BASIC PRINCIPLES OF CANCER

By Dr. Swathi Swaroopa. B

Introduction

- ***Cancer (neoplasm, tumor, or malignancy) is not a single disease; rather, it is a group of diseases characterized by uncontrolled growth and spread of abnormal cells.***

- ***Cancer cells do not respond to the normal processes that regulate cell growth, proliferation, and survival, and they cannot carry out the physiologic functions of their normal differentiated (mature) counterparts.***
- ***Cancer cells are described as poorly differentiated or immature.***

- ***Other characteristics of cancer cells include their ability to inv ade adjacent normal tissues and break away from the primary tumor (metastasize) and travel through the blood or lymph to establish new tumors (metastases) at a distant site.***

- ***Their ability to stimulate the formation of new blood vessels (angiogenesis) and their endless replication potential further c ontribute to their continued growth and survival.***

- ***Cancers can arise in any tissue in the body and may be c lassified as benign or malignant.***

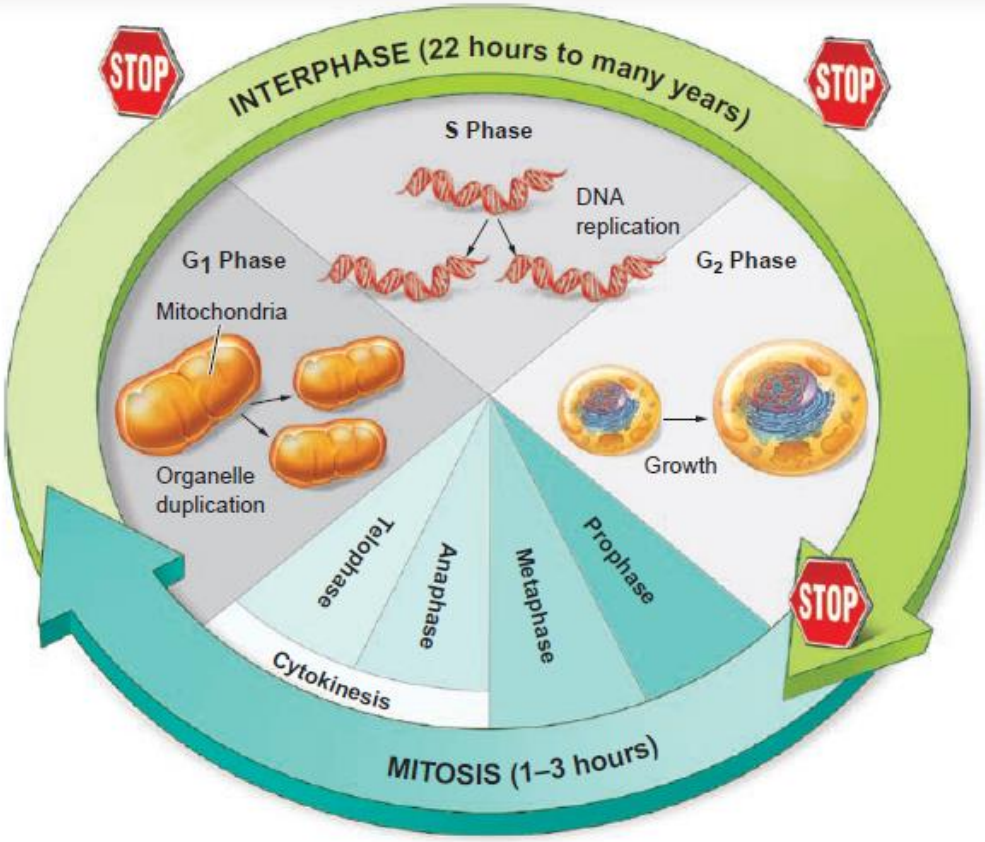
- ***Cancers arise from the transformation of a single normal cell***

- ***An initial "event" causes damage or mutation to the cell' s DNA.***

CELL CYCLE

- ***The cell cycle contains four phases (M, G1, S, and G2), e ach responsible for a different task necessary for cell div ision.***

- ***During the first activity phase, the M phase, the cell und ergoes mitosis, the process of cell division.***


STOP
INTERPHASE (22 hours to many years)
STOP
S Phase
DNA replication
G1 Phase
G2 Phase
Mitochondria
Organelle duplication
Growth
Telophase
Anaphase
Metaphase
Prophase
STOP
Cytokinesis
MITOSIS (1–3 hours)

- *After mitosis, the cell enters the first gap or resting phase (G1).*
- *During the G1 resting (or gap) phase, the cell makes the enzy mes necessary for DNA synthesis.*
- *The synthesis of DNA occurs during the S phase.*
- *After the S phase, the cell enters a second resting phase (G2).*
- *RNA and other proteins are synthesized to prepare for cell div ision during the Mphase.*

