MARROW

2024 NEET-SS

UPDATED PEDIATRICS NOTES

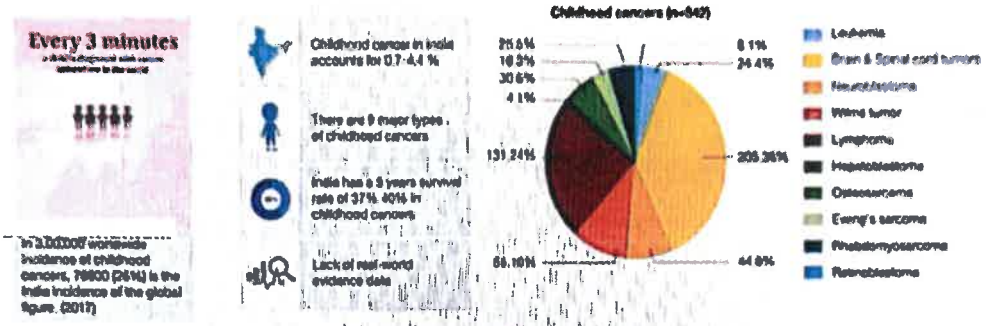
HEMATO ONCOLOGY

BASICS OF PAEDIATRIC ONCOLOGY

Active space

Introduction 00:00:23

Statistics :



80% of children with cancer will survive in high-income countries.
Only about 20% of children with cancer will survive in some low and middle income countries.

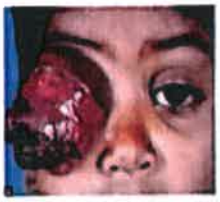
Roadblocks to improved cancer survival :

- Delayed diagnosis/misdiagnosis/no diagnosis.
- Lack of awareness.
- Overlap of signs and symptoms of cancer with other infectious diseases.
- Lack of diagnostic facilities.
- Symptoms of leukemia/lymphoma are often mistaken for more common nutritional deficiency/tuberculosis.
- Many patients are empirically started on ATT.
- Steroids are often used in peripheral centres without a diagnosis.

Retinoblastoma :

Early diagnosis : 100% survival.
Late diagnosis (Extraocular retinoblastoma) : 20-30% survival

Loss of red reflex : Early retinoblastoma.



Extraocular retinoblastoma (Late).

----- Active space -----

Cost of late diagnosis :

- Poor survival rates.
- High treatment cost.

Factors related to late diagnosis :

Patient related factors :

- Infants : Dependent on caregivers for a diagnosis.
- Adolescents : Ignoring the symptoms.

Health related factors :

- Lack of diagnosis.
- Lack of availability of cancer centres within reach.

Children at risk :

1. Infections :
   - EBV infection : Hodgkin Lymphoma, Burkitt lymphoma, Post transplant lymphoproliferative disorder (PTLD), nasopharyngeal cancer.
   - HIV : Kaposi sarcoma, B cell lymphoma.
   - Hep B and C : Hepatocellular carcinoma.
   - HPV : HPV associated cancer.
2. Immunodeficiency syndromes.
3. Patients receiving immunosuppressive therapy : Higher risk of malignancy (PTLD and lymphomas).
4. Pediatric solid organ transplant recipients who are on prolonged thiopurine therapy : PTLD.
5. Childhood cancer survivors.
6. Exposure to alkylating agent, anthracycline, topoisomerase inhibitors.
7. Exposure to radiation.

Signs and symptoms 00:10:31

Fever :

- Non specific symptom.
- One of the causes of prolonged fever of unknown origin (FUO) : Occult malignancy.
- 10% or less of patients with FUO as the only symptom are later diagnosed with a malignancy.

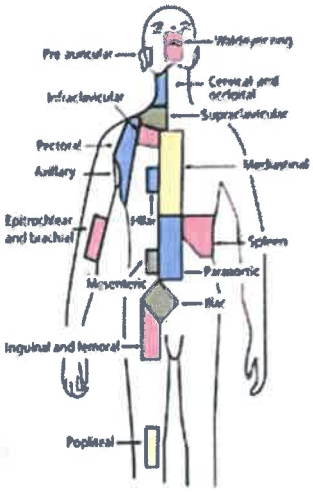
Feedback

Lymphadenopathy :

m/c cause : Reactive hyperplasia (Benign).

Enlarged lymph node could be due to :

- Intrinsic cellular components.
- Extrinsic cellular infiltration.



