Gynaecological Malignancies

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Overview

Genital tract tumors account for 15% of all female malignancies

Anatomical pathology:

- Vulva carcinoma
- Vaginal carcinoma
- Cervical carcinoma
- Uterine tumors
- Ovarian tumors

Vulva Carcinoma

- Affects elderly women
- 3% of genital tract cancers
- 95% of vulva tumors are squamous cell carcinoma
- Invasive cancer is preceded by vulva intraepithelial neoplasia (VIN) & graded from I, II and III in a manner similar to preinvasive carcinoma of the cervix
- SCC is associated with HPV type 16, 18, 31 or 33 infection. Same strains associated with SCC of vagina & cervix.
- Malignant melanoma of vulva accounts for 10% of vulva tumors.
- Pagets disease of vulva similar to Pagets disease of the breast. Associated with underlying adenocarcinoma of apocrine sweat glands.

Vaginal Carcinoma

- Vaginal squamous cell carcinoma accounts for 1% of all genital tract cancer in women.
  - Patients with vaginal carcinoma often have vulva or cervical carcinoma.
- Vaginal clear cell adenocarcinoma is seen in young women exposed to diethylstilbestrol (DES) during fetal development.
- Vaginal adenosis is thought to be a precursor of clear cell adenocarcinoma. Adenosis is characterised by mucosal columnar epithelial lined crypts in areas normally lined by stratified squamous epithelium.
- Sarcoma botryoides is a rare variant of rhabdomyoscarcoma.
  - Occurs in children <5.
  - Presents as multiple polypoid masses resembling "bunch of grapes" projecting into the vagina, often protruding from vulva.

Cervical Carcinoma

- Accounts for 20% of gynaecolocal cancers
- Associated with HPV types 16, 18, 31 & 33 infection.
- Peaks in middle aged women
- Early sexual activity and multiple sexual partners associated with increased incidence.
- Other risk factors: sexual worker, low socio-economic status, cigarette smoking and promiscuity.
- Introduction of Papanicolaou (PAP) cytological screening has significantly reduced mortality.
- HPV vaccine now available

Pathology & Pathogenesis

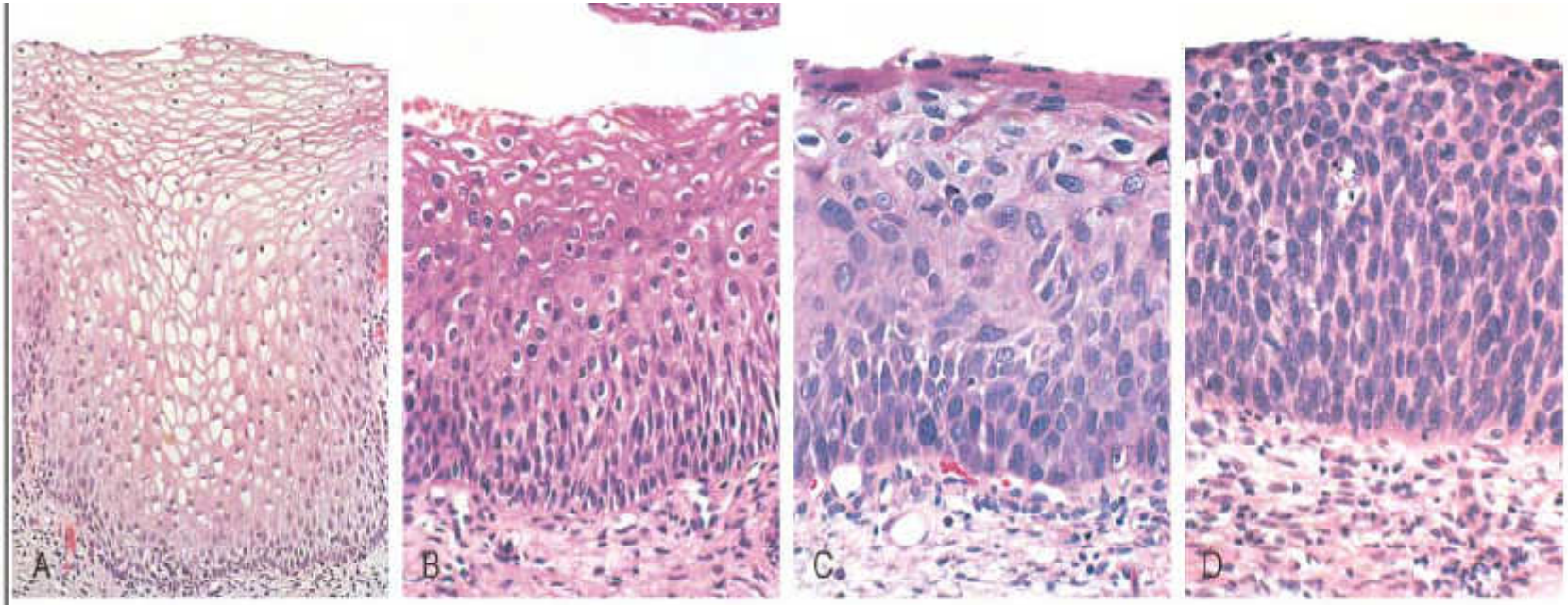
Pathology:

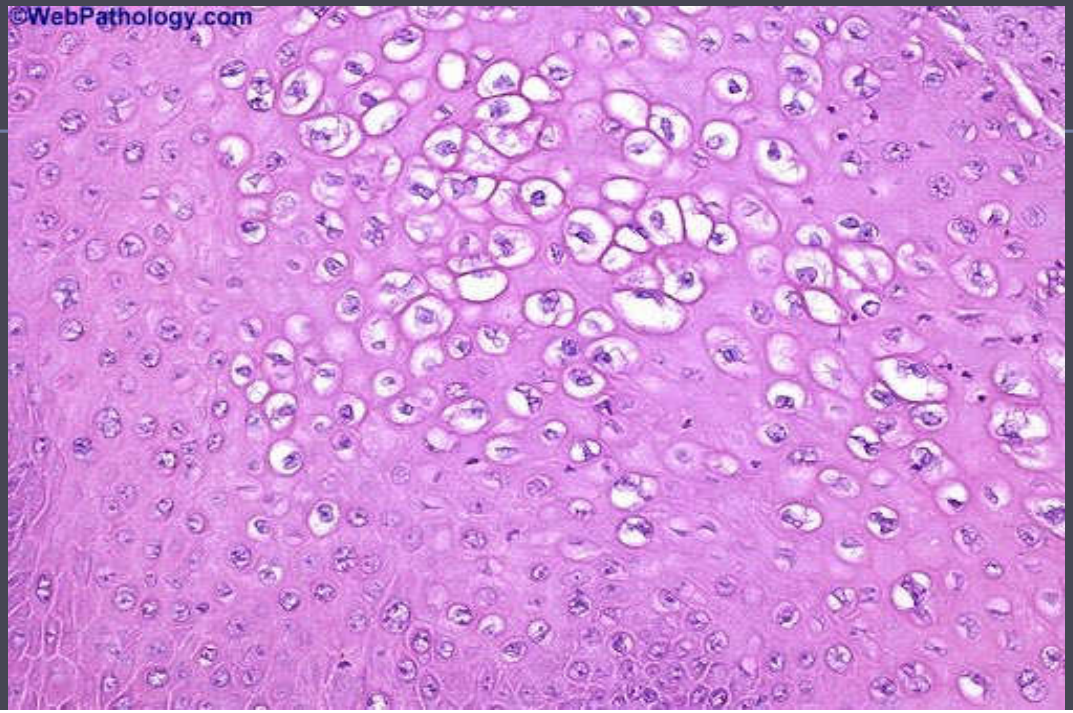
- Squamous cell carcinoma common type (95%)
- Adenocarcinoma accounts for 5% of cases only
- Role of HPV:
  - Dysplastic cells exhibit koilocytosis (as in HPV induced condonyloma acuminatum).
  - HPV genomic squences often intergrated into genomes of dysplastic or malignant cervical epithelial cells (HPV – 16, 18, 31, 33). HPV associated with 90% of cases.
  - HPV viral proteins E6, E7 bind & inactivate gene products of p53 & Rb respectively. Both tumor suppressor genes. Gene Products are tumor suppressor proteins.

