Reproduction Block

Pathology Practicals

Prepared by:

- *Prof. Ammar Al Rikabi*
- *Dr. Sayed Al Esawy*

Head of Pathology Department: Dr. Hisham Al Khalidi

Objectives:

At the end of the practical classes, the medical students should be able to:

- Know the normal structure of the male and female genital systems.
- Acquire the knowledge about the gross appearances and histopathological features of the following diseases in the Male and Female genital systems and breast.

Contents:

1st Practical *(Male Genital System):*

- Testicular Atrophy.
- Seminoma of the testis.
- Embryonal carcinoma and teratoma of testis.
- Prostatic Hyperplasia.
- Adenocarcinoma of the prostate.

2nd Practical *(Female Genital System)* :

- Uterine Leiomyomata.
- Endometrial hyperplasia and carcinoma.
- Endometriosis.
- Cervical dysplasia and carcinoma.
- Acute salpingitis.

3rd Practical *(Ovarian & Breast diseases):*

- Ovarian cysts and breast masses.
- Dermoid cysts (Teratoma) of the ovary.
- Breast diseases (Fibroadenoma, invasive ductal carcinoma and Paget's disease of the nipple)

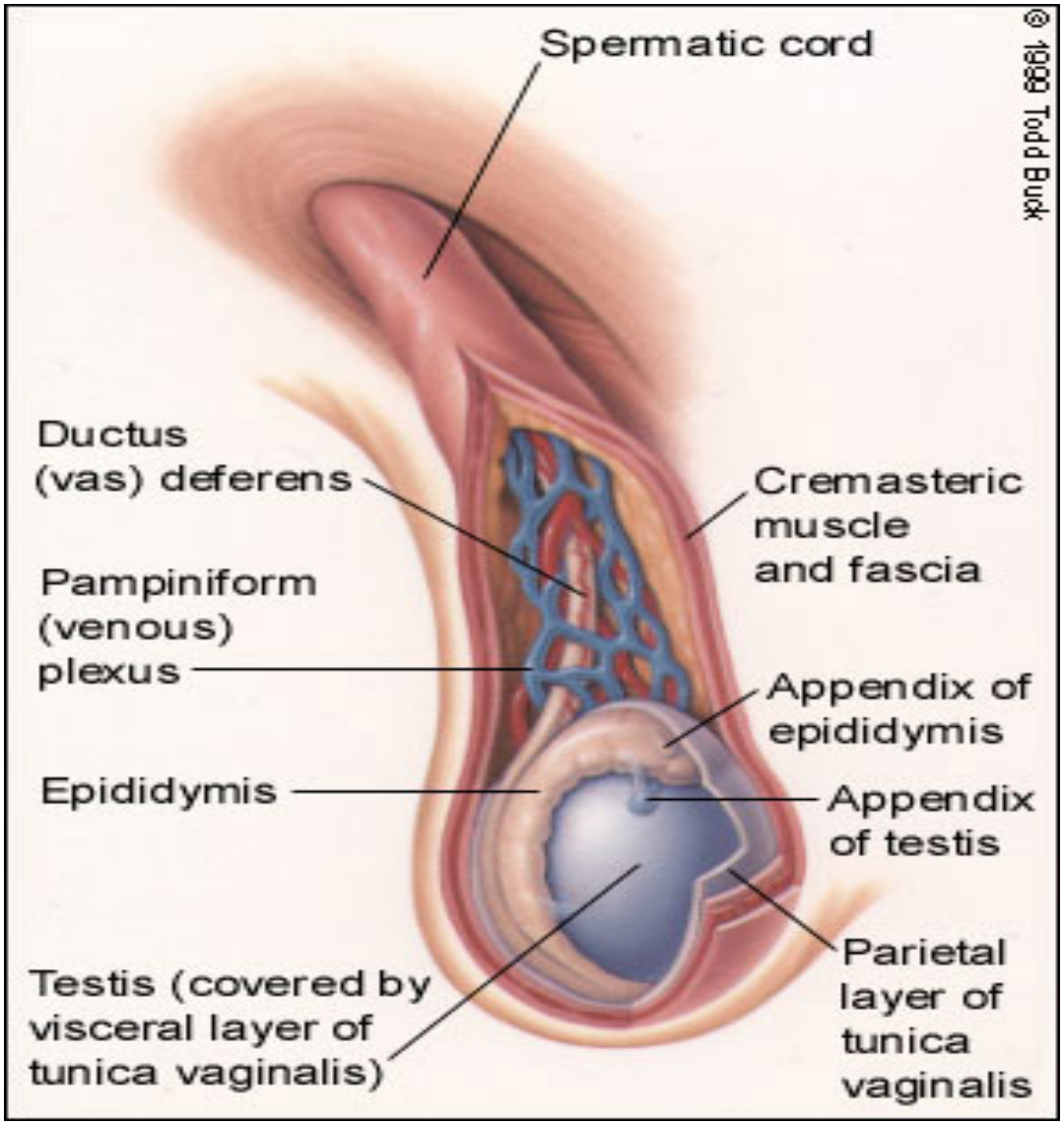
1st Practical Session

MALE GENITAL SYSTEM

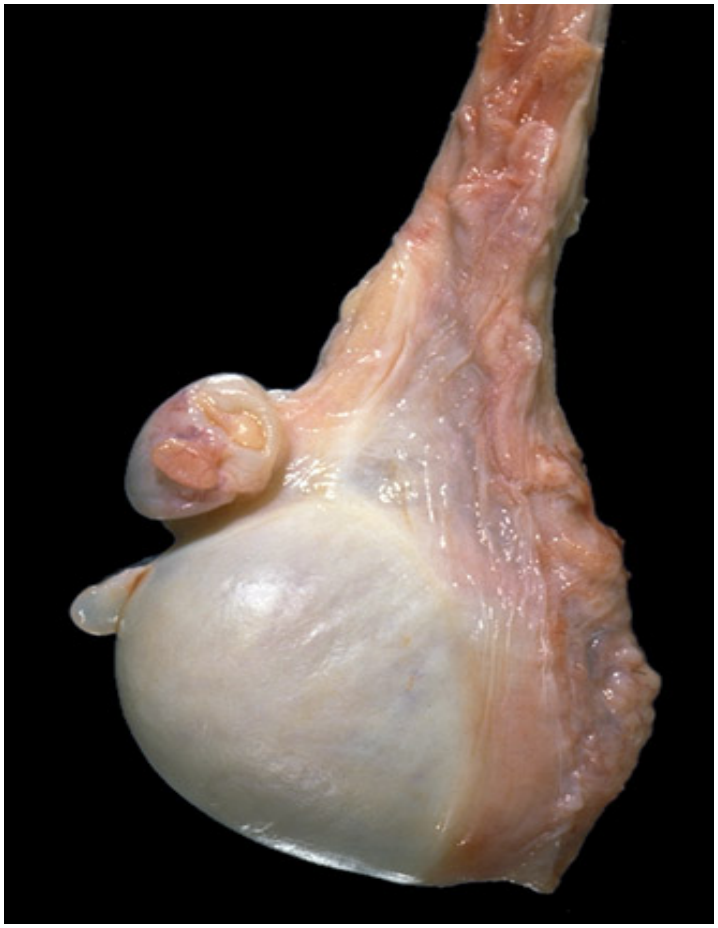
TESTIS

Normal Anatomy and Histology

Diagram of Normal Testis

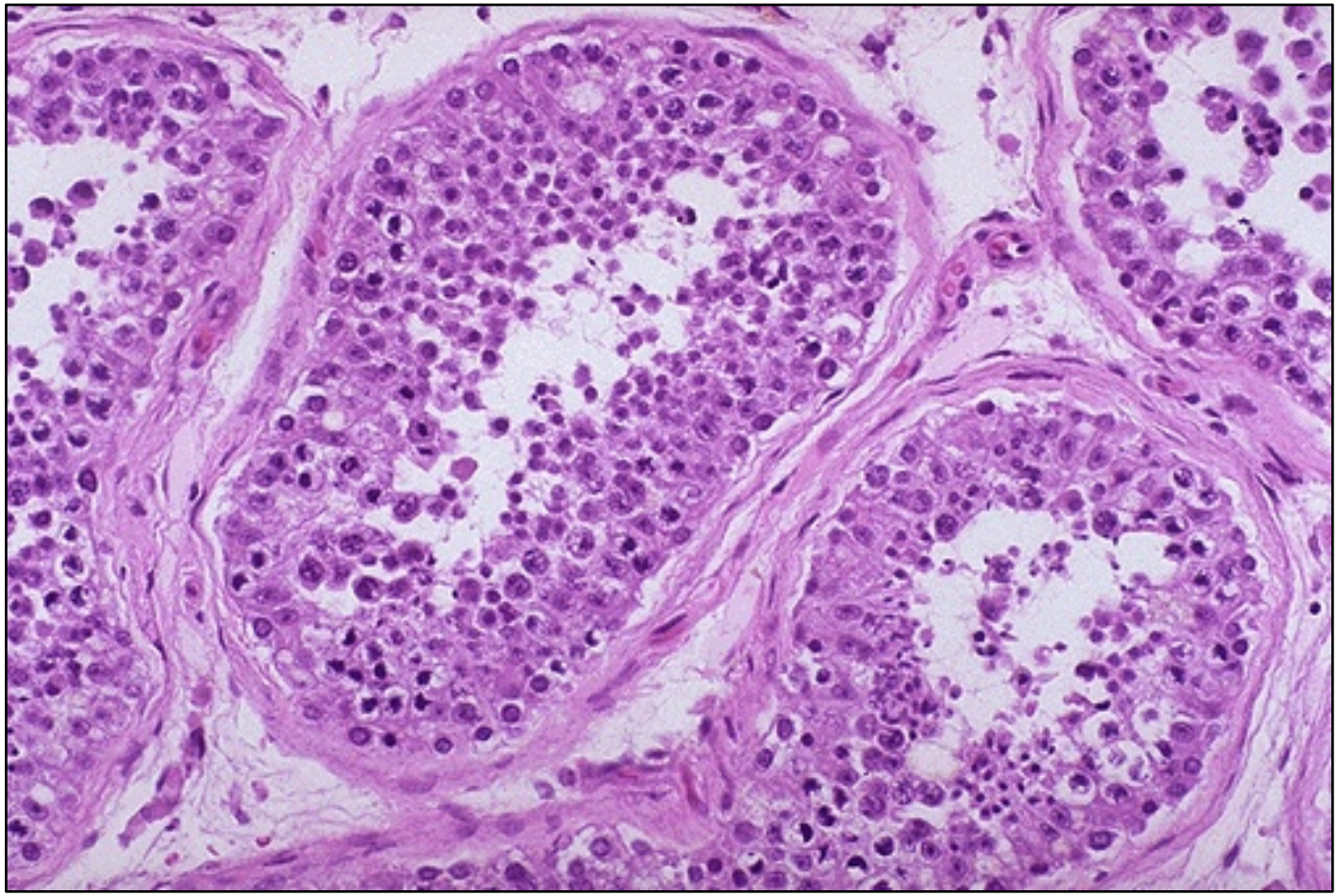


Anatomy of Normal Testis - Gross



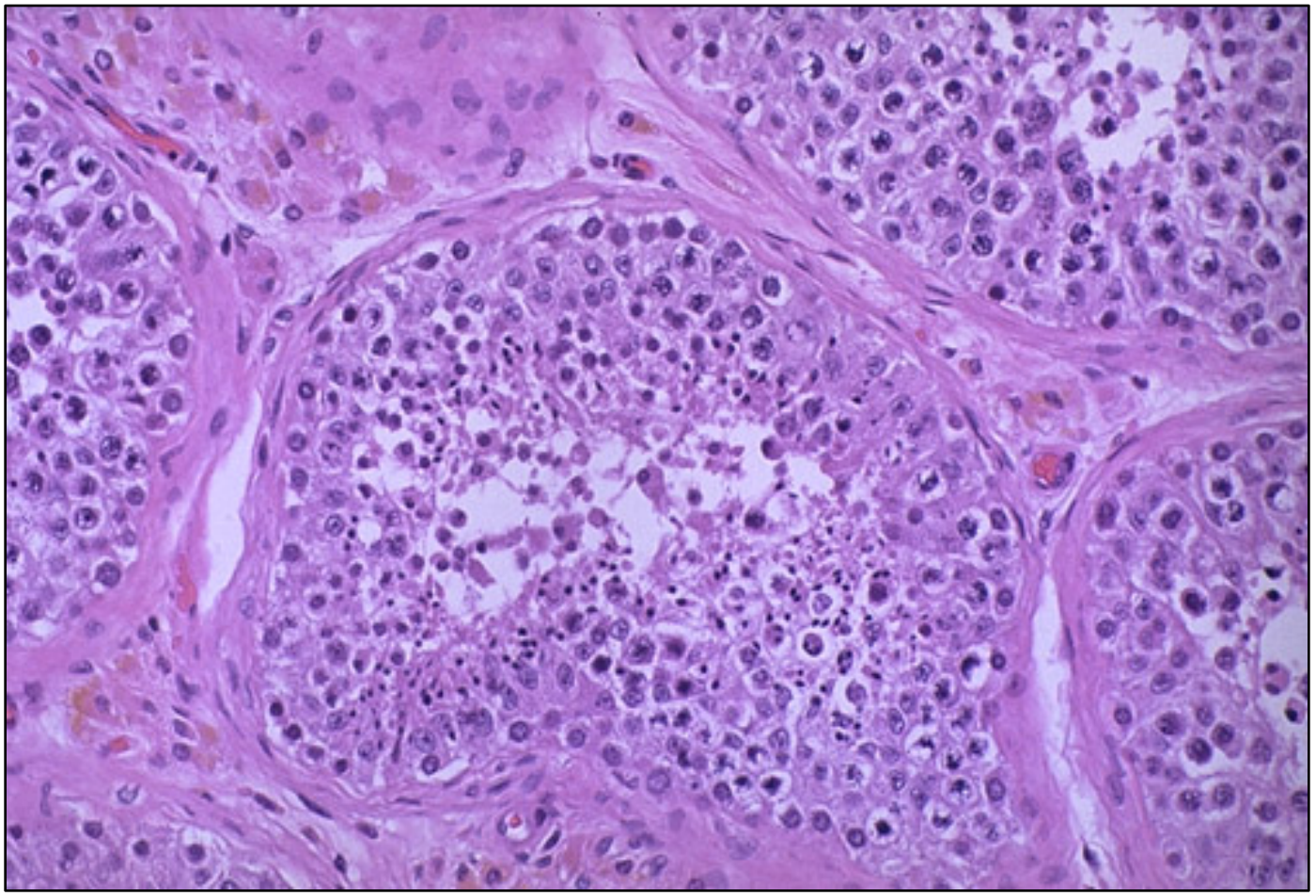
Here is a normal testis and adjacent structures. Identify the body of the testis, epididymis, and spermatic cord. Note the presence of two vestigial structures, the appendix testis and the appendix epididymis.

Histology of Normal Testis - LPF



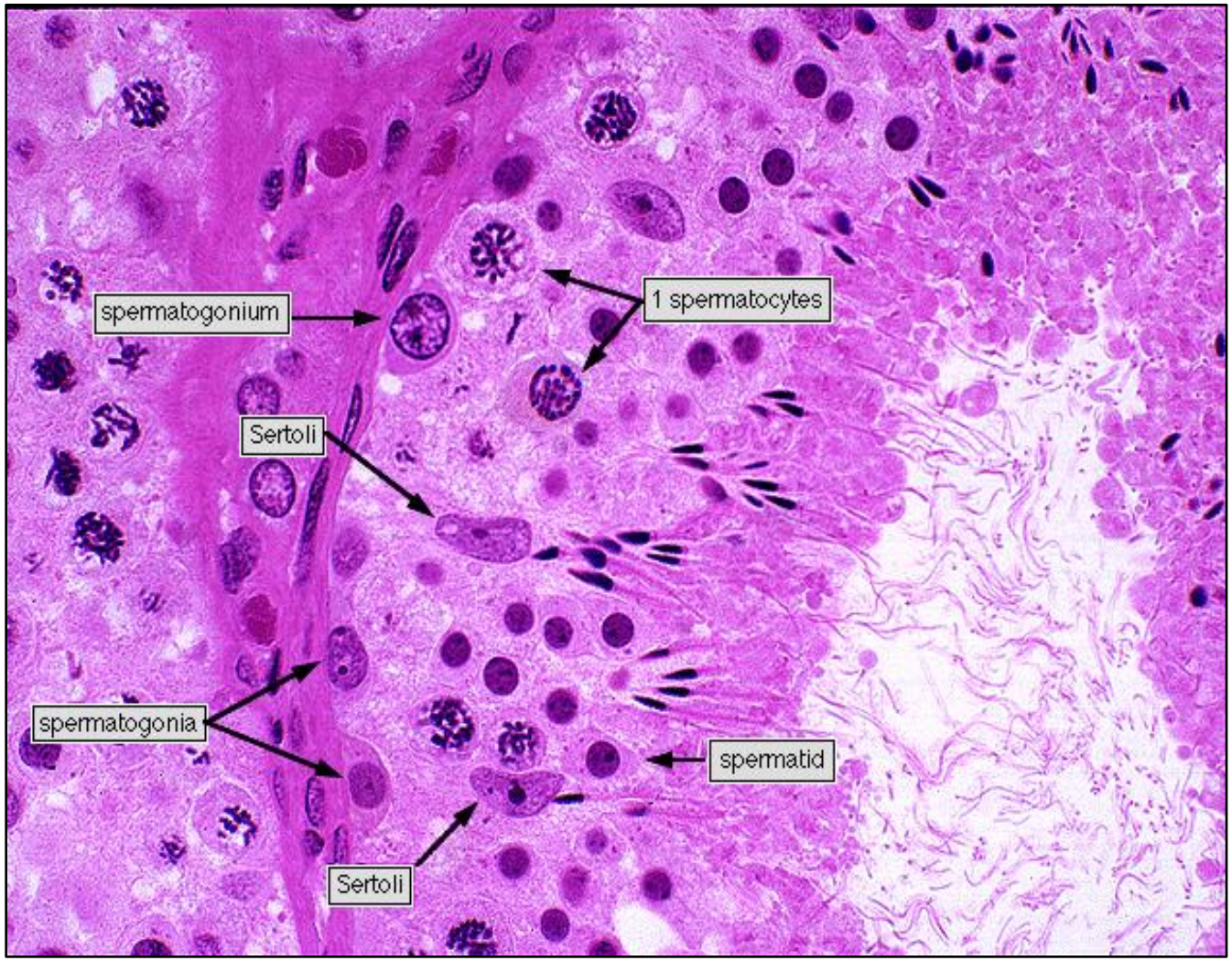
The seminiferous tubules have numerous germ cells. Sertoli cells are inconspicuous. Small dark oblong spermatozoa are seen in the center of the tubules.

Histology of Normal Testis - LPF



Pink Leyding cells are seen here in the interstitium. Note the pale golden brown pigment as well. There is active spermatogenesis.

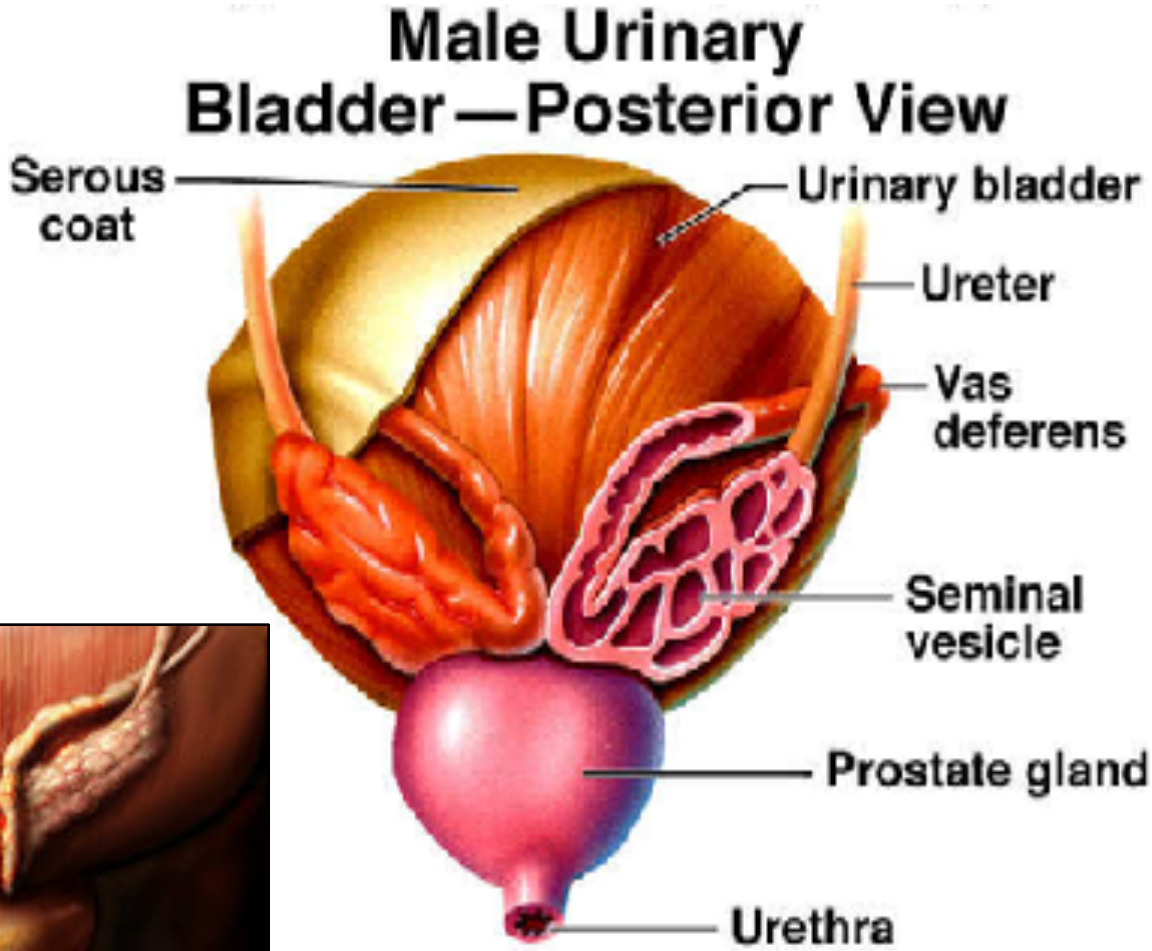
Histology of Normal Testis - HPF



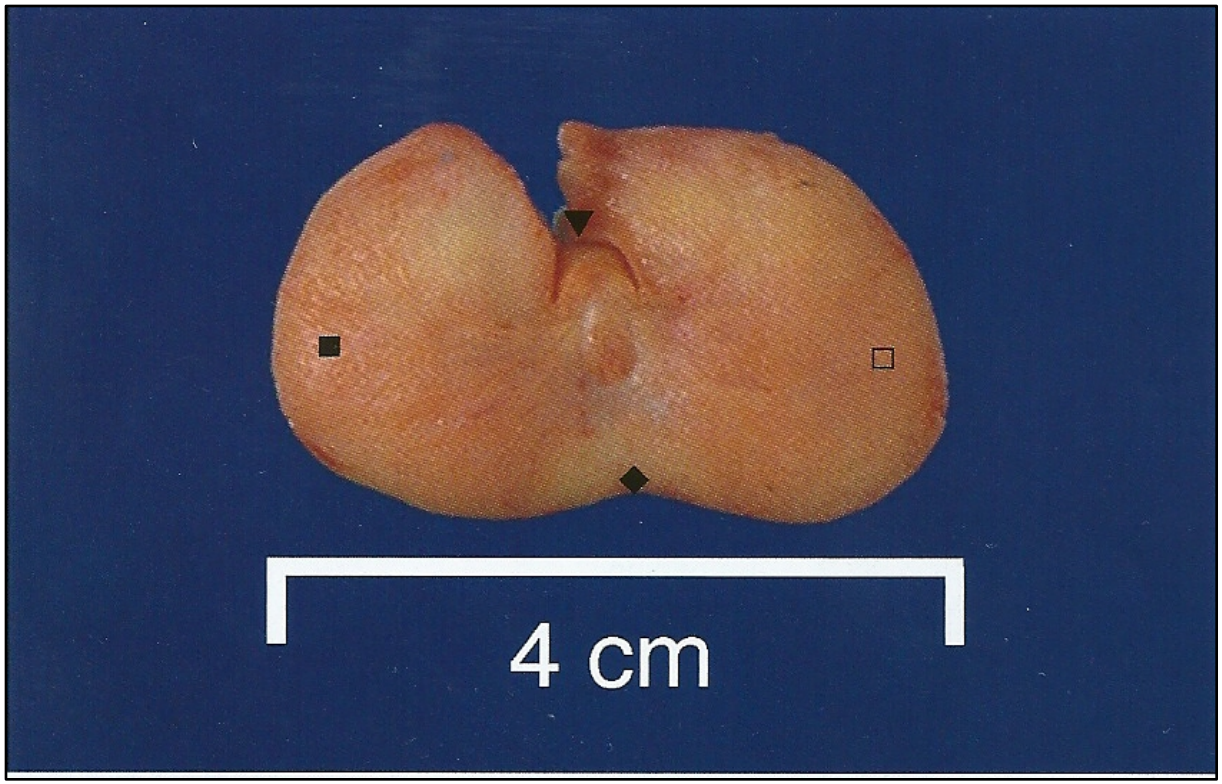
PROSTATE

Normal Anatomy and Histology

Diagram of Prostate and Seminal Vesicle

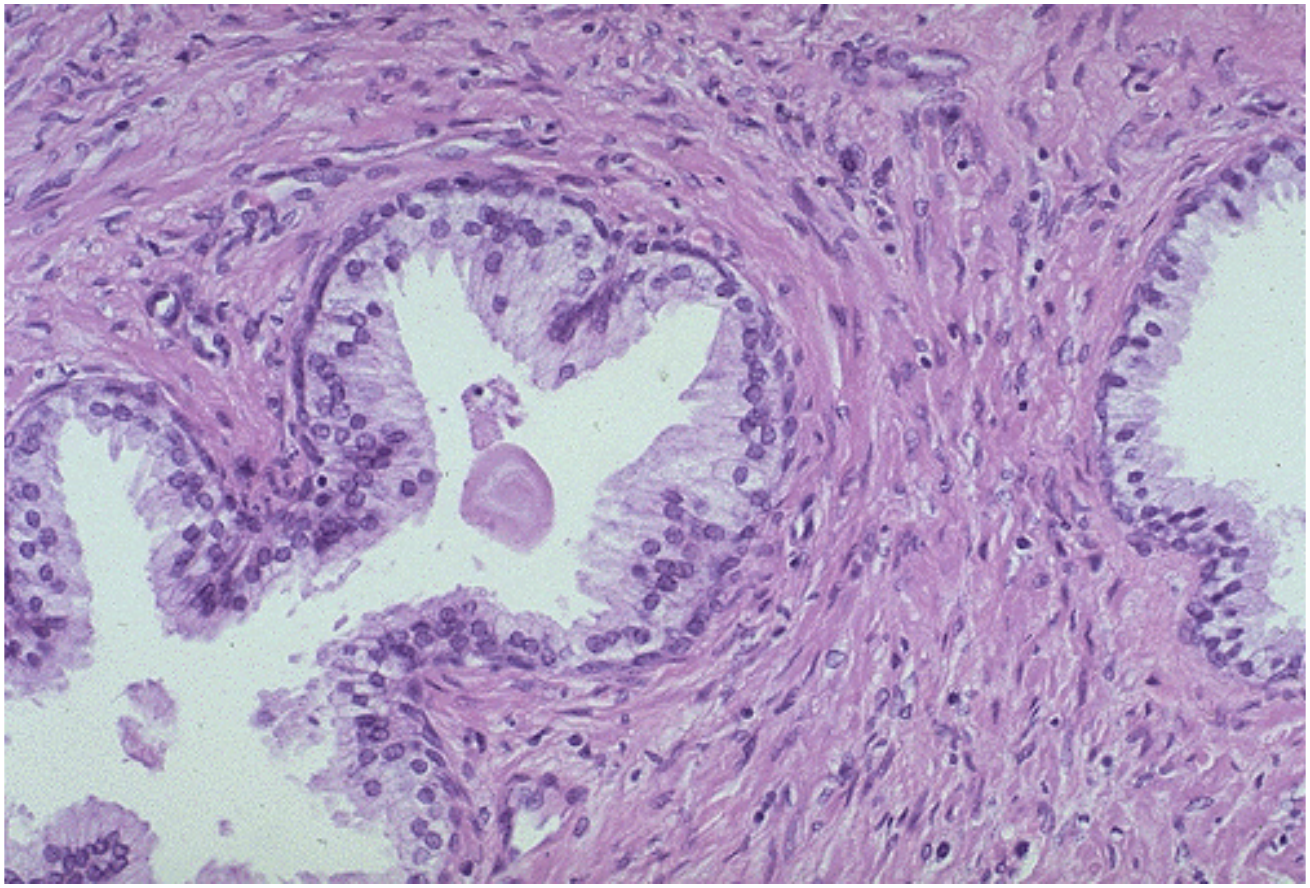


Normal Prostate - Gross



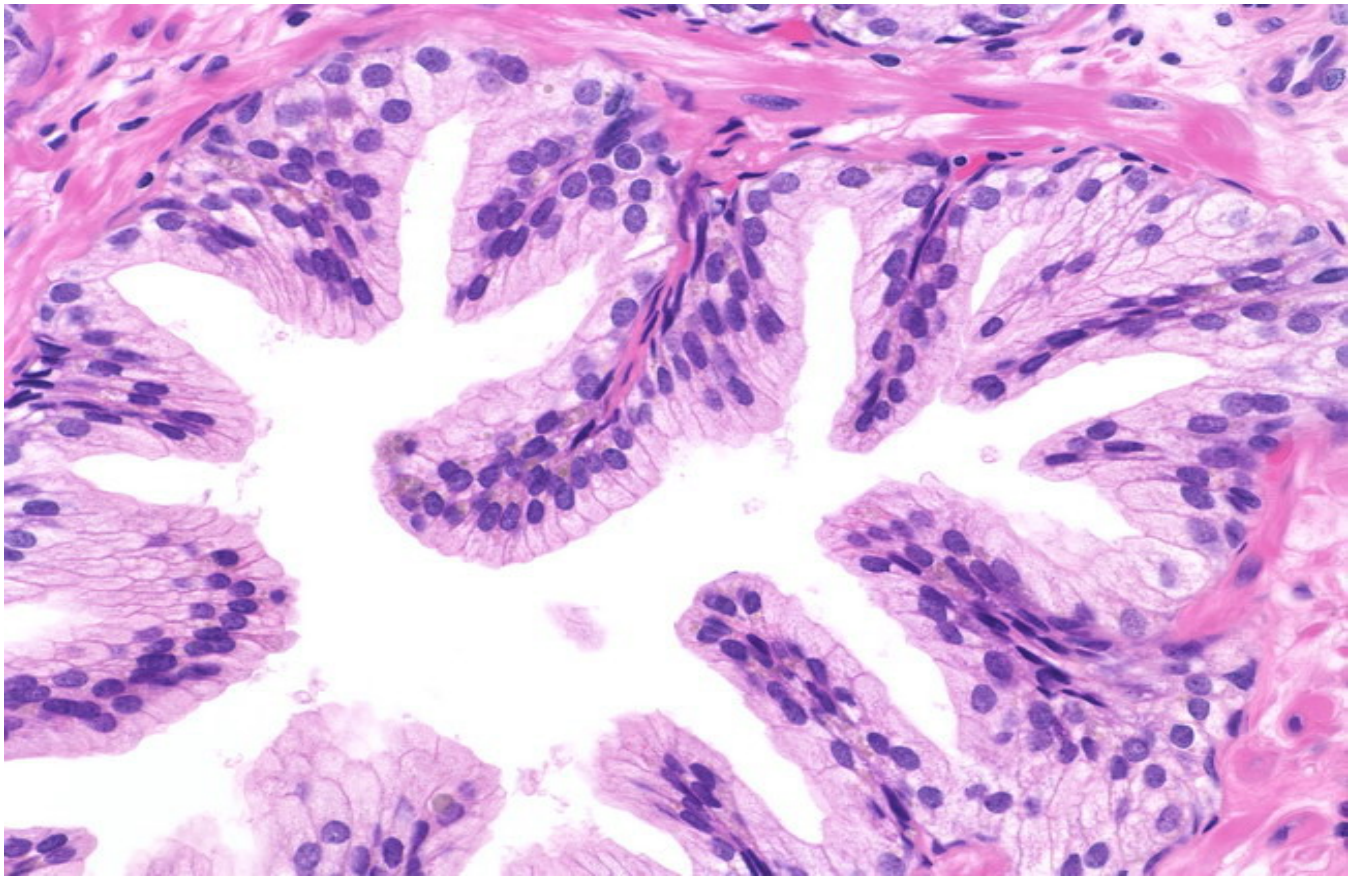
A normal prostate gland is about 3 to 4 cm in diameter.
This is an axial transverse section of a normal prostate. There is a central urethra(▼), at the depth of the cut made to open this prostate anteriorly at autopsy, with the left lateral lobe (■), the right lateral lobe (□) , and the posterior lobe (◆). Consistency is uniform without nodularity.

Normal Prostate Histology - LPF



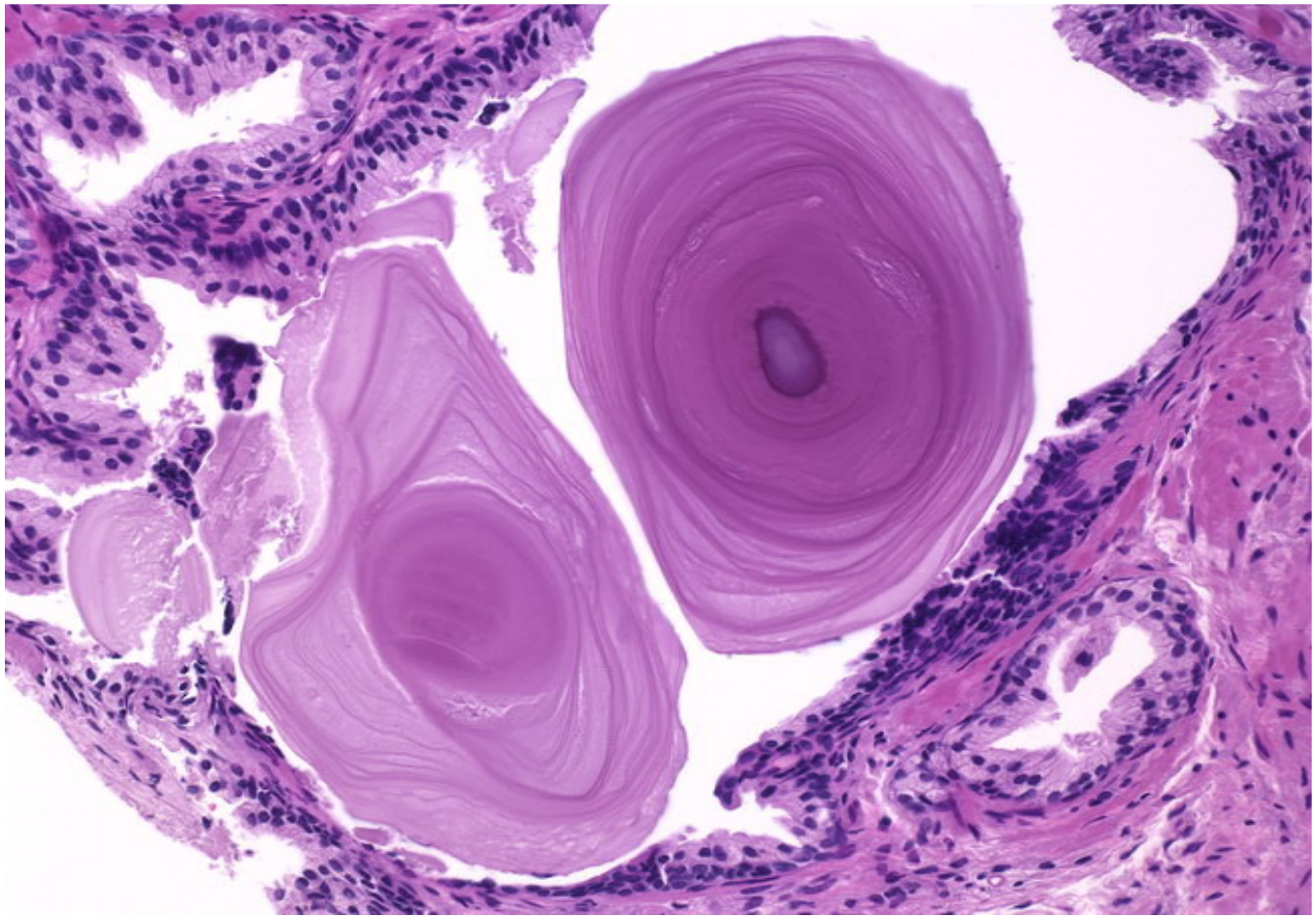
A small pink concretion (typical of the corpora amylacea seen in benign prostatic glands) appears in the gland just to the left of center. Note the well-differentiated glands with tall columnar epithelial lining cells. These cells do not have prominent nucleoli.