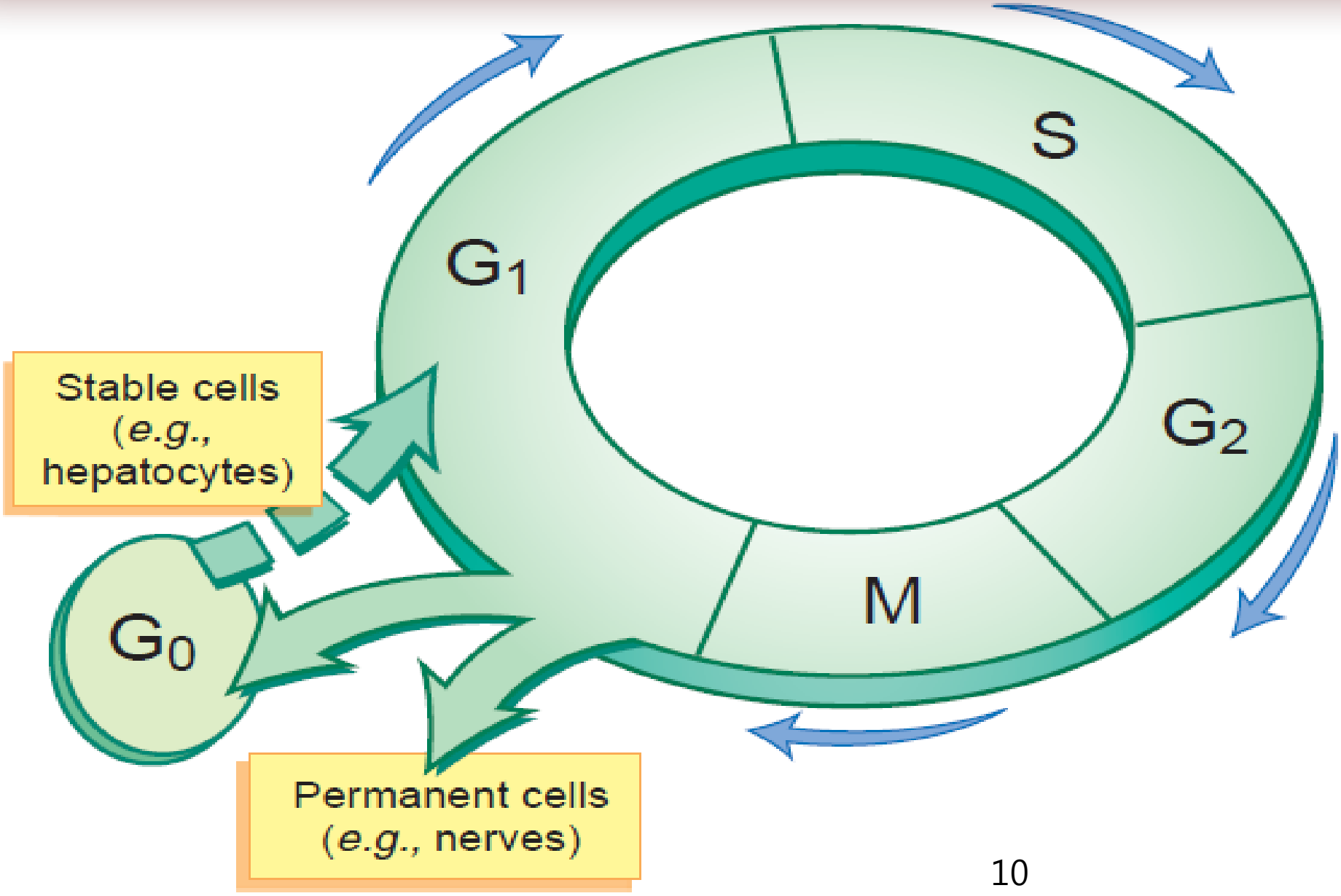
- *The cells that complete mitosis may either continue to proceed through the cell cycle to divide again or mature into specialized cells and eventually die, or enter a third resting phase called G0*

- *G0 is the stage after mitosis during which a cell may leave the cell cycle and either remain in a state of inactivity or reenter the cell cycle at another time*

- *Labile cells, such as blood cells and those that line the gastrointestinal tract, do not enter G0 but continue cycling.*

- ***Stable cells*, such as hepatocytes, *enter G0* after mitosis but can reenter the cell cycle when stimulated by the los s of other cells.**

- ***Proliferation* of normal cells is *carefully controlled* to bal ance the *loss* of mature functional cells with the *product ion* of new cells.**


S
G1
G2
M
G0
Stable cells
(e.g.,
hepatocytes)
Permanent cells
(e.g., nerves)

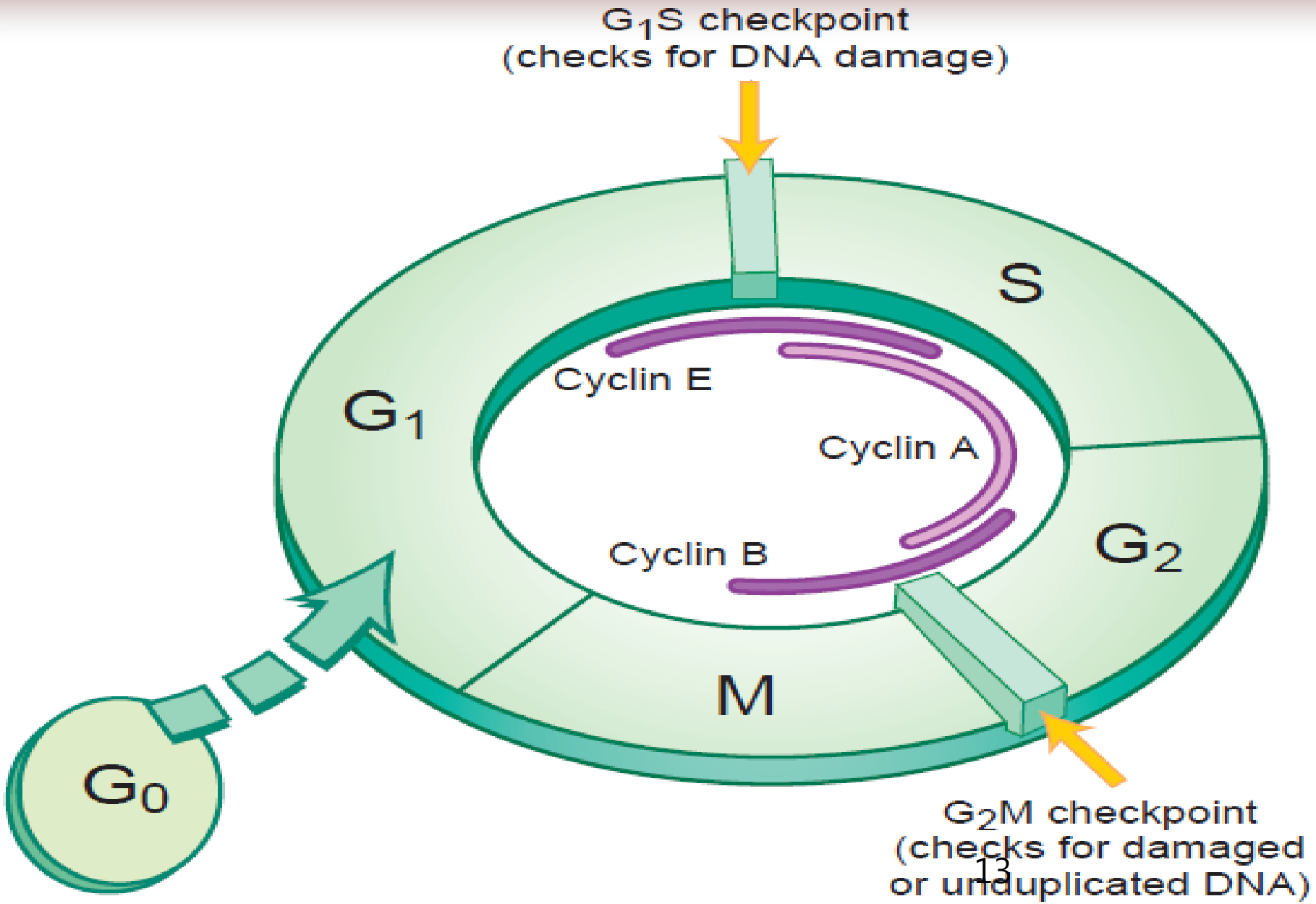
- ***The transition of cells through the cell cycle is an ordered, tightly regulated process, which involves a series of checkpoints that assess these signals and the number and integrity of the cells***