Cervical Carcinoma

Pathological findings:

- Most tumors originate from the transitional zone.
- Invasive squamous cell carcinoma is preceded by cervical intraepithelial neoplasia (CIN) a curable condition.
- CIN I – mild dysplasia. Maturation limited to basal and parabasal layers.
- CIN II – moderate dsyplasia
- CIN III – carcinoma in-situ. Atypical cells through the entire thickness of the epithelium,


A
B
C
D
Normal
CIN I
CIN II
CIN III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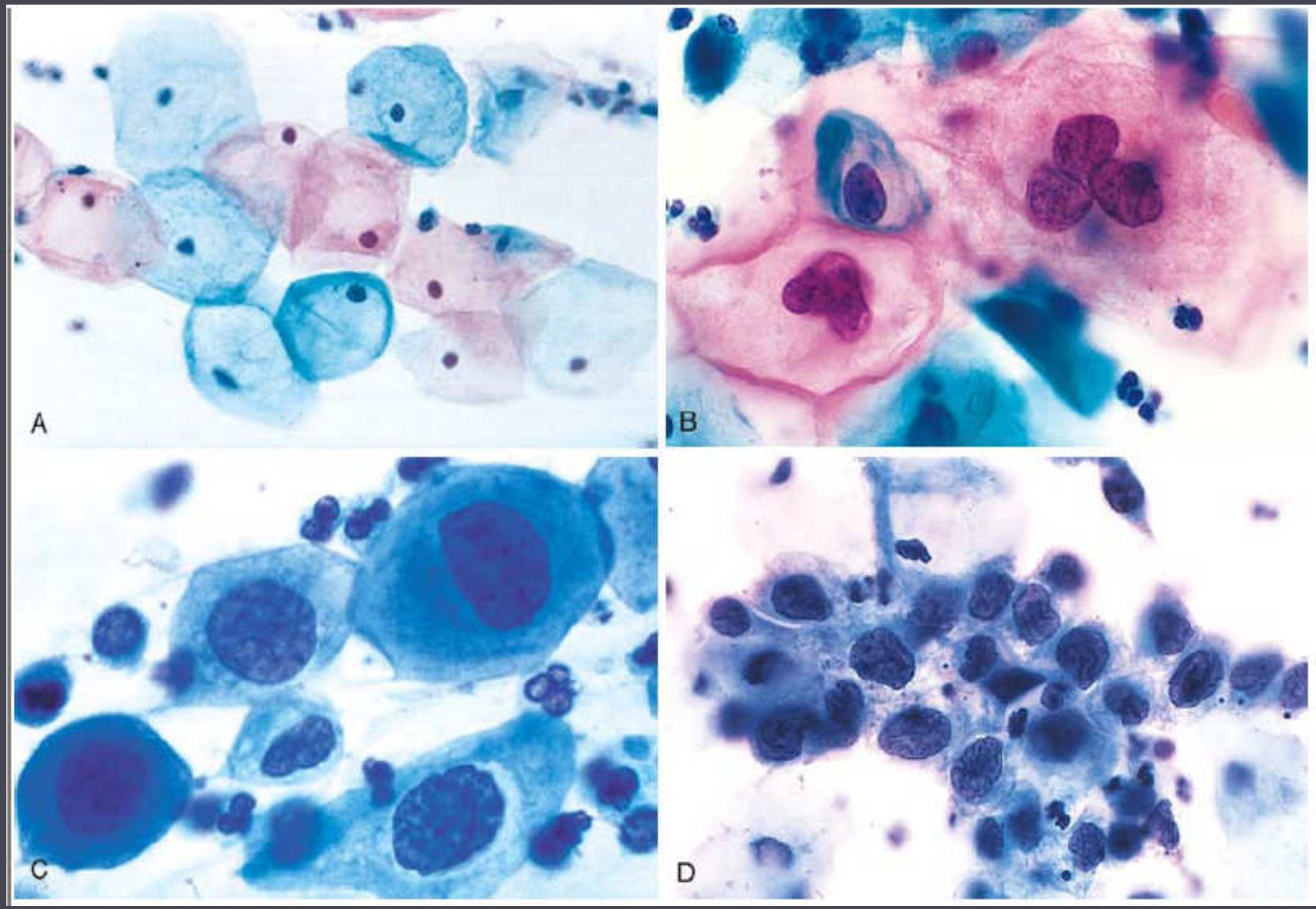
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Uterine Carcinoma

