Neoplasia

Lectures: 11 - 15

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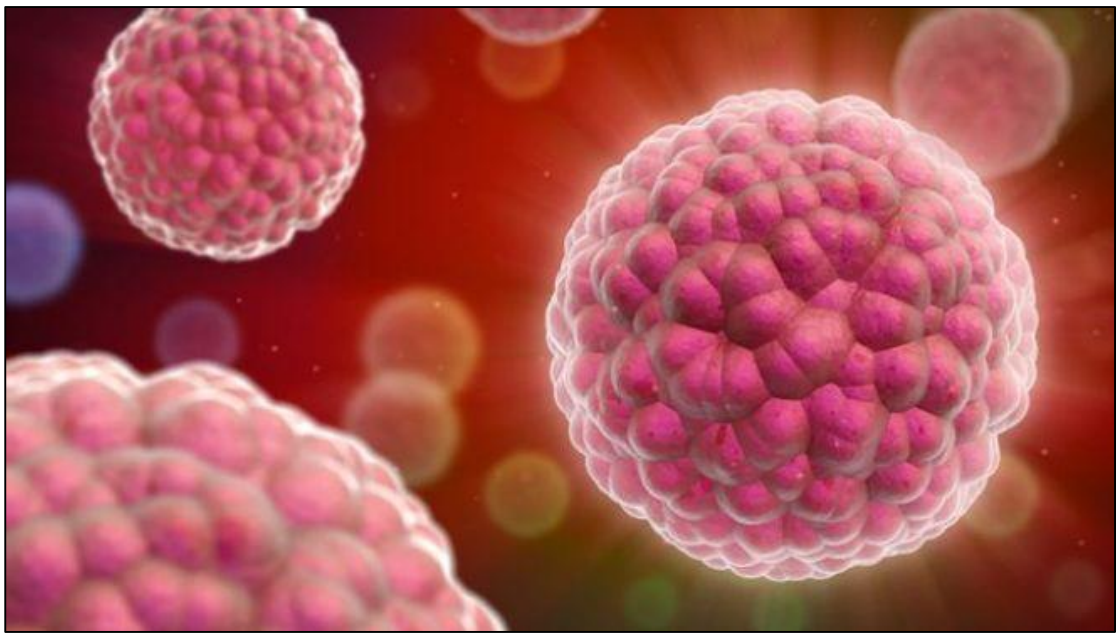

PATHOLOGY

TEAM 433

OBJECTIVES:

- Define neoplasia and its nomenclature.
- Compare and contrast benign and malignant tumors.
- Knowing the differences between metastasis, dysplasia & neoplasia.
- Know the carcinogenesis.
- Recognize the epidemiologic data of cancer distribution in regard to age, race, geographic factors, and genetic backgrounds.
- List some inherited syndromes with a genetic predisposition to cancer.
- Define host defense against cancer
- Define tumor grade and clinical stage.

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Important terms:

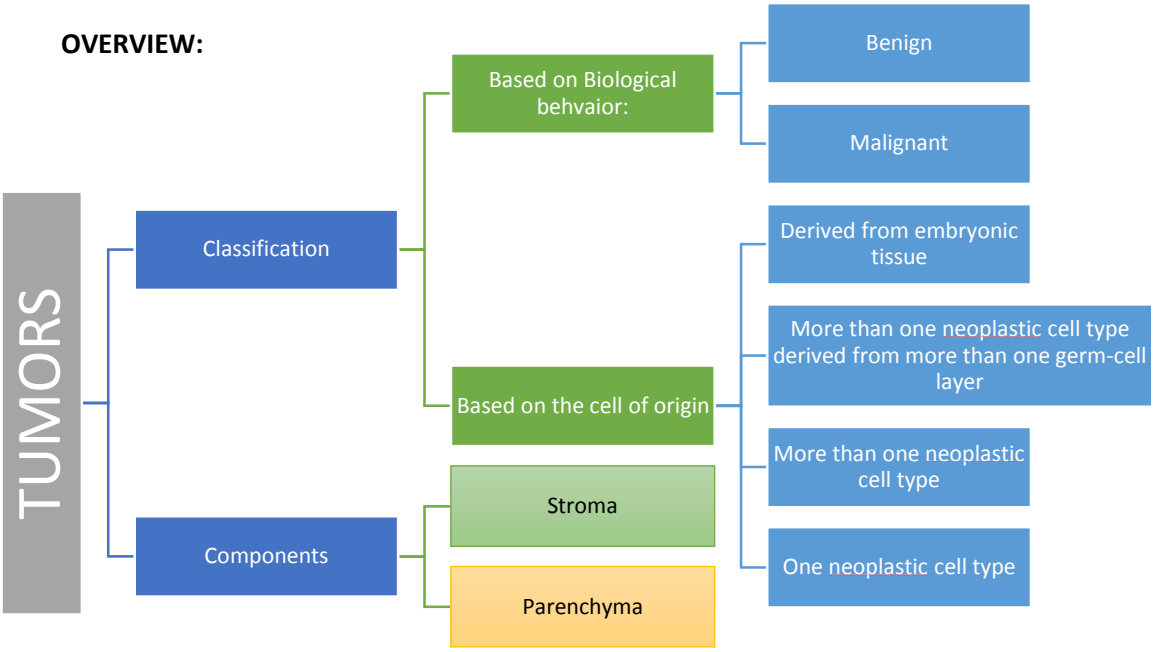
Neoplasia = new growth
Neoplasm = tumor = swelling = oncos
The study of tumors = Oncology
Pleomorphism: Variation in size.
Hyperchrmasia (dark cell).
High nuclear/cytoplasm ratio (N/C ratio).

TUMORS:

Definition:

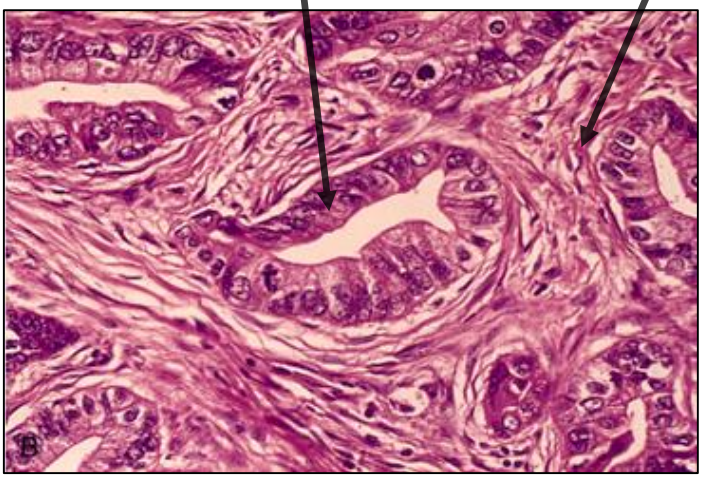
An abnormal and an uncoordinated growth of a normal tissue that persists in the same excessive manner after the cessation of the stimulus, which evoked (triggered) the change.

OVERVIEW:



Parenchyma:
- Made up of **neoplastic** (new-grown) cells.
- Determines the biological **behavior** of the tumor.
- From which the tumor derives its name.

Stroma:
- Made up of **non-neoplastic**, it is made of host-derived connective tissue and blood vessels.
- Carries the blood supply.
- Provides **support** for the growth of the parenchyma.



1st: Types of tumors based on biological behavior.

	Benign	Malignant
Features	- Remain localized (cannot spread to distant sites). - Generally can be locally excised (استئصال). - Patient generally survives (NOT FATAL).	- Can invade and destroy adjacent (Near) structure. - Can spread to distant sites. - Cause death (if not treated).
Differentiation and anaplasia?	Well differentiated	Begin as a well differentiated in process to anaplastic
Growth Rate	Grows slowly, it's affected by blood supply, hormonal effects & location.	Grows faster Correlate with the level of differentiation
Local Invasion	- Remain localized. - Cannot invade. - Usually capsulated.	- Progressive invasion. - Destruction. - Usually not capsulated.
Metastasis?	NO METASTASIS; because it remains localized	- Generally, the more anaplastic and the larger the primary tumor, the more likely is metastasis. - **Three pathways**: 1- Lymphatic spread. 2- Hematogenous spread. 3- Seeding of the body cavities.

Differentiation: the extent to which the parenchymal cells of the tumor resemble their normal counterparts morphologically and functionally.

- Well differentiated: closely resemble their normal counterparts
- Moderately differentiated
- Poorly differentiated
- Undifferentiated (**Anaplasia**)

Metastasis: the development of secondary implants discontinuous with the primary tumor, possibly in remote tissues.
- Cancers have different ability to metastasize
- Approximately 30% patients present with clinically evident metastases.

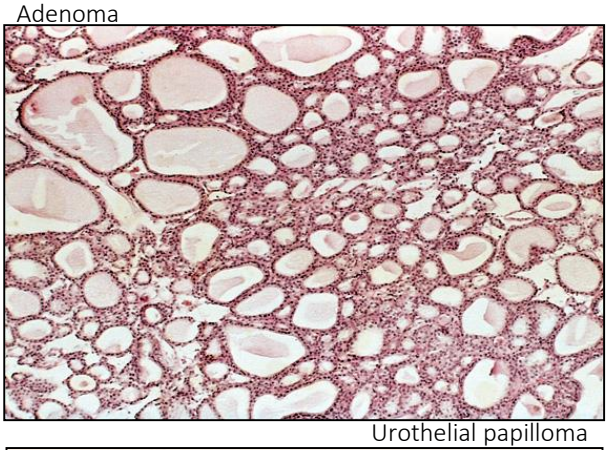
- **Lymphatic** spread:
  Favored by carcinomas.
  Breast carcinoma → axillary lymph nodes.
  Lung carcinomas → bronchial lymph nodes.
- **Hematogenous** spread:
  Favored by sarcomas.
  Also used by carcinomas.
  Veins are more commonly invaded.
  The liver and lungs are the most frequently involved secondary sites.

2nd: Nomenclature.

