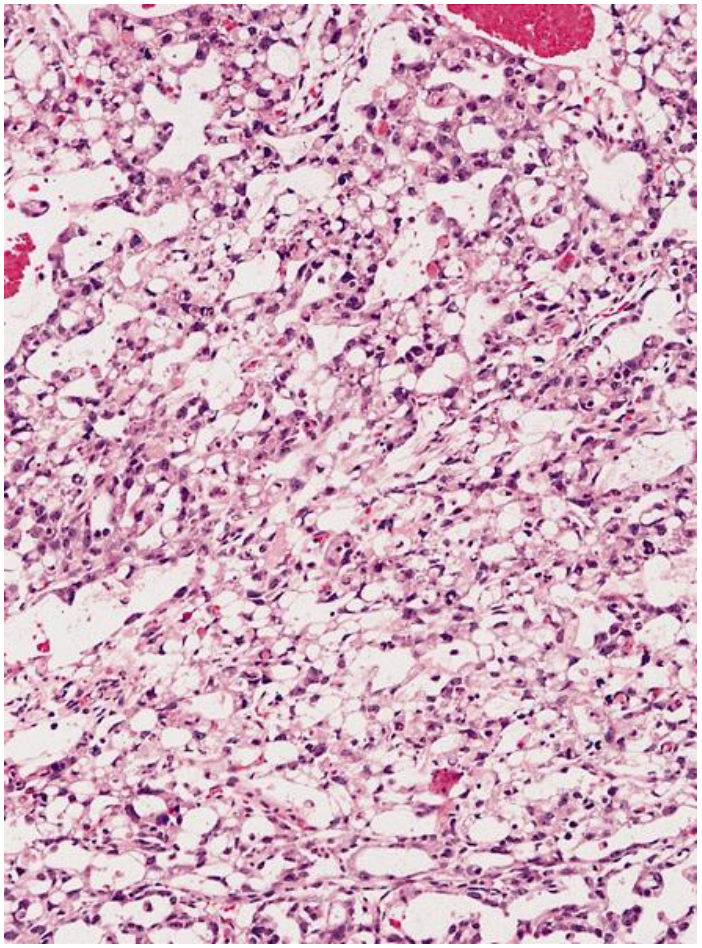


Fig. 13-29

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Most tumors have a reticular pattern characterized by a loose meshwork of communicating spaces lined by primitive tumor cells with cytoplasm that is typically clear, containing glycogen and occasionally, lipid. The hyperchromatic, irregular, large nuclei have prominent nucleoli; mitotic figures are usually numerous. Reticular areas frequently merge with microcystic or macrocystic areas. The presence of Schiller- Duval bodies (single papillae, lined by primitive epithelium, with fibrovascular cores containing single vessels and occupying spaces lined by hobnail cells) are characteristic of yolk sac tumor