- Uterus most common site for gynaecological malignant tumors and often seen in older women (post-menopausal).
- Endometrial Carcinoma of uterus accounts for 50% of all gynaecological cancers
- Risk factors: nulliparity, obesity, diabetes mellitus & hyperrestrinism (prolonged estrogen stimulation causing endometrial hyperplasia)
- Pathology: 95% are adenocarcinomas. Preceded by high grade endometrial dysplasia & hyperplasia.
- **Abnormal vaginal bleeding (post-menopausal) or spotting is the common clinical presentation. Needs endometrial biopsy. "Red Flag" in post-menopausal women. Biopsy mandatory!!**

Myometrial tumors: Leiomyoscarcomas is rare malignant tumor that enlarges the uterus. Arises de novo.

Rare: endometrial stromal sarcoma (stromaL cells) & mixed mullerian tumors (glandular & stromal cells)

TABLE 19-1 *Comparison of Tumors of the Female Reproductive System*

Type	Behavior	Location	Comments
Condyloma acuminatum (venereal wart)	Benign	Vulvovaginal, perianal, sometimes cervical	Most often multiple; etiologic agent HPV (types 6 and 11)
Squamous cell carcinoma	Malignant	Vulva	May be preceded by atypical hyperplastic dystrophy
Clear cell adenocarcinoma	Malignant	Vagina	Peak incidence in teenagers and young women exposed in utero to DES
Squamous cell carcinoma	Malignant	Vagina	Uncommon location for primary squamous cell carcinoma; more often due to extension of squamous cell carcinoma of the cervix
Squamous cell carcinoma	Malignant	Uterine cervix	Squamocolumnar junction most frequent site of origin; often preceded by dysplasia; HPV (types 16, 18, 31, and 33) is suspected to be the etiologic agent
Leiomyoma	Benign	Uterine corpus	Most frequently occurring neoplasm of women; most often multiple; increases in size during pregnancy; regresses with menopause
Endometrial carcinoma	Malignant	Uterine corpus	Peak incidence in older age group; predisposed by estrogen stimulation; incidence increasing
Cystadenoma, serous or mucinous	Benign	Ovary	
Cystadenocarcinoma, serous or mucinous	Malignant	Ovary	Rupture of mucinous form can lead to pseudomyxoma peritonei
Mature teratoma (dermoid cyst)	Benign	Ovary	Most frequent ovarian tumor
Choriocarcinoma	Malignant	Ovary or gestational tissue	Increased hCG in serum and urine
Fibroma	Benign	Ovary	Can be associated with Meigs syndrome (ovarian fibroma, ascites, and hydrothorax)
Granulosa cell tumor	Benign	Ovary	Estrogen-secreting
Krukenberg tumors	Malignant	Ovaries	Metastatic replacement of ovaries with signet-ring cells from primary malignant tumor elsewhere (often from the stomach)

HPV = human papillomavirus; DES = diethylstilbestrol; hCG = human chorionic gonadotropin.

Ovarian Tumors

- Classified by WHO based on **site of origin** of tumor.