- ***In most cells, there are several checkpoints in the cell cycle, at which time the cycle can be arrested if previous events have not been completed.***

- ***For example, the G1/S checkpoint monitors whether the DNA in the chromosomes is damaged by radiation or chemicals, and the G2/M checkpoint prevents entry into mitosis if DNA replication is not complete.***

- ***The cyclins are a family of proteins that control entry and progression of cells through the cell cycle.***

- ***They function by activating proteins called CDKs.***


G1S checkpoint
(checks for DNA damage)
S
G1
Cyclin E
Cyclin A
Cyclin B
G2
M
G0
G2M checkpoint
(checks for damaged
or unduplicated DNA)

- ***Cyclins bind to proteins called cyclin-dependent kinases (CDKs).***
- ***The cyclin–CDK complexes are regulated by the binding of CDK inhibitors (CKIs).***
- ***The CKIs are particularly important in regulating cell cycle checkpoints during which mistakes in DNA replication are repaired***
- ***If insufficient amounts of cyclins or CDK are present during any phase, the cell will not enter the next phase..***

- *A decline in the level of the CDK complex signals the end of the phase.*
- *Cyclin–CDK complexes generate phosphate groups from molecules of adenosine triphosphate (ATP)*
- *Transfer them to a protein called a retinoblastoma protein (pRb).*
- *Phosphorylated pRb promotes cell cycle progression*

- ***CDK inhibitors* inhibit cell proliferation by *dephosphorylating pRb***

- ***Proto-oncogenes* and *tumor-suppressor genes* provide t he *stimulatory* and *inhibitory signals*, respectively, that *r egulate the cell cycle.***

- ***Protooncogenes* encode for *normal cell proteins* such as growth factors, growth factor receptors, growth factor si gnaling molecules, and transcription factors that promot e cell growth or increase growth factor–dependent signa ling**

- ***Growth and proliferation** of normal cells are influenced by proteins, known as **growth factors**.*

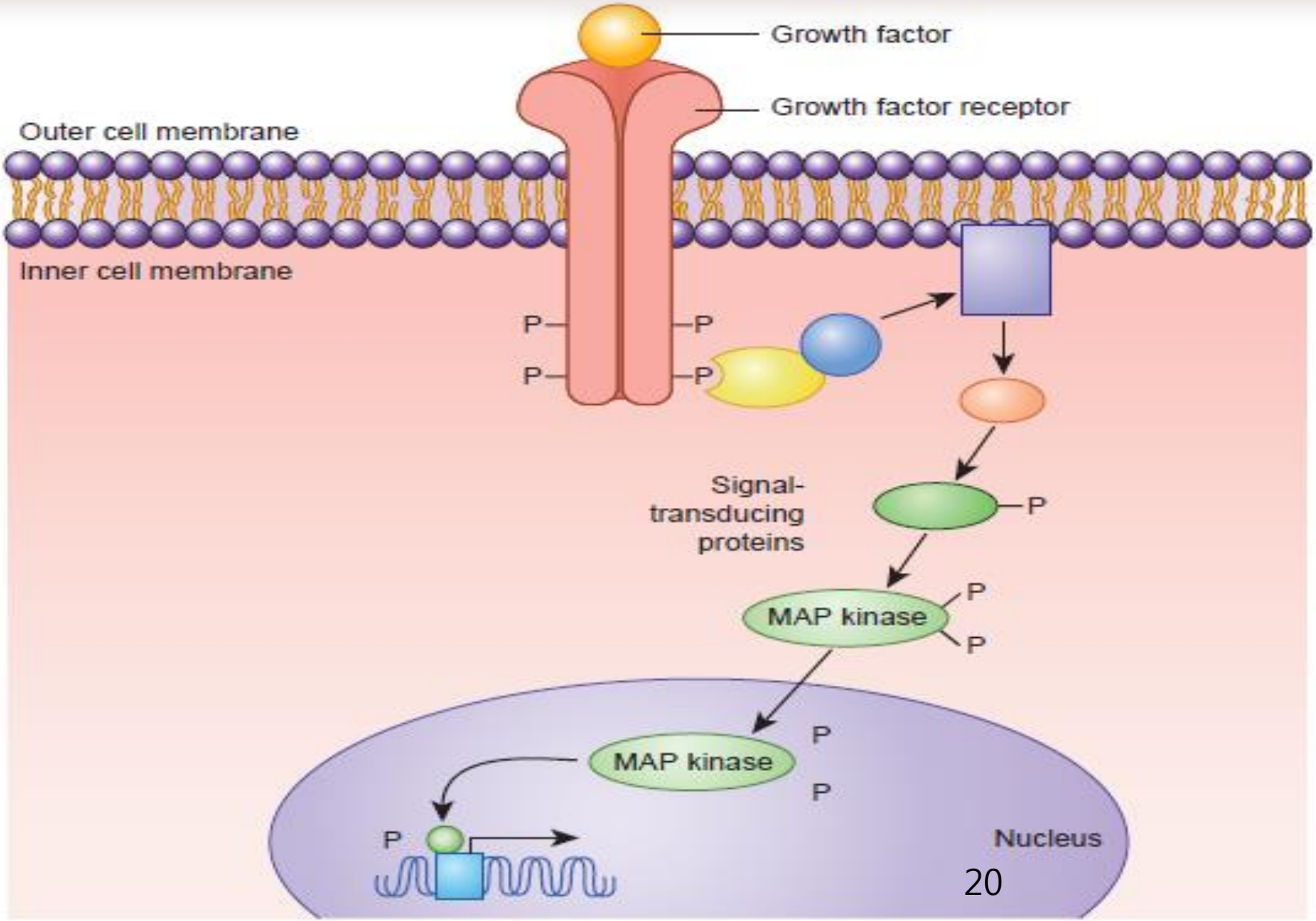
- ***When growth factors bind to receptors** on the cell surface, they activate a series of enzymes within the cell that stimulate **cell signaling pathways and gene transcription.***

- ***These genes encode for proteins** that regulate **cell growth** and **proliferation**.*

- ***The coordination and integration of cellular signaling processes are referred to as signal transduction.***

- ***Proto-oncogenes are responsible for encoding several components of signal transduction pathways.***

- ***Abnormal forms or excessive quantities of these stimulatory proteins disrupt normal cell growth-signaling pathways, leading to excessive growth and proliferation and, ultimately, a malignant transformation.***


Growth factor
Growth factor receptor
Outer cell membrane
Inner cell membrane
P
P
P
P
Signal-
transducing
proteins
P
MAP kinase
P
P
MAP kinase
P
P
P
Nucleus

