Neoplasia

kamran

- **Neoplasia**-new growth
  - Abnormal mass of tissue with growth that exceeds and is uncoordinated with that of the surrounding normal tissues; autonomous
- **Tumor**-synonymous with neoplasm
- **Cancer**-common term for malignant neoplasm
- **In common medical usage**, a neoplasm is often referred to as a ***tumor,*** and the study of tumors is called ***oncology*** (from *oncos,* "tumor," and *logos,* "study of")

NEOPLASIA

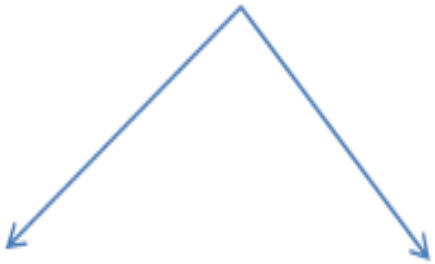
- Literally means “New Growth”
- Willis defined it as “ an abnormal mass of tissue the growth of which exceeds and is uncoordinated with that of the normal tissues and persists in the same excessive manner after the cessation of the stimuli which evoked the chance
- Genetic disorder but epigenetic changes occur and both lead to alter the functional expression of genes involved in growth, survival & senescence
- All tumors-clonal
- Fundamental to the origin of all neoplasms are heritable changes that allow excessive and unregulated proliferation that is independent of physiological growth-regulatory stimuli

❖ Growth Disorders

Non-neoplastic
(secondary)
Controlled and reversible

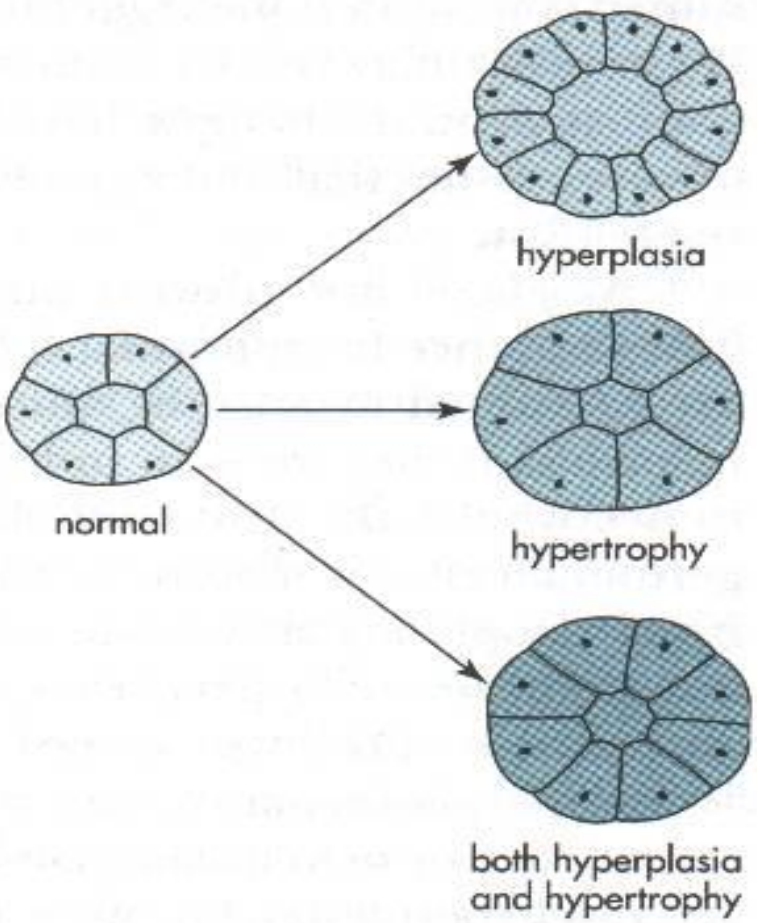
- Hypertrophy
- Hyperplasia
- Metaplasia
- Dysplasia?

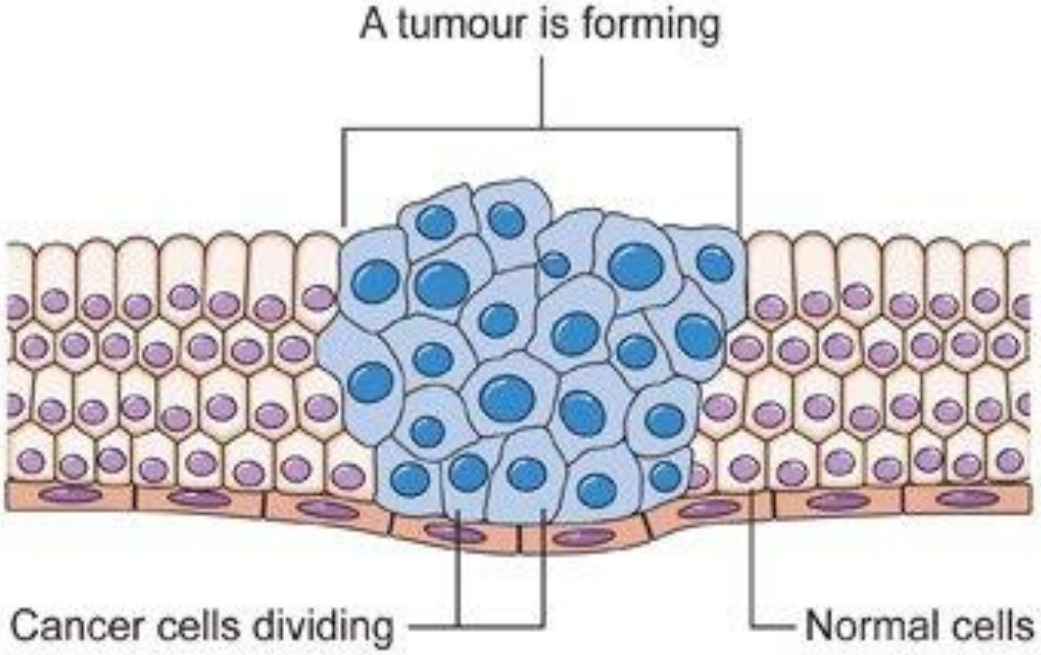
Neoplastic (Tumor)
(primary)
Uncontrolled and irreversible



Benign
Localized, noninvasive

Malignant
Spreading, invasive


hyperplasia
normal
hypertrophy
both hyperplasia
and hypertrophy


A tumour is forming
Cancer cells dividing
Normal cells

Cancer

- Refers to all malignant neoplasms
- May arise from most organs
- Morbidity and mortality vary by type of CA
- Many are curable or treatable; Hodgkin's lymphoma - highly curable but pancreatic cancers-always fatal
- Ranks 2nd to CV disease as leading cause of death
- Affects all age groups
- Causes more deaths in children age 3–15than any other disease
- Emotional and physical suffering is more agonizing

- 1 out of 3 Americans will develop cancer in their lifetime; 1 in 4 deaths in US is due to cancer
- Most common in all: Skin CA
- Men: prostate, lung, colorectal
- Women: Breast, lung, colorectal
- Lung cancer is leading cause of CA death in US—resistant to treatment

WHO 2014

Pakistan

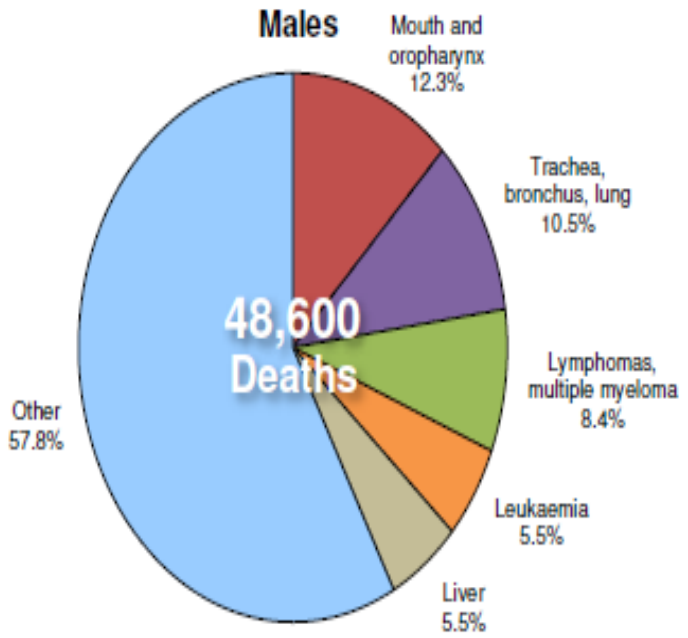
Total population: 179,000,000

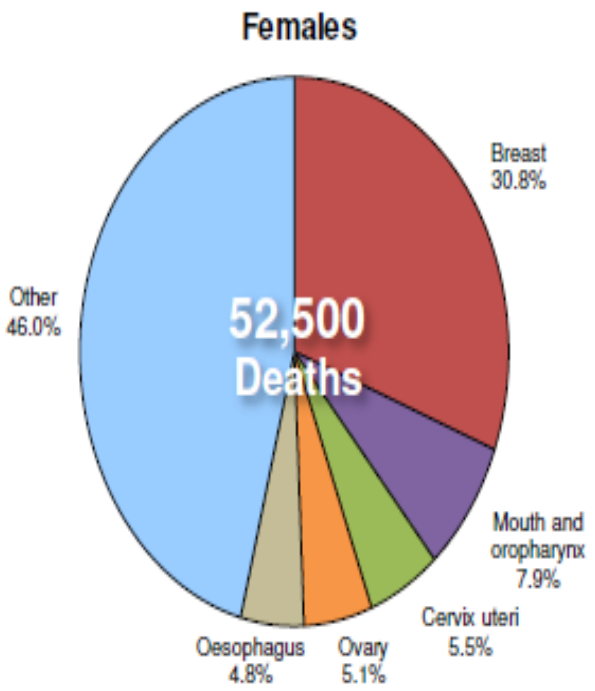
Income group: Lower middle

Total deaths: 1,332,000

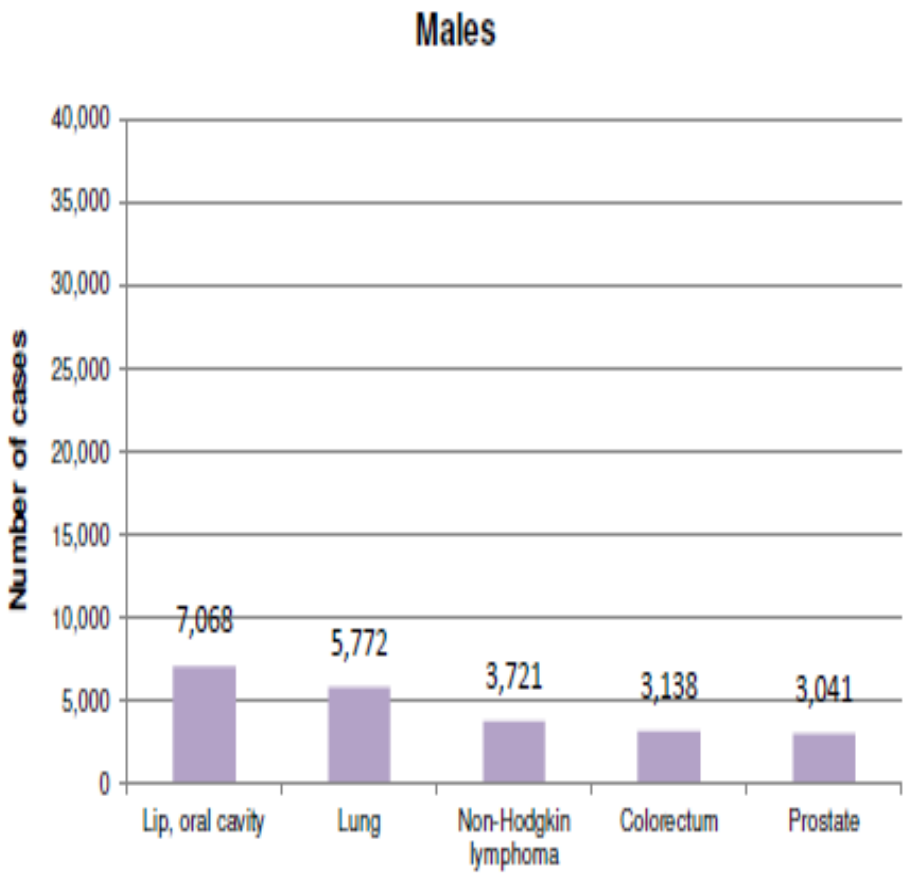
Life expectancy at birth: Total:65 Males:64 Females:66

