CHAPTER (5)

DISORDERS OF GROWTH AND NEOPLASIA

ILOs:
After this lecture, student should be able to:

- *Describe hyperplasia, metaplasia, and dysplasia-to carcinoma in situ and invasive carcinoma sequence.*
- *Contrast neoplastic growth with hyperplasia, metaplasia, and dysplasia (adaptations).*
- *Classify tumors according to their tissue of origin, morphological criteria and behavior.*
- *Differentiate the morphology and behavior of benign, locally malignant and frank malignant tumors.*
- *Describe basic histopathological changes of malignant neoplasms.*
- *Differentiate the morphology and behavior of carcinoma and sarcoma*
- *Explain the four basic gross features of carcinoma.*
- *Clarify molecular pathways, clinical significance of invasiveness and metastasis.*
- *Express the pathways utilized by tumors in metastatic spread.*
- *Analyze theories of neoplastic transformation.*
- *Discuss the process of neoplastic transformation.*
- *Apply general features on certain common benign and malignant neoplasms.*

Growth: It is the process of increase in size resulting from the synthesis of specific tissue components that may occur through:

- Increase in numbers of cells (as in embryogenesis),
- Increased size of individual cells (as in skeletal muscle),
- Increase in intercellular tissue components, as in bone and cartilage.
- Combined patterns of all (as in embryological development).

Differentiation: It is the process whereby a cell develops a distinct specialized function and morphology (phenotype) that was not present in the parent cell.

DISORDERS OF GROWTH AND DIFFERENTIATION

Cells adapt to acceptable changes in their environment by modification of their metabolism and growth pattern (increased or decreased cell activity or altered structure).

I- Increased growth:

1. Hypertrophy: Increasing cell size without cell replication.
2. Hyperplasia: Increasing cell numbers by cell division.
3. A combination of both.

II- Decreased growth:

Atrophy.

III- Altered growth:

1. Metaplasia.
2. Dysplasia.

Hypertrophy:

Definition: Increased size and weight of organ due to increase in size of its cells, which have synthesized actively metabolic structural components, necessary for increasing the metabolism.

Types:

It may be physiological or pathological.

1. Physiological: Pregnant uterus due to hormone stimulation & muscle hypertrophy in athletes.
2. Pathological:
   a) Adaptive type: It affects the muscle coat of hollow organs due to increased intra-luminal pressure e.g.
      - Left ventricular hypertrophy due to hypertension or aortic valve stenosis.
      - Urinary bladder hypertrophy due to stricture of the bladder neck.
   b) Compensatory type: If one of a paired organ is out of function or surgically removed, the other organ undergoes compensatory hypertrophy e.g. kidney enlargement when the other kidney is surgically removed.

Figure (5.1) Left ventricular hypertrophy.

Hyperplasia :

Definition: Increased size & weight of organ due to Increase in number of its cells (Increased cell division). Hyperplasia can occur in any cell type capable of division.

Types:

It may be physiological or pathological.

1. Physiological:
   a. Hormonal hyperplasia e.g. mammary glands & genitalia at puberty due to estrogen stimulation.
   b. Compensatory e.g. bone marrow hyperplasia after hemorrhage.
2. Pathological:
   a. Hormonal hyperplasia e.g. endometrial hyperplasia in repeated anovulatory cycles and benign prostatic hyperplasia due to estrogen stimulation.
   b. Lymphoid hyperplasia in response to antigenic stimulation.

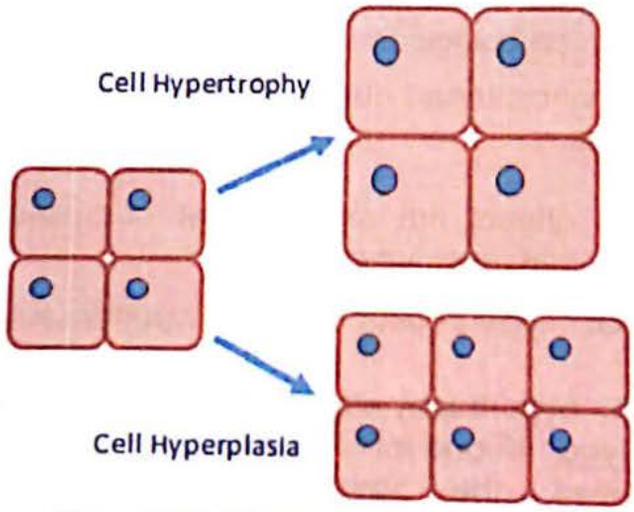

Figure 5.2 Cell hyperplasia and cell hypertrophy.

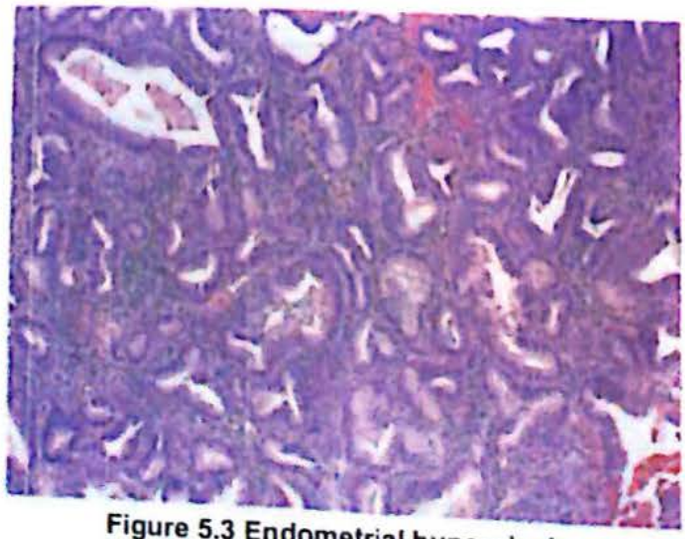

Figure 5.3 Endometrial hyperplasia.

Atrophy:

Definition: Decrease in size of cells with decrease in size and weight of organ after organ had reached its adult size.

Types:

It may be physiological or pathological.

1. Physiological:
   a. Localized atrophy as thymus after puberty and breasts after menopause.
   b. Generalized atrophy in case of senility. Aging results in diminution in organ size & function e.g. brown atrophy of the heart.
2. Pathological:
   a. Localized atrophy:
      i. Hormonal atrophy due to loss of hormonal stimulation e.g. breast atrophy following bilateral excision of ovaries.
      ii. Vascular atrophy e.g.:
         - Renal atrophy due to atherosclerosis of renal artery.
         - Atrophy of the vertebral bodies due to pressure atrophy by aneurysm.
      iii. Neuropathic atrophy: Atrophy of limb muscles due to loss of innervation as in poliomyelitis activity or diminished function ends in atrophy of muscle
      iv. Disuse atrophy: e.g. muscles after prolonged immobilization after a fracture of bone.
   b. Generalized atrophy: It affects all organs. Heart is small, skin is wrinkled due to loss of elastic fibers, bones and muscle are week, and teeth fall. e.g.
      - Decreased anabolism in cases of chronic malnutrition and starvation.
      - Increased catabolism as in advanced stages of malignancy (cachexia) and thyrotoxicosis.

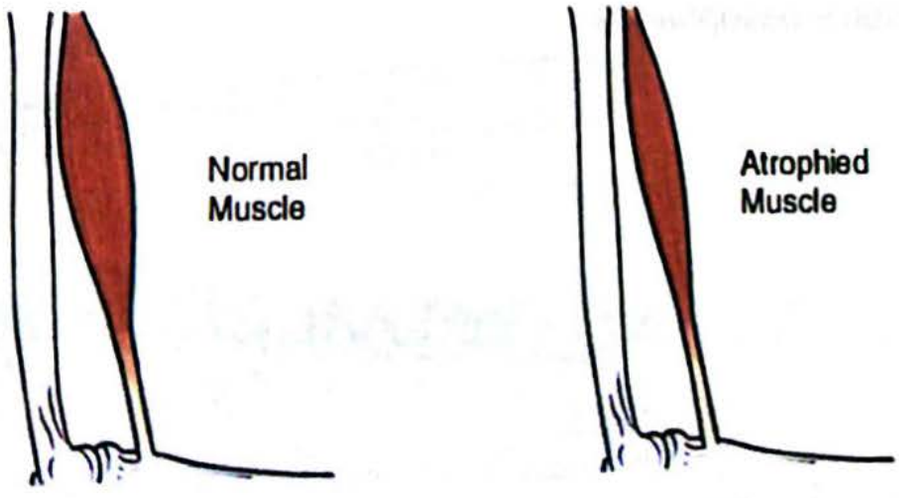

Figure (5.4) Muscle atrophy.

Metaplasia:

Definition: Transformation of one mature differentiated cell type to another of the same histologic type in response to an injurious agent, which is more resistant to chronic injury.
It is often associated with an increased risk of malignancy (e.g. squamous cell carcinoma associated with squamous metaplasia in bronchi).

Etiology, Pathogenesis and Types:

A. Epithelial Metaplasia:

1. Squamous Metaplasia: Transformation of columnar or transitional cells to squamous epithelium e.g.
   - Respiratory epithelium of the trachea and bronchi in smokers.
   - Transitional bladder epithelium in the presence of stones, and in the presence of ova of the Schistosoma haematobium.

   Leukoplakia: Transformation of columnar or transitional cells to keratinized squamous epithelium, which is tougher e.g. bilharzial epithelial UB changes & chronic cervicitis.
   - Gross: Thick irregular white mucosal patches related to chronic irritation
   - Microscopic: Squamous epithelium keratinization and subepithelial chronic inflammation.
2. Intestinal Metaplasia: Transformation of columnar cells to mucus secreting cells like those of intestine e.g. gastritis and at the edges of peptic ulcers. Or the replacement of the normal squamous epithelium of the oesophagus by columnar epithelium (glandular metaplasia) e.g. Barrett's oesophagus.