Yolk sac tumor

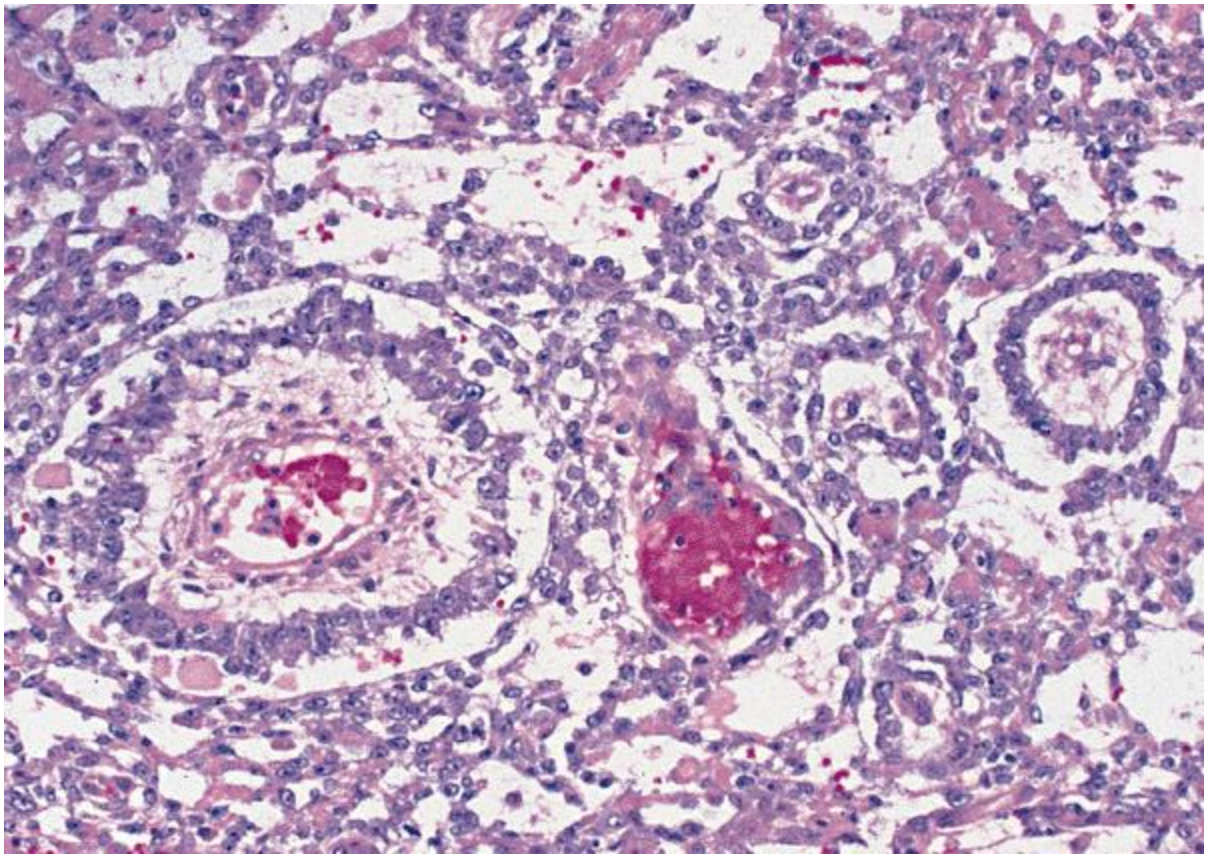


Reticulated pattern. The most common form.

Fig. 4-26

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Yolk sac tumor

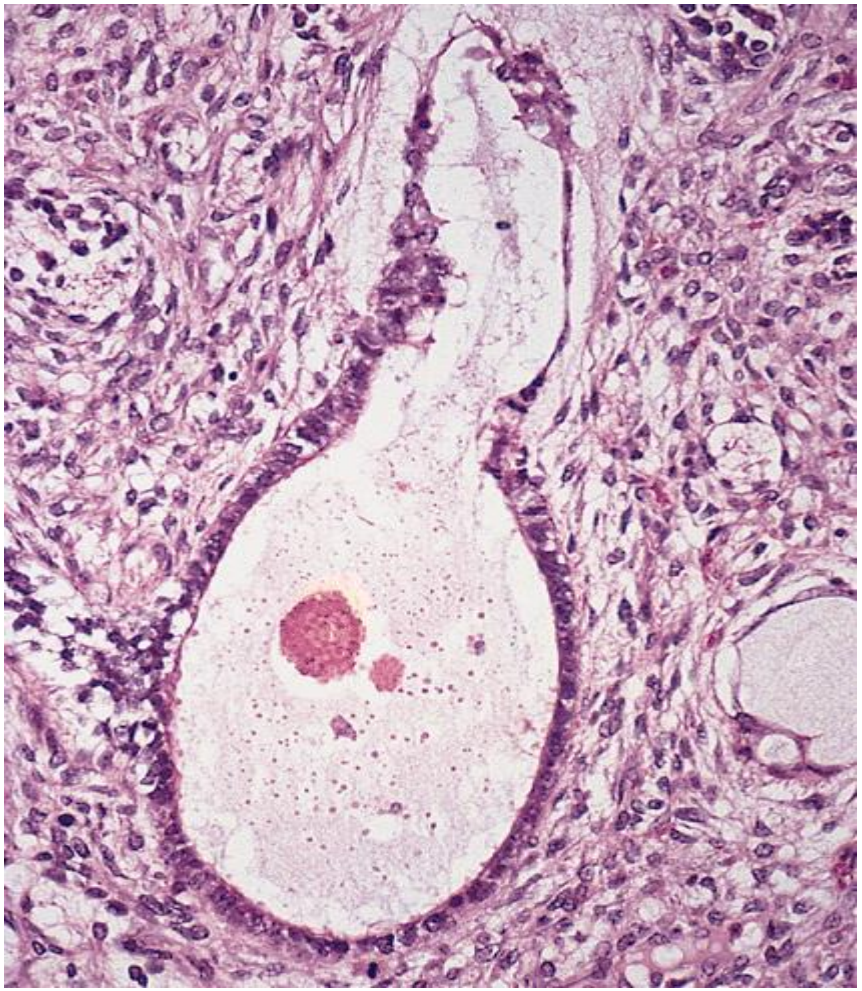


Endodermal sinus pattern.

Fig. 4-32

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

Yolk sac tumor



Polyvesicular vitelline pattern.

Fig. 4-47

T. M. Ulbright, M. B. Amin, R. H. Young, “Tumors of the testis, adnexa, spermatic cord, and scrotum. Atlas of Tumor Pathology, Third Series, Fascicle 25. Armed Forces Institute of Pathology, Washington, DC. 1999.

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Choriocarcinoma

- More commonly of placental origin
- An example of extraembryonic differentiation of malignant germ cells.
- It is generally held that a germ cell origin can be confirmed only in prepubertal females, because after this age an origin from an ovarian ectopic pregnancy cannot be excluded.
- Most ovarian choriocarcinomas exist in combination with other germ cell tumors, and pure choriocarcinoma is extremely rare.
- Produce HCG abundantly

Sex cord stromal tumors

- Derived from the ovarian stroma, which in turn is derived from the sex cords of the embryonic gonad.
- The undifferentiated gonadal mesenchyme produces Sertoli and Leydig cells in the male and granulosa and theca cells in the female gonads
- May present as precocious puberty
- Granulosa and theca cells normally secrete estrogens.
- Tumors are feminizing.
- Leydig cells normally secrete androgens.
- Tumors are masculinizing.