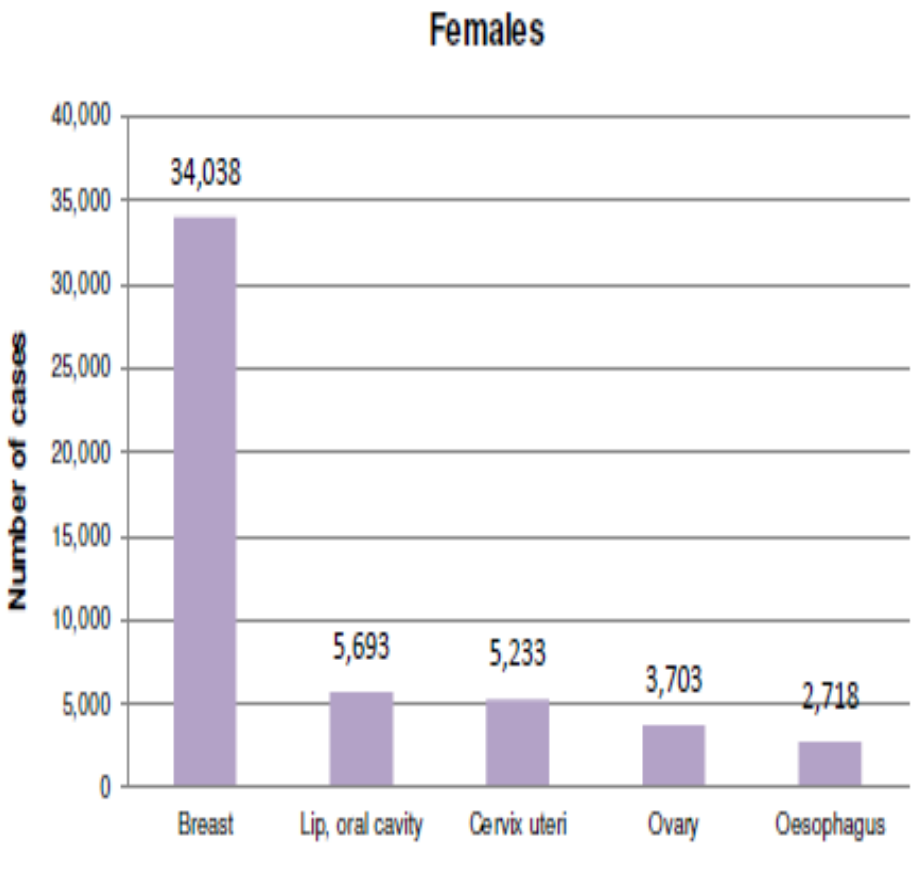
Cancer Mortality Profile*



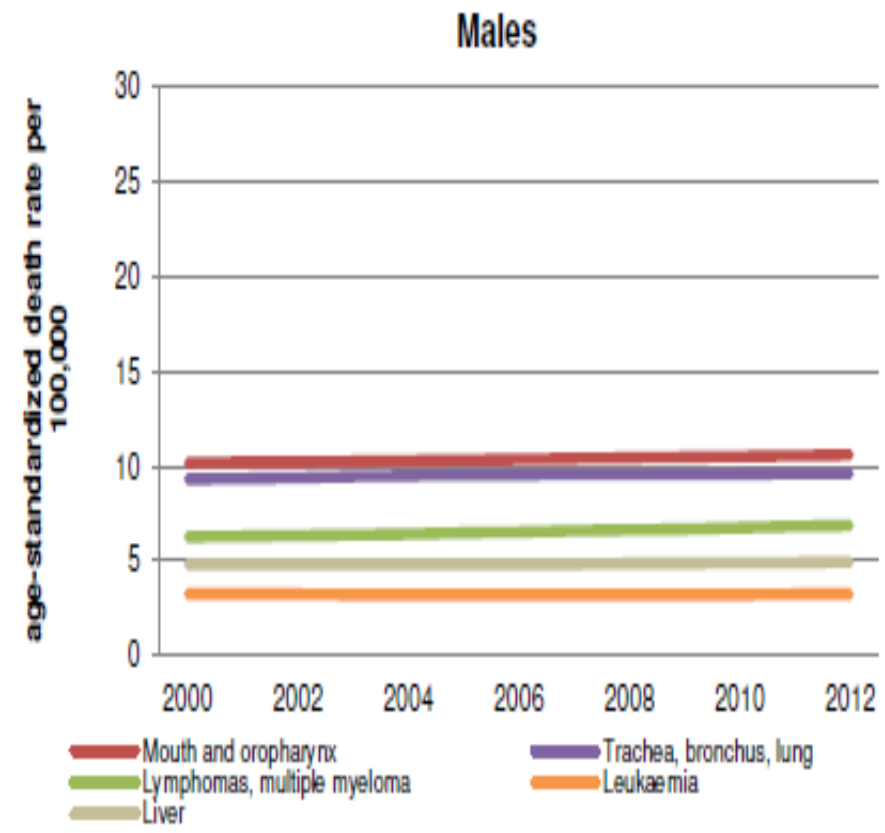


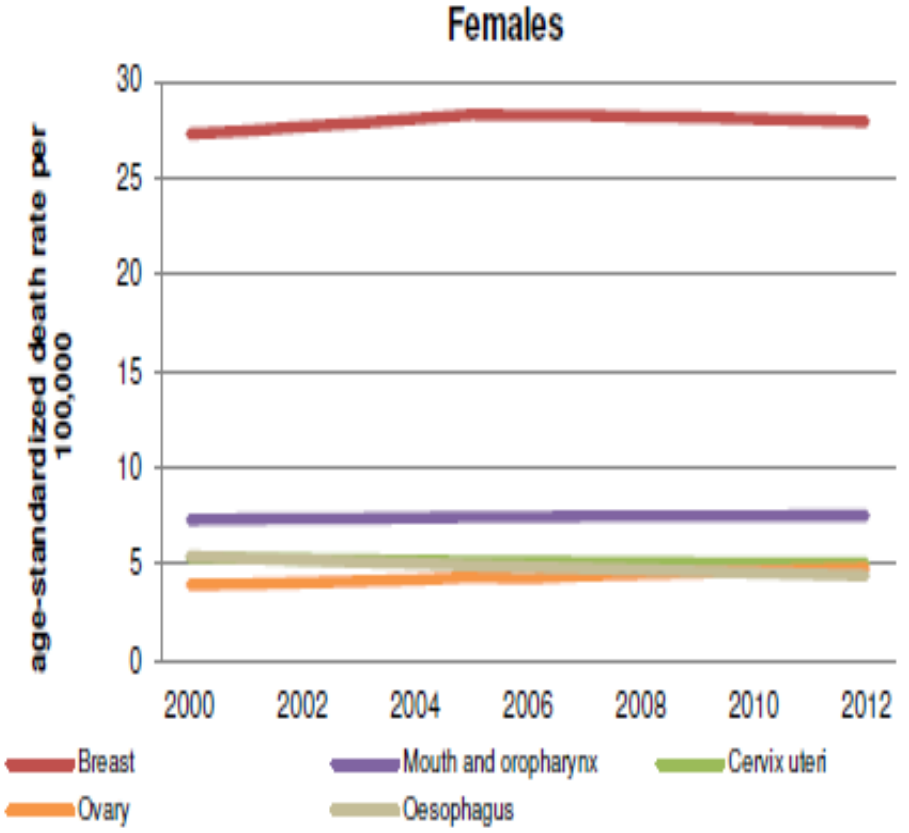
Cancer Incidence





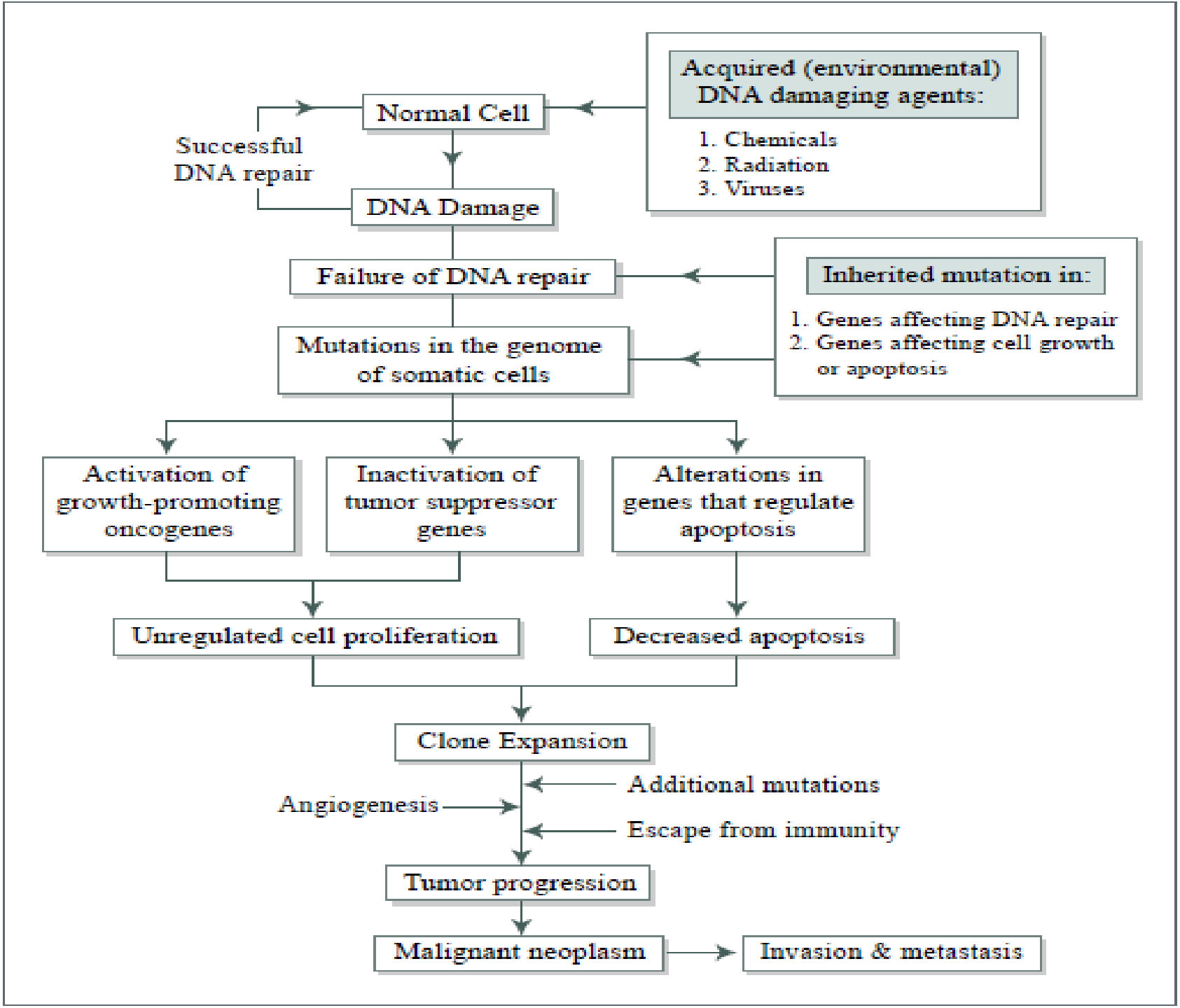
Age-Standardized Cancer Mortality Trends*





Adult Risk Factors

	Males	Females	Total
Current tobacco smoking (2011)	37.6%	7.4%	22.7%
Total alcohol per capita consumption, in litres of pure alcohol (2010)	0.1	0.0	0.1
Physical inactivity (2010)	18.5%	29.7%	24.0%
Obesity (2014)	3.3%	6.4%	4.8%
Household solid fuel use (2012)	-	-	62.0%


Acquired (environmental) DNA damaging agents:
1. Chemicals
2. Radiation
3. Viruses
Normal Cell
Successful DNA repair
DNA Damage
Failure of DNA repair
Inherited mutation in:
1. Genes affecting DNA repair
2. Genes affecting cell growth or apoptosis
Mutations in the genome of somatic cells
Activation of growth-promoting oncogenes
Inactivation of tumor suppressor genes
Alterations in genes that regulate apoptosis
Unregulated cell proliferation
Decreased apoptosis
Clone Expansion
Additional mutations
Angiogenesis
Escape from immunity
Tumor progression
Malignant neoplasm
Invasion & metastasis