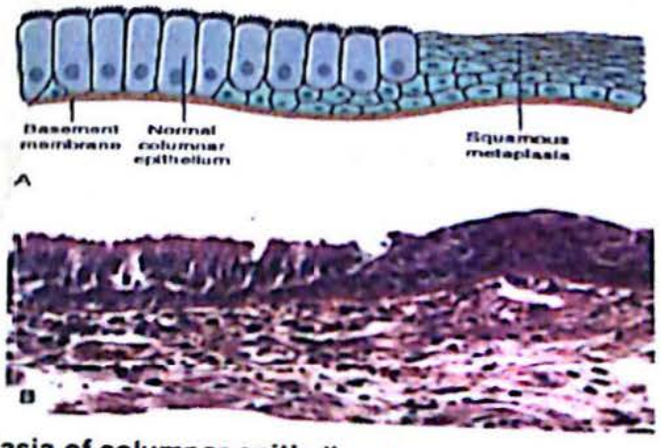

Figure (5.5) Metaplasia of columnar epithelium to squamous epithelium in bronchus.

B. Mesenchymal Metaplasia:

Fibroblasts exposed to chronic injury change into osteoblasts or chondroblasts.e.g. Myositis ossificans; muscle fiber injury causing necrosis results in granulation tissue. The fibroblasts of which undergo osteoblastic metaplasia.

Dysplasia:

Definition: It is non-neoplastic disordered proliferation of cells, usually induced by prolonged cell irritation.

Sites:

1. Mucous membranes of the cervix uteri, bronchi, oral cavity, urinary bladder, colon and gall bladder.
2. Epidermis.

Gross: Nonspecific gross appearance.
Microscopic: is characterized by:

1. Loss of cell pattern: i.e. Normal orderly arrangement (polarity), with increase in layers of immature cells.
2. Cellular pleomorphism (different shapes & sizes) and nuclear hyperchromasia (increased nuclear color).
3. Increased mitosis.
4. Grades: Dysplasia may be low grade or high grade depending on the degree of cellular atypia.
   - Low grade dysplasia affects the basal third of the epithelium.
   - High grade dysplasia affects the lower two-thirds up to the whole thickness.

Prognosis & Clinical significance:

- Low grade dysplasia is commonly reversible when the irritating cause is removed.
- High grade dysplasia and carcinoma in situ (intra epithelial malignancy not invading the basement membrane) are pre-invasive phase of malignancy.

Carcinoma in Situ (CIS):

Definition: Carcinoma in situ (CIS) represents a pre-invasive stage of carcinoma and is characterized by severe epithelial atypia (severe dysplasia) without invasion of the basement membrane (separating it from potential routes of metastases i.e. blood vessels and lymphatics).
Once the basement membrane is invaded the CIS phase ends and actual malignant tumor starts.

Microscopic features: CIS is essentially a microscopic change characterized by:

- Diffuse cellular atypia involving the whole thickness of the affected epithelium. The cells are pleomorphic with dark nuclei and numerous mitoses. Their architectural orientation (polarity) is disturbed.
- No invasion of basement membrane.

Fate: Progression into invasive carcinoma occurs after a variable time (usually years).

Examples of common sites of CIS:

1) Bladder
2) Cervix
3) GIT
4) Mammary gland
5) Skin

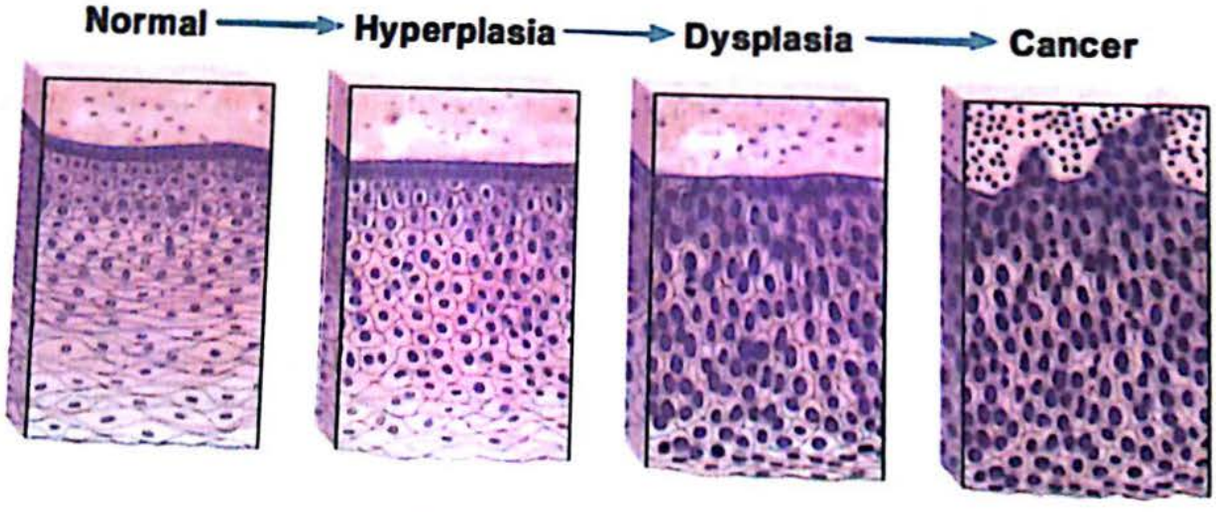

Figure (5.6) Change of normal cells to cancer.

NEOPLASIA

Definition: A neoplasm (tumor) is a new growth forming an abnormal mass, caused by autonomous self-controlling proliferation of cells which is irreversible, uncontrolled, unlimited, progressive & purposeless.

Table (5.1) Difference between hyperplasia and neoplasia

HYPERPLASIA	NEOPLASIA
- Excited by a stimulus - Reversible, i.e. pathological hyperplasia stops and disappears if the stimulus abates. - Proliferated cells are normal-shaped. - May be useful (e.g. compensatory hyperplasia).	- A stimulus is not always detected. - Irreversible, i.e. cell proliferation is unlimited and progresses independent of any stimuli. - Proliferated cells in case of malignant neoplasia are abnormal-shaped. - Harmful.

Any Tumor has Two Basic Components:

- **The transformed (neoplastic) cells:** Cells which have undergone genetic damage.
- **The supporting stroma & vessels:** Non-transformed elements derived from the host in response to factors released from the tumor, e.g. angiogenesis factor.

Classification of Tumors

A. According to their behavior:

1. Benign Tumors.
2. Malignant Tumors.
3. Intermediate Tumors.

B. According to cell of origin (Histogenetic Classification):

1. Epithelial tumors.
2. Mesenchymal tumors.
3. Others.

Characteristics of Benign Tumors

In general benign tumors appear to be genetically simple, harboring fewer mutations than cancer cells and genetically stable, changing little in their genotype over time.

A. Tumor Structure:

Gross Features:

- Tumor Margins: well defined.
- Cut section of the tumor: commonly uniform with no hemorrhage or necrosis.
- A tumor arising inside a solid organ appears globular or ovoid & often becomes surrounded by a fibrous capsule composed of a rim of condensed connective tissue.

Microscopic Features:

- Cell Differentiation: Cellular differentiation is the extent to which tumor cells resemble comparable normal cells. In benign tumors, the cells are perfectly differentiated i.e. closely mimic the corresponding normal cells, e.g. fat cells in lipoma resembles normal fat cells in subcutaneous tissue. Mitosis is rare or absent.
- Histologic Differentiation: This is the degree of resemblance of the structural pattern of the tumor to that of the normal tissue. In benign tumors, the tumor cells exhibit structural patterns similar to the normal tissue. Thus adenoma of thyroid consists of acini almost similar to those of normal thyroid gland.
- Other Features: Hemorrhage and necrosis are extremely rare.

B. Rate of Growth: It is often slow.

C. Local Invasion & Metastases (Distant Spread):

- Benign tumors do not have the capacity to infiltrate, invade or metastasize to different sites.
- Benign tumors **are well circumscribed** and most are capsulated. This capsule probably is derived from the stroma of the host tissue as the parenchymal cells undergo atrophy under the pressure of the expanding tumor. Some benign tumors do not have a capsule e.g. a leiomyoma.
- Most benign tumors do not recur if well excised.

D. Prognosis: Benign tumors have good prognosis, but in certain locations can have serious effects (see later).

Characteristics of Malignant Tumors

A. Tumor Structure:

Gross Features:

1. Tumor Margins: Irregular or ill- defined.
2. Cut section of the tumor: often shows areas of hemorrhage and necrosis.

3. A tumor inside a solid organ appears as an irregular non-capsulated mass. However, very rarely a malignant tumor may acquire a capsule (mostly incomplete & microscopically shows frequent foci of tumor invasion).

Microscopic Features:

4. Cellular Anaplasia (lack of differentiation): Malignant cells show grades of cellular atypia, referred to as anaplasia, ranging between mild to marked. Anaplasia is characterized by:
   1. **Cellular pleomorphism:** Malignant cells vary in size & shape. However some tumors are monomorphic.
   2. **Nuclear pleomorphism:** Nuclei may be irregular or bizarre shaped.
   3. **Nuclear enlargement & hyperchromatism:** Due to increased synthesis of DNA, the nuclei appear dark (hyperchromatic) & the nucleo-cytoplasmic (N/C) ratio is increased approaching 1:1 (normally N/C ratio is approximately 1:5).
   4. **Nucleoli** may be prominent.
   5. **Abundant mitoses** & frequently abnormal mitotic figures (e.g. tripolar spindles).
   6. **Tumor giant cells** containing a single large polypoid nucleus or multiple nuclei.

5. Histological differentiation: In addition to cytologic abnormalities, anaplastic cells usually fail to develop recognizable patterns of orientation to one another (i.e., they lose normal polarity). They may grow in sheets, with total loss of common structures, such as glands or stratified squamous architecture.
   Carcinoma may be graded as well differentiated (grade I), moderately differentiated (grade II), poorly differentiated (grade III) & undifferentiated (grade IV). Better differentiated tumors tend to show less marked cellular anaplasia & grow slower. On the other hand undifferentiated tumors show great cellular anaplasia & grow faster. Undifferentiated (grade IV) carcinoma is sometimes termed anaplastic carcinoma.

- Other Features: Hemorrhage and necrosis are common.