Fibrothecoma

- 4% of ovarian tumors
- 90% unilateral
- Solid, encapsulated, gray-white masses
- Composed of well-differentiated fibroblasts and a scant interspersed collagenous stroma. Focal areas of thecal differentiation may be identified.
- 40% associated with ascites and right hydrothorax (Meig's syndrome)
- Generally benign

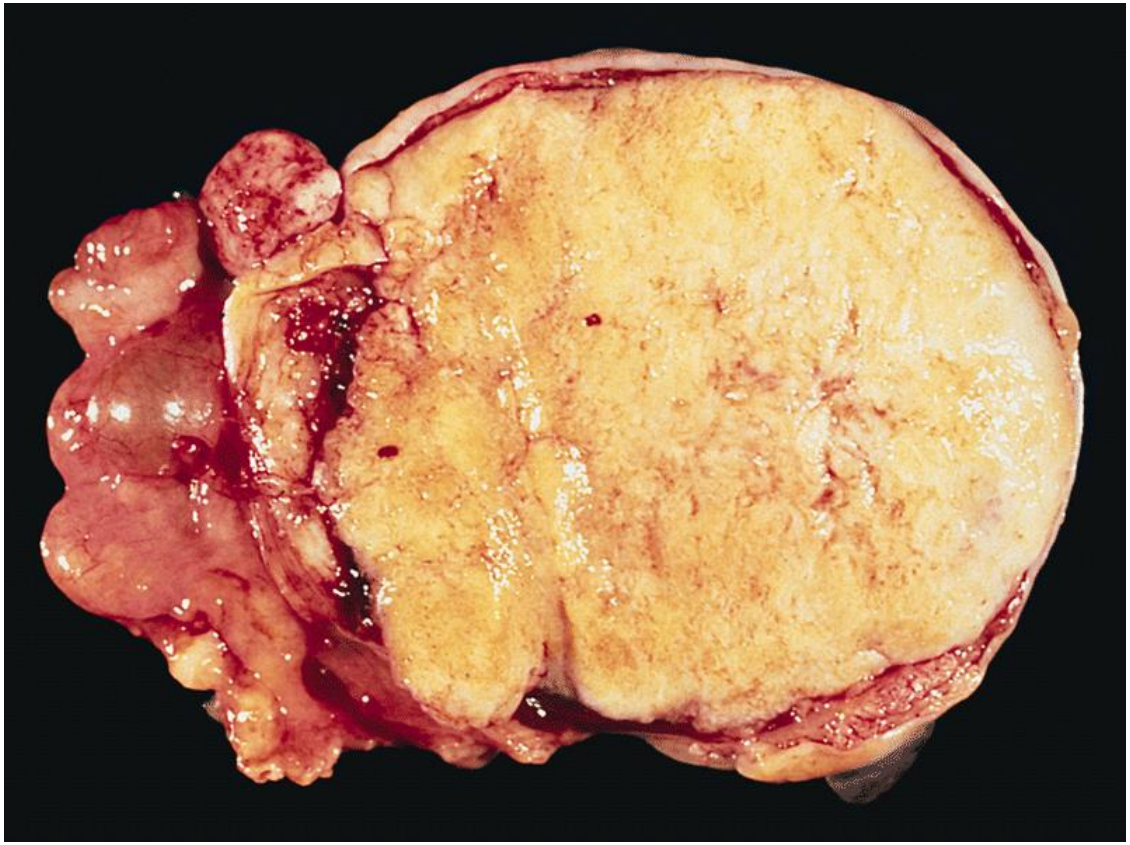
Granulosa-theca cell tumors

- 5% of all ovarian tumors
- Commonly bilateral.
- 40-70 years of age.
- May metastasize
- If in pre-puberty, cause precocious feminization
- Rarely, masculinization.
- May see postmenopausal bleeding.
- Inhibin levels elevated
- 97% of adult type have FOXL2 mutation (controls granulosa cell development)
- Juvenile type of different origin

Granulosa-theca cell tumors

- Tumors that are hormonally active have a yellow coloration to their cut surfaces, due to intracellular lipids.
- Characterized by small, cuboidal to polygonal cells that grow in anastomosing cords, sheets, or strands.
- Small, distinctive, glandlike structures filled with an acidophilic material recall immature follicles (Call-Exner bodies).
- Occasionally, there is a predominant thecoma component that consists of clusters or sheets of cuboidal to polygonal cells.
- Luteinized change may occur.