- Tumors of surface epithelial origin
  - e.g. serous cystadenocarcinoma
- Tumors of germ cell origin
  - e.g. Teratoma
- Tumors of ovarian sex cord-stromal origin
  - e.g. granulosa –theca cell tumor
- Tumors metastatic to the ovary
  - e.g. Krukenberg tumors

Classification of Ovarian Tumors

Table 24–3. OVARIAN NEOPLASMS (1993 WHO CLASSIFICATION)

Surface epithelial-stromal tumors
Serous tumors
  Benign (cystadenoma)
  Of borderline malignancy
  Malignant (serous cystadenocarcinoma)
Mucinous tumors, endocervical-like and intestinal type
  Benign
  Of borderline malignancy
  Malignant
Endometrioid tumors
  Benign
  Of borderline malignancy
  Malignant
  Epithelial-stromal
    Adenosarcoma
    Mesodermal (müllerian) mixed tumor
  Clear cell tumors
    Benign
    Of borderline malignancy
    Malignant
  Transitional cell tumors
    Brenner tumor
    Brenner tumor of borderline malignancy
    Malignant Brenner tumor
    Transitional cell carcinoma (non-Brenner type)

Sex cord–stromal tumors
Granulosa-stromal cell tumors
  Granulosa cell tumors
  Tumors of the thecoma-fibroma group
Sertoli-stromal cell tumors; androblastomas
Sex cord tumor with annular tubules
Gynandroblastoma
Steroid (lipid) cell tumors

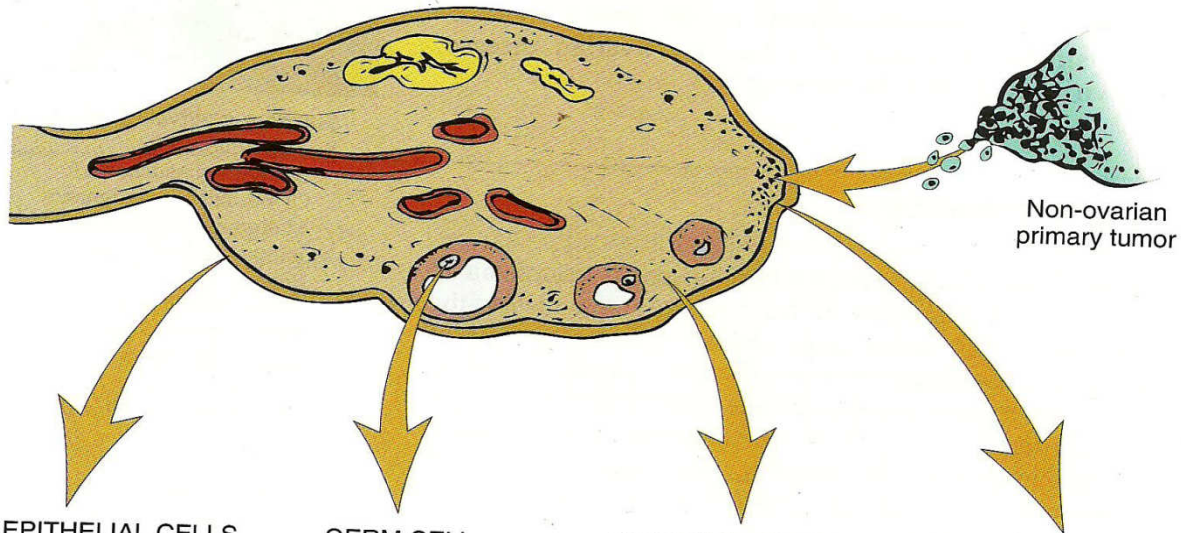
Germ cell tumors
Teratoma
  Immature
  Mature (adult)
    Solid
    Cystic (dermoid cyst)
  Monodermal (e.g., struma ovarii, carcinoid)
Dysgerminoma
Yolk sac tumor (endodermal sinus tumor)
Mixed germ cell tumors

Malignant, not otherwise specified

Metastatic nonovarian cancer (from nonovarian primary)

REF: Robins Pathological Basis of Diseases, 7th Ed.

