

CANCER

What is cancer?

- Cancer is medically called Malignant Neoplasm.

It involves unregulated cell growth.

In cancer, cells grow continuously and uncontrollably which forms malignant tumors and invade nearby parts of the body.

Cancer generally spreads through lymphatic system or blood stream.

There are several types of cancer depending on the organ they effect. They possess same common properties of:

1. Abnormal cell growth
2. Capacity to invade other tissues
3. Capacity to spread to distant organs via blood or lymph.

- The body is made up of trillions of living cells. These cells grow divide and die in an orderly fashion. This process is regulated and controlled by DNA. In an adult person most cells divide to replace the damaged or dying cells or to repair tissues injuries.
- When cells at particular site starts to grow out of control, they may become cancerous. Cancer cell growth is different from normal cell growth. Instead of dying, cancer cells continue to grow and form new abnormal cells.
- **Tumor**- Any abnormal swelling, lump or mass inside body.
- **Neoplasm** – Scientific term to describe abnormal proliferation of genetically altered cells.

- Types of cancer or tumor



Malignant Tumor

In Malignant Tumor cells grow uncontrollably and invade neighboring tissues.

It is Cancerous and are usually named using

-carcinoma, -sarcoma, -blastoma as a suffix

Eg- Liver : hepatocarcinoma

Breast cancer : mammary ductal carcinoma

Benign Tumor

In Benign Tumor cells do not grow uncontrollably and do not invade neighboring tissues.

It is Non cancerous and can be removed.

Benign tumors are named using *-oma* as suffix with the organ name as the root.

Eg- BT of uterus smooth muscle: Leiomyoma

- Some cancer do not form tumors.
Eg: *Leukemia* – cancer of blood and bone marrow.
- Local symptoms may occur due to the mass of the tumor or its ulceration.
Eg: *Lung cancer* : blockage of bronchus resulting in cough & pneumonia.
Esophageal cancer: narrowing of esophagus and difficult to swallow.
Colorectal cancer : narrowing or blockage in bowel.
- Tumor with ulceration can cause bleeding which if it occurs in *lungs* will lead to coughing up blood.
Blood in bowel causes anemia
Blood in bladder leads to urine with blood
Blood in uterus causes vaginal bleeding

- Other types of cancer:

- 1) Carcinoma : cancer that begins in the skin or tissue that covers internal organs.

eg: *Adenocarcinoma* – a malignant epithelial tumor arising from glandular structure which are constituent parts of most organs of the body.

Esophageal cancer, Colorectal cancer.

- 2) Sarcoma: cancer that begins in bone, cartilage, fat, muscles, Blood vessels or other connective or supportive tissue.
- 3) Leukemia : cancer that starts in blood forming tissues like bone marrow and causes large number of abnormal blood cells to be produced and enter the blood.
- 4) Lymphoma & myeloma : cancer that begins in the cells of immune system.
- 5) CNS cancer : cancer that begins in the tissues of brain and spinal cord.

- 6) Germ cell tumor : tumor derived from totipotent cells. In adults most often found in testes & ovary. In children it is found in tip of tailbone
- 7) Blastic tumor/ Blastoma : a tumor which resembles an immature or embryonic tissue.

Metastasis : The distant spread of malignant tumor from its site of origin by three routes blood lymph and body cavities.

Eg : carcinoma- via lymphatic
sarcoma – via blood stream

- **Origin of cancer**

All cancer begins in cells, the body's basic unit of life.

The body is made up of many types of cells. These cells grow and divide in a controlled way to produce more cells to keep the body healthy. When cells become old and damaged they die and are replaced by new ones.

But sometimes this orderly process goes wrong. Genetic material i.e DNA of cell is changed or damaged due to which normal cell growth and division change, as a result mutation takes place. Hence cells do not die when required and new cells form when body not needed. These extra cells form mass of tissue called tumor.

- Flow chart representation

Genetic Material – DNA of cells damage/change



Normal cell growth and division change



Mutation occurs



Cells do not die when required and new cells form
when not needed



These extra cells form mass of tissue called tumor

Pathophysiology

Genetic alteration- Cancer is the disease of failure of tissue growth regulation. Gene which regulate the cell growth and differentiation when altered, then normal cell transform to a cancer cell.