Hallmarks of Cancers

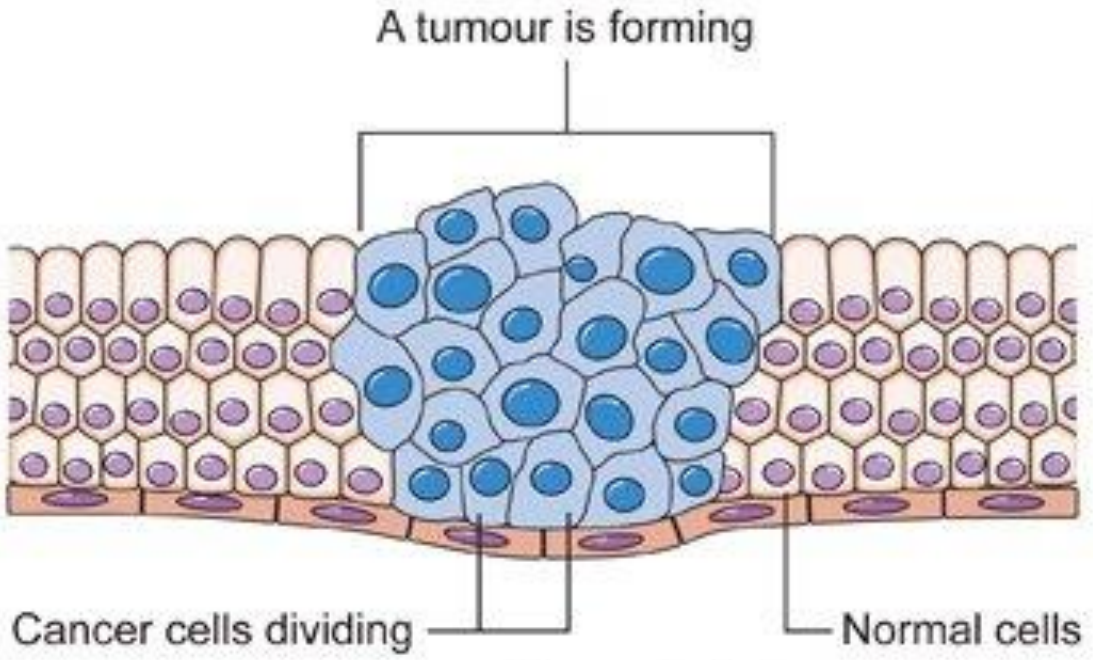
- Self sufficiency in growth signals - autonomous and unregulated
- Lack of response to growth inhibitory signals that control non-neoplastic cellular proliferations such as hyperplasias;
- Evasion of cell death, allowing cancer cells to survive under conditions that induce apoptosis in normal cells
- Limitless replicative potential, making cancer cells immortal
- Development of angiogenesis to sustain cancerous growth
- Ability to invade local tissues and spread to distant sites
- Reprogramming of metabolic pathways—specifically, a switch to aerobic glycolysis even when there is abundant oxygen; &
- Ability to evade the immune system

Characteristics of Normal Cells

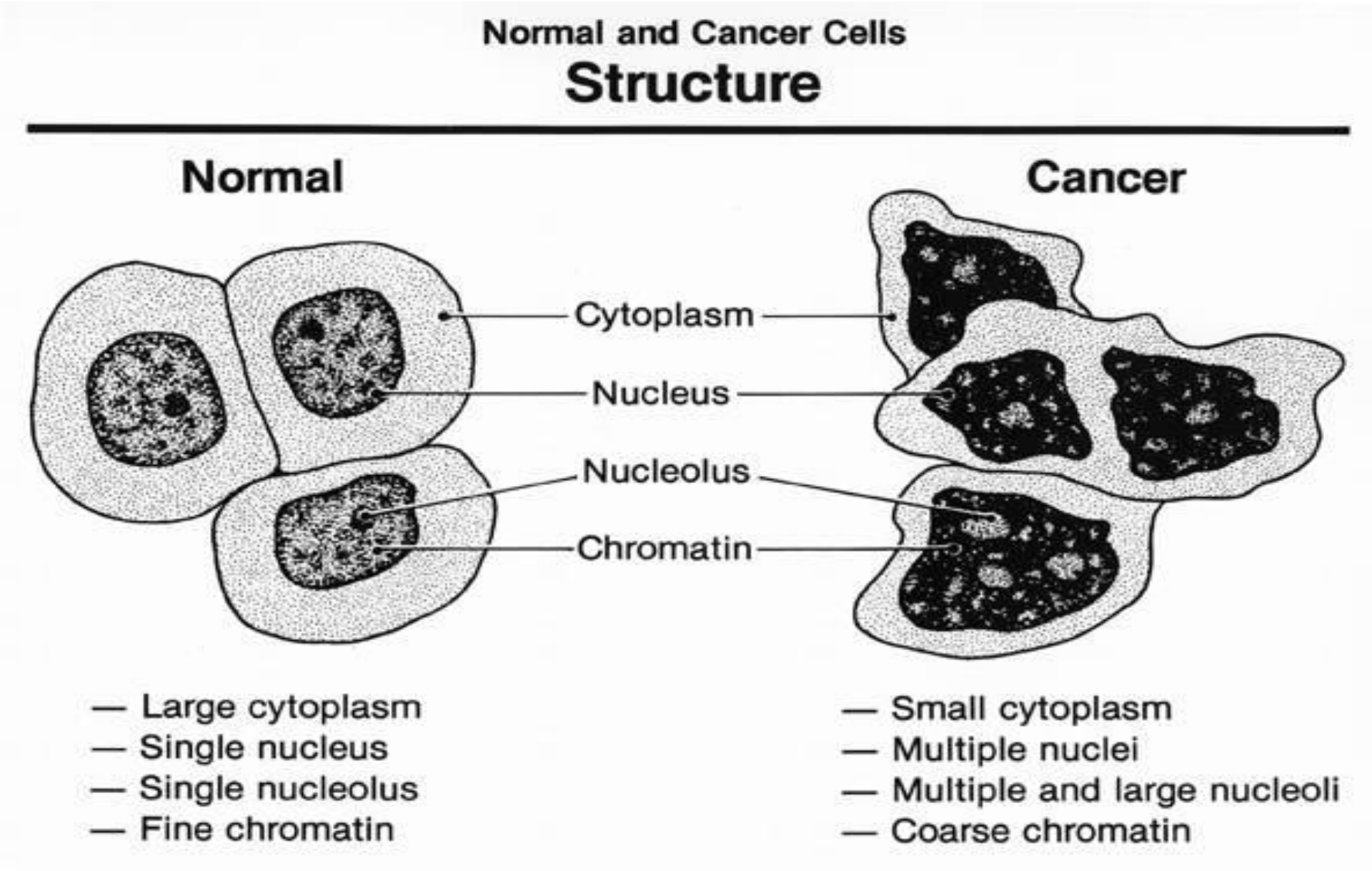
- Reproduce themselves exactly
- Stop reproducing at the right time
- Stick together in the right place
- Self destruct if they are damaged
- Become specialized (differentiated) or 'mature'

Characteristics of Cancer Cells

- Cancer cells don't stop reproducing
- Cancer cells don't obey signals from other cells
- Cancer cells don't stick together
- Cancer cells don't specialize or differentiate , but stay immature



Comparing Normal and Cancer Cells



❖ *What is Dysplasia?*

Dysplasia is a disordered but ***non-neoplastic*** *proliferation of* ***epithelia***

It is a *loss in the uniformity of individual cells and in their architectural orientation*

Features of dysplastic cells:

- Considerable **pleomorphism** (variation in size and shape)
- **Hyperchromatic nuclei**, abnormally **large** for the size of the cell
- **Mitotic figures** are more abundant than usual and appear in abnormal locations

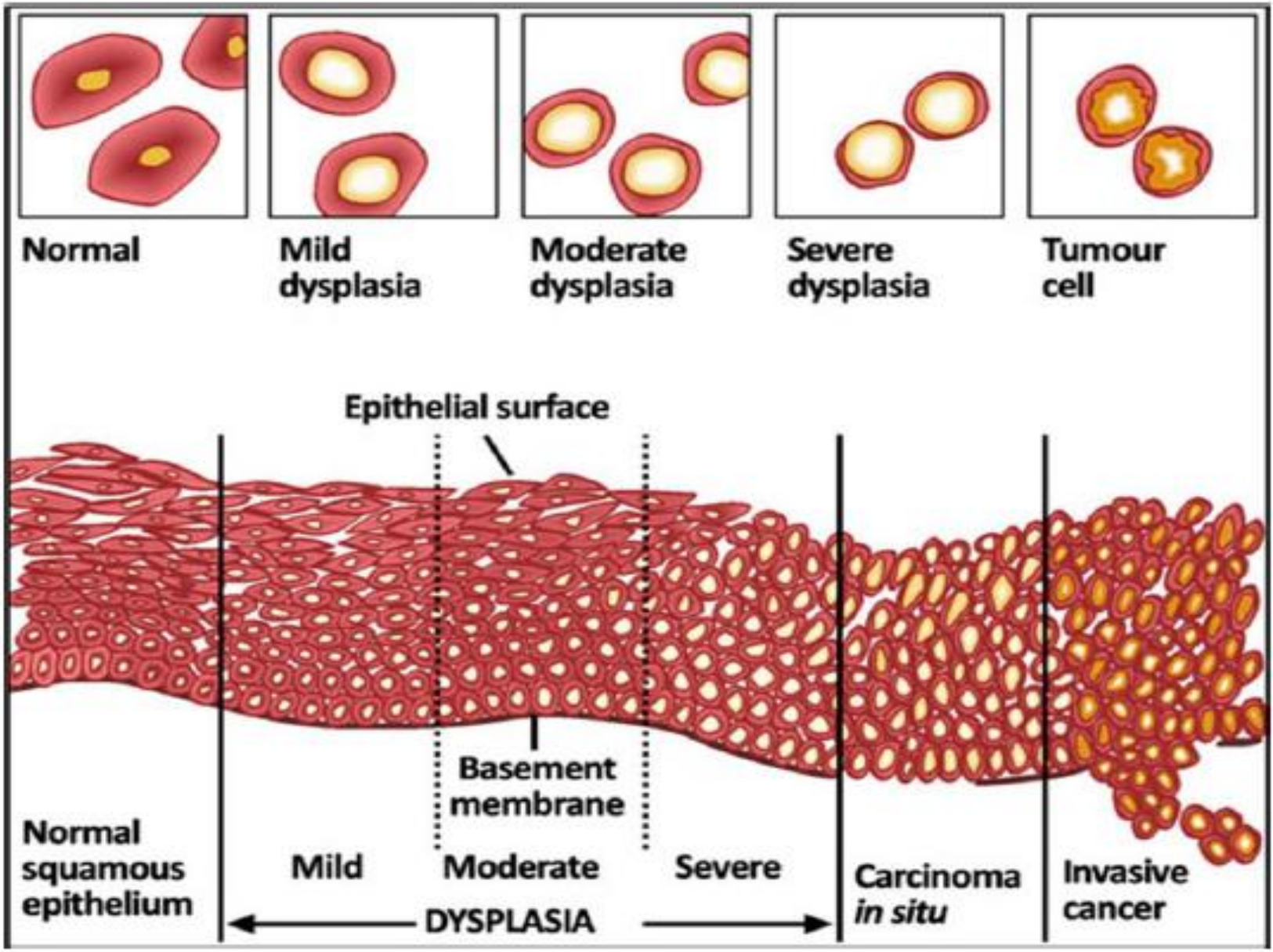
(In dysplastic stratified squamous epithelium, mitoses are not confined to the basal layers)

- Considerable architectural **anarchy**

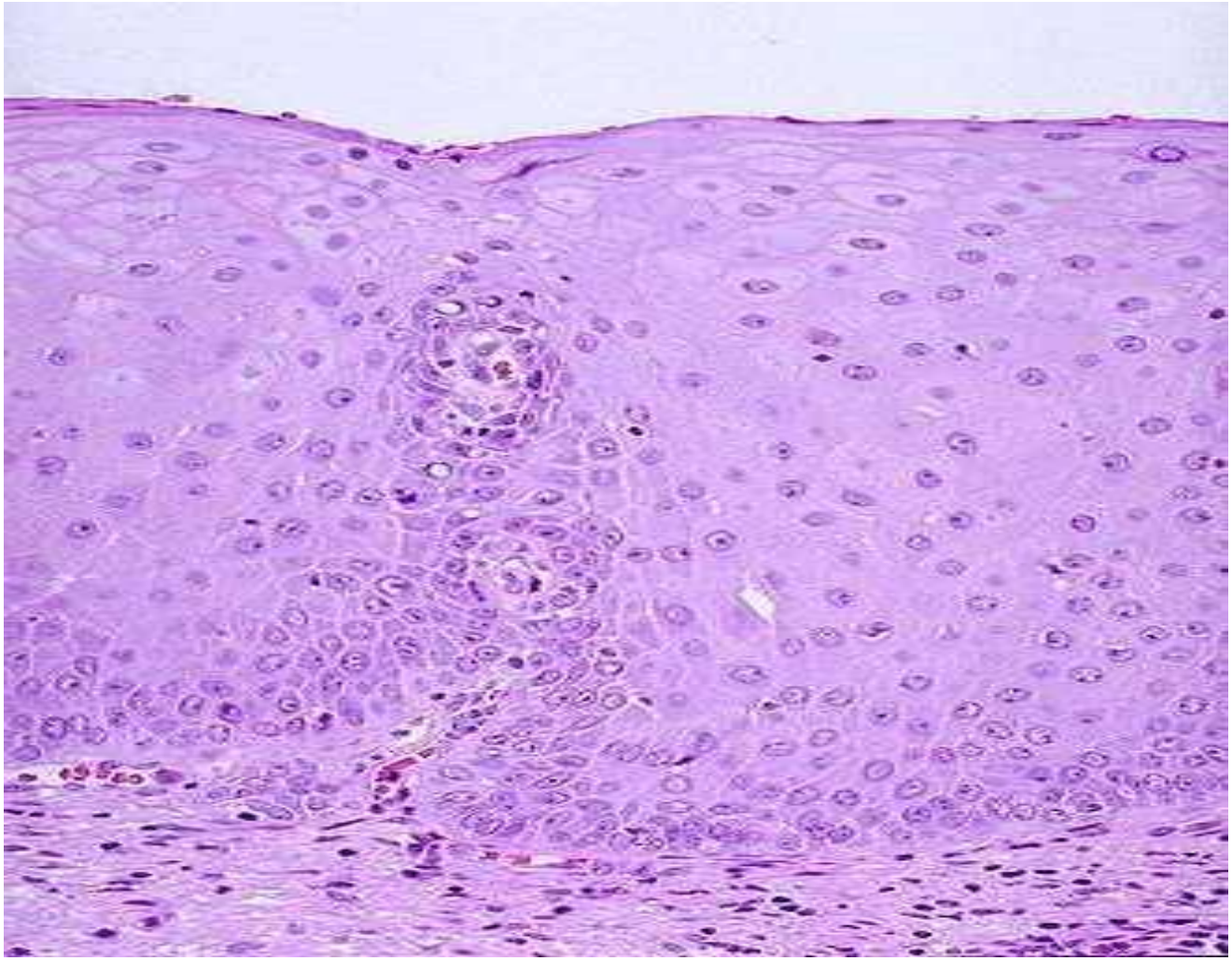
The term dysplasia without qualifications does not indicate cancer, and dysplasia does not necessarily progress to cancer.