Lymphadenopathy.

Significant lymphadenopathy :

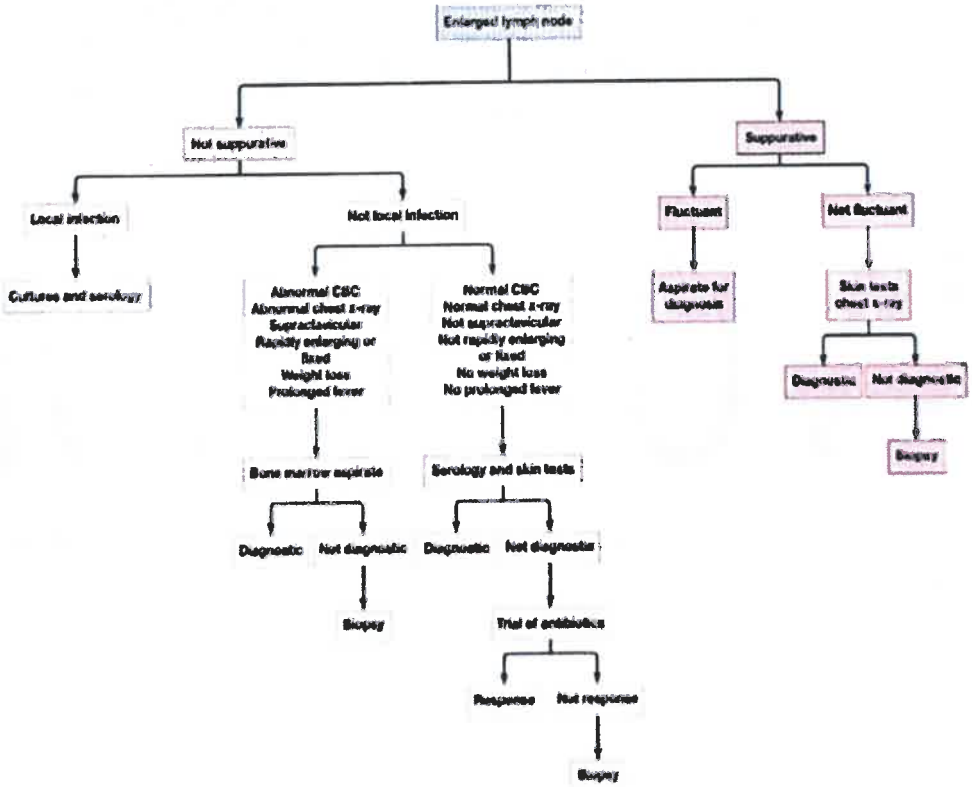
- Cervical >1 cm.
- Axillary >1 cm.
- Epitrochlear >0.5 cm.
- Inguinal >1.5 cm.

Generalized lymphadenopathy : Significant lymphadenopathy of 2 or more noncontiguous lymph nodes.

Note :

- Palpable supraclavicular nodes should always be considered abnormal.
- Left-sided (Virchow) nodes suggest metastases from an intra-abdominal malignancy (Neuroblastoma).
- Right-sided nodes suggest intrathoracic disease.

Lymphadenopathy Evaluation



Active space

Indications of lymph node biopsy :

- Chronic, persistent, progressive adenopathy in the absence of any infectious etiology.
- Any nodes >2.5 cm in diameter in the absence of signs of infection.
- Supraclavicular adenopathy.
- Systemic symptoms.

Cautions for lymph node biopsy :

- Avoid upper cervical and inguinal areas : Commonly d/t infections.
- Lower cervical and axillary nodes are more reliable.
- Largest node should be biopsied.
- Node should be removed intact with the capsule.
- Lymph node should be immediately submitted to the pathologist fresh or in sufficient tissue culture to prevent the tissue from drying out.
- The node must not be left in strong light (Subject to heat) and should not be wrapped in dry gauze (Drying) : may produce a drying artefact.
- Fresh and frozen samples should be set aside for additional studies, as noted later.

Intracranial mass :

Red flag signs of headache :

- Recurrent early morning vomiting.
- Headache that awakens the child from sleep.
- Incapacitating headache.
- Enlargement of head size (In infants).
- C/F associated with raised ICT (Intracranial tension).