B. Rate of growth: It is often rapid.

C. Local Invasion & Metastases (Distant Spread):

- Cancers grow by progressive infiltration, invasion and destruction of the surrounding tissue. They do not develop well-defined capsules. The infiltrative mode of growth makes it necessary to remove a wide margin of surrounding normal tissue during surgical excision. These margins have to be examined carefully by surgical pathologists for presence of cancer cells.
- Metastases: Metastases are secondary implants of a tumor that are discontinuous with the primary tumor and located in remote tissues. More

than any other feature, the property of metastases identifies a neoplasm as malignant.

D. Prognosis:

- Malignant tumors spread (see later).
- Recurrence after surgical excision is very common either from tumor cell remnants (not removed with the excised tissue) or from a new neoplastic transformation.
- Malignant tumors are serious & cause death. (see later)

Table (5.2) Main differences in the characteristics of benign and malignant tumors.

Benign Neoplasms	Malignant Neoplasms
-Resemble tissue of origin and are well differentiated.	-Poorly or completely undifferentiated.
-Generally slow growing.	-Generally grow faster.
-Expansile growth, well circumscribed and have a capsule.	-Poorly circumscribed and invade the surrounding normal tissue.
-Benign tumors remain localized to the site of origin.	-Malignant tumors metastasize to different sites.

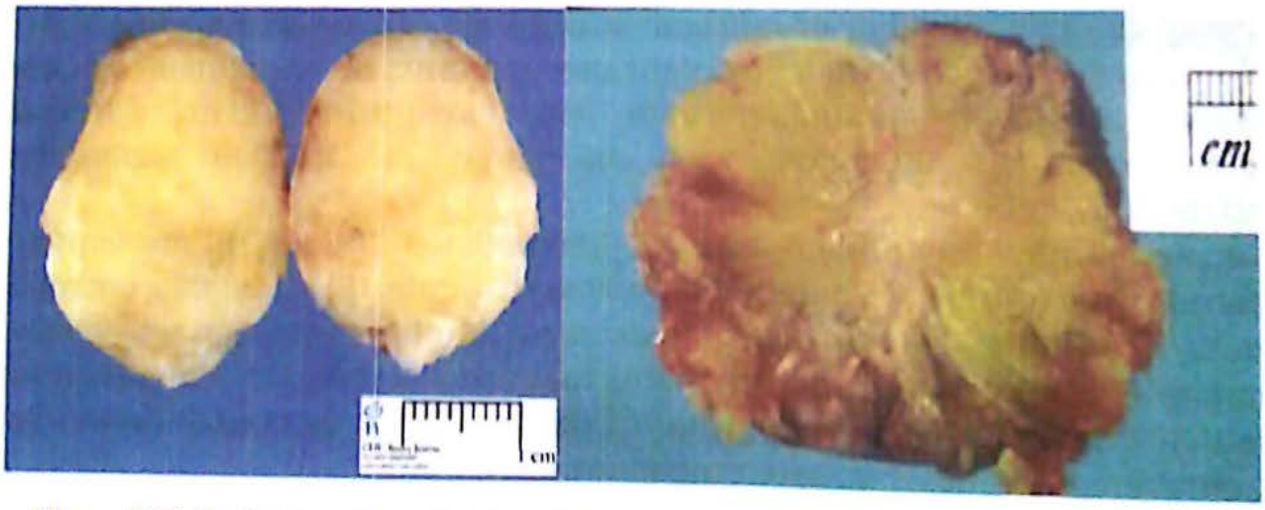

Figure (5.7) Benign tumor on the *left:* well defined and encapsulated; malignant tumor, on the *right*: irregular infiltrating the fat.

Routes (Pathways) of Spread of Malignant Tumors

1. **Local (Direct) Spread:** Tumor cells invade adjacent structures in direct continuity e.g. cancer tongue can directly spread to the floor of mouth.
2. **Distant Spread (Metastasis):**

A. Lymphatic Spread: Occurs more commonly with carcinomas than sarcomas.

i. Lymphatic Embolism:

- Malignant cells invade the wall of lymphatic vessels forming tumor emboli and reach the lymph node.
- Spread from one node to another may occur by efferent lymphatics.
- Grossly: The affected nodes are enlarged & hard. They may become fused & fixed.
- Microscopically the metastatic deposit resembles the primary tumor from which it is derived.
- Progressive spread by the lymphatic route may ultimately lead to tumor emboli within the main lymphatic ducts (thoracic duct), from which tumor emboli reach the venous circulation causing hematogenous spread.

ii. Lymphatic Permeation: The tumor cells grow as solid columns inside lymphatics leading to lymphatic obstruction and lymphatic oedema. Example: Breast carcinoma spread by permeation of axillary lymphatics leads to edema of the whole arm

N.B. Enlargement of nodes near a primary neoplasm does not always imply cancerous involvement. The necrotic products of the neoplasm and tumor antigens often evoke immunologic responses in the nodes, such as hyperplasia of the follicles (lymphadenitis) and proliferation of macrophages in the subcapsular sinuses (sinus histiocytosis). Thus, histopathologic verification of tumor within an enlarged lymph node is required.

Sentinel Lymph Node:

A "sentinel lymph node" is the first regional lymph node that receives lymph flow from a primary tumor. It can be identified by injection of blue dyes or radiolabeled tracers near the primary tumor. Biopsy of sentinel lymph nodes allows determination of the extent of spread of tumor and can be used to plan treatment.

B. Hematogenous (Blood) Spread:

- Emboli derived from primary tumors of organs drained by systemic veins (vena cava) e.g. breast, and kidney reach the right side of the heart and through the pulmonary arteries reach the lungs causing lung metastases.
- Emboli derived from tumors of lungs (whether primary or metastatic) are carried through pulmonary veins to left side of heart and systemic arterial circulation causing metastases in different organs as liver, bones, brain ... etc.
- Emboli derived from tumors of organs drained by the portal vein (tumors of gastrointestinal tract) give rise to liver metastases. Further spread from liver gives rise to emboli that reach the hepatic veins and then through inferior vena cava to lungs ... etc.
- Tumors arising from organs near the vertebral column can embolize through the paravertebral plexus, this pathway is probably involved in the frequent vertebral metastases of carcinomas of thyroid and prostate.

- Certain cancers have a propensity for invasion of veins. Renal cell carcinoma often invades the branches of the renal vein and then the renal vein itself, from where it may grow in a snake-like fashion up the inferior vena cava, sometimes reaching the right side of the heart.

Pathology of Organ Metastases:

The most common sites of metastases include the liver, lungs, bones & brain.

Metastases are rare in muscles , spleen, pancreas & intestine.

Gross picture: Metastases appear as scattered round nodules of variable sizes.

Microscopic picture: Metastases resemble the primary tumor from which they are derived.

Bone metastases: are commonly osteolytic but in case of cancer prostate it may be osteosclerotic (new bone formation is stimulated around the metastatic deposit, since malignant cells of prostatic origin secrete phosphatase).

C. Seeding of Body Cavities (Transcoelomic Spread):

When the serosal covering of an organ is infiltrated by malignant cells of a tumor within this organ, some of these cells may detach and become implanted on the serosal surface on other sites. This may be associated with hemorrhagic effusion. Transcoelomic spread includes:

1. **Transperitoneal spread** from carcinoma of stomach, colon, pancreas etc... cause metastatic peritoneal/omental nodules accompanied by hemorrhagic ascites. In females, carcinoma of stomach (or colon) may be associated with bilateral ovarian metastases, termed "Krukenberg tumors" which were considered to represent transcoelomic spread. *They are now believed to be due to retrograde lymphatic or blood spread, since Krukenberg tumors can also occur in case of cancers of breast, urinary bladder & biliary tract.*
2. **Transpleural and transpericardial spread** from lung or breast cancer resulting in metastases on the diaphragm accompanied by hemorrhagic pleural or pericardial effusion.
3. Malignant tumors of brain may give rise to tumor cells within the CSF leading to metastases within the lining of the ventricles, base of skull and spinal cord.

D. Other methods of spread:

- **Transluminal spread:** malignant cells detached from transitional carcinoma of the renal pelvis may become implanted in the mucosa of urinary bladder forming secondary deposits.
- **Surgical implantation/Innocculation:**
  a. Instruments contaminated with malignant cells during surgical management of a tumor may transfer tumor cells into the surgical wound causing secondary tumor deposits.

b. Implantation from carcinoma of lower lip may lead to a secondary tumor in the upper lip.

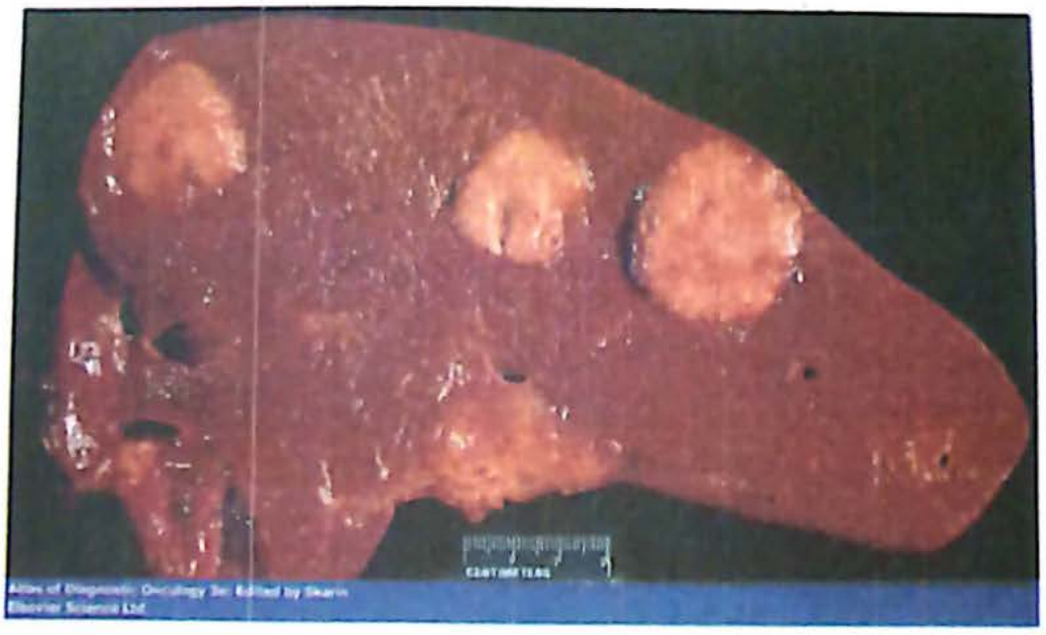

Figure (5.8) Liver metastases.