Normal Prostate Histology - HPF



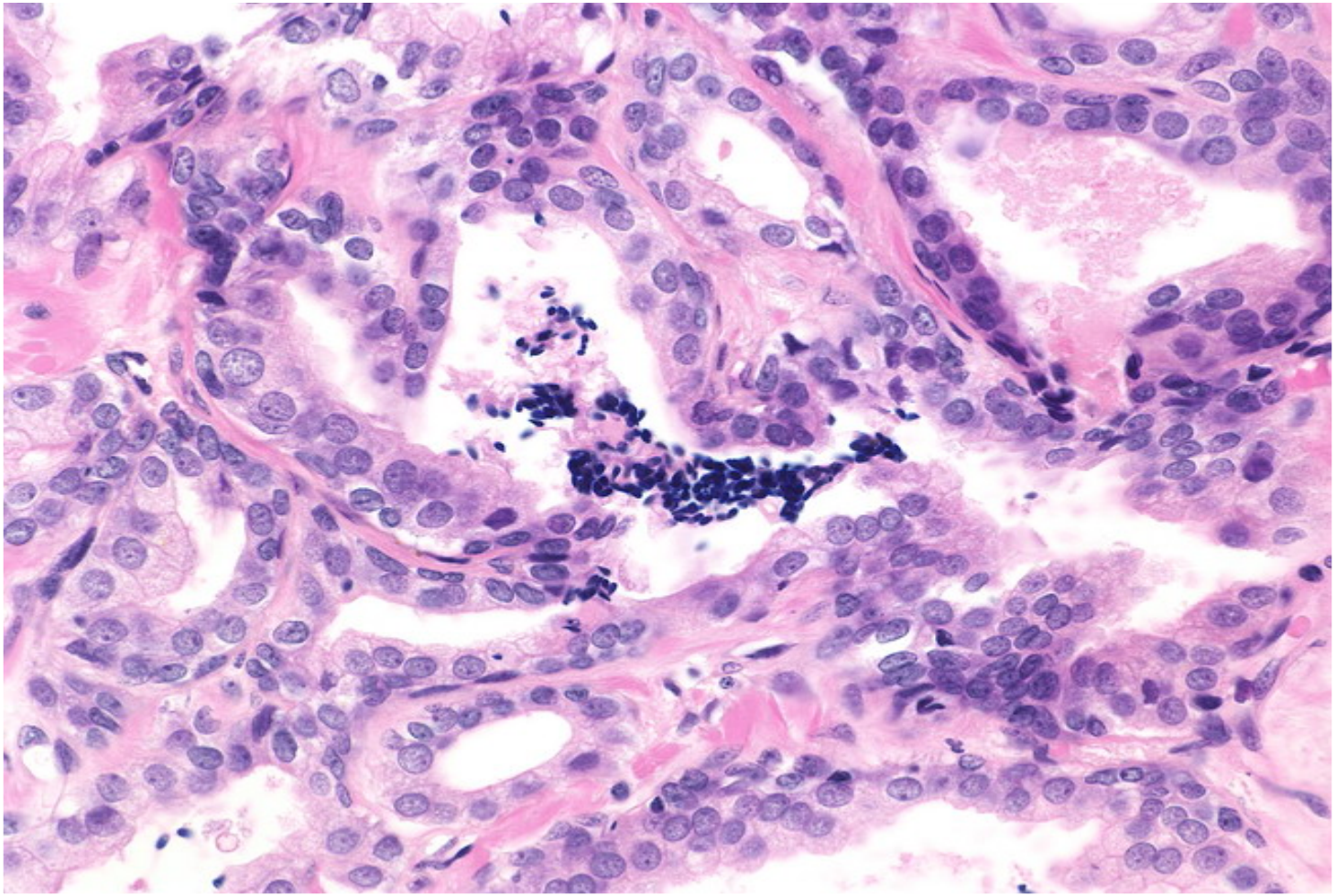
In this benign gland, the luminal contour shows tufts and papillary infoldings. The tall secretory epithelial cells have pale clear cytoplasm and uniform round or oval nuclei. Prominent nucleoli are not seen. Many basal cells can be identified

Corpora Amylacea in Prostate - HPF



Corpora amylacea are inspissated secretions that may have a lamellated appearance. Usually they are pink or purple in appearance. Sometimes they may be golden-brown

Sperms in Normal Prostate Biopsy – HPF

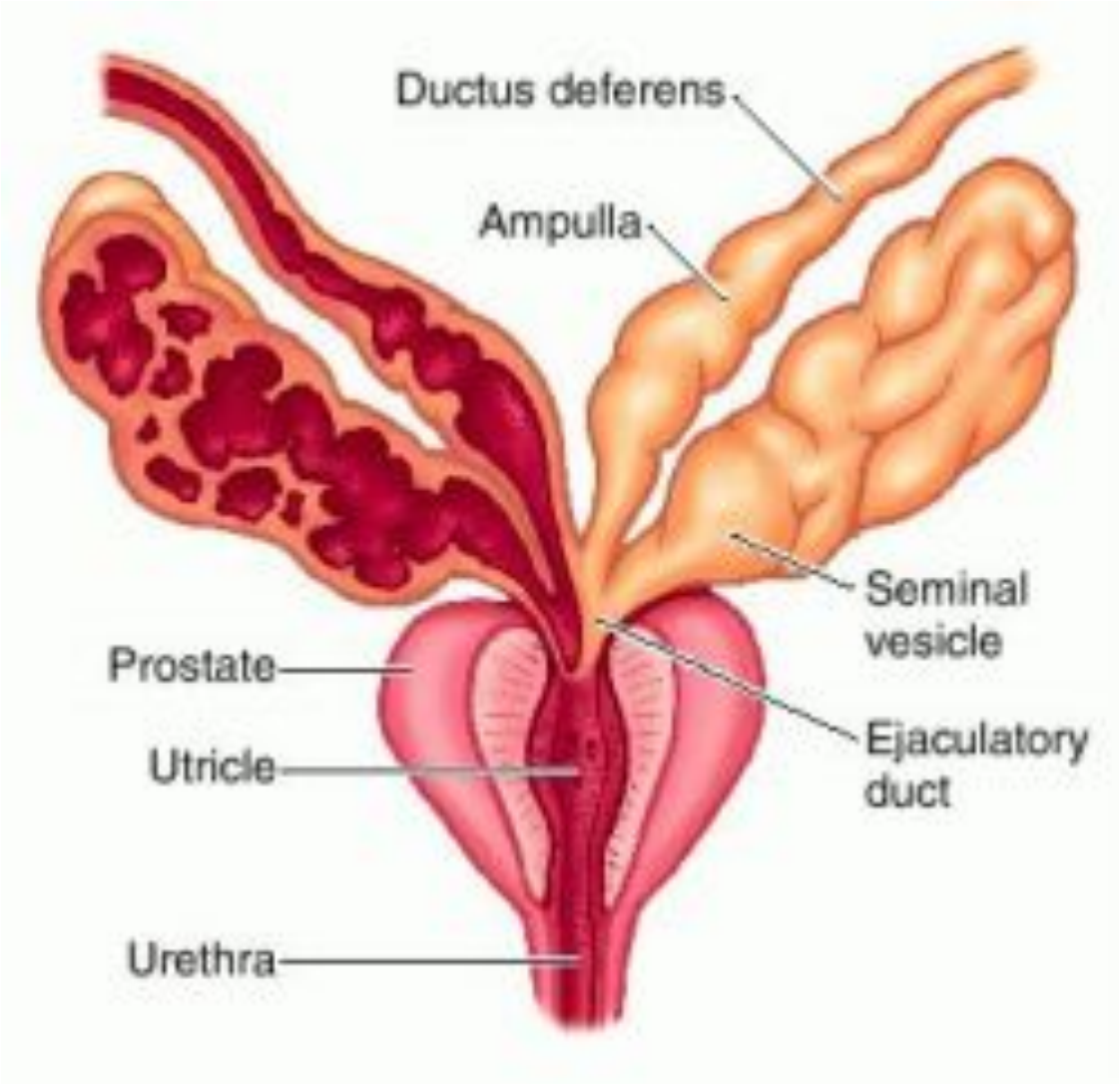


Spermatozoa are seen in approximately 1% of prostate needle biopsies (unpublished personal observation).

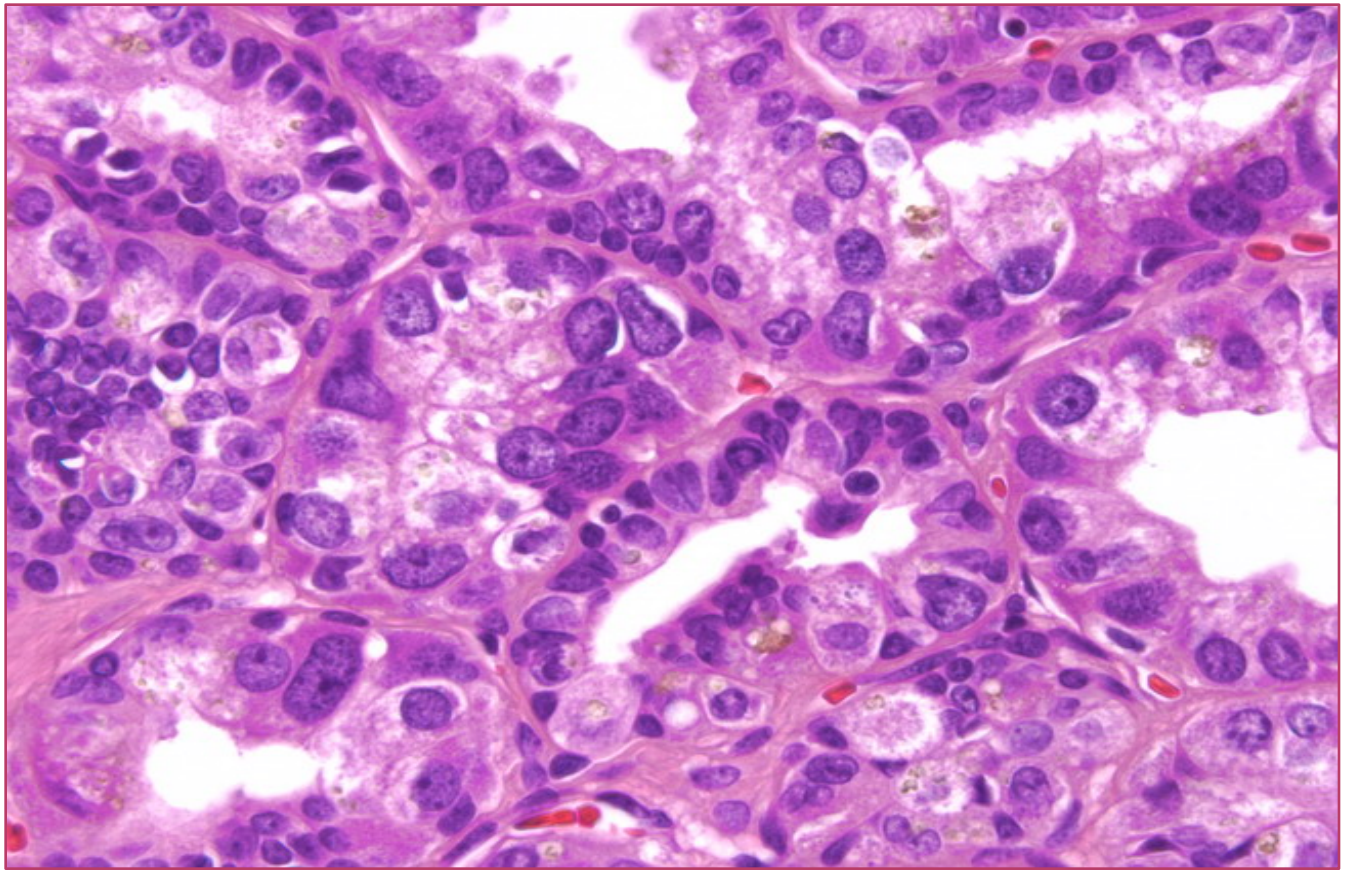
SEMINAL VESICLE

Normal Anatomy and Histology

Diagram of Seminal Vesicle



Normal Seminal Vesicle – HPF



Highly atypical cells are a normal finding in the seminal vesicles of about 80% of older men. The nuclei are large, irregular, hyperchromatic & show prominent nucleoli.
The atypia is degenerative and not observed in the seminal vesicles of young men

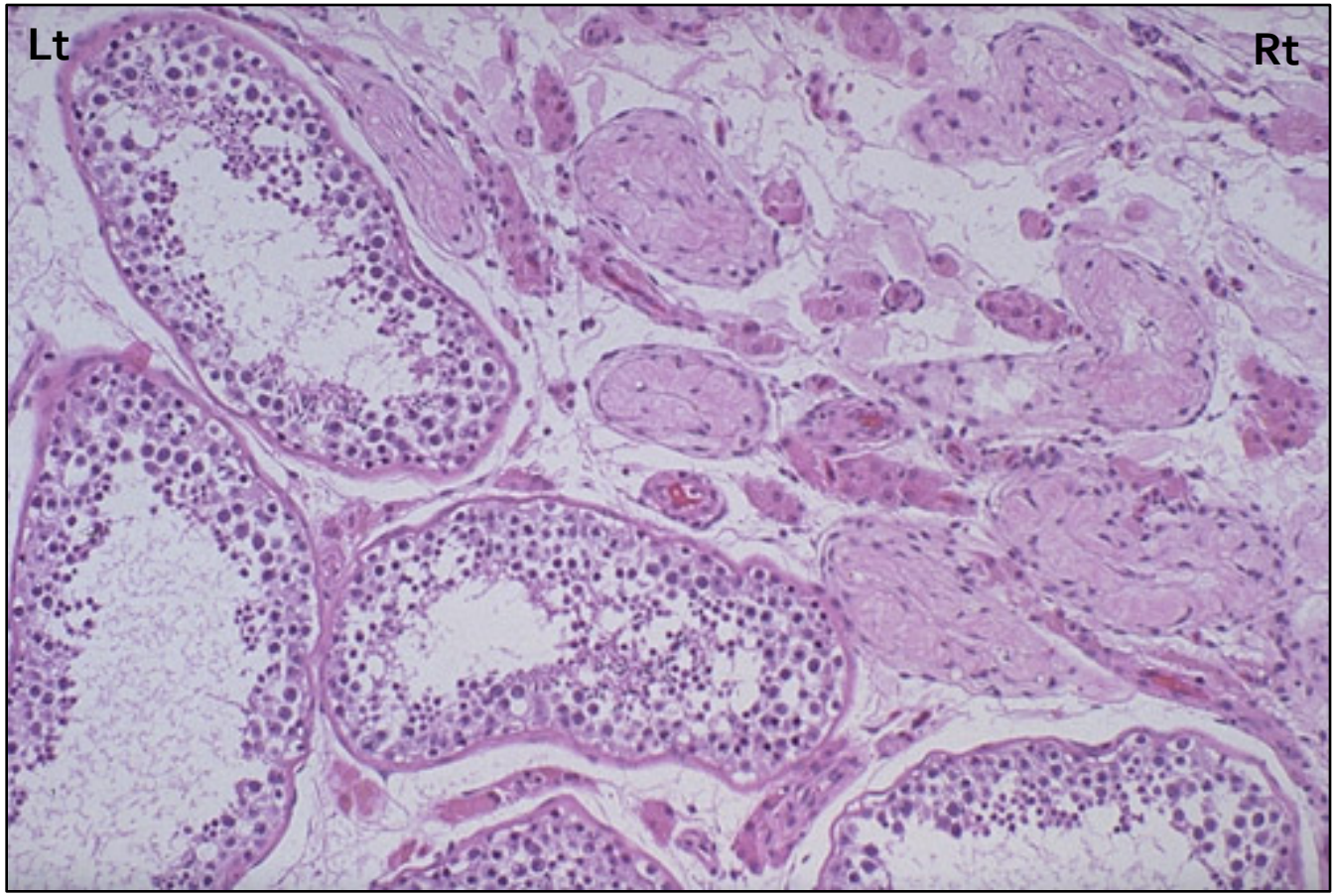
HISTOPATHOLOGY OF THE TESTIS

Testicular Atrophy

Normal vs Atrophied Testis - Gross

On the left is a normal testis. On the right is a testis that has undergone atrophy. Bilateral atrophy may occur with a variety of conditions including chronic alcoholism, hypopituitarism, atherosclerosis, chemotherapy or radiation, and severe prolonged illness.

Normal vs Atrophied Testis - Microscopic



There is focal atrophy of tubules seen here to the upper right. The most common reason for this is probably childhood infection with the mumps virus, which produces a patchy orchitis

Seminoma of the Testis

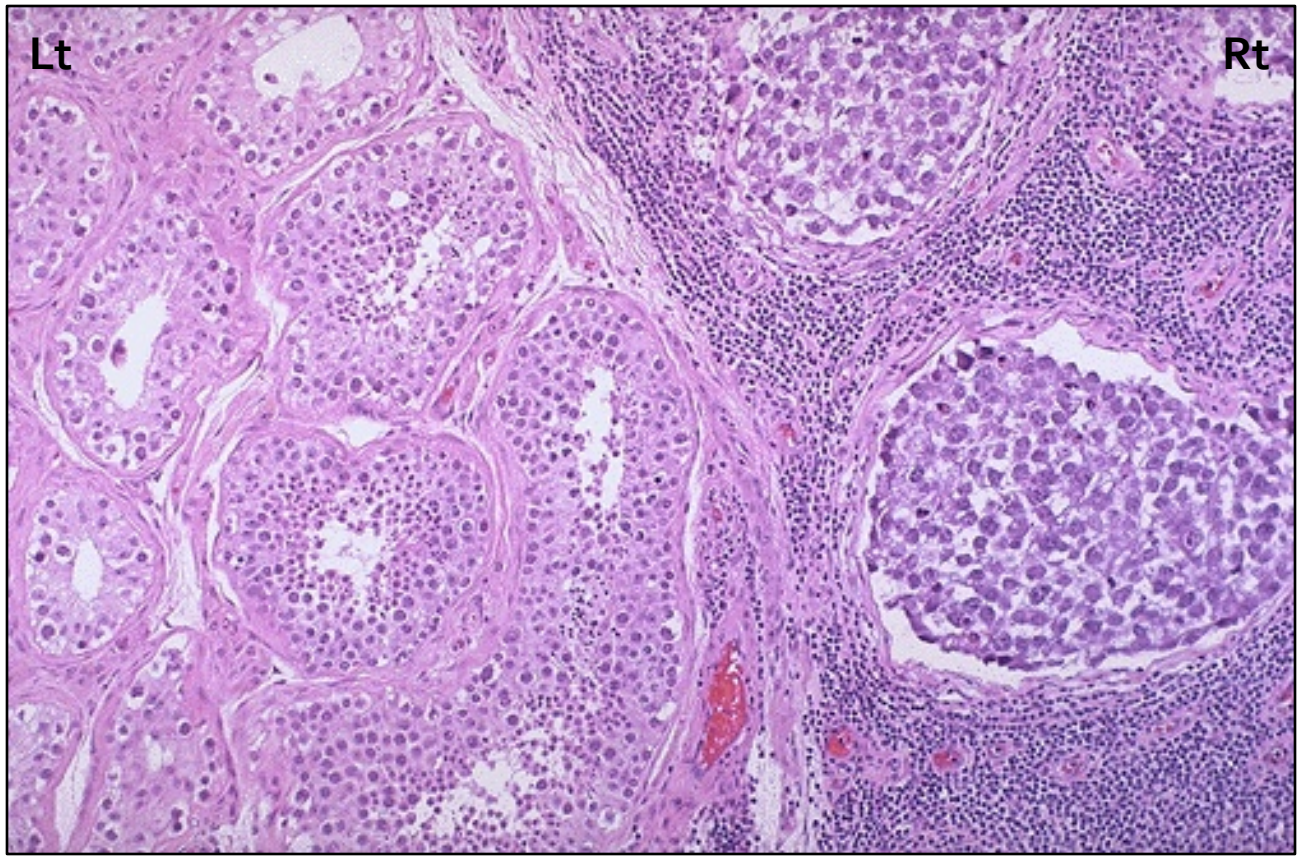
Seminoma of the Testis - Gross

Normal testis appears to the left of the mass. Pale and lobulated testicular mass with bulging and potato like cut surface with attached and congested spermatic cord . Most important risk factor is cryptorchidism (undescended testicle) .

Seminoma of the Testis - Gross

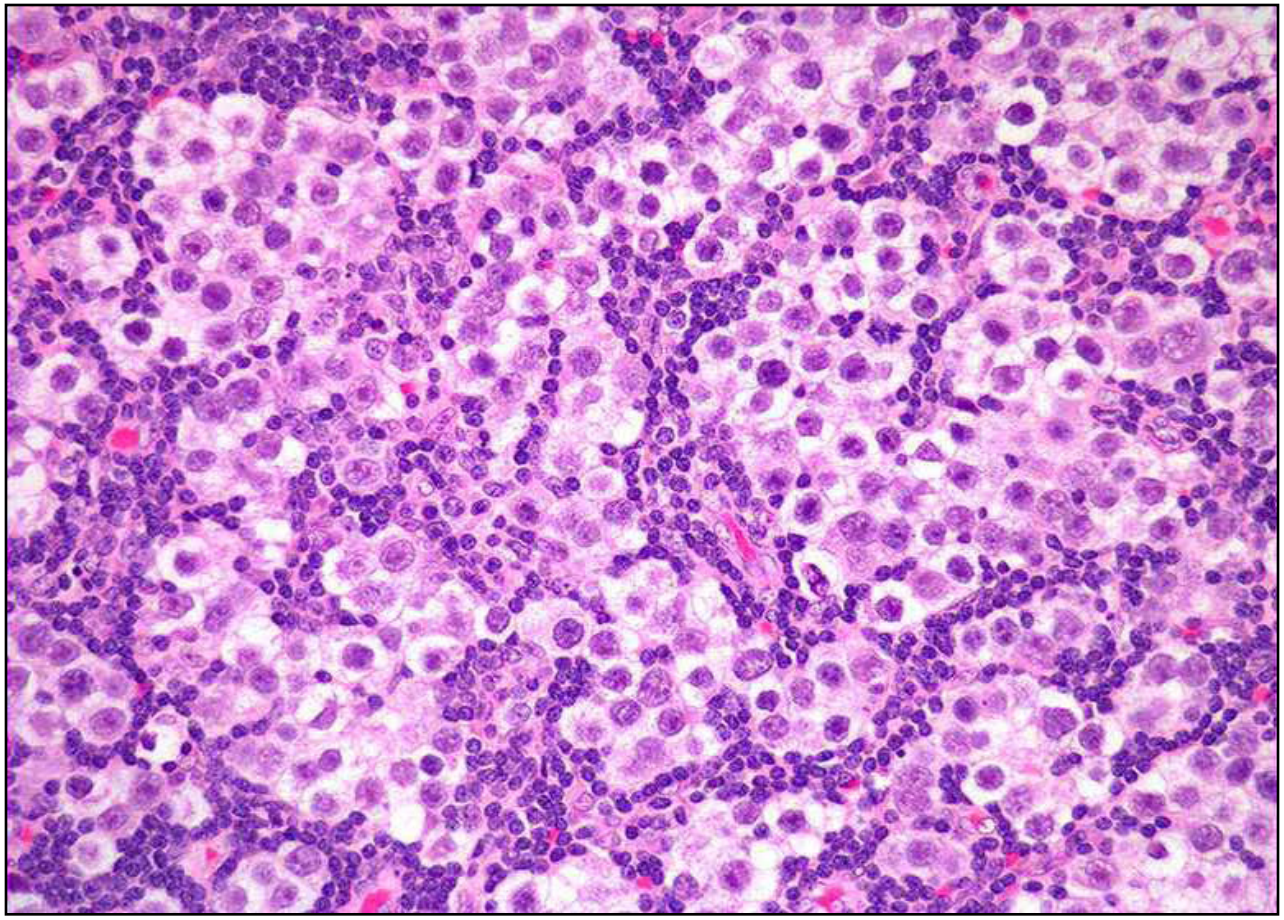
- *Pale and nodular tumor.*
- *Surrounding normal yellowish testicular cut surface.*

Seminoma vs Normal Testis - LPF



Normal testis appears at the left, and seminoma is present at the right.
Note the difference in size and staining quality of the neoplastic nests of cells compared to normal germ cells.
Note the lymphoid stroma between the nests of seminoma.

Seminoma of the Testis - HPF



- *Malignant germ cells.*
- *Large vesicular nuclei.*
- *Prominent nucleoli.*
- *Lymphocytes.*

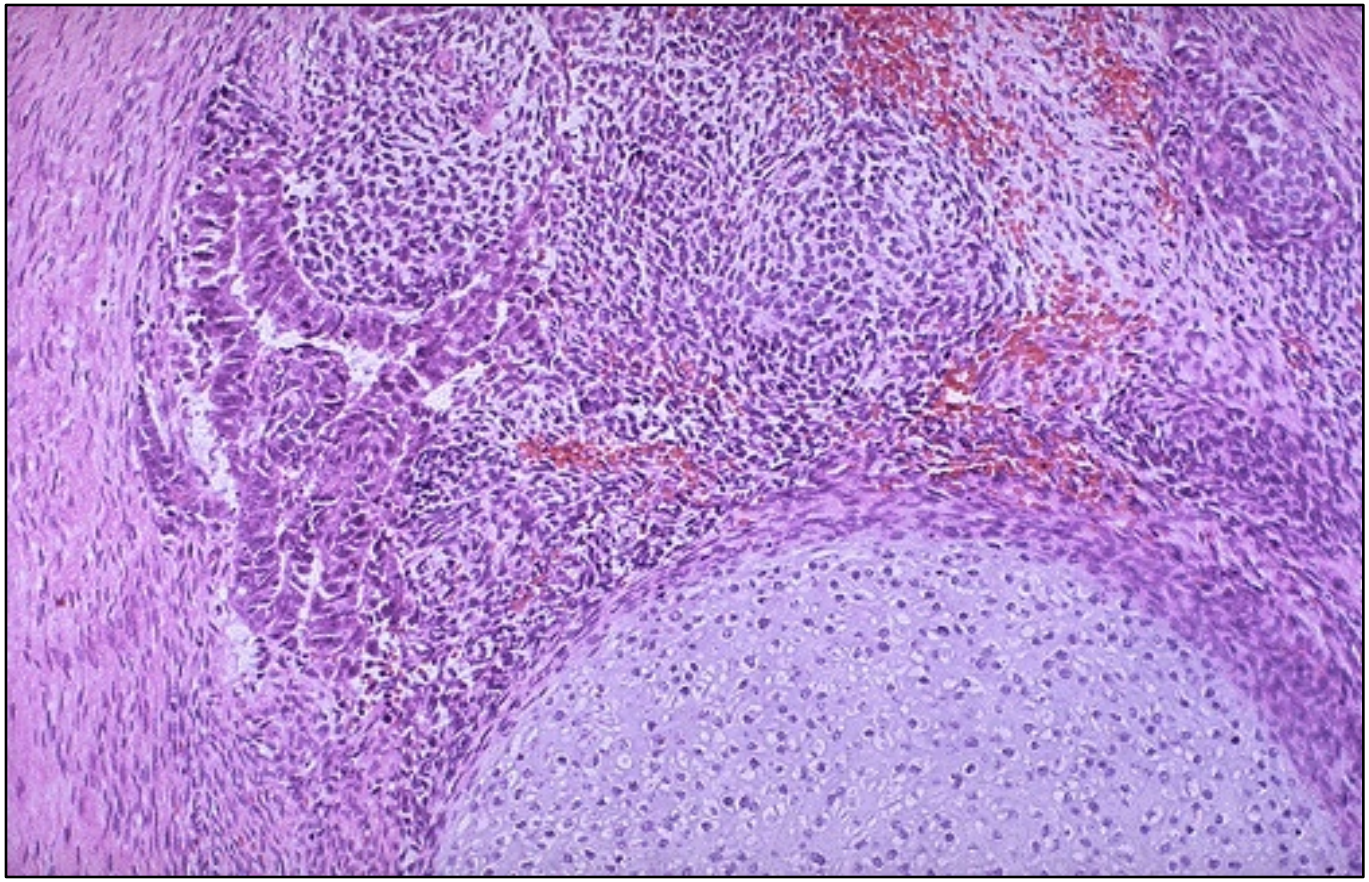
Embryonal Carcinoma & Teratoma of the Testis

Malignant mixed germ cell tumor or Embryonal Carcinoma & Teratoma - Gross

Partly solid and partly cystic and hemorrhagic tumor.

Here is an embryonal carcinoma mixed with teratoma in which islands of bluish white cartilage from the teratoma component are more prominent. A rim of normal brown testis appears at the left.

Malignant mixed germ cell tumor or Embryonal Carcinoma & Teratoma - Gross



- *Cartilage.*
- *Malignant glandular tissue consistent with embryonal carcinoma.*

Tumor	Peak Patient Age (yr)	Morphology	Tumor Marker(s)
Seminoma	40–50	Sheets of uniform polygonal cells with cleared cytoplasm; lymphocytes in the stroma	10% of patients have elevated hCG
Embryonal carcinoma	20–30	Poorly differentiated, pleomorphic cells in cords, sheets, or papillary formation; most contain some yolk sac and choriocarcinoma cells	Negative (pure embryonal carcinoma)
Yolk sac tumor	3	Poorly differentiated endothelium-like, cuboidal, or columnar cells	90% of patients have elevated AFP
Choriocarcinoma	20–30	Cytotrophoblast and syncytiotrophoblast without villus formation	100% of patients have elevated hCG
Teratoma	All ages	Tissues from all three germ cell layers with varying degrees of differentiation	Negative (pure teratoma)
Mixed tumor	15–30	Variable, depending on mixture; commonly teratoma and embryonal carcinoma	90% of patients have elevated hCG and AFP

AFP, alpha fetoprotein; hCG, human chorionic gonadotropin.

PROSTATE

Prostatic Hyperplasia

Prostatic Hyperplasia - Gross

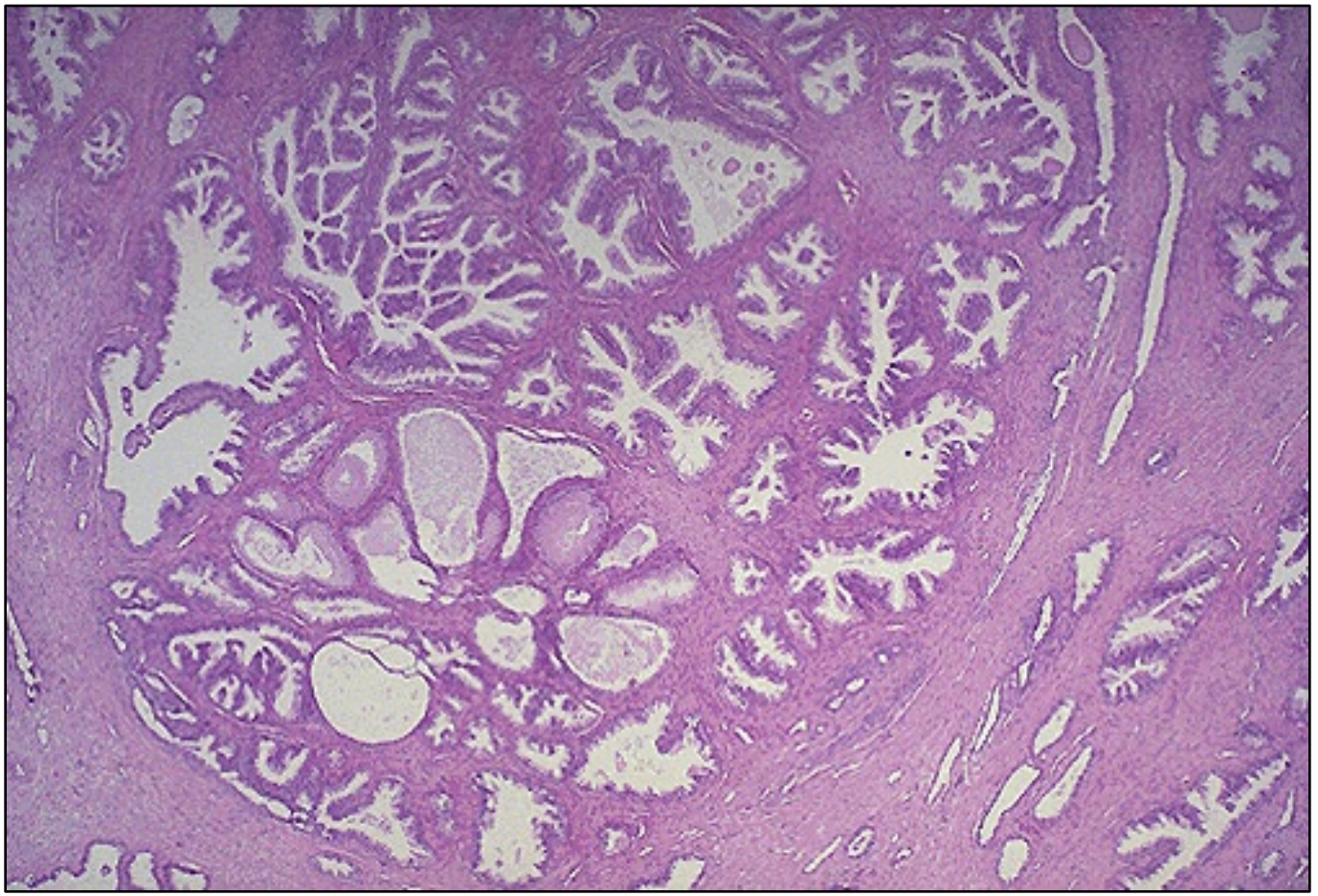
Enlarged lateral lobes, and median lobe that obstructs the prostatic urethra that led to obstruction with bladder hypertrophy, as evidenced by the prominent trabeculation of the bladder mucosa. Obstruction with stasis also led to the formation of the yellow-brown calculus (stone).

Prostatic Hyperplasia - Gross

Central and periurethral parts.