Granulosa cell tumor

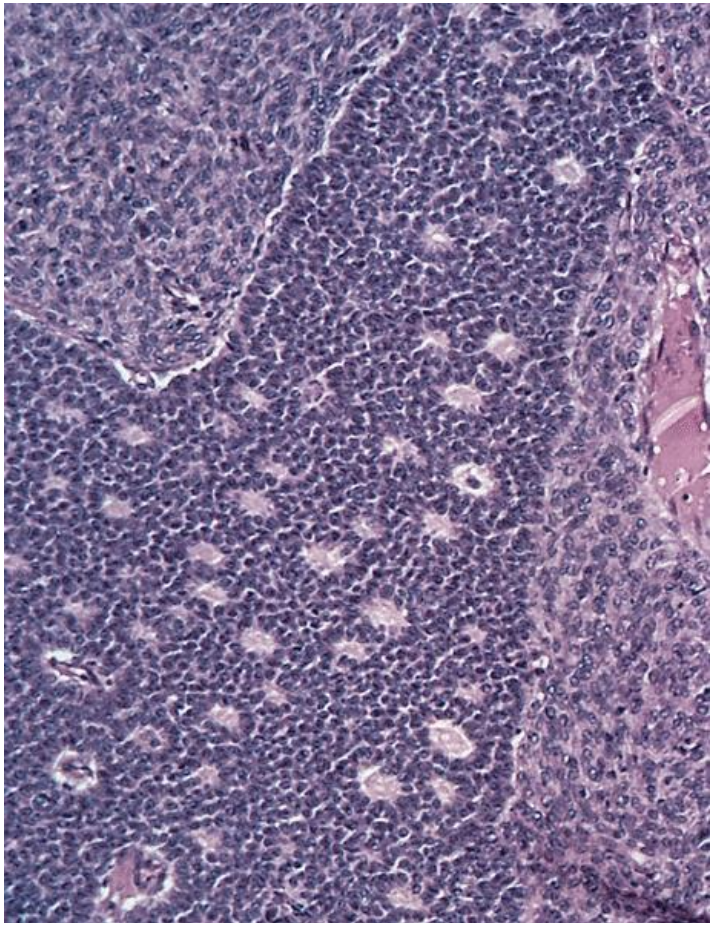


The sectioned surface is uniformly solid and yellow.

Fig. 9-2

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Granulosa cell tumor

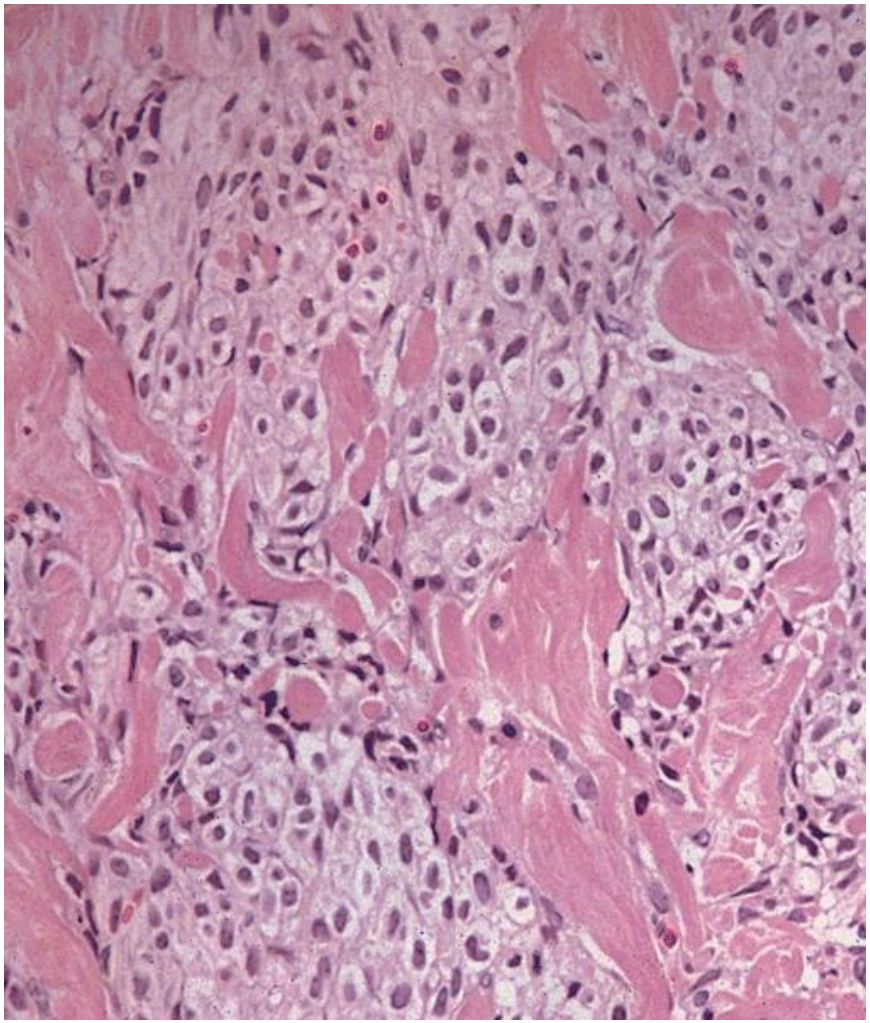


A large, discrete island of granulosa cells contains numerous Call- Exner bodies and is surrounded by a diffuse pattern of granulosa cells.

Fig. 9-7

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Theca cell tumor



The cytoplasm is abundant and vacuolated or pale and dense; it usually contains moderate to large amounts of lipid. The nuclei vary from round to spindle shaped and typically exhibit little or no atypia; mitotic figures are absent or infrequent. Rarely, large bizarre nuclei with a degenerative appearance are seen. Hyaline plaques are often conspicuous.

Fig. 10-3

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Sertoli-Leydig cell tumor

- Teens and twenties
- Unilateral
- Often functional
- Commonly produce masculinization or defeminization
- Produce testosterone as well as other androgens.
- A few have estrogenic effects.

Sertoli-Leydig cell tumor

- Hirsutism, voice change (deepens), acne, and clitoromegaly.
- DICER1 mutations suggests the genesis of male-directed stromal cells may involve abnormalities of gene expression related to dysregulation of miRNAs.
- Rarely metastasize.
- Hysterectomy with bilateral salpingo-oöphorectomy may be curative.

Sertoli-Leydig cell tumor

- Solid, yellow
- Well-differentiated tumors show tubules composed of Sertoli cells or Leydig cells interspersed with stroma.
- The intermediate forms show only outlines of immature tubules and large eosinophilic Leydig cells.
- The poorly differentiated tumors have a sarcomatous pattern with a disorderly disposition of epithelial cell cords. Leydig cells may be absent.

