1. Endometrial Hyperplasia

Abnormal endometrial gland **proliferation** resulting in an **increase in Gland/stroma ratio**; induced by **persistent, prolonged estrogenic stimulation of the endometrium.** The risk of developing carcinoma depends on the severity of the **hyperplastic changes** and **associated cellular atypia.**

Risk factors	Clinically
• Anovulatory menstrual cycles (*failure of ovulation*) • Excessive endogenous production of estrogen. • Exogenous administration of estrogenic steroids *without counter balancing progestins* over a long period of time, Obesity, Western diet, Nulliparity, Diabetes mellitus • Hypertension & hyperestrinism. Mutations in the PTEN tumor suppressor gene	• **Mild type** of hyperplasia tends to occur in **younger patients**. • The more severe type of hyperplasia occurs mainly in **peri- and postmenopausal women. (significant premalignant potential).** • Patients with endometrial hyperplasia usually present with **abnormal uterine bleeding.**

Simple hyperplasia		Complex hyperplasia	
Without atypia	**With atypia**	**Without atypia**	**With atypia**
(cystic hyperplasia): Glands are varibly shaped and sized and cystically dilated with abundant cellular stroma and give a "Swiss Cheese" appearance. Rarely progress to adenocarcinoma.	Same as the other one but with **cytologic atypia**.	Proliferation of endometrial glands resulting in complex **crowded glands** with papillary infoldings and irregular shapes. The epithelial cells remain cytologically **normal**.	Complex proliferation of endometrial glands with atypia. The nuclei show loss of polarity and are enlarged and rounded and may have **irregular nuclear membranes**.

Endometrial carcinoma: A common neoplasm in women. Overall it is the fifth commonest cancer in women.

FEATURES	TYPE I	TYPE II	Clinical features of both:
Histologic type	Endometrioid adenocarcinoma	Serous or clear cell carcinoma	▪ Most are between 50 and 60 years. ▪ Many tend to be **nulliparous and obese**. ▪ Manifests as abnormal **vaginal bleeding** and **excessive leucorrhea**. ▪ With progression, the uterus **enlarges**. ▪ Usually slow to metastasize.
Age	Premenopausal and perimenopausal (50-60 yrs)	Post-menopausal (~ 70 yrs)	
Unopposed estrogen	Present	Absent	
Precursor lesion	Hyperplasia with atypia	Endometrial intraepithelial carcinoma	
Growth	Slow growing	Rapidly progressing	
Grade	Low	High	
Myometrial invasion	Usually superficial	Usually deep	
Prognosis	Favorable	Poor	
Genetic alterations noted	PTEN, microsatellite instability	P53 mutations	
Microscopy	Resemble normal endometrium, shows **mucinous**, **tubal** (ciliated), and **squamous diffrentation**	small tufts and papillae, much **greater cytologic atypia** and are **more poorly differentiated**	

Leiomyoma (fibroid) of uterus

A benign tumor of smooth muscle in **myometrium.** It's an **estrogen responsive** tumor. **shrinks** in postmenopausal woman. Types are: **Submucosal**, **Intramural**: most common, **Subserosal** fibroids & **Pedunculated** ones **"parasitic leiomyoma"**.

Clinical features	Morphology
Asymptomatic or irregular abnormal bleeding (submucosal most commonly)	Whorled, grey-white cut surfaces. Interlacing bundles of smooth muscle cells with collagenous stroma between bundles. No Mitotic figures, Foci of fibrosis & Calcification

Leiomyosarcoma: It is the malignant tumor of the smooth muscle. Sites include the uterus and soft tissue Poor prognosis.

2. Ovarian cysts

Chocolate cyst /Endometriotic cyst	The ovary is the most frequent site of endometriosis. And chocolate cyst is a blood-filled cyst of the ovary. It is due to endometriosis in the ovary with **hemorrhage**.
Corpus luteum cyst	Results from hemorrhage into a persistent **mature** corpus luteum.
Theca lutein cyst/ hyperreactio luteinalis	Are thin walled cysts **lined by luteinized theca cells.** They are associated with high levels of circulating gonadotropins (e.g. pregnancy, hydatidiform mole, etc).
Follicular cyst	Arise from the ovarian follicles & are due to distension of un-ruptured Graafian follicle

Ovarian Tumors: grow **silently** and go undetected in the early stage when it is still curable. Most of the patients already have **metastasis** at the time of **diagnosis**

		Types	Morphology		Info
Serous tumors	**Surface epithelial tumors**	Type	Info	Morphology	The **most common type** of ovarian tumors & the most common group of epithelial tumors. The tumor cells are of serous nature. **Benign lesions** are usually encountered in patients between 30 and 40 years of age, and **malignant serous tumors** are more commonly seen between 45 and 65 years of age.
		serous cystadenoma	• Commonly large, **cystic**, thin-walled, and unilocular. • Lined by **serous cells** and **contain thin, clear yellow fluid**. 25% **bilateral**	• Serosal covering is smooth and glistening. • A single layer of **tall columnar epithelial cells. Psammoma bodies**	
		Borderline	**Cystic with a thin wall and a smooth surface**, but often have multiple papillary excrescences (**grape-like clusters**), protruding into the lumen in places.	Exhibit **less** cytologic atypia and little or no stromal invasion. They may seed the peritoneum, but those implants usually are "**noninvasive**."	
		cystadenocarcinoma	• The **commonest** malignant ovarian tumor • **Partly cystic and partly solid with prominent excrescences, often with necrosis and hemorrhage** & usually present with ascites due to abdominal metastases. • Some develop from **tubal intraepithelial carcinoma**. • Develop rapidly. Most have mutations in *TP53*	• The surface has nodular irregularities representing areas in which the tumor has penetrated into the serosa. • Cystic spaces usually are filled with a clear serous fluid. • Papillary formations are complex and multilayered • Nests or undifferentiated sheets of malignant cells invade the axial fibrous tissue	
Mucinous		-	Can be very large, bilaterality is uncommon, typically cystic (multicystic), multilocular and filled with **thick sticky, viscous mucoid fluid.** The tumor cells are **mucin-producing cells** **Malignant tumors:** we see complex structures, including solid areas of growth, cellular stratification, cytologic atypia, serosal penetration and stromal invasion		**10% malignant. 80% benign & 10% borderline.**
Endometrioid tumors		-	They have **a tubular gland** that **resembles the endometrium** so the name endometrioid (endometrium-like). Form 10 to 20% of all ovarian tumors; **Most** are malignant (carcinomas). May be solid or cystic & are bilateral in about 30% of cases. Mutations in the PTEN tumor suppressor gene can be seen. Some come with endometrial carcinoma in the uterus and / or **endometriosis in the ovaries**		
Brenner		-	**Most are benign**. Uncommon, solid, unilateral ovarian tumor consisting of **transitional cell type epithelium** Smoothly encapsulated and gray-white on cut section		

		Morphology	Info
Thecoma-Fibroma	**Sex cord stromal tumors**	Pure theca cell tumors produce estrogen Fibromas **do not produce estrogen** except when mixed with thecomas. They are solid tumors, vary in color from white to yellow. Fibromas are whiter, harder with whorled cut surface.	▪ Unilateral, almost always **benign**. Very rarely malignant Any age; they can be either pure thecomas, pure fibromas or fibrothecomas (mixture of both). ▪ Some are associated with ascites and hydrothorax called as **Meig's Syndrome**
Granulosa cell		▪ Unilateral, solid and cystic; **Produce estrogen.** ▪ About 5 to 25% show **malignant** behavior	Adult form is more in **postmenopausal women**. The juvenile form is seen the **first 3 decades,** can present **with isosexual precocity**. Can present with abnormal vaginal bleeding; & can be associated with **endometrial hyperplasia and carcinoma.**
Sertoli-leydig		▪ Rare tumors of **low malignant potential**; **All ages**; Unilateral yellowish solid tumor. ▪ Produces androgens and present with virilization in 1/3 of cases (oligomenorrhea, **amenorrhea**, loss of female secondary sex characteristics with hirsutism, clitoromegaly, deepening of voice)	