- *Pale, gray, nodular cut surface or nodules.*
- *Narrow "slit like" urethra.*

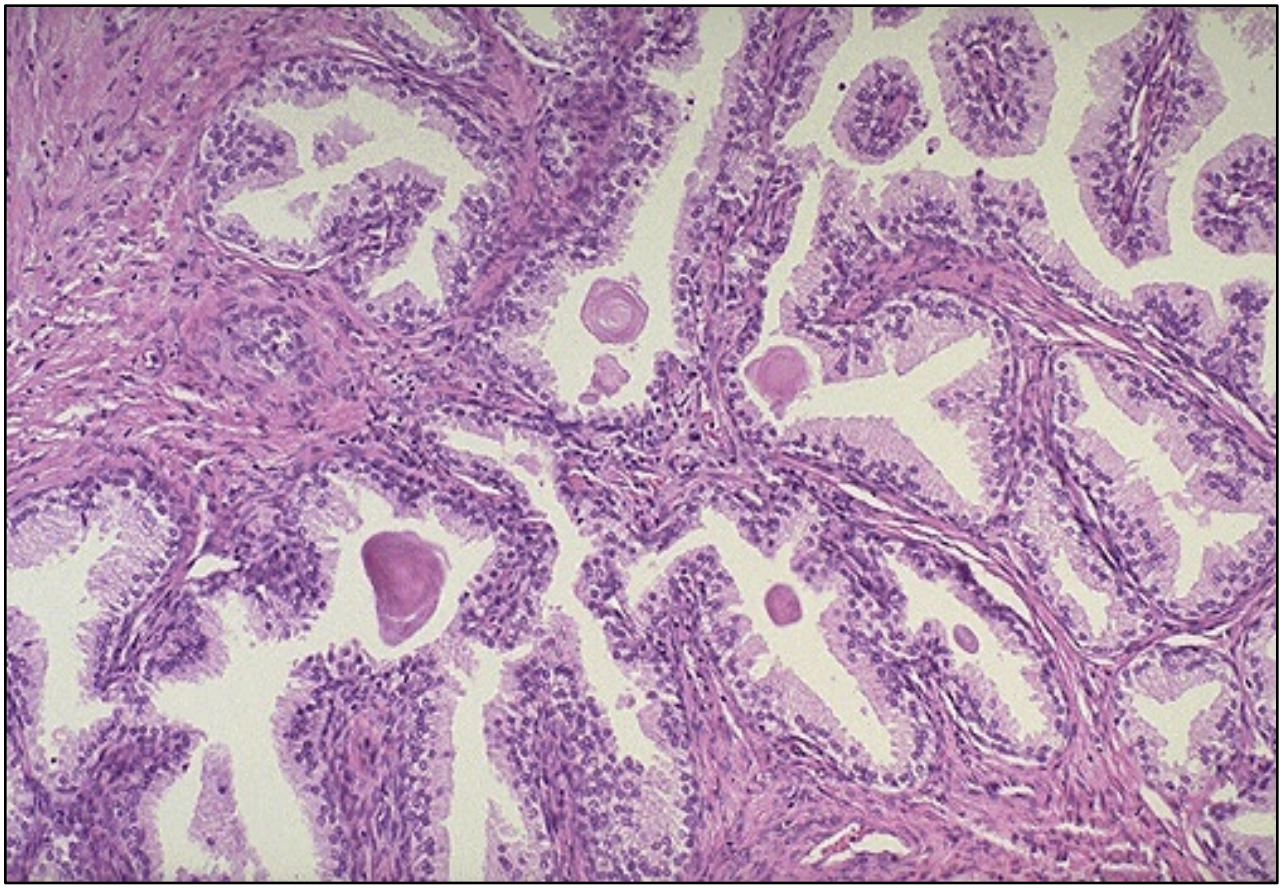
Prostatic Hyperplasia - LPF



Microscopically, benign prostatic hyperplasia can involve both glands and stroma, though the former is usually more prominent. Here, a large hyperplastic nodule of glands is seen

Prostatic Hyperplasia - HPF

Nodules of hyperplastic prostatic glands and stroma.

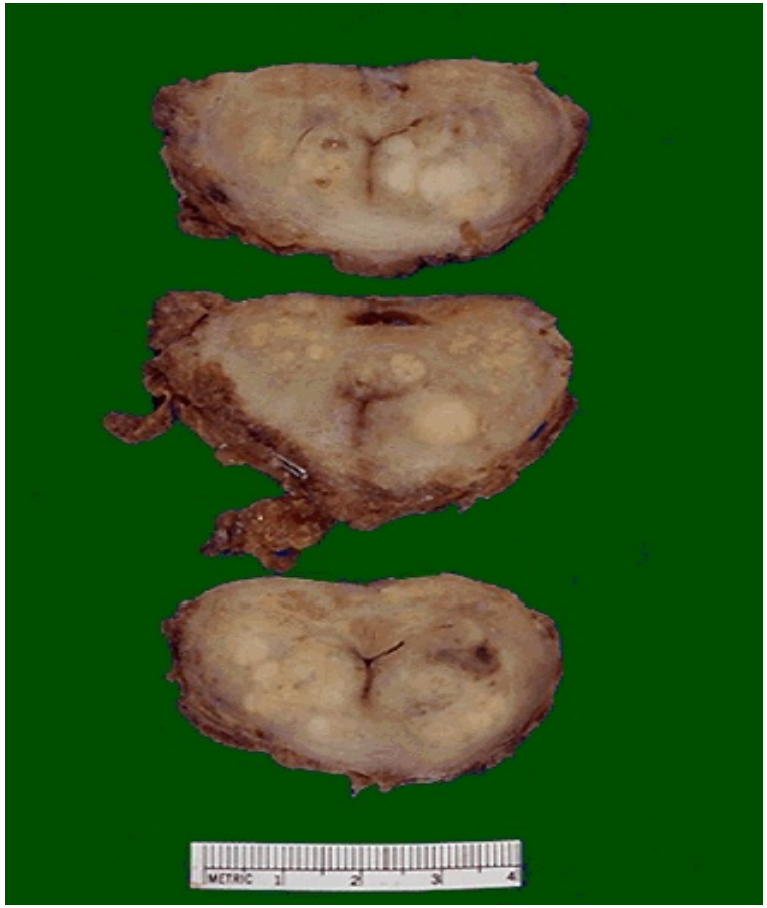


The enlarged prostate has glandular hyperplasia. The glands are well-differentiated and still have some intervening stroma. The small laminated pink concretions within the glandular lumens are known as corpora amylacea

Adenocarcinoma of Prostate

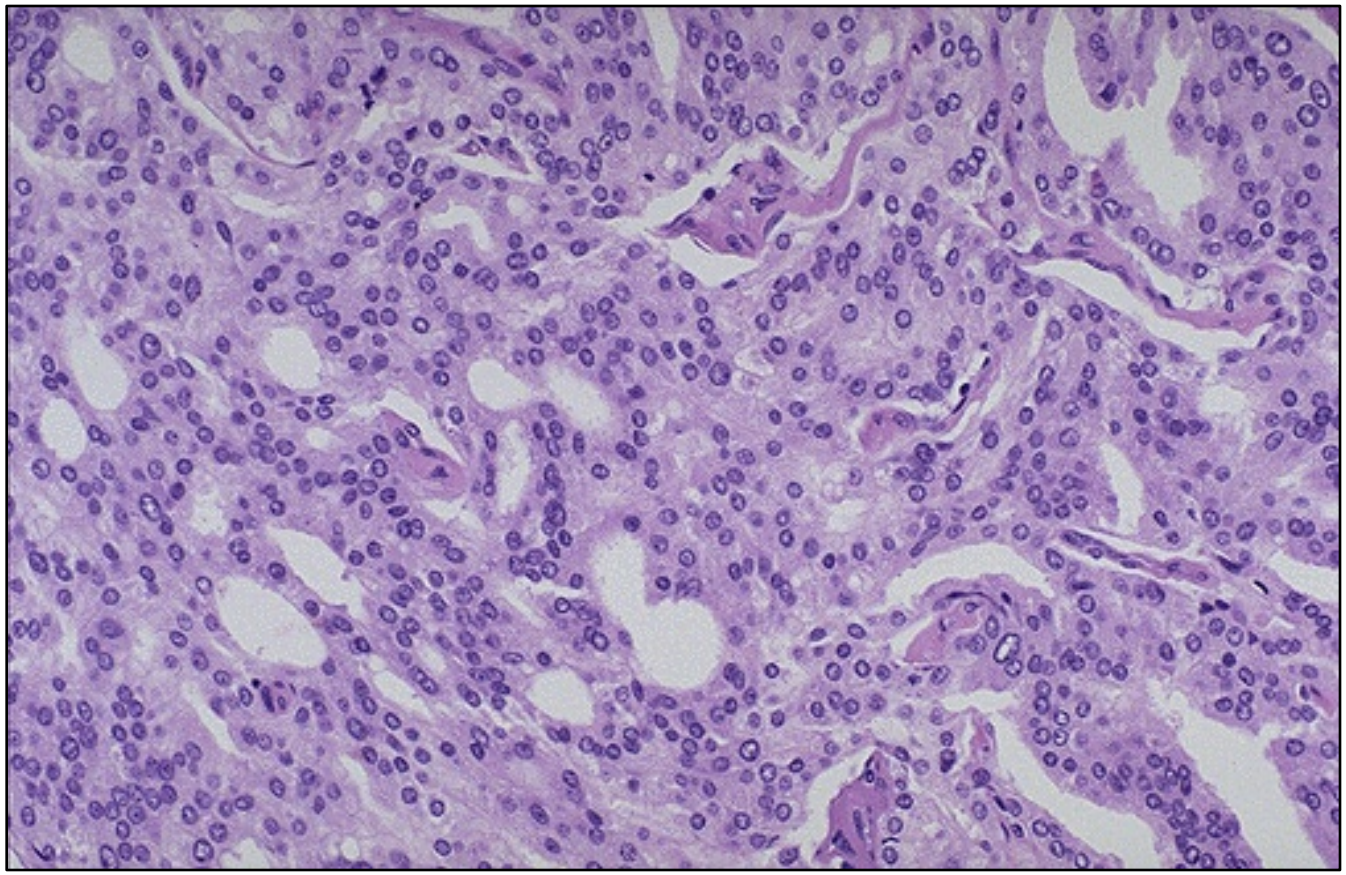
Adenocarcinoma of the Prostate - Gross

Usually affect Peripheral parts



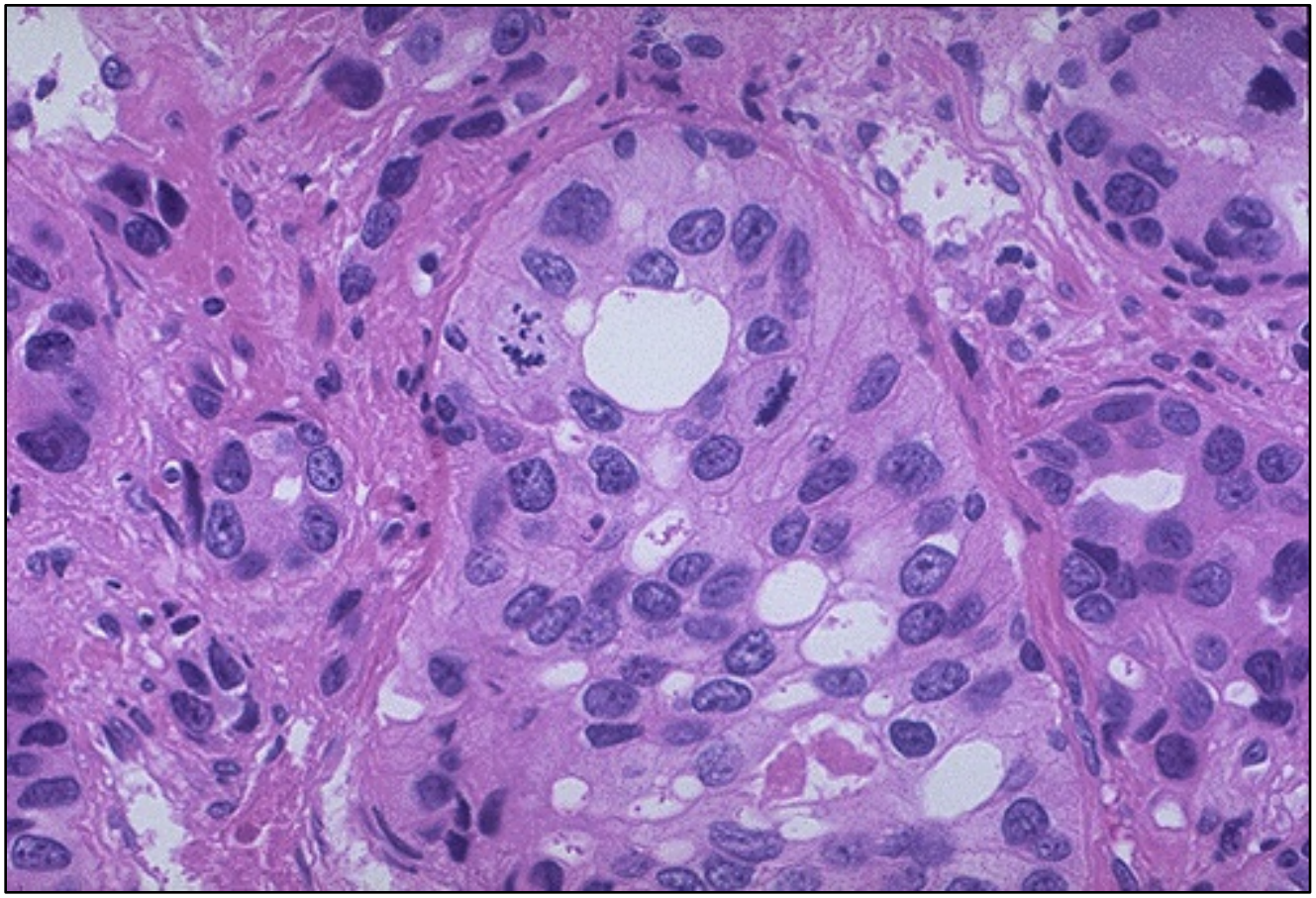
Several pale and yellowish nodules are seen in the posterior and periurethral parts of the prostatic gland.

Adenocarcinoma of the Prostate - MPF



At high magnification, the neoplastic glands of prostatic adenocarcinoma are still recognizable as glands, but there is no intervening stroma and the nuclei are hyperchromatic.

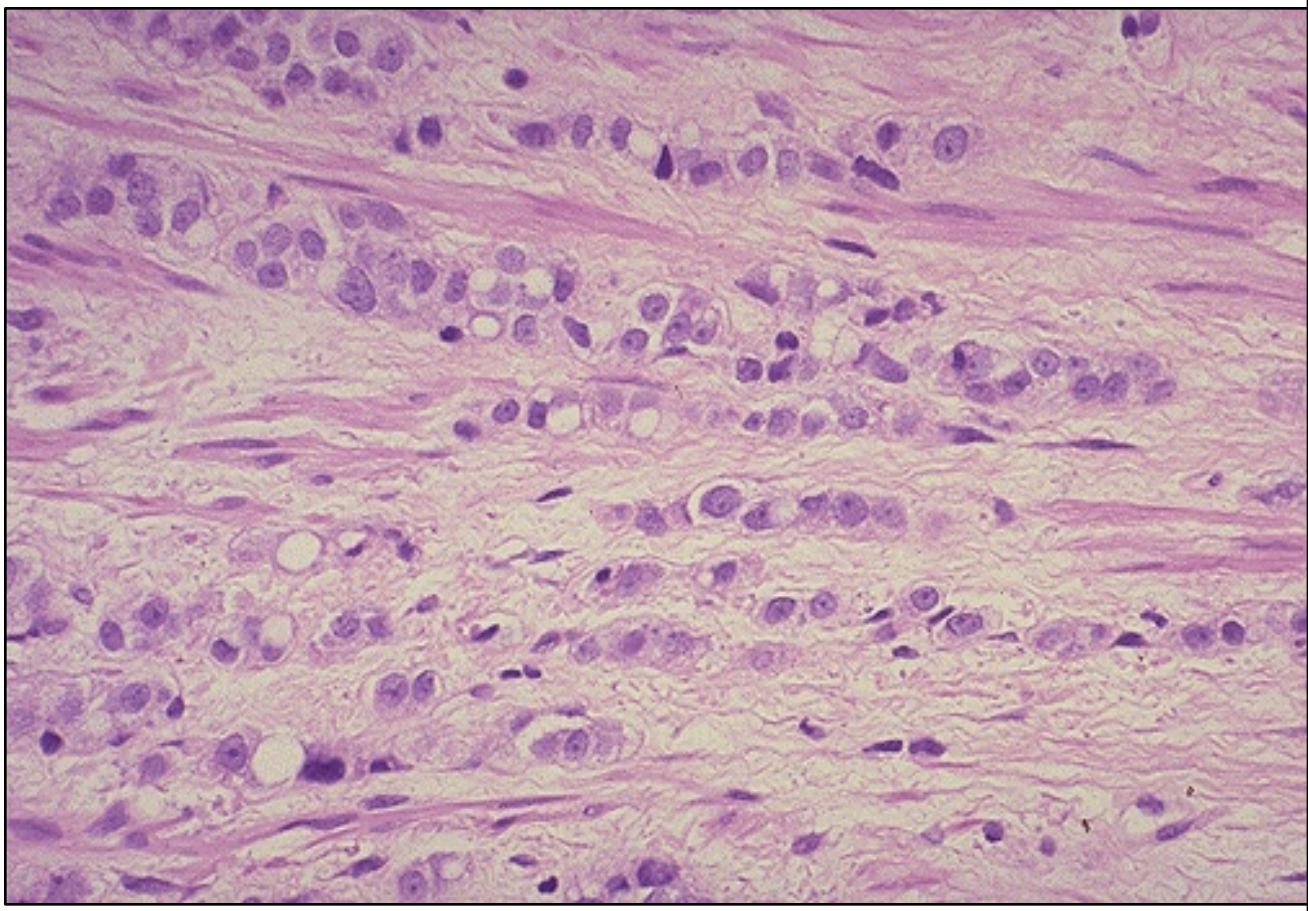
Adenocarcinoma of the Prostate - HPF



At high magnification, this poorly differentiated prostatic adenocarcinoma demonstrates cells with nucleoli and mitotic figures.

Adenocarcinoma of the Prostate - HPF

Diagnosis: Prostatic adenocarcinoma.
Grade: High grade, poorly differentiated.



Poorly differentiated malignant cells.

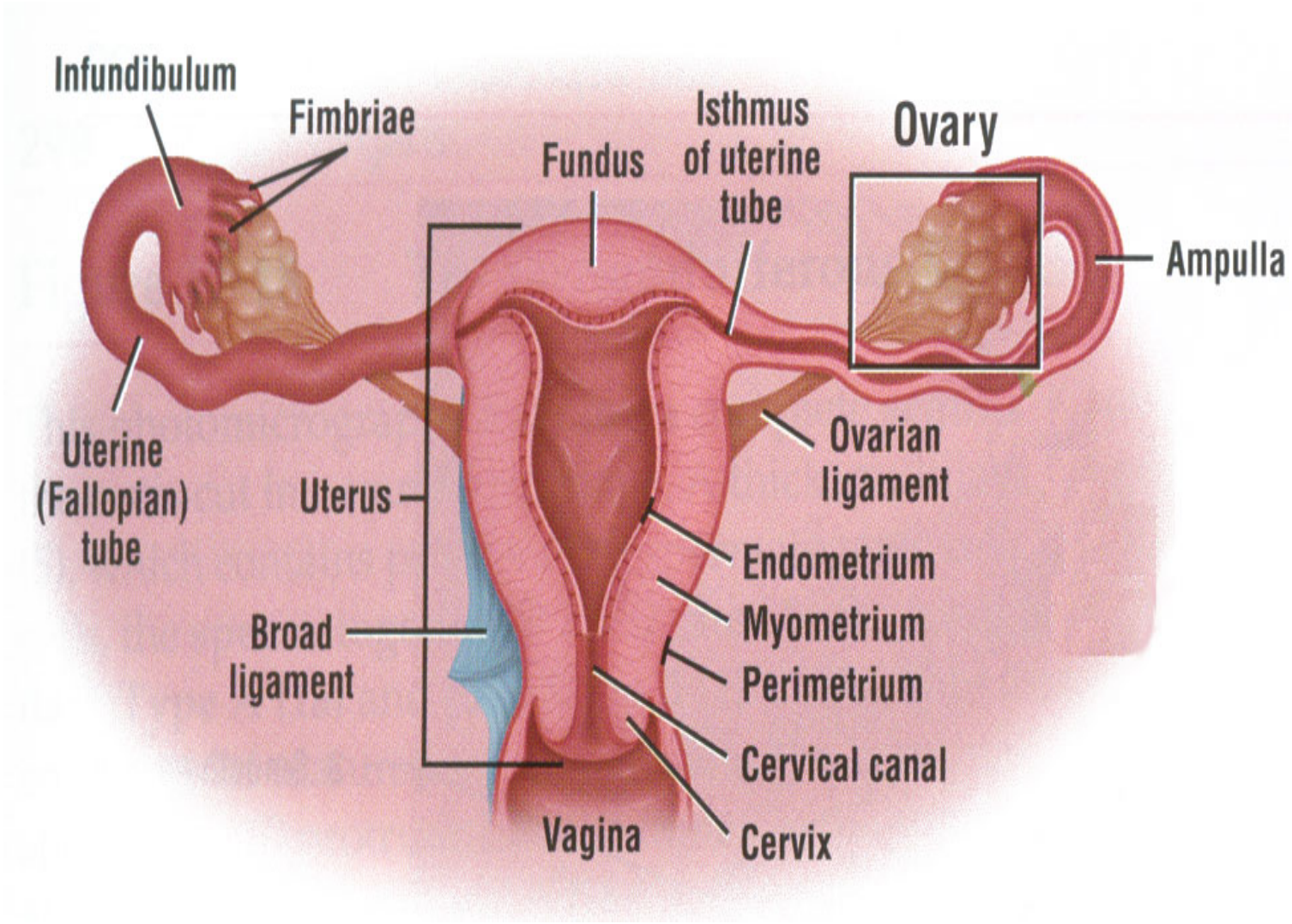
Prostate cancer is graded by the Gleason system. According to this system, prostate cancers are stratified into five grades on the basis of glandular patterns of differentiation. Grade 1 represents the most well-differentiated tumors and grade 5 tumors show no glandular differentiation. Since most tumors contain more than one pattern, a primary grade is assigned to the dominant pattern and a secondary grade to the next most frequent pattern. The two numerical grades are then added to obtain a combined ***Gleason score***. Tumors with only one pattern are treated as if their primary and secondary grades are the same, and, hence, the number is doubled. Thus the most differentiated tumors have a Gleason score of 2 (1 + 1) and the least differentiated tumors merit a score of 10 (5 + 5).

2nd Practical Session

FEMALE GENITAL SYSTEM

Normal Anatomy and Histology

Female Reproductive System - Diagram



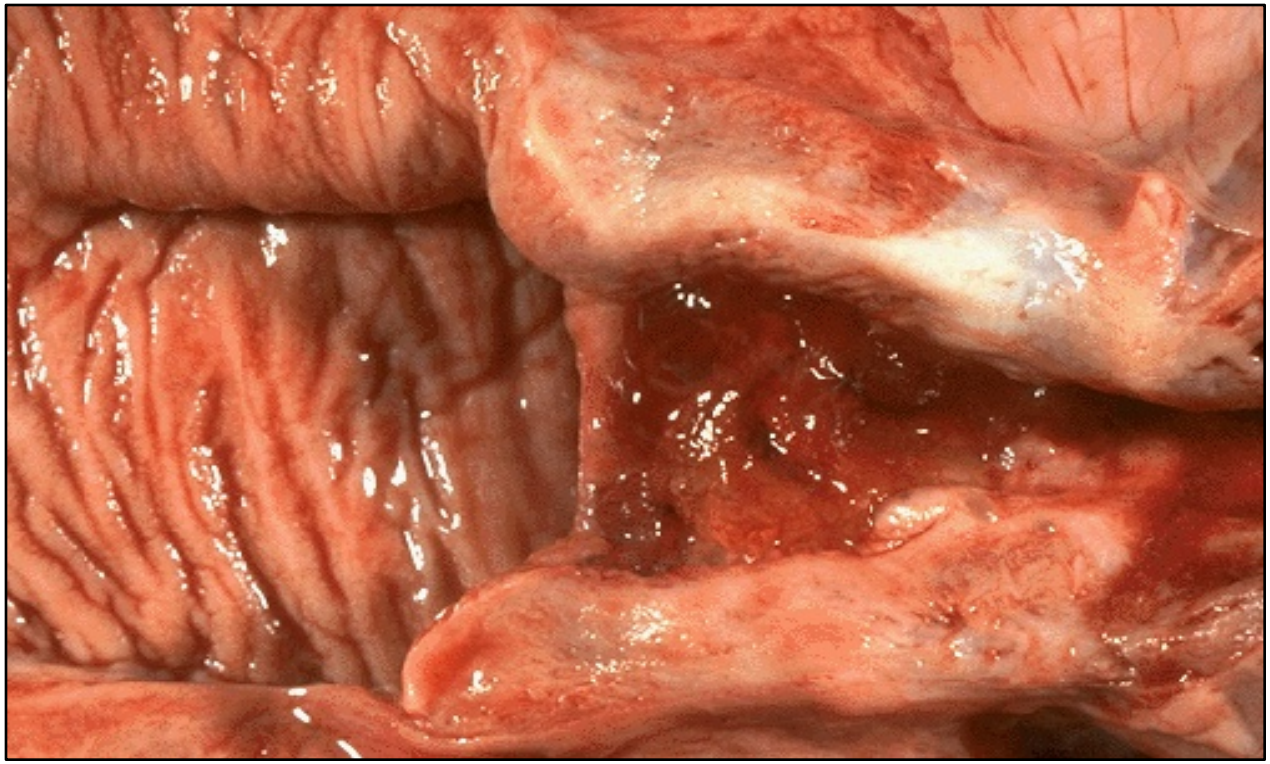
Female Reproductive System - Gross

Uterus with Cervix, Ovaries and Fallopian Tubes

Normal Uterine Cervix - Gross

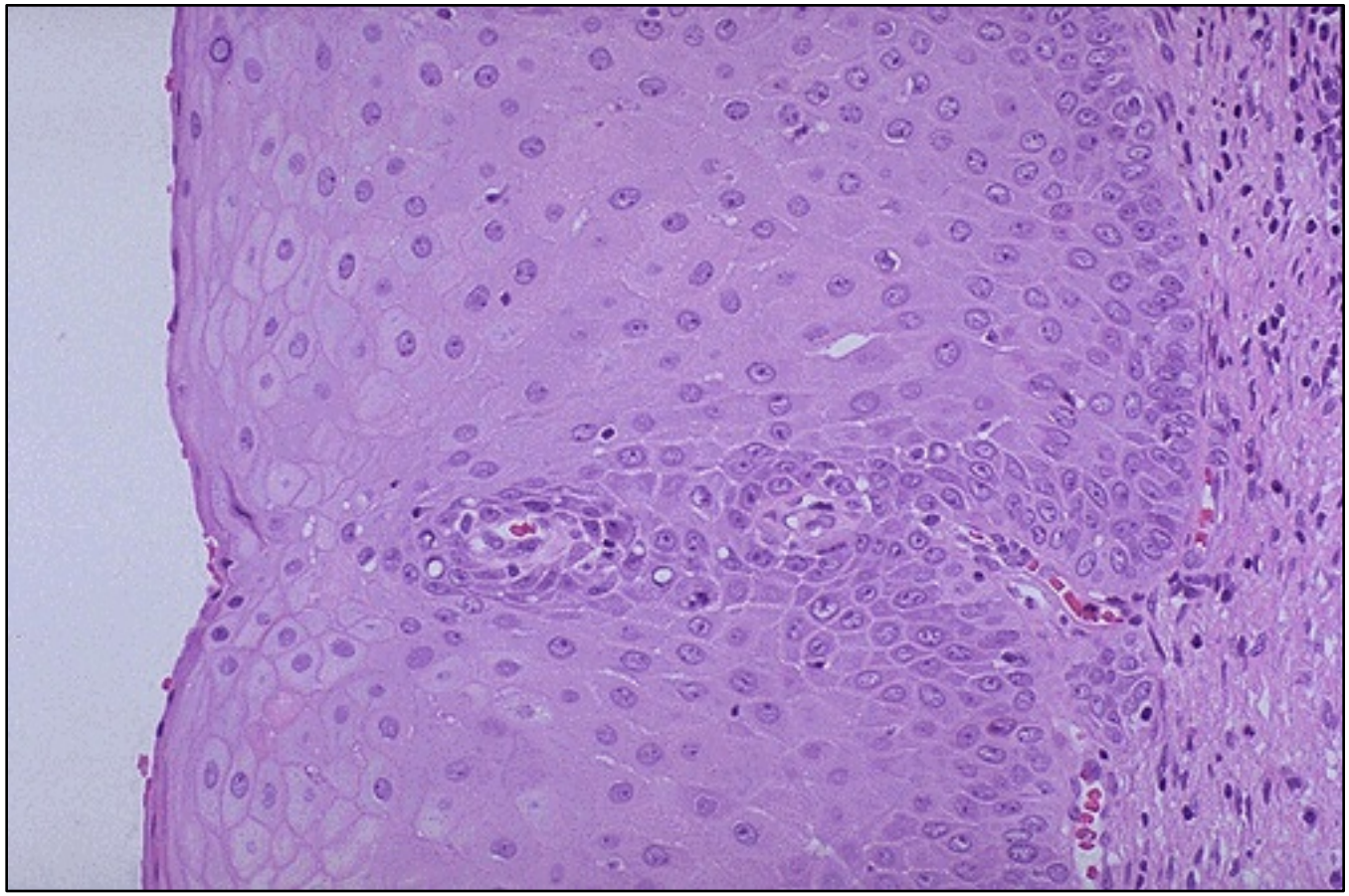
Normal cervix with a smooth, glistening mucosal surface. There is a small rim of vaginal cuff from this hysterectomy specimen. The cervical os is small and round, typical for a nulliparous woman. The os will have a fish-mouth shape after one or more pregnancies

Normal Vagina & Cervix - Gross Cut section



The normal adult vaginal mucosa with a wrinkled appearance that is seen in women of reproductive years appears at the left. The cervix has been opened to reveal an endocervical canal leading to the lower uterine segment at the right that has an erythematous appearance extending to the cervical os consistent with chronic inflammation.

Normal Cervical Mucosa - HPF



This is normal Ectocervical non-keratinizing squamous epithelium. The squamous cells show maturation from the basal layer to the surface

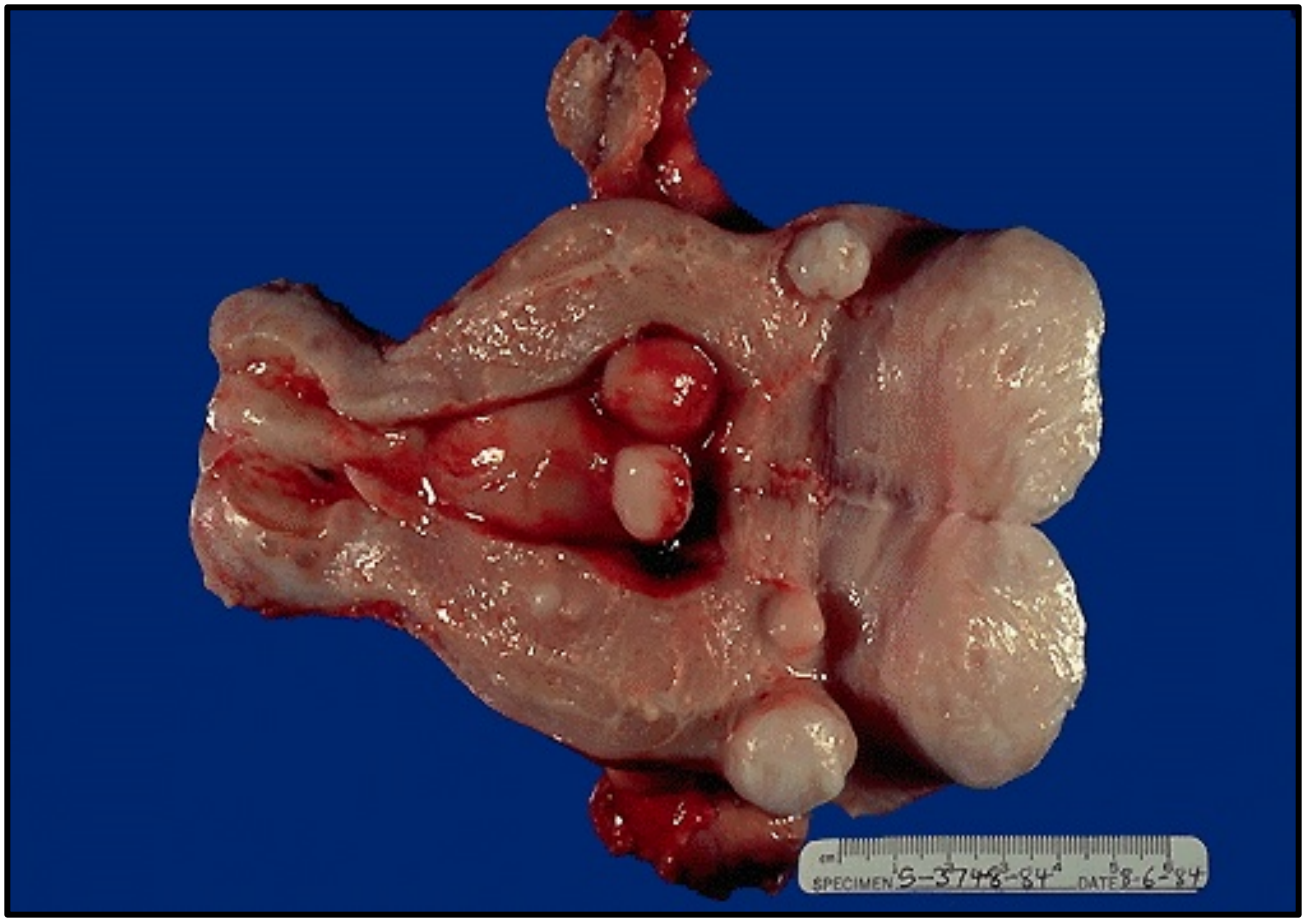
UTERUS

GROSS and HISTOPATHOLOGY

ENDOMETRIUM

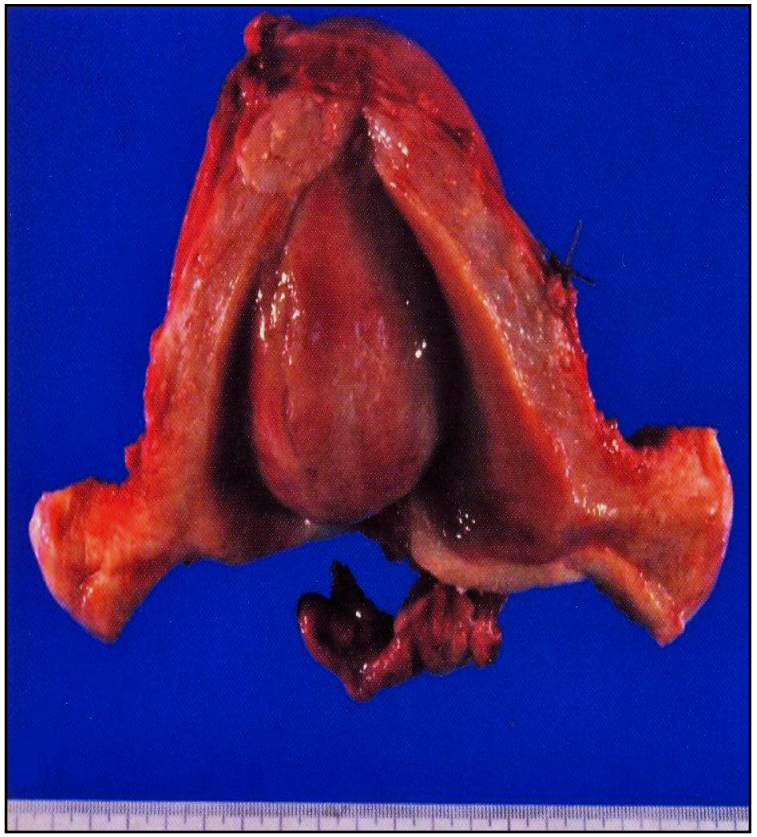
Uterine Leiomyomata

Multiple Uterine Leiomyomata - Gross



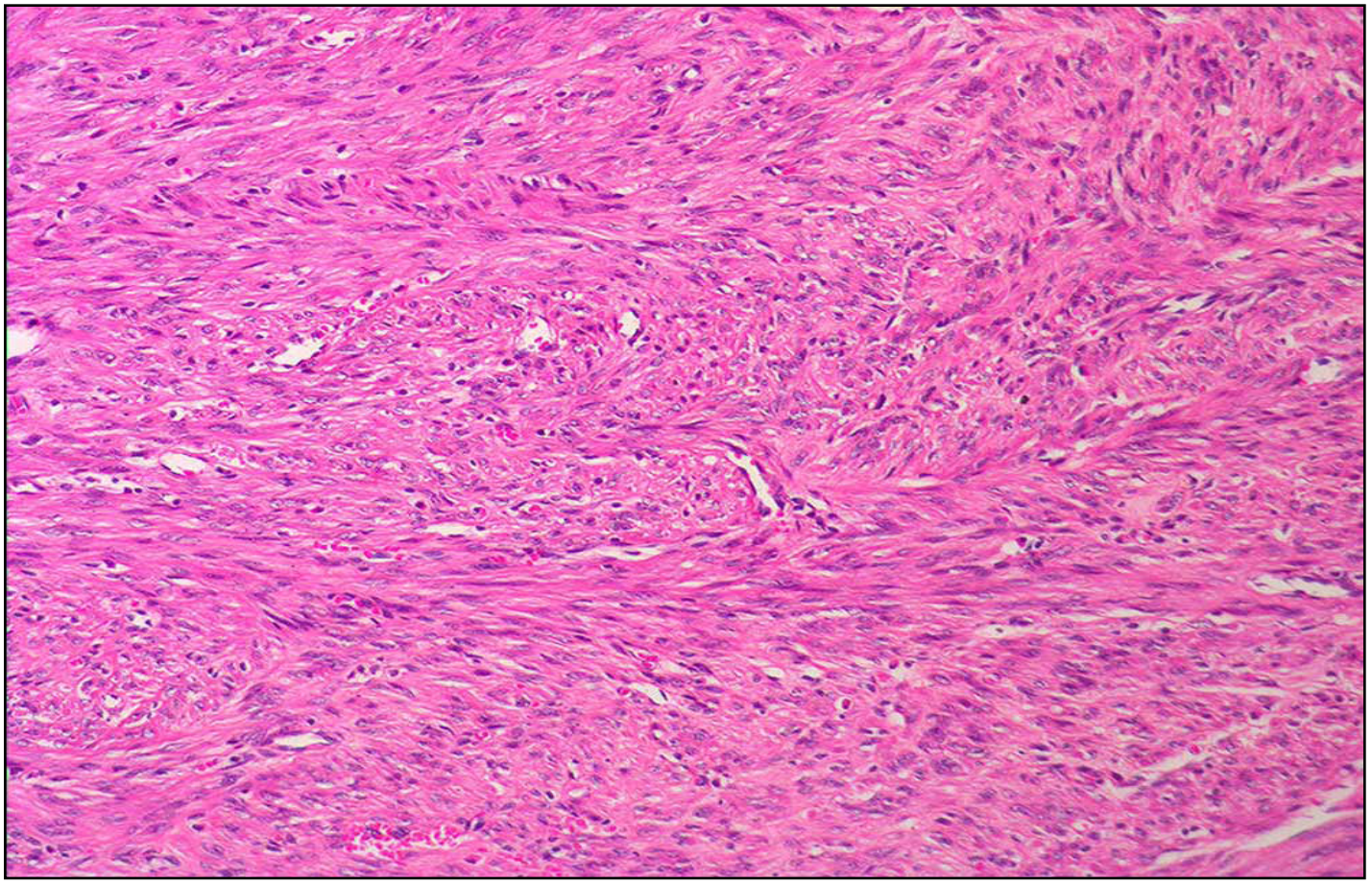
Smooth muscle tumors of the uterus are often multiple. Seen here are submucosal, intramural, and subserosal leiomyomata of the uterus.