Oncogene- are the genes which promote cell growth and reproduction.

Tumor suppressor genes- are the genes which inhibit cell division and survival.

Inappropriate overexpression of normal oncogenes/under expression or disabling of tumor suppressor gene causes Malignant transformation.

Genetic changes can occur through mutation i.e change in nucleotide sequence of genomic DNA, which causes gain or loss of entire chromosome through errors in *mitosis*.

- DNA virus or retrovirus cause integration of genomic material which can result in disruption of a single gene.
- Replication of enormous data contained within DNA of living cells result in some errors.
- If significant error occurs, the damaged cell can self destruct through programmed cell death called Apoptosis.
- if the error control process fails then the mutation will survive and be passed along to daughter cells.

- **Carcinogenesis**

Carcinogenesis is also called Oncogenesis or tumorigenesis.

It is a process by which normal cells are transformed into cancer cells.

Cell division is a physiological process which maintain balance between proliferation and programmed cell death in form of apoptosis.

Carcinogenesis is caused by mutation and epimutation of genetic material of normal cells, which upsets the normal balance between proliferation and cell death.

More than one mutation to certain classes of gene are required for carcinogenesis.

Large scale mutation : it involves gain or deletion of a portion of chromosome. Genomic duplication occurs when a cell gains many copies of a small chromosomal region containing one or more oncogenes and genetic material.

Translocation occurs when 2 separate chromosomal regions become abnormally fused.

Eg: translocation of chromosome 9 & 22 occurs in chronic myelogenous leukemia and results in production of protein called tyrosine kinase.

Small scale mutation : it include point mutation, deletion and insertion which occurs in promoter of a gene and affect its expression and alter the function of protein product.

Epimutation : it include methylation or demethylation of the CpG islands of the promoter regions of genes which results in repression or de-repression of gene expression.

Causes of cancer :

90-95% is due to Environment causes.

5-10 % is due to Genetic causes.

Environmental causes include: tobacco – 25-30%

Diet & obesity – 30-35%

Infection – 15-20%

Radiations – 10%

Stress & lack of physical activity

- 1) Tobacco & cancer – Tobacco smoking is associated with many forms of cancer and causes 90% of lung cancer. It causes cancer in lungs, larynx, stomach, head , neck, bladder, kidney, esophagus, pancreas. Tobacco smoking contains 50 known carcinogens including *nitrosamines and polycyclic aromatic hydrocarbons*.
- 2) Diet and exercise – Diet, physical inactivity and obesity are related to 30-35% of cancer deaths.

Diet that are low in vegetables, fruits and whole grains or high in red meat are linked with cancer.

Eg: High salt diet – Gastric cancer

Betel nut chewing – oral cancer

3) Infection – A virus that can cause cancer is called oncovirus.

Eg: Viral infection cancer:

Human papilloma virus- cervical carcinoma

Epstein-Barrvirus – B cell lymphoproliferative disease

Nasopharyngeal carcinoma

Kaposi sarcoma herpesvirus – Kaposi's sarcoma: a malignant tumor arising from blood vessel in the skin and appear as purple plaques or nodules.

Hepatitis B and C virus – Hepatocellular carcinoma

Human T cell leukemia virus 1 – T cell leukemias.

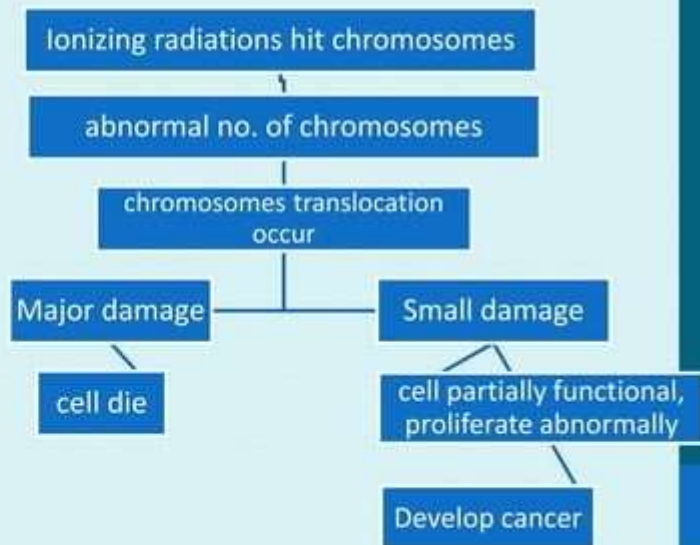
Eg: Bacterial: Helicobacter pylori- Gastric carcinoma

Eg: Parasitic : Clonorchis sinensis – MT of bile ducts.

