Step pathology

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Pathpedia

Neoplasia

Neoplasia

Abnormal mass of tissue, its growth exceeds normal rate & persist after cessation of stimuli, neoplastic cells are transformed cells that depend on normal cells for their metabolic needs

Benign

- Localized, don't spread, amenable to local resection

Epithelium:

Surface epithelium
- » Papilloma

Glandular or secretory
- » Adenoma

Mesenchymal:

Fat
- » Lipoma

Fibrous tissue
- » Fibroma

Smooth muscles
- » Leiomyoma

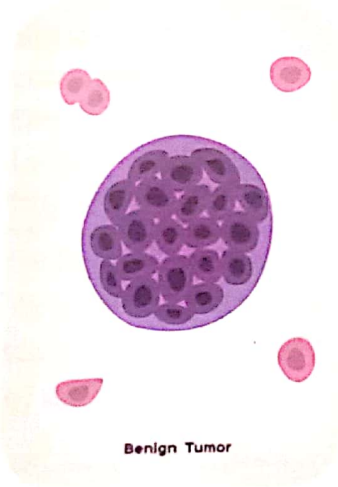
Striated muscles
- » Rhabdomyoma

Cartilage
- » Chondroma

Bone
- » Osteoma

Blood vessels
- » Haemangioma

Lymph vessels
- » Lymphanigoma



Benign Tumor

Malignant

- Can invade & destroy adjacent structures, metastasized, lead to death

Epithelium carcinoma:

Surface epithelium
- » SCC
- » Basal CC
- » Transitional CC

Glandular or secretory
- » Adenocarcinoma
- » Mucoidcarcinoma
- » Signet ring carcinoma

Mesenchymal sarcoma:

Fat
- » Liposarcoma

Fibrous tissue
- » Fibrosarcoma

Smooth muscles
- » Leiomyosarcoma

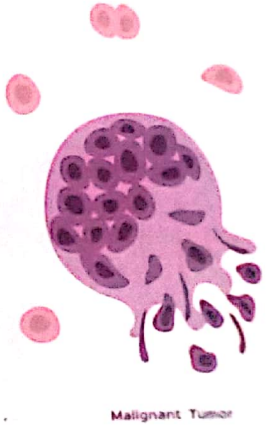
Striated muscles
- » Rhabdomyosarcoma

Cartilage
- » Chondrosarcoma

Bone
- » Osteosarcoma

Blood vessels
- » Angiosarcoma

Lymph vessels
- » Lymphanigosarcoma



Malignant Tumor

Characteristics of tumors

1. Microscopic features

Microscopic pattern

Epithelial:
- Acini / sheets / columns / cords
- Arranged in solid / papillary pattern
- In a vascular CT stroma

Mesenchymal:
- Bundles / whorly / fascicles
- Separated by IC matrix substance

Criteria of malignancy
- *Loss of palrity*
- *Pleomorphism*
- *N:C ratio*
- *Aniso nucleosis*
- *Hyperchromatism*
- *Nucleolar changes*
- *Mitotic figures*
- *Tumor giant cells*
- *Cytoplasmic charges*
- *Chromosomal abnormalities*

Differentiation & anaplasia

Differentiation:
- Extent of morphological & functional resemblance of tumor cells to normal cells

Mixed pattern
» Pleomorphic adenoma → salivary glands
» Fibroadenoma → breast
» Carcionsarcoma → uterus

Benign
» Well-differentiated

Malignant
» Well-differentiated
» Moderate differentiated
» Undifferentiated
» Anaplastic

Anaplasia:
- Dedifferentiation
- Loss of structural & functional differentiation of normal cells failure of differentiation

Tumor angiogenesis & stroma

Angiogenesis:
- Formation of new blood vs from the pre-existing one
- To provide nourishment to a growing tumor

Stroma Collagenous tissue:

Scanty
- Soft-fleshy→ Sarcoma/lymphoma

Excessive
- Hard-grilty → IDC of breast "desmoplasia"
- its growth stimulated by b-FGF secreted by tumor cells

Inflammatory reaction

- Ulceration with 2ry infection
- Cell-mediated immune respons
→ Chronic inflammatory Reactio or granulomatous reaction
e.g.: seminoma

Criteria of malignancy

Cells

Loss of polarity:
- Disrupted orientation of cells
- Nuclei tend to be away from BM

Pleomorphism
- Variation is size & shape of tumor cells
- Pleomorphism & differentiation

Mitotic figures
- Poorly differentiated cells show normal or abnormal mitotic figures "tripolar – qudripolar, multipolar spindles"

Tumor giant cells
- Multinucleated cells
- Giant cells with single large & bizarre nucleus

Functional changes
- *Better diff & normal function e.g.: well differentiated SCC → keratin*
- *Anaplastic SCC → (No) keratin*

Nucleus

↑ Nucelo: cytoplasmic ratio (N:C)
- From (1:4-1:6) to (1:1)

Anisonucleosis "an-iso-nucleois"
- Nuclei show variation in size & shape

Hyperchromatism
- ↑ Amount of nucleoprotein
- Dark stained nuclei

Chromosomal abnormalities
- Most tumors show DNA aneuploidy ↑ number of chromosome → ↑ size of nuclei
- All tumors have abnormal genetic composition & transmit it to their progeny e.g.: Philadelphia chromosome in CML (chronic myeloid leukemia)

Nucleoli

Nucleolar changes:
- ↑ Nuclear protein synthesis
  - » Prominent nucleolus
  - » Multiple nucleoli

Epithelial Dysplasia

Chronic irritation / inflammation:
- Disordered cellular proliferation

Criteria:
- ↑ Number of layers of epithelial cells
- Loss of polarity
- Cellular & nuclear pleomorphism
- Nuclear hyperchromatism
- ↑ N/C ratio
- ↑ Mitotic activity in abnormal location

Classification
- Mild: lower 1/3
- Moderate: lower 2/3
- Severe: > lower 2/3

→ Reversible

Sites: "most common"
- Uterine cervix
- Resp. tract
- GIT mucosa

Carcinoma insitu:
- "preinvasive carcinoma": dysplastic change involving entire epithelial thickness withou invasion of BM

Characteristics of tumors

2. Rate of growth

Benign:
- Slowly
- Months → years

Exceptions:
- **Leiomyoma of uterus**
  - » ↑ by estrogens
  - » ↑↑ during pregnancy
- **Pituitary adenoma**
  - » Locked in sella turcica → Progressive enlargement → Compression of blood supply → Shrinkage & necrosis