Tumor suppressor genes include the

- *Retinoblastoma (RB) gene, which normally prevents cell division that encodes for pRb*
- *P53 gene, which normally becomes activated in DNA-damaged cells*
- *p53 gene is responsible for temporarily arresting cell growth in response to biochemical or molecular damage until the DNA damage can be repaired*
- *If the damage cannot be repaired, apoptosis (programmed cell death) occurs to prevent genetically damaged cells from growing uncontrollably.*

Etiolpathogenesis of Cancer

- ***The causes of cancers are very diverse and complex. It is useful to discuss causation in terms of:***

  - ***The genetic and molecular mechanisms that are in volved and that characterize the transformation of normal cells to cancer cells***

  - ***The external and more contextual factors such as a ge, heredity, and environmental agents that contrib ute to the development and progression of cancer.***

Cancer-Associated Genes

Originate with genetic damage or mutation

- ***Gene overactivity***
  - ✓ ***Protooncogenes***
- ***Oncogenes arise from normal genes called proto-oncogenes through genetic alterations such as chromosomal translocations, deletions, insertions, and point mutations.***

- ***Gene underactivity***
  - ✓ ***Tumor suppressor genes***
    - ❖ ***P53 gene***
    - ❖ ***Retinoblastoma (RB) gene***

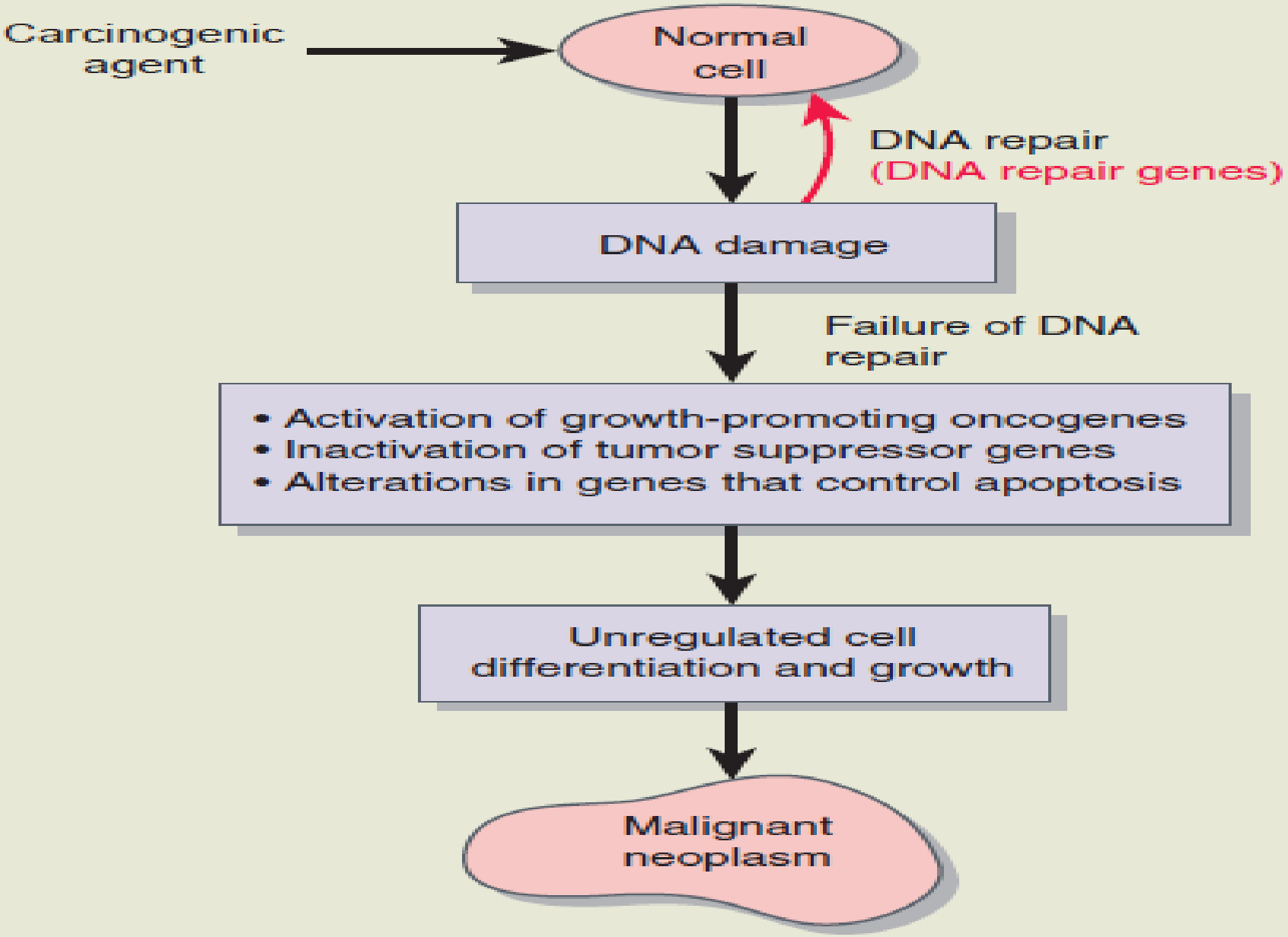
Etiology of Cancer

Carcinogenic Risk Factor	Associated Cancer(s)
Environmental	
Ionizing radiation (radon gas emitted from soil containing uranium deposits)	Leukemia, breast, thyroid, lung
Ultraviolet radiation	Skin melanoma
Viruses	Leukemia, lymphoma, nasopharyngeal, liver, cervix
Occupational	
Asbestos	Lung, mesothelioma
Chromium, nickel	Lung
Vinyl chloride	Liver
Aniline dye	Bladder
Benzene	Leukemia
Lifestyle	
Alcohol	Esophagus, liver, stomach, oropharynx, larynx
Dietary factors	Colon, breast, gallbladder, gastric
Tobacco	Lung, oropharynx, pharynx, larynx, esophagus, bladder

TABLE 130-1 Selected Drugs and Hormones Known to Cause Cancer in Humans

Drug or Hormone	Type of Cancer Caused
Alkylating agents (e.g., chlorambucil, mechlorethamine, melphalan, nitrosoureas)	Leukemia
Anabolic steroids	Liver
Analgesics containing phenacetin	Renal, urinary bladder
Anthracyclines (e.g., doxorubicin)	Leukemia
Antiestrogens (tamoxifen)	Endometrium
Coal tars (topical)	Skin
Estrogens	
Nonsteroidal (diethylstilbestrol)	Vagina/cervix, endometrium, breast, testes
Steroidal (estrogen replacement therapy, oral contraceptives)	Endometrium, breast, liver
Epipodophyllotoxins (etoposide, teniposide)	Leukemia
Immunosuppressive drugs (cyclosporine, azathioprine)	Lymphoma, skin
Oxazaphosphorines (cyclophosphamide, ifosfamide)	Urinary bladder, leukemia