Multiple Uterine Leiomyomata - Gross



A well demarcated tumour mass in the muscle coat of uterus without a definite capsule.

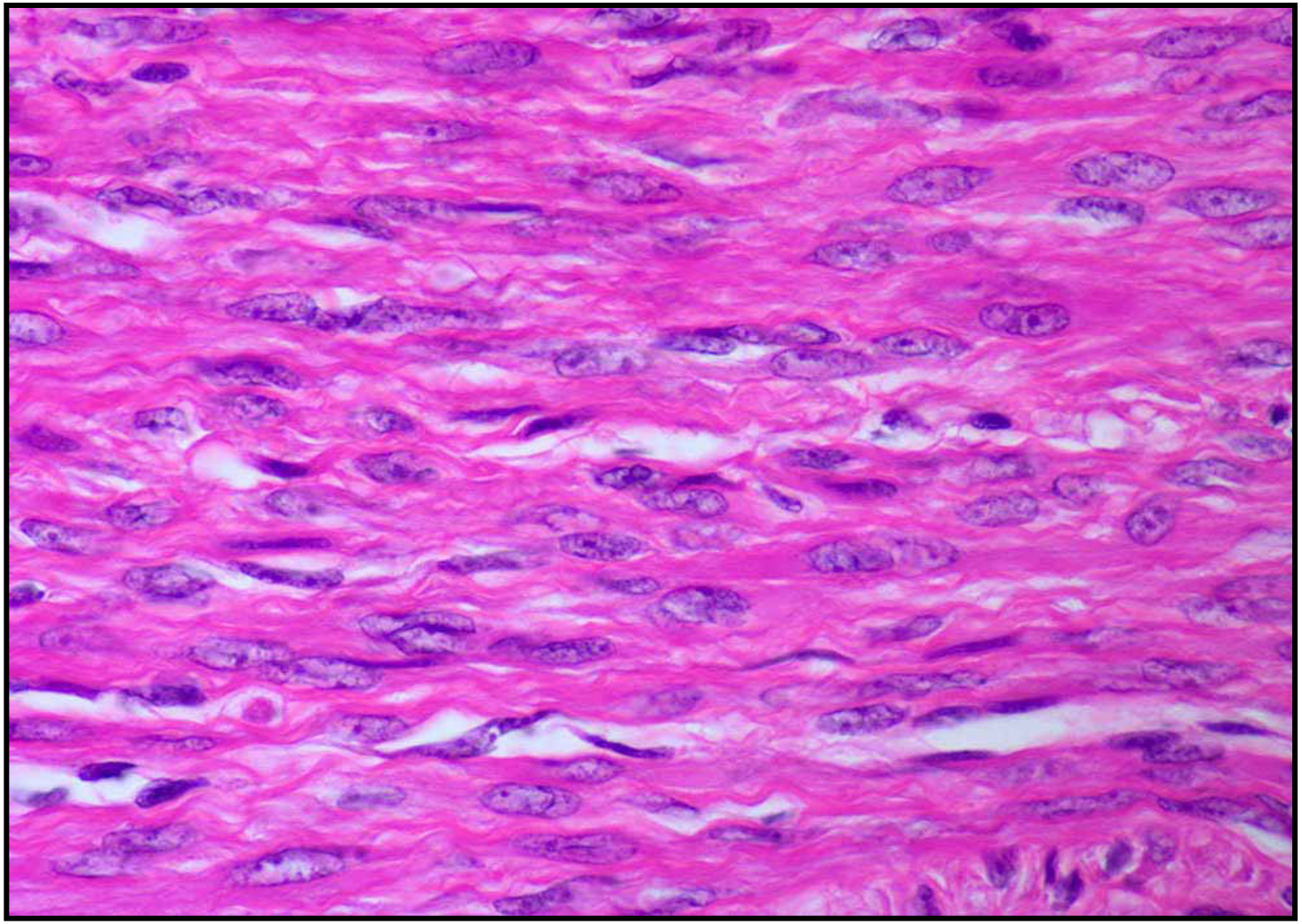
Uterine Leiomyoma – LPF



Tumour consists of interlacing bundles of smooth muscle and fibrous tissue.

The muscle cells are spindle shaped with elongated nuclei and eosinophilic cytoplasm.

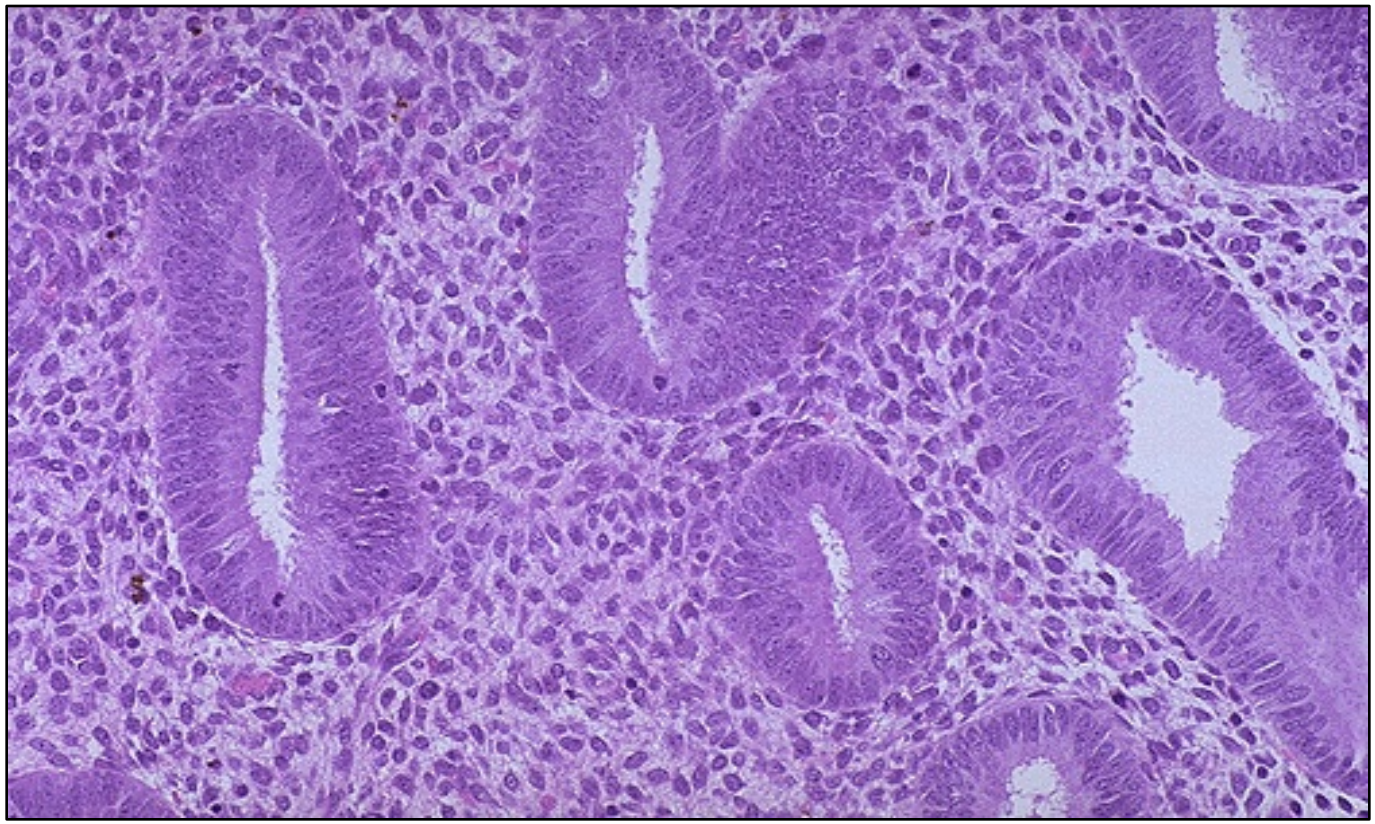
Uterine Leiomyoma – HPF



The muscle cells are spindle shaped with elongated nuclei and eosinophilic cytoplasm

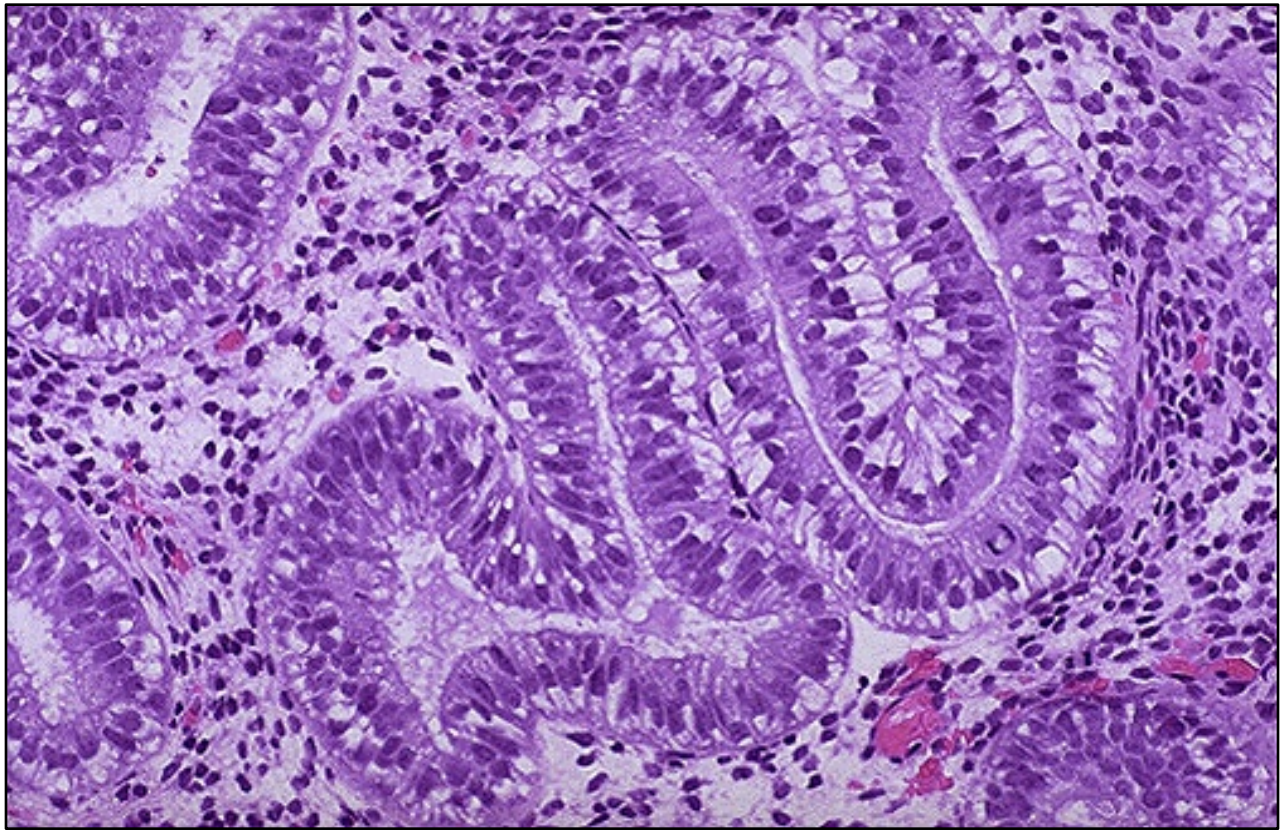
Endometrial Hyperplasia & Carcinoma

Normal Proliferative Endometrium



Normal proliferative endometrium in the menstrual cycle. The proliferative phase is the variable part of the cycle. In this phase, tubular glands with columnar cells and surrounding dense stroma are proliferating to build up the endometrium following shedding with previous menstruation.

Early Secretory Endometrium



The appearance with prominent subnuclear vacuoles in cells forming the glands is consistent with post-ovulatory day 2 of luteal phase. The histologic changes following ovulation are quite constant over the 14 days to menstruation and can be utilized to date the endometrium.

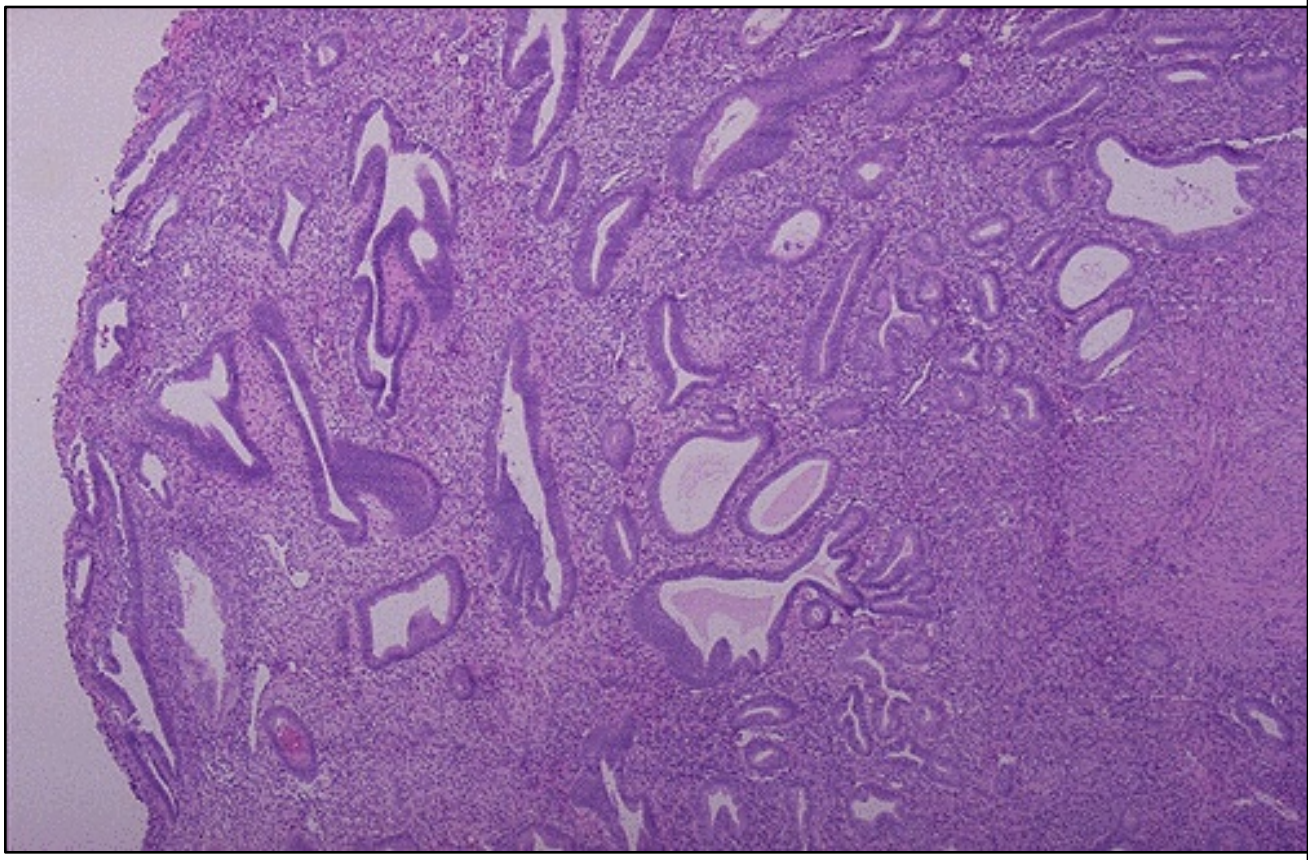
Endometrial Hyperplasia - Gross

- **Thick and hyperplastic endometrium.**
- **Areas of hemorrhage.**

The endometrial cavity is opened to reveal lush fronds of hyperplastic endometrium. Endometrial hyperplasia and carcinoma usually results with conditions of prolonged estrogen excess and can lead to metrorrhagia (uterine bleeding at irregular intervals), menorrhagia (excessive bleeding with menstrual periods), or menometrorrhagia.

Endometrial Hyperplasia without atypia (Simple and cystic endometrial hyperplasia). - LPF

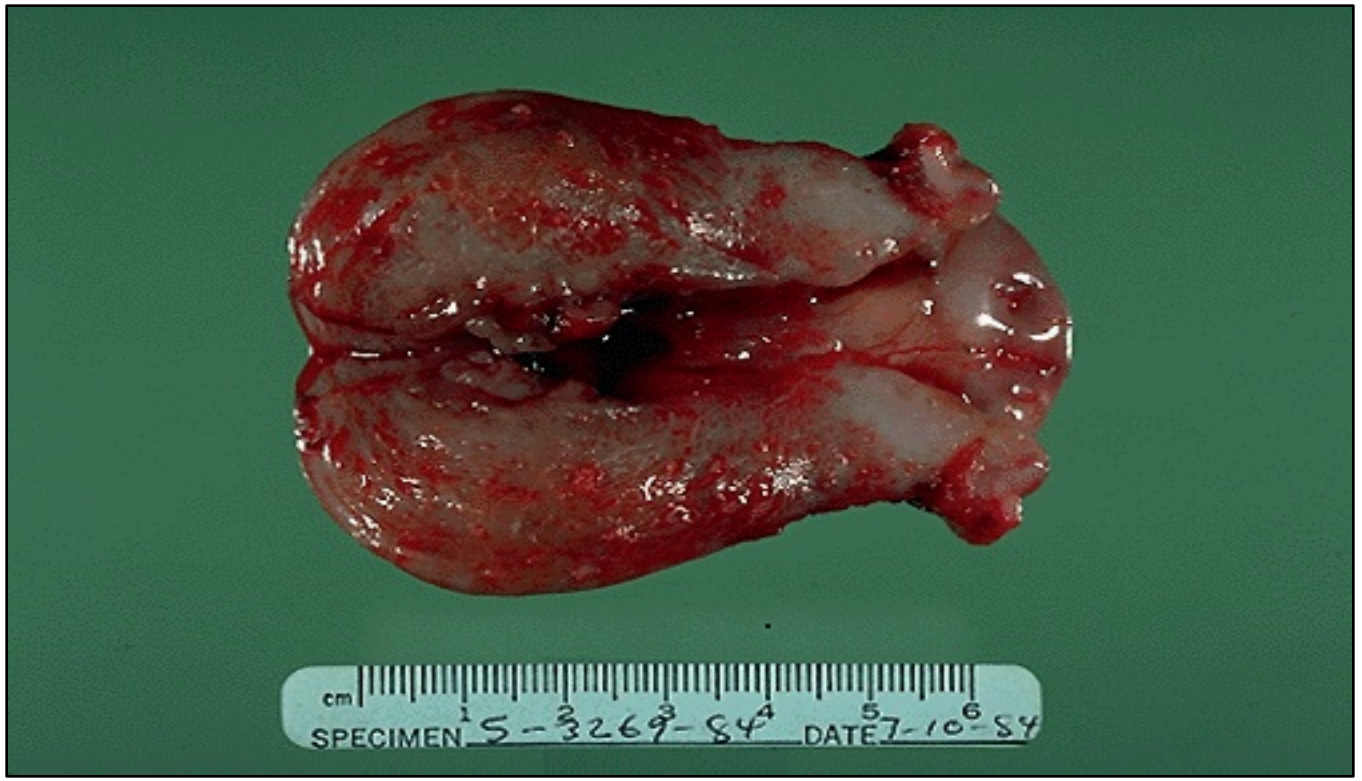
- Cystic and elongated glands.
- Increased glands to stromal ratio.
- Irregular glands lined by columnar cells.



The amount of endometrium is abnormally increased and not cycling as it should. The glands are enlarged and irregular with columnar cells. Can cause bleeding, but are not thought to be premalignant.

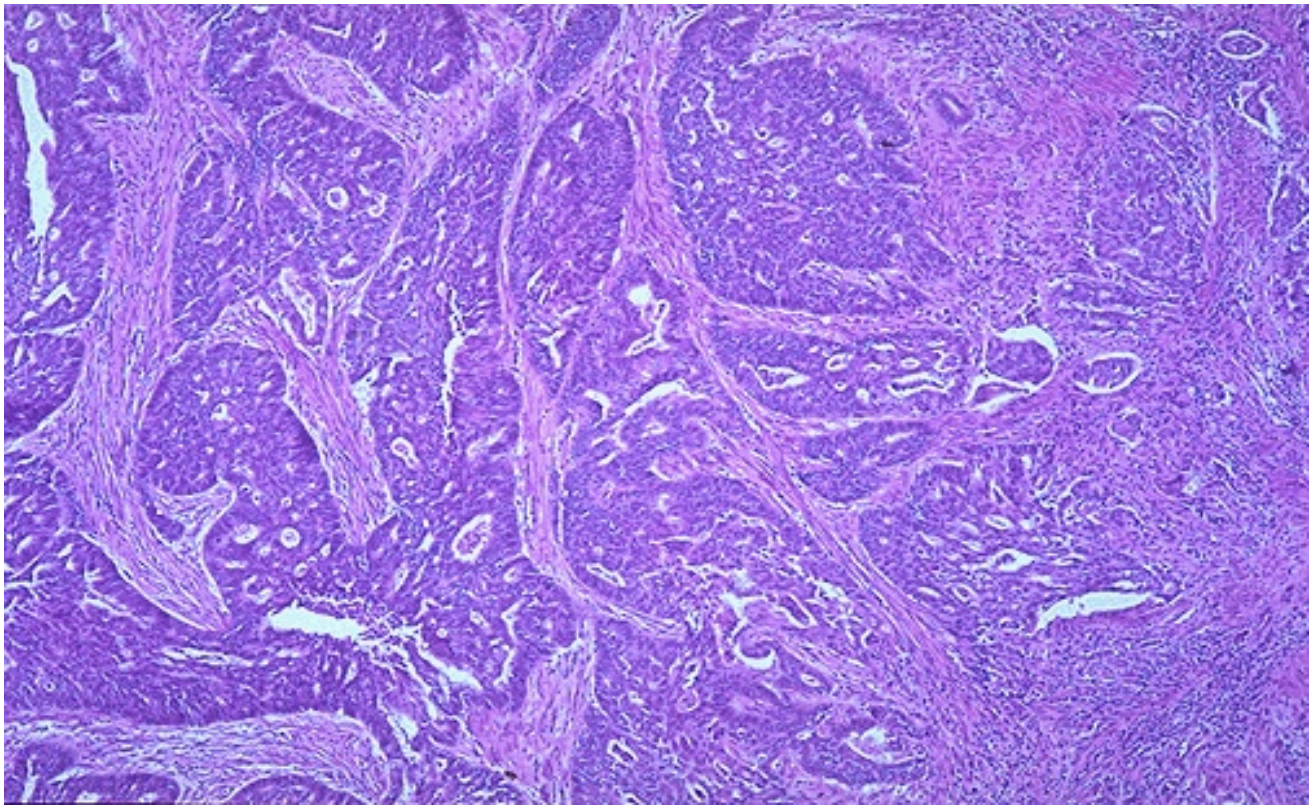
Endometrial hyperplasia is placed in two categories based on the presence of cytologic atypia: hyperplasia without atypia and hyperplasia with atypia. Hyperplasia without cellular atypia carries a low risk (between 1% and 3%) for progression to endometrial carcinoma, whereas hyperplasia with atypia, also called endometrial intraepithelial neoplasia (EIN), is associated with a much higher risk (20%–50%).

Endometrial Adenocarcinoma - Gross



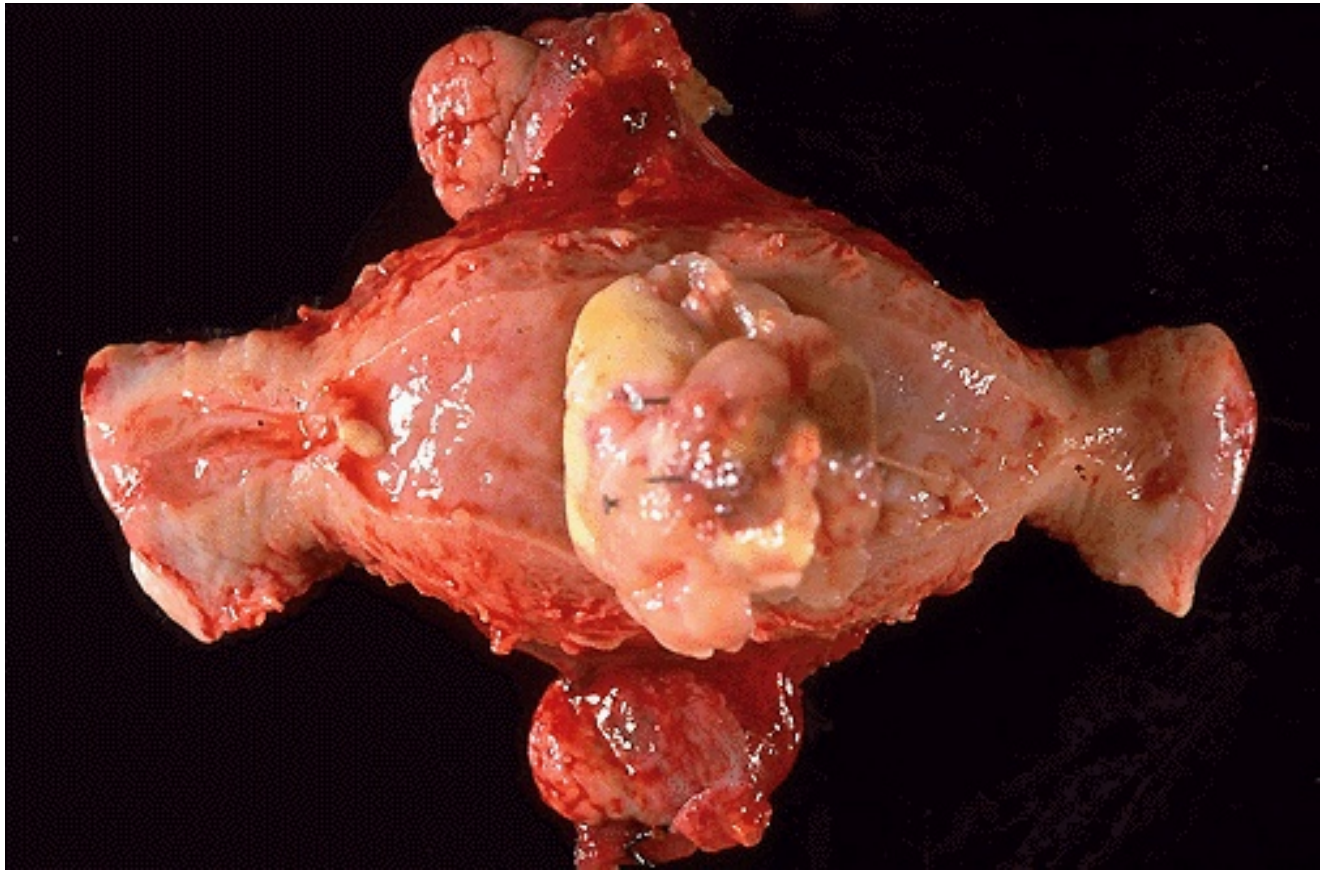
This uterus is not enlarged, but there is an irregular mass in the upper fundus that proved to be endometrial adenocarcinoma on biopsy. Such carcinomas are more likely to occur in postmenopausal women. Thus, any postmenopausal bleeding should make you suspect that this lesion may be present.

Endometrial Adenocarcinoma - LPF



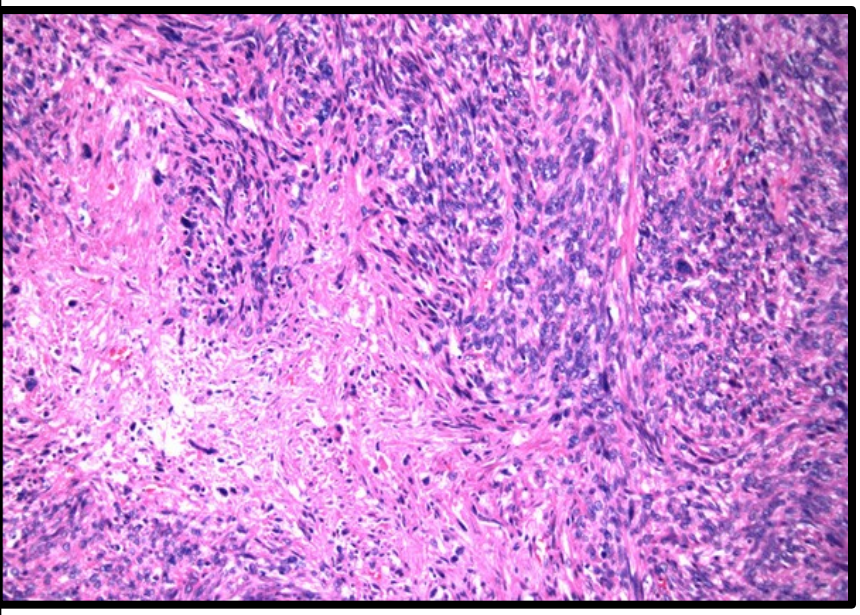
This is an endometrial adenocarcinoma which can be seen invading into the smooth muscle bundles of the myometrial wall of the uterus. This neoplasm has a higher stage than a neoplasm that is just confined to the endometrium

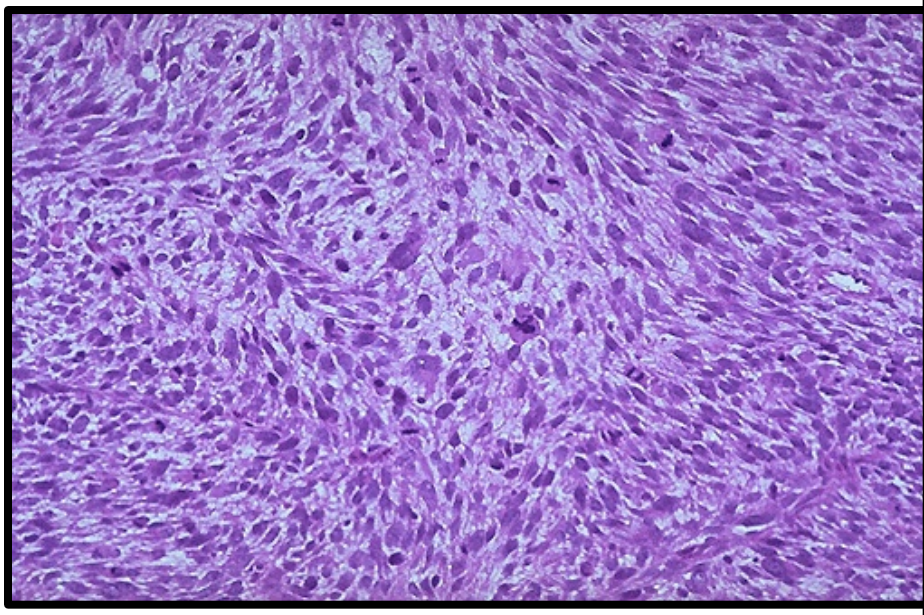
Endometrial Leiomyosarcoma - Gross



- *Large pale irregular mass.*
- *Protruding from myometrium.*

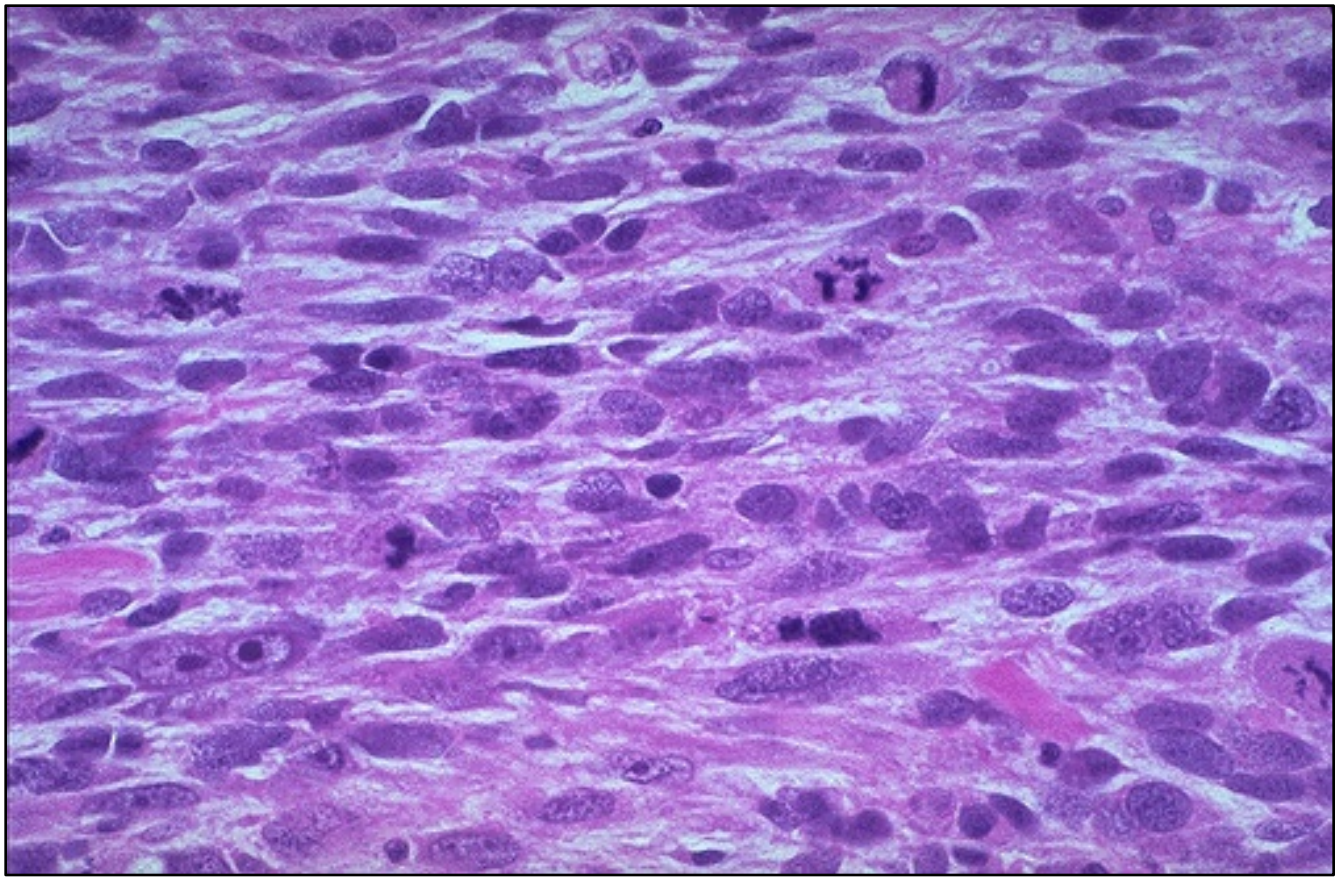
Endometrial Leiomyosarcoma - LPF





The cells have much more pleomorphism /hyperchromatism, increased mitoses and necrosis compared to the benign leiomyoma.