Malignant:
- Progressive & rapid
- ***Rapidly growing tumors***
  - » *Central areas of ischemic necrosis*
- ***Some tumors after a period of slow growth***
  - » *Suddenly rapidly growing*
- ***Poorly differentiated***
  - » *Aggressive growth pattern*
- ***Some tumors***
  - » *Disappear spontaneously*
  - » *By necrosis due to host immunity leaving 2ry metastatic implants e.g. choriocarcinoma, malignant melanoma*

3. Local invasion "direct spread"

Benign:
- Localized, doesn't infiltrate or invade surrounding
- Grow by expansion
- Mass with fibrous capsule
- Some are without capsule:
  Leiomyoma of uterus → well demarcated by zone of compressed normal myometrium

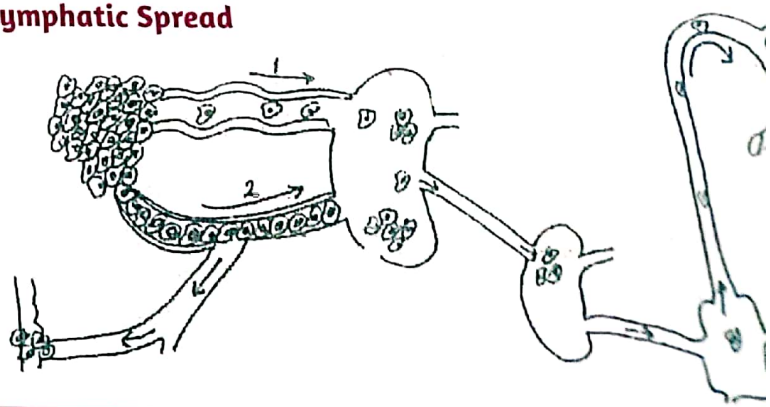
Malignant:
- Infiltrative
- Grow by invasion destruction, penetration
- No capsule
  Some are "partially encapsulated" but M/P reveals infiltration e.g. Follicular carcinoma of thyroid

4. Metastasis "distant spread"

Def.:
Development of 2ry cancerous growth by transmission of cancerous cells from 1ry tumor → remote tissues

- Metastasis & invasiveness are the most important feature to distinguish malignant from benign
- ↑ anaplasia & size → ↑ metastatic spread
- BCC of skin & most CNS tumors → rarely metastasia
- Most osteogenic sarcomas → metastasize to lungs at presentation
- 30% of malignant tumors have evident metastatic deposits at presentation while another 20% have occult metastasis

Lymphatic Spread



Methods of spread of malignant tumors

1. Lymphatic spread

Routes:

- **Lymphatic emboli:**
  - » Malignant cells detach → emboli → along lymph → draining LNs → lodge in sub-capsular sinus → grow → whole LN replaced by tumor
- **Lymphatic permeation**
  - » Tumor cells grow along the lymphatic channel as continuous solid columns to the nearest LN

Generally:

- **Carcinomas** → early lymphatic / **Sarcomas** → early blood
- **Regional LN metastasis:** are the 1st to be involved e.g. carcinoma of breast → axillary lymph nodes first
- but may be "reactive regional lymphadenitis" by necrotic products of tumor and tumor antigens
- **Sentinel LN:** 1st regional lymph node → biopsy help in determination of extent of lymphatic spread
- **Retrograde spread:**
  - » Lymphatic obstruction → spread against flow of lymph
  - » Unusual sites → supraclavicular "Virchow's" LN as in "prostate–colon–stomach" cancers
- **Krukenberg:** bilateral nets in ovaries → stomach – colon – ILC of breast

2. Haematogenous spread

Routes:

- For sarcomas, but some carcinomas (kidney, liver, prostate, thyroid)

Arteries:

- Rarely invaded due to thick wall & elastic lamina
  - » **(Veins)** are frequently invaded → thrombus → emboli

Circulation:

- Systemic → lung
- Portal → liver

Renal cell carcinoma:

- Renal vein → IVC → Rt. Side of the heart

Sites:

- LLBBRR: liver-lung, brain – bone – renal – supra renal

Spleen / heart / SK muscles:

- Generally do not allow tumor metastasis to grow

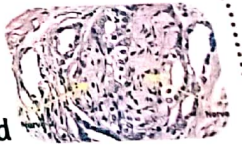
3. Body cavities

Trans coelomic: Spread of malignant cells via seeding of the surface of peritoneal cavity pleural & pericardial spaces. e.g.: (ovarian → peritoneal) (mesothelioma → pleural)

CSF:

- Meduloblastoma – ependymoma → ventricles → CSF → meningeal surfaces within brain or spinal cord

4. Perineural spread



- Neoplastic invasion of nerves
- Painful & has poor prognosis
- Least resistance pathway for tumor growth mediated by: neurotrpophic GFs & metalloproteinases by cancer cells
- **Adenoid cystic carcinoma of saliuary - Protastatic adenocarcinoma**

5. Intra-epithelial spread

- **Breast:** duct → lobules and vice versa
- **Kidney** → ureters → lower urinary tract
- **Endometrium** → Fallopian tube → ovaries

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Features differentiating benign from malignant tumors

Feature	Benign	Malignant
I- Gross features		
· Boundaries	• Encapsulated or well circumscribed	• Poorly-circumscribed & irregular
· Surrounding tissue	• Often compressed	• Usually invaded
II- Microscopic features		
· Differentiation	• Usually well-differentiated & resembles tissue of origin closely	• Range from well to poorly differentiated
· Criteria of malignancy	• Not present	• Present
· Functional changes	• Usually well-maintained	• May be retained, or lost
· Chrom. abnormalities	• Infrequent	• Invariably present
· III- Growth rate:	• Usually slow	• Usually rapid
· IV- Local invasion	• Often compresses the surrounding tissues without invading or infiltrating them	• Usually infiltrate & invade the adjacent tissue
· V- Metastasis	• Absent	• Frequently present
· VI- Prognosis	• Local complications	• Local & metastatic complications