Intermediate Tumors (Locally Malignant Tumors).

Some malignant tumors are locally invasive and destructive but rarely give rise to metastases (previously termed locally malignant tumors). Such tumors usually grow slowly, can recur after surgical excision, but have a better prognosis than malignant tumors that metastasize.

Examples:

1. Basal cell carcinoma of the skin.
2. Giant cell tumor of bone (osteoclastoma).
3. Adamantinoma.
4. Some neuroendocrine tumors as carcinoid tumor.
5. Chordoma
6. Some tumors of CNS as craniopharyngioma.

Histogenetic Classification of Tumors and their Nomenclature

The major categories are:

- Tumors arising from epithelial cells
- Tumors arising from mesenchyme
- Tumors arising from lymphoid and hematopoietic organs
- Miscellaneous tumors

Table (5.3) Histological Classification of Tumors

Tissue of Origin	Benign	Malignant
A. Epithelium		
1. Surface epithelium.		
a. Stratiffed squamous	Squamous cell papilloma	Squamous cell carcinoma
b. Transilional	Transilional cell papilloma	Transilional cell carcinoma
c. Ducts of glands	Duct papilloma	Duct carcinoma
d. Mucosa of GIT	Adenomalous polyp	Adenocarcinoma
2. Glandular epithelium		
Endocrine & Exocrine glands	Adenoma	Adenocarcinoma
B. Mesenchyme		
1. Connective tissue		
a. Fibrous	Fibroma	Fibrosarcoma
b. Adipose	Lipoma	Liposarcoma
c. Primitive mesenchyme	Myxoma	.....
d. Bone	Osteoma &osteoblasloma	Osteosarcoma.
e. Cartilage	Chondroma, osteochondroma	Chondrosarcoma
2. Smooth muscle	Leiomyoma	Leiomyosarcoma
3. Striated muscle	Rhabdomyoma	Rhabdomyosarcoma
4. Endothelium	Angioma	Angiosarcoma
5. Mesothelium	Rare	Mesothelioma
6. Synovium		Synovial sarcoma
C. Others		
1. Pigmented cells	Nevus (benign melanoma)	Malignant melanoma
2. Trophoblast	Vesicular mole	Choriocarcinoma
3. Totipotent cells	Teratoma, mature (benign)	Teratoma, immalure (malignant)
4. Embryonic cells		Embryonic rumors
5. Lymphoid & hemopoeitic		Lymphoma & leukemia
6. Schwann cells	Schwannoma	Malignant peripheral sheath tumor

A. Benign Epithelial Tumors:

Benign epithelial tumors: Papilloma, Adenoma.

1. Papilloma:

Definition: A papilloma is a benign epithelial tumor, growing on any surface that produces microscopic or macroscopic finger-like fronds.

Microscopic Picture:

- They have a branching fibrovascular core covered by proliferated epithelium.
- Papillomas are rarely inverted endophytic pushing the basement membrane and grow inwards, compressing the subepithelial tissues without invasion, e.g. inverted papillomas of urinary bladder & nose.

Papillomas are classified according to type of epithelium into:

i. Squamous Cell Papilloma:

Definition & origin: A benign tumor of stratified squamous epithelium.
Sites: Skin, lip, tongue, oral mucosa, pharynx, larynx, oesophagus, cervix, vagina & anal canal.
Gross Picture: A small sessile or pedunculated projection. With progressive tumor growth, its surface becomes thrown into branching folds → complex papillary pattern.
Microscopic Picture: Connective tissue cores covered by thick proliferated stratified squamous epithelium exhibiting acanthosis (increased prickle cell layers) and hyperkeratosis.
Complications: May rarely change into squamous cell carcinoma.

ii. Transitional Cell Papilloma (Villous Papilloma):

Definition & origin: A benign tumor arising from urothelium (transitional mucosa of urinary tract). It is strongly pre-malignant. (see systemic pathology)

Columnar Cell Papilloma: These are papillomas arising from columnar epithelium e.g. **duct papilloma** arising from the epithelium of major ducts, e.g. of breast or pancreas (systemic pathology)

2. Adenoma:

Definition and origin: A benign tumor arising from glandular epithelium (acini and /or small ducts).

Sites:

- ***Exocrine or endocrine glands*** (breast, ovary, salivary glands, pancreas, thyroid, pituitary, adrenal glands... etc)
- ***Mucosal glands:*** e.g. GIT & endometrium (mucosal adenoma, adenomatous polyp). (see below)

i. Adenomas of Endocrine or Exocrine Glands:

Gross Picture: In solid organs, an adenoma appears as a capsulated globular or ovoid mass. Cut section may be solid, cystic or cystic with small projecting papillae.

Microscopic Picture: Several Patterns:

- **Simple adenoma (tubular adenoma):** Consists of proliferated glands lined by cuboidal or columnar epithelium, separated by fibrovascular stroma. Example: pancreatic adenoma.
- **Fibroadenoma:** Consists of glandular & wide stromal proliferations. Breast is the main site.
- **Cystadenoma:** In some types of adenoma, secretions are retained leading to cystic dilatation of the proliferated acini. Example: ovarian cystadenoma.
- **Papillary Cystadenoma:** It is a cystadenoma in which the epithelial lining of the cyst proliferates forming papillae. Example: papillary cystadenoma of the ovary.

Complications:

- Adenoma of endocrine glands may function e.g. thyroid adenoma may cause thyrotoxicosis.
- Malignant change (adenocarcinoma).

ii. Adenomas of Mucosal Glands:

Gross Picture: Adenomas of mucosal glands such as the colon may project on the surface of mucosa into the colonic lumen and is called a polyp. A polyp may be sessile or pedunculated.

Microscopic Picture: It is covered by columnar epithelium and the core contains proliferated glands, so it is called adenomatous polyp. Some adenomas of the colon may acquire a papillary architecture and are called villous adenomas.

B. Malignant Epithelial Tumors:

Malignant epithelial tumors are called ***carcinomas***. These comprise:

Carcinoma of surface epithelium:

1. Squamous cell carcinoma.
2. Basal cell carcinoma.
3. Transitional cell carcinoma.

Carcinoma of glandular epithelium: These are termed adenocarcinoma, e.g. adenocarcinoma of the breast, stomach or colon.

Squamous Cell Carcinoma:

Definition & Origin: A malignant tumor of stratified squamous epithelium.

Sites:

a. Skin.
b. Squamous mucous membranes as lip, tongue, mouth, pharynx, larynx, oesophagus, cervix, vagina & anal canal.
c. Other mucous membranes on top of squamous metaplasia e.g. squamous cell carcinoma of urinary bladder on top of squamous metaplasia due to bilharziasis.

Predisposing factors:

- Prolonged exposure to sun.
- Squamous metaplasia & leukoplakia.

Gross Picture: Several patterns:

- Fungating polypoid pattern.
- Ulcerative pattern: An irregular ulcer with raised raised everted edges, rough necrotic floor and indurated base.
- Infiltrative pattern.

Microscopic Picture:

- The dermis or submucosa is infiltrated by malignant epithelial cells which in well differentiated neoplasms form "cell nests".
- These cell nests consist of malignant cells that replicate the organization of the normal epidermis i.e. the periphery of these nests shows basal cell differentiation, followed by prickle cells then granular cells with the center of the nests showing whorly keratin (keratin pearls).
- In less differentiated neoplasms, fewer cell nests are formed & in anaplastic carcinoma, no cell nests may be detected.

Broder's Grading of Squamous Cell Carcinoma:
Grade I: 75-100% of the tumor consists of cell nests.
Grade II: 50-75% cell nests.
Grade III: 25-50% cell nests.
Grade IV: 0-25% cell nests.

Spread: Local, lymphatic and by blood.

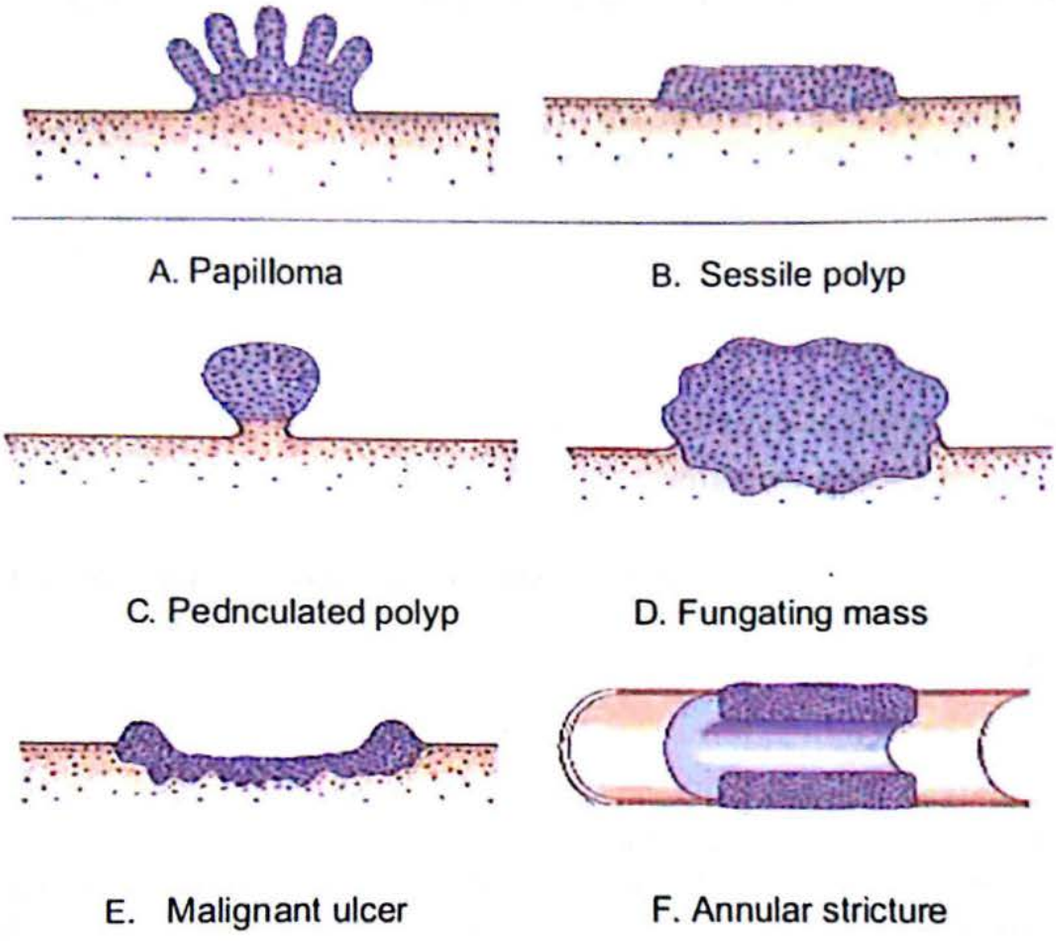

Figure (5.9) Gross appearance of surface epithelial tumors: A,B,C benign; D,E,F:malignant

Adenocarcinoma:

Definition and origin: These are malignant tumors arising from glandular epithelium either of:

1. The mucosal surfaces (as gastrointestinal mucosa, endometrium or endocervix).
2. Glandular organs (endocrine or exocrine glands as prostate, ovary, mammary gland, salivary glands... etc).