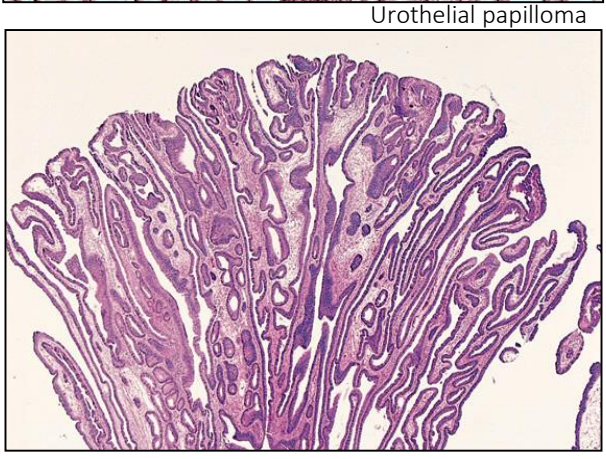
Benign Tumors		Malignant Tumors	
Arising from mesenchymal tissue: **Type of cell + (-oma)** **fibrous tissue**: Fibro + oma= Fibroma. **fatty tissue**: Lipo + oma= lipoma. **Cartilage:** Chondro + oma= chondroma. **Smooth muscle**: Leiomyo + oma= leiomyoma. **skeletal muscle:** Rhabdomyo + oma= rhabdomyoma.	**Arising from epithelial tissue:** - **Adenoma**: benign epithelial neoplasms producing gland pattern OR derived from glands but not necessarily exhibiting gland pattern. - **Papilloma**: benign epithelial neoplasms growing on any surface that produce finger-like pattern under the **microscope** or **macroscopically** - **Polyp**: a mass that projects above a mucosal surface to form a **macroscopically** visible structure.	Arising from mesenchymal tissue: +**SARCOMA** **Fibrous tissue**: **Fibro**sarcoma **From bone**: **Osteo**sarcoma **From cartilage**: **chondro**sarcoma	**Arising from epithelial tissue:** +**CARSINOMA** - Squamous cell carcinoma - Renal cell adenocarcinoma. - Cholangiocarcinoma.

Carcinomas arising from any epithelium of the body that exhibit squamous differentiation are termed squamous cell carcinoma.

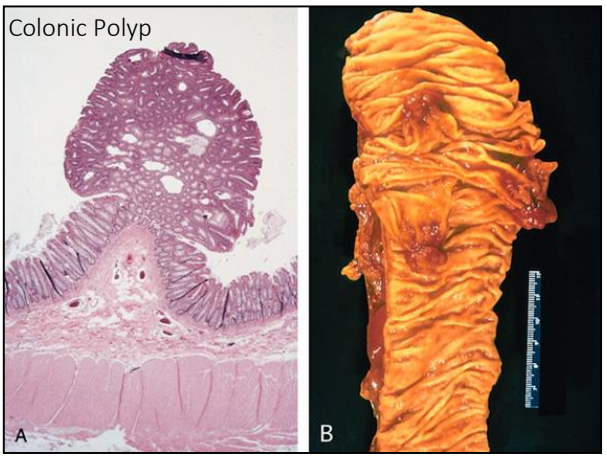
Adenoma



Urothelial papilloma



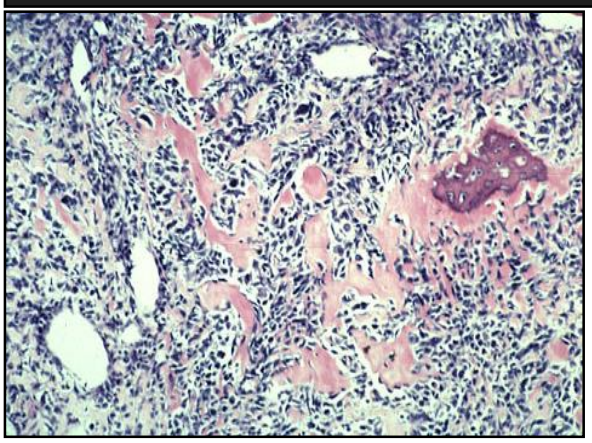
Colonic Polyp



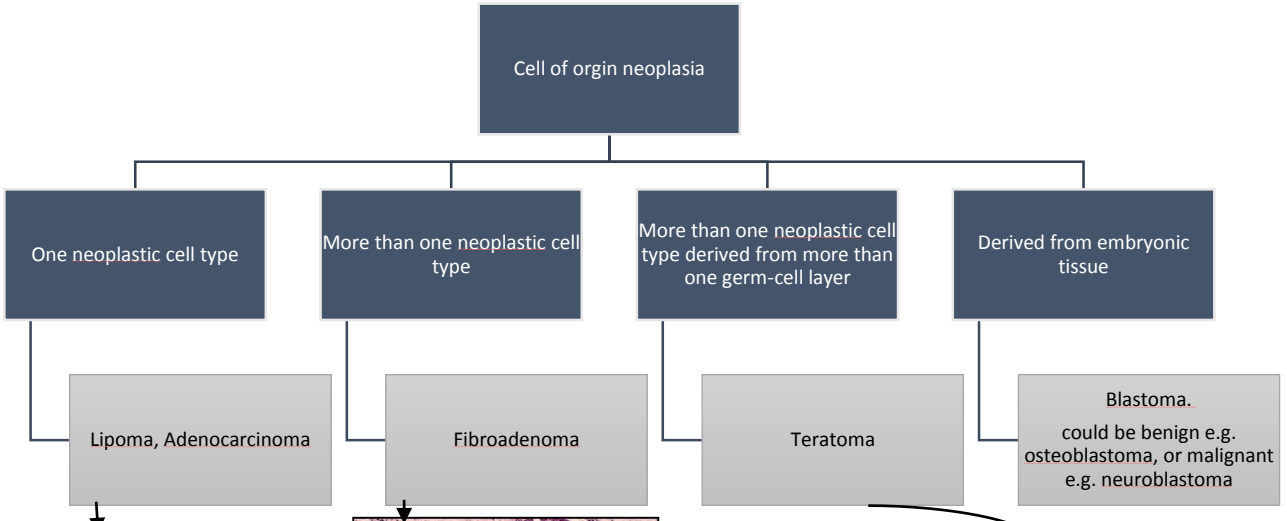
Exceptions for nomenclature:
The name of these exceptions shows that they are benign tumors **BUT** in fact they are malignant.
For example:

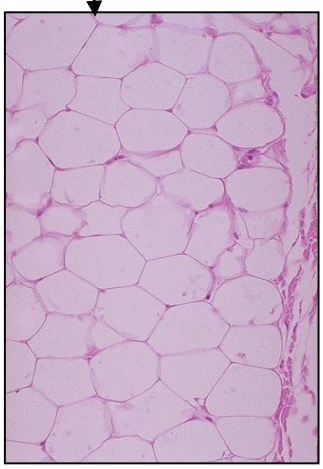
- Melanoma (skin): The benign tumor of melanocytes called nevus.
- Mesothelioma (mesothelium): Mesothelium: lining the body cavities of the body
- Hepatoma (Liver cells)
- Seminoma (Testis)
- Lymphoma (Lymphoid tissue)

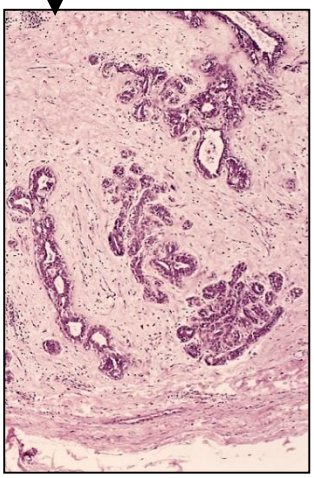
Osteosarcoma

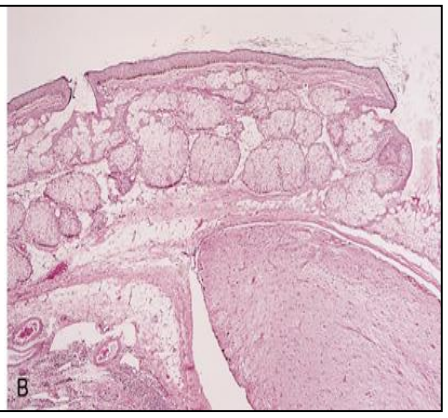


3rd: Types of tumors based on cell of origin.









Teratoma:

- *Teratoma contains recognizable mature or immature cells or tissues representative of more than one germ-cell layer and sometimes all three.*
- *Teratomas originate from totipotential cells such as those normally present in the ovary and testis.*
- *Such cells have the capacity to differentiate into any of the cell types found in the adult body. So they may give rise to neoplasms that mimic bone, epithelium, muscle, fat, nerve and other tissues.*
- *Most common sites are: ovary & testis*
- *If all the components parts are well differentiated, it is a benign (mature) teratoma. If less well differentiated, it is an immature (malignant) teratoma.*

WHAT ARE HAMARTOMAS AND CHORISTOMA?

THEY ARE **Malformation** and **not neoplasm.**

They are distinguished from neoplasms by the fact that they do not exhibit continued growth. They are group of tumor-like tissue masses which may be confused with neoplasms.

Hamartoma: A mass composed of cells native to the organ
e.g. pulmonary hamartoma.

Choristoma: a mass composed of normal cells in a wrong location
e.g. pancreatic choristoma in liver or stomach.

4th: Dysplasia.

A NON-NEOPLASTIC caused by loss in the uniformity of the individual cells and a loss in their architectural orientation that occur mainly in the epithelia.

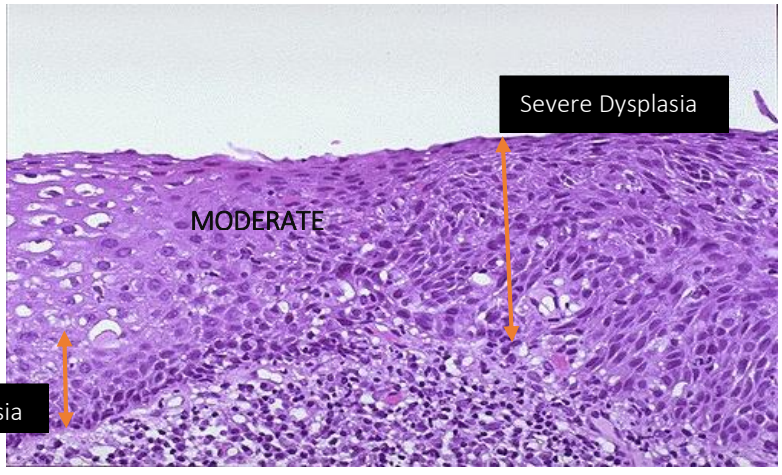
Features:

1- Pleomorphism.
2- Hyperchrmsia.
3- Increased mitosis.
4- Loss of polarity.
5- Disordered maturation.
6- Nuclear abnormality:

- Increased N/C ratio.
- Irregular nuclear membrane.
- Increased chromatin content.
- Cytoplasmic abnormalities: due to failure of normal maturation.