Feature	Carcinoma	Sarcoma
· Origin	• Malignant tumor of epithelial origin	• Malignant tumor of mesenchymal origin
· Vascularity	• Less vascular	• Highly vascular
· Rate & mode of growth	• Less rapid, grows more by infiltration	• Rapid, grows by expansion & infiltration
· Consistency	• Usually firm	• Soft & fleshy
· Cut section	• Grayish white with areas of haemorrhage & necrosis	• Homogenous grey with areas of hge & necrosis
· Microscopic	• Tumor cells are arranged in masses or acini separated by CT stroma	• Highly cellular with scanty stroma separating individu
· Spread	• Early by lymphatic, blood spread is usually late	• Early by blood
Prognosis	• Relatively better	• Worse

Tumors of epithelial tissues

Benign

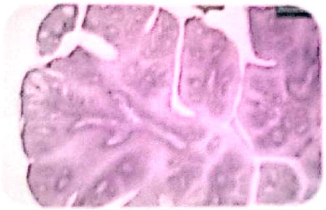
Papilloma

Origin:
- Surface

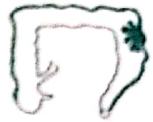
Gross:
- Sessile or pedunculated
- Simple / breached / finger – like, surface may be ulcerated

Microscopic:
- Central vascular CT core covered by surface e.p.: squamous / transitional / columnar

Complications:
- Ulceration
- Hge
- Infection
- Malignancy



Adenoma



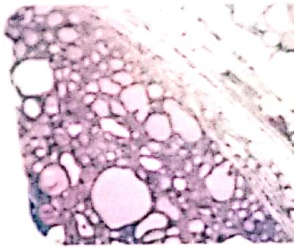
Origin:
- Glandular

Gross:
- Solid organ → well encaps. Mass
- Hollow organ → adenomatous polyp projection into lumen
- Cystadenoma of ovary → cystic mass d.t. accumulated secretion
- Epithelial proliferation in cystic mass → papillary formation e.g. papillary cystadenoma

Microscopic:
- Tissue similar to the gland of its origin

Complications:
- Hyper secretion of hormone
- Malignancy

Sites:
- Endocrine glands: thyroid – adrenal
- MM: GIT – bronchi
- Ovary – breast – sebaceous glands



Squamous cell carcinoma

Sites:

- Squamous epithelium of skin, lip, tongue larynx
- On top of metaplasia: UB-GB

Gross:

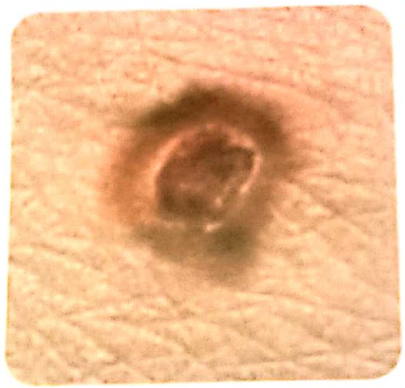
- Fungating mass
- Large malignant ulcer "CCC" by raised everted edges, necrotic floor, hard indurated base
- Infiltrating mass

Microscopic:

- Irregular masses of malignant Cells
- Central keratinization "cell nest"
- Separated by fibrous tissue

Histological broder's grading system:

- *GI: WD "≥50% cell nest"*
- *GII: mod. "25-50%, cell nests"*
- *GIII: poor "<25% cell nests"*
- *GIV: undifferentiated "no cell nest"*



- Most common form of skin cancer arising in the basal cells of epidermis
- Slowly growing (months – years)
- Men are affected twice as often as women
- Although it rarely metastasize it can infiltrate deeper structure (bone → local damage) (rodent ulcer)

Sites:

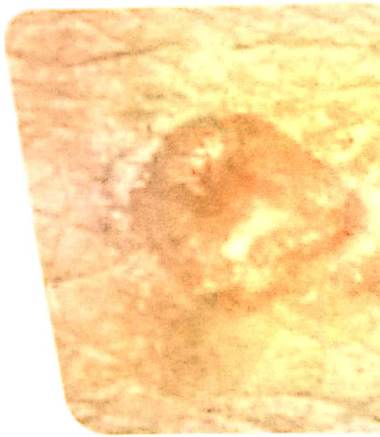
- Skin: face – scalp – back – neck – shoulders – hands
- Face: above the line drawn between angle of mouth and lobule of ear (sun exposed area)

Gross:

- Start as small fleshy nodules → ulceration
- Ulcer has inverted beaded edges with indurated base

Microscopic:

- Dermis → infiltrated by regular masses of basaloid cells with peripheral Palisading nuclei
- Cells → hyperchromatic nuclei & scanty cytoplasm
- Nests of tumor cells → surrounded by fibrous stroma
- Surface ulceration

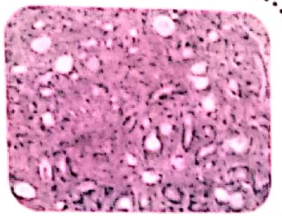


Causes:

- Chronic exposure to sunlight
- Arsenic
- Radiation

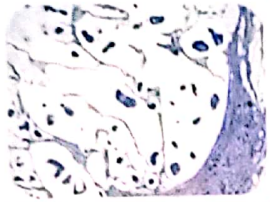
2. Glandular Epithelium

Adenocarcinoma



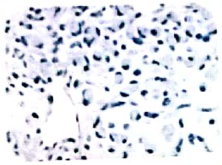
- From glandular epithelium
- WD → malignant acini separated by CT stroma
- Poor differentiated → malignant cells & few acini
  "differentiation depends on number of malignant

Mucoid adenocarcinoma



- Extra-cellular mucin secretion
  - » Colorectal
  - » Breast

Signet ring carcinoma



- Intra-cellular mucin secretion
  - » Gastric carcinoma

Connective tissue tumors

Benign
- Fibroma
- Lipoma
- Chondroma
- Osteoma

Malignant
- Fibro-sarcoma
- Liposarcoma
- Chondrosarcoma
- osteosarcoma

Gross
- Well circumscribed

MP
- Tissue similar to the original tissue

Organ Tropism

- Arrest of tumor emboli in specific organ related to expression of tumor molecules or chemokines by tumor cells whose receptors are expressed on endothelial cells of target organ

e.g.: Cancer (lung, kidney, thyroid, prostate, breast) → bone metastasis
- Bronchus → (liver –adrenal – brain)
- Seminoma → lung
- Sarcomas → lung, liver, bone

Locally Malignant tumors

- Tumor of unknown (behavior – borderline – locally aggressive)
- Definition: group of malignant tumors which spread locally only i.e. there is no distant spread or metastasis.