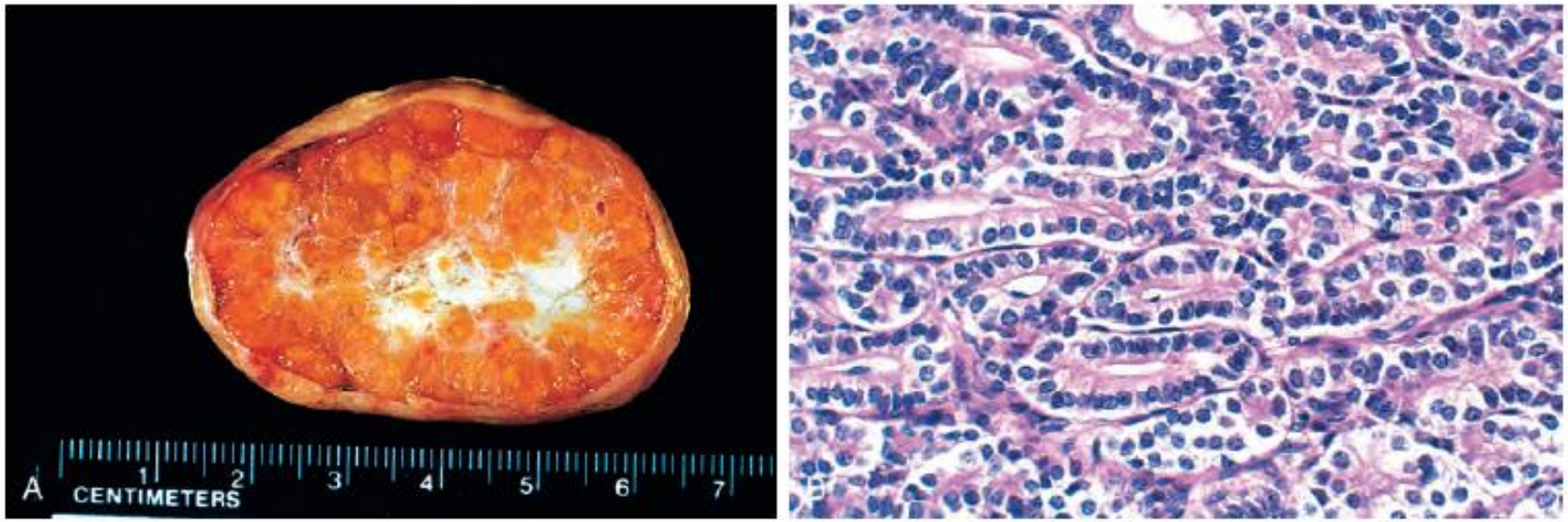
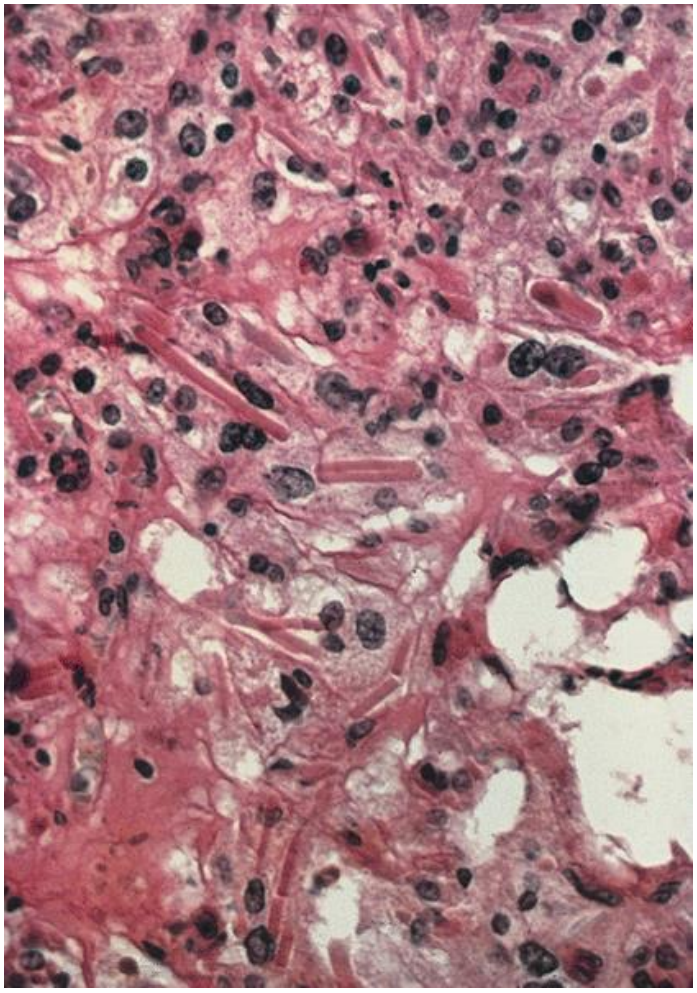


Figure 22-45 Sertoli cell tumor. **A,** Gross photograph illustrating characteristic golden-yellow appearance of the tumor. **B,** Photomicrograph showing well-differentiated Sertoli cell tubules. (Courtesy Dr. William Welch, Brigham and Women's Hospital, Boston, Mass.)