IMPORTANT NOTES:

- Dysplasia does not mean cancer.
- Dysplasia does not necessarily progress to cancer.
- Dysplasia may be reversible.
- If dysplastic changes involve the entire thickness of the epithelium it is called: **CARCINOMA IN-SITU**



Clinical significance of dysplasia:

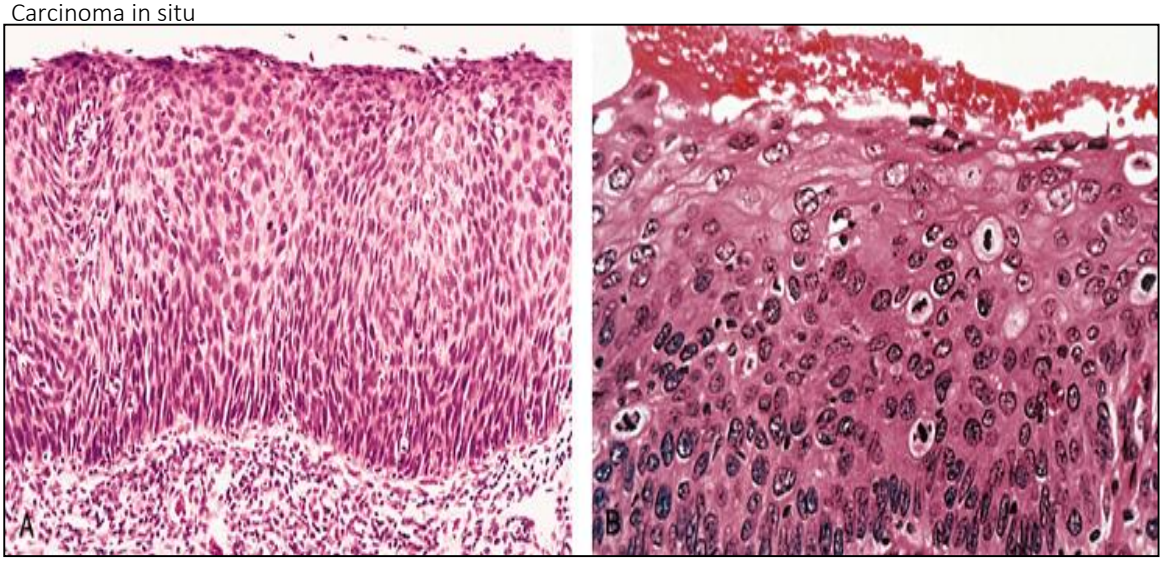
- It is a premalignant condition.
- The risk of invasive cancer varies with:
  1- Grade of dysplasia (mild, moderate, sever).
  2- Duration of dysplasia.
  3- Site of dysplasia.

Differences between dysplasia and cancer: **Lack of invasiveness & Reversibility.**

Carcinoma in-situ:

- *An intraepithelial malignancy in which malignant cells involve the entire thickness of the epithelium without penetration of the basement membrane.*
- *Applicable only to **epithelial neoplasms**.*
- *A true neoplasm with all of the features of malignant neoplasm except invasiveness.*

Carcinoma in situ



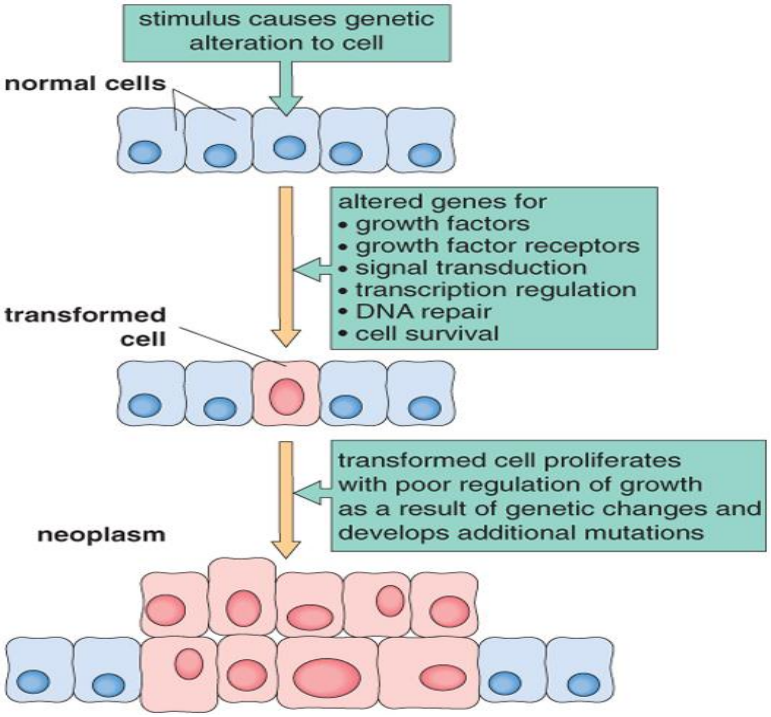
A, Low-power view shows that the entire thickness of the epithelium is replaced by atypical dysplastic cells. There is no orderly differentiation of squamous cells. The basement membrane is intact, and there is no tumor in the subepithelial stroma. B, High-power view of another region shows failure of normal differentiation, marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface.

5th: Carcinogenesis.

It is a multistep process at both the phenotypic and the genetic levels.
It starts with a genetic damage (which lead to mutation) due to:

- Environmental
  - Chemical
  - Radiation
  - Infectious
- Inherited

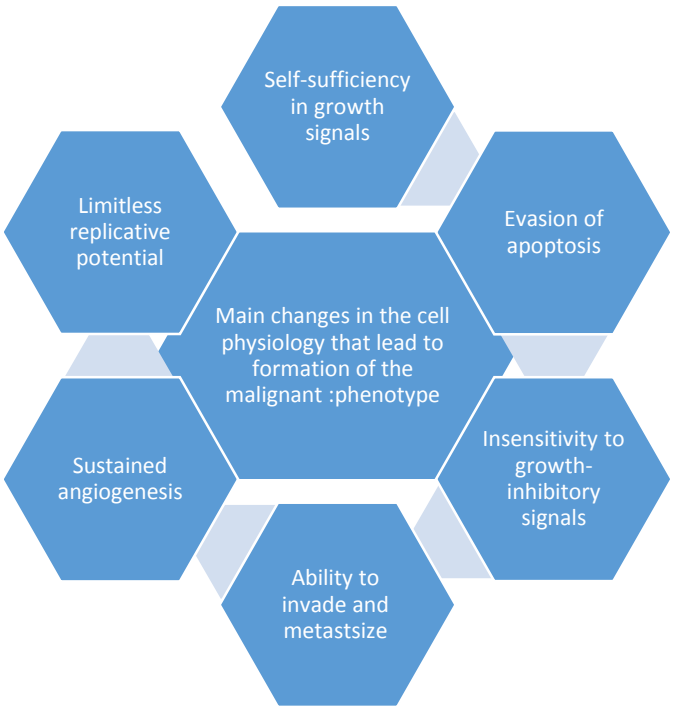
A single cell which has the genetic damage undergoes neoplastic proliferation (clonal expansion) forming the tumor mass.



The Genetic damage targets these regulatory genes:

1. Growth promoting **proto-oncogenes.**
2. Growth inhibiting (supressors) genes.
3. Genes regulating apoptosis.
4. DNA repair genes.

Changes in cell physiology:



Proto-oncogene, oncogene & oncoprotein?

A proto-oncogene is a normal gene that have many different functions in the cell. Some proto-oncogenes provide signals that lead to cell division.
Oncogen is a Gene that promote autonomous cell growth in cancer cells.
Oncoprotein is a protein encoded by an oncogene which can cause the transformation of a cell into a tumor cell if introduced into it.

1- Self-sufficiency in growth signals:

- They are derived by mutations in proto-oncogene

{ Proto-oncogene » mutation » oncogene }

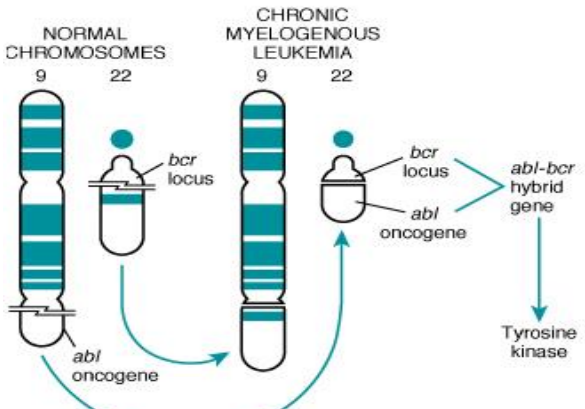
- They are characterized by the ability to promote cell growth in the absence of normal growth-promoting signals.
- The products are **oncoproteins.**

THE MECHANISM:

The Process	Details
1. *Binding of a **growth factor** to its receptor on the cell membrane.*	Growth factors: Cancer cells are capable to synthesize the same growth factors to which they are responsive e.g. 1- Sarcomas » TGF-α 2- Glioblastoma » PDGF
2. *Activation of the **growth factor receptor** leading to activation of signal-transducing proteins.*	Receptors » mutation » continuous signals to cells and uncontrolled growth. Receptors » overexpression » cells become very sensitive » hyper-responsive to normal levels of growth factors. E.g. 1- Epidermal Growth Factor (EGF) Receptor family. 2- HER2: - Amplified in breast cancers and other tumors (most important of them breast and gastric cancer). - High levels of HER2 in breast cancer indicate poor prognosis - Anti- HER2 antibodies are used in treatment (25% of breast cancer cases are positive for HER2).
3. *Transmission of the signal to the nucleus.*	They receive signals from activated growth factors receptors and transmit them to the nucleus. E.g.: RAS & ABL
4. *Induction of the DNA transcription.*	Mutations may affect genes that regulate transcription of DNA » growth autonomy E.g. MYC MYC is a regulator gene that codes for a transcription factor. MYC protooncogene produce MYC protein when cell receives growth signals. MYC protein binds to DNA leading to activation of growth-related genes. Normally, MYC decrease when cell cycle begins, but in tumors there is sustained expression of MYC » continuous proliferation. - Burkitt Lymphoma; MYC is deregulated due to t(8,14). Lymphoma: malignant tumor of lymphoid tissues.
5. *Entry in the cell cycle and cell division.*	Cyclins and [cyclins- dependent kinases (CDKs)] - Progression of cells through cell cycles is regulated by CDKs after they are activated by binding with cyclins. - Mutations that deregulate cyclins and CDKs » cell proliferation. - Cyclin D genes are overexpressed in breast, esophagus and liver cancers. - CDK4 is amplified in melanoma and sarcomas - Cell cycle controlled by cell Cyclins and CDKs. These mediators have genes which responsible to push the cycle temporarily from G1 to S, and they will stop, again ycle is abnormal, they will get the same result. (autonomies cell)