- 4) Radiations : causative radiations are both ionizing and non-ionizing UV radiations.

Sources of radiations – Medical imaging, Radon gas.

Mechanism of Action:



Non ionising radiations – UV rays, mobile radiations.

Radon : A radioactive gas released from normal decay of elements like uranium, thorium and radium in rocks, soil. Radon decay quickly giving off cancerous radioactive particles.

- 5) Physical agents : Asbestos causes mesothelioma: tumor of pleura, peritonium or pericardium. other elements are cobalt, nickel, crystalline silica, hair dyes, formaldehyde.
- 6) Hormones : Increase in sex hormones(contraceptives, menopausal hormones) can cause cancer.
Diethylstylbesterol – synthetic form of estrogen which can cause breast cancer if taken during pregnancy.

TREATMENT

1. Surgery
2. Radiation Therapy
3. Chemotherapy
4. Targeted Therapy
5. Immunotherapy
6. Hormonal Therapy
7. Angiogenesis Inhibitor

1. **SURGERY** – Non haematological cancer can be cured if entirely removed by surgery. But if cancer has already spread to other sites in the body i.e Metastasis, then removing all cancer by surgery is not possible.

Initially cancer grows locally and then spread to lymph nodes and then to rest of the body. So for small cancer surgery became popular treatment.

- Eg : for Breast cancer – Mastectomy surgery
for prostate cancer - prostatectomy

Goal of surgery is the removal of only tumor or removal of entire organ.

Surgery is often necessary for *staging* also. (Staging means determining the extent of disease whether metastasized to lymph nodes.)

Drawback – sometimes when any single cancer cell is left, it can grow and cause cancer again called recurrence.

2) **RADIATION THERAPY** – also called Radiotherapy.

- It is the medical use of Ionizing Radiation as a part of cancer treatment to control malignant cells.
- Radiotherapy is used for curative therapy or adjuvant cancer treatment or palliative treatment (where cure is not possible and aim is to control disease or provide symptomatic relief).
- Total Body Irradiation (TBI) is a radiotherapy technique used to prepare the body to receive bone marrow transplant.

- MOA of Radiotherapy-

Radiotherapy works by damaging the DNA.

Photon, electron, proton, neutron or ion beam directly or indirectly ionize the atoms which make up the DNA chain.



Indirect ionization happens as a result of ionization of water to form free radicals (hydroxyl radicals)



DNA damage.

Breaking the DNA on both strands is necessary because cells have mechanism to repair DNA damage.



DNA damage is inherited to cancer cells



Damage accumulate to cancer cells



Cancer cell die or reproduce more slowly

Uses – 1) In malignant tumor as primary therapy.

2) In non-malignant conditions as –

- *Trigeminal neuralgia* : brief paroxysms of searing pain felt in the distribution of trigeminal nerve branches in the face.
- Severe thyroid eye disease
- Pterygium : a triangular overgrowth of the cornea.
- Pigmented villonodular synovitis : inflammation of synovium membrane that lines the joint capsule.
- Prevention of keloid scar growth : an overgrowth of fibrous scar tissue following trauma to the skin.
- Prevention of heterotopic ossification (osteogenesis).

- Radiotherapy is commonly combined with surgery, chemotherapy, hormone therapy.

Major Limitation : cells of solid tumor become more deficient in oxygen because solid tumor usually outgrow their blood supply and cause a low oxygen state called *Hypoxia*.

More hypoxia the tumor more resistant to radiation because oxygen makes the radiation damage to DNA permanently.