Adapted from Compagni and Christofori[4] and Cotran et al.[5]


Carcinogenic agent
Normal cell
DNA repair (DNA repair genes)
DNA damage
Failure of DNA repair
• Activation of growth-promoting oncogenes
• Inactivation of tumor suppressor genes
• Alterations in genes that control apoptosis
Unregulated cell differentiation and growth
Malignant neoplasm

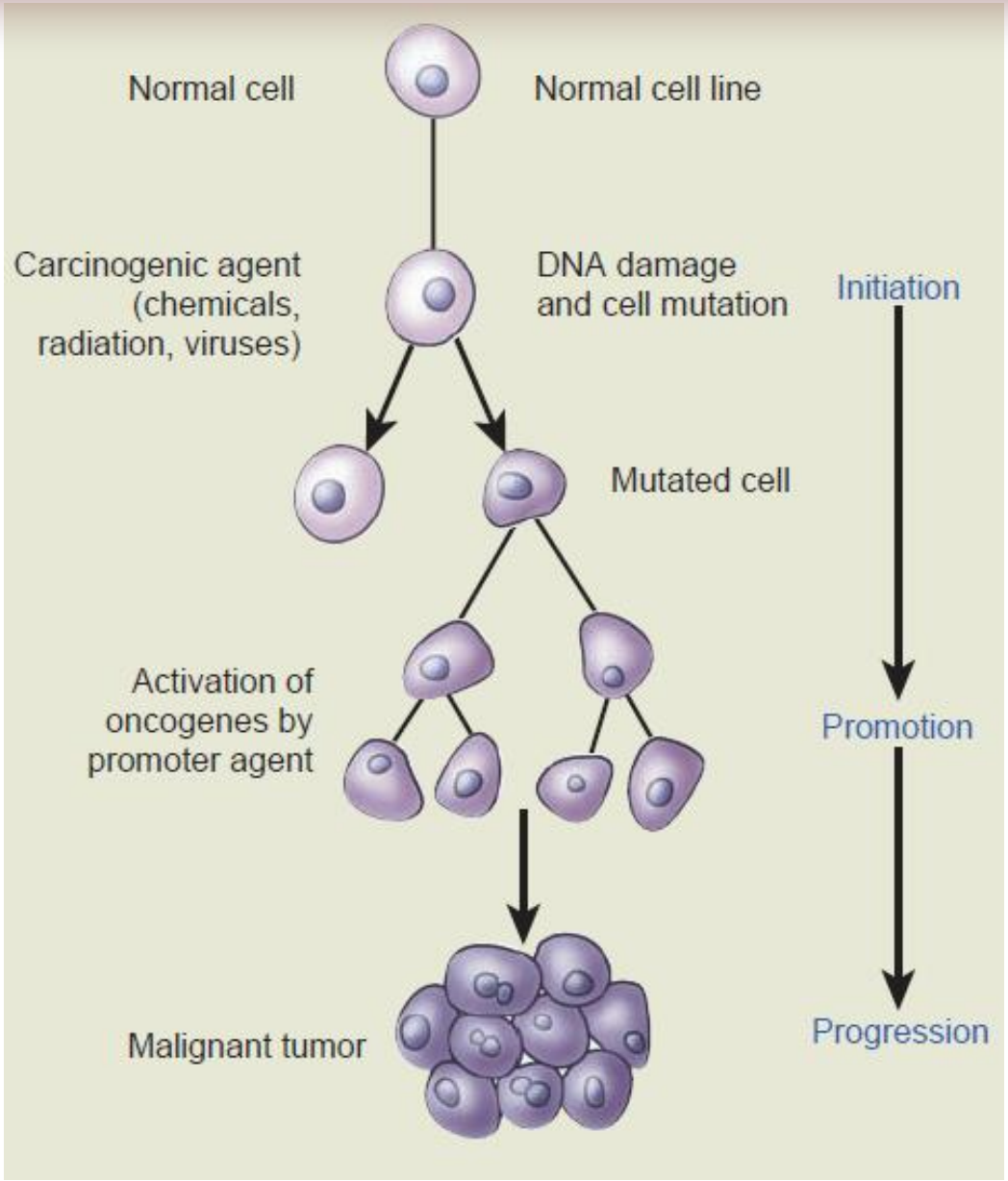
CARCINOGENESIS

- ***Carcinogenesis is the process by which normal cells are t ransformed into cancer cells.***

- ***If the balance of stimulatory and inhibitory growth signa ls becomes dysregulated, carcinogenesis may occur***

- ***In carcinogenesis, normal mechanisms such as apoptosis and senescence (aging) do not function properly and ca nnot control excessive cell division.***

- ***Hence Carcinogenesis is a multistep process that include s initiation, promotion, conversion, and progression.***


Normal cell
Normal cell line
Carcinogenic agent (chemicals, radiation, viruses)
DNA damage and cell mutation
Initiation
Mutated cell
Activation of oncogenes by promoter agent
Promotion
Malignant tumor
Progression

Pathology of Cancer

- Origin of tumor
- Tumor characteristics
- Invasion and Metastasis

Origin of Tumor

- ***Tumors may arise from any of four basic tissue types:***

✓ ***Epithelial tissue***

✓ ***Connective tissue (i.e., muscle, bone, and cartilage)***

✓ ***Lymphoid tissue***

✓ ***Nerve tissue***

Tumor Characteristics

i. Noncancerous growths that are often encapsulated, localized, and indolent.
ii. Cells of benign tumors resemble the cells from which they developed.
iii. These masses seldom metastasize, and once removed they rarely recur.