Tumors of ovaries



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

REF: Robins Pathological Basis of Diseases, 7th Ed.

Tumors of surface epithelial Origin

- Serous tumors
  - Serous cystadenocarcinoma:
  - Accounts for 50% of ovarian carcinomas. Frequently bilateral.
  - Single cyst with serous fluid
- Mucinous tumors
  - Mucinous cystadenocarcinoma:
  - Tumor through rapture can result in pseumyxoma peritonei, multiple tumor implants all producing intraperitoneal mucinous material.
  - Multiloculated cyts with mucin
- Endometrioid tumors: cells resemble endometrium but malignant.
- Clear cell tumors – rare. Almost always malignant.

Germ cell tumors

- Account for 25% of ovarian tumors.
- High in women younger than 25 years of age.
- Teratomas: demonstrate tissue elements derived from 2 or 3 embryonic layers. Embryonal layers – ectoderm, endoderm & mesoderm.
- Observed in 3 distinct catergories
  - Mature - dermoid cyst. Benign. 20% ovarian tumors. 90% of germ cell tumors. Contains hair, tooth, cartilage, bone etc.
  - Immature - aggressive malignant tumor & includes immature cellular elements.
  - Monodermal teratoma – contains single element. Common one is struma ovarii consisting of hyperfunctioning thyroid tissue.
- Dysgerminoma (ovarian counterpart of serminoma)
- Endodermal sinus (yolk sac tumor)
- Choriocarcinoma – secretes hCG. Primary ovarian tumor. Highly metastatic. Unresponsive to chemotherapy in contrast to those arising from placental tissue.

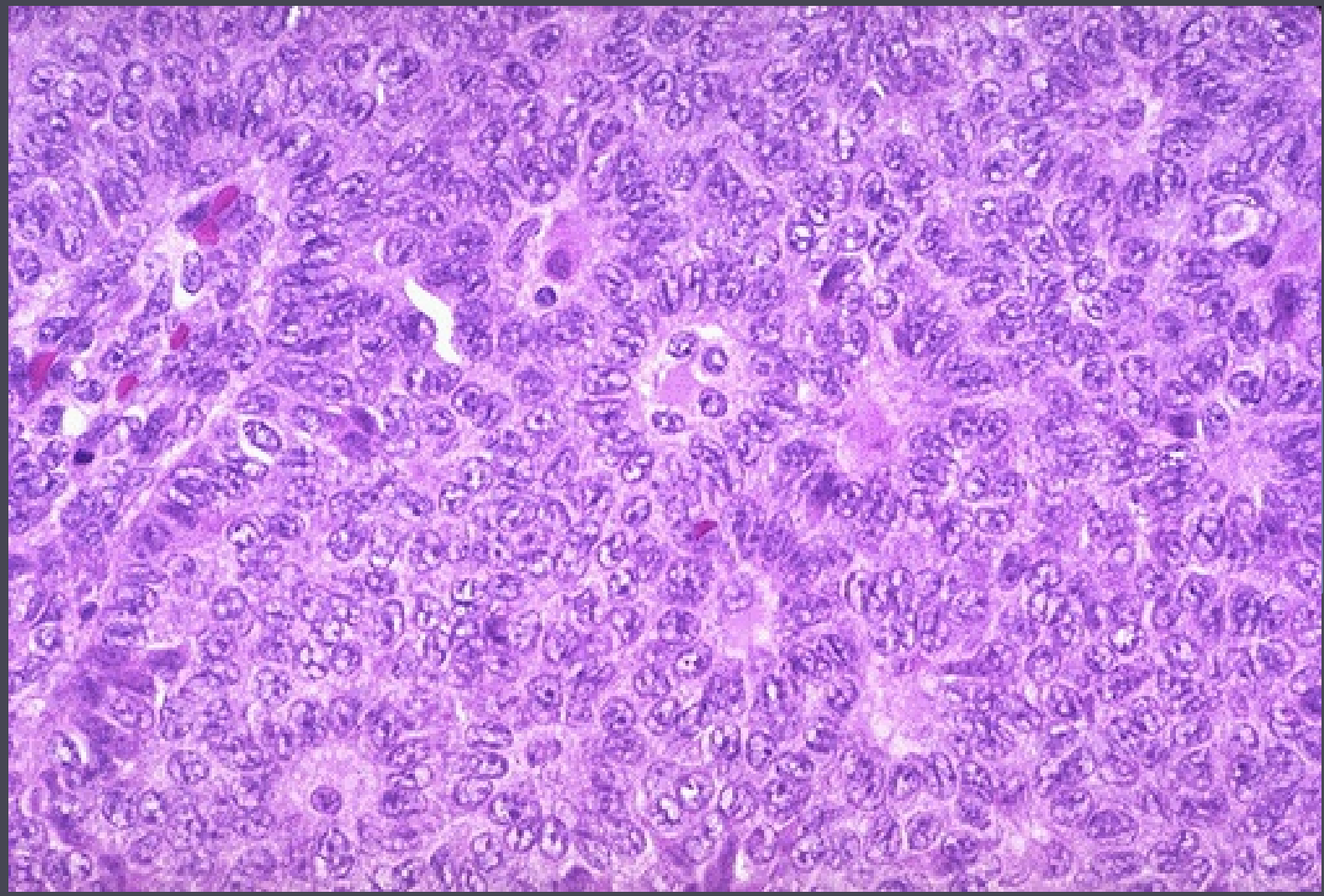
Ref: Internet Pathology Library, Mercer University