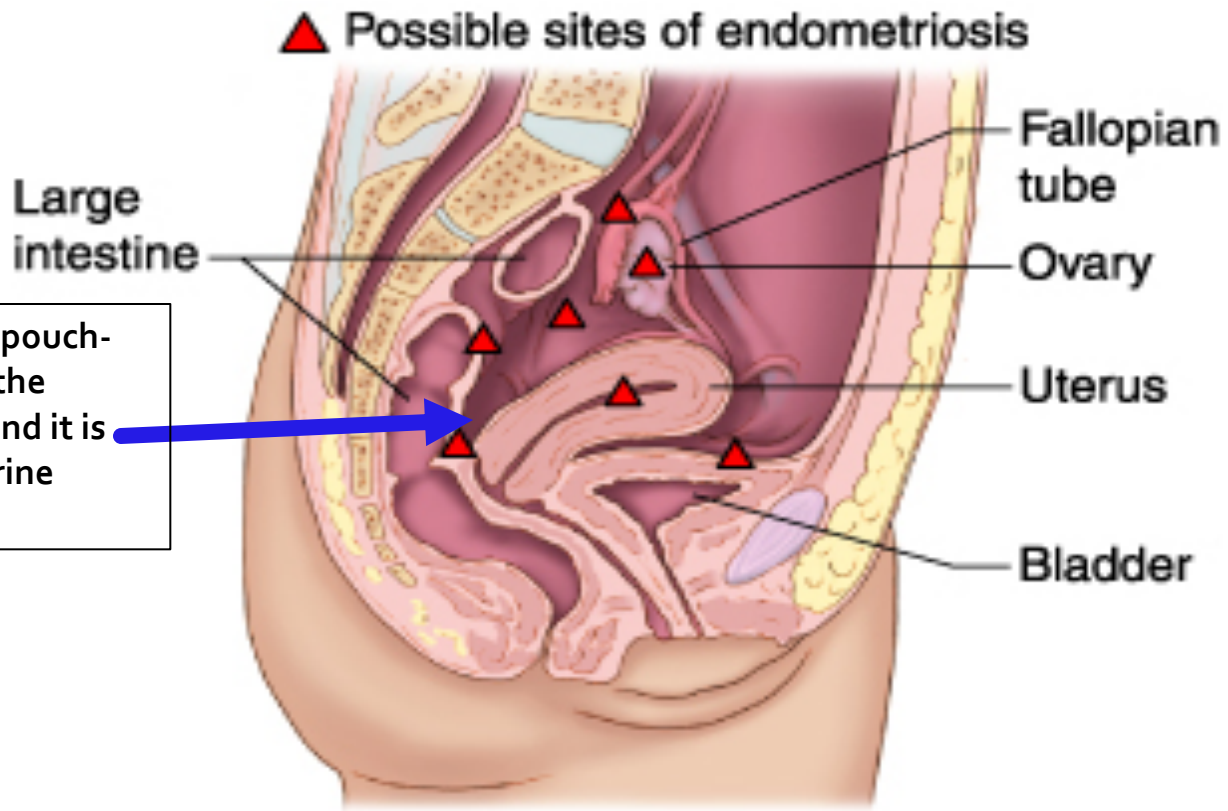
Endometrial Leiomyosarcoma - HPF



- *Nuclear and cellular pleomorphism.*
- *Mitoses.*
- *Spindle cells*

ENDOMETRIOSIS

Endometriosis sites - Diagram



Pouch of Douglas: a pouch-like space between the rectum and uterus and it is also called rectouterine pouch.

Endometriosis, a chronic noncancerous disorder of the female reproductive system, develops when the endometrium grows outside the uterus. Common sites for endometriosis include ovaries, fallopian tubes, external genitalia (vulva), ligaments supporting the uterus, intestine, bladder, cervix, and vagina.

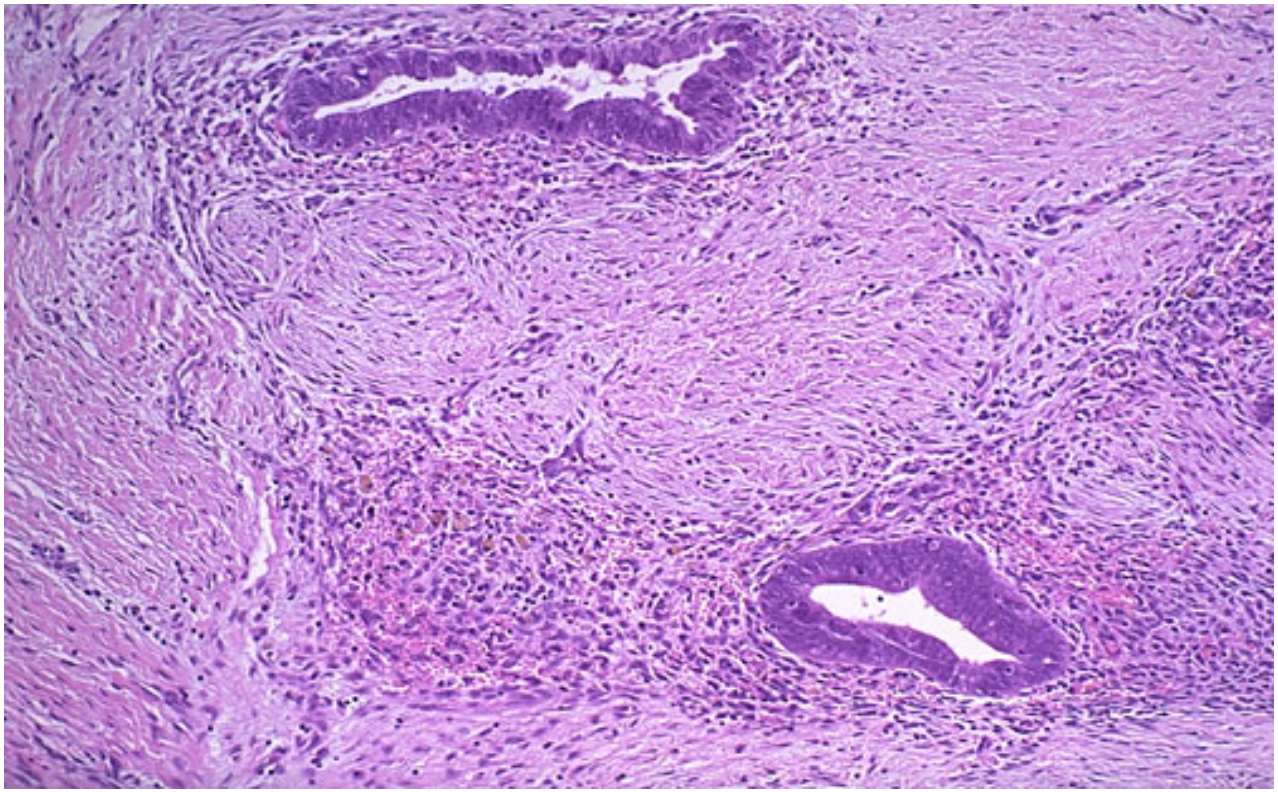
Endometriosis - Gross

Grossly, in areas of endometriosis the blood is darker and gives the small foci of endometriosis the gross appearance of "powder burns". Small foci are seen here just under the serosa of the posterior uterus in the pouch of Douglas.

Endometriosis - Gross

Upon closer view, these five small areas of endometriosis have a reddish-brown to bluish appearance. Typical locations for endometriosis may include: ovaries, uterine ligaments, rectovaginal septum, pelvic peritoneum, and laparotomy scars

Endometriosis - HPF Microscopy

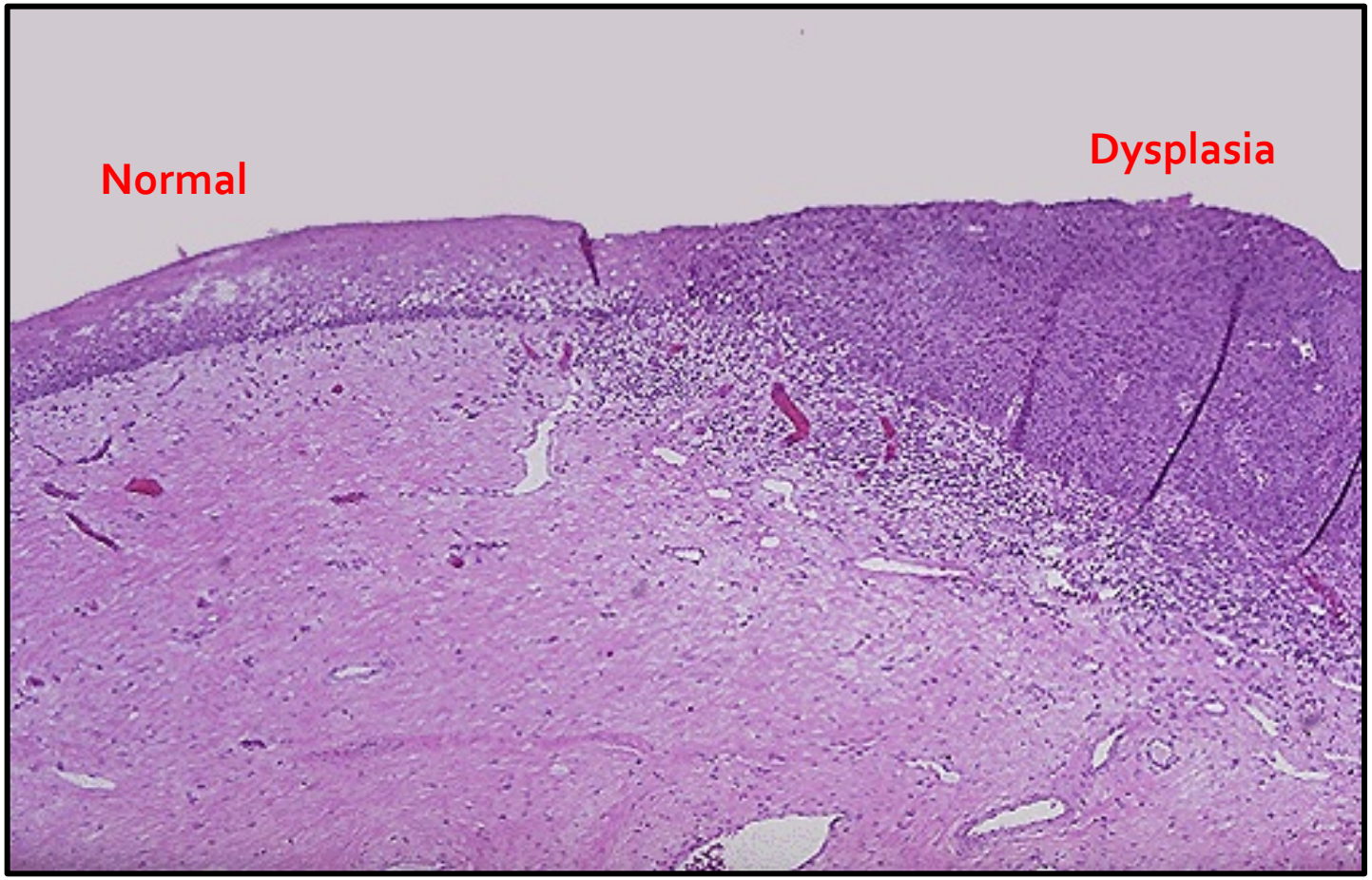


- Endometrial glands along with stroma.
- Fibrosis.

UTERINE CERVIX

Cervical Dysplasia & Cervical Carcinoma

Normal and Dysplastic Cervical Squamous Epithelium

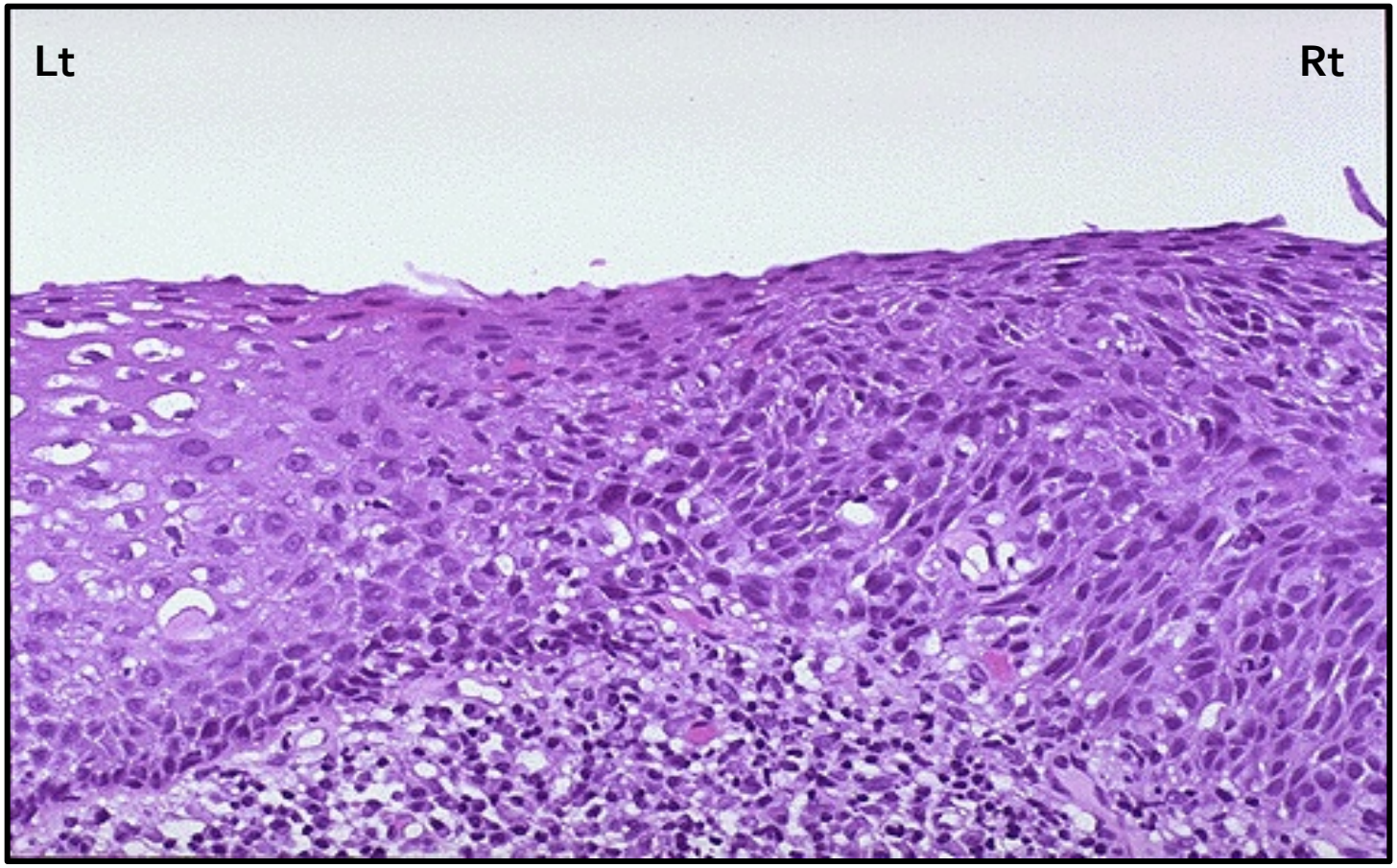


Diagnosis:

- *Uterine cervical squamous dysplasia.*
- *CIN (cervical intraepithelial neoplasia).*

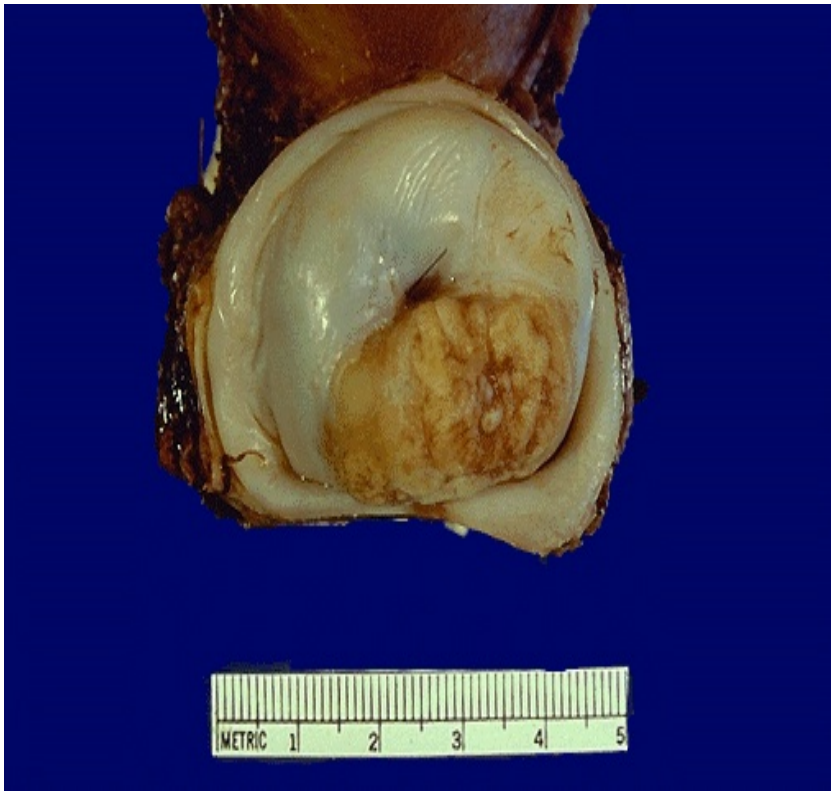
The normal cervical squamous epithelium at the left transforms to Severely dysplastic ectocervical squamous epithelial (high grade dysplasia) diffuse atypia and less maturation with underlying chronic inflammation

Endocervical Squamous Dysplasia



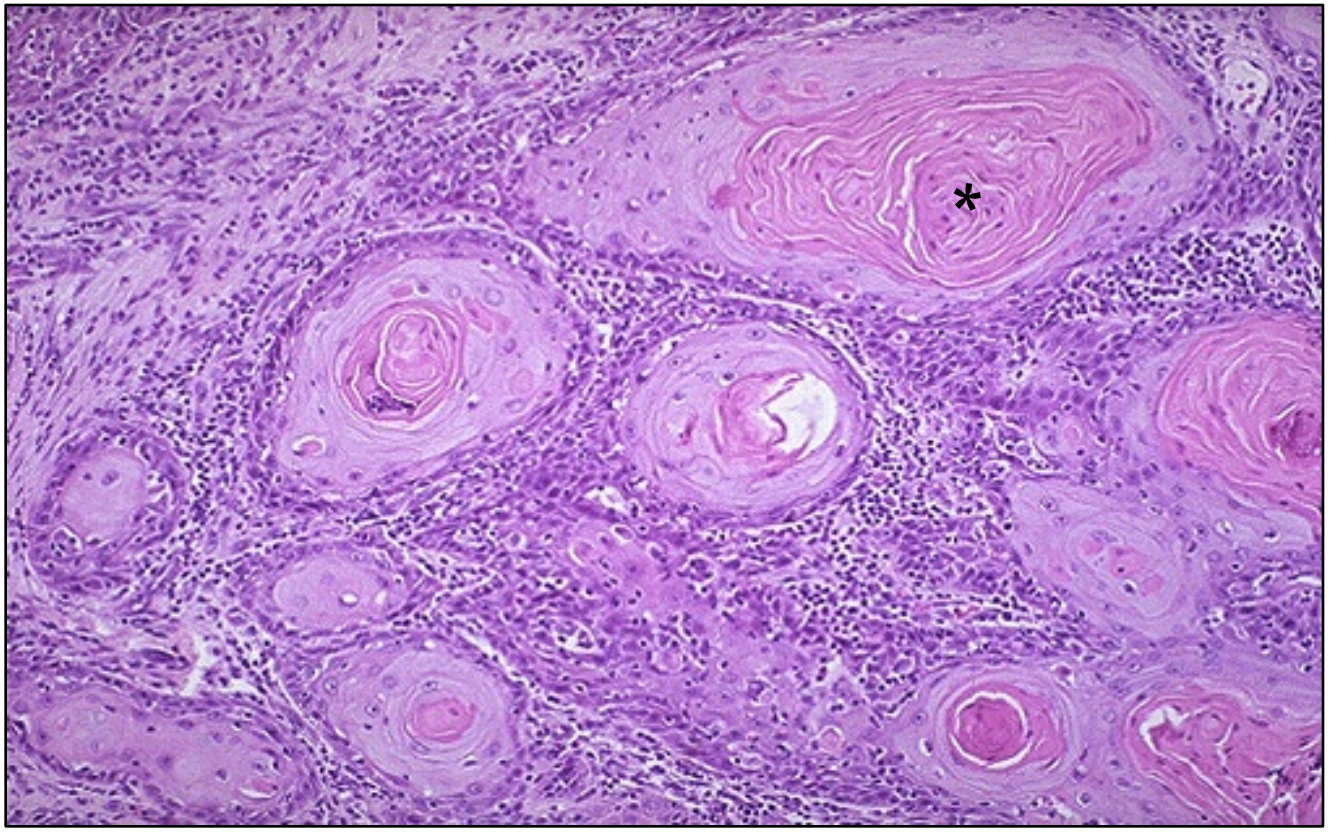
- *Dysplastic cells/nuclei.*
- *Large and dark nuclei.*
- *Disordered cells, loss of polarity.*
- *Chronic inflammatory cells.*

Cervical Squamous Cell Carcinoma



This is the gross appearance of a cervical squamous cell carcinoma that is still limited to the cervix (stage I).
The tumor is a fungating red to tan to yellow mass.

Cervical Squamous Cell Carcinoma - HPF

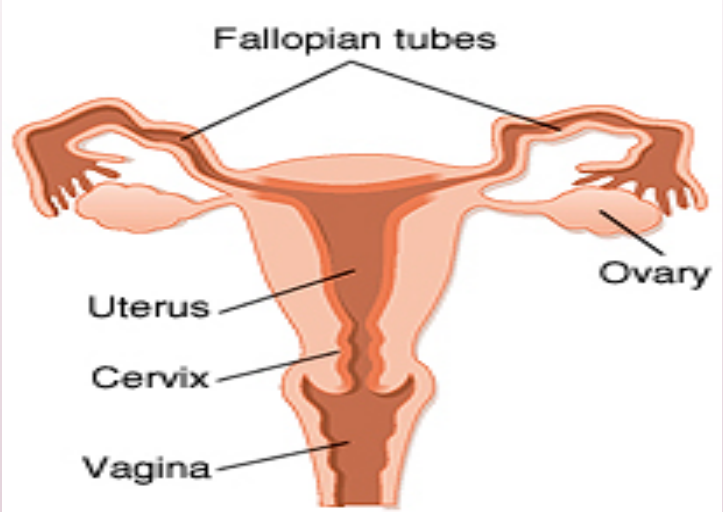


At high magnification, nests of neoplastic squamous cells are invaded through a chronically inflamed stroma. This cancer is well-differentiated, as evidenced by keratin pearls (*) within nests of tumor cells. However, most cervical squamous carcinomas are non-keratinizing.

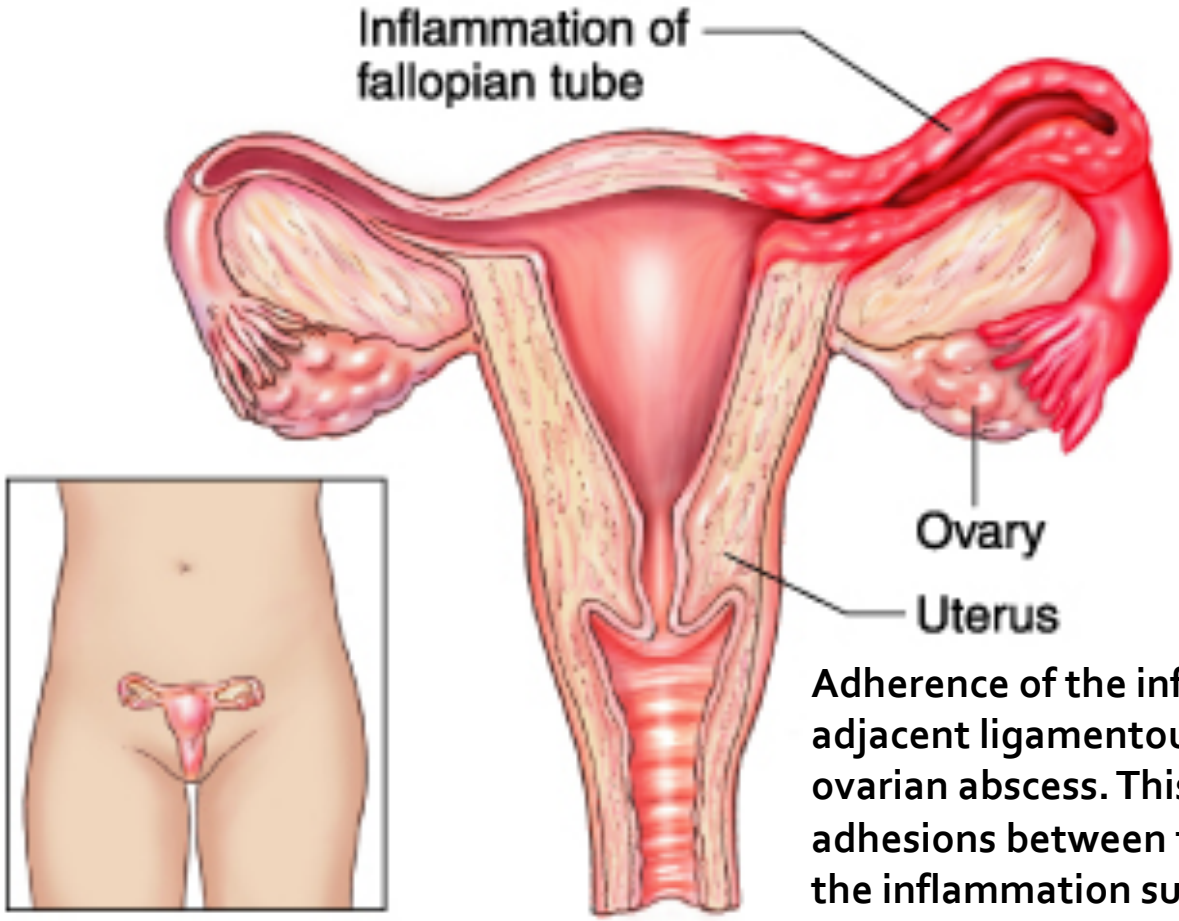
Important risk factors for the development of CIN and invasive carcinoma thus are directly related to Human Papilloma Virus (HPV) exposure and include:

- *Early age at first intercourse.*
- *Multiple sexual partners.*
- *Male partner with multiple previous sexual partners.*
- *Persistent infection by high-risk strains of papillomavirus.*

FALLOPIAN TUBES



Normal vs Inflamed Fallopian Tube

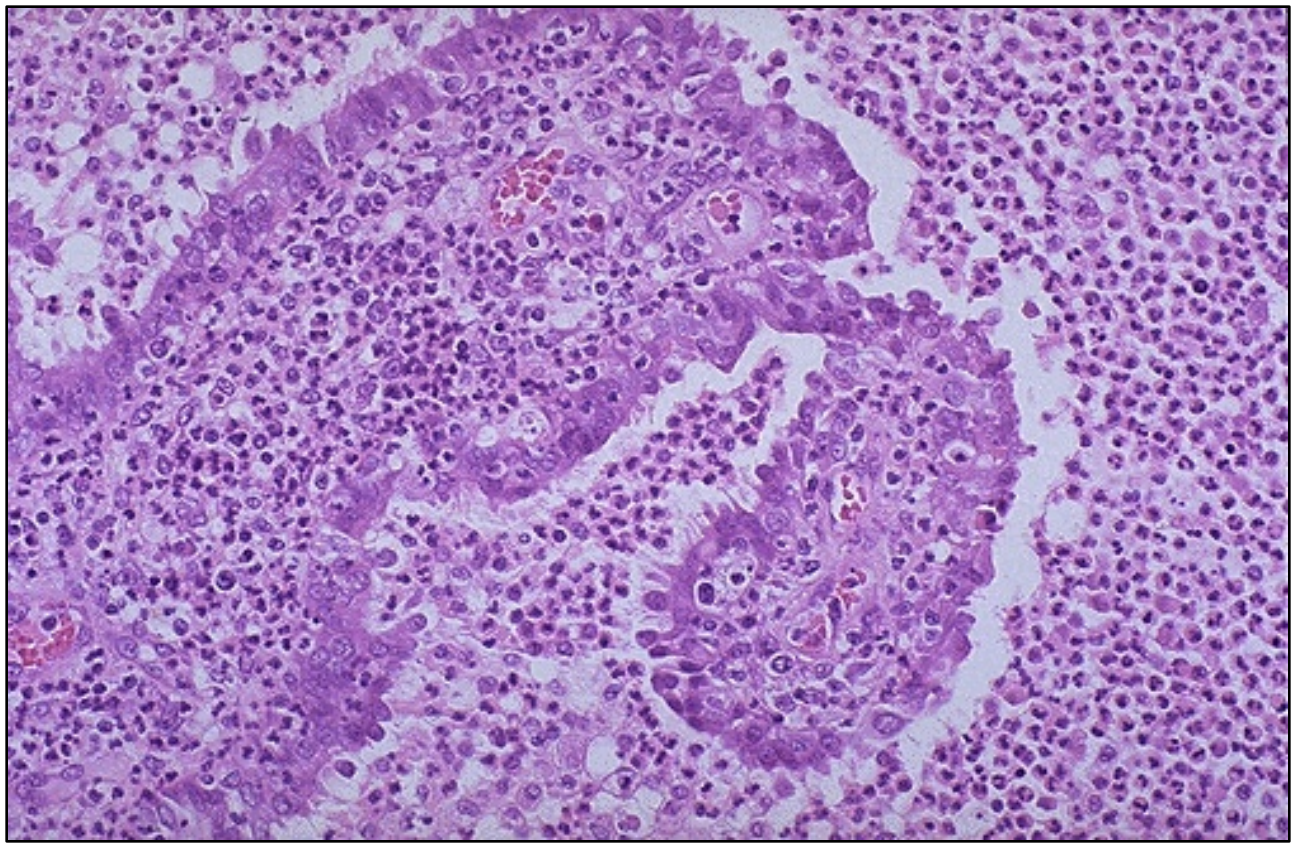


Adherence of the inflamed tube to the ovary and adjacent ligamentous tissues may produce a tubo ovarian abscess. This may in turn result in adhesions between the ovary and the tubes when the inflammation subsides. Even more serious are adhesions of the tubal plicae, which are associated with increased risk of tubal ectopic pregnancy. Damage to or obstruction of the tubal lumina may produce permanent sterility.

Acute Salpingitis - Gross

Acute salpingitis: Excised congested swollen fallopian tube with hemorrhagic patches

Acute Salpingitis - Microscopic

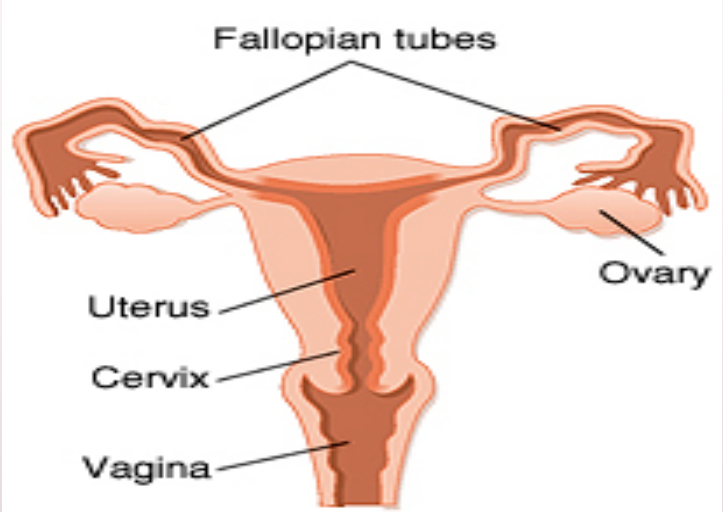


A remnant of ciliated tubal epithelium is seen here surrounded and infiltrated by numerous neutrophils. This is acute salpingitis. Neisseria gonorrheae was cultured.