Other ovarian tumors

- Hilus cell tumors (pure Leydig cell tumors)
- Derived from clusters of polygonal cells arranged around hilar vessels.
- Unilateral
- Large lipid-laden Leydig cells with distinct borders and characteristic cytoplasmic structures (Reinke crystalloids).
- Masculinizing as produce testosterone
- Pregnancy luteoma
- Resembles corpus luteum
- May produce virilization in pregnant patients and their female infants.

Leydig cell tumor



A prominent fibrous stroma subdivides the tumor into cellular lobules. Many of the nuclei have enlarged, hyperchromatic, bizarre nuclei. Elongated eosinophilic crystals of Reinke are conspicuous in the cytoplasm of several
tumor cells.

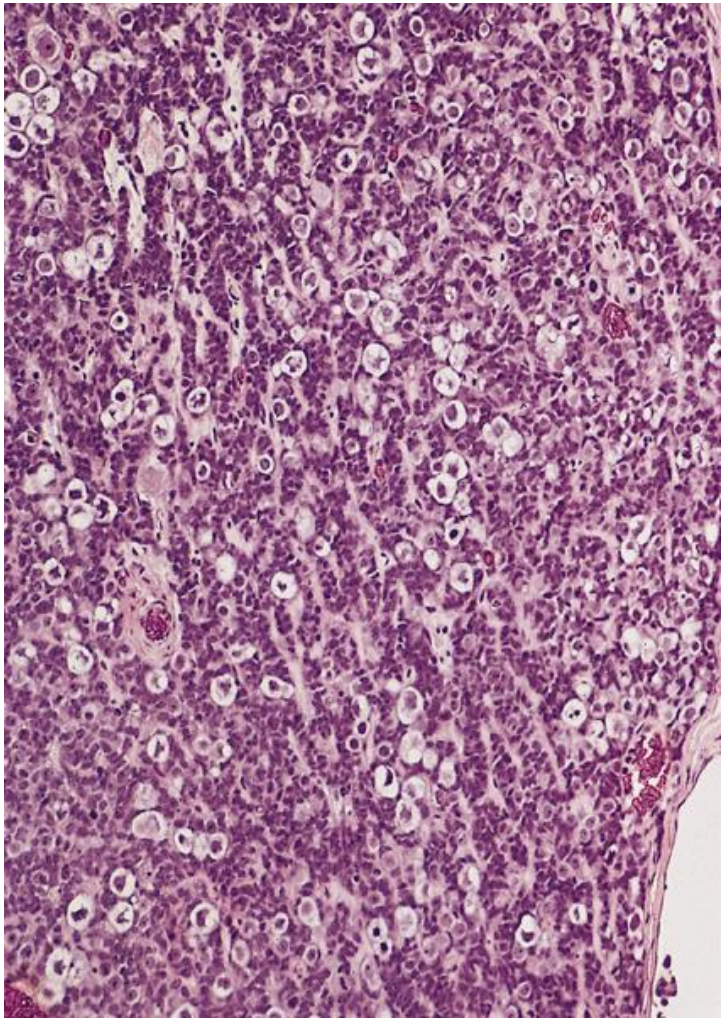
Fig. 12-11

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Other ovarian tumors

- Gonadoblastoma
- Composed of germ cells and sex cord-stroma derivatives resembling immature Sertoli and granulosa cells.
- It occurs in individuals with abnormal sexual development and in gonads of indeterminate nature.
- 80%, phenotypic females
- 20%, phenotypic males with undescended testicles and female internal secondary organs.
- A coexistent dysgerminoma occurs in 50% of the cases.

Gonadoblastoma



An admixture of germ cells and smaller cells with abundant clear cytoplasm are scattered within long, anastomosing cords and trabeculae.

Fig. 16.6

Scully, Robert E, Young, Robert H, Clement, Phillip B. Tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Atlas of Tumor Pathology, Third Series, Fascicle 23. Armed Forces Institute of Pathology. Washington, D.C, 1998

Undifferentiated tumors

- Among undifferentiated cancers, some mimic undifferentiated carcinomas of other organs (lung)
- One aggressive type associated with hypercalcemia typically arises in the first decades.
- Metastatic tumors from the gastrointestinal tract may simulate primary mucinous carcinomas.