Teratoma	**Germ Cell Tumors**	Type	Info	Morphology	
		Mature cystic	**Benign**, most common GCT & teratoma. Typically occurs during reproductive years composed of mature elements of the ectoderm, endoderm and mesoderm. Complications include **torsion (acute surgical emergency)**, rupture, infection or limbic encephalitis	Cystic tumor, unilateral (mostly right-sided), filled with sebaceous material, hair and occasionally teeth.	Majority in the first 2 decades. The younger the patient, the greater the likelihood of malignant behavior. Benign mature type is more than the malignant immature one.
		Monodermal (specialized teratoma)	▪ Composed predominantly of one tissue element. ▪ Most common type is **"struma ovarii*",** which is mature thyroid tissue (may cause hyperthyroidism). The thyroid tissue can sometimes become malignant. Sometimes a carcinoid tumor can arise from it.		
		Immature	○ **Malignant** rare neoplasms, occurs in children and young adults (mean age is 18). Like mature teratoma but they contain **immature or embryonal tissues** especially immature **neuroepithelium**. ○ Usually a unilateral, solid, bulky and pedunculated by areas of necrosis tumor	Presence of **immature elements** or minimally differentiated cartilage, bone, muscle, nerve, or other tissues. Particularly ominous are foci of **neuroepithelial differentiation**	

Dysgermi-noma	**Germ Cell Tumors**	Unilateral and solid mass. Looks exactly like its counterpart in testis (Seminoma) & brain (germinoma)	Uncommon, All malignant, Between 10 to 30yrs of age **PLAP positive & Highly sensitive to radiation therapy**
Endodermal sinus tumor		Elevated serum α-fetoprotein and α-1-antitrypsin. **Positive immunostain for α-fetoprotein Schiller-Duval bodies**	AKA yolk sac tumor. Under 30 years of age. Can be a component of a mixed germ cell tumor. **Radioresistant** but responds to combination chemotherapy.
Embryonal Carcinoma		Unilateral, solid tumor with hemorrhage and necrosis **CD 30 immunostain positive.**	Rare, aggressive, highly malignant, 2^{nd}-3^{rd} decades (children and young adults) & **radioresistant** but responds to chemotherapy. Usually occurs in (mixed GCT).
Chorio-carcinoma		**Elevated serum hCG levels; HCG immunostain positive** Unilateral, solid, hemorrhagic tumor, composed of malignant cytotrophoblast and syncytiotrophoblast.	A tumor of the placenta appears in the ovaries, Rare aggressive, highly malignant, metastasizes widely through the **bloodstream**; **Radioresistant AND chemoresistant**. Usually occurs with other GCTs (mixed GCT). Can present in the ovaries as ovarian tumor

Metastatic Carcinoma in the ovaries

- Older ages, Mostly Bilateral and sometimes very large. Primary tumor can be from **Gastro-intestinal tract (most common),** breast and lung.
- One of the most classic forms of metastatic carcinoma involving the ovaries is the **Krukenberg tumor (producing bilateral ovarian masses)**. This tumor is a metastatic carcinoma composed of signet ring cells in a fibrous background. **The most common sites of origin is the GIT (stomach, colon and appendix).**

3. Testicular Diseases:

Epididymitis: inflammation of epididymis. Orchitis: inflammation of testis. Inflammatory conditions are generally more common in the epididymis than in the testis. However, some infections, notably syphilis, may begin in the testis with secondary involvement of the epididymis.

1-Nonspecific epididymitis and Orchitis:

Features:	Microscopic findings:
Uncommon in children, gram negative rods Man <35 Chlamydia trachomatis and Neisseria (STD) | Man>35 E. Coli and Pseudomonas	Testis are swollen and congested with edema. Neutrophils, macrophages, lymphocyte infiltration. Sparing of leydig cells.

2-Granulomatous (autoimmune) epididymitis &orchitis:

Features	Microscopic
• **Unilateral** testicular mass • May be in response to disintegrated sperm, post-infectious, due to trauma or sarcoidosis. • Several conditions including infection and autoimmune injury (Tuberculosis is most common) may elicit it.	Granulomatous inflammation with plasma cells lymphocytes

3- Gonorrhea

Gonococcal infection can spread from urethra to prostate, seminal vesicles and then to epididymis and testis leading to suppurative orchitis and even abscess.

4- TB

Tuberculosis begins in the epididymis and spreads to the testis.
There is associated tuberculous prostatitis and seminal vesiculitis
Microscopic: Caseating Granulomas and caseous necrosis.

Testicular tumors:

The most important cause of firm, painless enlargement of testis. Peak incidence between the ages of 20 and 34 years. Most common tumors of men.

Germ cell tumor

- Between 15 to 30 years of age. these are the most common tumor of men.
- Most are highly aggressive cancers.
- Most of them can be cured with current therapy.
- Most GCTs originate from precursor lesions called intratubular germ cell neoplasia (it is like carcinoma-in-situ).
- (e.g., cryptorchidism, dysgenetic gonads).
- These in situ lesions can be found in grossly "normal" testicular tissue adjacent to GCTs in mostly all cases.

Clinical Features:
Patients present most frequently with a painless testicular mass that (unlike enlargements caused by hydroceles) is non-translucent.

Predisposing factors of GCTs:

- Cryptorchidism
- androgen insensitivity syndrome & testicular dysgenesis
- Genetic factors
- Strong family predisposition

1. Seminoma

-Most common type of testicular tumors , Almost never occurs in infants, Peak incidence in the 30s, highly sensitive to radiation therapy. **Minimally elevated serum hCG**

Metastasis

- Iliac and paraaortic lymph node
- Hematogenous spread can occur

Morphology

- Uniform cells divided into lobules by delicate fibrous septa containing lymphocytes, collagen within cytoplasm.
- A lymphocytic infiltrate usually is present. Positive for PLAP, OCT4 stain and c-kit (CD117)

2. Spermatocytic seminoma Uncommon, slow growing with no metastasis. Over age 65, excellent prognosis. No lymphatic infiltration.

Non-Seminomatous germ cell tumors (NSGCT):

	Morphology		Info
1- Embryonal Carcinoma	Info: Positive for cytokeratin (CK) and CD30 stain	Morphology: Smaller than seminoma, poorly demarcated. Variegated with foci of necrosis and hemorrhage. Large cells with basophilic cytoplasm.	More aggressive than seminomas. Metastasizes early via both lymphatic and hematogenous routes. Can be seen in GCTs. Pure embryonal carcinomas account for 2-3% of all testicular GCTs.
2-Yolk Sac Tumor	• low cuboidal to columnar epithelial cells forming microcysts. • **Schiller-Duval bodies.** • **Gross:** Non-encapsulated, homogenous, yellow white, mucinous		Most common tumor in infants and children up to 3 years of age ، Patients have elevated serum alpha fetoprotein (AFP). Positive for alphafetoprotein (AFP) and alpha-1- antitrypsin stain.
3-Chorio-carcinoma	Small cuboidal cells، eosinophilic syncytial cells containing multiple dark, pleomorphic nuclei; represent **cytotrophoblastic** and **syncytiotrophoblastic** differentiation, respectively. Prominent hemorrhage and necrosis; Malignant trophoblastic (placental) tissue (cyto-trophoblastic and syncytio-troblastic cells) (placenta-like tissue, but villi are absent).		• Highly malignant tumor. Elevated serum (HCG). • Pure choriocarcinoma of the testis is extremely rare, and the tumor is much more common as a component of mixed GCT. • Positive for human chorionic gonadotropin (HCG) stain.
4- Teratoma	• Usually large 5 -10 cm. • Heterogeneous appearance with solid and cystic areas. • Can show bone, cartilage and teeth grossly. • Composed of bizarrely distributed collection of different type of cells or organ structures (heterogeneous). **Mature teratoma:** If the cellular/organ tissue is mature looking **Immature teratoma:** If some of the cellular/organ tissue component is immature (sharing histologic features with fetal or embryonal tissues) **Behavior:** • In infants and children, mature teratomas are benign and immature teratoma is considered malignant. • In post-pubertal male, all teratomas are regarded as malignant, and capable of metastasis, regardless of whether the elements are mature or not.		• It is a tumor composed of different types of cells or organ components. Any age, infancy to adult life. • **Pure form:** is common in infants and children second to yolk sac tumor (in this age group). But is rare in **adults** & occurs as part of mixed GTC. • Any of the following cell types of various organs can be present: neural/brain, cartilage, bone, squamous epithelium, hair, glandular cells, smooth muscle, thyroid tissue, bronchial epithelium of lung, pancreatic tissue etc. • If any of the cellular/organ tissue undergoes non-germ cell type of malignant transformation, it's called as **teratoma with malignant transformation** (rare) e.g. squamous cell carcinoma or adenocarcinoma.