3RD PRACTICAL SESSION

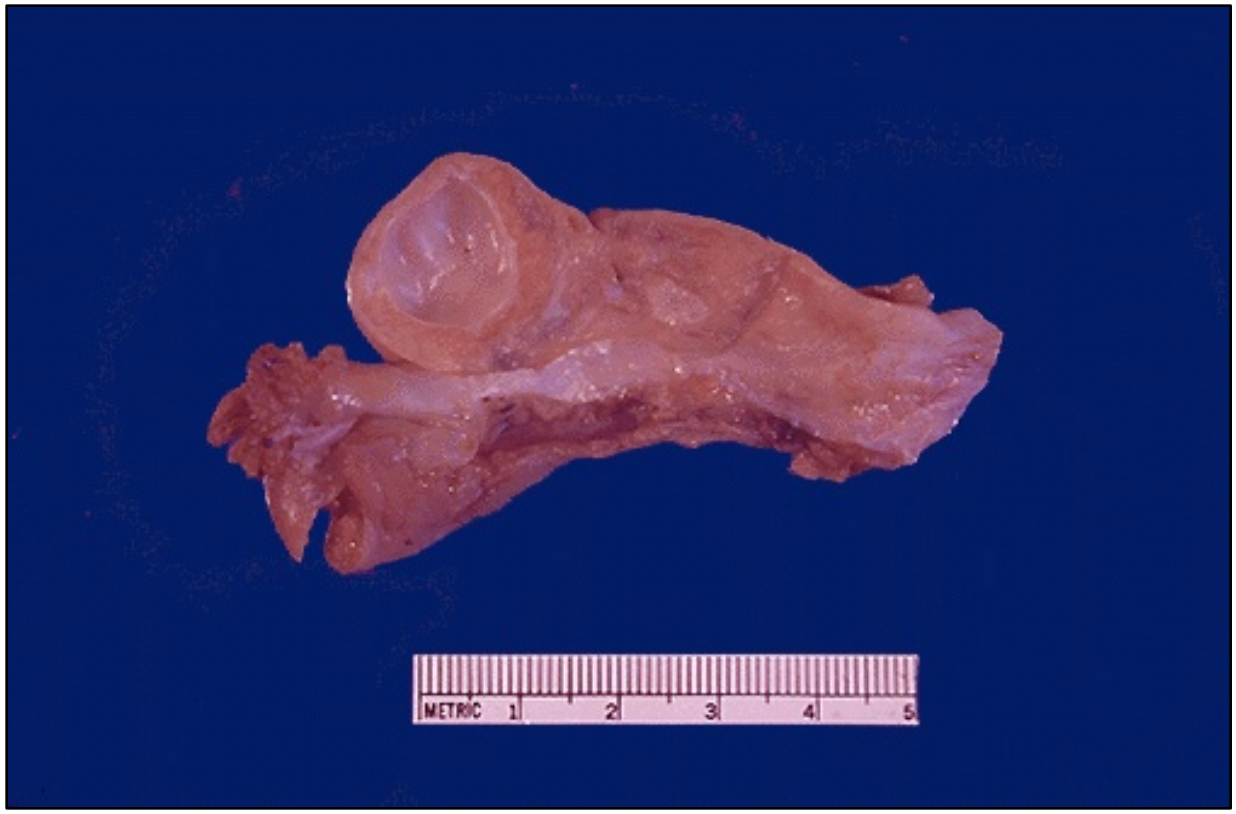
Ovarian Cysts and Breast Masses

OVARIES



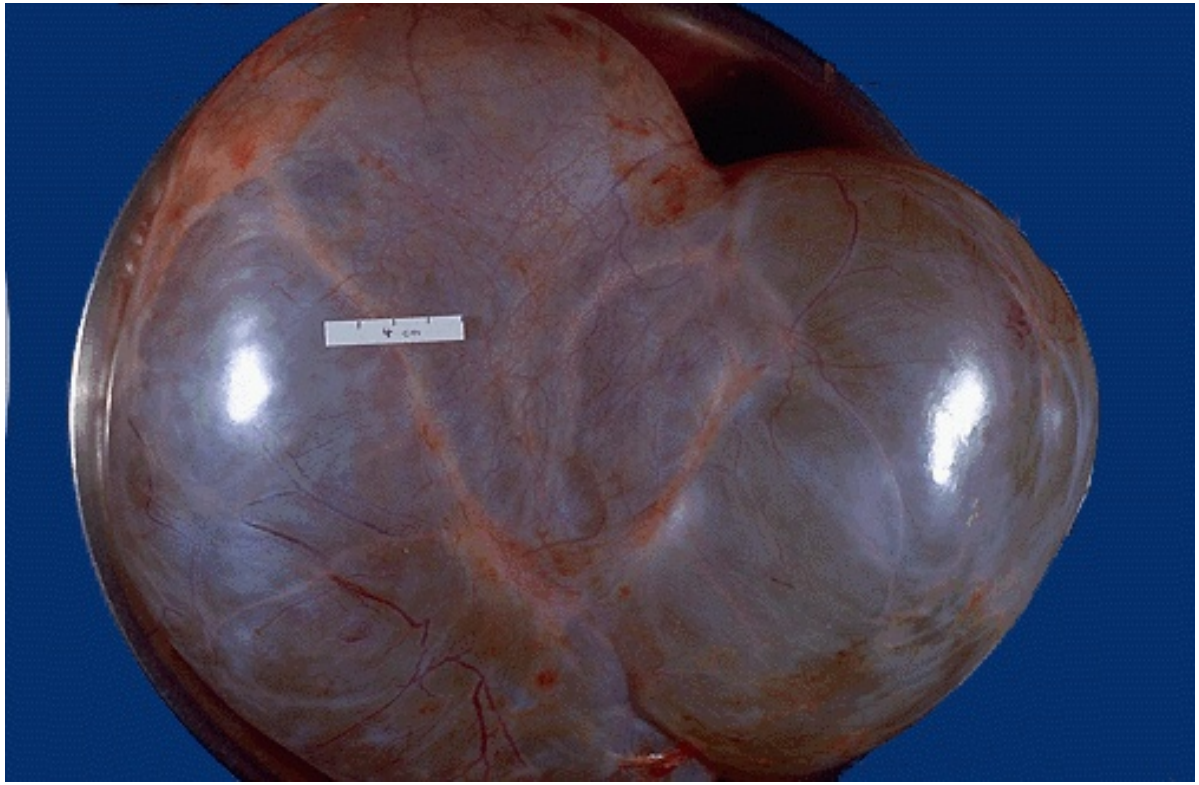
OVARIAN CYST

Benign Ovarian Cyst - Gross



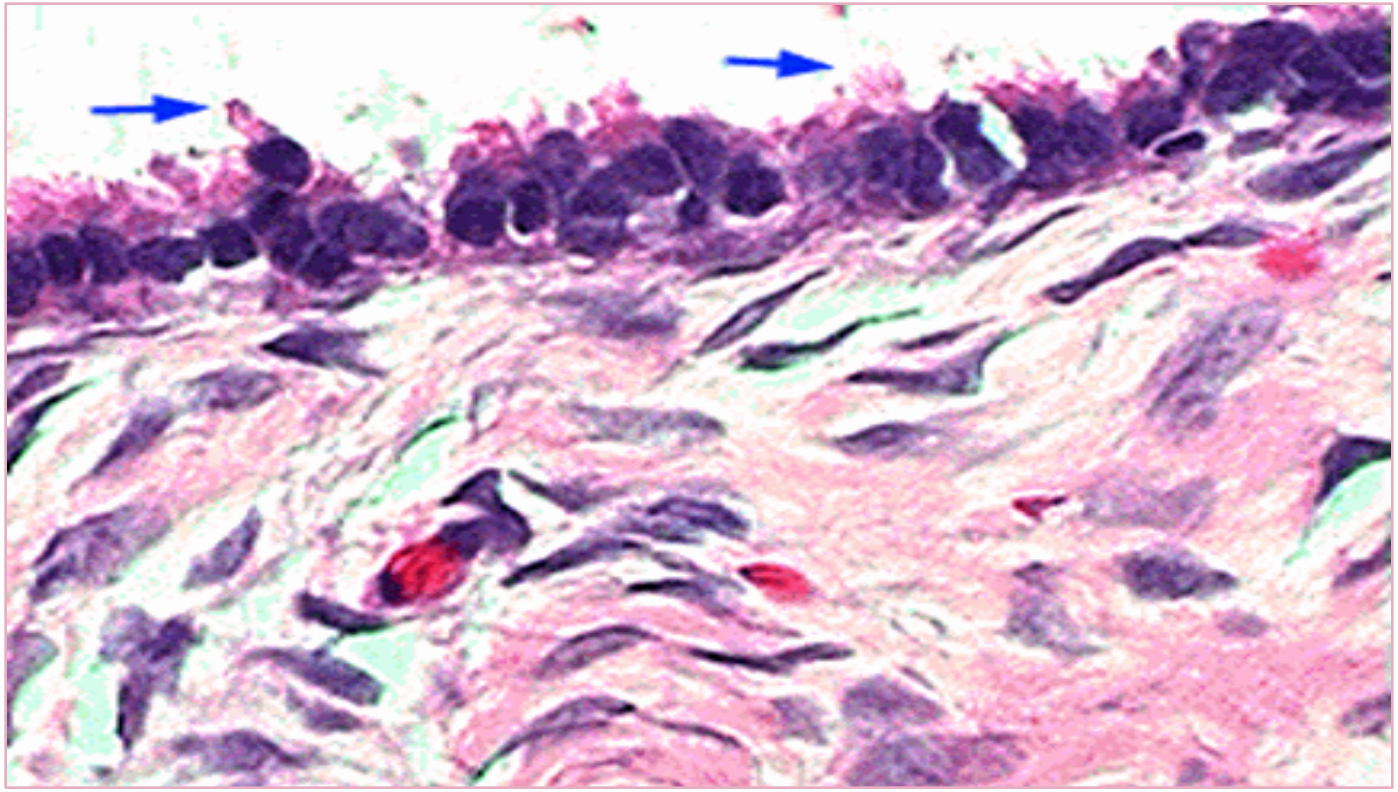
Here is a benign cyst in an ovary. This is probably a follicular cyst. Occasionally such cysts may reach several centimeters in size and, if they rupture, can cause abdominal pain.

Serous Cystadenoma of the Ovary



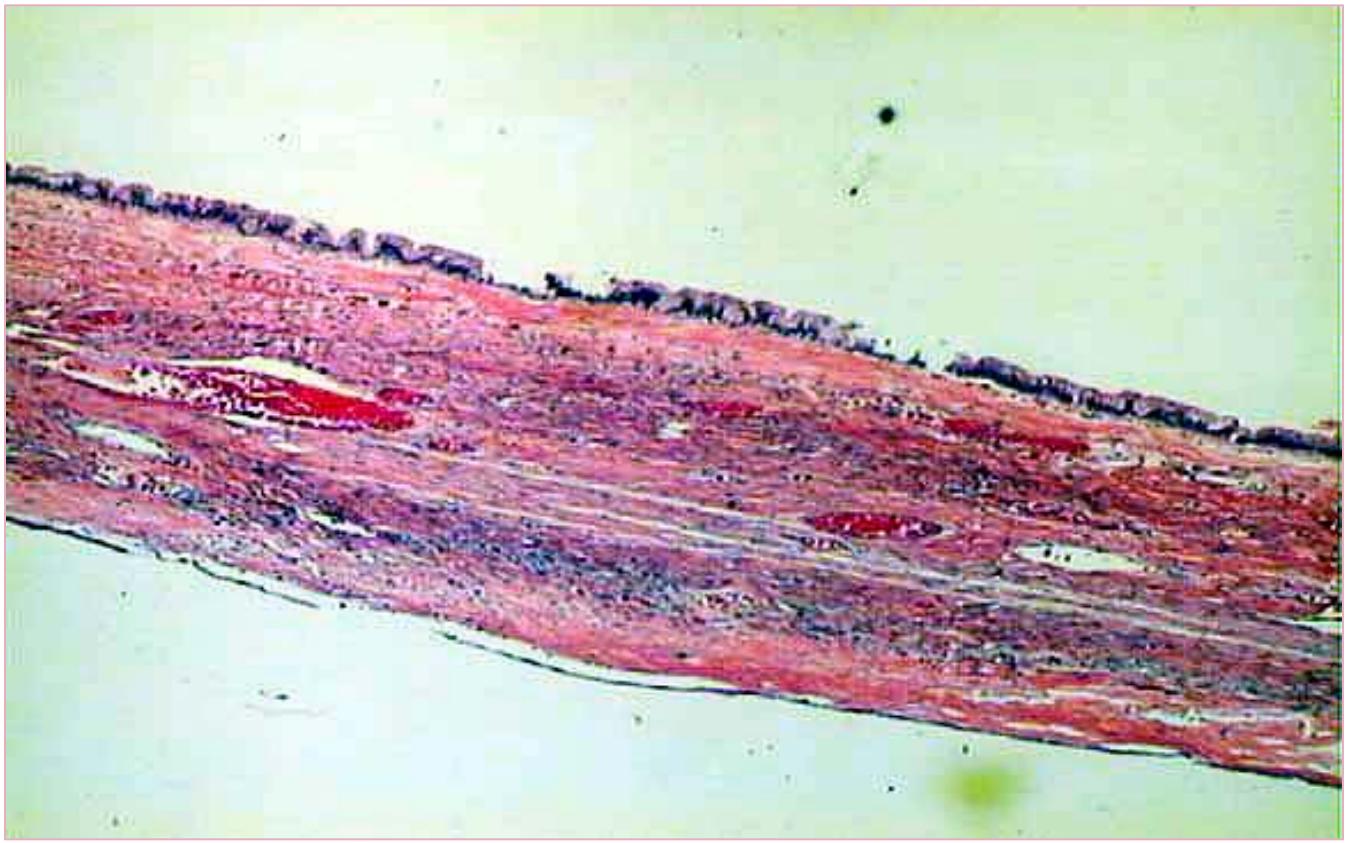
Benign epithelial tumors of the ovary can reach massive proportions. The serous cystadenoma seen here fills a surgical pan and dwarfs the 4 cm ruler.

Serous Cystadenoma of the Ovary - HPF



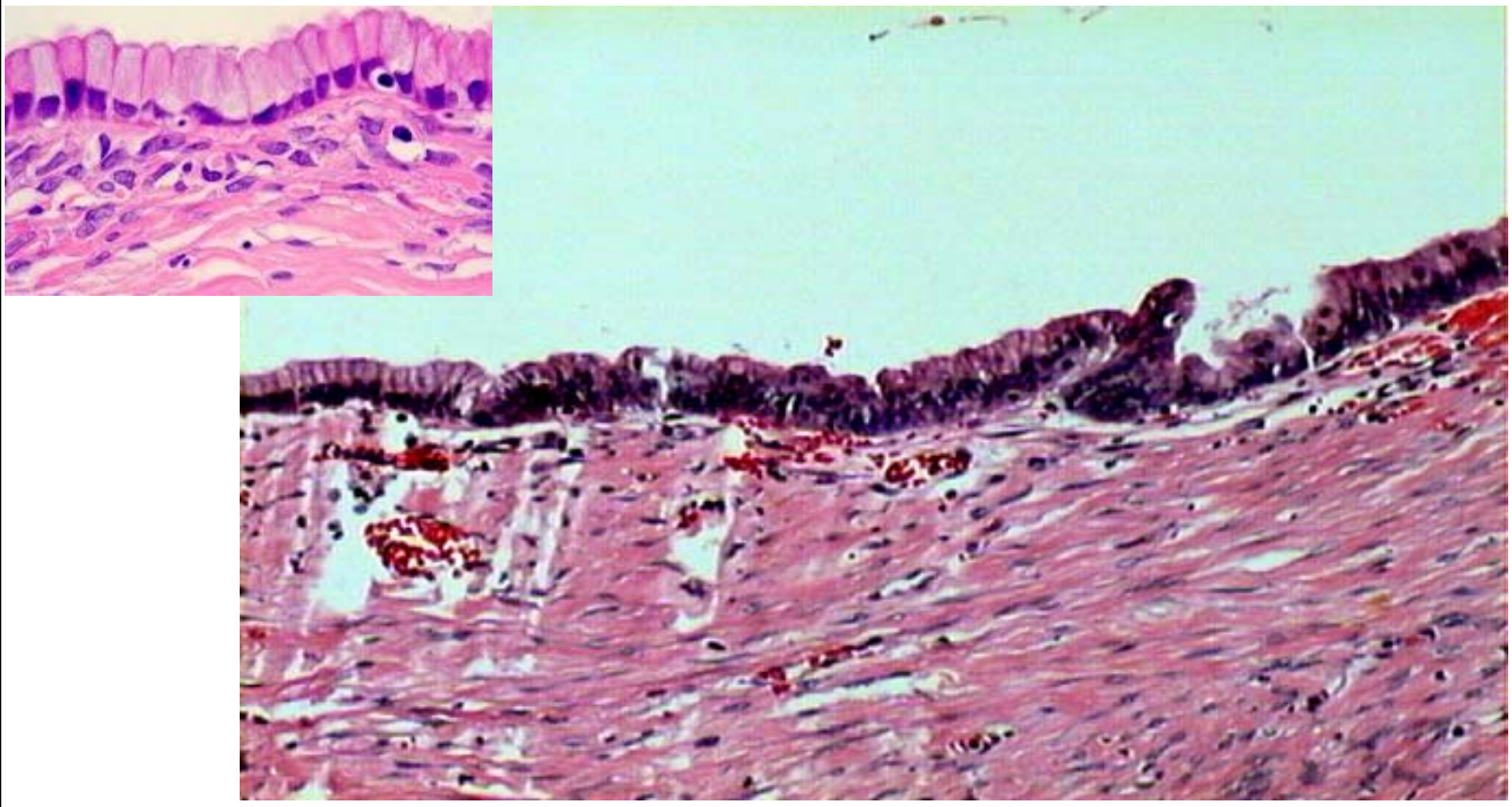
- *The blue arrows point to cilia.*
- *The cells have dark nuclei without nucleoli or mitoses.*
- *The cytoplasm is eosinophlic and ciliated like tubal epithelium.*
- *The stroma contains spindly fibroblasts*

Mucinous Cystadenoma of the Ovary - LPF



Microscopy shows the thin wall lined by a single layer of mucin-secreting columnar cells with a basally-placed spherical small nucleus

Mucinous Cystadenoma of the Ovary - HPF



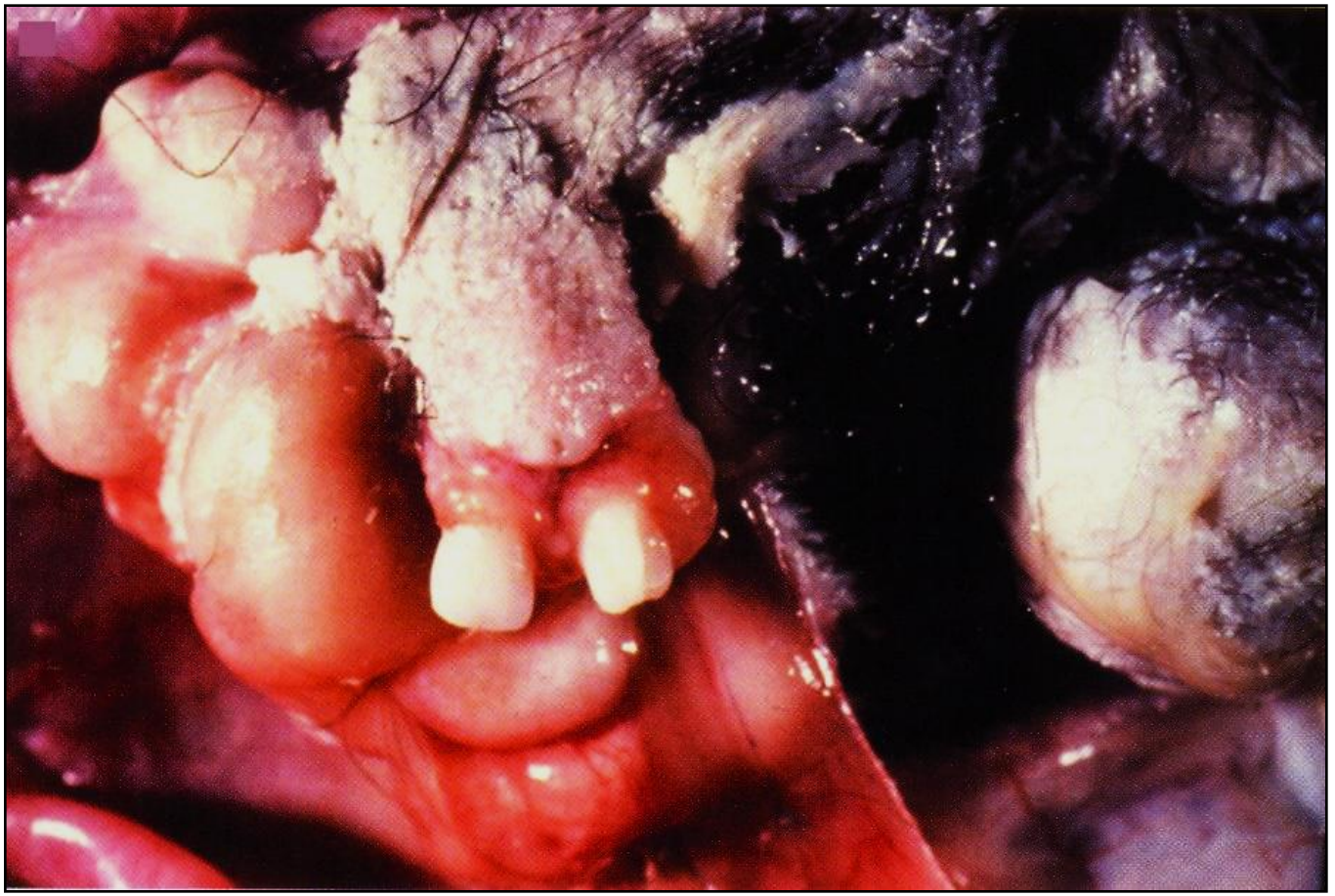
High power shows the thin wall lined by a single layer of mucin-secreting columnar cells with a basally-placed spherical small nucleus

Dermoid Cyst (Teratoma) of the Ovary

Ovary: Mature Cystic Teratoma

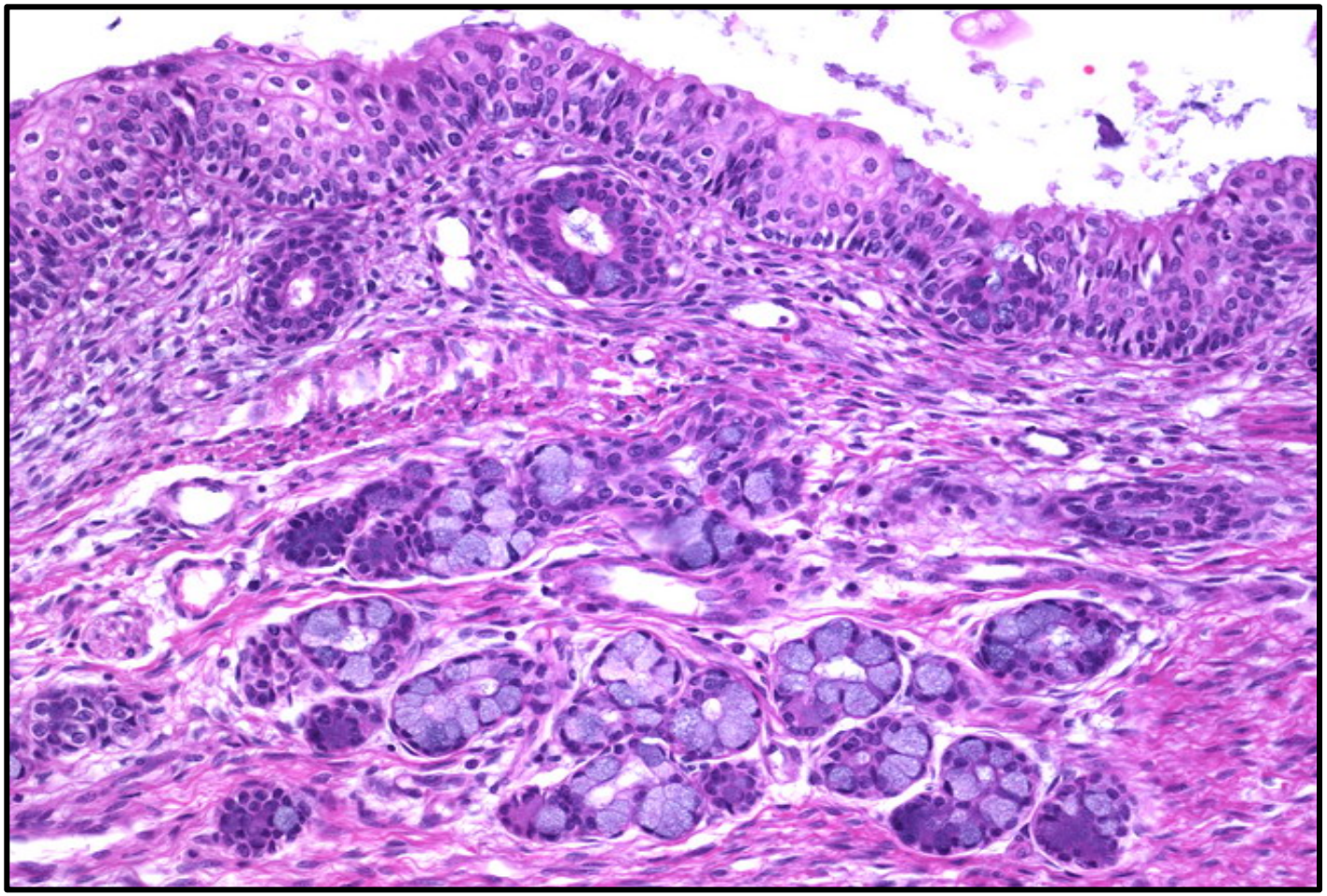
This 4.0 cm dermoid cyst is filled with greasy material (keratin and sebaceous secretions) and shows tufts of hair. The rounded solid area at the bottom is called Rokitansky's protruberance. Microscopically, it also showed foci of neural tissue (Immature Cystic teratoma).

Ovary: Mature Cystic Teratoma



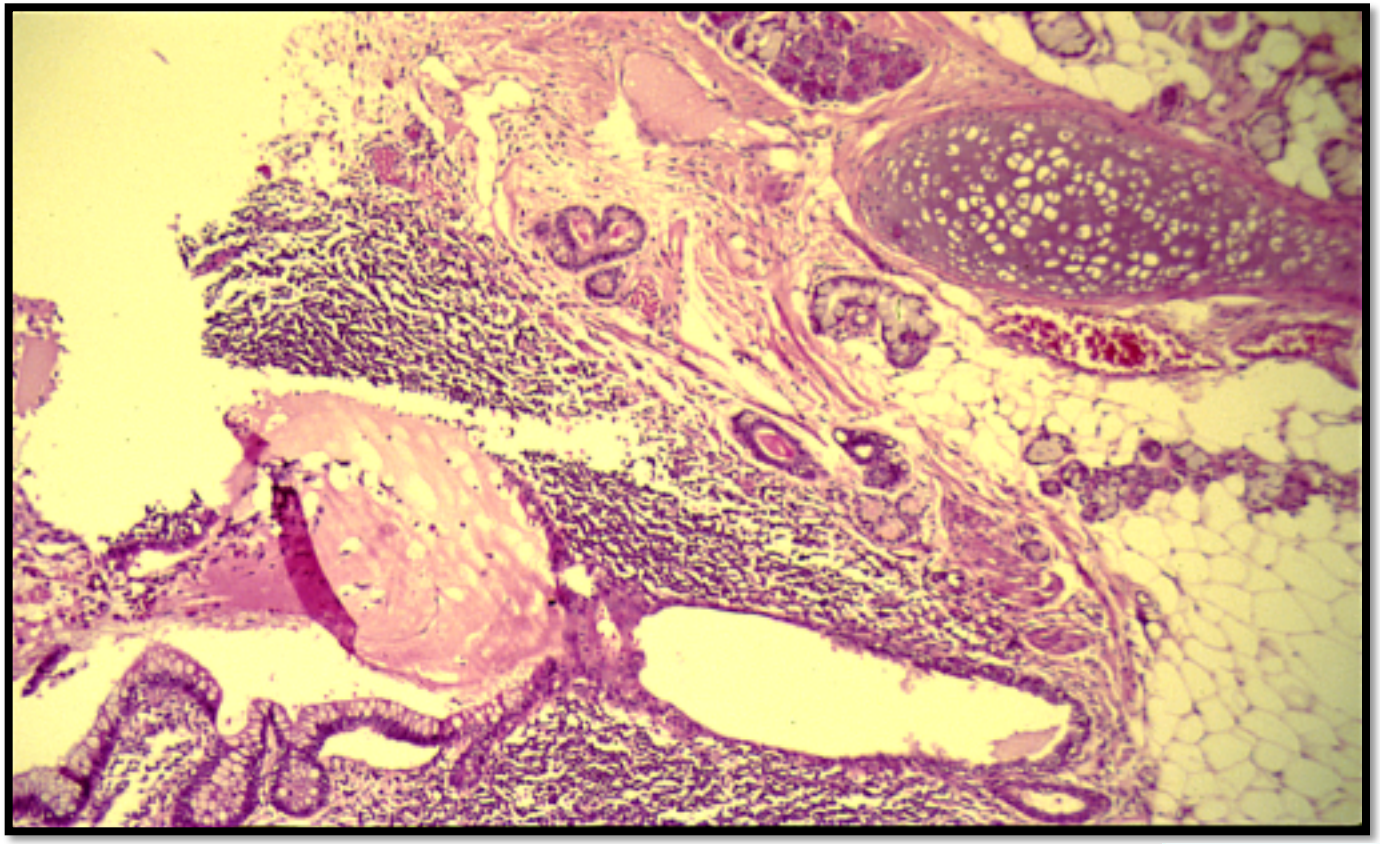
- Skin.
- Nail.
- Hairs.
- Teeth.

Ovary: Mature Cystic Teratoma



This image shows skin and mucinous glands in a mature solid teratoma of the ovary

Ovary: Mature Cystic Teratoma



- *Cartilage*
- *Fatty tissue.*
- *Columnar epithelium.*
- *Mucous and serous gland.*

ECTODERM (outer layer of embryo)

- Epidermis of skin and its derivatives (including sweat glands, hair follicles)
- Nervous and sensory systems
- Pituitary gland, adrenal medulla
- Jaws and teeth
- Germ cells

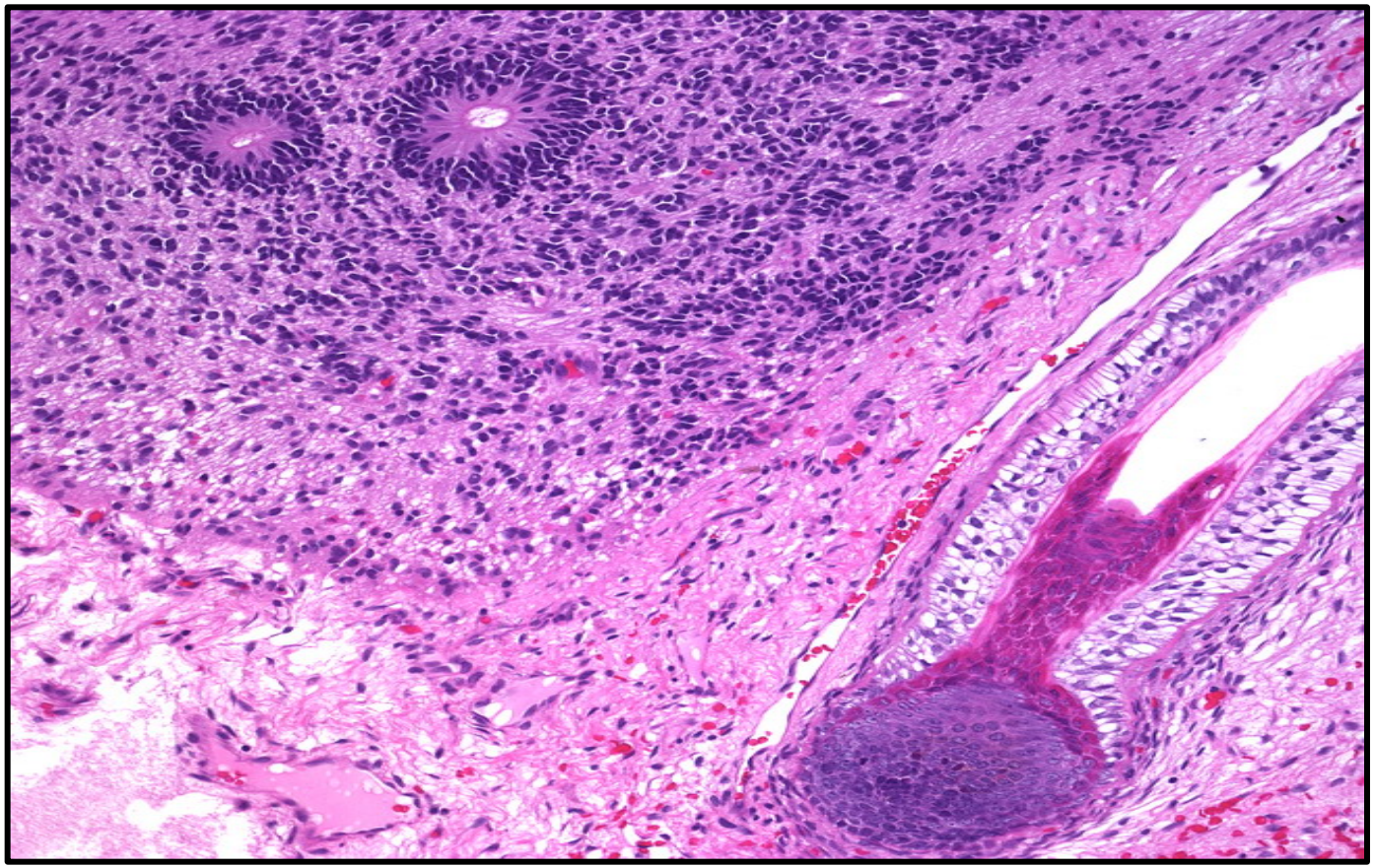
MESODERM (middle layer of embryo)

- Skeletal and muscular systems
- Circulatory and lymphatic systems
- Excretory and reproductive systems (except germ cells)
- Dermis of skin
- Adrenal cortex

ENDODERM (inner layer of embryo)

- Epithelial lining of digestive tract and associated organs (liver, pancreas)
- Epithelial lining of respiratory, excretory, and reproductive tracts and ducts
- Thymus, thyroid, and parathyroid glands

Ovary: Immature Cystic Teratoma

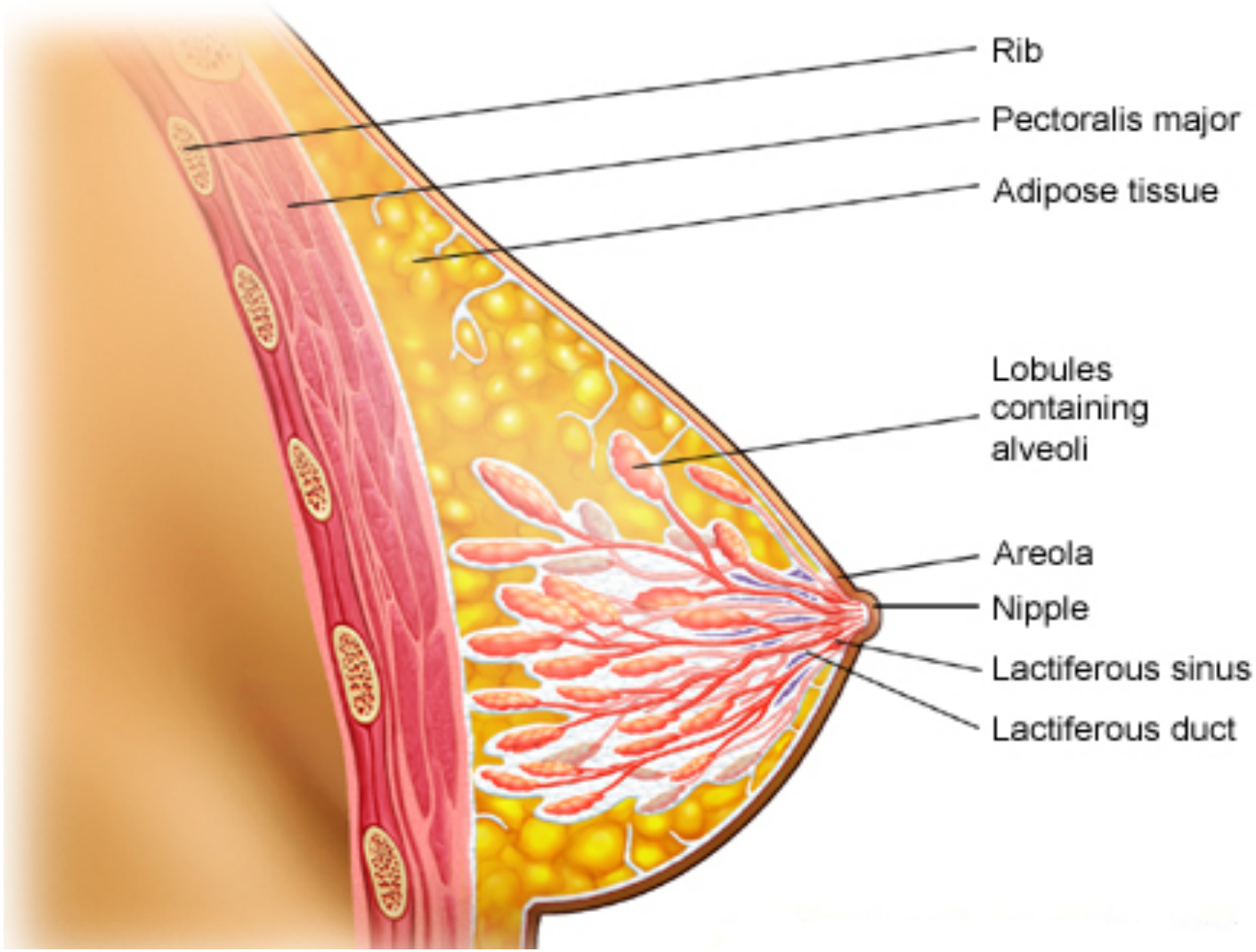


Ovarian teratoma showing neuroepithelial tubules and rosettes (immature component) adjacent to a hair follicle (mature component). They consist of epidermis, hair follicles, sweat and sebaceous glands and neuroectodermal derivatives