Gross Picture:

- In mucous surfaces, the tumor pattern may be:
  a) Fungating polypoid pattern.
  b) Malignant ulcer type.
  c) Infiltrative pattern (annular and diffuse subtypes).
- In endocrine and exocrine glands, the tumor forms an irregular infiltrative growth. (Carcinos=crab in Greek)

Spread:

1. Local
2. Distant spread by :

a. Lymphatics.
b. Blood (late).
c. Transcoelomic.

Microscopic Types:

1. **Adenocarcinoma:**

- In well differentiated adenocarcinoma, the malignant cells show acinar arrangement. These malignant acini differ from the normal acini in several respects:
  - They are irregular with no definite basement membranes.
  - Their lumens are irregular.
  - The cells show malignant features (describe).
  - They exist in abnormal sites (as submucosa, musculosa or serosa) due to infiltration.
  - They may be cystically dilated (cystadenocarcinoma) if the malignant cell secretions are retained. Some malignant cells may show papillary proliferations (papillary adenocarcinoma or papillary cystadenocarcinoma).
- Less differentiated adenocarcinomas show less degrees of acinar differentiation.

2. **Mucin secreting carcinomas:** Two types:

a. **Mucinous adenocarcinoma (mucoid or colloid Carcinoma):** This is an adenocarcinoma with abundant *extracellular mucin* secretion
b. **Signet ring cell carcinoma:** The malignant cells show *intracytoplasmic mucin* that pushes the nuclei eccentrically. No acinar differentiation.

3. ***Carcinoma simplex*** (undifferentiated carcinoma, spheroidal cell carcinoma). These are malignant tumors of glandular origin that neither exhibit acinar differentiation nor secrete mucin. Malignant cells form solid groups

Sites:

- Most common in breast
- Less common in other glandular sites mainly GIT.

Gross & Microscopic Features:

a. **Scirrhous Carcinoma:** Grossly the tumor is firm, gritty & ill-defined. Microscopically malignant cells are rounded and form small-sized solid groups surrounded by dense stroma.
b. **Medullary Carcinoma (encephaloid carcinoma):** Grossly the tumor is more expansile and better defined than scirrhous carcinoma and appears relatively soft. Microscopically, malignant cells are rounded

and form large-sized solid groups usually with more marked necrosis and little fibrous stroma.

Spread: As adenocarcinoma, describe (1- local spread 2-Distant spread).

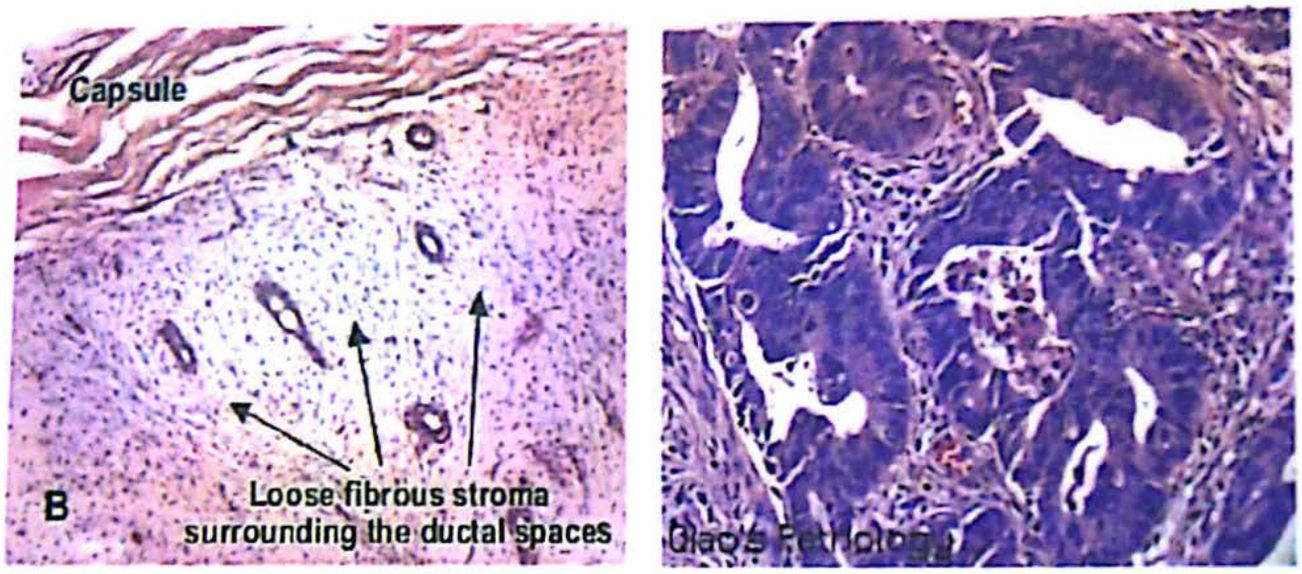

Figure (5.10) ***Left:*** **Fibroadenoma** showing regular glands separated by stroma, and surrounded by CT capsule. ***Right:*** **Adenocarcinoma** showing irregular glands lined by multiple layers of pleomorphic cells with hyperchromatic nuclei.

C. Connective Tissue Tumors and Other Mesenchymal Tumors

These are either benign or malignant.

1. Benign Mesenchymal Tumors:

These are named according to the cell or tissue of origin with a suffix "oma" e.g.

- *Fibroma:* benign tumor of fibroblasts.
- *Lipoma:* benign tumor from fat cells (lipocytes) of adipose tissue.

2. Malignant Mesenchymal Tumors:

These are called sarcomas.

- Sarcomas are more common in adolescents and young adults.
- They form large bulky fleshy masses (sarc= Flesh in greek).
- They are more expansile than carcinomas, with infiltration at the edges.
- They spread early by blood.

Table (5.4) Major Differences between Carcinoma and Sarcoma.

Carcinoma	Sarcoma
Definition: Malignant tumor of epithelium	***Definition:*** Malignant tumor of mesenchyme.
Most common form of malignancy.	Much less common than carcinoma.
Age: Usually (but not always) above age of 40 years.	**Age:** Usually (but not always below age of 20 years.
Growth rate: Rapid **Mode of growth:** Infiltrative & expansile.	**Growth rate:** Faster than carcinoma. **Mode of growth:** as carcinoma, but its rapid rate of growth gives it a more expansile appearance.
Gross Features:	***Gross Features:***
1. Size is usually less bulky than sarcoma.	1. Most sarcomas form bulky masses.
2. Consistency: Usually hard.	2. Consistency: Usually soft and fleshy.
3. Color is usually grayish.	3. Color is tinged pink due to richer vascularity.
4. Appearance: Irregular infiltrating growth.	4. Large, bulky ,expansile
Microscopic Features:	***Microscopic Features:***
1. Cellular anaplasia: Usually less marked than sarcoma.	1. Cellular anaplasia is generally greater than carcinoma.
2. Cell cohesion: Neoplastic cells exhibit variable grades of cohesion. This is however poor in anaplastic carcinomas. Connective tissue surrounds groups of cells and not individual cells.	2. Cell cohesion is often absent and the tumor cells occur singly. CT and extracellular matrix surrounds individual cells.
3. Blood vessels are less and better formed than in sarcoma.	3. Blood vessels are more numerous and thin- walled.
4. Hemorrhage, necrosis and secondary changes are usually less profound than in sarcoma.	4. Hemorrhage, necrosis and secondary changes as hyaline and myxomatous changes are common.
Distant spread	***Distant spread***
1) Usually slower than sarcoma 2) Occurs early by lymphatics then later by blood.	1) Usually faster than carcinoma 2) Occurs early by blood & rarely (10%) by lymphatics.

D.Tumors arising from Lymphoid and Hemopoietic Organs:

Tumors arising from lymphoid tissue are called ***lymphoma.***

Tumors arising from leukocyte forming cells in the bone marrow are called ***leukemia.***

E. Other Tumors:

I. Teratoma:

Definition, origin & sites:

Teratoma is a composite tumor containing structures derived from ectoderm, mesoderm & endoderm. It arises from primitive germ cells or totipotent cells that may exist in post-natal life in some places as ovary, testis, sacrococcygeal region & mediastinum. The structure of teratoma is foreign to the site from which it arises.

Origin:

- During early fetal development the primitive structural cells are called totipotent cells which can give rise to all three embryonic cell types (ectoderm, endoderm and mesoderm). Through action of placental chemical organizers, organs are formed from these primitive cells & the later progressively disappear.
- Sometimes some primitive totipotent cells that are directed towards the gonads (totipotent germ cells) persist in the gonads or arrest along the line of their migration (midline: base of skull, mediastinum, sacrococygeal ... etc) and remain in their primitive state without prenatal maturation.
- The born fetus is usually structurally normal. However if the totipotent cells proliferate in postnatal life, they give rise to a tumor composed of a mixture of ectodermal, endodermal and mesodermal structures, but these structures will not form mature organs (due to lack of placental chemical organizers).