Mild-to-moderate changes that do not involve the entire thickness of epithelium may be ***reversible****, and with removal of the putative inciting causes, the epithelium may revert to normal.*

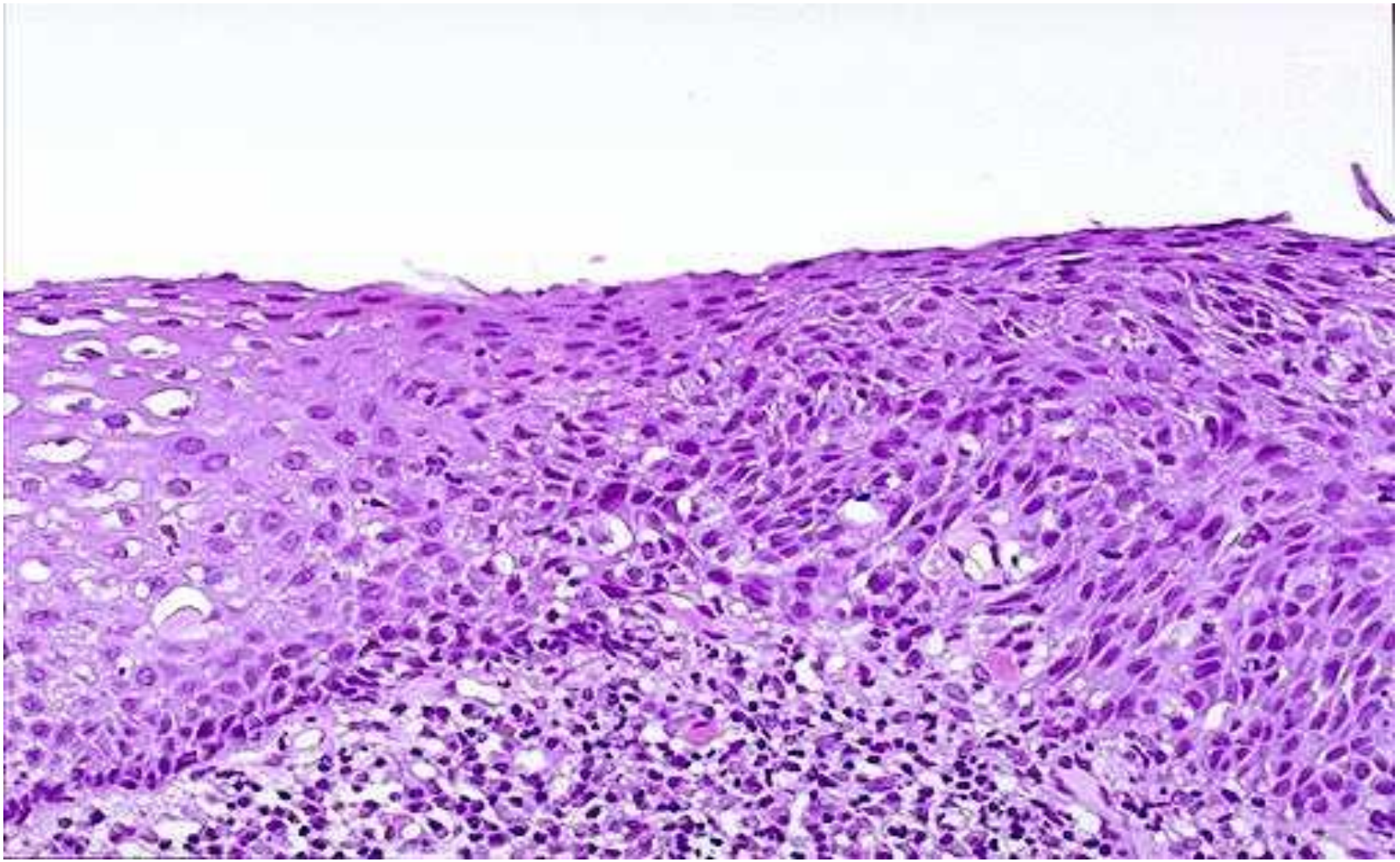
❖ *From Dysplasia to Cancer*



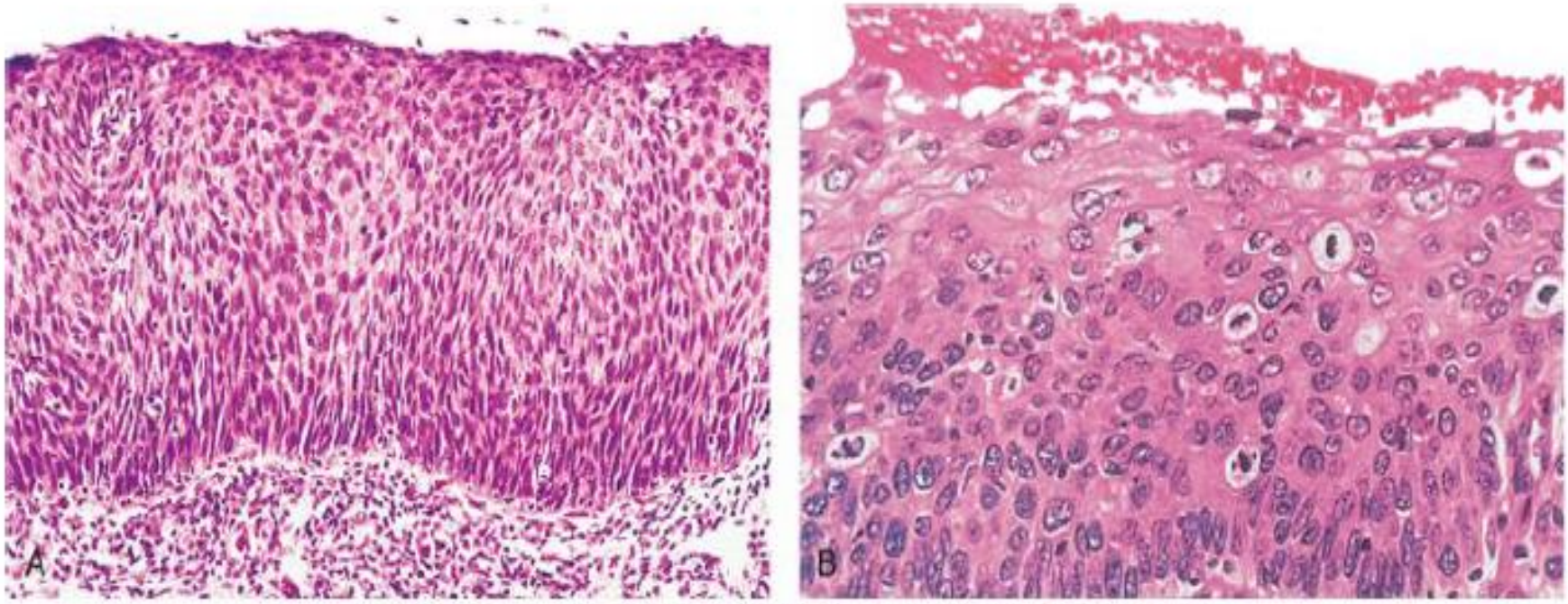
normal epithelium



dysplasia



❖ *Carcinoma in situ*



A, Low-power view shows the entire thickness of the epithelium is replaced by atypical dysplastic cells. There is no orderly differentiation of squamous cells. The basement membrane is intact, and there is no tumor in the subepithelial stroma.

B, High-power view of another region shows failure of normal differentiation, marked nuclear and cellular pleomorphism, and numerous mitotic figures extending toward the surface

When dysplastic changes are marked and involve the **entire thickness of the epithelium**, the lesion is referred to as ***carcinoma in situ***, a **pre-invasive stage of cancer**

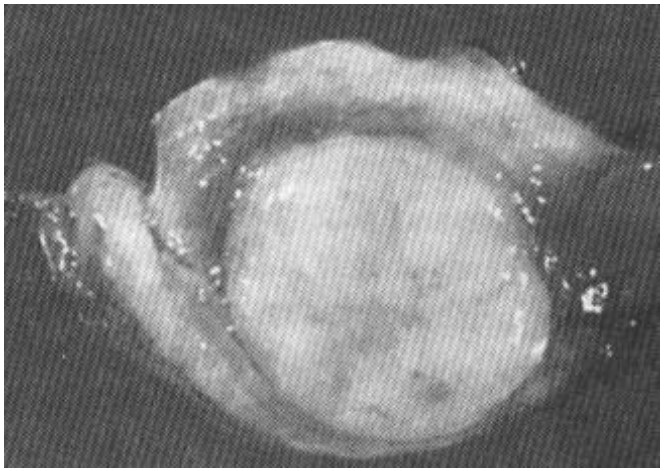
Benign vs Malignant

Benign

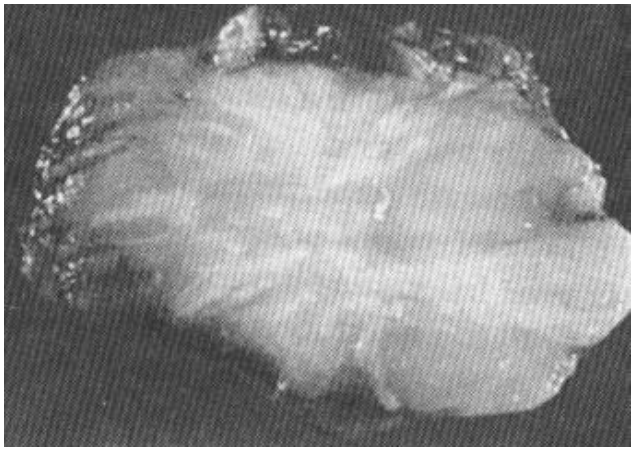
- Well defined; often encapsulated
- Appear similar to cell of origin
- Does not spread to other tissues
- Slow growth
- Usually not fatal

Malignant (Cancer)

- Very invasive with vague borders
- Dedifferentiated – appear to be very immature version of cell of origin
- Metastasis – spreads via blood or lymph to other tissues/organs
- Rapid growth
- High fatality rate