Mixed GCT

- Mixed Germ Cell Tumors are quite common. About half of testicular tumors are composed of a mixture of GCTs.
- The common combinations/mixtures are: Teratoma + embryonal carcinoma +/- yolk sac tumor o Seminoma + embryonal carcinoma

Clinical features	Info
• Present as a painless enlarging mass in the testis. Generally, any solid testicular mass should be considered neoplastic. • GCTs secrete hormones and enzymes that can be detected in blood (HCG, AFP, and lactate dehydrogenase). • Biopsy of a testicular tumor is associated with a risk of tumor spillage therefore it is not recommended. • GCTs can spread by direct extension to the epididymis, spermatic cord, or scrotal sac. • Lymphatic spread is common (Retroperitoneal and para-aortic nodes are first to be involved) • Hematogenous spread to Lung, liver, Brain, and bones. Seminomatous tumors are radiosensitive. • Non-seminomatous tumors are chemosensitive and respond very well to chemotherapy. • The standard management of solid testicular tumors is radical orchiectomy.	• More than 95% of patients with seminoma can be cured. 90% of patients with non-seminomatous tumors can achieve complete remission with aggressive chemotherapy, and most can be cured. • The rare pure choriocarcinoma is the most aggressive non-seminomatous tumor. Pure • choriocarcinoma has a poor prognosis.

4. Benign Prostatic Hyperplasia

- Characterized by proliferation of both stromal and epithelial elements, with resultant enlargement of the gland and, in some cases, urinary obstruction.
- Extremely common lesion in men over age 50. Its frequency rises progressively with age, 20% in men > 40yrs, up to 70% by age 60, and 90% by age 80.

Pathogenesis	Clinical Features
Related to androgen; hence, it does **not** occur in males castrated before the onset of puberty or in men with genetic diseases that block androgen activity. **(DHT):** the ultimate mediator for prostatic growth. It increases the proliferation of stromal cells and inhibits epithelial cell death.	Some only present with acute urinary retention & others present with lower urinary tract obstruction (caused by prostatic enlargement). In some, BPH leads to **complete urinary obstruction**, with resultant painful distention of the bladder. Symptoms are: ↑ **urinary urgency, frequency**, **dysuria**, hydronephrosis, **nocturia** and **hesitancy** & **infection.**

Morphology

Grossly	Microscopically
Enlargement, **nodularity** due to **glandular** and **fibro-muscular** proliferation. Nodular hyperplasia begins in the **inner** aspect of the prostate gland, the **transition zone.** (**not** a premalignant lesion). It compresses the wall of the urethra resulting in a **slit-like orifice.**	The main feature of BPH is nodularity; The nodules can either be: **Purely stromal nodules (fibromuscular element) or Fibroepithelial** with **both** glandular and fibromuscular component: aggregation of glands (small, large & cystically dilated), lined by 2 layers of epithelium surrounded by fibromuscular stroma. The glandular lumina often contain inspissated, proteinaceous secretory material known as **corpora amylacea**. Diagnosis of BPH **cannot** be made on needle biopsy. it's made up on radiology only.

Prostatic Adenocarcinoma

- The **most common form** of cancer in men, disease of men over age 50. **Androgens** are believed to play a major role in the pathogenesis.
- **Risk factors:** Age, race, family history, hormone level (androgens), environmental influences, and acquired somatic mutations.
- Just like BPH, it does not develop in males castrated before puberty. **Prostatic intraepithelial neoplasia (PIN):** precursor lesion for invasive carcinoma

Pathogenesis (factors playing a role are?)	Clinical Features
Heredity: ↑ risk among first-degree relatives of patients with prostate cancer. **Environment** & **Acquired somatic mutations**: TMPRSS2 gene **TMPRSS2-ETS fusion genes.** The **most common** are mutations that inactivate the tumor suppressor gene **PTEN**, which acts as a brake on **PI3K** activity	Asymptomatic, very small and are discovered incidentally. Most arise in the **peripheral zone**, therefore, the urinary symptoms occur late. Patients may present with back pain caused by vertebral metastases. PSA (Prostate Specific Antigen) levels are important in the diagnosis and management of prostate cancer. **It gives us an idea about wither it is BPH or prostatic cancer** A transrectal **needle biopsy** is required to confirm the diagnosis.

Morphology

Grossly	Microscopically
Tumor is firm, gray-white, gritty and is palpable. **Metastasis:** Spread by **direct** local invasion and through blood stream and lymph (**periprostatic** tissue, **seminal vesicles** and the **base** of the urinary bladder). Hematogenous extension occurs to the bones (commonly vertebra), is frequent late in the disease and is typically osteoblastic.	▪ Most produce well-defined gland patterns. More advanced lesions appear as firm, gray-white lesions with ill-defined margins that infiltrate the adjacent gland. ▪ The malignant glands are lined by a single layer of cuboidal or low columnar epithelium with large nuclei and one or more large nucleoli. Nuclear pleomorphism is **not** marked. The outer basal cell layer typical of benign glands is absent. No branching or papillary infolding. Mitotic figures are uncommon. ▪ Commonly there is **perineural invasion**. With increasing grade, irregular or ragged glandular structures, cribriform glands, sheets of cells, or infiltrating individual cells are present.

Gleason Grading and Scoring: It's a histological grading and scoring system for prostatic adenocarcinoma done on the microscopic level.

There are five grades (1 to 5) depending on the degree and pattern of differentiation as seen microscopically (in which they range from, grade 1= well-differentiated to grade 5= very poorly differentiated). The two **most common** types of grades seen in the biopsy for each cancer case are added to produce a combined Gleason score.

- Staging in prostate cancer depends on the TNM system. It is the most important indicator of prognosis.

5. Cervix

Cervicitis

Non-infectious	Infectious
Asymptomatic, cervix appears red & swollen. Inflammatory cells. **Squamous metaplasia** is common in chronic cervicitis. Some glands dilate to form cysts filled with mucin called Nabothian cysts.	▪ Can be caused by various organisms (discussed below) ▪ Most often involves the endocervix. ▪ May be asymptomatic & may manifest as vaginal discharge or itching.