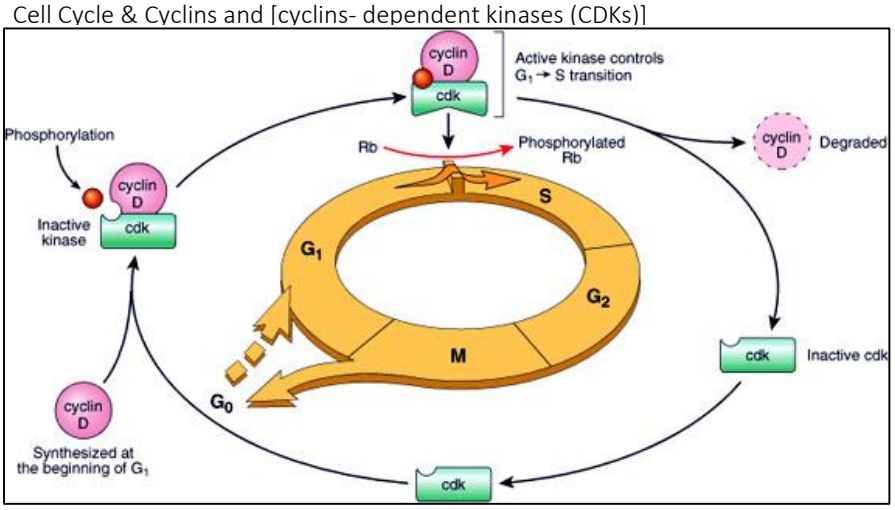
RAS:
- 30% of all human tumors contain mutated RAS gene
- E.g. colon, Pancreas cancers
- Mutations of the RAS gene is the most common oncogene abnormality in human tumors
- Mutations in RAS --- cells continue to proliferate

ABL:
- proto-oncogene has a tyrosine kinase activity
- Its activity is controlled by negative regulatory mechanism E.g. chronic myeloid leukemia (CML) : t(9,22) ---ABL gene transferred from ch. 9 to ch. 22 Fusion with BCR ---> BCR-ABL
BCR-ABL has tyrosine kinase activity(oncogenic)



CML patients are treated with (Gleevec or Glivec) which is inhibitor of ABL kinase
CML: Chronic myelogenous (or myeloid) leukemia
Gleevec: we use it with CML and other tumors in GIT.

Cell Cycle & Cyclins and [cyclins- dependent kinases (CDKs)]

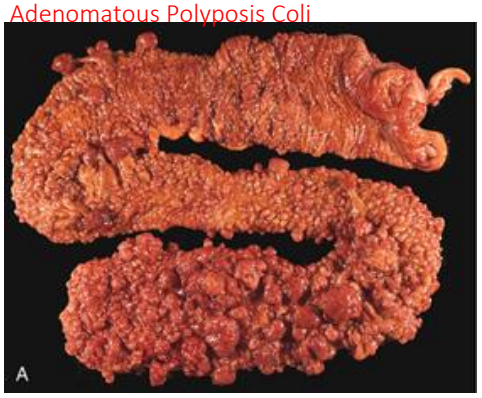


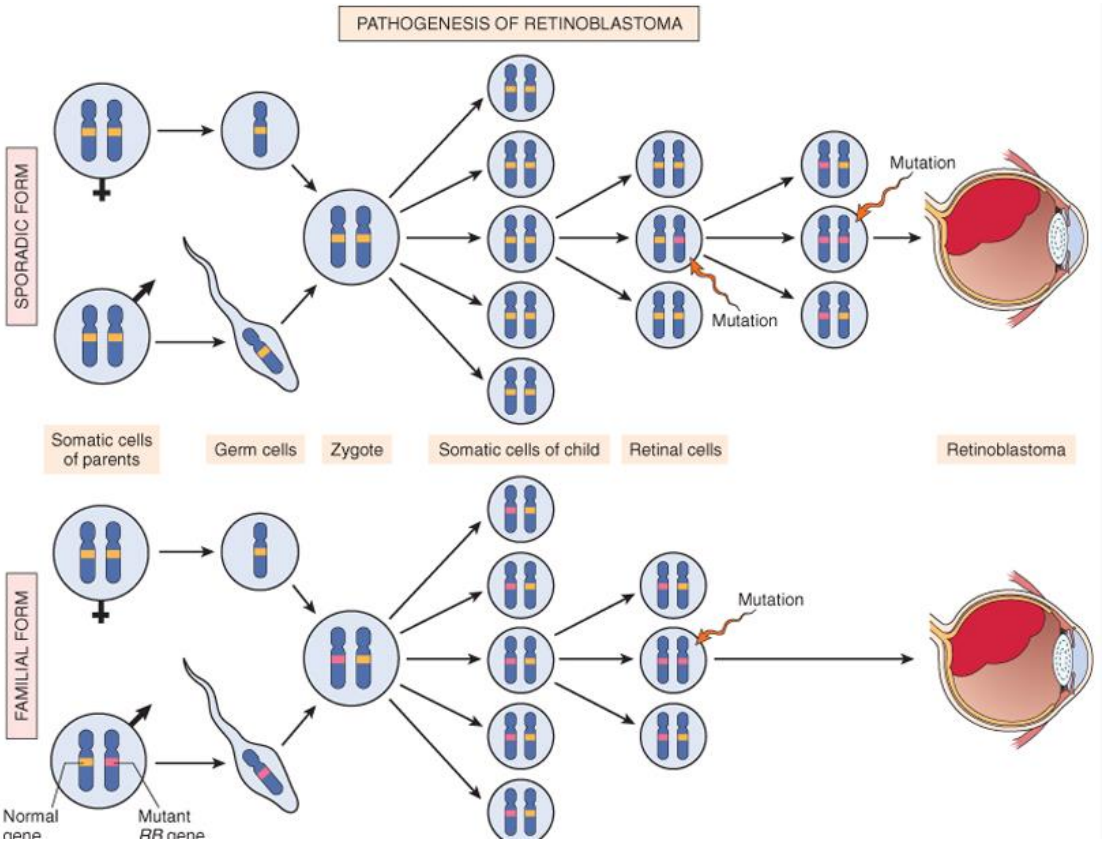
2- Insensitivity to growth-inhibitory signals.

Tumor suppressor genes control (apply brakes) cells proliferation.
If **mutation** caused disruption to them » cell becomes **insensitive** to growth inhibition » uncontrolled **proliferation**
Examples: **APC, RB, TGF-b & P53.**

APC: Adenomatous polyposis coli	**RB (retinoblastoma) gene:**	**Transforming Growth Factor- b pathway: (TGF-b)**	**P53: "The Guardian of the Genome"**
- APC is tumor suppressor gene. - APC **gene loss** is very common in colon cancers. - It has anti-proliferative action through inhibition of b-Catenin that activate cell proliferation. - Individuals with mutant APC develop thousands of colonic polyps One or more of the polyps will progress to colonic carcinoma APC mutations are seen in 70% to 80% of sporadic colon cancers	- First tumor suppressor gene discovered - It was discovered initially in **retinoblastomas**. - Found in other tumors, e.g. breast cancer. - RB gene is a DNA-binding protein located on chromosome **13**. - It exists in " active " and " inactive" forms: 1- If **active »** stop the advancing from G1 to S phase in cell cycle. 2- If cell is stimulated by growth factors **» inactivation** of RB gene **»** brake is released **»** cells start cell cycle [G1 **»** S**»** M] then RB gene is activated again.	- It is an inhibitor of proliferation. - It regulate RB pathway. - Inactivation of TGF-b lead to cell proliferation. - Mutations in TGF-b pathway are present in 100% of pancreatic cancers & 83% of colon cancers.	- It has multiple functions Mainly: - Tumor suppressor gene (anti-proliferative). - Regulates apoptosis. - P53 senses DNA damage. - Causes G1 arrest to give chance for DNA repair. - Induce DNA repair genes If a **cell with damaged DNA** cannot be repaired, it will be directed by P53 to undergo apoptosis. - With loss of P53, DNA damage goes unrepaired. - Mutations will be fixed in the dividing cells, leading to **malignant** transformation.

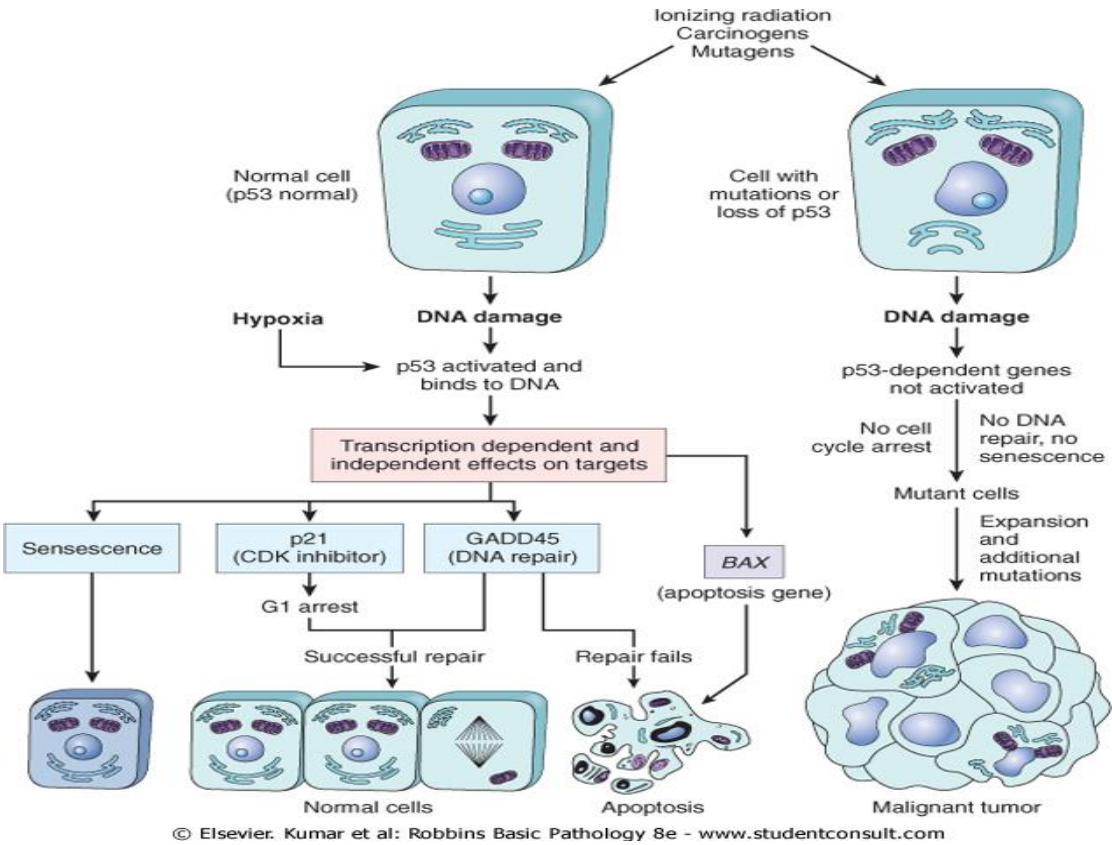
Adenomatous Polyposis Coli



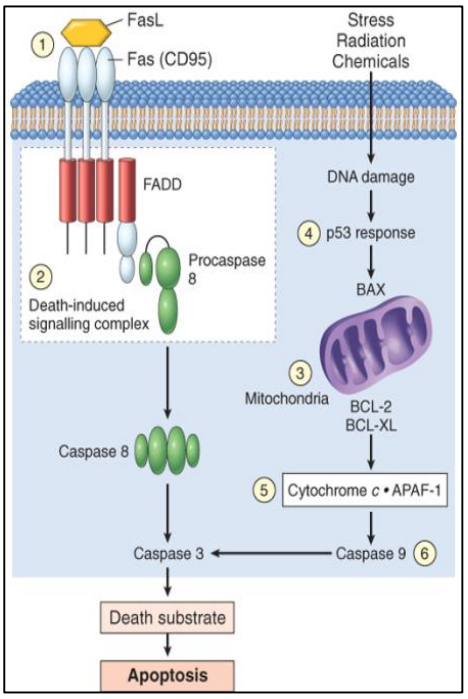


- Retinoblastoma is an uncommon childhood tumor.
- Retinoblastoma is either sporadic (60%) or familial (40%).
- Two mutations required to produce retinoblastoma.
- Both normal copies of the gene should be lost to produce retinoblastoma.