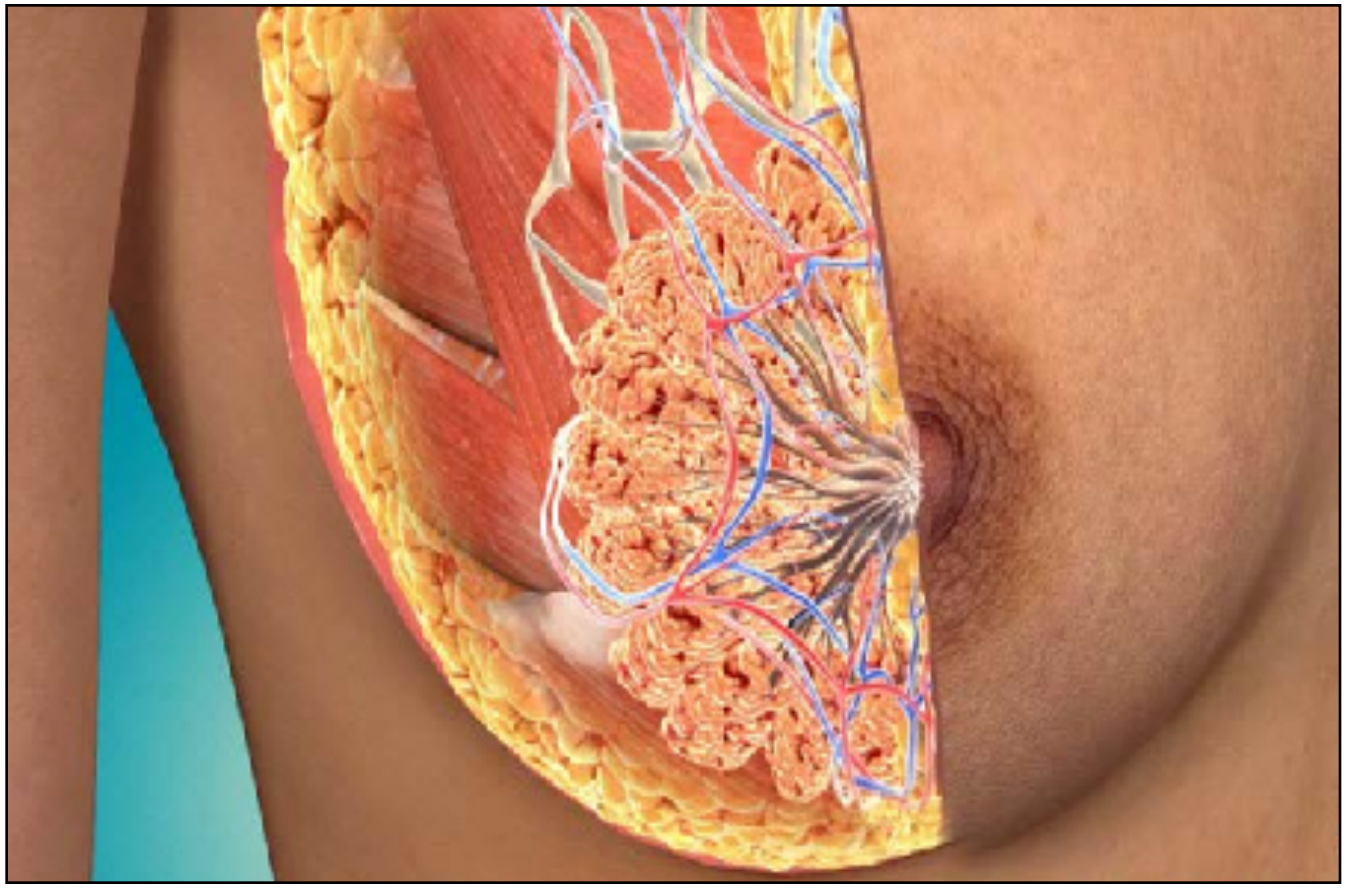
Neoplasm	Peak Incidence	Usual Location	Morphologic Features	Behavior
Germ Cell Origin				
Dysgerminoma	Second to third decade of life Occur with gonadal dysgenesis	Unilateral in 80–90%	Counterpart of testicular seminoma Solid large to small gray masses Sheets or cords of large clear cells separated by scant fibrous strands Stroma may contain lymphocytes and occasional granulomas	All malignant but only one third aggressive and spread; all radiosensitive; 80% cure rate
Choriocarcinoma	First 3 decades of life	Unilateral	Identical to placental tumor Often small, hemorrhagic focus with two types of epithelium: cytotrophoblast and syncytiotrophoblast	Metastasizes early and widely. Primary focus may degenerate, leaving only metastases In contrast with gestational tumors, ovarian primaries are resistant to chemotherapy
Sex Cord Tumors				
Granulosa-theca cell	Most postmenopausal, but may occur at any age	Unilateral	May be tiny or large, gray to yellow (with cystic spaces) Composed of mixture of cuboidal granulosa cells in cords, sheets, or strands and spindled or plump lipid-laden theca cells Granulosa elements may recapitulate ovarian follicle as Call-Exner bodies	May elaborate large amounts of estrogen (from thecal elements) and so may promote endometrial or breast carcinoma Granulosa element may be malignant (5% to 25%)
Thecoma-fibroma	Any age	Unilateral	Solid gray fibrous cells to yellow (lipid-laden) plump thecal cells	Most hormonally inactive A few elaborate estrogens About 40%, for obscure reasons, produce ascites and hydrothorax (Meigs syndrome) Rarely malignant
Sertoli-Leydig cell	All ages	Unilateral	Usually small, gray to yellow-brown, and solid Recapitulates development of testis with tubules or cords and plump pink Sertoli cells	Many masculinizing or defeminizing Rarely malignant

Breast Diseases

Diagram of the Normal Breast

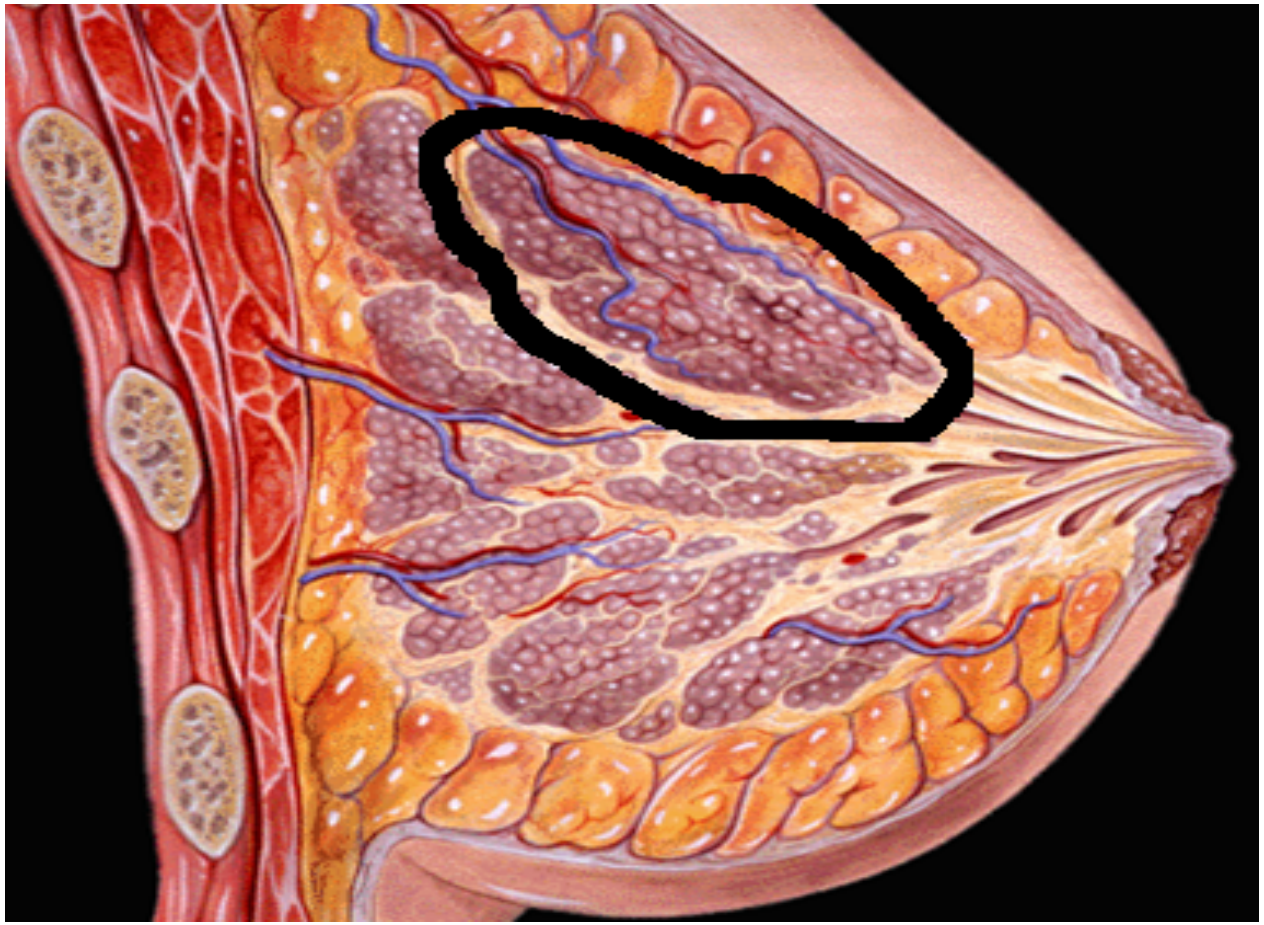


Anatomy of Normal Female Breast



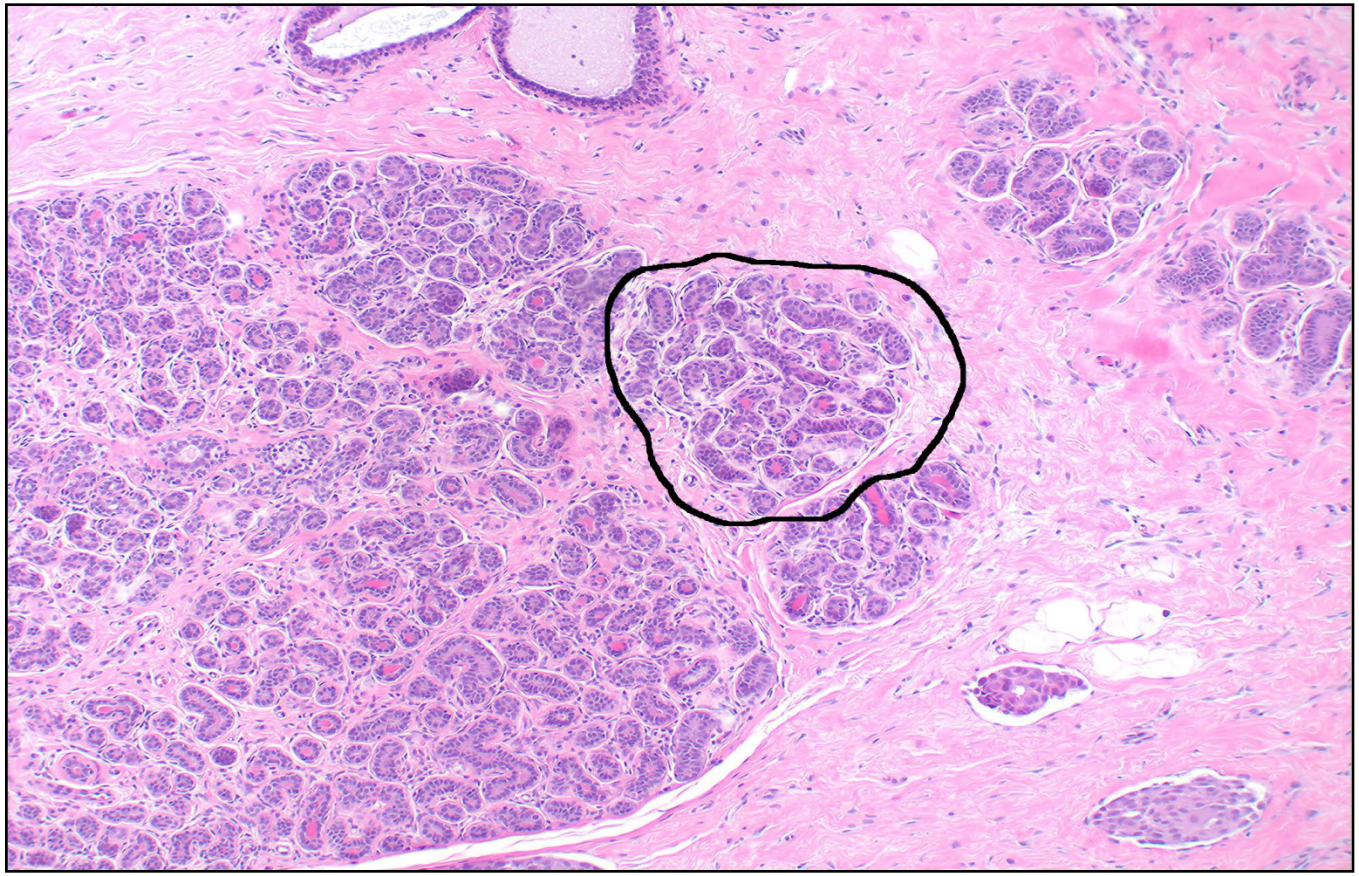
***From inside outwards** : Pectoralis muscles, Adipose tissue , Lobules containing alveoli (acini), Lactiferous ducts, Lactiferous sinus, Nipple , Skin covering the breast with dark colored Areola around the nipple.*

Normal Breast Lobe



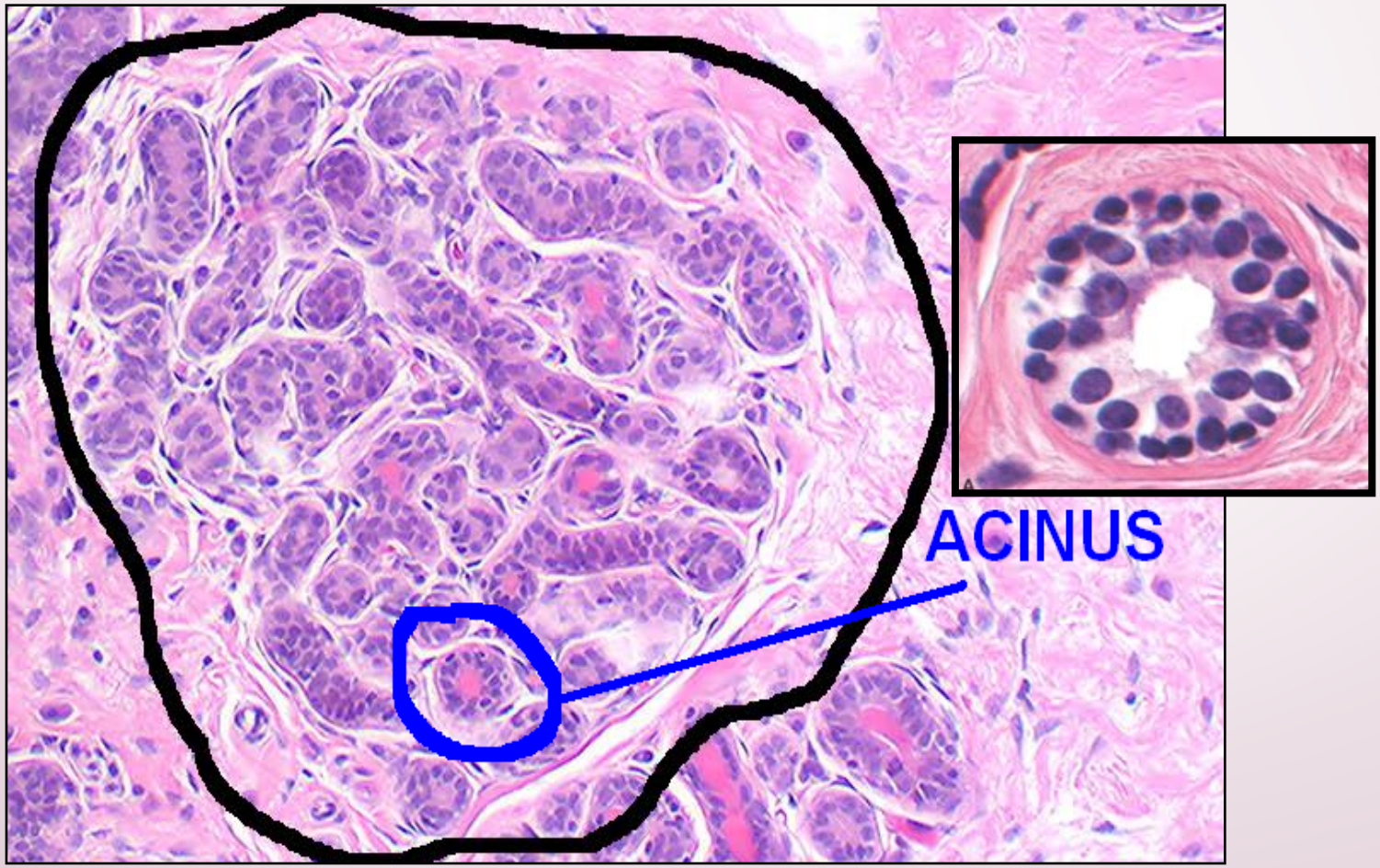
There are an average of about 10 LOBES per breast. The suspensory ligament separates lobes.

Normal Histology of Breast– LPF



Normal histology of breast tissue consists of the lobules. Within the lobules are small acini. Lobules are connected to intralobular ductules and interlobular ducts. Lobules are surrounded by loose connective tissue sensitive to sex hormones.

BREAST ACINUS – HPF Microscopy



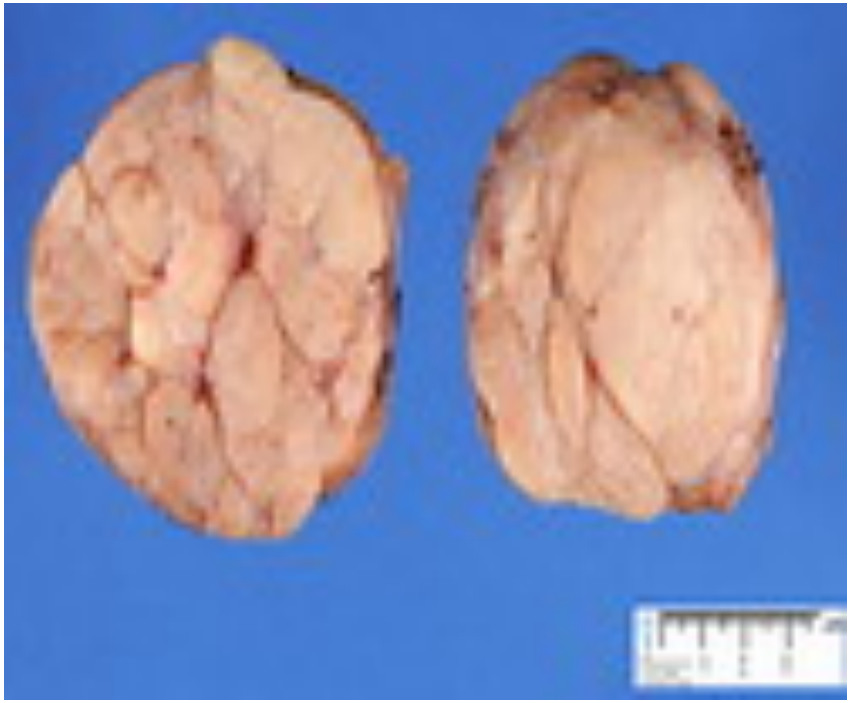
Each lobule contains several acini. Acini are also known as alveoli similar to pulmonary alveoli but the difference here it is secretory but in the lungs it is respiratory.

GROSS AND HISTOPATHOLOGY

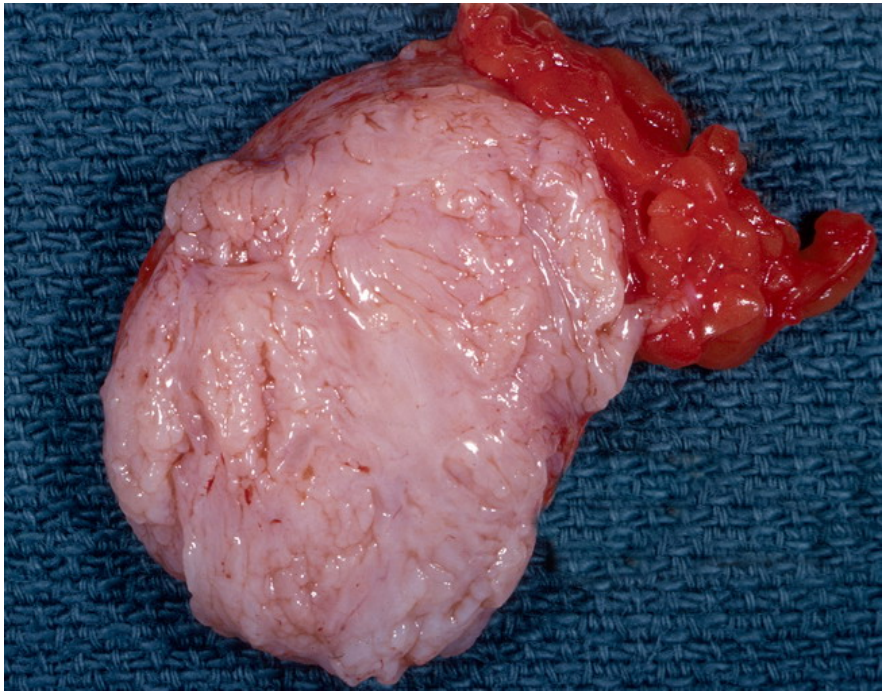
Fibroadenoma

Fibroadenoma of the Breast - Gross

Fibroadenoma of the breast has a benign behavior with good prognosis

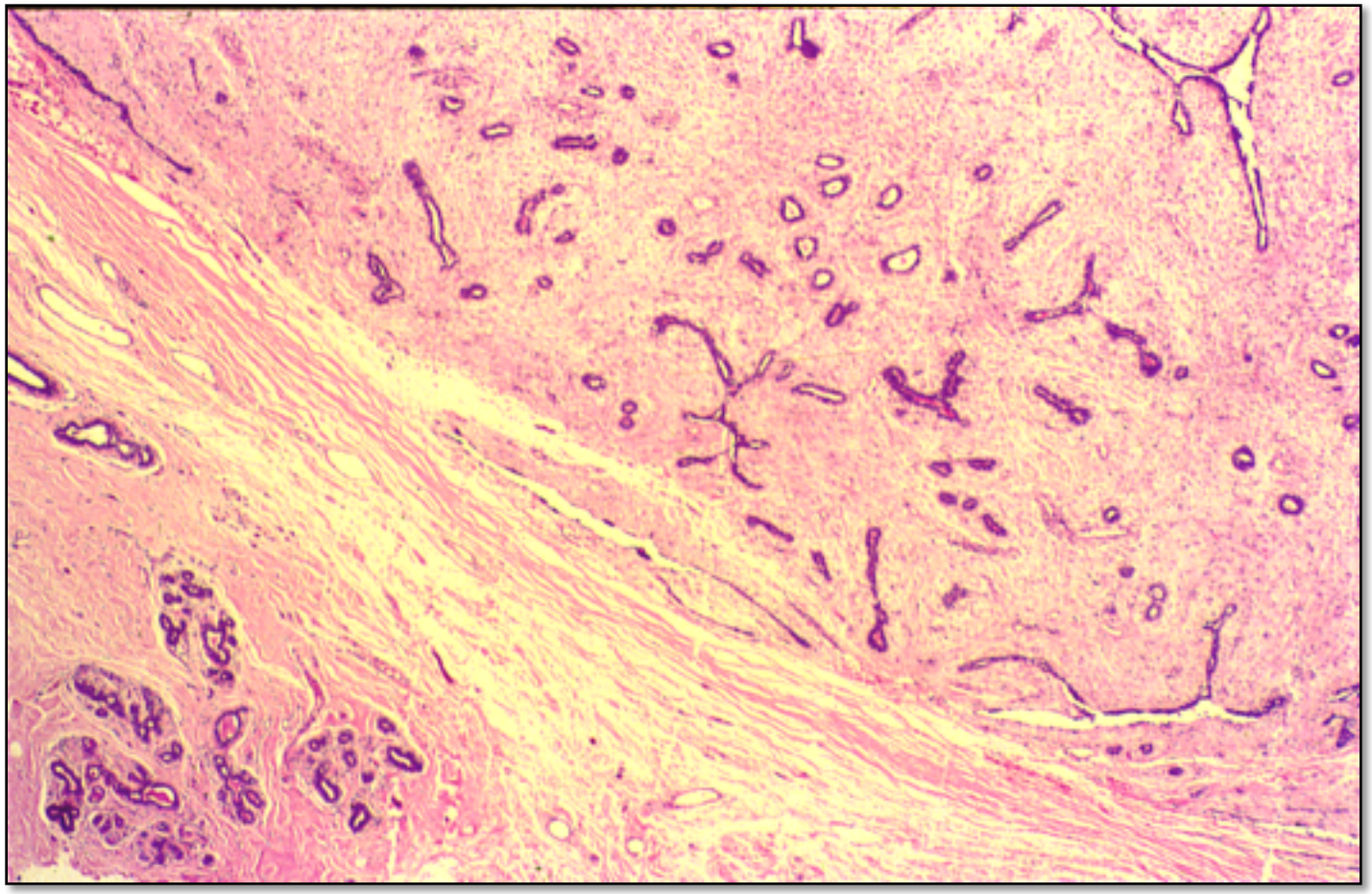


Multiple fibroadenomas with smooth, circumscribed borders



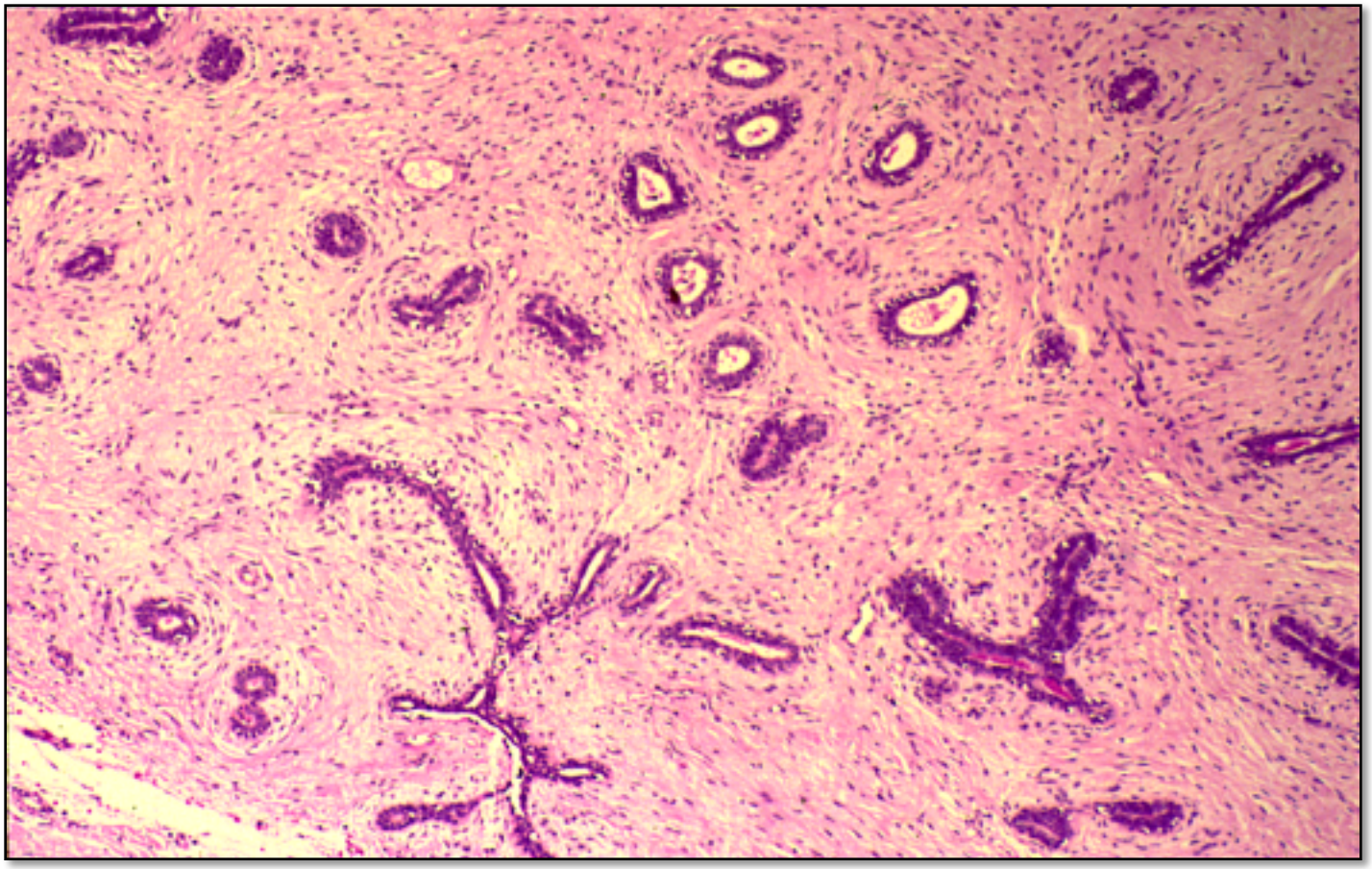
Well circumscribed and bulging white mass .The cut surface is lobulated with slit-like spaces

Fibroadenoma of the Breast- LPF



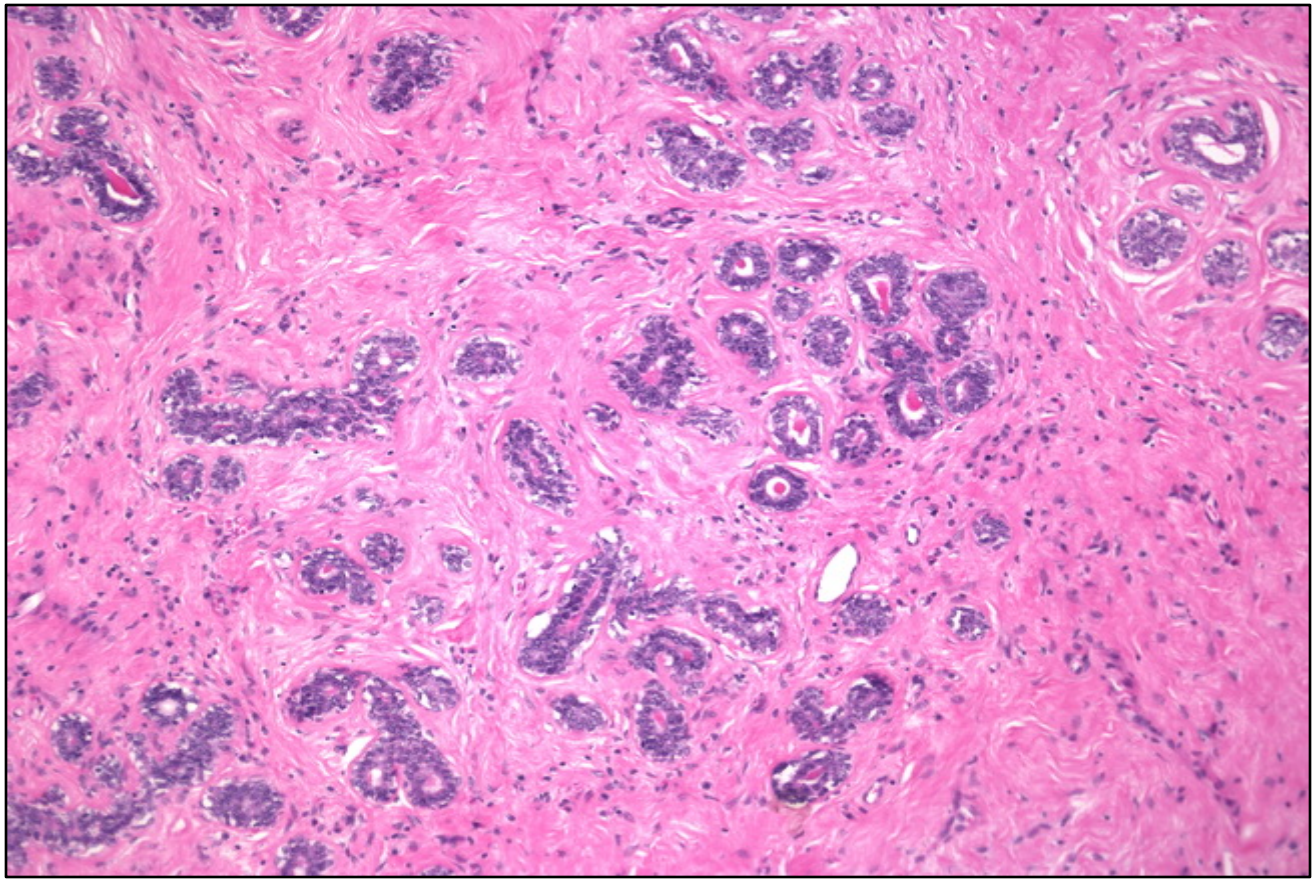
A tumour shows proliferation of both glandular tissue and fibrous tissue with intracanalicular and pericanalicular fibrous and ductular tissue growth pattern .