Risk group	Clinical definition	Probability of brain tumor %	Diagnostic strategy
Low	Headache >6 months and no neurologic symptoms.	0.01	No imaging. Clinical follow-up and medical treatment.
Intermediate	Migrane HA and no neurologic symptoms.	0.4	CT, MRI followed by biopsy or surgery.
High	Headache <6 months and one clinical predictor of space occupying lesion.	4	MRI followed by biopsy or surgery.

Feedback

Abdominal masses :

Palpable abdominal mass : m/c presenting feature.

Age of patient :

- Neonatal period : Congenital malformation of GI and GU system.
- Childhood : Malignant.

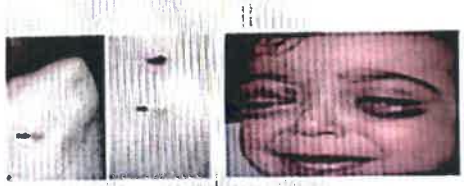
Site :

Upper abdomen	Mid abdomen	Lower abdomen
Neuroblastoma. Wilms tumor. Hepatoblastoma. Lymphoma.	Lymphoma. Sarcoma. Germ cell tumor.	Germ cell tumor. Sarcoma. Lymphoma.

History and physical examination :

Systemic symptoms :

- Periorbital ecchymosis (Racoon eyes).
- Subcutaneous nodules.
- Bone pains.



Subcutaneous nodules, periorbital ecchymosis.

Investigations :

- Ultrasound abdomen.
- Mass arising from liver : Serum alpha fetoprotein (AFP).
- Tumour markers : β-HCG.

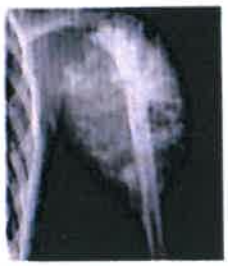
Bone pain :

Localized bone pain with limping :

- Osteosarcoma.
- Ewing sarcoma.

Features of malignant bone tumor :

- Cortical erosion.
- Irregular mass.
- Periosteal reaction.
- White zone of transition.



Malignant bone tumor.

Diffuse bone pain is a cardinal feature of acute leukemia.

Differential diagnosis : Juvenile rheumatoid arthritis.

	Acute leukemia	JRA
Symptom manifestation	Worse at night.	Morning stiffness.
Involvement	Bones and joints.	Joints.
Constitutional symptoms	Present.	Present/absent.

Acute leukemia vs juvenile rheumatoid arthritis (JRA).

Mediastinal tumors

00:23:11

Parts of mediastinum :

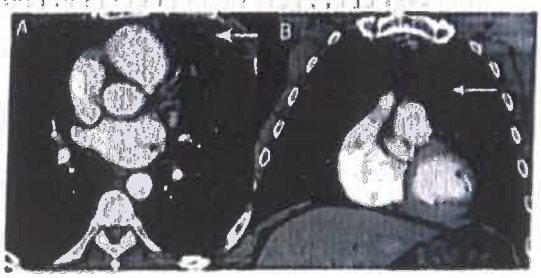
Anterior mediastinum : Anteriorly by the sternum and posteriorly by pericardium.

Parts of mediastinum

middle mediastinum : Between the anterior border of pericardium and an imaginary line drawn 1 cm posterior to the anterior border of the vertebral bodies.

Posterior mediastinum : Anteriorly by an imaginary line drawn 1 cm posterior to the anterior border of the vertebral bodies and posteriorly by the posterior paravertebral gutters.

Anterior mediastinal mass :

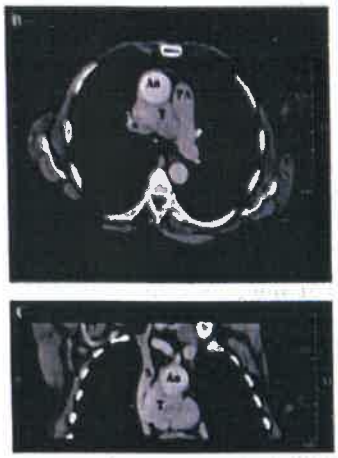


Anterior mediastinal mass.