N.B.: Teratomas may be benign or malignant.

Age: Any age; children, young adults or elderly.

Types:

A. Mature teratoma (Benign Teratoma):

Grossly: Mature teratomas are commonly cystic (DERMOID CYST) Commonest in ovary, usually large. It consists of a dermoid ridge which is a solid part covered by skin, and contains different tissue and structures (e.g. teeth). The rest of the tumor is cystic and contains sebaceous material and tufts of hair.

Microscopically: These tumors consist of a haphazard mixture of mature ectodermal structures such as skin, neuroglial cells & teeth, mature endodermal structures such as thyroid tissue & other types of glandular epithelium & mature mesodermal structures such as cartilage, bone, adipose tissue, fibrous tissue, muscle ... etc. It maybe cystic & consist predominantly of skin & hairs (dermoid cyst).

Malignant transformation occurs in 1 % of mature teratomas (any type of malignancy, but squamous cell carcinoma is the most common).

B. Immature teratoma (Malignant Teratoma):

It consists of a varied amount of immature tissues (immature cartilage, neuroepithelium, glands... etc).
The degree of malignancy and spread is proportionate to the degree of immaturity.
According to the proportion of immature to mature structures, this group is subtyped as grade I, grade II & grade III.

C. Monodermal teratomas (Specialized Teratomas):

These are teratomas that differentiate along the line of a single abnormal tissue.

Examples:

a) Struma ovarii: A benign ovarian teratoma composed of thyroid tissue.
b) Ovarian or testicular choriocarcinoma: A malignant placental epithelial tumor.

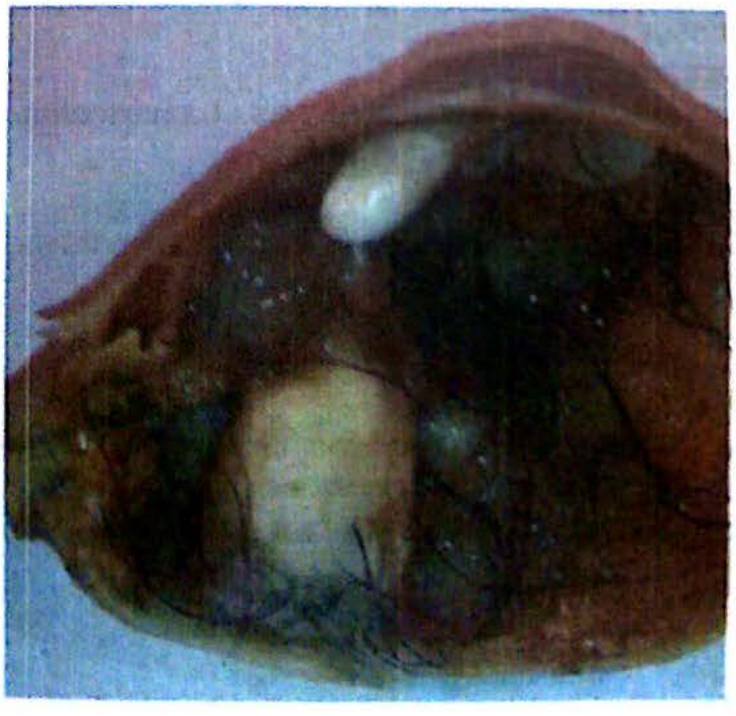

Figure (5.11) Ovarian teratoma (Dermoid cyst) showing hair and teeth.

II. EMBRYONIC TUMORS:

Definition, origin and age:

Malignant tumors derived from embryonic cell remnants in infants and young children. Occasionally, the cells may show some differentiation towards the tissues which normally arise from their related cell type.

Structure: They consist of primitive embryonic (undifferentiated) malignant small round cells.

Examples:

1. Neuroblastoma of adrenal medulla & sympathetic ganglia.
2. Retinoblastoma of eye.
3. Nephroblastoma of kidney.
4. Hepatoblastoma of liver.
5. Medulloblastoma of brain.

TUMOUR-LIKE LESIONS

HAMARTOMA

This is a tumor-like developmental malformation formed of noncapsulated mature tissues of the affected organ (not foreign to them), but arranged haphazardly. It usually stops growing after puberty. Some hamartomas are precancerous.

Examples of hamartomas:

1- Lung hamartoma (a mixture of cartilage, smooth muscle and bronchial mucosal tissue).
2- Kidney hamartoma.
3- Angiomas are now considered as hamartomas rather than true neoplasms.
4- Pigmented nevi.
5- Exostosis (osteochondromas) & neurofibromatosis are regarded as hamartomatous malformations.

CHORISTOMA

Choristoma is a congenital anomaly consisting of a heterotropic rest of cells. For example: a small nodule of well-developed and normally organized pancreatic tissue may be found in the mucosa of the stomach, duodenum or small intestine.

EPIDEMIOLOGY OF CANCER

Study of cancer patterns in population

The incidence of cancer varies with geography, age, race, and genetic background.

1. Cancer incidence and mortality by site and sex:

In men, cancers of prostate, lung and colon are leading causes of cancer death.
In women, cancers of breast, lung and colon are leading causes of cancer death.

2. Geographic and environmental Factors:

Environmental factors significantly affect occurrence of specific forms of cancer in different parts of the world.
Examples of environmental factors:

- Cigarette smoking causes cancer lung.
- Prolonged exposure to sun (UV rays) leads to skin cancer as in farmers.
- Occupational exposure to carcinogens as asbestos, arsenic, nickel,...
- Chronic alcohol consumption leads to alcoholic cirrhosis and hepatocellular carcinoma.

3. Age:

In general, the frequency of cancer increases with age; this may be explained by:

- Accumulation of successive mutations with prolonged exposure to carcinogens.
- The decline in immune competence with aging.

Most carcinomas occur after the age of 55 years. Prostatic cancer is almost present in every male above the age of 100 years.

Certain malignant tumors are common in infants and children, e.g. acute leukemia, retinoblastoma, neuroblastoma and Wilm's tumor.

4. Genetic Predisposition to cancer: divided into 3 categories:

A. Autosomal dominant inherited cancer syndromes:

Inheritance of a single mutant gene, usually a point mutation in one allele of cancer suppressor gene.
Transmission: Autosomal dominant.
Only specific sites or tissues are affected.
Examples:

- Retinoblastoma: 40% are familial; one defective allele of RB gene is inherited in germ line, therefore it is present in all somatic cells and the other allele is lost in retinoblasts by somatic mutation. They develop retinoblastoma and also show increased risk of developing other certain malignancies.

- Those born with one mutant allele of adenomatous polyposis coli (APC) tumor suppressor gene develop innumerable adenomatous polyps in the colon (familial adenomatous polypi). When the other allele is lost by somatic mutation, one or more polyps develop cancer (100% of cases will develop colon carcinoma by the age of 50).

B. Defective DNA repair syndromes*:* A group of cancer predisposing conditions characterized by defects in DNA repair and resultant genomic instability→ increased predisposition to environmental carcinogens. Examples: xeroderma pigmentosum. Also BRCA1 and BRCA2 account for 80% of cases of familial breast cancer.

C. Familial cancers*:* Familial clustering of specific forms of cancer, but role of inherited predisposition may not be clear in an individual case. Examples: breast cancer, ovarian cancer, colon cancer other than familial adenomatous polypi.

5. **Non hereditary predisposing conditions (Acquired preneoplastic disorders):** Some chronic diseases may lead to precancerous lesions. Examples include:
   A. Chronic inflammatory diseases *as:*
      - Bilharziasis of the urinary bladder.
      - Ulcerative colitis.
      - Atrophic gastritis
      - Radiodermatitis
      - Tertiary syphilis of tongue
      - Lupus vulgaris (cutaneous T.B)
   B. Gall stones and urinary stones
   C. Hyperplastic, metaplastic and dysplastic lesions as leukoplakia, endometrial hyperplasia, mammary hyperplasia and cervical dysplasia.
   D. Some Benign Tumors e.g. villous bladder papilloma & GIT adenomatous polyps.
   E. Others as liver cirrhosis, varicose ulcers, Paget's disease of bone, undescended testis.

MOLECULAR BASIS OF CANCER

- Cancer is a genetic disorder caused by DNA mutations that are mostly acquired spontaneously or induced by environmental insults (initiating mutation).
- These genetic mutations are passed to daughter cells upon cell division.
- Most tumors are monoclonal.
- It is thought that these mutations provide the cells with survival advantages over the neighboring cells and allow them to dominate the population (Darwinian selection).

Carcinogenesis (tumorigenesis):

Tumor results from the accumulation of complementary mutations in a stepwise fashion over time (multistep process). Once established, tumors evolve genetically during their outgrowth and progress under the pressure of Darwinian selection (survival of the fittest).

Carcinogenesis is a multistep process:

1-**Initiation:** Induction of certain irreversible changes in the genome of the cells. These initiated cells are not transformed cells and do not have growth autonomy. They just have altered DNA (gene mutation) and are called latent tumor cells.

2-**Promotion:** Promoters enhance the proliferation of initiated cells, an effect that may contribute to the acquisition of additional mutation.

3-**Neoplastic transformation**: Abnormal differentiation occurs and the cells undergo continuous purposeless uncontrolled irreversible proliferation.

During this process, there is competition among tumor cells for access to nutrients, and subclones with the capacity to overgrow their predecessors tend to "win" this Darwinian contest and dominate the tumor mass, only to be replaced by other, still malignant subclones. This pernicious tendency of tumors to become more aggressive over time is referred to as tumor progression. As a result, even though malignant tumors are clonal in origin, by the time they become clinically evident their constituent cells are often extremely heterogeneous genetically.

Four classes of normal regulatory genes are the principal targets of cancer-causing mutations:

- The growth promoting proto-oncogenes.
- The growth-inhibiting tumor suppressor genes.
- Genes that regulate programmed cell death (apoptosis).
- Genes involved in DNA repair.

Accumulation of mutations gives rise to a set of properties that have been called "hallmarks of cancer. These include:

1. The growth of cancer cells become autonomous and are unregulated by physiological signals (self -sufficiency).
2. Lack of response to growth inhibitory signals.
3. Evasion of cell death.
4. Unlimited replication potential, thus making cancer cells immortal.
5. Development of angiogenesis to sustain the growth of cancer cells.
6. Ability to invade local tissues and spread to distant sites.
7. Ability to evade the immune system.