	Candidiasis (moniliasis)	Trichomoniasis	Chlamydia trachomatis
Info	Common involves cervix & vagina	**Sexually transmitted (STD)**	The most common **STD** in the developed countries.
Caused By	Candida albicans	Trichomonas vaginalis	• **May coexist with N. gonorrhoeae infection**. • A frequent cause of pelvic inflammatory disease. • **Can cause lymphogranuloma venereum**
Associated with	**DM, pregnancy, antibiotic therapy**, oral contraceptive use & immunosuppression.	• **Greenish-yellow frothy** and **foul smelling vaginal discharge** • **Painful urination**, dyspareunia. • vulvovaginal **itching or irritation.**	
Characteristics	**White** patchy mucosal lesions with thick curdy white discharge and vulvovaginal pruritis. Ulcers.		Most often asymptomatic. But in symptomatic cases there is a mucopurulent cervical discharge with a reddened, congested and edematous cervix. It may be associated with urethritis.
Cytology Smear	Shows **fungal colonies in the form of spores** and **branching pseudohyphae** on the cervical epithelium. Chronic inflammatory cells are present.	Found in Pap-stained vaginal smears in a background of inflammatory cells. A saline wet preparation shows the motile trophozoites.	

	HSV	Human papilloma virus (HPV)
Info		**Common** in cervix. Associated with increased risk of **subsequent cervical cancer**.
Associated with	**Herpes simplex virus type 2** accounts for **majority** of genital herpes cases and is **spread by sexual contact**. It produces vesicles and ulcers that can involve the cervix, vagina, vulva, urethra and perianal skin.	May cause any of the following **depending on the serotype:** 1) **Condyloma**: develops in the squamous epithelium of the cervix. The lesions may be flat or exophytic condylomma acuminatum. Usually caused by **HPV serotypes 6 and 11.** 2) **Mild dysplasia:** usually caused by "low risk" HPV **serotypes, 6 & 11**. 3) **High- grade dysplasia:** caused by **"high risk" HPV (types 16 and 18) and moderate risk HPV (types 31, 33 and 35).** **Koilocytes:** Squamous epithelial cells that have undergone structural change due to infection of the cell by HPV. They show **koilocytosis or koilocytic atypia which is the following cellular changes:** - Nuclear enlargement, Irregular nuclear membrane, Nuclear hyperchromasia. & Perinuclear halo (clear area around the nucleus).

Cervix carcinoma

Most tumors of the cervix are of epithelial origin. Most common cervical cancer is **squamous cell carcinoma**. Other types are adenocarcinoma, neuroendocrine carcinoma, etc. Use of **PAP screening has lowered the incidence of invasive cancer** and it's the most successful cancer screening test ever developed.

Cause	Risk factors
HPV; it's the **number one reason** for abnormal cells of the cervix (detected in most precancerous lesions). - A skin virus, which results in warts & precancerous lesions. - **High risk types of HPV**: 16, 18, 31, 33, 35, 39, 45, 52, 56, 58, and 59. - **Low risk types of HPV:** 6, 11, 42, 44 . These types result in condylomas.	Early age at first intercourse or multiple sexual partners. A male partner with multiple previous sexual partners. Persistent infection by high risk HPV, Low socioeconomic groups & Rare among virgins and multiple pregnancies.

Precancerous lesions

CIN	Histology, graded as:
CIN peaks in incidence at about 30 years of age, whereas invasive carcinoma peaks at about 45yrs	**CIN I:** Mild Dysplasia. With HPV associated koilocytotic atypia (in the superficial layers). Lower 1/3rd of the squamous epithelium is replaced by pleomorphic cells. **CIN II:** Moderate Dysplasia. Lower 2/3rd of the epithelium is replaced by pleomorphic cells (delayed keratinocyte maturation). **CIN III:** Severe Dysplasia and Carcinoma in situ (CIS). There is diffuse atypia and loss of maturation. All levels of the epithelium are replaced by pleomorphic cells, **(full thickness)**

SIL & PAP screening test	General rules
Cytologic examination can detect precancerous SIL long before any abnormality can be seen, using the PAP test.	**Should start at the age 21**. **For women between age 21-29:** cytological screening pap test should be done every 3 years **For women between age 30-64:** there are 2 possibilities: Only cytology screening pap test is done every 3 years or Co-testing in which cytology screening pap test is done along with DNA in-situ hybridization HPV testing, every 5 years.

Invasive Cervical carcinoma

- Most are **Squamous cell carcinomas (SCC),** which generally evolve from pre-cancer CIN/SIL lesions. The remainder are Adenocarcinoma.
- SCC appears in increasingly younger women, now with a peak incidence at about 45 years, about 10-15 years after detection of their precursors.
- Keep in mind that the progression of CIN to invasive carcinoma is unpredictable and requires **HPV infection** as well as mutations in genes such as **LKB. Risk factors for progression include:** Cigarette smoking & HIV

Morphology	Clinical Course
▪ Mainly in the transformation zone, and range from microscopic foci of early stromal invasion to grossly frank tumors encircling the cervical Os. ▪ The tumors may be invisible or exophytic ▪ Tumors encircling the cervix and penetrating the underlying stroma produce a **barrel cervix**, which can be identified by direct palpation.	Patients on schedule with their PAP screening test ▸ HPV is detectable by molecular methods in nearly all cases of CIN and cervical carcinoma. ▸ Many of cervical cancers are diagnosed in early stages (& vast majority in the pre-invasive phase). Patients who have never had a PAP screening test or haven't for years ▸ More advanced cases & Symptomatic, with patients coming to medical attention for unexpected vaginal bleeding, leukorrhea, painful coitus (dyspareunia), or dysuria.

Signs and symptoms

Early stage	Late stage (advanced)
Early stages of cervical cancer → completely asymptomatic. **If symptomatic: Vaginal bleeding, contact bleeding, or cervical mass**, Leukorrhea & **dyspareunia**, or dysuria.	Loss of appetite & Weight loss, Fatigue, Pelvic, back & leg pain, Swollen legs, Heavy bleeding from the vagina, Bone fractures & **Leakage of urine or faeces from the vagina (rarely).**

Metastasis:	(advanced) it may be present in the abdomen, lungs or elsewhere. Extension into the parametrial soft tissues can affix the uterus to the surrounding pelvic structures.

Mortality: Strongly related to tumor stage & Most patients with advanced disease die because of local invasion not distant metastasis (eg. renal failure).

Polycystic Ovarian Disease (PCOD): Other names include polycystic ovarian syndrome and Stein-Leventhal syndrome.

Bilateral enlargement of ovaries by multiple small cysts, chronic anovulation and clinical manifestations secondary to excessive production of estrogens and androgens (mainly androgens), affecting both ovaries. The initial abnormality resulting in the syndrome is not known but is believed to be related to hypothalamus-pituitary dysfunction leading to oversecretion of luteinizing hormone (LH). LH in turn stimulates the ovary to produce excess androgens. Secretion of follicle stimulating hormone (FSH) is inhibited resulting in suppression of ovulation with follicle cyst formation. High level of LH, testosterone & estrogen; and low FSH.

Clinical Appearance	Women with PCOS are at risk for the following
The usual clinical presentation is a young woman (between 15 and 30 years) with: Virilism due to excessive amounts or effects of androgenic (masculinizing) hormones, Secondary amenorrhea with anovulation, Oligomenorrhea or irregular menses or amenorrhea, Infertility, Hirsutism, Obesity & Acne	Acanthosis nigricans (patches of darkened skin under the arms, in the groin area, on the back of the neck), Endometrial hyperplasia and endometrial cancer, Insulin resistance (in T2DM), Cardiovascular disease, Depression/Anxiety, Dyslipidemia, Weight gain, High blood pressure, Autoimmune thyroiditis, Strokes & Miscarriage.