Benign	Malignant
Teratoma	Non-Hodgkin's lymphoma
Cystic hygroma	Hodgkin's disease
Haemangioma	Teratoma with yolk sac tumour
Thymic cyst	Seminoma
	Desmoid
	Sarcoma
	Thymoma

Causes of anterior mediastinal mass.

middle mediastinal mass :

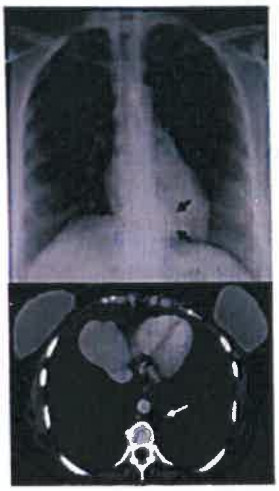


Benign	Malignant
Bronchogenic cyst (Tracheal duplication cyst)	Hodgkin's disease
Teratoma	Non-Hodgkin's lymphoma
Plasma cell granuloma	Teratoma
Cardiac rhabdomyoma	Rhabdomyosarcoma
	Other sarcomas

Causes of middle mediastinal mass.

Middle mediastinal mass.

Posterior mediastinal mass :



Benign	Malignant
Ganglioneuroma	Neuroblastoma,
Neurofibroma	Ganglioneuroblastoma
Enterogenous cyst	Neurofibrosarcoma
Teratoma (Rare)	Sarcoma
Lipoma	Liposarcoma
Leiomyoma	Leiomyosarcoma
	Sarcoma

Causes of posterior mediastinal mass.

Posterior mediatinal mass.

Lung tumors

00:26:03

Primary malignancies of the lung and tracheobronchial tree : Rare.
Inflammatory myofibroblastic tumor : M/C lung tumor in pediatrics.
Bronchial carinoid : Intense contrast enhancement related to their fibrovascular stromal component.
Mucoepidermoid carcinoma.
Bronchogenic carcinoma.

Pleuropulmonary blastomas (PPB) :

Type I :

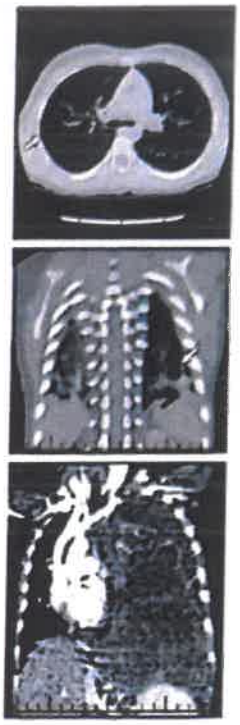
- Purely cystic tumors occurring <2 years of age.
- Median age of 10 months, 5-year DFS : 90%.

Type II :

- Cystic and solid tumors.
- Median age of 35 months.

Type III :

- Solid tumors, median age of 41 months.
- Surgical resection is recommended if feasible, followed by chemotherapy and/or radiation therapy, intracavitary chemotherapy.
- 5-year DFS : 50-60%.
- Associated with germline pathogenic DICER1 variants.
- Susceptible to other tumors :
  - Cystic nephromas.
  - Ovarian stromal sex cord tumors.
  - Thyroid and other endocrine tumors.
  - Embryonal rhabdomyosarcoma.
  - Brain tumors.



Pleuropulmonary blastomas.

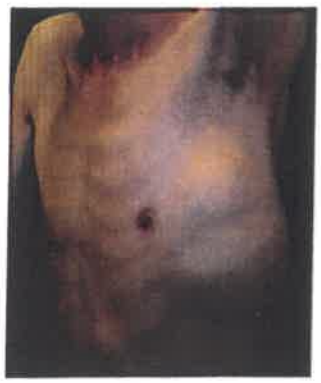
Chest wall tumors

00:27:22

May arise from bone or soft tissues.
m/c : metastatic rib lesions (Neuroblastoma, Langerhans cell histiocytosis, lymphoma, leukemia).

m/c paediatric chest wall primary malignancies :

- Rhabdomyosarcoma.
- Extraosseous Ewing sarcoma.
- PNET of the chest (Askin tumor).



Chest wall tumor.

Primary bone malignancies :

- Ewing sarcoma.
- Osteosarcoma.

May arise from the ribs, thoracic vertebrae, or scapulae and manifest as chest wall masses.

Non malignant chest wall masses :

- Neurofibromas.
- Hemangiomas, vascular malformations.

- Aneurysmal bone cysts.
- Osteochondromas.
- Healing rib fractures.
- Osteomyelitis.
- Developmental variations of the thoracic cage.

Indications of immediate evaluation of back pain :

- Bowel/bladder dysfunction.
- Paresis.
- Gait abnormalities.
- Paraesthesia.

Risk of spinal cord compression : Emergency.

Immediate MRI scanning.

Start dexamethasone.