Benign

i. **Invade and destroy the surrounding tissue.**

ii. **The cells of malignant tumors are genetically unstable and loss of normal cell architecture results in cells that are atypical of their tissue or cell of origin.**

iii. **Malignant tumors tend to metastasize, and consequently, recurrences are common after removal or destruction of the primary tumor.**

Malignant

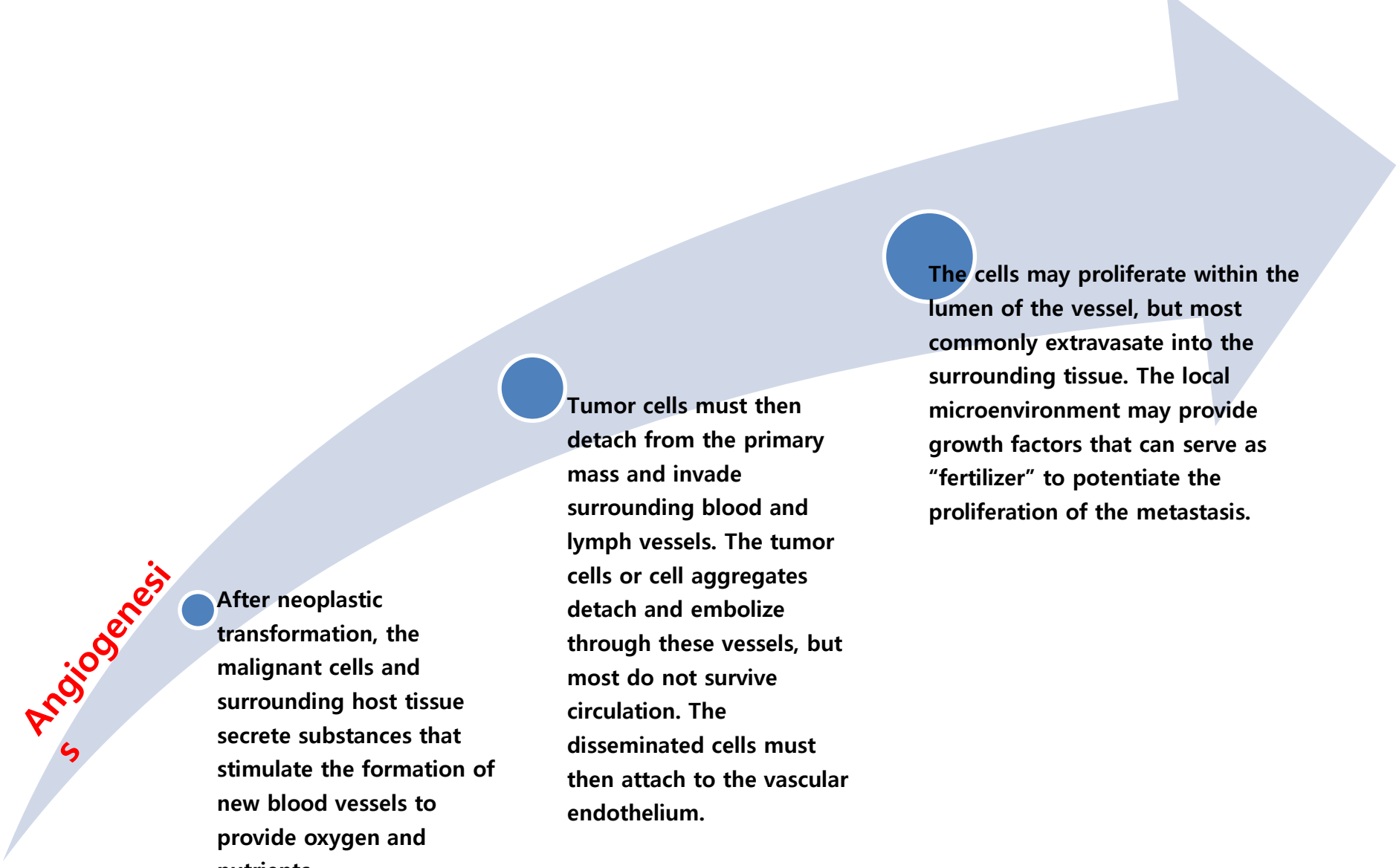
Invasion & Metastases

- Cells must break away from the primary tumor and travel to other sites in the body to form metastases
- Normally, cells adhere to one another and the extracellular matrix.
- The cell-to-cell adhesion molecules are called cadherins
- Cell-to-extracellular matrix molecules are called integrins.
- In cancer cells, these molecules are often absent, allowing tumor cells to easily move away from the primary tumor mass.

Metastases cont....

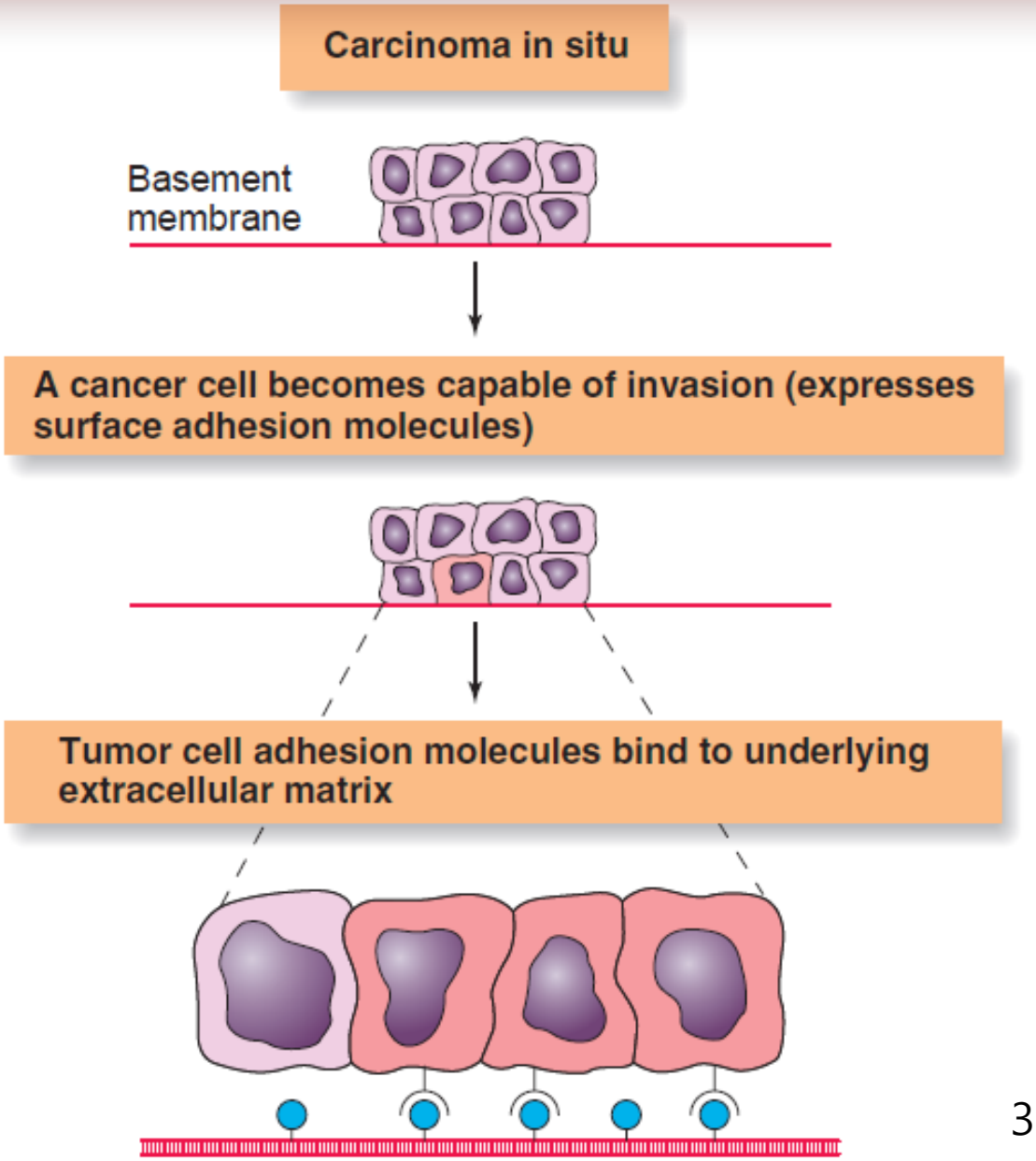
- The blood vessels and the lymphatics are the primary pa thways by which cells metastasize
- After a cancer cell establishes a metastatic site, it must a gain undergo angiogenesis to ensure continued growth.
- Together, angiogenesis and hematogenous or lymphatic spread help cancer cells invade healthy tissues