Morphology

Ovaries		Endometrium
Gross	**Microscopic**	**Microscopic**
Ovaries are 2 times the normal size with many subcortical and cortical cysts measuring 0.5 to 1.5 cm in diameter	The outer portion of the cortex is thickened and fibrotic (cortical stromal fibrosis) with multiple cysts underneath. The follicular cysts usually have a prominent theca interna layer. Corpora lutea are frequently absent due to the anovulation.	The unopposed estrogenic due to chronic anovulation leads to a hyper estrogenic state; hence, endometrium may show a variety of appearances ranging from mild hyperplasia to complex hyperplasia to atypia to endometrial adenocarcinoma.

Endometriosis:

It is the presence of ectopic endometrial glands and stroma outside the uterus. **Non-neoplastic.** Usually found on the peritoneal surfaces of the reproductive organs and adjacent pelvic organs. The most frequent location is the **ovary** (approx. 50%) followed by the pouch of Douglas & uterine ligaments.
Occasionally involves cervix, vagina, perineum, bladder, large bowel and the umbilicus. Rare lesions are seen in as far as small bowel, kidneys, lungs, nose and brain. It has been reported in men. The sites involved were the bladder, scrotum and prostate. **Like** the uterine endometrium, it is **responsive** to the hormonal variations of the menstrual cycle, and bleeds during menstruation. Therefore, in endometriosis there is menstrual type bleeding at the site of the ectopic endometrium, resulting in blood filled areas (e.g. chocolate cysts).

Clinical behavior	Clinical features	Morphology
Benign with no malignant potential. May recur after surgical excision but the risk is low. **Complications:** Infertility & Adhesion	• Depend on the site of endometriosis, often result in infertility. • Dysmenorrhea, cyclic abdominal pain and dyspareunia are common symptoms. Usually there is severe menstrual-related pain. • Usually appears as multiple red or brown (due to hemosiderin) 1-5mm nodules (some may form larger masses or cysts). Dense fibrous adhesions may surround the foci. • Repeated hemorrhage into the ovary with each menstrual cycle produces cysts, filled with chocolate-brown material "chocolate cyst". With time the ovaries become totally cystic and turn into large cystic masses filled with chocolate brown fluid.	Ectopic endometrial glands and endometrial stroma are present. Denatured blood from previous bleeding is present. • **Macrophages** containing **hemosiderin** (siderophages) are present. • When endometriosis develops in a muscular organ, the smooth muscle around it is often hyperplastic. **Theories behind pathogenesis:** The regurgitation theory; The metaplastic theory & vascular or lymphatic dissemination theory

Adenomyosis:

- This is defined as the presence of endometrial glands and endometrial stroma in the myometrium of the uterus. **More common** in the posterior wall than the anterior wall (but it may affect both walls in the same uterus).
- The disease is primarily a disorder of parous women and is uncommon in the nullipara.
- The aberrant presence of endometrial tissue induces reactive hypertrophy of the myometrium, resulting in an enlarged, globular uterus, often with a thickened uterine wall. It is associated with menorrhagia and severe dysmenorrhea. In 1/3rd of the patients: there are no symptoms.
- **If extensive**: the lesions produce myometrial thickening with small yellow or brown cystic spaces containing fluid or blood; **Do not undergo cyclic bleeding.**
- **Less severe than endometriosis. Clinical behavior:** A benign condition with no known malignant potential that regresses after the menopause.

7. Trophoblastic diseases

Ectopic pregnancy

Sites

- Over 90% of ectopic pregnancies occur in the fallopian tubes (tubal pregnancy) Other sites of pregnancy include the ovaries, abdominal cavity and uterine cervix.

Ovarian pregnancies: when the ovum is fertilized just as the follicle ruptures (rare).
Gestation within the abdominal cavity: when the fertilized egg drops out of the fimbriated end of the oviduct and implants on the peritoneum.

Risk Factors

Pelvic inflammatory disease/infections/salpingitis: One of the most common causes & Organisms like N. gonorrhea and chlamydia infect the reproductive organs.
History of: Previous ectopic pregnancy, Multiple sexual partners or **Infertility**: **Smoking**, **In-utero diethylstilbestrol** (DES) exposure, Abdominal/pelvic **surgery** or **tubal ligation** surgery, **Intrauterine tumors and endometriosis**, Congenital **anomaly** of the tubes.
Intrauterine device users

Clinical Features

A woman with an ectopic tubal pregnancy may present with pelvic pain or abnormal bleeding following a period of amenorrhea. The majority will present as an emergency with tubal rupture and hemorrhagic shock.
Tubal ectopic pregnancy: fallopian tubes are the most common location for ectopic pregnancies and any factor that retards passage of the ovum through the tubes predisposes to tubal ectopic pregnancy. In about half of the cases, it is due to chronic inflammation and scarring in the oviduct.

Diagnosis

- **Clinical:** Abdominal/pelvic ultrasound shows mass (gestational sac) within fallopian tube, plus positive HCG levels
- **Microscopic**: Placental tissue or fetal parts.

Spontaneous abortion

- Miscarriages that occur before the sixth week of gestation are called *early pregnancy loss* or *chemical pregnancy*.
- Miscarriages that occur after the sixth week of gestation are called *clinical spontaneous abortion.* Most miscarriages occur during the first 13 weeks of pregnancy.

Causes

- Most miscarriages occur during the first trimester. The cause of a miscarriage cannot always be determined.
- Miscarriages can occur for many reasons: genetic, uterine abnormalities, hormonal abnormalities, collagen vascular disease (e.g. SLE), reproductive tract infections, and congenital (present at birth) abnormalities of the uterus. **Chromosomal abnormalities** of the fetus are the most common cause of early miscarriages.

Diagnosis

Confirmed via ultrasound and by the examination of the passed tissue microscopically for the products of conception. Genetic tests may also be performed to look for chromosomal anomalies.

Gestational trophoblastic Disease

A group of related disorders in which there is an abnormal proliferation of placental trophoblasts.

- **Divided into:** Benign non-neoplastic lesions, Hydatidiform moles & Neoplastic lesions. The maternal age above **40 years has 5 times more risk** of trophoblastic disease compared to the mothers below 35 years. Most women who have had GTD **can have normal pregnancies later**. Most GTD produces the **beta subunit of human chorionic gonadotropin (HCG). Serum HCG** is elevated in pregnancy (normal and ectopic) but in GTD it is **markedly** elevated. However, in normal pregnancy the HCG levels drop after 14 weeks of gestation, but in GTD the serum HCG levels continue to rise even after 14th weeks.

Hydatidiform Mole	Risk Factors of hydatidiform moles
An abnormal fertilization resulting in an abnormal placenta due to excess of paternal **(from father)** genes. It is caused by abnormal gametogenesis and fertilization. ▪ Results in the formation of enlarged and edematous placental villi, which fill the lumen of the uterus. ▪ Passage of tissue fragments, which appear as small grapelike masses, is common. The serum HCG concentration is **markedly elevated**, and are **rapidly** increasing.	**Maternal age:** girls < 15 years of age and women > 40 are at higher risk. Ethnic background: higher in Asian women. Women with a prior hydatidiform mole have a **20-fold** greater risk of a subsequent molar pregnancy than the general population.