Examples:
- Basal cell carcinoma of the skin (rodent ulcer)
- Adamantinoma of the jaw
- Carcinoid tumor of the appendix
- Astrocytoma of the brain
- Craniopharyngioma of pituitary gland
- Giant cell tumor of bone (grade I and II)

Tumors of blood vessels

Haemangioma

- M/C: benign neoplasm – (M/C) tumor of infancy or childhood
- Maybe localized or diffuse "angiomatosis"

Capillary

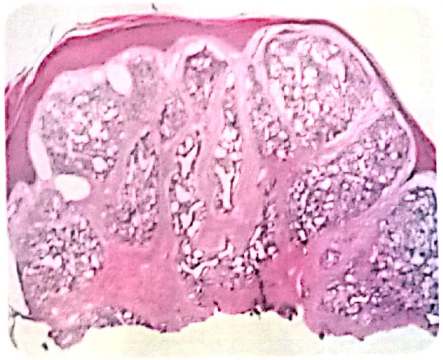
Incidence
- More common

Age
- First few years of life

Site
- Skin, S.C tissue

Gross
- Irregular red patch of skin

MP
- Proliferated capillary – type vessels
- Lined by flattened endothelial cells
- Separated by F.t. stroma



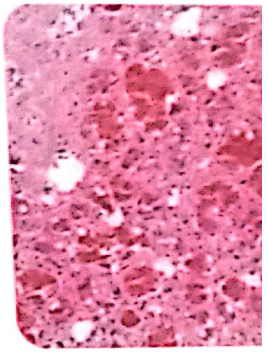
Cavernous

Incidence
- Less common

Site
- Same + internal organs "liver"

Gross
- Ill defined bluish mass

MP
- Large irregular vascular spaces
- Lined by flattened endothelial cells
- Separated by f.t. stroma



Tumors of lymphatics (Cavernous lymphangioma)

Site
- Head, neck, axilla, mediastinum, viscera

M/P
- Large irregular endothelial lined spaces filled with lymph
- Focal lymphocytic infiltrate is noted

Cystic hygroma
- Cavernous lymphangioma of the neck of new born

Tumors of melanocytes

Navus

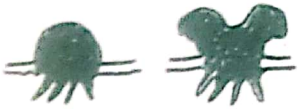
Site
- Skin of face, neck, back, etc...

Gross
- Well – demarcated colored papule
- Papillomatous lesion

MP
- Junctional
- Intradermal
- Compound

Melanoma

Site
- Skin of face, neck, back, etc...



Gross
- Elevated pigmented nodule
- Rapidly grows, tend to ulcer

MP
- Malignant melanocytes containing melanin growing from basal epidermis → dermis

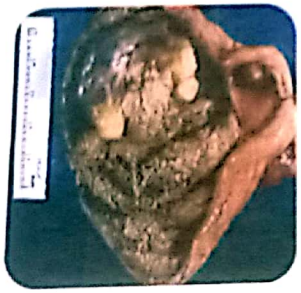
Spread
- Local - lymphatic - blood

Prognosis
- Depends on the depth of invasion

Teratomas

- Tumors originating from totipotent cells (germ cells & embryonic cells)
- Can differentiate into any of cell types: (bone - epithelium - muscle - fat - nerve & other tissues)

Sites
- Germ cells: ovary & testis - congenital or not
- Embryonic rests: "midline": brain - ant. mediastinum - retroperitoneum - sacrococcygeal (congenital)



Types
- **Benign** "mature" well-differentiated
- **Immature:**
  - » Immature "fetal type" tissues, Behave in a malignant fashion
- **Mature teratoma with malignant transformation** rare - M/C: SCC

Monodermal teratoma:

Mature teratoma, consists predominantly of one type of mature tissue

"Struma ovarii" → thyroid tissue

Embryonic tumors "blastomas"

- More common in infants & children < 5 yrs

Examples:
- » Medulloblastoma "cerebellum"
- » Retinoblastoma "retina"
- » Neuroblastoma "adrenal medulla"
- » Nephroblastoma "kidney"
- » Hepatoblastoma "liver"

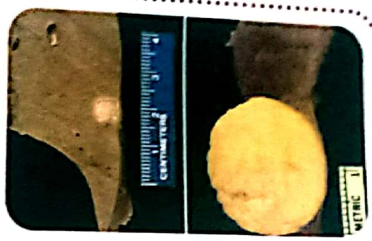
- Primitive embryonal cells which appear round or oval, with dark stained nuclei
- Arise from embryonal or partially diff. cells that hasn't yet fully develop

Choriostoma or heterotopia

- Congenital anomaly
- Normal cells / tissues in abnormal locations
- E.g.: normal pancreatic tissue in stomach or small intestine

Hamartoma

- Tumor-like formation
- Mass of disorganized but mature tissues
- Normally present in the affected part
- Often with 1 element predominating
- Grow at the same rate of surroundings
- Different parts:
  - » Lung → formed of islands of cartilage bronchi, blood vessels → disorganized but mature
  - » Liver → formed of hepatocyte, blood vessels, bile ducts disorganized but mature
- Asymptomatic & discovered accidently



Grading & staging of cancer

Two systems to predict tumor behavior, prognosis & guide therapy

Grading

Histologic / microscopic degree of differentiation

Based on:

- Degree of differentiation
- Number of mitosis within the tumor
  - » Grade I: well-differentiated
  - » Grade II: moderately – differentiated
  - » Grade III: poorly – differentiated
  - » Grade IV: undifferentiated or anaplastic
- This correlates to tumor aggressiveness

Staging

Clinical / extent of spread of tumor

Based on:

- Clinical examination
- Radiological exam: CT., MRI, PET
- Histopathological examination
- TNM system:
  - » T: Primary tumor size
  - » N: Extent of regional LN involvement
  - » M: Metastases
- With greater clinical value than grading

Tis	In situ, non-invasive (confined to epithelium)
T1	Small (<2cm), minimally invasive within primary organ site
T2	Larger (2-5cm), more invasive within the primary organ site
T3	Larger (5-10 cm) &/or invasive beyond margins of primary organ
T4	Very large (>10cm) &/or very invasive, spread to adjacent organs

N0	No LN involvement
N1	Regional LN involvement
N2	Extensive regional LN involvement
N3	More distant LN involvement
M0	No distant metastases
M1	Distant metastases present