- ***Initially after neoplastic transformation, the malignant cells and surrounding host tissue secrete substances that stimulate the formation of new blood vessels to provide oxygen and nutrients. This process is known as angiogenesis or neovascularization***

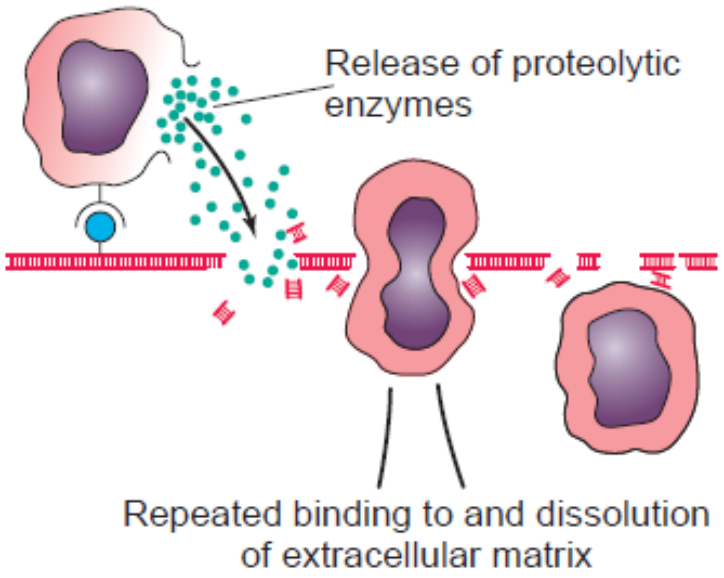

Angiogenesis
After neoplastic transformation, the malignant cells and surrounding host tissue secrete substances that stimulate the formation of new blood vessels to provide oxygen and nutrients.
Tumor cells must then detach from the primary mass and invade surrounding blood and lymph vessels. The tumor cells or cell aggregates detach and embolize through these vessels, but most do not survive circulation. The disseminated cells must then attach to the vascular endothelium.
The cells may proliferate within the lumen of the vessel, but most commonly extravasate into the surrounding tissue. The local microenvironment may provide growth factors that can serve as “fertilizer” to potentiate the proliferation of the metastasis.

- *At every step of the way, the potential metastatic cell must fight the host immune system. Last, the metastasis must again initiate angiogenesis to ensure continued growth and proliferation.*

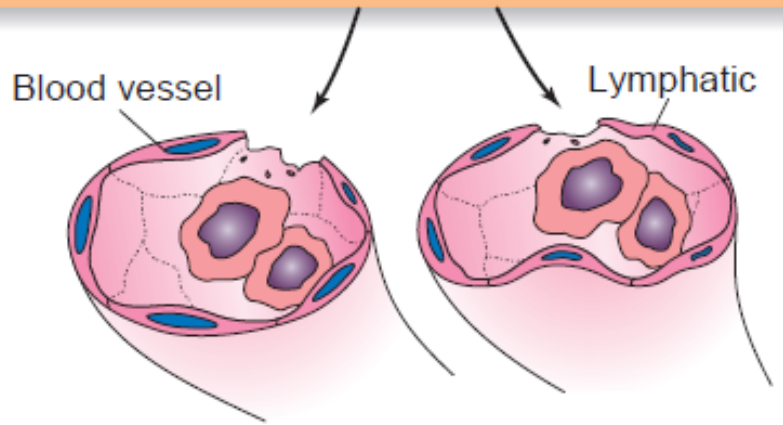
- *Because angiogenesis has been recognized as a critical element in primary tumor growth as well as metastasis, it has become a target for development of new anticancer agents*


Carcinoma in situ
Basement membrane
A cancer cell becomes capable of invasion (expresses surface adhesion molecules)
Tumor cell adhesion molecules bind to underlying extracellular matrix

Tumor cells disrupt and invade extracellular matrix



Tumor cells metastasize by way of blood vessels or lymphatics



Cancer cells

- *Less dependent on receiving stimulatory signals from ex ternal growth factors*

- *Capable of immortality through their ability to maintain their telomeres indefinitely and Possess unlimited replic ation potential (activate telomerase)*

- *Balance between cell renewal and loss of mature (senesc ent) cells is disrupted (due to oncogenes and tumor sup pressor genes)*

- ***Develop new blood vessels to obtain nutrients and to sp read to distant sites (metastasize).***

- ***Secrete growth factors (VEGF, PDGF, bFGF) that stimulate the growth of the new blood vessels (angiogenesis) fro m existing blood vessels***

- ***The regulation and function of cyclins, CDK, and inhibito ry proteins may be disrupted by a malignant transforma tion***

- ***Deletion of the RB gene**, a tumor suppressor gene that encodes for **pRb** if this molecule becomes inactive, **excessive cell proliferation can occur.***

- ***Loss or mutation of a second tumor suppressor gene, p53**, is also common in human cancers, and is associated with the **resistance** of cancer cells to undergo **cell cycle arrest or apoptosis***