- P53 is called the "**guardian of the genome**".
- 70% of human cancers have a defect in P53.
- It has been reported with almost all types of cancers: e.g. lung, colon & breast.
- In most cases, mutations are **acquired**, but can be **inherited**. E.g. Li-Fraumeni syndrome



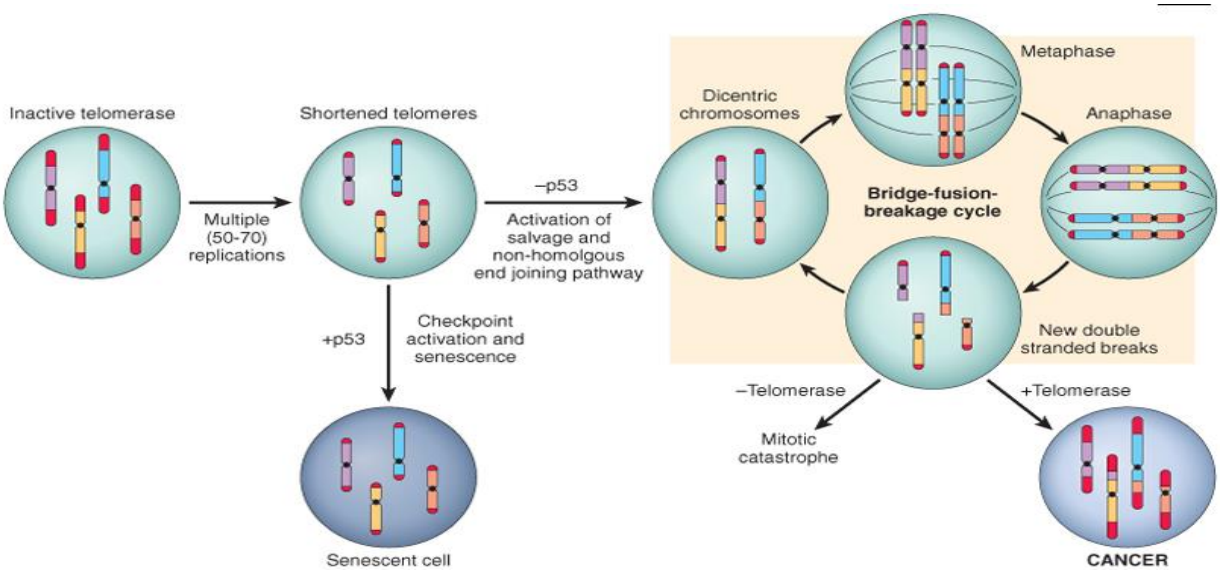
3- Evasion of apoptosis:



- Mutations in the genes regulating apoptosis are factors in malignant transformation.
- Genes that promote and inhibit apoptosis control cell survival.
- Reduced CD95 level inactivate death & induced signaling cascade that cleaves DNA to cause death » tumor cells are less susceptible to apoptosis.
- DNA damage induced apoptosis (with the action of P53) can be blocked in tumors.
- Loss of P53 and up-regulation of BCL2 prevent apoptosis e.g. follicular lymphoma.

4- Limitless replicative potential:

- Normally there is progressive shortening of telomeres at the ends of chromosomes.
- Telomerase is active **in normal stem cells** but absent in somatic cells.
- **In tumor cells**: activation of the enzyme telomerase, which can maintain normal telomere length.



5- Sustained angiogenesis

- Neovascularization has two main effects:
  1- Perfusion supplies oxygen and nutrients.
  2- Newly formed endothelial cells stimulate the growth of adjacent tumor cells by secreting growth factors, e.g. : PDGF, IL-1
- Angiogenesis is required for metastasis

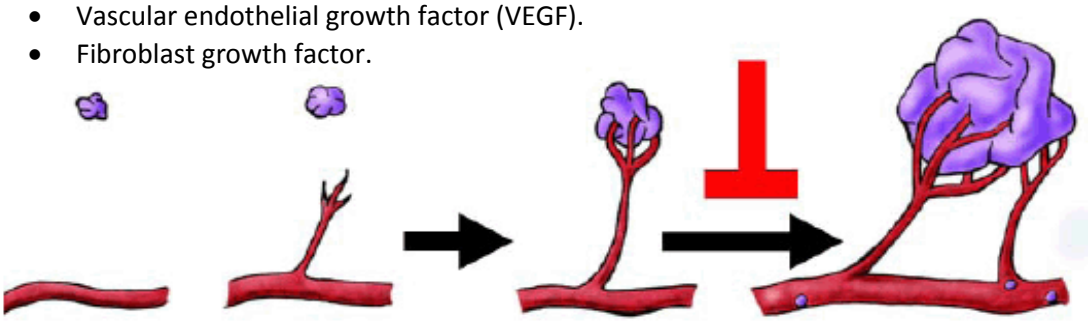
How do tumors develop a blood supply?

Tumor-associated angiogenic factors.

These factors may be produced by tumor cells or by inflammatory cells infiltrating the tumor e.g. macrophages.

Important factors:

- Vascular endothelial growth factor (VEGF).
- Fibroblast growth factor.



6- Ability to invade and metastsize:

Two phases:

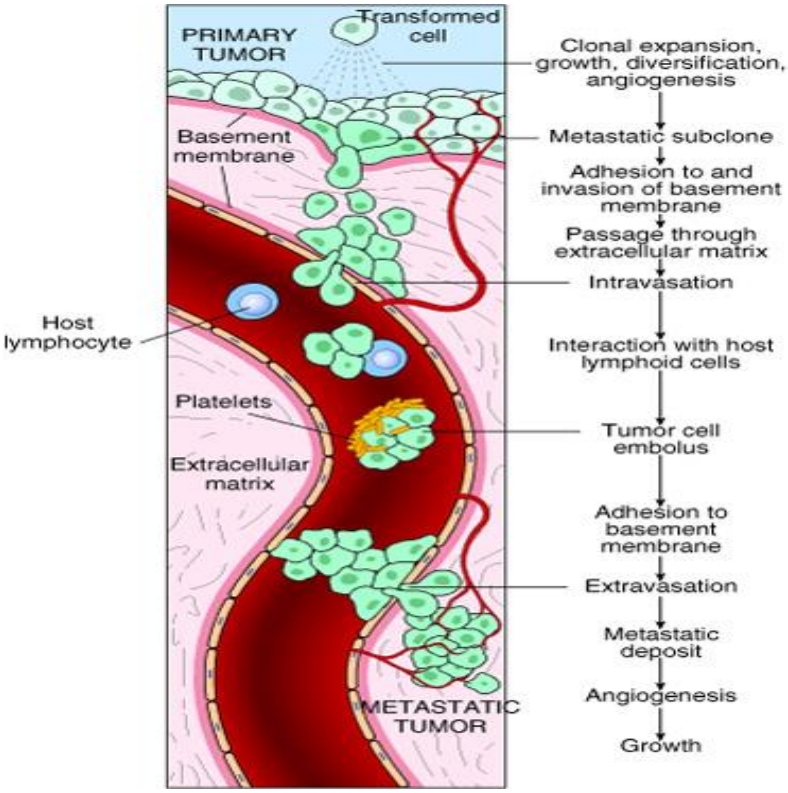
1- Invasion of extracellular matrix
2- Vascular dissemination and homing of tumor cells

Invasion of ECM:

A. Malignant cells first breach the underlying basement membrane
B. Traverse the interstitial tissue
C. Penetrate the vascular basement membrane
D. Gain access to the circulation

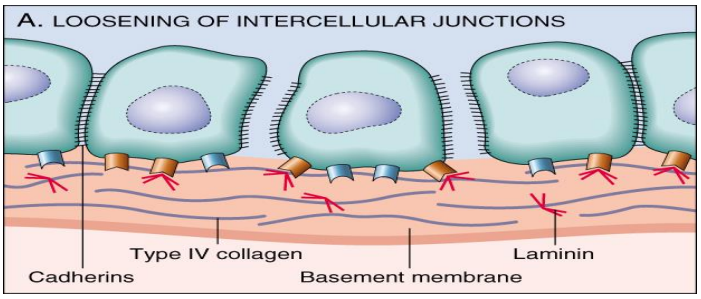
Vascular dissemination and homing of tumor cells:

- May form emboli.
- Most travel as single cells.
- Adhesion to vascular endothelium extravasation.