Epidemiology & predisposition to neoplasia

1. Cancer incidence

- M/C cancers in ♀ : breast & lung
- M//C cancers in ♂ : prostate & lung
- ↓ Death rate:
- Cancer → d.t. early diagnosis
- Cancer stomach → ↓ expose to dietary Carcinogens

2. Geographic & environmental factors

- Cancer risk (65% environmental – 35% genetic)
- Breast cancer: 4 times in SA > Japan
- Liver cell carcinoma: most lethal cancer in Africa
- e.g.: • Sunlight • Asbestos • Certain occupations & diet
- Smoking & alcohol

3. Age

- Generally; cancer & age
- d.t.: - ↑ somatic mutations
  - ↓ immune response
- Most cancer: 55-75 yrs
- Rate ↑: after 75
- Cancer cause death in 10% of children <15 years

4. Hormones

- Estrogen:
  - » Estrogen therapy / estrogen -secreting tumors → endometrium
  - » OCP → breast & liver cell adenoma
- Anabolic steroids
  - » Benign & malignant tumors of the liver
  - » Gonadal atrophy and infertility in males

5. Familial & genetic factors

Inherited cancer syndromes "autosomal dominant"

- Rb → retinoblastoma (40%)
- NF1&2 → Neurofibromatosis 1&2
- BRCA1&2 → breast & ovary
- P53 → Li-Fraunmenti $
- APC → familial adenomatous polyposis / colon cancer

Inherited AR $ of defective DNA repair

- Xeroderma pignemtosum

Familial cancer

- Breast
- Ovary
- Malignant melanoma
- Colon
- Brain
- Pancreas

6. Acquired pre-neoplastic disorders

- Persistent regenerative cell replication:
  - » SCC: margin of unhealed wound e.g. old burn scar (marjolin's ulcer)
  - » HCC: liver cirrhosis
- Hyperplastic & displastic proliferation:
  - » Endometrial carcinoma → atypical endometrial hyperplasia
  - » Bronchogenic carcinoma → dysplastic bronchial epi. In smokers
- Chronic atrophic gastritis → gastric carcinoma
- Chronic ulcerative colitis → cancer colon
- Leukoplakia of oral cavity & vulva → SCC
- Some benign tumors → villous adenom of colon → adenocarcinoma
  → neuro-fibromatosis → sarcoma

7. Sex

- Generally, cancer more common in males
- Except: breast, GB, thyroid, organs of each sex

Normal, Genes regulating normal growth of cells **4 Classes**

Proto-oncogenes
Normal - growth promoting gene

Anti-oncogenes
Growth suppressor gene

Apoptosis
Regulatory genes
Programmed cell death

DNA repair genes
Repair DNA damage in mitosis of damage of other 3 classes

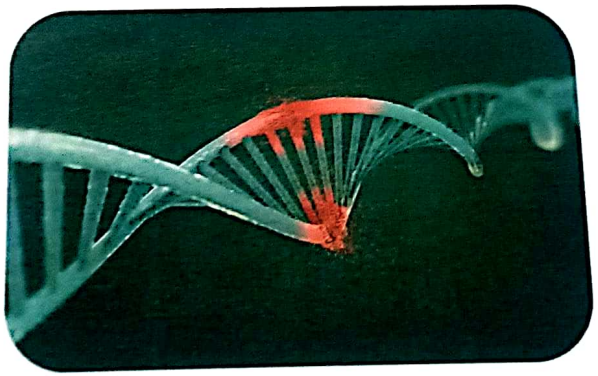
Gene damage

Activation of growth promoting gene
- Proto-oncogene normal → oncogene (mutant)
- Cellular transformation
- Single allele is enough = dominant oncogene
- Product → oncoprotein

Inactivation of tumor suppressor gene (anti-oncogene)
- Proliferation of transformed cells
- Both alleles must be damaged = recessive
- Called promoters → mutation of these gene release cellular proliferation

Alteration in apoptois regulatory genes
- Dominant as oncogenes
- Recessive as suppressor genes

Failure of DNA repair genes
- Failure to repair non lethal DNA damage → mutation spread of one of the previous three classes → neoplastic transformation



Oncogenes

They're genes whose products: oncoproteins, are associated with neoplastic transformation

- Normal proto-oncogenes (normal cell growth genes) transform into oncogenes (cancer cell proliferation gene) by one of three mechanisms:

Structural damage

Point mutation:

- Single base mutation
- e.g. RAS oncogene in cancer lung, colon, pancreas (adenocarcinoma)
  RAS → rat sarcoma gene

Chromosomal translocation:

- Transfer of a chromosomal protein carrying a proto-oncogene → independent of growth control
  - » Philadelphia chromosome in chronic myeloid leukemia C-ABL translocation
    No. 9 → 22
  - » Burkitt lymphoma C-MYC translocation from chromosome
    No. 8 → no. 14
    MYC → from isolated virus myelocytomatosis