Side effects : (a) Acute - Damage to epithelial surface, swelling, edema, infertility(no gametes formation), generalized fatigue.

(b) Long term – fibrosis, hair loss, dryness, fatigue, cancer.

Dose : The amount of radiation is measured in Gray (Gy)

Curative dose – solid epithelial tumor : 60 to 80 Gy

lymphoma tumor : 80 to 100 Gy

Preventive dose – Breast, head & neck cancer : 45 to 60 Gy in 1.8 to 2 Gy fractions.

- Types of Radiation Therapy :

Three main divisions of radiotherapy are –

1. External Beam Radiotherapy (EBRT/ XBRT) or Teletherapy.
2. Brachytherapy or sealed source radiotherapy.
3. Unsealed source radiotherapy.

EBRT is the radiotherapy given outside the body.

Sealed & unsealed – radioactive material delivered inside the body.

Conventional External Beam Radiotherapy : 2DXRT is delivered via 2 dimensional beams using linear accelerator machines.

Virtual simulation, 3-D conformal radiotherapy & intensity modulated radiotherapy – this radiotherapy delineate tumors in 3-D using CT or MRI scan.

Radioisotope therapy (RIT) – Radiotherapy can be delivered through infusion (in blood stream) or ingestion also.

Eg: For neuroblastoma - infusion of metaiodobenzyl guanidine.

For thyroid cancer – infusion of oral iodine-131

For neuroendocrine tumors – infusion of Lutetium-177

3) CHEMOTHERAPY –

chemotherapy means use of chemical agents to destroy cancer cells.

It has the ability to treat widespread and metastatic cancer. While radiotherapy and surgery are confined to specific areas only.

How do chemotherapeutic drugs work?

For chemotherapeutic agents the potential target is cancer cell, which should be differentiated from normal tissues. Hence the differentiation evolved was that cancer cells grow at a rate faster than normal cells.

Therefore the conclusion came was that *cell growth cycle* should be the target for chemotherapeutic drugs. Fast growing cells would be affected the most while slow growing the least. This is the basis of many chemotherapeutic agents. Looking towards the side effects hair follicles, skin, gastrointestinal lining cells are also affected as they are the fast growing cells.

Administering the recommended amt. of drugs(chemo) may prove to be too toxic to metabolize & excrete. So patients with kidney or liver damage are given chemo on precautions.

- Cell cycle- cell cycle is the sequence of steps a cell goes through in order to copy its genetic material and divide into 2 cells.

The cell cycle is divided into 4 phases – G_1 S G_2 M

A chemotherapeutic agent may be –

cell cycle specific: acts in only one phase of the cycle.

cell cycle nonspecific: acts in all phases of cell cycle.

G_1 phase : most active in protein synthesis. Cellular DNA is tightly coiled and is not actively being transcribed (copied).

S phase : is the synthetic phase of cell cycle. DNA replication is most active in this phase.

G_2 phase : when mostly RNA is actively produced.

M phase : mitosis/cell division occur in this phase.

So by knowing the phase an agent works in, we are able to combine agents that work in different phases to achieve most tumor killing.

- Chemotherapeutic drugs (classification) :
 - (a) Cytotoxic drugs (drugs acting directly on cells) – alkylating agents, Ethylenimine, Alkyl sulfonate, nitrosoureas, triazines.
 - (b) Antimetabolites – Folate antagonist, purine antagonist, pyrimidine antagonist.
 - (c) Vinca alkaloids
 - (d) Taxanes
 - (e) Epidophyllotoxins
 - (f) Camptothecin analogue
 - (g) Antibiotics
 - (h) Miscellaneous
- Alkylating agents : are nitrogen mustard & cell cycle non specific. Binds to –ve charged sites on DNA like oxygen, nitrogen, ph, sulphur so that steps of cell duplication(transcription, replication, base pairing) are altered. Also alkylating agents cause alkylation of DNA & DNA strands break. Cellular activity stops and cell dies.
Risks- sperm production ↓, menstruation cease, permanent infertility.