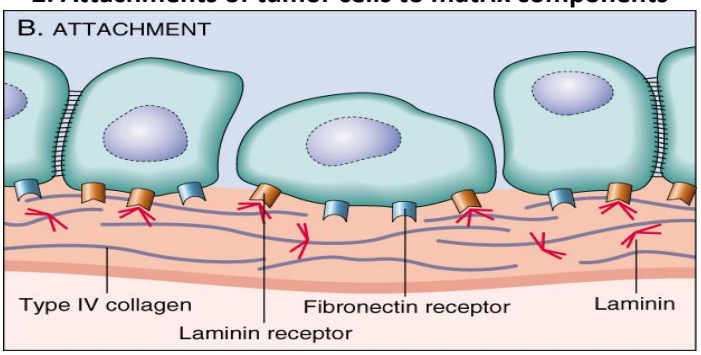


Invasion of the ECM has four steps:

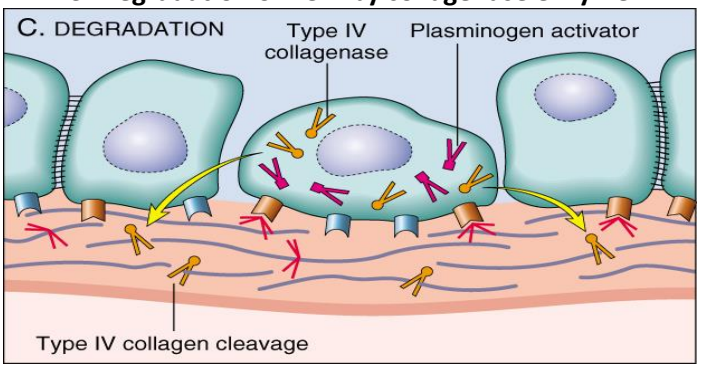
1. Detachment of tumor cells from each other



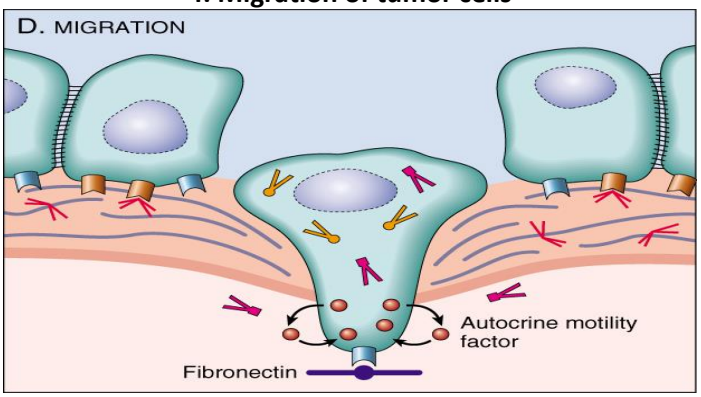
2. Attachments of tumor cells to matrix components



3. Degradation of ECM by collagenase enzyme

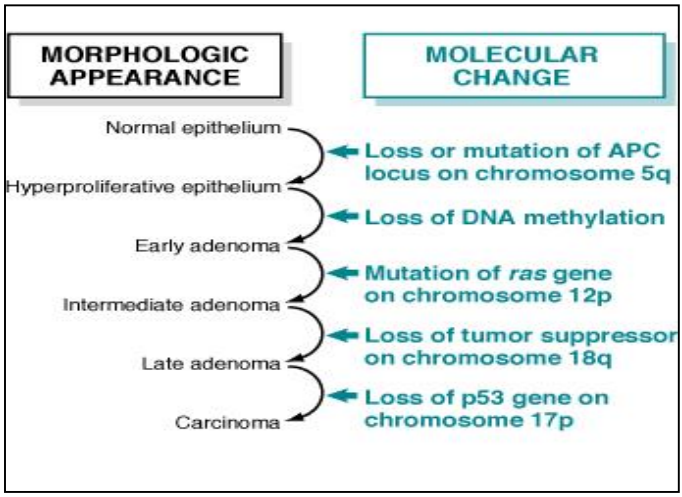


4. Migration of tumor cells



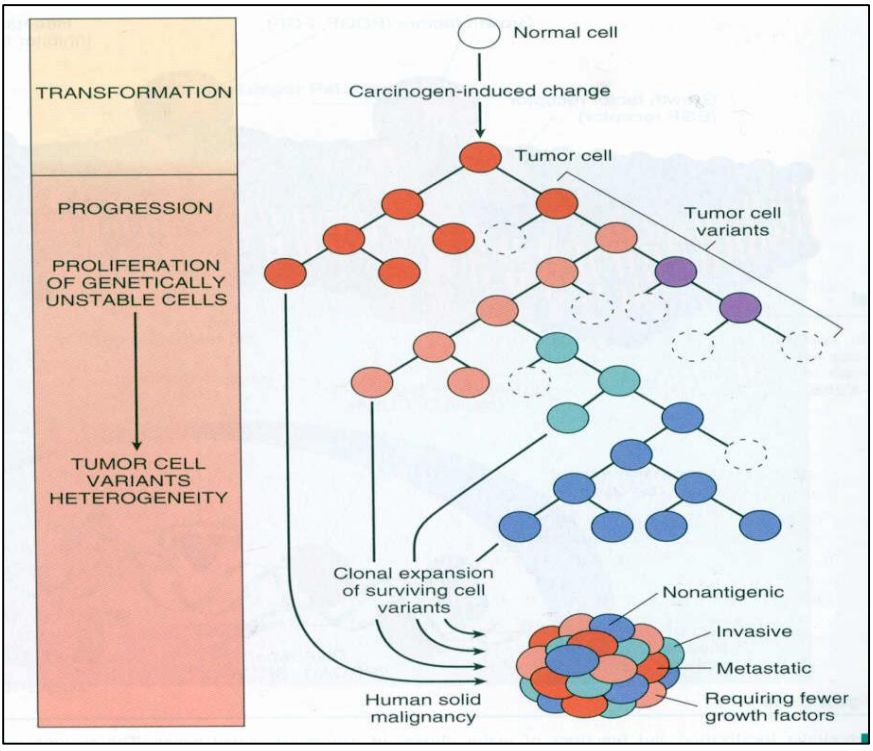
6th: Molecular Basis of multistep Carcinogenesis:

- Cancer results from accumulation of multiple mutations
- All cancers have multiple genetic alterations, involving activation of several oncogenes and loss of two or more tumor suppressor genes



7th: Tumor progression.

- Many tumors become more aggressive and acquire greater malignant potential. This is called "tumor progression" **not increase in size**.
- By the time, the tumor become clinically evident, their constituent cells are extremely heterogeneous.



8th: Genomic Instability.

- Enabling malignancy due to defect in DNA repair genes.

Examples:

1- Hereditary Nonpolyposis colon carcinoma (HNPCC).
2- Xeroderma pigmentosum.
3- **Familial breast cancer.** ⟶

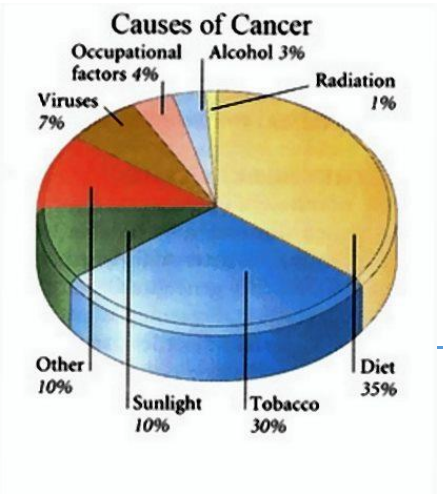
Familial breast cancer:
- Due to mutations in BRCA1 and BRCA2 genes.
- These genes regulate DNA repair.
- Account for 80% of familial breast cancer.
- They are also involved in other malignancies.

9th: Karyotypic Changes in Tumors.

Translocations	In CML: t(9,22) "Philadelphia chromosome” In Burkitt Lymphoma: t(8,14). In Follicular Lymphoma: t(14,18).
Deletions	
Gene amplification	Breast cancer : HER-2

10th: Carcinogenic Agents.

- Chemicals
- Radiation
- Microbial agents



1- Chemical Carcinogens:

- **Natural or synthetic.**
- **Direct reacting or indirect.**
- **Indirect → need metabolic conversion to be active and carcinogenic.**
- **Indirect chemicals are called " procarcinogens " and their active end products are called " ultimate carcinogens"**
- **All direct reacting and ultimate chemical carcinogens are highly reactive as they have electron-deficient atoms. Thus, they react with the electron rich atoms in RNA, DNA and other cellular proteins.**

Mechanism of action of chemical carcinogens:

- Most of them are mutagenic. I.e. cause mutations.
- RAS and P53 are common targets.

Alkylating agents	Polycyclic hydrocarbons:	Aromatic amines : B-naphthylamine	Some azo dyes	Other substances
	- Cigarette smoking. - Animal fats during broiling meats. - Smoked meats and fish.	cause bladder cancer in rubber industries and aniline dye.	used to color food also can cause bladder cancer	- Nitrosamines and nitrosamides are used as preservatives. They cause gastric cancer - Aflatoxin B: prduced by *Aspergillus* (fungi) growing on improperly stored grains. It cause hepatocellular carcinoma

2- Radiation Carcinogenesis:

Radiation has mutagenic effects: chromosomes breakage, translocations, and point mutations.

1- UV rays of sunlight. | **2- X-rays.** | **3- Nuclear radiation.** | **4- Therapeutic irradiations.**

UV rays of sunlight:

- Can cause skin cancers: melanoma, squamous cell carcinoma, and basal cell carcinoma.
- It is capable to damage DNA.
- With extensive exposure to sunlight, the repair system is overwhelmed » skin cancer
- They cause mutations in P53 gene.

3- Viral Carcinogenesis:

- Viral and Microbial onco-genesis:
  - DNA viruses.
  - RNA viruses.
  - other organisms.

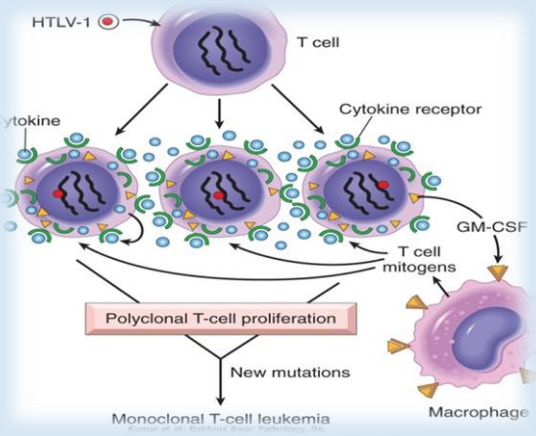
    - carry genes that induce cell replication as part of the viral life cycle
    - host cell has endogenous genes that maintain the normal cell-cycle
    - Viral infection mimics or blocks these normal cellular signals necessary for growth regulation

RNA Oncogenic viruses:

Human T-Cell Leukemia Virus type 1 (HTLV-1)

- RNA retrovirus targets / transforms T-cells
- causes T-Cell leukemia/Lymphoma
- Endemic in Japan and Caribbean
- Transmitted like HIV but only 1% of infected develop T-Cell leukemia/Lymphoma
- 20-30 year latent period

- No cure or vaccine
- Treatment : chemotherapy with common relapse



DNA Oncogenic Viruses:

- **virus DNA forms stable association with host's DNA**
- **transcribed viral DNA transforms host cell**

Examples:

1. **Human papilloma viruses (HPV)**
2. **Epstein-Barr (EBV)**
3. **Hepatitis B (HBV)**
4. **Kaposi sarcoma herpes virus.**

other organisms:

Helicobacter Pylori:

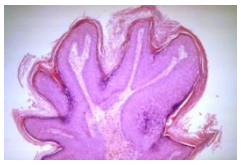
bacteria infecting stomach implicated in:

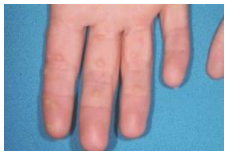
1. **peptic ulcers**
2. **gastric lymphoma**
3. **Mucosal Associated Lymphoid Tumor (MALT)**
4. **gastric carcinoma**

11th: DNA Oncogenic Viruses

❖ Human Papillomavirus (HPV)

- **HPV causing benign tumors:** types 6, 11





- 70 types
- **squamous cell carcinoma of:**
  1. cervix
  2. anogenital region
  3. mouth
  4. Larynx
- **sexually transmitted:**
- **Cervical cancer :** 85% have types 16 and 18
- **Genital warts:** Types 6 and 11.
- **HPV causing malignant tumors:**
- types 16, 18, 31
- vDNA integrates w/ host
- **HPV (types 16 and 18)**
- over-expression of Exon 6 and 7
- **E6 protein binds to Rb tumor suppressor :**
- replaces normal transcription factors
- decreases Rb synthesis
- **E7 protein binds to P53:**
- facilitates degradation of P53
- **HPV infection alone is not sufficient**

other risk factors:

- cigarette smoking
- coexisting infections
- hormonal changes

❖ Epstein-Barr Virus

- common virus worldwide
- Infects B lymphocytes and epithelial cells of oropharynx.
- causes infectious mononucleosis.
- EBV infection may cause malignancy .