Fibroadenoma of the Breast- HPF



Proliferation fibrous tissue is invaginating the ducts causing elongation, compression and distortion of the ducts which have slit-like lumen (intracanalicular).
At places fibrous tissue is arranged around the ducts (pericanalicular) and does not invaginate

Pericanalicular Fibroadenoma of Breast



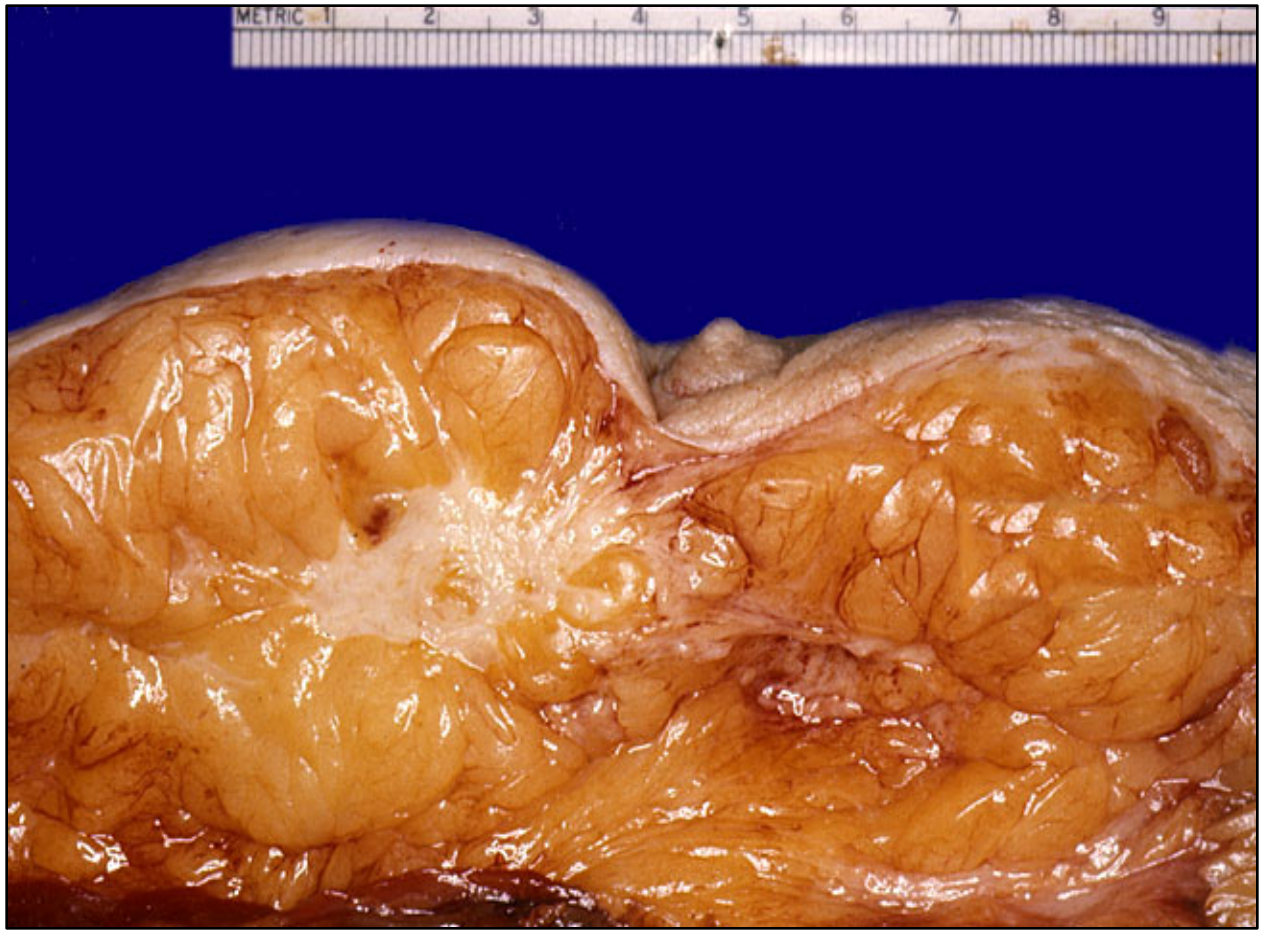
Pericanalicular Fibroadenoma: in histologic pattern, the glands maintain their round or oval profiles. There is no prognostic or clinical significance attached to the pericanalicular and intracanalicular patterns. Both may be seen within the same lesion

Carcinoma of the breast

Breast Cancer – Clinical Signs

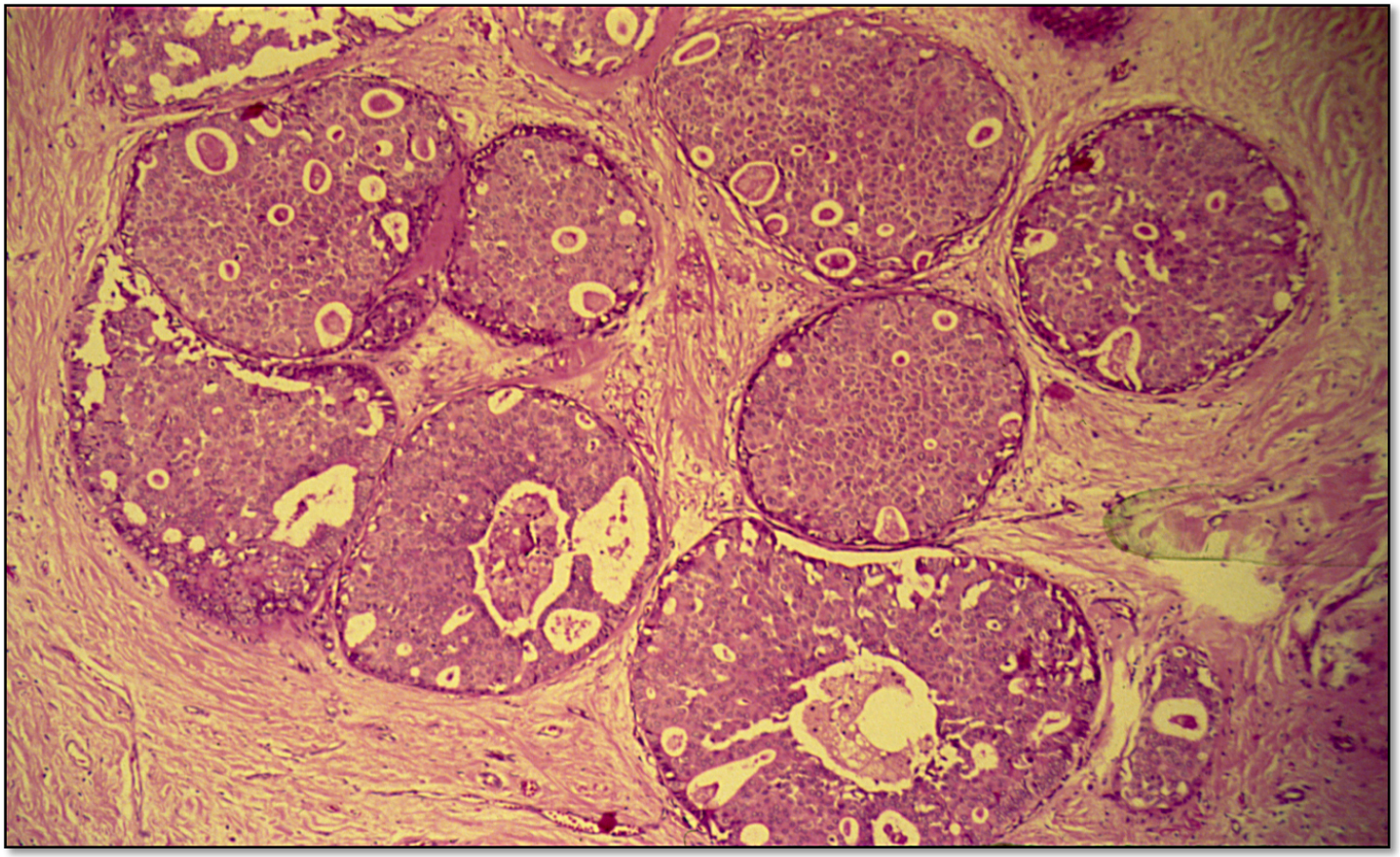
- *Inverted nipple.*
- *Skin dimpling or retraction.*

Breast Cancer – Gross Biopsy



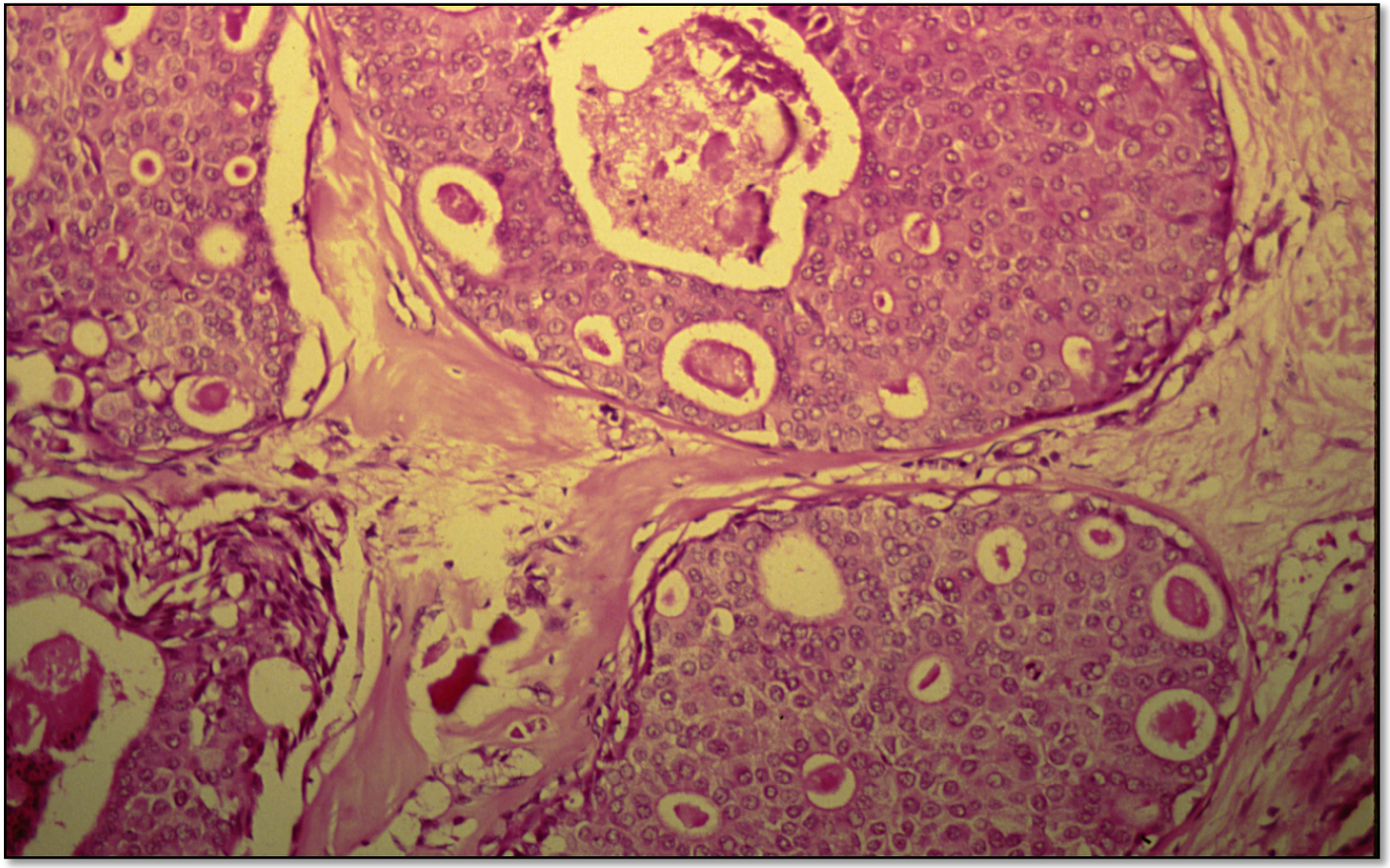
Ill-defined pale and firm nodule with overlying retracted nipple and surrounding skin .

Intraductal (In-situ) Carcinoma of the Breast- LPF



Cells are forming imperfect acini and shows a cribriform pattern. Small groups of cells in the center of many ducts are necrotic. No invasion of basement membrane of the ducts.

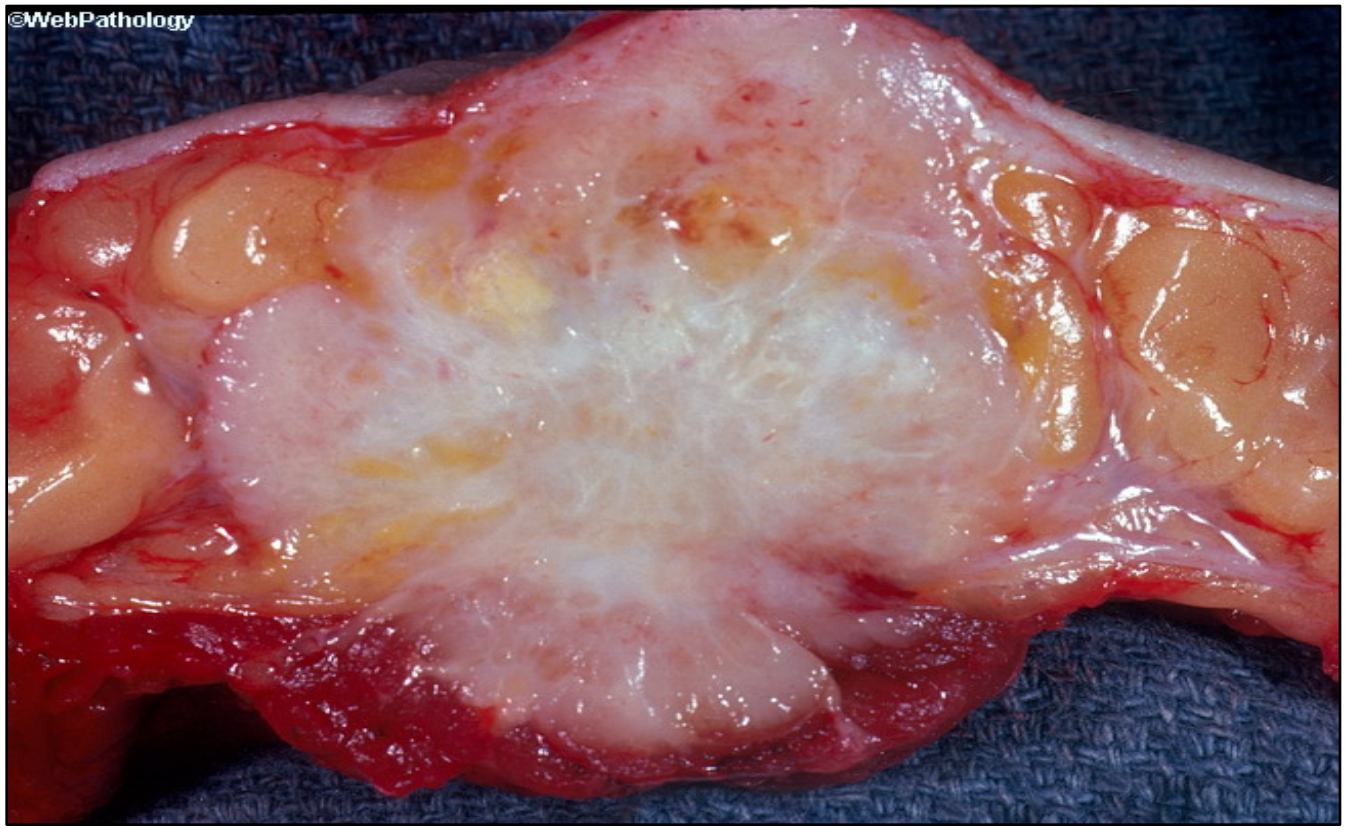
Intraductal Carcinoma (In-situ) of the Breast- HPF



The basement membrane is intact and clear and there is Central ("comedo") necrosis. Large ducts are distended by neoplastic/atypical ductal epithelial cells which are pleomorphic with large hyperchromatic nuclei and mitosis.

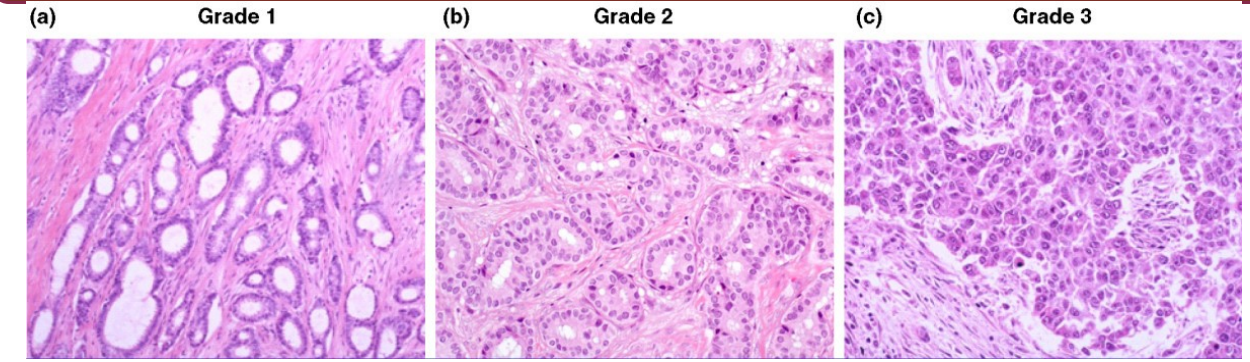
Invasive Ductal Carcinoma of the Breast

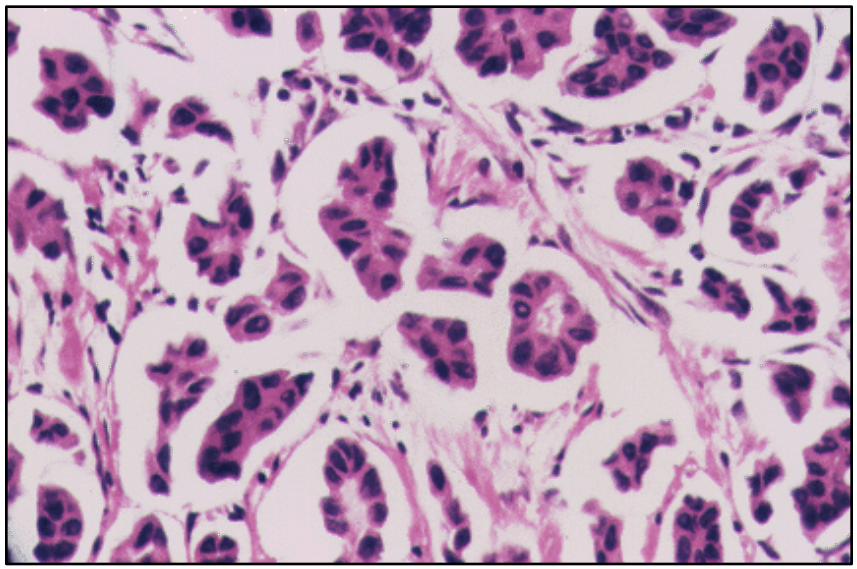
Invasive Ductal Carcinoma of Breast



In a typical invasive ductal carcinoma, the tumor is firm and poorly circumscribed with a yellowish gray cut surface. It cuts with a gritty sensation. It may show strands radiating into the surrounding fat.

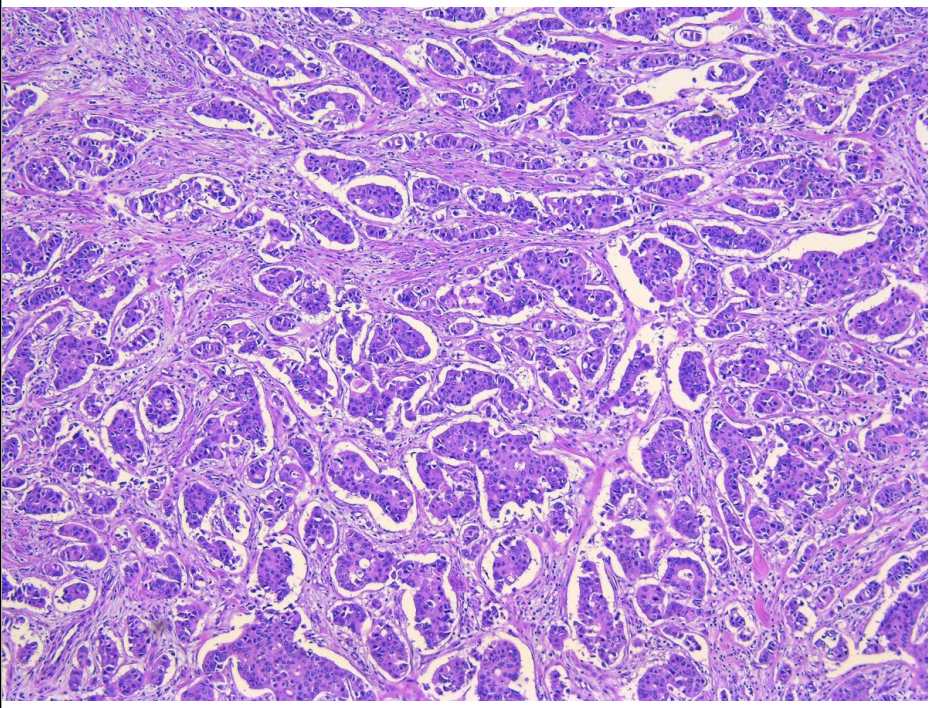
Invasive Ductal Carcinoma of Breast

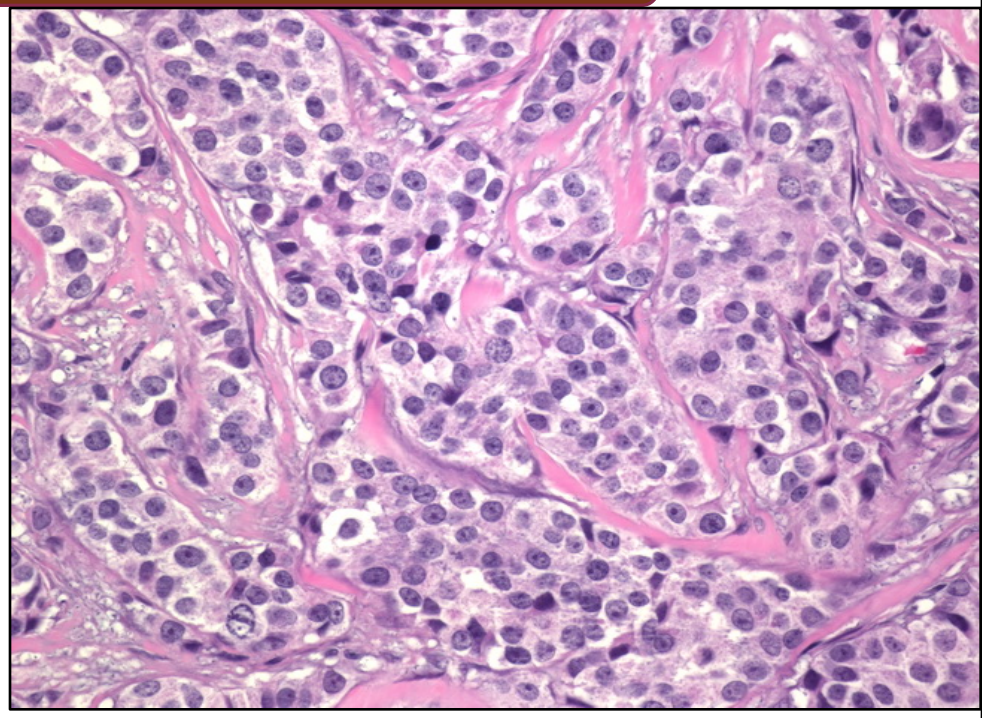




Microscopically , A well-differentiated ductal carcinoma made up of small acini and glands. Tumour cells are round to polygonal with deeply stained nuclei and occasional mitoses. Nuclear atypia is mild

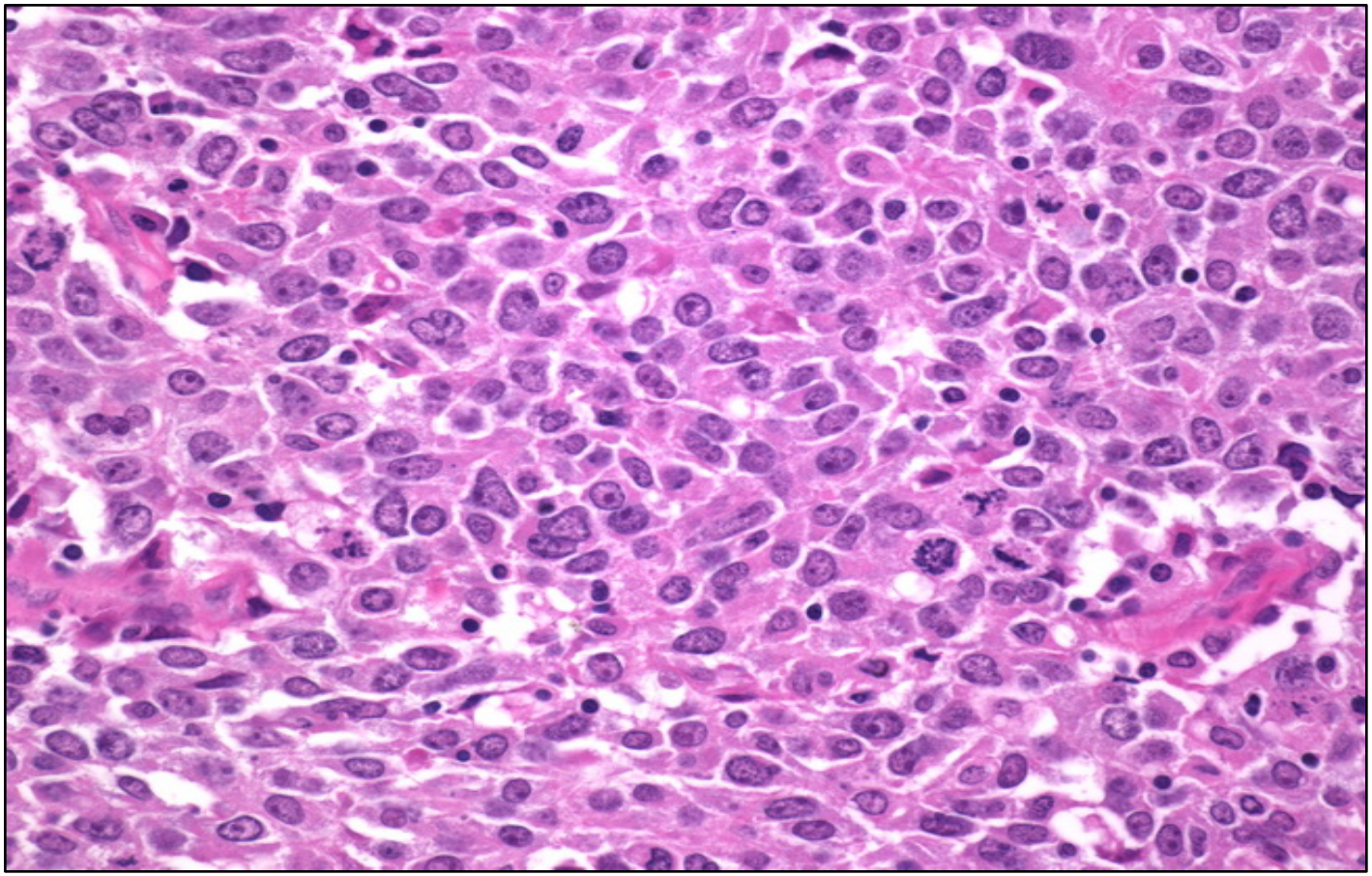
Invasive Ductal Carcinoma of Breast





- *Cords and sheets of pleomorphic tumor cells.*
- *Surrounding dense fibrous stroma.*
- *Scattered lymphocytes.*

Invasive Ductal Carcinoma of Breast



High grade invasive ductal carcinoma, The tumor cells are highly pleomorphic and show frequent mitotic figures with minimal tubular formation

Breast Cancer Risk Factors

Factor	Relative Risk
Well-Established Factors	
Geography	Varies in different areas
Age	Increases after age 30
Family history	
First-degree relative with breast cancer	1.2–3.0
Premenopausal	3.1
Premenopausal and bilateral	8.5–9.0
Postmenopausal	1.5
Postmenopausal and bilateral	4.0–5.4
Menstrual history	
Age at menarche <12 years	1.3
Age at menopause >55 years	1.5–2.0
Pregnancy	
First live birth from ages 25 to 29 years	1.5
First live birth after age 30 years	1.9
First live birth after age 35 years	2.0–3.0
Nulliparous	3.0
Benign breast disease	
Proliferative disease without atypia	1.6
Proliferative disease with atypical hyperplasia	>2.0
Lobular carcinoma in situ	6.9–12.0
Other Possible Factors	
Exogenous estrogens	
Oral contraceptives	
Obesity	
High-fat diet	
Alcohol consumption	
Cigarette smoking	

Prognosis of breast cancers is influenced by the following variables the first three of which are components of the tumor-node-metastasis (TNM) staging classification:

Tumor invasion and size.

- *Extent of lymph nodes involvement.*
- *Distant metastases.*
- *Histologic grade.*
- *Oestrogen and progesterone receptors.*
- *Overexpression of Her2-neu.*

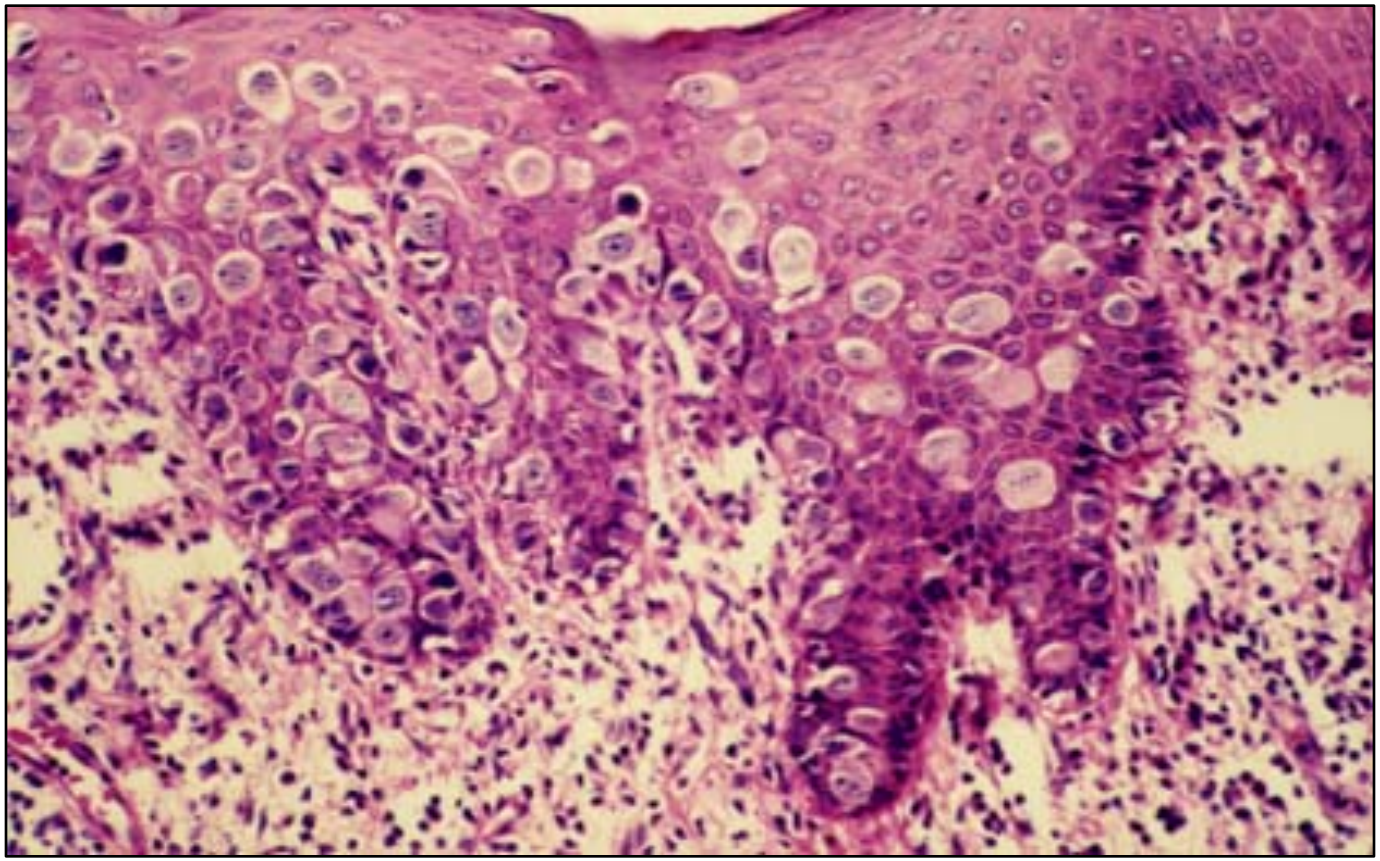
Paget's Disease of the Nipple

Paget's Disease of the Nipple - Gross

- **Redness, hyperemia.**
- **Erosion of the epidermis.**

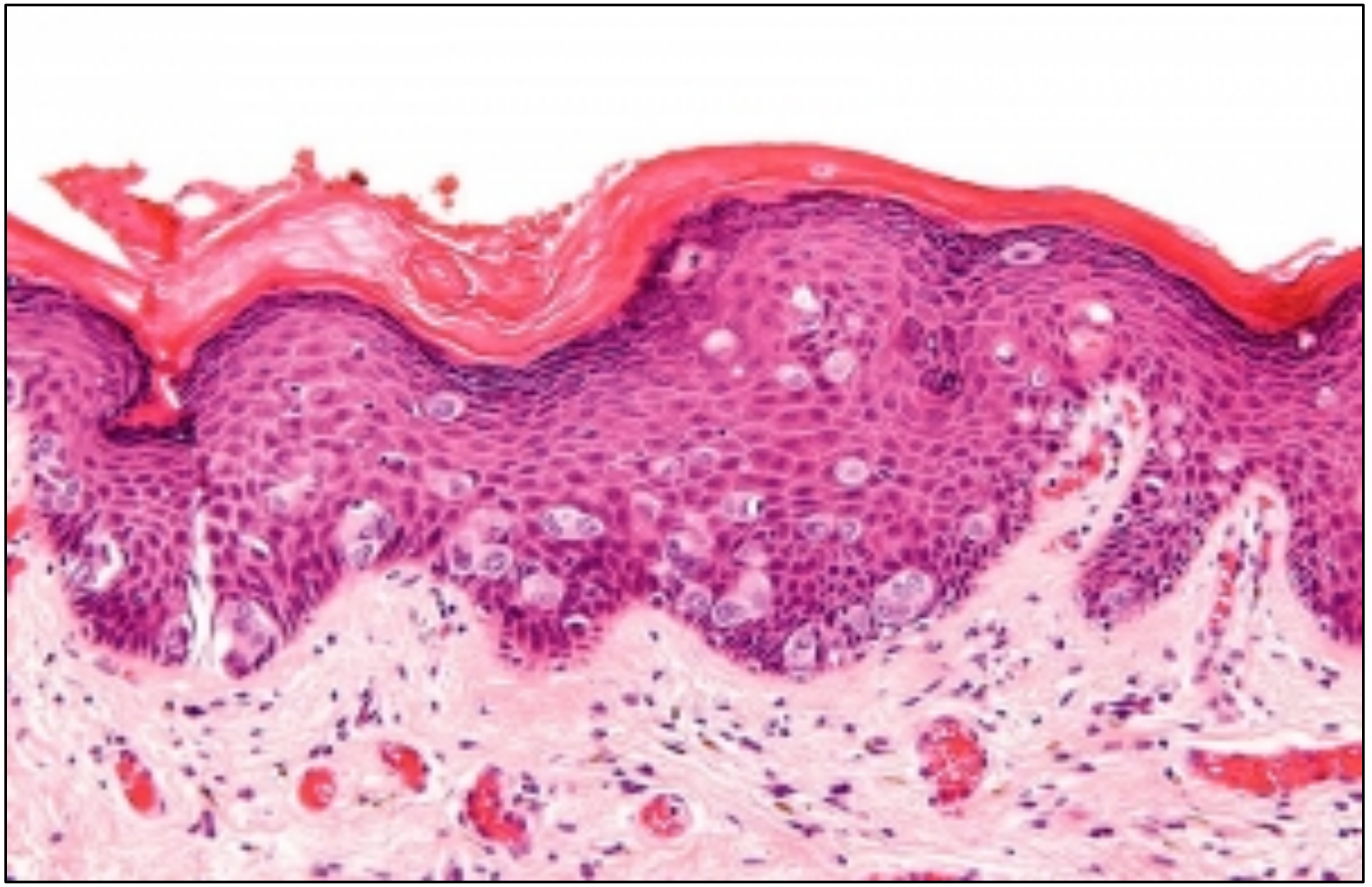
Paget's disease is a nipple lesion associated with underlying ductal carcinoma-in-situ (DCIS) or Invasive ductal carcinoma. Clinically, the lesion is eczema-like with hyperemia and erosion of the epidermis. Initially centered on the nipple, they may later involve the areola.

Paget's Disease of the Nipple- HPF



Paget's disease of nipple. Paget's cells have pale, vacuolated cytoplasm and large nuclei and migrate through the epidermis from parabasal cell layers upward. Notice the highest concentration in the deep layers of epidermis.

Paget's Disease of the Nipple- HPF



Hyperkeratosis of epidermis and chronic inflammation in the dermis are common. Ulceration and invasion of epidermis by ductal carcinoma cells (Paget cells), present between basal cells in elongated rete pegs.

GOOD LUCK