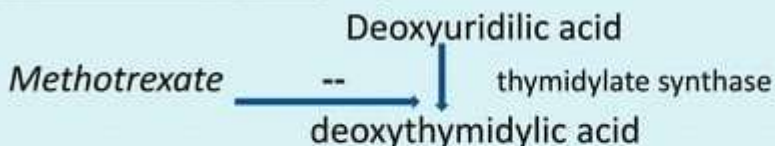
- **Antimetabolite** : They completely inhibit utilization of the normal substrate or get themselves incorporated to form dysfunctional macromolecule.

Eg: *methotrexate* : is cell cycle specific and kills cells in S-phase, primarily inhibits DNA synthesis but also affects RNA & protein synthesis.

Risks- megaloblastic anemia, pancytopenia(↓ in WBC, RBC, Platelets)

- **Purine Antagonist** : inhibits the formation of adenine & guanine nucleotides. Eg: *mercaptopurine(6-MP)*, *Thioguanine (6-TG)*

- **Pyrimidine antagonist** : Eg: Methotrexate



So in the absence of deoxythymidylic acid DNA synthesis fails.

- **Camptothecin analogue** : binds to DNA topoisomerase I, so DNA strand breaks. Acts in S-phase and arrest cell cycle in G₂ phase.

- Vinca alkaloid : are mitotic inhibitors.

↓
Binds to tubulin protein & prevent the assembly of microtubules.

↓
Cause disruption of mitotic spindle

↓
Chromosomes fail to move apart during mitosis

↓
Metaphase arrest occur.

Eg: *Vincristine*- used in:

Lymphosarcoma : a malignant tumor of lymph nodes.

Hodgkin's disease : form of lymphoma characterised by painless enlargement of one or more groups of lymph nodes in neck, axillae, groin, chest, abdomen.

Ewing's sarcoma: a malignant tumor of bone.

Vinblastin – used in Hodgkin's disease and testicular sarcoma.

- Taxanes : same as Vinca alkaloids.

Eg: paclitaxel

Chemotherapy administration : most common routes are mouth, vein, muscle. Chemotherapy can be administered directly in a specific cavity i.e intracavitary, in abdomen- intraperitoneal, in lung – intrapleural, in CNS- intrathecal.

Additional pretreatment actions such as increased IV fluids or administration of anti-nausea medicines are needed to decrease the side effect.

- 4) **TARGETED THERAPY** : it refers to a medication that targets a specific pathway in the growth and development of tumor. The target themselves are typically various molecules in the body known to play role in cancer formation.

Types- 1) Tyrosine kinase inhibitor – it is a receptor which when blocked prevents the cascade of reaction and prevent tumor survival.

2) Angiogenesis inhibitor – like normal cells tumor cells also need blood supply to perform vital cellular functions. Inhibiting angiogenesis (formation of blood vessels) can inhibit the growth of tumor cells.

3) Proteasome inhibitors – proteasome is a structure inside cell which breaks down the protein which are supposed to degrade & recycle. Inhibiting this enzyme can arrest the tumor cell growth.

5) **IMMUNOTHERAPY** : it does not interfere with growth by binding to target but it triggers immune signals.

Antigens on cancer cell surface are captured by antibodies (specific) which leads to antitumor immune reaction. These Ab are monoclonal.

When there is a radioisotope attached these drugs are called radioimmunotherapy.

Eg : Alemtuzumab – chronic lymphocytic leukemia.

Beracizumab – colon cancer.

6) **HORMONAL THERAPY** : by administering hormones (steroid), endocrine system is manipulated and particular hormone activity is inhibited due to which certain cancer cells cease growing or they die.

It is used in breast cancer, prostate cancer, endometrium cancer, adrenal cortex cancer.

Inhibitors of hormone synthesis –

a) Aromatase inhibitors – used for breast cancer in postmenopausal women. At menopause, estrogen production in ovaries stops, but other organs continue to produce estrogen by the help of aromatase.

Aromatase action inhibited \rightarrow estrogen level \downarrow \rightarrow apoptosis of hormone responsive cancer cell.

Eg : Letrozole, anastrozole.

b) GnRH analogue – Gonadotropin releasing hormone analogue can be used to induce a complete castration i.e complete suppression of estrogen & progesterone from ovaries and testosterone production from male testes.

Eg : leuprolide, goserelin