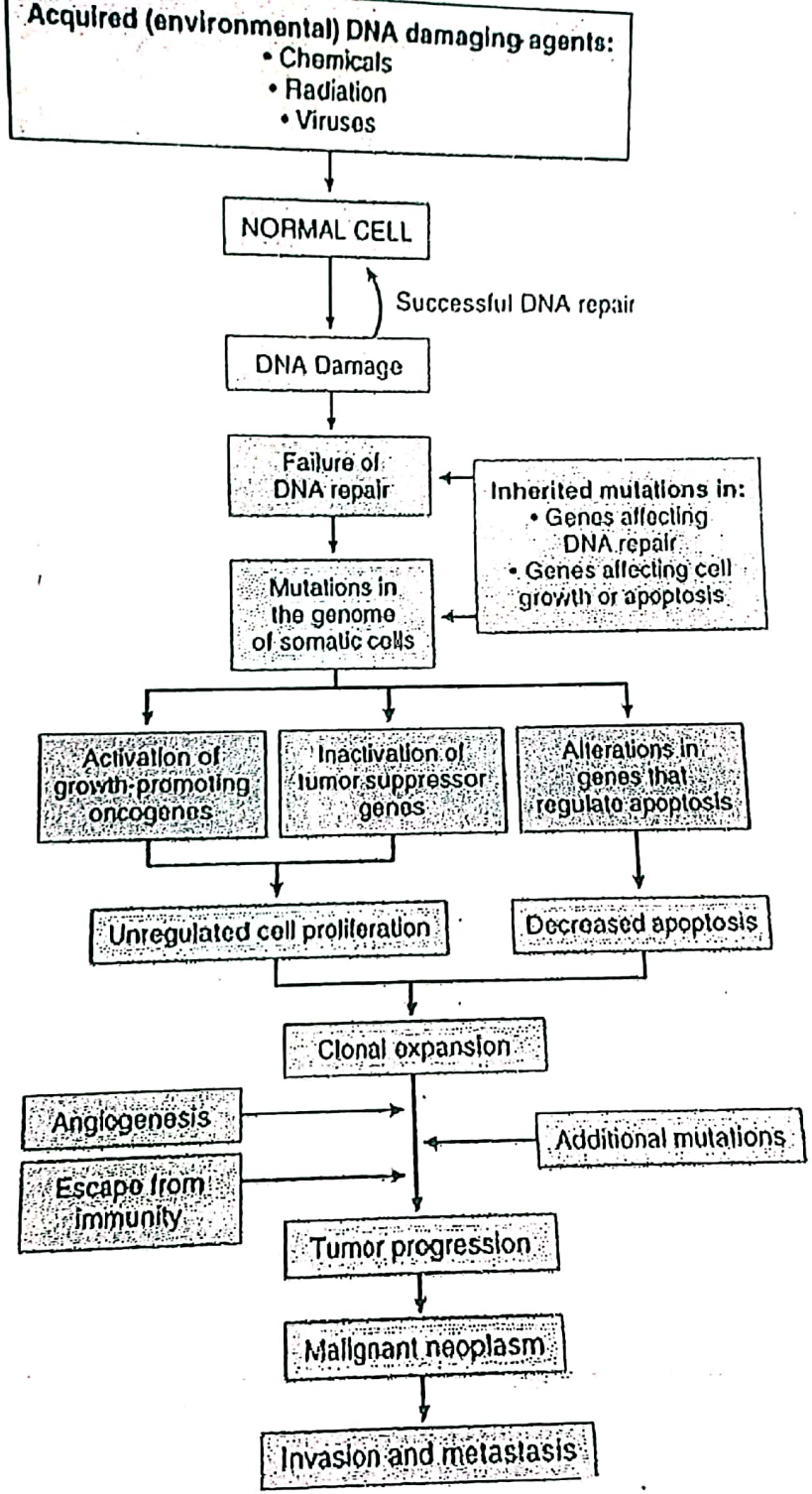
Number

Gene amplification:

- Increase number of copies of DNA sequences in proto-oncogenes → ↑ mRNA → ↑ gene expression → autonomous cellular proliferation
- e.g.: ERB-B2 (HER2/neu) in breast & ovary HER2/neu → human epidermal growth factor receptor type 2

Gene deletionL

- Deletion to one nucleotide



Properties of cancer cell

- Excessive & autonomous growth
- ↓ Sensitivity to growth inhibition

- Avoid cellular aging
- Escape cell death
- DNA damage & repair system
- Cancer progression & heterogeneity clonal aggressiveness
- Multi step phenomenon
- Micro RNAs in cancer

- *Continuous perfusion & sustained angiogenesis*
- *Ability to invade & metastasize*

1. Excessive autonomous growth

A) Growth Factors

- Normal cell requires GF stimulation to go proliferation.
- GF made by a cell to action a neighboring cell (paracrine)
- Cancer cells have (growth self sufficiency) by
  - » ↑ Expression of GF oncoproteins
  - » ↑ Ability to make GF to which they respond
- e.g.: glioblastomas make PDGF & its receptor
- Many sarcomas make TGF-α & its receptor

B) GF receptor

- GF are transported intracellularly by cell surface receptor

Mutation: of receptor protein → stimulation of cell growth in the absence of GF

Overexpression: Of GFRs → cancer cell ↑ response to normal levels of GF. EGF receptor family: ERB2/ HER2 neu → breast cancer

C) Signal transduction

- Proteins transduce from R on cell surface to nucleus to activate intracellular growth signals
- e.g. RAS m.c. mutated proto-oncogenes

D) Nuclear transcription factor

- Signal transduction pathways
- → nucleas → regulate DNA transcription → induce cell enter 5 phase.
- Mutation of these genes → ⊕ growth → autonomy

Example of mutated nuclear transcription factor:

- C.Myc translocation in Burkitt Lymphoma
- N.Myc amplified in neuroblastoma
- L.Myc amplified in small cell lung carcinoma

E) Cell cycle regulatory proteins

- Cell cycle is normally under regulation of cyclin s & cyclin dependent kinases (CDK) and inhibitors (CDKI)
- ⊕ of CDK by cyclin → cell progression into diff. phases of cell cycle.
- Cyclins are synthesized and degraded rapidly .
- Mutation in cyclins & CDKs are important cancer growth promoting signals
- e.g.: cyclin D amplified in Mantle cell lymphoma
- CDK4 amplified malignant melanoma

2. ↓ Sensitivity to growth inhibitory signals

Inactivation of tumor suppressor genes

- Tumor suppressor genes → proteins → (-) cells proliferation
- Recessive → both copies must be lost
- Familial → one damaged copy is inherited
  → the other copy is lost by somatic mutation
- Sporadic → both copies lost by somatic mutation

RB gene

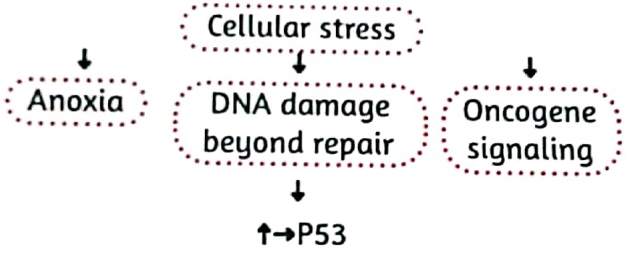
Retinoblastoma:

- Location: long arm Ch. (9-13)
- Normal function: produce protein
- That binds DNA and (-) proliferation by controlling G, to S check point
- Most cancers have disabled Gi check point ether by damaged RB or genes that affect RB function as cyclin D
- Both alleles on must be lost (recessive) → retinoblastoma
- Homozygous pair in cancer breast, lung, bladder
- Carcinogenic virus bind RB gene and (-) it as HPV

P53

Guardian of genome :

- Location: short arm. chromosome 17
- Normally found in ↓ amount and accumulates in DNA damage