	Complete Hydatidiform Mole	Partial Hydatidiform Mole
Results from	Fertilization of an **empty ovum** that lacks maternal DNA. Most commonly, a haploid (23X) set of paternal chromosomes duplicates to 46XX (the most common type in CM) The characteristic feature is **complete lack of maternal chromosomes.** 10% are 46XY because of dispermy. It's a genetically abnormal placenta with hyperplastic trophoblasts, **without fetus or embryo.**	Fertilization of a **normal single ovum**/egg (23,X) by two normal spermatozoa, each carrying 23 chromosomes, or by a single spermatozoon that has not undergone meiotic reduction and bears 46 chromosomes (the pregnancy has **too much paternal DNA**). It's a genetically abnormal placenta with a resultant mixture of large and small villi with slight hyperplasia of the trophoblasts, filling the uterus. In contrast to a complete mole, **embryo/fetal parts may be present**. The fetus associated with a partial mole usually **dies after 10 weeks' gestation**, and the mole is aborted shortly thereafter.
Symptoms	- Fast rate of abdominal swelling (due to **rapid increase in uterine size**) mistaken for normal pregnancy but the uterus is disproportionately large for that stage of pregnancy. Some vaginal bleeding, severe nausea and vomiting. **HCG levels are elevated**.	- It makes up **15–35% of all moles** - **Uterine size usually small** or appropriate for gestational age **Serum HCG levels are high but not as high as complete mole.**
Signs	**Uterus is distended and filled with swollen/large villi** with prominent trophoblastic cell proliferation. No embryo, or fetal tissue is present. Grossly it looks like a bunch of grapes.	Grossly the genetically abnormal placenta has a mixture of large chorionic villi and normal-appearing smaller villi.
CA	Chromosomal analysis shows 46XX karyotype and all the chromosomes come from the male/paternal side i.e. it is an **androgenetic pregnancy with no maternal DNA.**	**Shows 69XXY in 58%** (The most common type in PM) (i.e. 3 haploid sets also called as **triploidy**) 40% are 69XXX & 2% are 69XYY.
Fertili-zation	90% of the time, a single sperm of 23 chromosomes fertilizes a egg that has lost its chromosomes. It then duplicates resulting in **46XX** (all paternal)	Have **69 chromosomes** (triploidy gestation), of which one haploid set (23,X) is maternal and two haploid (23,X+23X=46X) sets are paternal in origin.
US	Will show a "cluster of grapes" appearance or a "snowstorm" appearance, signifying an abnormal placenta.	-
Tx	**Evacuation** of uterus by **curettage** and sometimes **chemotherapy**. With appropriate therapy **cure rate is very high.**	**Evacuation** of uterus by **curettage** and sometimes **chemotherapy**
Compli-cations	Uterine hemorrhage, perforation, Trophoblastic embolism, and infection, Few patients develop an invasive mole & The most important complication is the **development of choriocarcinoma**, which occurs in about **2%** of patients after the mole has been evacuated.	It almost **never evolves into choriocarcinoma** **Prognosis**: Risk for development of choriocarcinoma very low. **Follow-up is mandatory**.

Invasive Mole

- When the villi of a hydatidiform mole extends/infiltrates into the myometrium of the uterus.
- The mole sometimes enters into the veins in the myometrium, and at times spreads via the vascular channels to distant sites, mostly the lungs (note: death from such spread is unusual). It occurs in about **15% of complete** moles and rarely in partial mole.
- Can cause hemorrhage and uterine perforation.

Choriocarcinoma

Malignant tumor of placental tissue, composed of a proliferation of malignant anaplastic cuboidal cytotrophoblast and syncytiotrophoblast, **without villi formation.** An aggressive malignant neoplasm characterized by **very high levels of serum HCG. Aneuploidic**, spreads early via blood to the lungs and vagina, brain, liver, or kidneys. Lymphatic invasion is uncommon. Responds well to chemotherapy but choriocarcinoma that affects the gonads' prognosis is poor.. About half the choriocarcinoma are preceded by **complete hydatidiform** mole. Others are preceded by a partial mole (rare), 25% from abortion, ectopic pregnancy and **occasionally normal term pregnancy.**

8,9- Breast pathology

Clinical presentation of breast disease:
1)Pain (may be cyclical with menses or non-cyclical) 2) Palpable masses 3) Nipple discharge: Milk discharge (Not with malignancy) blood or serous discharge (common with benign lesion) **Mammographic screening:** Densities & calcification

Inflammatory lesion of the breast

Acute mastitis	Periductal
Associated with breast feeding (1st month); Commonly caused by staph. Aureus & The breast is erythematous, painful & fever is often present	• Not associated with lactation. • strong association with cigarette smoking.

Benign epithelial lesions

1- Non proliferative Breast Changes (Fibrocystic Change/disease)

Features	Microscopic
Most common disorder of the breast. Age: 20-55yrs, decreases progressively after menopause. Can produce palpable breast mass, mammographic densities, calcifications, or nipple discharge. May also present with cyclical pain; No increased risk of cancer.	Cysts formation with apocrine metaplasia (benign); Fibrosis & adenosis

2- Proliferative Disease without Atypia

Features	Subtypes
Rarely form palpable masses; Detected as small mammographic densities; Incidental finding; Risk for cancer is 1.5 – 2 times normal	Epithelial hyperplasia; Sclerosing adenosis; Complex sclerosing lesions/radial scar; Papillomas & Proliferative variant of fibrocystic disease.

proliferative disease without atypia's histological entities:

Epithelial hyperplasia	Papilloma	Complex sclerosing lesions/radial scar	Sclerosing adenosis
Defined as the presence of more than 2 layers & can range from mild, moderate to severe/florid. Both epithelial and myoepithelial cells proliferate. Can be seen in the ducts and the lobules. When it is seen in fibrocystic disease: it is called as proliferative type/variant of fibrocystic disease.	Rises from the ductal epithelium. It is more common in the **large lactiferous ducts** ➢ **Large duct (central):** usually solitary and situated in the lactiferous duct & Patients present with bloody nipple discharge and sometimes a subareolar palpable mass. ➢ **Small duct (peripheral)** commonly multiple and located deeper within the ductal system & Small duct papillomas have been shown to increase the risk of subsequent carcinoma.	• Stellate lesions characterized by a central nidus of entrapped glands in a hyalinized stroma. • present as an irregular mammographic density and closely mimic an invasive carcinoma both mammographically and grossly.	Commonly seen as an incidental microscopic finding but may occasionally present as a palpable mass that is mistaken clinically for cancer. Calcification is commonly seen in the lesion, so even on mammography it can mimic cancer. It is almost always associated with other forms of fibrocystic change. Myoepithelial cells are intact (deference from cancer) Microscopically: adenosis and stromal fibrosis in the lobule which leads to compression and distortion of the lobule.

3- Proliferative breast disease with atypia (Atypical hyperplasia) (the worst)

- Risk for cancer is 4-5 times normal
- Atypical hyperplasia is a cellular proliferation resembling ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) but lacking sufficient qualitative or quantitative features for a diagnosis of carcinoma in situ.
- Include two entities: 1. Atypical ductal hyperplasia 2. Atypical lobular hyperplasia

Breast Carcinoma:

- Carcinoma of the breast **is one of the most common cancer in women**.
- Mammographic screening has dramatically increased the detection of small invasive cancers.
- DCIS by itself is almost exclusively detected by mammography, so the incidence of DCIS is increased with the use of mammography.
- The mortality rate has started to decline. Currently only 20% of the women with breast cancer are expected to die of the disease. (Because you detect it early and treat it early with high cure rate)

Rick factors

- Age, exposure to estrogen, First Degree relative with Breast Cancer, Radiation exposure, Obesity and Dietary factors, Race & Geographic influence
- History of breast cancer, History of Other Cancer & Benign breast disease

Hereditary Breast Cancer: (family history) A family history of breast cancer in a first-degree relative & About 25% of familial cancers (or around 3% of all breast cancers) can be attributed to two autosomal-dominant genes: BRCA1 and BRCA2.
Sporadic cancer: Related to hormone exposure, most of these cancers occur in postmenopausal women and overexpression of estrogen
Protective MECHANISMS: Exercise & breast feeding

Carcinoma in Situ: has **not** invaded beyond the basement membrane and is therefore incapable of metastasis.