Acquired capabilities of cancer cells that differ from normal cellular function

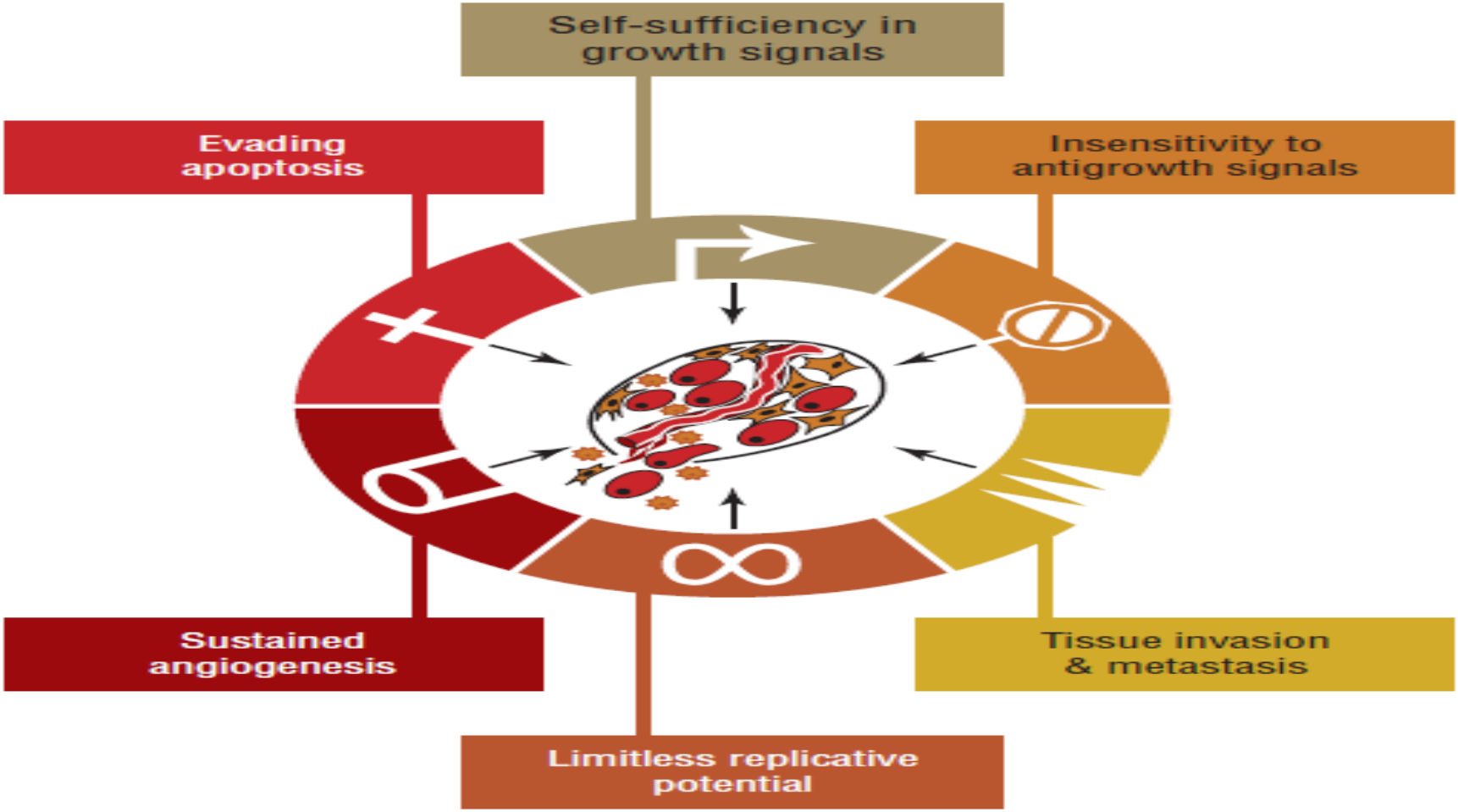


FIGURE 130-2. Functional capabilities acquired by cancer cells including angiogenesis, self-proliferation, insensitivity to antigrowth signals and limitless growth potential, metastasis; and antiapoptotic effects. It is thought that most, if not all cancer cells acquire these functions through a variety of mechanisms, including activation of oncogenes and mutations in tumor suppressor genes. *(This article was published in Cell, Vol. 100(1), Hanahan D, Weinberg RA, The Hallmarks of Cancer, Pages 57–70, Copyright Elsevier.)*

The presentation in adults may include any of cancer's seven warning signs as well as pain or loss of appetite

TABLE 130-5 Cancer's Seven Warning Signs

Change in bowel or bladder habits
A sore that does not heal
Unusual bleeding or discharge
Thickening or lump in breast or elsewhere
Indigestion or difficulty in swallowing
Obvious change in wart or mole
Nagging cough or hoarseness
If YOU have a warning signal, see your doctor!

American Cancer Society Study Communicating Cancer Information Through Mass Distribution Leaflets—an American Cancer Society Study. CA Cancer J Clin 1967;17:291–293.

Diagnosing and staging of Cancer

The definitive diagnosis of cancer relies on the procurement of a sample of the tissue or cells suspected of malignancy and pathologic assessment of this sample. This sample can be obtained by numerous methods, including biopsy, exfoliative cytology, or fine-needle aspiration. A tissue diagnosis is essential, because many benign conditions can masquerade as cancer. Definitive treatment should not begin without a pathologic diagnosis.

Staging of Cancer

- ***The most commonly applied staging system for solid tumors is the TNM classification, where T = tumor, N = node, and M = metastases.***

- ***A numerical value is assigned to each letter to indicate the size or extent of disease. The designated rating for tumor describes the size of the primary mass and ranges from T1 to T4.***

- ***Nodes are described in terms of the extent and quality of nodal involvement (N0 to N3).***

- ***Metastases are generally scored depending on their presence or absence (M0 or M1).***

Staging of Cancer

- ***To simplify the staging process, most cancers are classified according to the extent of disease by a numerical system involving stages I through IV. Stage I usually indicates localized tumor, stages II and III represent local and regional extension of disease, and stage IV denotes the presence of distant metastases.***

- ***The assigned TNM rating translates into a particular stage classification. For example, T3N1M0 describes a moderate to large-sized primary mass, with regional lymph node involvement and no distant metastases, and for most cancers is stage III.***

Staging of Cancer

TNM Classification	
Primary Tumor (T)	
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm but not >5 cm in greatest dimension
T3	Tumor >5 cm in greatest dimension
T4	Tumor of any size with direct extension to chest wall or skin
Regional Lymph Nodes (N)	
N0	No regional lymph node metastasis
N1	Metastasis to movable ipsilateral axillary lymph node(s)
N2	Metastasis to ipsilateral axillary lymph node(s) fixed to one another or other structures
N3	Metastasis to ipsilateral internal mammary lymph node(s)

Staging of Cancer

Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis (includes metastasis to i psilateral supra-clavicular lymph nodes)

Stage Grouping			
Stage I	T1	N0	M0
Stage II_A	T0	N1	M0
	T1	N1	M0
	T2	N0	M0

Staging of Cancer

Stage II_B	**T2**	**N1**	**M0**
	T3	N0	M0
Stage III_A	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage III_B	T4	N0, N1, N2	M0
Stage III_C	Any T	N3	M0
Stage IV	Any T	Any N	M1

THANK YOU