Gross: Teratoma

Tumors of ovarian sex-cord-stromal origin

- Rare. Peak incidence in women 25-45.
- Granula cell tumors:
  - Secretes oestrogen & can cause precocious puberty. In post menopausal will cause endometrial hyperplasia.
  - Adults results in endometrial hyperplasia or endometrial carcinoma.
  - Tumor consists of small cuboidal deeply staining granulosa cells arranged in anastomotic cords.
- Sertoli-Leydig cell tumor (androblastoma, arrhenoblastoma): secretes androgen thus can cause virilism (masculinisation).
  - Can be benign or malignant.

Micro: Granulosa cell tumor



Ref: Internet Pathology Laboratory, Mercer University

http://library.med.utah.edu/WebPath/webpath.html#MENU

Metastatic Tumors to Ovary

- Uterus
- Fallobian tube
- Contralateral ovary
- Pelvic peritoneum
- Breast
- GIT (including biliary tract & pancrease)
- Krukenberg tumor – ovarian metastasis from GIT adenocarcinoma. Often from stomach.
  - Characterised by mucin secreting **signet-ring** cells replacing both ovaries.

Diagnosis

- Biopsy
- EUA
- Tumor markers where appropriate
- Medical imaging – USS, CT, MRI

- Prognosis variable between type of cancer and clinical stage.
- All malignant cancer outcome measured in 5 year survival rates from time of diagnosis with & without treatment.

End

- Robins Pathological Basis of Diseases – what ever edition you have.

- PDF format of presentation & study guides will be available on:

www.pathologyatsmhs.wordpress.com

Useful website: http://library.med.utah.edu/WebPath/

Work through study guides.

Study Guide

- List the germ cell tumors in order of frequency of occurrence, from most common to least common.
- Describe the pathology of each of the germ cell tumors.
- Differentiate the benign from the malignant germ cell tumors.

Study Guide

- Describe the pathology of each of the sex cord tumors.
- How is diagnosis confirmed?
- What are the common malignant tumors that metastasis to the ovaries?
- What is a Krukenberg tumor? Describe the macroscopic and microscopic features of this tumor

Study Guide

- List the 5 year survival rates for all the malignant cancers coverered in this seminar.