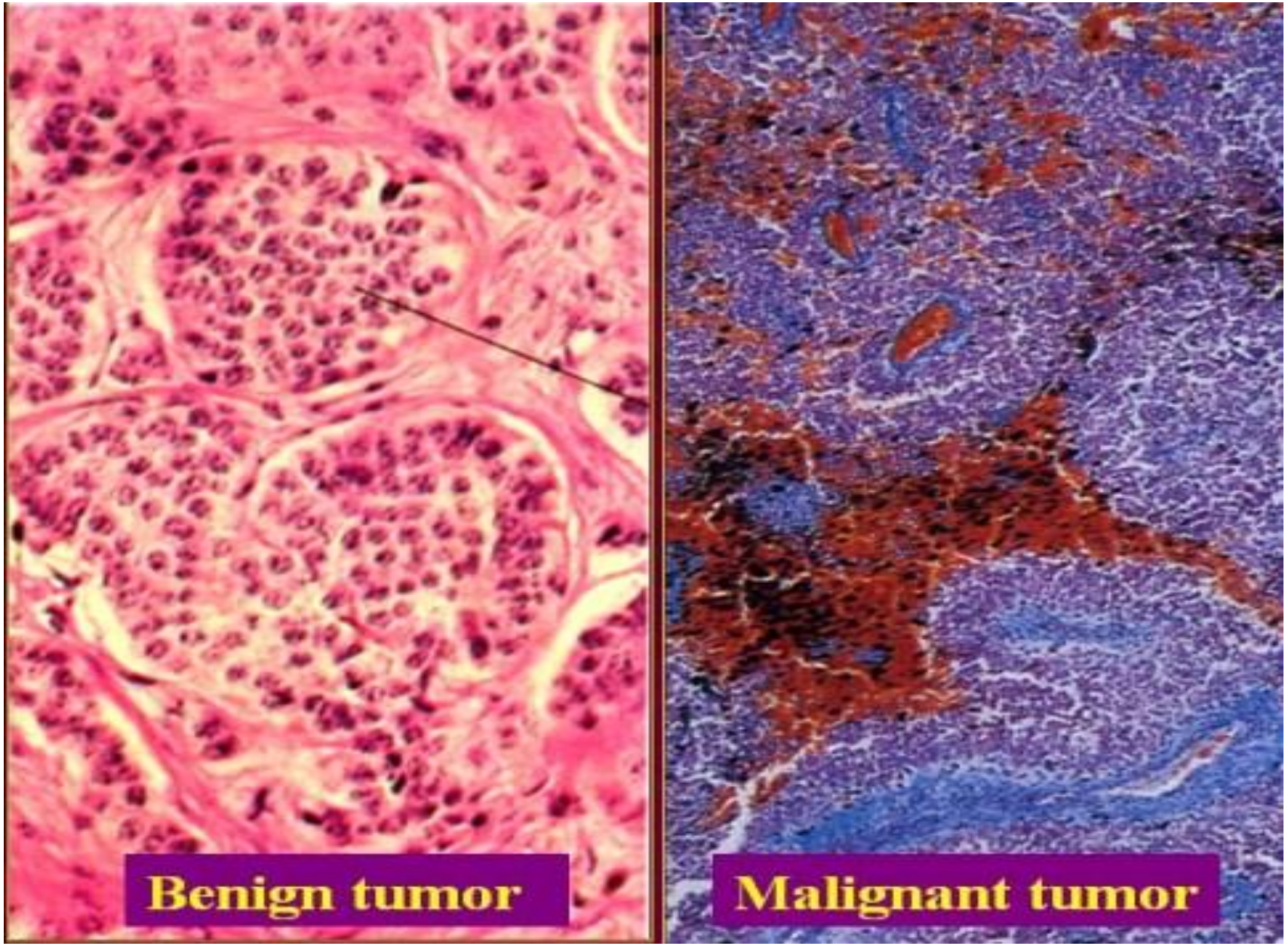


Benign



Malignant

Note: Death is usually due to complications caused by cancer


Benign tumor
Malignant tumor

Nomenclature-Benign Tumor

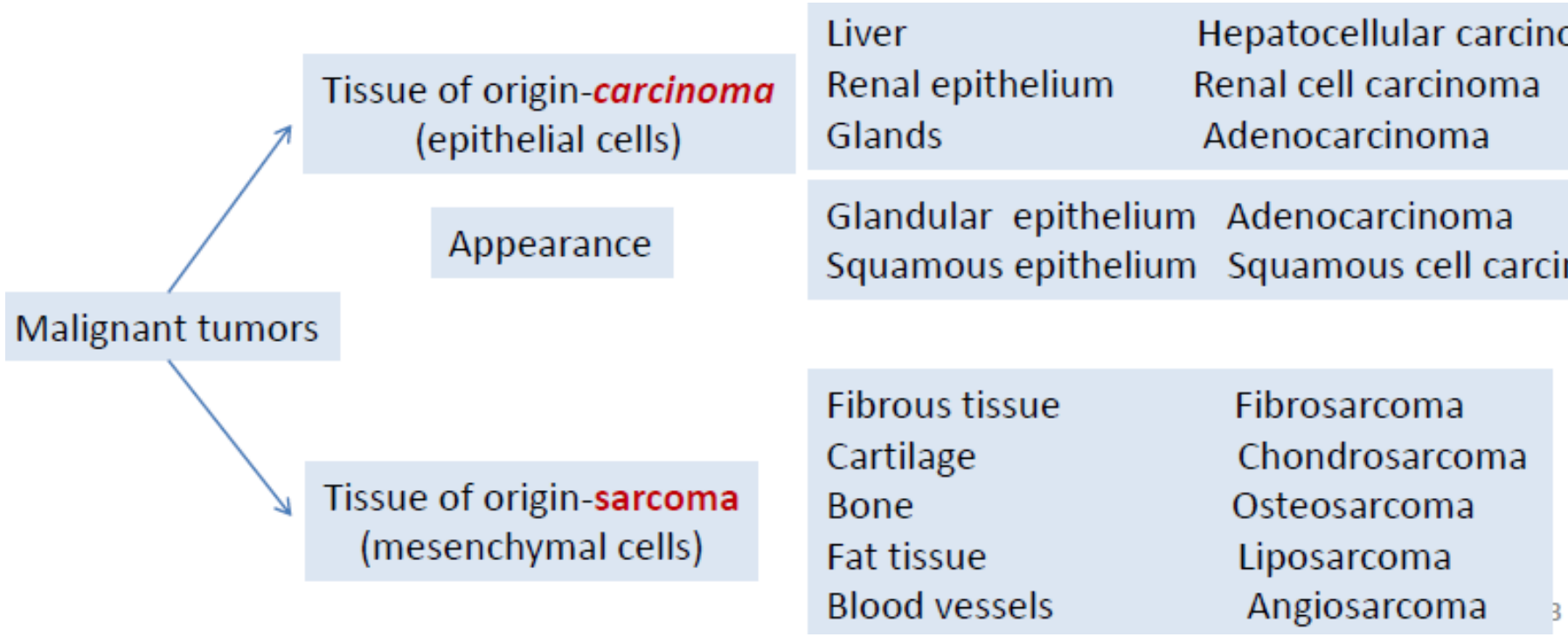
Benign tumors → Tissue of origin-oma

Fibrous tissue	Fibroma
Cartilage	Chondroma
Bone	Osteoma
Glands	Adenoma
Epithelium	Papilloma

- Epithelial: sometimes on their microscopic pattern & sometimes on their macroscopic pattern
- Others include:
  - Polyp : benign tumor projecting over mucosal surface
  - Cystadenoma : benign epithelial tumor forming hollow cystic mass

- Mesenchymal
  - Chondroma: benign cartilaginous tumor
  - Leiomyoma: benign smooth muscle tumor
  - lipoma: benign tumor of fat
  - Fibroma: benign tumor of fibrous tissue
- Mixed
  - Benign Mixed Tumor –divergent differentiation of stem cell (pleomorphic adenoma)
  - Fibroadenoma – neoplastic fibrous component
- More than one germ cell layer
  - Benign teratoma – mature components

Nomenclature-Malignant Tumor



- Epithelia is derived from all 3 germ layers
- Mesoderm: *Epithelial- carcinoma
  *Mesenchymal- Sarcomas
  *Hematolymphoid tumors (leukemias and lymphomas)

- Carcinomas that grow in a glandular pattern are called *adenocarcinomas*
- Those that produce squamous cells are called *squamous cell carcinomas*
- Sometimes, the tissue or organ of origin can be identified as in renal cell carcinoma or cholangiocarcinoma
- Sometimes the tumor shows little or no differentiation and must be called *poorly differentiated or undifferentiated carcinoma*
- Cancer derived from same cell, i.e., monoclonal; but sometimes the tumor cells undergo *divergent differentiation,* creating so called *mixed tumors*

- The best example of mixed tumor is salivary gland containing epithelial components dispersed throughout a firomyxoid stroma, sometimes harboring islands of cartilage or bone
- Since the above diverse elements are thought to derive from epithelial cells or myoepithelial cells, or both, and the preferred designation for these neoplasms is *pleomorphic adenoma*
- Fibroadenoma of the female breast is another common mixed tumor
- Teratoma is a mixed tumor
- Inconsistency in nomenclature:
- - lymphoma/leukemia
- - Mesolithioma, melanoma & seminoma

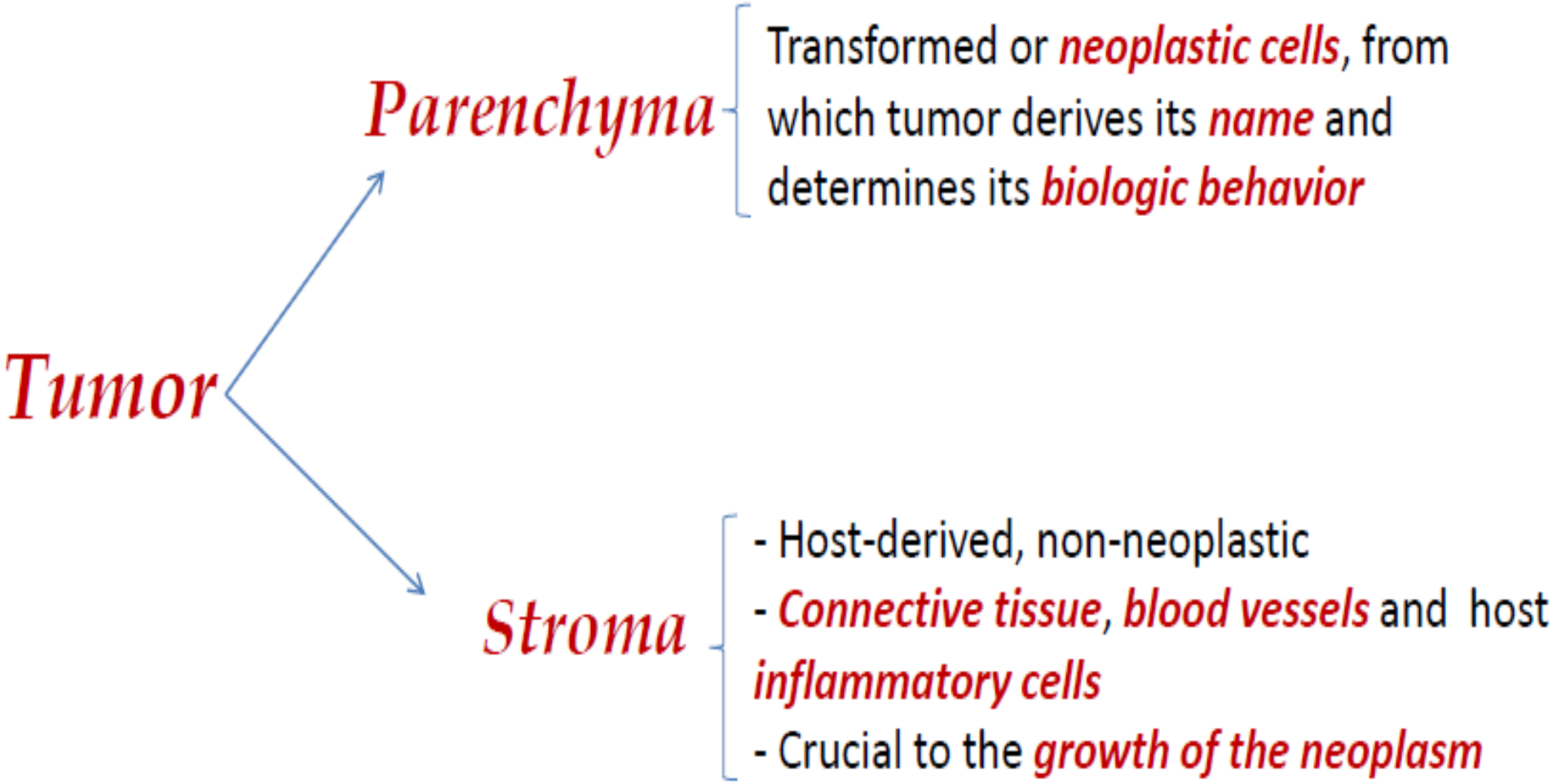
Tissue of Origin	Benign	Malignant
Composed of One Parenchymal Cell Type		
Connective tissue and derivatives	Fibroma	Fibrosarcoma
	Lipoma	Liposarcoma
	Chondroma	Chondrosarcoma
	Osteoma	Osteogenic sarcoma
Endothelial and related tissues		
Blood vessels	Hemangioma	Angiosarcoma
Lymph vessels	Lymphangioma	Lymphangiosarcoma
Mesothelium		Mesothelioma
Brain coverings	Meningioma	Invasive meningioma
Blood cells and related cells		
Hematopoietic cells		Leukemias
Lymphoid tissue		Lymphomas
Muscle		
Smooth	Leiomyoma	Leiomyosarcoma
Striated	Rhabdomyoma	Rhabdomyosarcoma
Tumors of epithelial origin		
Stratified squamous	Squamous cell papilloma	Squamous cell or epidermoid carcinoma
Basal cells of skin or adnexa		Basal cell carcinoma
Epithelial lining of glands or ducts	Adenoma	Adenocarcinoma
	Papilloma	Papillary carcinomas
	Cystadenoma	Cystadenocarcinoma
Respiratory passages	Bronchial adenoma	Bronchogenic carcinoma
Renal epithelium	Renal tubular adenoma	Renal cell carcinoma
Liver cells	Liver cell adenoma	Hepatocellular carcinoma
Urinary tract epithelium (transitional)	Urothelial papilloma	Urothelial carcinoma
Placental epithelium	Hydatidiform mole	Choriocarcinoma
Testicular epithelium (germ cells)		Seminoma
		Embryonal carcinoma
Tumors of melanocytes	Nevus	Malignant melanoma