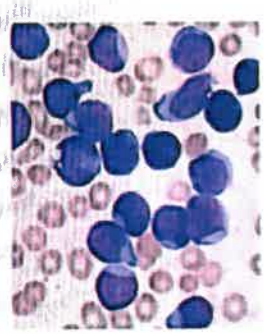
Peripheral blood abnormalities 00:29:33

Investigations :

1. Complete blood counts :

- Pancytopenia/bicytopenia.
- Leukocytosis.

2. Peripheral smear (PS) : Presence of blasts.



Blast cells on PS.

3. Bone marrow studies :

Indications for bone marrow studies :

- Patients with pancytopenia/more than one depressed cell line.
- Presence of blasts on peripheral smear.
- Presence of leucoerythroblastic changes on PS.
- Association with unexplained lymphadenopathy, bone pain, or hepatosplenomegaly.
- Association with an anterior mediastinal mass.

Diagnosis of leukemia :

- ≥20% bone marrow lymphoblasts in bone marrow study.
- Peripheral blood sample may be substituted if a sufficient level of circulating lymphoblasts is present.

Stains to distinguish lymphoblasts from myeloblasts :

- Wright-Giemsa-stained bone marrow aspirates.
- Hematoxylin and eosin (H&E) stained biopsies.

Features of lymphoblast :

- High nucleus-to-cytoplasm ratio.
- Absence of nucleoli
- Smaller size.

4. Flow cytometry.

5. Immunophenotyping :

B cells : CD10, CD19, CD20, CD45, Kappa, lambda.

T cells : CD2, CD3, CD4, CD5, CD7, CD8, CD45.

Myelomonocytic cells : CD11b, CD13, CD14, CD15, CD16, CD33, CD34, CD45, CD117, HLA-DR.

6. Chromosomal analysis and banding :

Essential for the identification of aneuploidy, microscopic chromosomal anomalies, and some translocations.

Common translocation in ALL :

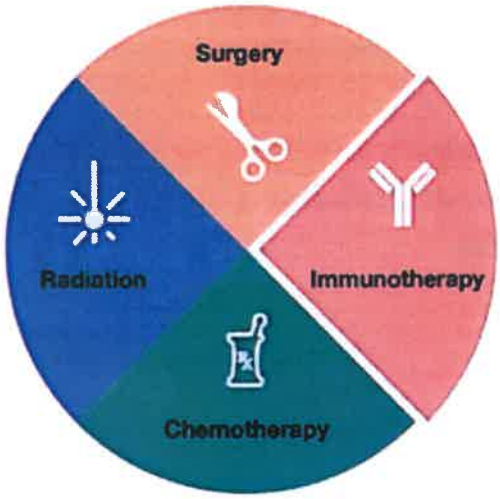
- t(12 ; 21) : m/c translocation in childhood ALL, favorable prognosis.
- t(1 ; 19) : Bad prognosis.
- t(9;22) : Very poor outcome.
- 11q23 rearrangements : Poor outcome.
- t(5;14).

Used for risk stratification

Note :

In case of suspicion of leukemia, do not give steroids during a blood transfusion or in case of transfusion reaction as it can delay the diagnosis.

Modalities of treatment :



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THE GOAL OF THE GLOBAL INITIATIVE IS TO ACHIEVE AT LEAST A

60% SURVIVAL

AND TO REDUCE SUFFERING FOR ALL CHILDREN WITH CANCER BY 2030.

1 MILLION CHILDREN WITH CANCER CAN BE SAVED IN THE NEXT DECADE.

Key home message :

- Childhood cancer is a highly curable disease.
- Increase awareness about symptoms and signs of childhood cancer.
- Early diagnosis.
- Early referral to the pediatric oncology unit.

Feedback

EPIDEMIOLOGY AND MOLECULAR BIOLOGY OF PAEDIATRIC CANCER

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Introduction 00:00:17

Tissue homeostasis depends on the regulated cell division and self-elimination (Programmed cell death) of each of its constituent members except its stem cells.

A tumor arises as a result of :

- Uncontrolled cell division.
- Failure for self-elimination.

Alterations in genes responsible for the deregulated control mechanisms that are the hallmarks of cancer cells :

- Proto-oncogenes.
- Tumor supressor genes.
- DNA stability genes/DNA repair genes.

Genes involved 00:01:18

Oncogenes :

It is a proto-oncogene → mutated → Leads to signals that cause uncontrolled growth ie., cancer.

mechanism of oncogenes.