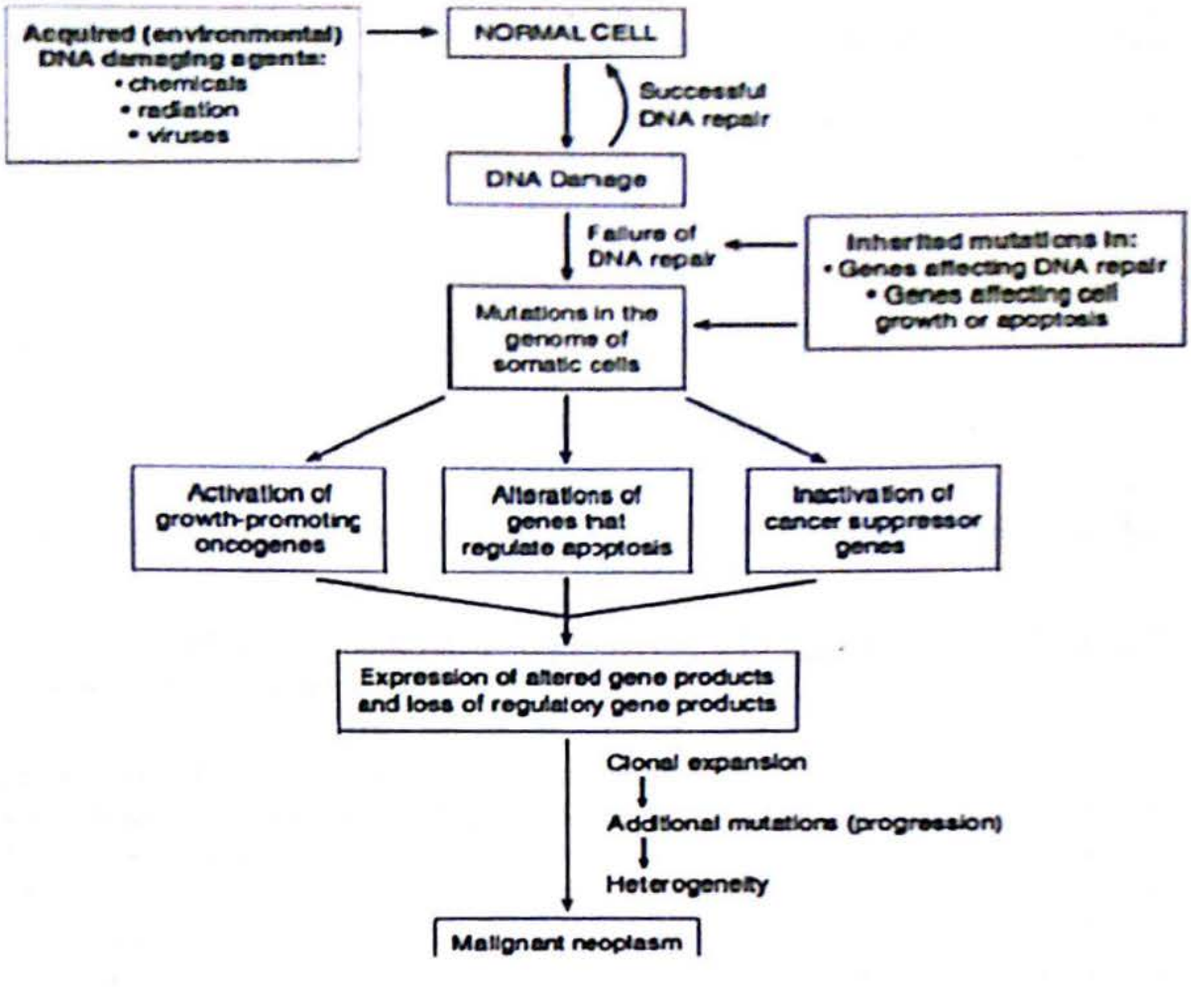

Figure (5.12) Carcinogenesis process.

Oncogenes:

1. **Proto-oncogenes:** These are normal cellular genes that encode proteins that drive cell proliferation.

The transformation of proto-oncogenes into cancer-causing oncogenes occurs by one of three mechanisms:

a) **Point mutations**, possibly due to exposure to cancer-causing chemicals.
b) **Chromosomal translocations**, where during cell divisions, a part of a certain chromosome (with its genes) is relocated into another chromosome leading to gene fusion or change in the sequence of genes, finally resulting in activation and transformation of proto-oncogenes.
c) **Gene amplification:** this is reduplication of proto-oncogenes.

Oncogenes encode synthesis of proteins called oncoproteins. These oncoproteins are produced in transformed (neoplastic) cells independent of growth factors or other external signals.

Examples of oncogenes:
- ERBB2 encodes a growth factor receptor, HER2. The ERBB2 gene is amplified in certain breast carcinomas, leading to overexpression of the HER2 receptor. A high level of HER2 protein in breast cancer is an indication of poor prognosis and generally respond to target therapy with anti-HER2 antibodies (Herceptin).
- RAS Mutations: Normal RAS proteins are located in the inner aspect of the plasma membrane. Point mutations of RAS family genes constitute the most common type of abnormality involving proto-oncogenes in human tumors. 90% of pancreatic adenocarcinomas and cholangiocarcinomas contain a RAS point mutation, as do about 50% of colon, endometrial, and thyroid cancers and about 30% of lung adenocarcinomas and myeloid leukemias.
- MYC oncogene (transcription factor): MYC is amplified in some breast, colon, lung, and many other carcinomas. Also in neuroblastomas. Translocations of MYC occur in Burkitt lymphoma.

2. Cancer Suppressor Genes:
Tumor suppressor genes are usefully placed into two general groups, "governors" and "guardians."
- ***"Governors"*** are classic tumor suppressor genes, such as retinoblastoma gene (RB), where mutation of the gene leads to transformation by removing an important brake on cellular proliferation.
- ***"Guardian"*** genes are responsible for sensing genomic damage. The response of these genes is to arrest proliferation to allow for DNA repair or, if the damage is too great to be repaired, the induction of apoptosis.

TP53, the so-called "guardian of the genome," is a prototypic tumor suppressor gene of this type. Mutation of TP53 does not directly transform cells, as loss of guardian function has no direct effect on cellular proliferation or apoptosis.
Instead, loss of the guardian genes permits and accelerates the acquisition of mutations in oncogenes and tumor suppressor genes that can lead to the development of cancer.

3. Genes that regulate programmed cell death (apoptosis):
Accumulation of neoplastic cells may result from mutations in the genes that regulate apoptosis.
- In the adult, cell death by apoptosis is a protective mechanism. A cell with genomic injury can be induced to die, eliminating the chance that such a cell might go on to give rise to a neoplasm.
  e.g. In greater than 85% of follicular B-cell lymphomas, the anti-apoptotic gene BCL2 is overexpressed due to a (14; 18) translocation.

Unlimited Replicative Potential:

- Most normal human cells have a capacity of 60 to 70 doublings. After this the cells lose the capacity to divide and enter a non-replicative senescence. This phenomenon is related to progressive shortening of telomeres at the ends of chromosomes. With each cell division, telomeres are shortened, and beyond a certain point, loss of telomeres leads to massive chromosomal abnormalities and death.
- Tumor cells must develop ways to avoid cellular senescence; this is acquired by activation of the enzyme telomerase, which can maintain normal telomere length. In 85% to 95% of cancers, there is up-regulation of the enzyme telomerase. Telomerase is active in normal stem cells but is absent from most somatic cells.

Sustained Angiogenesis:

- Tumor-associated angiogenic factors may be produced by tumor cells and inflammatory cells that infiltrate tumors.
- The two most important angiogenic factors are **vascular endothelial growth factor (VEGF)** and **basic fibroblast growth factor**.
- Tumor cells not only produce angiogenic factors but also induce antiangiogenic molecule. Tumor growth is controlled by the balance between angiogenic factors and antiangiogenic factors.
- The wild-type P53 inhibit angiogenesis by inducing the synthesis of the antiangiogenic molecule. Mutational inactivation of both P53 alleles (a common event in many cancers), the levels of antiangiogenic molecule drop precipitously, tilting the balance in favor of angiogenic factors.
- **VEGF inhibitors** are used to treat a number of advanced cancers and prolong the clinical course but are not curative

Ability to invade local tissues and spread to distant sites:

Mechanism of Spread:

Malignant tumors spread locally to surrounding tissues and distantly to remote sites (metastases). Mechanism of spread includes:

a) Invasion of Extracellular Matrix (ECM): The following steps are included:

- **Loss of cellular cohesion:** Normal cells are glued together by molecules called cadherins. Tumor cells lose the normal cadherin expression, allowing them to detach (loosening up).
- **Attachment of tumor cells (through receptors) to matrix components**; mainly to laminin of basement membrane and fibronectin of the interstitial tissue. Attachment to ECM promotes the next steps.
- **Degradation of the ECM** by proteolytic enzymes secreted by the tumor cells or by stimulated host cells (fibroblasts & macrophages). Several enzymes are released as type IV collagenase (causing lysis of basement membranes of epithelia and of vessels) and cathepsin D (causing

degradation of interstitium). Degradation of ECM is very important for the tumor cells to create passage ways for their migration.

- **Migration (mobility) of tumor cells (by pseudopodia)**. This is mediated by tumor-derived cytokines (mobility factors) such as "autocrine mobility factor". The process may be helped by acquiring negative charges on surface of tumor cells causing their repulsion and loss of contact inhibition.

b) Vascular Dissemination and Homing of Tumor Cells:

- Tumor cell mobility allows cells to come in contact with blood vessels.
- Tumor cells can penetrate lymphatics, capillaries & venules, but rarely arterioles (thick-walled).
- Once the tumor cells cross the vascular basement membranes, they reach circulation as tumor emboli.

  Fate of tumor emboli:

  a) Most tumor emboli are destroyed by immune mechanisms.

  b) The surviving tumor cells adhere to platelets. This affords them some protection from antitumor host immune cells.

  c) Finally the surviving tumor cell emboli get impacted in small vessels, where they adhere to the endothelium, cross the basement membrane (by mechanisms similar to those described above) & settle in the new site (homing). In their new sites, tumor cells proliferate forming metastatic deposits (metastasis, secondary tumors).