RELATED TERMINOLOGIES

- **Hamartoma :** Excessive but focal overgrowth of cells and tissues native to the organ in which it occurs. Cellular elements are mature, but do not produce normal architecture
  - Hamartroma of lung
  - Angiomas
  - Pigmented nevi

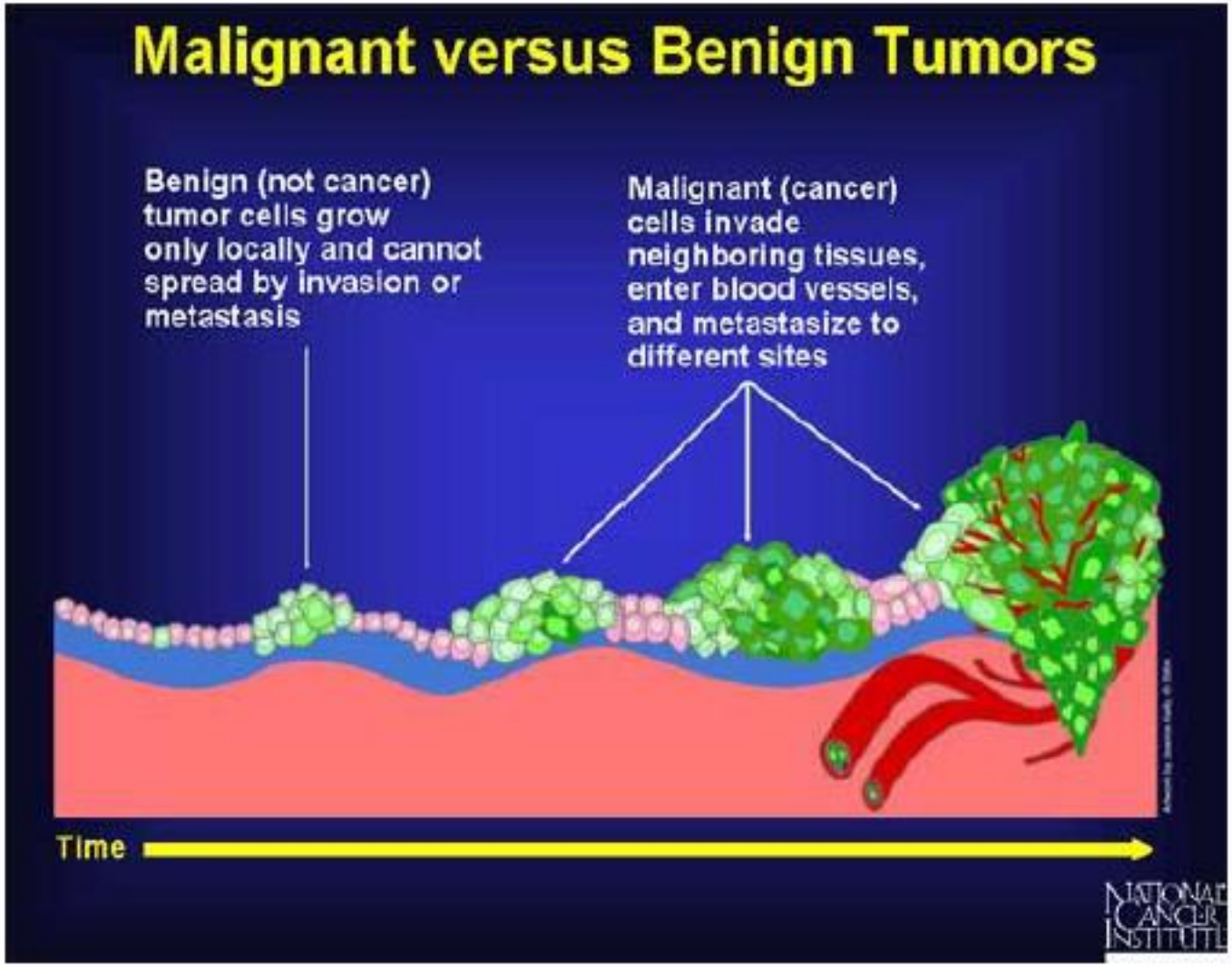
- **Choristoma (Heterotopia) :** Normal cells or tissues, that are present in abnormal locations
  - Pancreatic cells in the wall of stomach or intestine
  - Nests of adrenal cells in kidney , lung or ovaries

❖ Tumor Components



Characteristics Of Benign & Malignant Neoplasms

- The terms “benign” and “malignant” describe the biologic behavior of a tumor
- The biologic behavior is characterized by degree of differentiation of the tumor , rate of growth (and rate of cell death) , infiltration of surrounding tissue, and dissemination to distant sites

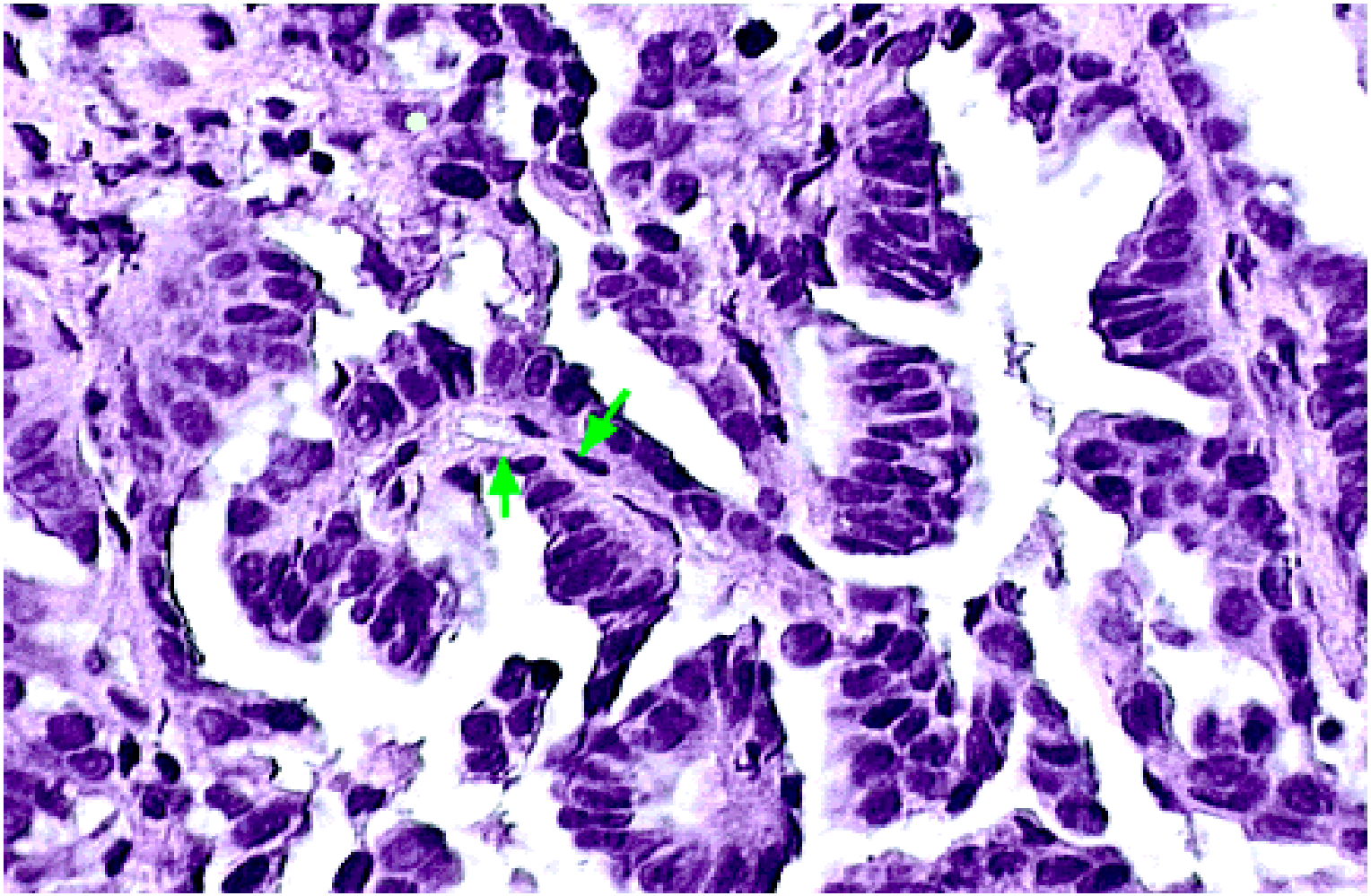


There are four fundamental features by which benign and malignant tumors can be distinguished: ***differentiation and anaplasia***, ***rate of growth***, ***local invasion***, *and* ***metastasis***.

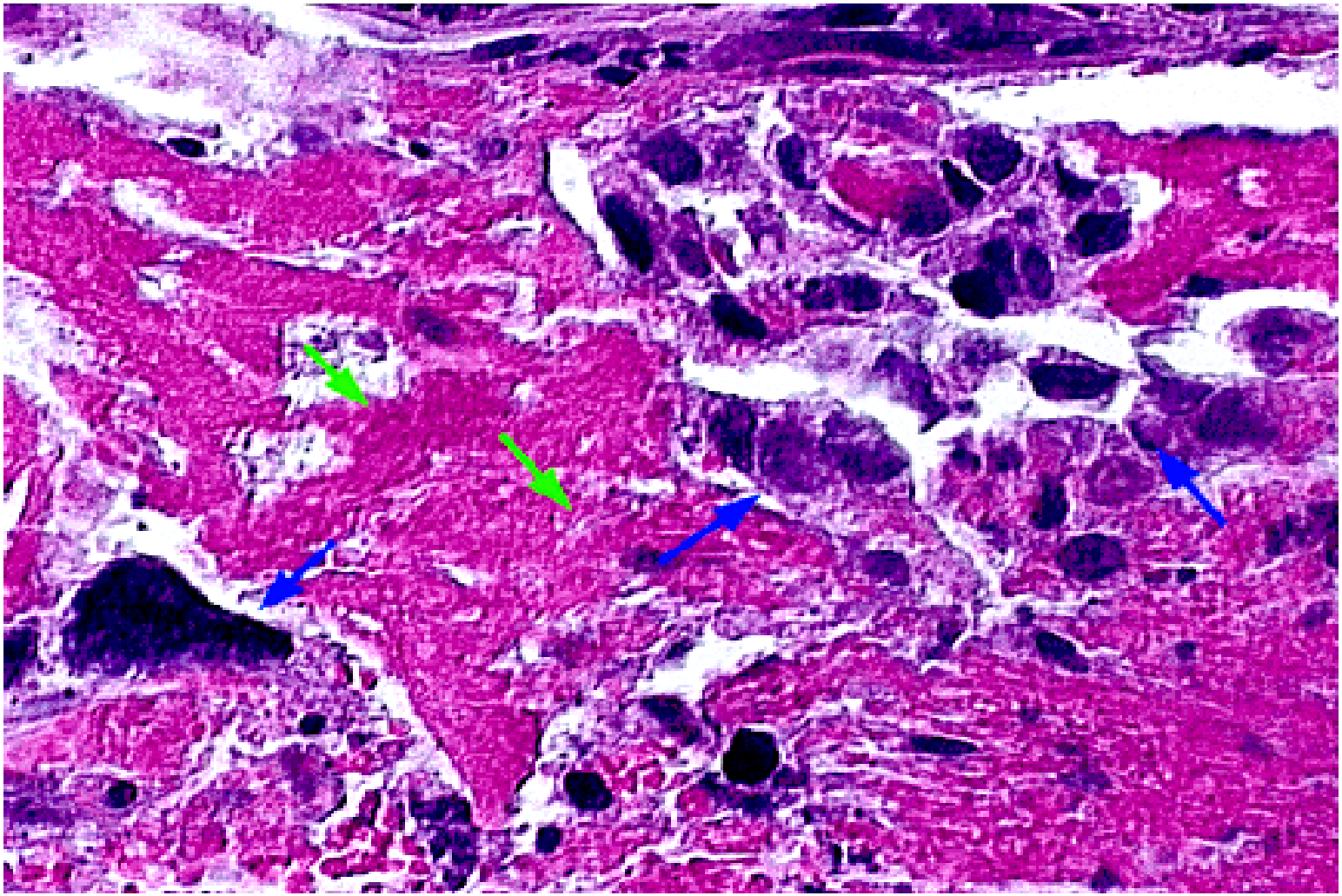
Differentiation & Anaplasia

- Differentiation and anaplasia are characteristics seen only in the parenchymal cells that constitute the transformed elements of neoplasms
- Well-differentiated tumors contain cells that resemble the normal cells of origin, e.g., lipoma
- Poorly-differentiated or undifferentiated tumors contain cells that do not resemble their normal counterparts (ancillary studies may be needed to determine the cell of origin)

well-differentiated



poorly-differentiated



Benign neoplasms are composed of well-differentiated cells that closely resemble their normal counterparts.

Lipoma: mature fat cells laden with cytoplasmic lipid vacuoles

Chondroma: mature cartilage cells that synthesize their usual cartilaginous matrix

Mitoses are usually rare and are of normal configuration.

Malignant neoplasms are characterized by a wide range of parenchymal cell differentiation: well differentiated- moderately well differentiated- undifferentiated.