Ductal Carcinoma in Situ (DCIS):

Features	Sub types	Diagnosis	Prognosis
Non-invasive proliferation of malignant cells within the duct system without breaching the underlying basement membrane.	• **Comedo (central necrosis)** has essentially a 100% chance of becoming invasive if left untreated. ***It*** is characterized by large central zones of necrosis with calcified debris. Less commonly causes mammographic density. • **Cribiform** (cells arranged around "punched-out" spaces) **papillary, Micropapillary solid** (cells fill spaces)	Mammography: DCIS frequently shows micro-calcifications and it's the sensitive diagnostic procedure for detecting DCIS • Majority are not palpable	high risk of development of subsequent invasive carcinoma. The tumor distends and distorts the ducts. Often multifocal-malignant cells can spread widely through the ductal system without breaching the basement membrane risk of recurrent DCIS following treatment

Lobular Carcinoma in Situ (LCIS):

Features	Histology	Prognosis
LCIS is malignant proliferation of cells lobules and is always an incidental finding in breast biopsy performed for another reason 1. LCIS does not form a palpable mass and can not be detected clinically on palpation or on gross pathological examination. 2. Microcalcifications in LCIS are infrequent and so mammography is not useful for detection. Not like the DCIS • LCIS tends to be multicentric and bilateral and therefore subsequent carcinomas can occur both breasts. • LCIS is a marker of increased risk of carcinoma in both breasts and a direct precursor of some cancers.	Monomorphic population of small, rounded cells fills and expands the acini of lobules. The underlying lobular architecture can still be recognized.	If LCIS is left untreated, about 30% of women develop an invasive cancer within 20 years of diagnosis. The invasive cancer that develops is usually lobular (but can be ductal too).

Paget's Disease:

Info	Prognosis
Paget's disease of the breast is a rare type of breast cancer that is characterized by a red, scaly eczematous lesion on the nipple and surrounding areola. • **Pruritus** is common and it might be mistaken for eczema. The **hallmark** is the infiltration of the epidermis by malignant cells called Paget cells which is large ductal neoplastic cells with abundant cytoplasm, pleomorphic nuclei and prominent nucleoli. The cells usually stain positively for mucin. • Paget cells extend from DCIS within the ductal system into nipple skin without crossing the basement membrane. • Palpable mass can be seen in 50% of women with Paget disease indicating an underlying invasive carcinoma nearby.	Based on the underlying carcinoma and is not affected by the presence of Paget disease.

Invasive breast carcinoma:

- Palpable mass. About 1/2 of the patients will have axillary lymph node metastases.
- Larger carcinomas may be fixed to the chest wall or cause dimpling of the skin.
- Lymphatics may become involved and the lymphatic drainage of that area and the overlying skin gets blocked causing lymphedema and thickening of the skin, a change referred to as peau d'orange.
- The lymphatic drainage will accumulate inside the breast and When the tumor involves the central portion of the breast, retraction of the nipple may develop.
- On mammography, invasive carcinomas commonly present as a **density**.
- Invasive carcinomas presenting as mammographic calcifications without an associated density are usually very small in size.
- The term "inflammatory carcinoma" refers to the clinical presentation of a carcinoma extensively involving dermal lymphatics, resulting in an enlarged erythematous breast. The diagnosis is made on clinical grounds and does not correlate with a specific histologic type of carcinoma

Invasive Ductal Carcinoma, NOS:

Features

- The commonest type of breast cancer, forming up to 80% of these cancers.
- Most of these tumors induce a marked fibroblastic (desmoplastic) stromal reaction to the invading tumor cells producing a palpable mass with hard consistency (scirrhous carcinoma). And therefore a palpable mass is the most common presentation.
  The tumor shows an infiltrative attachment to the surrounding structures and may cause dimpling of the skin (due to traction on suspensory ligaments) or nipple retraction.

Morphology

Microscopic:
- The tumor cells are large and pleomorphic usually within a dense stroma. They are adenocarcinomas and so they show glandular formation but can also be arranged in cords or sheets of cells.
- The tumors range from well differentiated to moderate or poorly differentiated.

Gross:
- Tumor is firm, hard, with an irregular border.
- Cut surface: gritty and shows irregular margins with stellate infiltration (sometimes it can be soft and well demarcated) and in the center there are small foci of chalky white stroma and occasionally calcifications.

Invasive Lobular Carcinoma:

Features

- It is the second most common type of invasive breast cancer forming up to 10% of breast cancers.
- The tumor may occur alone or in combination with ductal carcinoma.
- It tends to be bilateral and multicentric
- The amount of stromal reaction to the tumor varies from marked fibroblastic (desmoplastic) response to little reaction and therefore the presentation varies from a discrete mass to a subtle, diffuse indurated area. Most are firm to hard with irregular margins.

Histology

Single infiltrating malignant cells, forming a line often one cell width (called as indian file pattern) "single-file" strands or chains. No tubules or papillary formation.

Medullary Carcinoma:

- This subtype of breast cancer presents as a well circumscribed mass.
- May be mistaken clinically and radiologically for fibroadenoma
- It does not produce any fibroblastic (desmoplastic) reaction and therefore is soft and fleshy.

Histology:
The tumor is composed of solid sheets of malignant cells surrounded by many lymphocytes and plasma cells. There is scant fibrous stroma.

Colloid Carcinoma/ Mucinous carcinoma:

- Tends to occur in older women.
- It is sharply circumscribed, lacks fibrous stroma and is slow growing.
- Is soft and gelatinous and has a glistening cut surface.
- It may be in pure mucinous or mixed with another type of invasive breast carcinoma.
- The tumor is composed of small islands of tumors cells and single tumor cells floating in pools of extracellular mucin.

Treatment: Wide local excision & Radical mastectomy

Prognostic factors

Major factors

- Invasive or in situ disease
- Distant metastasis
- Lymph node metastasis (Axillary lymph node status is the most important prognostic factor for invasive carcinoma)
- Tumor Size (the second most important prognostic factor)
- Locally advanced disease
- Inflammatory carcinoma.

Minor factors

- Histological sub type (Infiltrating ductal and lobular carcinomas have the worst prognosis)
- Tumor grade (calculated using a grading system called modified Scarff-Bloom-Richardson (SBR) grading system)
- Tumor cells with estrogen and progesterone positive receptors (better prognosis)
- HRE2 (Respond very well to a chemotherapy drug named Trastuzumab (Herceptin))
- Lymphovascular invasion (Strongly associated with the presence of lymph node metastases)
- Proliferative rate (ki67 index. Faster it grows the worse the result)

Stromal Tumors:

Fibroadenoma:

Features

- The most common benign tumor of the female breast.
- It is composed of benign proliferation of both epithelial and stromal elements.
- Any age, most common before age 30
- Classic presentation: firm, **mobile lump** ("breast mouse").
- It may increase in size during pregnancy. It may stop growing and regress after menopause.
- The tumor is usually solitary but may be multiple and involve both breasts.
- The tumor is completely benign. FA are almost never malignant.
- Grossly: spherical nodules, sharply demarcated and circumscribed from the surrounding breast tissue and so is freely movable and can be shelled out. Size vary (1cm to 10 cm in diameter). Cut surface: pearl-white and whorled.

Histology: Tumor is composed of a *mixture of ducts* and *fibrous connective* tissue

Treatment: Lumpectomy (only the lump is removed).

Phyllodes tumor:

Features

- Phylloides tumors **can occur at any age**, but most present in the 40s and 50s, that is 10 to 20 years later than the average presentation of a fibroadenoma
- These tumors are much **less common** than fibroadenomas
- Most present as large palpable masses (usually 3 to 4 cm in diameter)
- They are fibro-epithelial tumors arranged in leaf like pattern with cellular stroma.
- They are usually **benign** or low-grade tumors that may **recur locally**. And therefore, are excised with wide margins to avoid the chances of local recurrences.
- High-grade Phyllodes tumors are **uncommon** and they behave aggressively, with frequent local recurrences and distant metastases.