- ↑ Genes arrest cell cycle
- ↑ Genes of DNA repair (if no repair → apoptosis)
- P53 ↑ RB gene → G1-S block stop the cycle → giving a chance to DNA repair
- Both alleles are lost
- Viruses → proteins → (-) P53 as HPV, EBV and HBV

Adenomatous polyposis coli β-catenin pathway

- Normal function
- Antiproliferative → destruction of cytoplasmic β-catenin protein
- Loss APC → ↑ β-catenin → nucleus → ↑ growth as a transcription factor
- In familial adenomatous polyposis $, inheritance of mutated APC gene → hundreds of colon polyps at young age → one or more of them → colon cancer
- Sporadic colon cancer → somatic loss of both APC gene alleles

3. Escape apoptosis

- In cancer cells, lost function of apoptosis due to mutation in genes regulating apoptosis
- e.g.: BCL2 follicular β-cell lymphomas

4. Overcoming cellular aging limitless replicative potential

- Normally with each cell division, telomeres are shortened till telomeres are lost → cell cycle arrest → stop mitosis by RB & P53 genes.
- In tumor cells → escape aging → enzyme telomerase → helps maintain telomere length → tumor cells avoid aging → mytosis doesn't stop
- Normally telomerase enzyme active in stem cells but absent in somatic cells.

5. Continued cancer perfusion sustained angiogenesis

- Tumors need angiogenesis for growth and metastasis
- Angiogenic factors [VEGF & bFGF by tumor cells] inflammatory cells that infiltrate tumor.
- Antiangiogenic:

Tumor growth is controlled by:

» Angiogenic factors

» Antiangiogenic factors (1. Thrombospondin-1) (2. Angiostatin)

- Angiogenesis (neovascularization) has dual effect on tumor growth:
  - » Supplies O2 & nutrients ?
  - » New endothelial cells → ↑ growth of tumor cells → by ↑ GF

Oncogene	Mode of activation	Associated tumors
1- Growth factors: • PDGF • TGF-α	 • Overexpression • Overexpression	 • Glioblastoma • Sarcoma
2- GFRs: • HER2	 • Amplification	 • Breast cancer
3- Signal transduction proteins: • RAS	 • Pont mutation	 • Lung, colon & pancreas
4- Nuclear regulating proteins: • C-MYC • N-MYC • L-MYC	 • Translocation • Amplification • Amplification	 • Burkitt's lymphoma • Neuroblastoma • Small cell lung carcinoma
5- Cyclins: • Cyclin D • CDK4	 • Amplification • Amplification	 • Mantle cell lymphoma • Malignant melanoma

6. Ability to invade and metastasize in two phases

Invasion of ECM

Four steps:

- Attachment of tumor cells by (-) of –cadherin
- Degeneration of ECM by ↑ proteolysis enzymes MMP. Cathepsin-D
- Attachment cleavage of ECM → ECM → generate site bind to receptors on tumor cells
- Migration of tumor cells (through release of cytokines by tumor cells as autocrine motility factors)

Vascular dissemination & homing

- In circulation tumor cells are vulnerable to destruction by immunity
- Circulate
  - » Single cells
  - » Tumor embolic aggregates and adheres to leucocytes & PLIs

Extravasation by :

- Adhesion to vascular endothelium
- Exit through BM → organ parenchyma
- Adhesion
- Invasion

7. DNA damage & repair

- *Repair genes are important to genome integrity*
- *Lost both copies of DNA repair genes → genome instability*
- *Inherited mutation of genes involved in DNA repair system → ↑ risk of developing cancer*

HNPCC Hereditary non polyposis colorectal cancer

» *Have defect in repair system and develop colon cancer*

Hereditary breast cancer

» *BRCA1, BRCA2 are found in familial breast cancer*

Xeroderma Pigmentosa

» *Are predisposed to sunlight induced melanoma BCC, SCC*

8. Cancer progression & heterogeneity clonal aggressiveness

- ↑ Size
- ↑ Histologic grade
- Necrosis: ↑ growth > bl. supply
- Invasion & metastasis
- Although cancer cells are monoclonal in origin, by time they acquire more & more mutations → multiple mutated subpopulations of more aggressive clones of cancer cells → more tendency to invade & metastasize.

9. Multistep carcinogenesis

- Accumulation of multiple mutation is important in carcinogenesis example: **colorectal cancer:**
  - » Epithelial hyperplasia → adenomas → malignant transformation
  - » (-)APC tumor suppressor gene → ↑ RAS → loss of tumor suppressor gene on chromosome 18 and loss of P53

10. MicroRNAs in cancer: OncomiRs

- They're endogenous, non-coding single strand RNA → negative regulator of genes
- oncomiRs perform as tumor suppressor or growth promoter in association with various tumor genes

Etiology of Cancer

Carcinogenic agent

Chemical

Indirect: require metabolic conversion to become active

- → polycyclic hydrocarbons as benzopyerene are formed in consumption of tobacco in cigarette smocking → lung cancer
- Also in smoked meats and fish.

Direct: no metabolic conversion alkylating agent in chemotherapy

- Mechanism: DNA damage → mutation of P53 & RAS

Radiation

- UV rays, X-ray, nuclear fission → radiation → carcinogen
- Radioactive elements → mc. Incidence of lung cancer 10 folds
- Ionizing radiation → acute & chronic myeloid leukemia
- Natural UV radiation → skin cancers melanoma, SCC, BCC
- Therapeutic irradiation of head & neck → papillary thyroid cancer

Mechanism

- Chromosomal breakage: DNA damage → DNA breaks
  - » Translocations
  - » Point mutations

- **HHV-8**
  - » Kaposi sarcoma (vascular neoplasma) high risk in AIDS patients & homosexual
- **3- HBV & HCV**
  - » Hepatocellular carcinoma

Mechanism

a) Immune mediated chro. inf.