Undifferentiated cells are called **anaplastic cells** and are considered a hallmark of malignancy!

- An example of well differentiated (WD)cancer is adenocarcinomas of the thyroid which may contain normal appearing follicles & difficult to distinguish from benign proliferations
- Malignant neoplasms that are composed of undifferentiated cells are said to be *anaplastic*

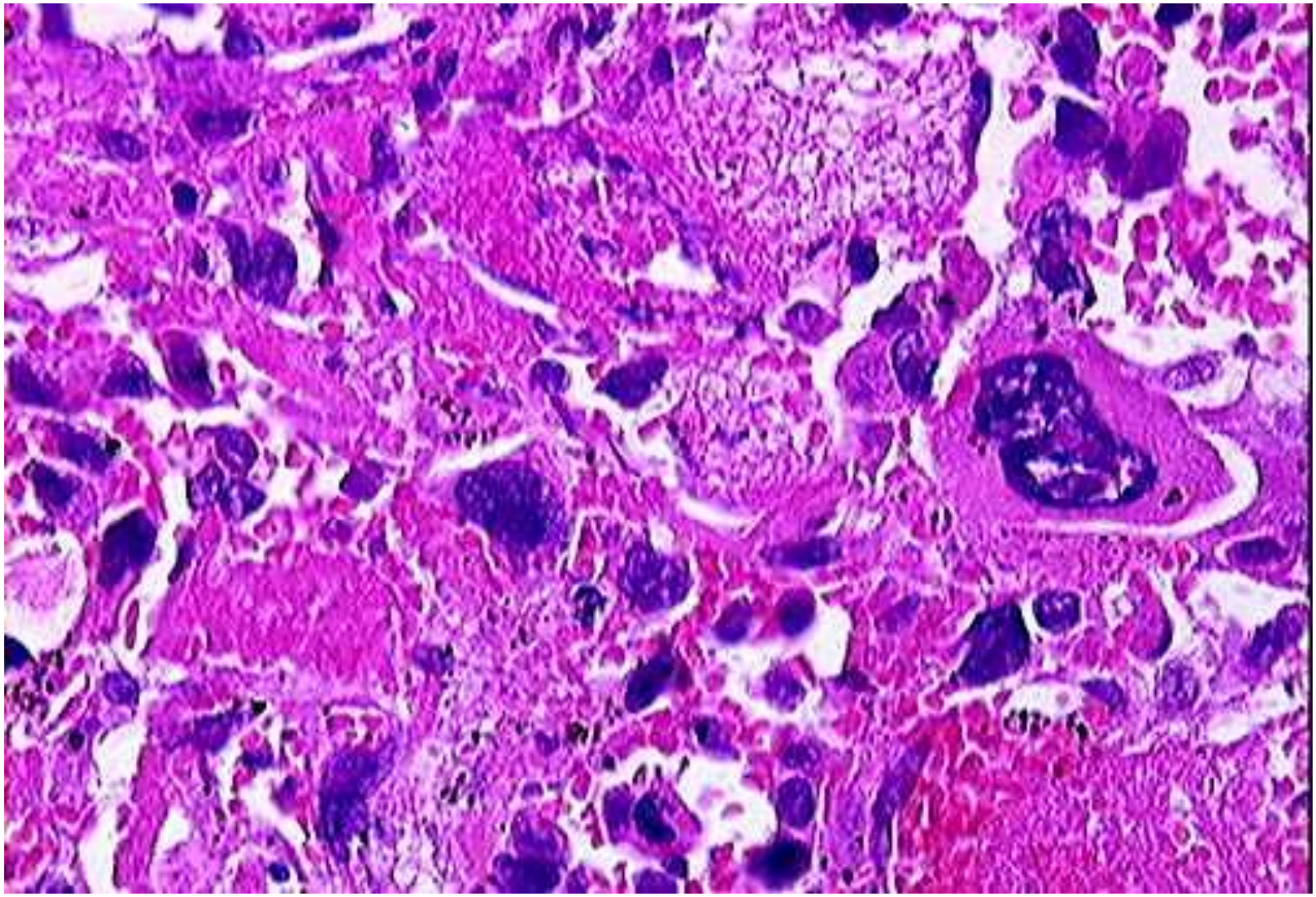
- Lack of differentiation, or anaplasia, is considered a hallmark of malignancy
- The term *anaplasia* literally means “backward formation”—implying dedifferentiation, or loss of the structural and functional differentiation of normal cells
- Between the two extremes lie tumors loosely referred to as *moderately well differentiated.*
- The stroma carrying the blood supply is crucial to the growth of tumors but does not aid in the separation of benign from malignant ones
- Certain cancers induce a dense, abundant fibrous stroma (desmoplasia), making them hard, so-called scirrhous tumors

- Functionally, a WD tumor cell retain its ability
- WD squamous cell carcinomas produce keratin
- WD hepatocellular carcinomas secrete bile
- On other hand, unanticipated functions emerge
- Some cancers may elaborate fetal proteins not produced by comparable cells in the adult
- Cancers of nonendocrine origin may produce so-called ectopic hormones, e.g., certain lung carcinomas may produce adrenocorticotropic ACTH, parathyroid hormone–like hormone, insulin, glucagon, and others
- Generally, *the more rapidly growing and the more anaplastic a tumor is, the less likely it is to have specialized functional activity*

❖**Features of Anaplasia:**

- Marked ***pleomorphism*** (variation in size and shape)
- *Nuclei are extremely* ***hyperchromatic*** (dark-staining) and large resulting in an increased nuclear-to-cytoplasmic ratio that may approach **1 : 1** instead of the normal 1 : 4 or 1 : 6.
- ***Giant cells*** that are considerably larger than their neighbors may be formed and possess either one enormous nucleus or several nuclei.
- *Anaplastic* ***nuclei are variable and bizarre in size and shape****.* The chromatin is coarse and clumped, and nucleoli may be of astounding size.
- ***Mitoses*** *often are numerous and distinctly atypical*
- Anaplastic cells usually ***lose normal polarity***: fail to develop recognizable patterns of orientation to one another

anaplasia



Rate of growth

- In general, benign and well-differentiated malignant tumors have a slower rate of growth than moderately-differentiated and poorly-differentiated malignant tumors
- The rate of growth of leiomyomas (benign smooth muscle tumors) of the uterus is influenced by the circulating levels of estrogen—may increase rapidly during pregnancy, then cease growing and becoming largely fibrocalcific after menopause
- Blood supply, site, and hormonal stimulation are factors that can affect the growth rate of tumors
- However, exceptions may exist

- Adenomas of the pituitary gland locked into the sella turcica have been observed to shrink suddenly probably due to compression of blood supply as tumor grows- necrosis occurs
- *The rate of growth of malignant tumors usually correlates inversely with their level of differentiation*
- Rapidly growing tumors are poorly differentiated
- Some grow slowly for years and then enter a rapid growth phase; Others relatively slowly and steadily
- Rapidly growing tumors often contain central areas of ischemic necrosis
- Cancer stem cells were identified in breast cancers, glioblastoma multiforme, & acute myeloid leukemia

Invasion

- Benign tumors usually grow by slow expansion
- Have no capacity to infiltrate, invade or metastasize and often encapsulated
- Vascular benign neoplasms of the dermis—neither encapsulated nor discretely defined
- For example, the leiomyoma of the uterus is discretely demarcated from the surrounding smooth muscle by a zone of compressed and attenuated normal myometrium, but there is no well developed capsule

- Malignant tumors usually infiltrate and may destroy surrounding tissue (cell surface and the extracellular matrix play an important role).
- They do not develop well defined capsules
- There are, however, occasional instances in which a slowly growing malignant tumor deceptively appears to be encased by the stroma of the surrounding host tissue, but microscopic examination usually reveals tiny crablike feet penetrating the margin and infiltrating adjacent structures

Metastasis

- *Metastases* are secondary implants of a tumor that are discontinuous with the primary tumor and located in remote tissues
- Indicates malignancy & a discontinuous spread
- Most malignant neoplasm metastasize except few; such as gliomas in the CNS, basal cell carcinoma in the skin and dermatofibrosarcoma in soft tissues (highly invasive but rarely metastasize)
- 30% cancers have been metastasized at the time of diagnosis and additional 20% have hidden mets
- Organs least favored for metastatic spread include striated muscles and spleen

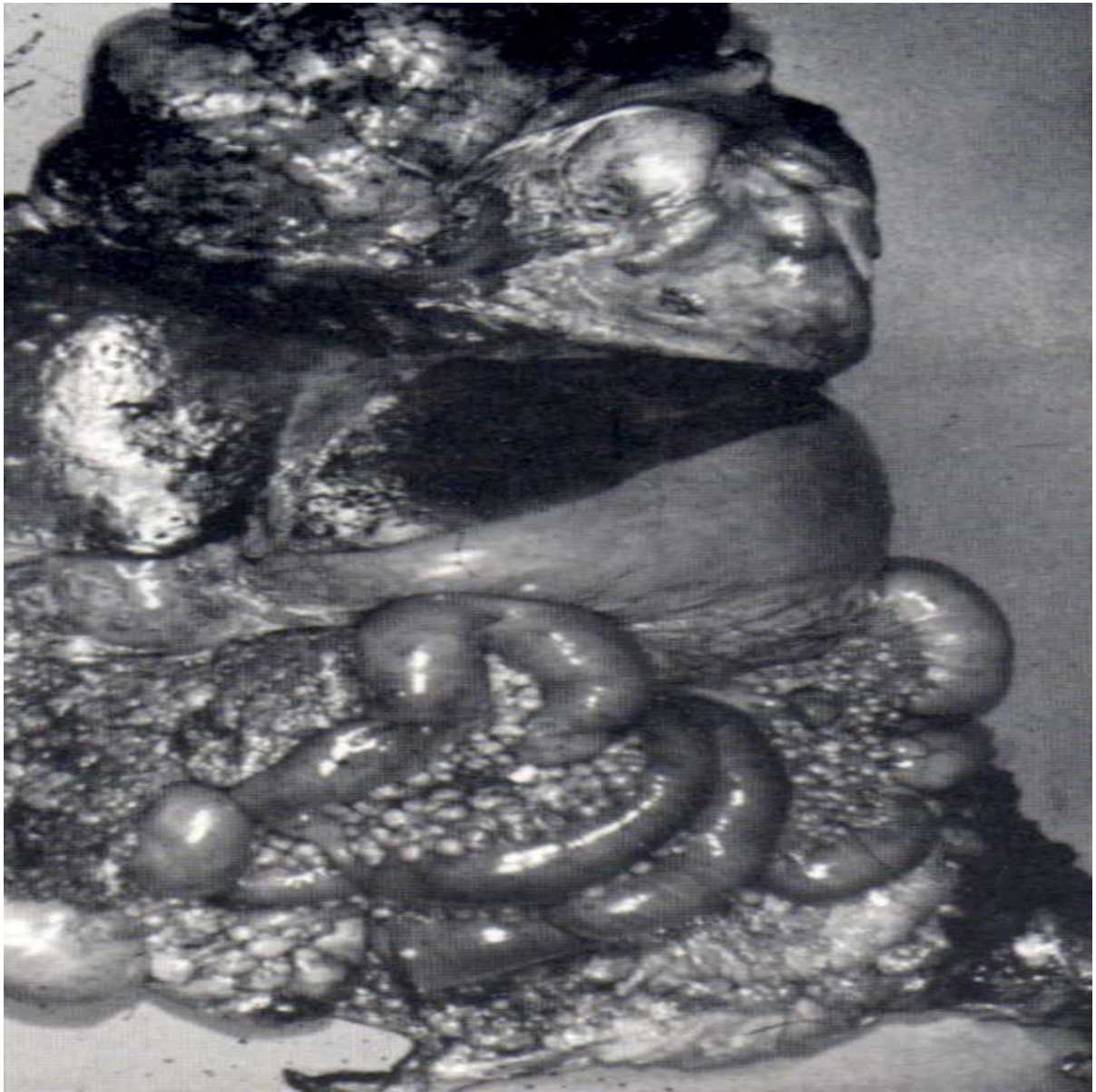
- Methods of metastasis include:

1. seeding of body cavities, e.g., neoplasm of the CNS such as a medulloblastoma or ependymoma or cancers of the ovary
2. lymphatic spread—more typical of carcinomas and
3. hematogenous spread is favored by sarcomas

- Numerous connections exist between the later two; so spread may involve both systems
- The pattern of lymph node involvement depends principally on the site of the primary neoplasm and the natural pathways of local lymphatic drainage
- Sentinel lymph node & skip metastases