Therapy

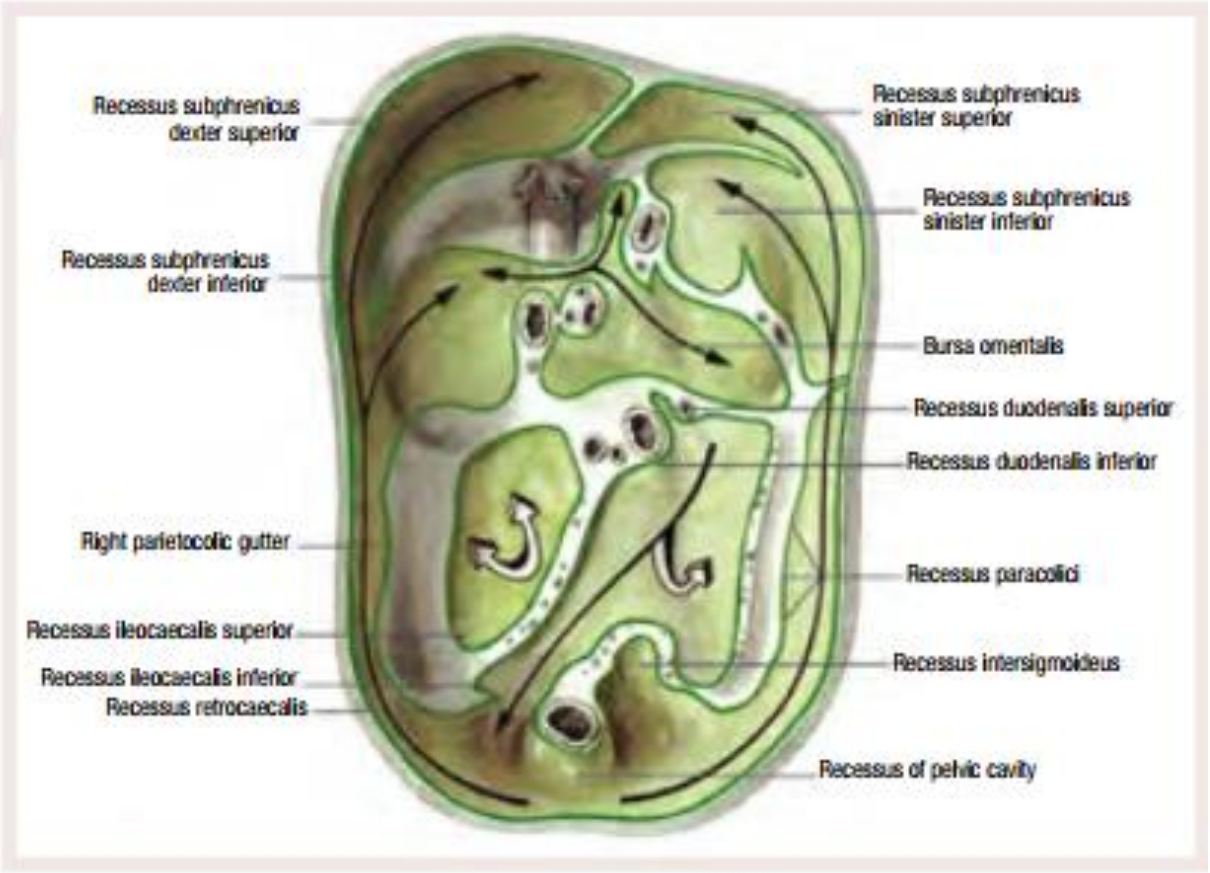
- Complete staging in assumed early-stage ovarian cancer consists of:
- Systematic assessment of the abdominal cavity
- Hysterectomy with bilateral salpingo-oophorectomy, omentectomy, appendectomy (in mucinous histology)
- Peritoneal mapping, peritoneal washing
- Systematic pelvic and para-aortic lymphadenectomy.
- Systematic lymphadenectomy results in detection of metastasis in 22% of patients, compared to 9% with lymph-node sampling only.

Therapy

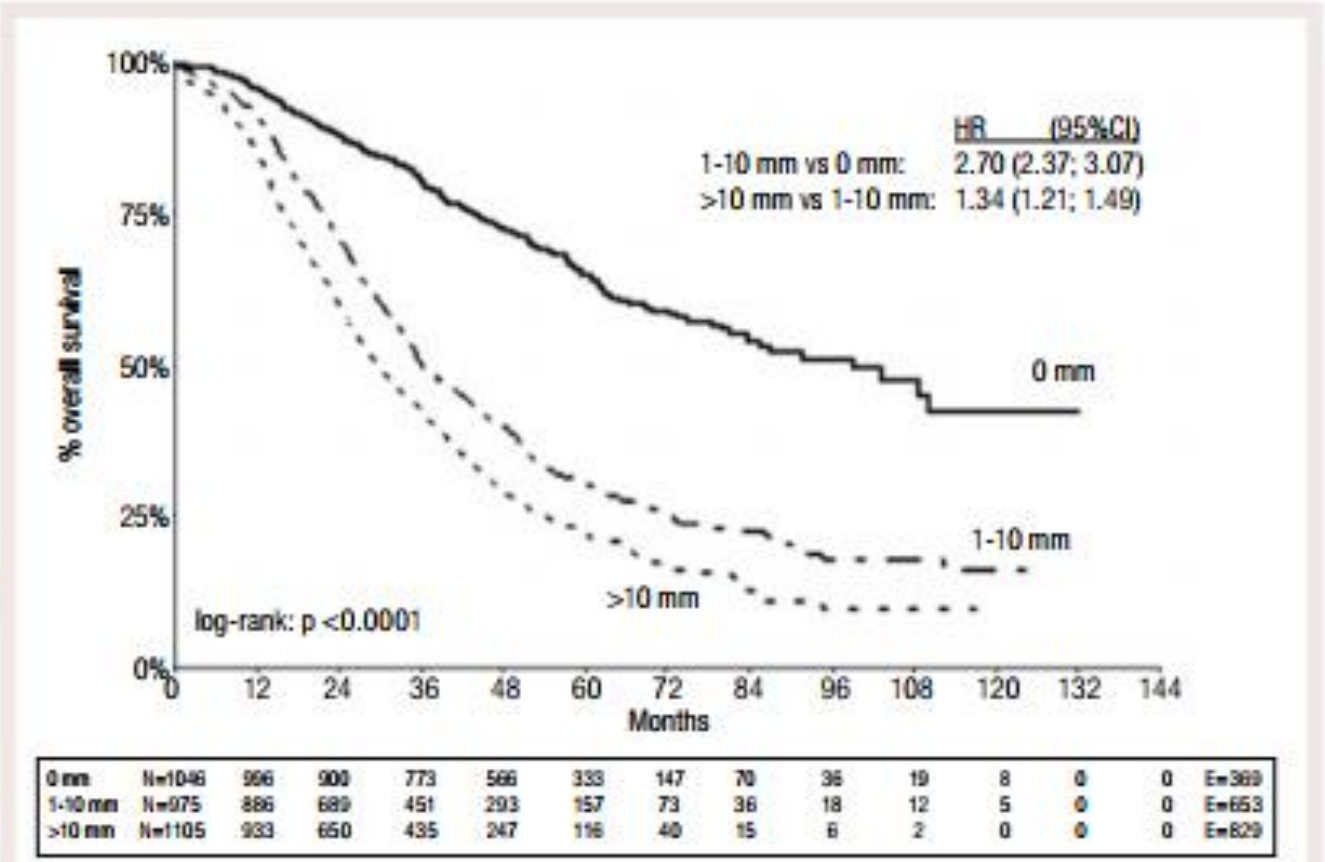
- In case of ovarian cancer confined to one of the ovaries, fertility-sparing surgery should be discussed with women with childbearing potential.
- The overall recurrence rate is higher in fertility-sparing surgery, however.
- Open incision surgery is the standard of care.
- Given the biology and tumor spread of ovarian cancer, complete tactile and visual exploration of the abdomen can only be performed through open surgery.
- Laparascopic and robotic surgery are not recommended