----- Active space -----

HER-2/neu :

- Encodes for a cell surface receptor that can stimulate cell division.
- Amplified in up to 30% of human breast cancers.

RAS :

- Involved in Kinase signaling pathways → Controls transcription of genes, regulating cell growth and differentiation.

MYC :

- Encodes transcription factor and controls expression of several genes.

SRC :

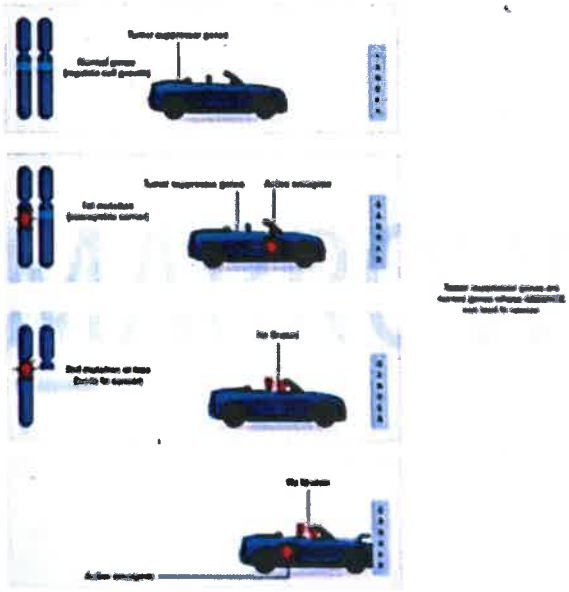
- First oncogene ever discovered.
- Is a tyrosine kinase → Regulates cell activity.

hTERT :

- Codes for telomerase → maintains chromosome ends.

Tumor suppressor gene :

- Segments of DNA that code for negative regulator proteins which keep the cell from undergoing uncontrolled division.
- Braking signals during phase G1 of the cell cycle, to stop or slow the cell cycle before S phase.
- Mutations in tumor suppressor genes cause loss-of-function, resulting in uncontrolled cell growth, i.e, cancer.



mechanism of tumor suppressor gene.

Examples of cancer predisposition genes and their associated syndromes :

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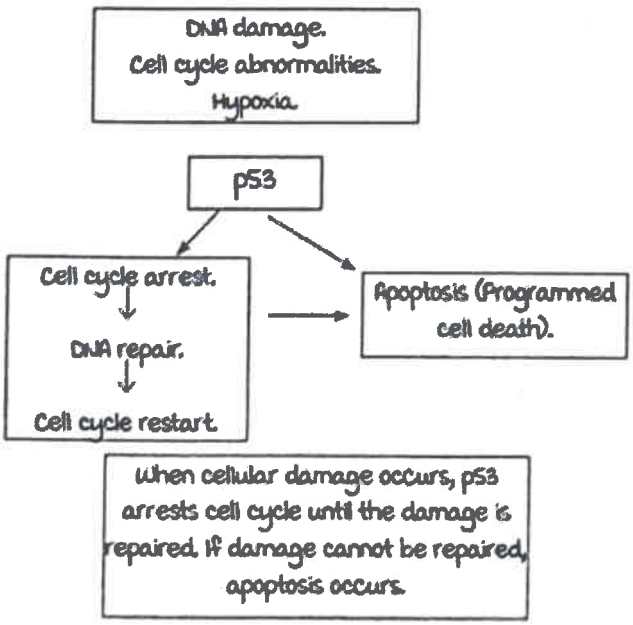
Tumor suppressor gene	Syndrome	Tumor
Rb	Retinoblastoma.	Retinoblastoma.
WT 1	Familial Wilm's tumor.	Wilm's tumor.
NIF 1	Neurofibromatosis type 1.	Neurofibroma, sarcoma.
NIF 2	Neurofibromatosis type 2.	Schwannoma, meningioma.
APC	Familial adenomatosis polyposis.	Tumors of colon, stomach and intestine.
p53	Li-Fraumeni syndrome.	Breast, lung, brain tumors, sarcoma.
VHL	Von Hippel-Lindau disease.	Tumors of kidney, adrenal.
E-CAD	Familial gastric cancer.	Tumor of stomach, breast.
PTCH	Gorlin syndrome.	Basal cell carcinoma.
PTEN	Cowden syndrome.	Hamartoma.
MEN 1	Multiple endocrine neoplasia.	Tumors of pituitary, pancreas and parathyroid.