10. HIV

Info

- **Human immunodeficiency virus (HIV)** is the causative agent for AIDS.
- HIV is a retrovirus of the lentivirus family that contains only RNA.
- The most common type of HIV infection is known as **HIV-1** and is the type that has led to the worldwide AIDS epidemic. There is also an HIV-2 that is much less common.
- The result of HIV infection is the destruction of the immune system.
- All HIV infected persons are at risk for illness and death from development of opportunistic infections and tumors and the inevitable manifestations of AIDS, and neurologic manifestations.

Modes of transmission

- It can be present in genital secretions, blood, and breast milk. NOTE: saliva, urine, tears, and sweat is of no major clinical importance.
- Primarily spreads as a sexually transmissible disease.
- HIV can be transmitted through parenteral route, e.g. Intravenous drug users sharing infected needles.
- Less common practices like use of instruments such as tattoo needles not properly disinfected also carries a potential risk. Health care workers with percutaneous exposures (needle puncture) to HIV-containing blood.
- Persons receiving multiple blood transfusions e.g. hemophiliacs. Screening of blood products for HIV has significantly reduced HIV transmission by this means.
- Can also be acquired as a congenital infection either perinatally or in infancy.
- Mothers with HIV infection can pass the virus transplacentally i.e. in utero at the time of delivery through the birth canal through breast milk.

Pathogenesis

The HIV virion expresses a cell surface protein/antigen called gp120. What does it do?

- Aids in the binding of the virus to the target cells.
- Responsible for attraction to CD4+ receptors. This function helps in entry of HIV into the host cell.
- Binds to two co-receptors CXCR4 and CCR5 on the host cell surface. They also assist in the entry of the virus into the host cell.

Once the virus enters the human body:

- It attaches itself to the target cell via the CD4 receptors on the surface of the target cell and therefore gains entry into the target cell. The T-lymphocytes have surface CD4 receptors (CD4+ T lymphocytes) to which HIV can attach to promote entry into the cell.
- Retroviruses are unable to replicate outside of living host cells because they contain only RNA and do not contain DNA. So once HIV infects a cell, it must use its reverse transcriptase enzyme to convert its RNA to host cell proviral DNA for replication. This HIV proviral DNA is then inserted into host cell genomic DNA by the integrase enzyme.
- Then the HIV provirus is replicated by the host cell to produce additional HIV virions which are released by surface budding.
- The infected cells undergo lysis with release of new HIV virions which can then infect additional cells.
- Macrophages and Langerhans cells are important both as reservoirs and vectors for the spread of HIV in the body including the CNS.
- In contrast with CD4+ T cells, macrophages are quite resistant to the cytopathic effects of HIV and therefore harbor the virus for long periods.
- The follicular dendritic cells (FDC's) in epithelia at sites of virus entry become infected (providing a reservoir), but are not destroyed.
- Once the infection extends to the lymph nodes, the HIV virions trapped in the processes of FDC's is passed on to CD4+ T cells through direct cell–cell contact.
- **The target cells are:** blood monocytes and tissue macrophages, T lymphocytes, B lymphocytes, natural killer (NK) lymphocytes, dendritic cells (i.e. the Langerhans cells of epithelia and follicular dendritic cells in lymph nodes), hematopoietic stem cells, endothelial cells, microglial cells in brain, and gastrointestinal epithelial cells
- In addition, **HIV can mutate easily.** This high mutation rate leads to the emergence of HIV variants within the infected person's cells that are more toxic and can resist drug therapy. Over time, different tissues of the body may harbor different HIV variants.

Diagnosis

- Test for HIV antibodies is done with a rapid test using (ELISA)
- If positive → confirm HIV infection with Western blot (IFA).
- The average HIV-infected person may take up to several weeks to become seropositive, and then may live up to 8 or 10 years, on average, before development of the clinical signs and symptoms of AIDS.

Primary infection

- Primary HIV infection may go unnoticed in at least half of cases or produce a mild disease which quickly subsides, or produce acute HIV infection, followed by a long clinical "latent" period lasting years.
- Primary acute HIV infections may include fever, generalized lymphadenopathy, pharyngitis, rash, arthralgia and diarrhea. These symptoms diminish over 1 to 2 months.

AIDS

The stage of clinical AIDS is reached years after initial infection and is marked by the development of one or more of the typical opportunistic infections or neoplasms common to AIDS.

Pathogenesis

- The primary target of HIV is the immune system, which is gradually destroyed. Clinically, HIV infection may appear "latent" for years.
- During this period there is ongoing immune system destruction but still enough of the immune system remains intact to provide immunity and prevent most infections.
- Latent infection of T cells (and macrophages) is an important feature; if latently infected CD4+ cells are activated (e.g., through intercurrent infection by other microbial agents), an unfortunate consequence is increased HIV proviral DNA transcription.
- This increased transcription leads to virion production and, in the case of T cells, also results in cell lysis. In addition, TNF, IL-1, and IL-6 produced by activated macrophages during normal immune responses can also lead to increased HIV gene transcription
- Eventually, when a significant number of CD4+ T lymphocytes have been destroyed and when production of new CD4 cells cannot match destruction, then failure of the immune system leads to the appearance of clinical AIDS.

Signs & Symptoms

The development is typically parallels laboratory testing for CD4 lymphocytes.

- When the CD4 lymphocyte count drops below 200/microliter, then the stage of clinical AIDS has been reached.
- This is the point at which the characteristic opportunistic infections and neoplasms of AIDS appear.
- The CD4+T cells to CD8+T cells ratio is also greatly reduced, often to less than 1.0.

Common complications:

- Infections e.g. pneumocystis jiroveci, CMV, mycobacteria, fungal etc.
- Neoplasms
- Miscellaneous e.g. lymphoid interstitial pneumonitis is a condition involving the lung that can be seen in AIDS in children.

Infections	Info
Pneumocystis jiroveci (formerly carinii)	• The most frequent opportunistic infection seen with AIDS. It commonly produces a pulmonary infection. • **Diagnosis** is made histologically by finding the organisms in cytologic (bronchoalveolar lavage) or biopsy (transbronchial biopsy) material from lung. • In the lung, there is soap bubble like intra-alveolar exudate and the organism appears as cyst like structures that are positive with silver stain.
CMV	Cytomegalovirus (CMV) infection causes pneumonia and can also cause serious disease in the brain and gastrointestinal tract. It is also a common cause for retinitis and blindness in persons with AIDS.
Mycobacterial infections	• Definitive diagnosis of mycobacterial disease is made by culture and PCR. • Mycobacterium tuberculosis & Mycobacterium avium complex (MAC) infection.
Fungal Infections	• Candidiasis of the esophagus, trachea, bronchi, or lungs. • Cryptococcus neoformans (produces pneumonia and meningitis), Histoplasma capsulatum, and Coccidioides immitis.
Other Infections	• Toxoplasmosis caused by *Toxoplasma gondii* is a protozoan parasite that most often leads to infection of the brain with AIDS. • Herpes simplex infection in the mucosa; Aspergillosis especially in the lung • Cryptosporidium and Microsporidium produce voluminous watery diarrhea in patients with AIDS. • Viral HIV encephalitis; Syphilis (primary, secondary and tertiary)
Malignant neoplasms	
Kaposi's sarcoma (KS)	• It is a sarcoma of the blood vessels & produces reddish purple patches or nodules over the skin and can be diagnosed with skin biopsy. • Visceral organ can also be involved with KS. It is associated with HHV-8 and on histology, it shows malignant spindle cells of vascular origin.
Malignant lymphomas	• Commonly it is B-cell Non Hodgkins Lymphoma. • They are typically of a high grade and often in the brain. They are very aggressive and respond poorly to therapy.

Done By: Nouf Altwaijri & Omar AlSuliman
Good Luck.