1. **Burkitt's Lymphoma**
2. **B cell lymphoma in immunosuppressed**
3. **Nasopharyngeal carcinoma**

Nasopharyngeal carcinoma:

- **Cancer of nasopharygeal epithelium.**
- **Endemic in South China, parts of Africa.**
- **100% of tumors contain EBV genome in endemic areas.**

Burkitt Lymphoma:

- **highly malignant B cell tumor**
- **sporadic rare occurrence worldwide**
- **most common childhood tumor in Africa**
- **all cases have t(8:14)**
- **causes B lymphocyte cell proliferation**
- **loss of growth regulation**
- **predisposes to mutation, esp. t(8:14)**

❖ Hepatitis B virus (HBV)

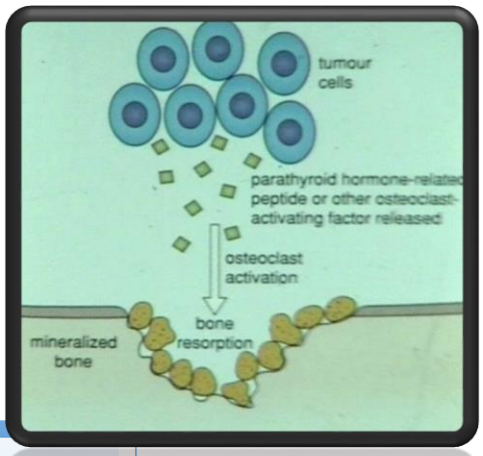
- **Strong association with Liver Cancer**
- **World-wide, but HBV infection is most common in Far East and Africa**
- **HBV infection incurs up to 200-fold risk to hepatocellular carcinoma**

12th: Host defense.

- **Tumor Antigens:**
  - Tumor-specific antigens: present only on tumor cells.
  - Tumor-associated antigens: present on tumor cells and some normal cells.

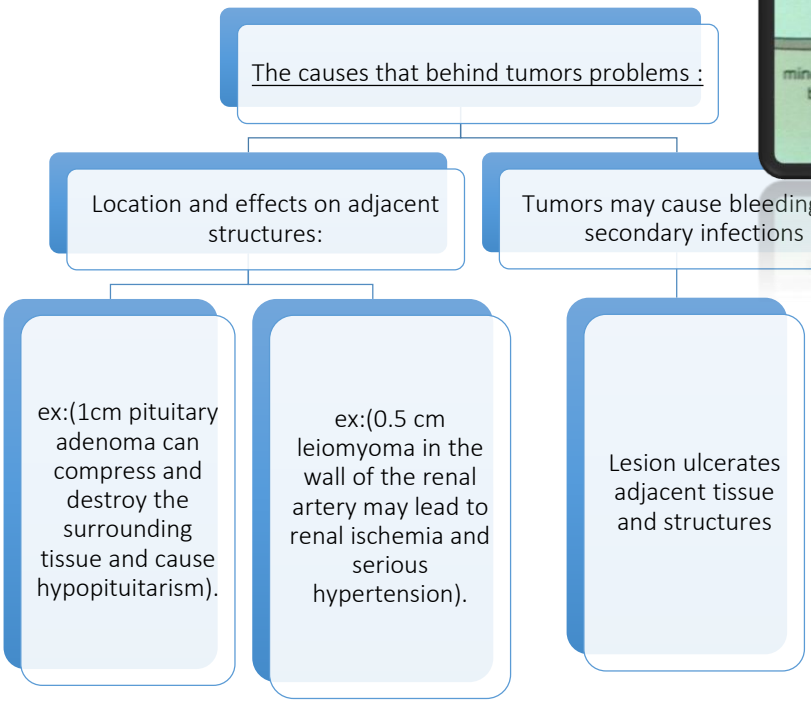
- **Tumor antigens may:**
  - Result from gene mutations: P53, RAS.
  - Be products of amplified genes: HER-2.
  - Viral antigens: from oncogenic viruses.
  - Be differentiation specific: PSA in prostate.
  - Onco-fetal antigens: CEA (especially large intestine cancer), Alpha-fetoprotein.
    - Normal embryonic antigen but absent in adults, and some tumors it will be re-expressed, e.g.: colon cancer, liver cancer.

- **Antitumor mechanisms involve:**
  - Cytotoxic T lymphocytes
  - Natural killer cells
  - Macrophages
  - Humoral mechanisms:
    - Complement system
    - Antibodies



13th: Clinical feature

- Effect of a tumor on the host
  - Secondary fracture: in weak bones.



- **Effects on functional activity (**Usually such activity is associated with **benign** tumors more than carcinomas.)

  - hormone synthesis occurs in neoplasms arising in endocrine glands:

1- Adenomas and carcinomas of β cells of the islets of the pancreas produce **hyperinsulinism.**

2- Some adenomas and carcinomas of the **adrenal cortex** elaborate corticosteroids.

  - **Aldosterone** induces sodium retention, hypertension and hypokalemia.

Cancer cachexia

- Usually accompanied by weakness, anorexia and anemia.
- Severity of cachexia, generally, is correlated with the size and extend of spread of the cancer.
- The origins of cancer cachexia are multifactorial:
  - anorexia (reduced calorie intake)
  - increased basal metabolic rate and calorie expenditure remains high.
  - **general metabolic disturbance**

Paraneoplastic syndromes:

- They are symptoms that occur in cancer patients and cannot be explained.
- They are diverse and are associated with many different tumors.
- They appear in 10% to 15% of patients.
- They may represent the earliest manifestation of an occult neoplasm.
- They may represent significant clinical problems and may be lethal.
- They may mimic metastatic disease.

- **The most common paraneoplastic syndrome are:**
  - Hypercalcemia.
  - Cushing syndrome.
  - Nonbacterial thrombotic endocarditis.
- **The most often neoplasms associated with these syndromes:**
  - Lung and breast cancers and hematologic malignancies.

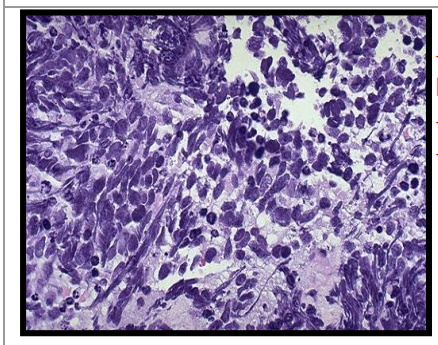
Paraneoplastic Syndromes

Syndrome	Mechanism	Example
Cushing's Syndrome	ACTH -like substance	Lung oat cell carcinoma
Hypercalcemia	Parathormone -like substance	- Lung squamous. - Cell carcinoma. - Renal cell carcinoma. - Breast carcinoma.

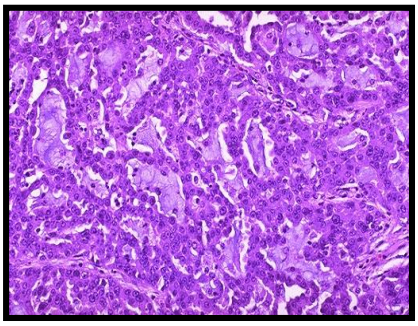
14th: Grading and Staging:

Grading

Grading of Malignant Neoplasms	
Grade	**Definition**
I	Well differentiated
II	Moderately differentiated
III	Poorly differentiated
IV	Nearly anaplastic



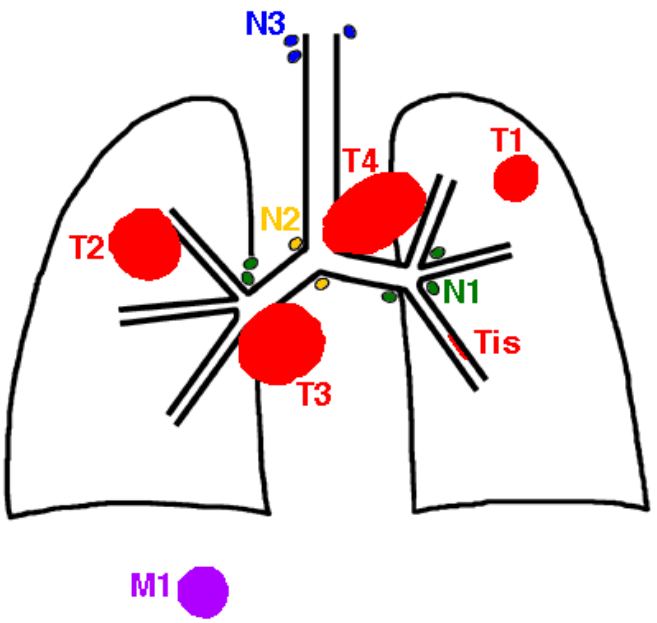
- Oat cell carcinima of the lung.
- Undifferenciated carcinoma.
- Grade IV.



- Adenocarcinoma of the colon.
- Well differentiated carcinoma.

Staging

Grading of Malignant Neoplasms	
Stage	**Definition**
T (primary tumor): T1, T2, T3, T4	Size(T)
N0, N1, N2, N3	Regional lymph nodes involvement
M0: There is no metastasis. **M1: There is metastasis.**	Presence or absence of distant metastasis (M)



Poorly differentiated neoplasms: have cells that are difficult to recognize as to their cell of origin.

Higher grade means a lesser degree of differentiation and the worse the biologic behavior. (Aggressive)

Oat cell: any of the small round or oval cells with a high ratio of nuclear protoplasm to cytoplasm that resemble oat grains and are characteristic of a small-cell lung cancer.