P53 gene :

Normal p53 :



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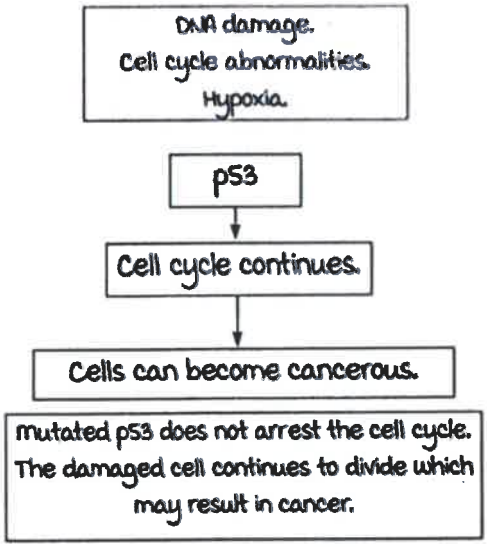
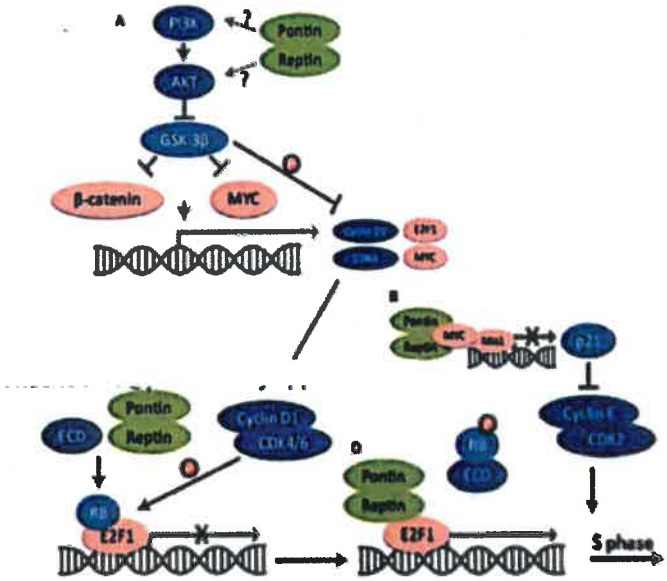
Mutated p53 :



Rb gene :

Also known as 'governor of the genome'.



Mechanism of Rb gene.

Mechanism :

i. Rb is phosphorylated by cyclin D/CDK4/6 complexes as cells leave G0 phase and enter the cell cycle.

ii. Moving through G1 phase, Rb becomes progressively more phosphorylated until R is reached.

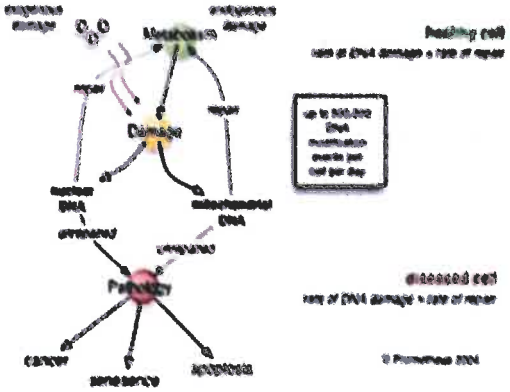
iii. Hyperphosphorylated Rb is no longer able to bind and inhibit its primary target, the E2F transcription factors.

iv. Hence, derepressed E2Fs are then free to upregulate expression of cell cycle related genes, cyclins E/A and CDKs.
v. Beyond the R point, Rb remains hyperphosphorylated throughout the rest of the cell cycle until it is dephosphorylated by protein phosphatase type 1 (PP1) at the end of mitosis.
vi. Homozygous deletions of Rb are necessary for the genesis of Rb.
vii. Rb gene mutations are also seen in :
- Subsets of osteosarcoma.
- Burkitt lymphoma.
- Glioblastoma multiforme.

Difference between tumor suppressor genes and oncogenes :

Property	Tumor suppressor genes	Oncogenes
Alleles mutated in cancer.	Both alleles.	One allele.
Germline transmission of mutant alleles.	Frequently seen.	Rare.
Somatic mutation involved in tumor formation.	Yes.	Yes.
Function of mutant allele(s).	Loss of function (Recessive allele).	Gain of function (Dominant allele).
Effects of cell growth.	Inhibit cell growth.	Promote cell growth.