- Some tumors show organ tropism. For example, prostatic carcinoma preferentially spreads to bone, bronchogenic carcinomas tend to involve the adrenals and the brain, and neuroblastomas spread to the liver and bones. Such organ tropism may be related to expression of adhesion molecules whose ligands are expressed by endothelial cells and the metastatic site or chemokine receptors on tumor cell surface.

Evasion of Immune Surveillance:

- Tumor cells can be recognized by the immune system as non-self and destroyed.
- Antitumor activity ismediated by predominantly cell-mediated mechanisms. Tumor antigens are presented on the cell surface by MHC class I molecules and are recognized by CD8+ cytotoxic T lymphocytes.
- Immunosuppressed patients have an increased risk for development of cancer, particularly types caused by oncogenic DNA viruses.
- In immune-competent patients, tumors may avoid the immune system by several mechanisms:
  - Selective outgrowth of antigen-negative variants.
  - Loss or reduced expression of histocompatibility antigens.
  - Immunosuppression-mediated by expression of certain factors (e.g.,TGF-β) by the tumor cells.

CARCINOGENIC AGENTS

Types of Carcinogens:

1) Chemical Carcinogens:

Most chemical carcinogens are mutagenic causing malignant transformation from mutations that affect proto-oncogene and tumor suppressor genes.

Examples:

- **Aromatic hydrocarbons** as 3,4 benzpyrene (exist in cigarette smoke) cause cancer lung.
- **Aromatic amines** as B naphthylamine: cause cancer bladder.
- **Asbestos**: cause mesothelioma.
- **Aflatoxins** (produced by Aspergillus flavus fungus) cause hepatic carcinoma.
- **Vinyl chloride** cause hepatic angiosarcoma.
- **Arsenic** causes skin cancer.

2) Physical carcinogens:

- **Prolonged exposure to ultraviolet rays** (sun) can cause skin malignancy (basal cell carcinoma, Squamous cell carcinoma, and melanoma).
- **Ionizing radiations**
  Ionizing radiation causes chromosome breakage, translocations, and less frequently point mutations, leading to genetic damage and carcinogenesis e.g. leukemia, osteosarcoma, skin malignancy and lung cancer.

3) Viruses:

Viruses may lead to development of cancer by:

- Integrating viral oncogenes into host DNA thus altering DNA.
- Producing proteins that inactivate products made by tumor suppressor genes.

Some viruses that have been implicated in causing neoplasms include:

- Epstein-Barr virus e.g.
  a. Burkitt's lymphoma
  b. Nasopharyngeal carcinoma
  c. other B cell lymphomas and some cases of Hodgkin's disease
- Hepatitis B virus causes hepatocellular carcinoma
- Human papilloma virus causes cervical carcinoma and some forms of carcinoma of skin cancers
- HTLV-1 (Human T lymphotropic virus I) causes T cell leukaemia/lymphoma.

4) **Hormones:** They cannot cause tumor initiation but may act as promoters. Examples:
- **Estrogen**: High levels of oestrogen (as in anovulation in adults & in cases of granulosa cell tumor of the ovary) can promote endometrial & mammary carcinoma.
- **Diethyl stilbosterol (DES)**: Administration of DES in a pregnant lady can promote vaginal adenocarcinoma (clear cell type) in her baby (if female) later on in life.
- **Androgens**: Androgen in high levels can promote prostatic carcinoma.
- **Role of contraceptive pills** in cancer breast is questionable. However they can lead to benign tumors of liver (hepatic adenoma)

CLINICAL ASPECTS OF NEOPLASIA

Benign tumors are not dangerous unless:
1. They arise in vital organs as brain e.g. a small pituitary adenoma can destroy the whole pituitary gland.
2. They arise in hollow organs (as intestine) causing obstruction.
3. They produce hormones as in tumors of endocrine glands e.g. adenomas from beta cells of pancreas can cause hyperinsulinism, sometimes fatal.
4. Some benign tumors may change malignant.

Malignant tumors are serious & cause death.
Causes of Death include:
1. Local organ destruction by direct spread.
2. Distant organ destruction by metastases.
3. Destruction of vital centers (brain tumors).
4. Obstruction of the lumen of hollow organs e.g. intestinal tumors.
5. Organ failure e.g.
   - Renal failure due to urinary obstruction (or bilateral renal tumors).
   - Liver failure & jaundice in case of primary or metastatic liver tumors.
6. Malnutrition due to:
   - Loss of appetite.
   - Interference with food intake (in cancer of GIT).
   - Chronic toxemia due to secondary bacterial infection.
   - Anaemia is common due to :
     a. Recurrent hemorrhages from the tumor.
     b. Bone marrow destruction by metastases.
     c. High tumor cell metabolism may lead to folic acid deficiency. Iron deficiency may also occur.
     d. Autoimmune hemolysis in some cases.
   - Cachexia:
     - This is marked decrease of body fat and lean body mass, weakness, anorexia and anemia.
     - There is some correlation between the size and extent of tumor spread and cachexia.

- Cachexia does not result due to nutritional demands of the tumor.
- Evidence indicates that cachexia result from the action of soluble factors such as cytokines produced by the tumor and the host (TNF secreted by macrophages or the tumor).

7. Some malignant tumors may secrete hormones:
   - Functioning endocrine tumor.
   - Para-neoplastic syndromes occur in 10% of cases. They are caused by abnormal products of the tumor e.g. lung carcinoma may produce ACTH causing Cushing's syndrome.
8. Hypercoagulability (migratory thrombophlebitis, disseminated intravascular coagulation, nonbacterial thrombotic endocarditis)

GRADING AND STAGING OF TUMORS

Grading:

- Grading of a cancer is based on the degree of differentiation of the tumor cells and, in some cancers, the number of mitoses or architectural features.
- Grading schemes differ for each type of malignancy, and generally range from two categories (low grade and high grade) to four categories.
- Although histologic grading is useful, the correlation between histologic appearance and biologic behavior is less than perfect.

Staging:

- The staging of solid cancers, determined by imaging or surgical exploration, is based on the size of the primary lesion, its extent of spread to regional lymph nodes, and the presence or absence of blood-borne metastases.
- The major staging system currently in use is the American Joint Committee on Cancer Staging.
- This system uses a classification called the TNM system—T for primary tumor, N for regional lymph node involvement, and M for metastases.

TNM staging varies for specific forms of cancer, but there are general principles:

- The primary lesion is characterized as T1 to T4 based on increasing size.T0 is used to indicate an in situ lesion.
- N0 would mean no nodal involvement, whereas N1 to N3 would denote involvement of an increasing number and range of nodes.
- M0 signifies no distant metastases, whereas M1 or sometimes M2 indicates the presence of metastases and some judgment as to their number.

- Staging is of greater value than grading, e.g.as regards choice of treatment and prognosis.

LABORATORY DIAGNOSIS OF CANCER

Morphologic Methods:

Several histologic and cytologic sampling of tumors are available e.g. Excision biopsy, fine needle aspiration and cytologic smears.

Immunohistochemistry:

- Immunohistochemistry is a powerful tool in determining the histogenesis of poorly differentiated tumors.
- Identification of different tumor types is by using antibodies against different specific proteins expressed by tumor cells e.g.:
  - Leucocyte common antigen (LCA) is detected in lymphomas.
  - Cytokeratins (CK) are present in carcinomas.
  - Vimentin is detected in sarcomas,
  - S100 protein is detected in tumors of schwann cells and malignant melanoma.
- Immunohistochemistry may be applied for identification of prognostic indicators e.g.:
  - Ki 67 is a proliferation marker. Highly proliferative tumors are more aggressive.
  - Detection of estrogen & progesterone receptor expression in cancer breast.
  - Detection of HER 2 (growth factor receptor) expression in cancer breast. Tumors with increased Her 2 receptors are more aggressive and are treated with anti Her 2 antibodies (Herceptin).

Tumor Markers:

Biochemical assays for tumor-associated enzymes, hormones, and other tumor markers in the blood cannot be used for definitive diagnosis of cancer; however, they contribute to the detection of cancer and in some instances are useful in determining the effectiveness of therapy or the appearance of a recurrence.

Table (5.5) The most common tumor markers used in diagnosis and follow up.

Tumor marker	Tumor type
Hormones	
Human Chorionic Gonadotrophin	Trophoblastic tumors
Calcitonin	Medullary carcinoma, thyroid
Oncofetal antigens	
Alpha feto-protein	Hepatocellular carcinoma
Carcino-embryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and heart
Antigens	
Prostatic specific antigens	Cancer prostate
Immunoglobulins	Multiple myeloma
Mucins and Other Glycoproteins	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer

Formative Assessment

MCQ

1) Which of the following is characteristic of hypertrophy
   a) Disordered atypical non-neoplastic cellular proliferation.
   b) Increase in the size of the cells.
   c) Uncontrolled autonomous cell growth.
   d) Increase in the number of the cells
2) After leg immobilization in plaster due to fracture, decrease in size of calf muscle is due to
   a) Atrophy
   b) Aplasia
   c) Hypoplasia
   d) Dystrophy
3) The following is true about adenoma except
   a) Benign mesenchymal tumor
   b) Are capsulated
   c) May secrete hormone
   d) May turn malignant

4) Serum tumor markers that can be used in diagnosis of neoplasia include all of the following except
   a) PSA
   b) Alpha feto protein
   c) Carcinoembryonic antigen
   d) P53
   e) CA125

EMQ

Match each of the following tumors or masses In column A with their corresponding name in column B. Each choice in column B may be used once, more than once or not at all.

1) Benign tumor of adipose tissue	a) Choristoma
2) Tumor of three germ cell layers foreign to the organ from which they arise	b) Embryoma
3) Non capsulated tissue mass not foreign to the organ in which they arise	c) Lipoma
	d) Rhabdomyoma
	e) Teratoma
	f) Hamartoma

SAQ

5) List routes of spread of malignant tumors
6) Name the 2 classes of tumor suppressor genes, describe how they work and give one example for each