TNM system

Staging of Malignant Neoplasms	
Stage	**Definition**
Tis	In situ, non-invasive (confined to epithelium)
T1	Small, minimally invasive within primary organ site
T2	Larger, more invasive within the primary organ site
T3	Larger and/or invasive beyond margins of primary organ site
T4	Very large and/or very invasive, spread to adjacent organs
N0	No lymph node involvement
N1	Regional lymph node involvement
N2	Extensive regional lymph node involvement
N3	More distant lymph node involvement
M0	No distant metastases
M1	Distant metastases present

15th:Laboratory Diagnosis

Morphologic methodes	Biochemical assays	Molecular diagnosis
- The gold standard of cancer diagnosis. - Several sampling approaches are available: ▪ **Excision or biopsy** ○ Frozen section ▪ fine-needle aspiration ▪ Cytological smears	- Useful for measuring the levels of tumor associated enzymes, hormones, and tumor markers in serum. - Useful in determining the effectiveness of therapy and detection of recurrences after excision. - Elevated levels may not be diagnostic of cancer (PSA prostate-specific antigen). - Only few tumor markers are proved to be clinically useful, example CEA and α- fetoprotein.	**- Polymerase chain reaction (PCR):** E.g. detection of BCR-ABL transcripts in chronic myeloid leukemia. **- Fluorescent in situ hybridization (fish):** It is useful for detecting chromosomes translocation characteristic of many tumors **Both PCR and Fish can show amplification of oncogenes (HER2 and N-MYC).** **- DNA microarray analysis:** - Expression of thousands of genes are studied. - Different tissue has different pattern of gene expression. - Powerful tool useful for subcategorization of disease e.g. Lymphoma - Confirmation of morphologic diagnosis. - Illustration of genes involved in certain disease and possible therapy.

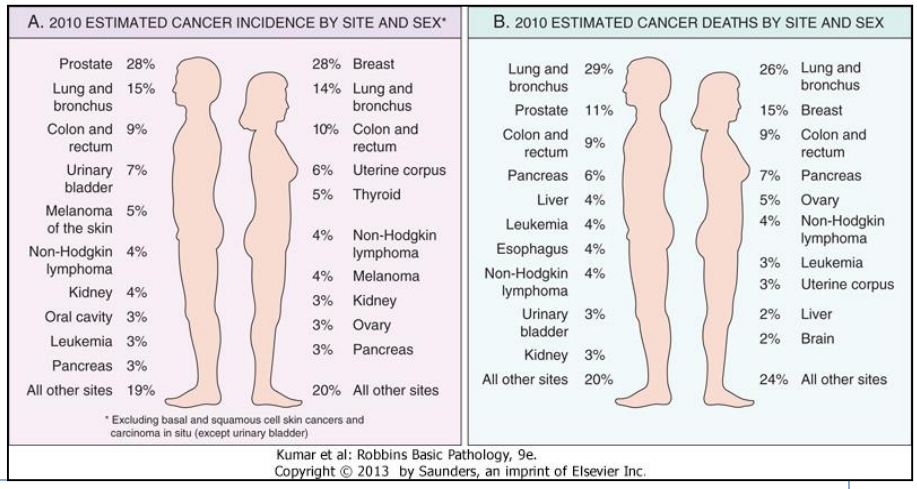
16th: Histological examination.

In the histological examination of a tumor you should look for :

1- Pleomorphism : variation in size
2- High nuclear/ cytoplasm ratio (N/C ratio)
3- Hyperchrmasia (dark cell)
4- Mitosis, abnormal one.

17th: Epidemiology.

- Will help to discover aetiology
- Planning of preventive measures
- To know what is common and what is rare.
- Development of screening methods for early diagnosis



Factor	Details
Geographic	- Rate of stomach carcinoma in Japan is seven times the rate in North America and Europe. - Breast carcinoma is five times higher in North America comparing to Japan - Liver cell carcinoma is more common in African populations.
Environmental	- Asbestos: mesothelioma. - Smoking: lung cancer. - Multiple sexual partners: cervical cancer. - Fatty diets: colonic cancer.
Age	- Generally, the frequency of cancer increases with age. - Most cancer mortality occurs between 55 and 75. - Cancer mortality is also increased during childhood. - Most common tumors of children: Leukemia, tumors of CNS. - Lymphomas, soft tissue and bone sarcomas.
Heredity	**Inherited Cancer Syndromes:** - Inheritance of a single mutant gene greatly increases the risk of developing neoplasm. - E.g. Retinoblastoma in children: 40% of Retinoblastomas are familial carriers of the gene have 10000-fold increase in the risk of developing Retinoblastoma. - E.g. multiple endocrine neoplasia. **Familial Cancers:** - All common types of cancers occur in familial form - E.g. breast, colon, ovary, brain - Familial cancers usually have unique features: 1- Start at early age. 2- Multiple or bilateral. 3- Two or more relatives.
Acquired preneoplastic disorders:	Some Clinical conditions that predispose to cancer: - Dysplastic bronchial mucosa in smokers » lung carcinoma. - Liver cirrhosis » liver cell carcinoma. - Margins of chronic skin fistula » squamous cell carcinoma.

18th: Cases

1- A 44-year-old woman notes a lump in her left breast while taking a shower. Her physician notes a 3 cm firm, irregular, non-movable mass located in the upper outer quadrant of her left breast on physical examination. A fine needle aspiration of this mass is performed. Cells obtained from the mass are examined cytologically and are consistent with infiltrating ductal carcinoma. The mass is removed with lumpectomy along with an axillary lymph node dissection. **Which of the following findings will best predict a better prognosis for this patient?**

A. The tumor cells are strongly estrogen receptor positive.
B. No metastasis are found in the sampled lymph nodes.
C. Flow cytometric analysis demonstrates aneuploidy and a high S-phase.
D. She has one relative who had a similar type of breast cancer.
E. The tumor has a high grade.

2- A 45-year-old healthy woman has a routine check of her health status. She has no chest pain, cough, or fever. A chest x-ray taken and shows a peripheral 2.5 cm diameter "coin lesion" in the right mid-lung field. **Which of the following biologic characteristics best distinguishes this lesion as a neoplasm, rather than a granuloma?**

A. Recurrence following excision
B. Rapid increase in size
C. Sensitivity to radiation or chemotherapy
D. Uncontrolled (autonomous) growth
E. Necrosis

3- A 48-year-old woman goes to her physician for a routine physical examination. A 4 cm diameter non-tender mass is palpated in her right breast. The mass appears fixed to the chest wall. Another 2 cm non-tender mass is palpable in the left axilla. A chest radiograph reveals multiple 0.5 to 2 cm nodules in both lungs. **Which of the following classifications best indicates the stage of her disease?**

A. T1 N1 M0
B. T1 N0 M1
C. T2 N1 M0
D. T3 N0 M0
E. T4 N1 M1

4- A study is performed to analyze characteristics of malignant neoplasms in biopsy specimens. The biopsies were performed on patients who had palpable mass lesions on digital rectal examination. **Of the following microscopic findings, which is most likely to indicate that the neoplasm is malignant?**

A. Pleomorphism
B. Atypia
C. Invasion
D. Increased nuclear/cytoplasmic ratio
E. Necrosis

5- Review of a series of surgical pathology reports indicates that a certain type of neoplasm is graded as grade I on a scale of I to IV. Clinically, some of the patients with this neoplasm are found to be stage I. **Which of the following is the best interpretation of a neoplasm with this stage I designation?**

A. Is unlikely to be malignant
B. Has probably arisen from epithelium
C. May spread via lymphatics
D. Has an in situ component
E. Is well-differentiated and localized

6- A child is born with a single functional allele of a tumor suppressor gene. At the age of five the remaining normal allele is lost through a point mutation. As a result, the ability to continue the transition from G1 to the S phase of cell cycle is lost. **Which of the following neoplasms is most likely to arise via this mechanism?**

A. Infiltrating ductal carcinoma of breast
B. Small cell anaplastic carcinoma of the lung
C. Retinoblastoma of eye
D. Cerebral astrocytoma
E. Chronic myeloid leukemia

7- A 50-year-old man has felt vague abdominal discomfort for the past 4 months. On physical examination he has no lymphadenopathy, and no abdominal masses or organomegaly can be palpated. Bowel sounds are present. An abdominal CT scan shows a 20 cm retroperitoneal soft tissue mass obscuring the left psoas muscle. A stool specimen tested for occult blood is negative. **Which of the following neoplasms is this man most likely to have?**

A. Melanoma
B. Hamartoma
C. Adenocarcinoma
D. Lymphoma
E. Liposarcoma

8- A 52-year-old man has had increasing fatigue for the past 6 months. On physical examination he has a palpable spleen tip. Laboratory studies show a WBC count of 189,000/microliter. The peripheral blood smear shows many mature and immature myeloid cells present. Cytogenetic analysis of cells obtained via bone marrow aspiration reveals a t(9:22) translocation. This translocation leads to formation of a hybrid gene that greatly increases tyrosine kinase activity. **Which of the following genes is most likely translocated to cause these findings?**

A. p53
B. Rb
C. c-abl
D. NF-1
E. k-ras

Answers

1- The answer is **B.** The lack of metastasis suggests a lower stage and a better prognosis.
2- The answer is **D**. A neoplasm is new, uncontrolled growth of cells.
3- The answer is **E.** She has a large invasive primary tumor mass with axillary node and lung metastasis.
4- The answer is **C**. Metastasis would be an even better indicator, but invasion suggests malignancy more than the other items listed here.
5- The answer is **E.** A well-differentiated and localized neoplasm usually has both a low grade and stage.
6- The answer is **C**. The Rb gene is the classic example of the 'two hit' mechanism for loss of tumor suppression. About 60% of these tumors are sporadic, while others are familial, and there is inheritance of a mutated copy of the Rb gene. Loss of the second copy in retinoblasts leads to the occurrence of retinoblastoma in childhood.
7- The answer is **E.** Sarcomas are big and bad. Retroperitoneum is a typical location.
8- The answer is **C**. This is the 'Philadelphia chromosome' of chronic myelogenous leukemia.

19th: General Questions.

Q1) Identify the types of carcinoma that can result from infection with the following DNA viruses.

1- Epsten –Barr virus (EBV)

Burkkit lymphoma, nasopharyngeal cancer.

2- Human papilloma virus (HPV)

Cervical cancer

3- Hepatitis B

Hepatocellular cancer

Q2) What is retrovirus?

An RNA virus that replicates by forming DNA via reverse transcriptase.

Q3) Name the following tumors:
Benign tumor of glandular breast tissue:

Breast cancer

Benign tumor of bone:

Osteoma

Malignancy of bone:

Osteosarcoma