DNA repair genes :
- Code for proteins whose normal function is to correct errors that arise when cells duplicate their DNA prior to cell division.
- Active throughout the cell cycle, particularly during G2 phase.
- Eg : BRCA 1 and BRCA 2.



BRCA I and BRCA mechanism.

Hallmarks of cancer 00:09:16

The important hallmarks are :

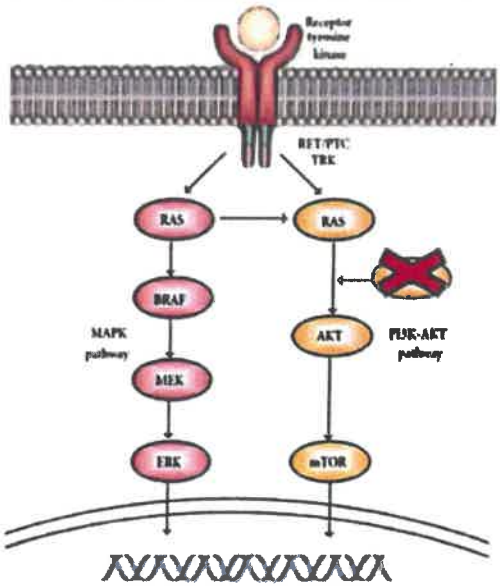
i. Sustained proliferative signalling.
ii. Evading growth receptors.
iii. Avoiding immune destruction.
iv. Enabling replicative immortality.
v. Tumor promoting inflammation.
vi. Activating invasion and metastasis.
vii. Tumor angiogenesis.
viii. Genome instability and mutation.
ix. Resisting cell death.
x. Deregulating cellular metabolism.

Sustained proliferative signalling :

Normal cells carefully control growth and division.

Cancer cells deregulate these signals of cell proliferation by :

- Synthesis of growth factors (Autocrine stimulation). Eg : PDGF and TGF-β .
- Overexpress receptors. Eg : EGFR.
- Show ligand-independent receptor activation by structural changes.
- Express different extracellular receptors.
- Independent from growth factors.
- Activation of downstream signaling pathways or the disruption of negative feedback mechanisms.



Mechanism of cell proliferation by RAS gene.

Antiproliferation :

- Normal tissues have multiple antiproliferative signals.
  Eg : Soluble growth inhibitors and immobilized inhibitors embedded in extracellular matrix & on surfaces of surrounding cells.
  These signals transition cell out of cell cycle to resting state (G0).
- Cancer cells evade the growth suppressor genes.
  Eg : Rb and p53 gene → Overrule the initiation or "turning off" of cell division.

Enabling replicative immortality :

- Normal cells → Limited replicative potential. After a number of divisions, they stop growing (Senescence).
- Mechanism of senescence : Due to limited number of telomeres (Restricting number of divisions).
- Telomerase adds hexanucleotide repeats (-TTAGGG) to end of telomeric DNA and prevent telomer shortening.
- Tumor cells have high telomerase enzyme → Telomere shortening prevented → Unrestricted cell division.

Cell death :

Forms of cell death :

- Apoptosis.

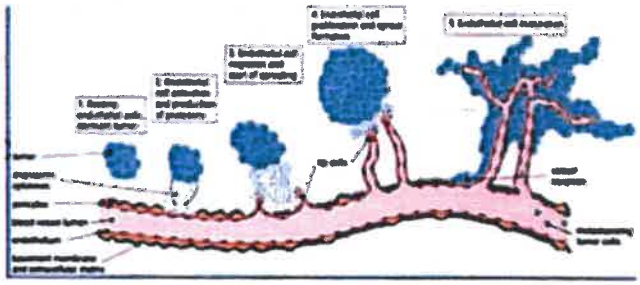
- Autophagy : Enables cells to break down cellular organelles and recycle them for biosynthesis and energy metabolism.
- Necrosis : Release contents into local tissue microenvironment.

mechanism to resist cell death :

- Loss of p53.
- Increase anti-apoptotic proteins.
- Decrease pro-apoptotic proteins.

Tumor Angiogenesis :

- Angiogenesis is the recruitment of new blood vessels to regions of chronically low blood supply, essential for the progression of solid tumors to malignancy.
- Tumors require oxygen, nutrients, and the ability to evacuate metabolic wastes and CO_2.
- VEGF was the first growth factor isolated that could stimulate proliferation and migration of blood vessel cell lining.



Tumor angiogenesis.

Invasion and metastasis :