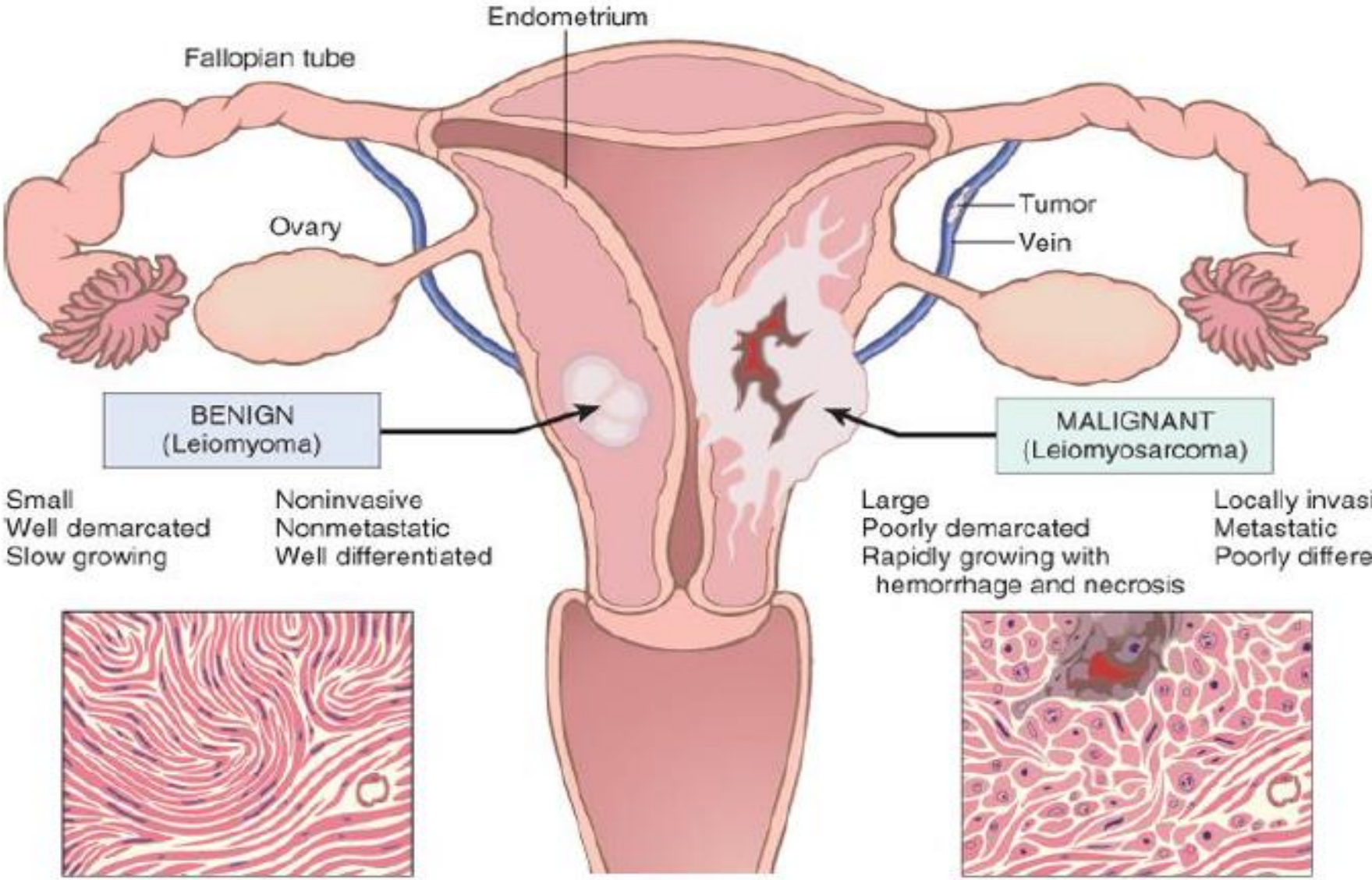
- The liver and lungs are the most frequently involved secondary site in hematogenous spread
- Certain carcinomas have a propensity to grow within veins, e.g., Renal cell carcinoma often invades the renal vein to grow in a snakelike fashion up the inferior vena cava, sometimes reaching the right side of the heart
- However, the secondary involvement may not wholly dependent on natural pathways of venous drainage
- 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
- Conversely, skeletal muscles, although rich in capillaries, are rarely the site of secondary deposits

metastatic ovarian carcinoma



metastatic adenocarcinoma

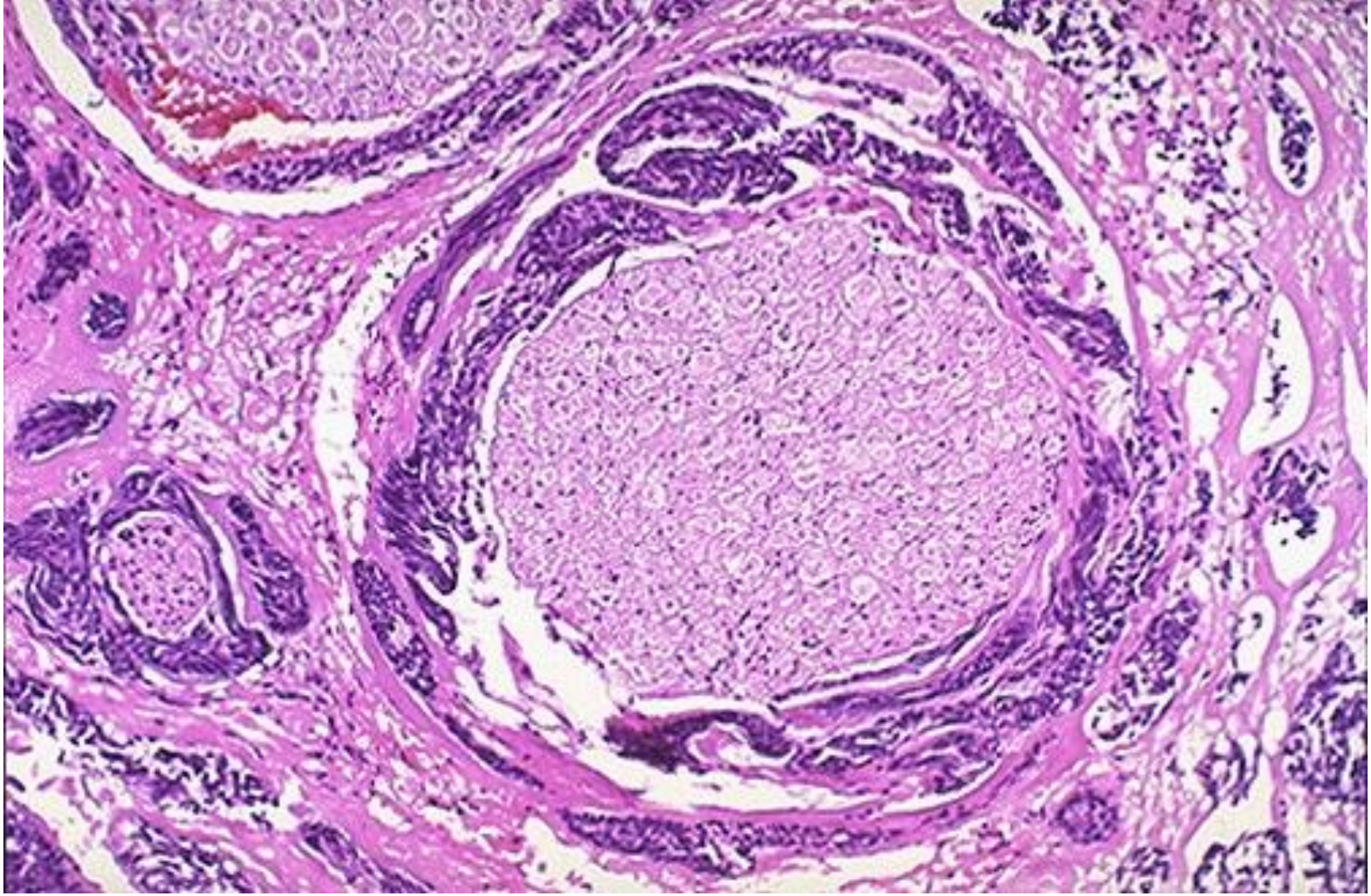
Summary of Characteristics of Benign & Malignant Neoplasms



Clinical Aspects of Neoplasia

- **B**oth malignant and benign tumors may cause problems because of:
- (1) location and impingement on adjacent structures,
- (2) functional activity such as hormone synthesis or the development of paraneoplastic syndromes,
- (3) bleeding and infections when the tumor ulcerates through adjacent surfaces,
- (4) symptoms that result from rupture or infarction
- (5) cachexia or wasting

- **Pain:**
  - Usually not in early stages
  - 60 – 80 % of terminally ill
  - Psychogenic, cultural and physiologic components
  - Due to pressure, obstruction, stretching, tissue damage or inflammation
- **Fatigue:**
  - sleep disturbances
  - biochemical changes
  - loss of muscle function



Branches of peripheral nerve are invaded by nests of malignant cells. This is often why pain associated with cancers is unrelenting.

- **Cancer Cachexia**:
- Many cancer patients suffer progressive loss of body fat and lean body mass, accompanied by profound weakness, anorexia, and anemia—a condition referred to as *cachexia*
- Current evidence indicates that cachexia results from the action of soluble factors such as cytokines produced by the tumor and the host, rather than reduced food intake
- It is suspected that TNF produced by macrophages in response to tumor cells or by the tumor cells themselves mediates cachexia

- TNF suppresses appetite and inhibits the action of lipoprotein lipase, inhibiting the release of free fatty acids from lipoproteins
- Additionally, a protein mobilizing factor called proteolysis-inducing factor, which causes breakdown of skeletal muscle proteins by the ubiquitin-proteosome pathway, has been detected in the serum of cancer patients
- Other molecules with lipolytic action also have been found
- No satisfactory treatment

- **Paraneoplastic Syndromes:**
- Symptom complexes that occur in patients with cancer and that cannot be readily explained by local or distant spread of the tumor or by the elaboration of hormones not indigenous to the tissue of origin of the tumor
- Appear in 10% to 15% of patients with cancer and their clinical significance implies:
  - The earliest manifestation of an occult neoplasm
  - The pathologic changes with substantial clinical illness which may even be lethal
  - In mimicking metastatic disease, thereby, confounding treatment.

- *The most common such syndromes are hypercalcemia, Cushing syndrome, and nonbacterial thrombotic endocarditis*
- Lung and breast cancers and hematologic malignancies are the major ones associated with these syndromes
- Hypercalcemia is multifactorial but the most important mechanism is the synthesis of a parathyroid hormone–related protein (PTHrP) by tumor cells
- TGF-α, a polypeptide factor derived from tumor cells activates osteoclasts, and the active form of vitamin D resulting in hypercalcemia
- Another possible mechanism for hypercalcemia is widespread osteolytic metastatic disease of bone

- Cushing syndrome usually is related to ectopic production of ACTH or ACTH-like polypeptides by cancer cells, as occurs in small cell cancers of the lung
- Sometimes one tumor induces several syndromes concurrently, e.g., bronchogenic carcinomas may intricate situation by producing products identical to or having the effects of ACTH, ADH, PTH, serotonin, hCG, and other bioactive substances
- Paraneoplastic syndromes also may manifest as hypercoagulability, leading to venous thrombosis and nonbacterial thrombotic endocarditis
- Other manifestations are clubbing of the fingers and hypertrophic osteoarthropathy in patients with lung carcinomas

- **Anemia: Due to**
  - chronic bleeding
  - malnutrition
  - medical therapies
  - malignancy in blood forming organs
- **Leukopenia and thrombocytopenia: Due to**
  - tumor invasion of bone marrow
  - chemotherapy or radiation
- **Infection:**
  - most significant cause of complications and death

Grading and Staging

- Grading is based on the microscopic features of the cells which compose a tumor and is specific for the tumor type.
- Staging is based on clinical, radiological, and surgical criteria, such as, tumor size, involvement of regional lymph nodes, and presence of metastases. Staging usually has prognostic value.

GRADING:

- Degree of malignancy is graded
- Score the degree of cellular and nuclear atypia (degree of tissue disorganization in tumor sections, biopsy or single tumor cells)
- G0= normal differentiation, no atypia (benign tumor)
- G1-G3= well differentiated to poorly differentiated (look at morphology, staining for specific markers and look at extent of proliferation)
- G4= cellular morphology completely different from normal tissue cells and pronounced atypia of cells and nuclei

Stages of cancer spread:

- Stage 1 – confined to site of origin
- Stage 2- cancer is locally invasive
- Stage 3 – cancer has spread to regional structure
- Stage 4- cancer has spread to distant sites

TNM system:

- tumor spread
- node involvement
- presence of distant metastasis

Staging may influence choice of treatment

TNM Staging System

- T= tumor size (T1-T4)
- N= extent of invasion of lymph nodes (N0-N1 or N2)
- M= extent of metastases (M0-M1 or M2)
- R= “resection margin”- after surgery necessary to know how much tumor has been removed [R0= tumor wholly contained within removed specimen]

Laboratory Diagnosis of Cancers

- Morphological Diagnosis:
  - Excision or biopsy, fine-needle aspiration, and cytological smears
  - Immunocytochemistry (immunohistochemical Staining)-
  - Flow cytometry
- Tumor Markers: less sensitivity & less specificity
  - PSA (prostate specific antigen), CEA (carcinoembryonic antigen), alpha fetoprotein
- Molecular diagnosis:
  - PCR-based techniques