Therapy

- A major principal of surgery in advanced ovarian cancer is the extraperitoneal en-bloc resection of the peritoneum together with the tumor.
- Resection of the sigmoid colon is necessary in about 60%–70% of patients
- The pelvis can be cleared of tumor with this approach.
- Surgical debulking important.
- Residual disease >1mm is associated with poor outcomes.



Sites of tumor spread in the peritoneum (green)



CI, Confidence interval; HR, hazard ratio.

Therapy

- Adjuvant platinum-based chemotherapy confers an overall survival benefit compared to observation for patients with FIGO Stage 1 ovarian cancer, especially in those with higher grade stage early cancers (G2/3 Stage 1b/c).
- Else, observation alone is acceptable if optimally staged,
- Chemotherapy with carboplatin and paclitaxel is now first line therapy for women with FIGO Stage II-IV ovarian cancer.

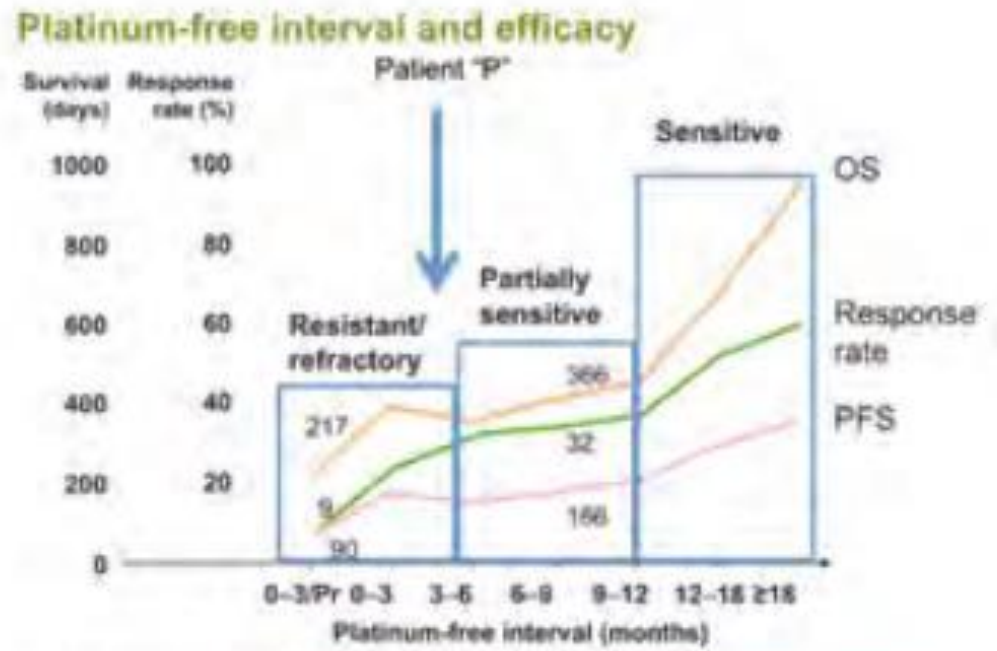
Therapy

- The addition of bevacizumab and increasing maintenance to 12 months improves overall survival in those with residual disease
- Intraperitoneal chemotherapy leads to better outcomes.
- 70% of Stage III/IV patients will relapse

Therapy

- A rising CA125 is not a reason to reinstitute chemotherapy (in the absence of the presence of demonstrable tumor)
- Maintenance with the PARP inhibitor, olaparib, improves progression free survival in patients with a germline BRCA mutation.
- There is no agreed upon therapy for platinum resistant tumors.

Rechallenge with platinum-based therapy



OS, Overall survival; PFS, progression-free survival.

Therapy

- 25% of chemotherapy treated germ cell tumor patients develop metabolic syndrome
- 2% germ cell tumors relapse after 2 years

Therapy

- Bevacizumab (Anti-VEGF) delays progression in recurrent ovarian cancer as well as in those women with residual tumors >1cm or who are Stage IV at diagnosis.
- Bevacimuzab and olaparpib (PARP inhibitor) enhance response in ovarian adenocarcinoma.