» Hepatocytes injury

» (+) of proliferation

» ROS → DNA damage

b) Activation of signal transduction pathway by HBX protein of HBV & HCV

c) Viral integration → rearrangements of chromosomes → multiple deletions of tumor supp. genes

Microbial Agents

A) Viral

RNA:

1- Hepatitis C virus

2- HTLV-1:

» Cause T cell leukemia / lymphoma has tropism for CD4 + T-cells

MOI: transmit infected T-cells via sexual intercourse, blood products & breast feeding

» Only 1% develop leukemia of 20 years period of latency

Mechanism:

» HTLV-1 genome encodes proteins → (-) tumor supp. Genes as (CKDIs & P53)

DNA

1- HPV:

» Type 16, 18 and 31 → SCC of cervix, anal, vulva & oropharyngeal cancers

Mechanism:

» Degrade BAX → (-) apoptosis

» Activates telomerase → avoid aging

» (-) CDKIs & (+)cyclins

» (-) P53

2- Herpes viruses:

- **EBV**
  - » Burkitt lymphoma / B-cell lymphoma / Hodgkin lymphoma / Nasopharyngeal carcinoma

Mechanism

» EBV gene products → B-cell proliferation

» (-) apoptosis by (+) BCL2

»(+) MYC oncogene

B) Bacterial

- H. pylori → gastric adenocarcinoma & MALT lymphoma

Mechanism

- Chronic inflammation
- (+) Cell proliferation
- ROS → DNA damage
- H. pylori → ch. Gastritis → gastric atrophy → intestinal metaplasia → dysplasia → carcinoma
- H. pylori → B-cell proliferation → accumulates mutations in growth regulatory genes → B. cell MALT lympoma

C) Fungal

- **Aspergellus flavus:** in stored grains → Aflatoxins → consumption → HCC especially if associated with HBV.

Mechanism

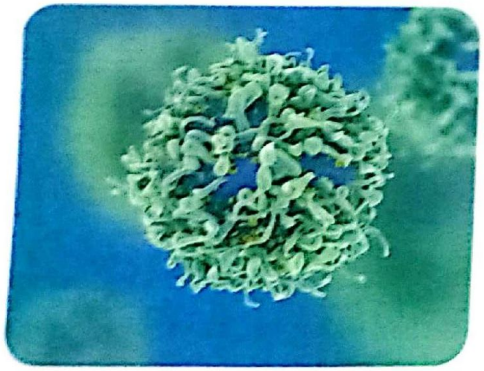
- (-) of P53

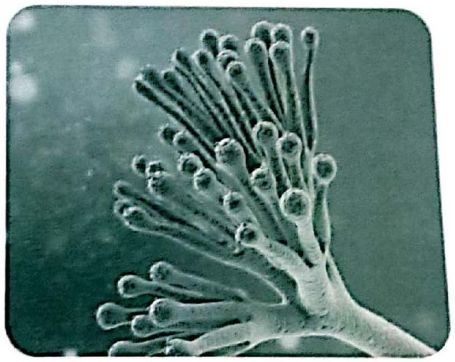
D) Parasitic

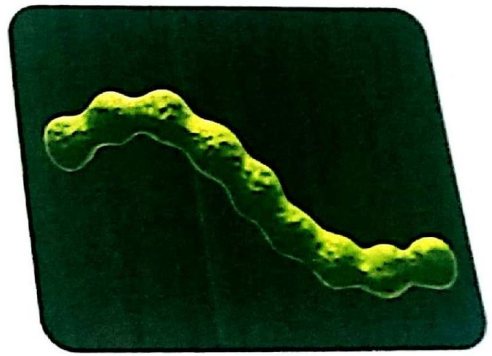
- **Schistosoma haematobium:** urinary bladder carcinoma.

Mechanism

- Tryptophan metabolites & activated nitroso compounds → DNA damage & mutations in P53 tumor suppressor gene







Clinical Features of Neoplasia

Local: according to size or location

Compression

- Pit. Adenoma → hypopituitarism
  leiomyoma in renal artery → HTN
- Bile duct / ampulla of vater → biliary obstruction

Mechanical obstruction

- Benign or malignant tumor in the gut → intussusception & IO

nfraction: ulceration – HgE and ry infection (very common)

Pedunculated ovarian tumor → torsion → infarction & Hge

ssue destruction

By 1ry and metastatic tumor

Hormone

- More common in benign than malignant neoplams in endocrine glands
- Adenoma or carcinoma in β-cells of pancreases→ ↑ insulin
- Adrenal cortex → corticosteroid

Fever FUO

As in

- Hodgkin
- RCC
- Osteosarcoma
- NB: exact mechanism is not known but mostly due to release of pyrogens by cancer cells

Cancer cachexia

- *Weight loss, weakness anorexia & anemia*

Causes?

- ↑ *BMR*
- *Release TNF α & IL-1 by cancer cells & MCs:*
  - » ↓ *Appetite*
  - » ↓ *FFA release from lipoproteins*
- ↑ Proteolysis inducing factor by tumor → ↑ breakdown of muscle
- ↑ Lipolytic factors

• Paraneoplastic $ symptoms not explained by local
• Distant spread of tumor or by release of hormones native to tissue of origin of the tumor 10-15% of cancers

docrinopathies:

IADH → small cell carcinoma of lung	→ ADH
lypercalcemia → breast cancer / RCC / SCC of lung	→ PTH
arcinoid $ → bronchial / pancreatic / gastric tumors	→ serotonin
olycythemia → RCC	→ erythropoietin
ushing $ → SCC of lung	→ ACTH

Vascular & hematologic

- Trousseau phenomenon → pancreatic / bronchogenic carcinoma → tumor products that activates clotting (procoagulating factors)
- Nonbacterial thrombotic endocarditis → metastatic adenocarcinoma → hypercoagulability
- Others: nephrotic $ → various cancers → ICs depositions

Laboratory Diagnosis of Cancer

Morphology

Histological

- Excision or biopsy
- Frozen section
- Fine needle aspiration
- Pap smear cytological (papanicolaou) smear used in CIS or dysplasia of cervix, used for identification of cancer cells in peritoneal, plural & CSF

Immunohistochemistry

- Cytokeratin +ve in carcinoma
- Vimentin +ve in sarcoma
- LCA +ve in lymphoma
- PSA → prostatic adenocarcinoma
- Er, Pr and HER2/NEU → +ve in breast carcinoma
- IHC can help in diagnosis prognosis and treatment of tumor

Flow cytometry

- Florescent Abs against cell surface molecules

- **Molecular profiling of tumors (DNA microarray analysis)** → measuring expression of several tumor genes

Tumor markers

- PSA prostatic specific antigen ↑ in prostatic adenocarcinoma
- CEA carcinogenic embryonic antigen ↑ in colorectal cancer and pancreatic cancers
- α fetoprotein ↑ in HCC & Yolk sac tumors of the gonads