LATE EFFECT,SECOND MALIGNANCY AND SURVEILLANCE IN PAEDIATRIC CANCER SURVIVORS

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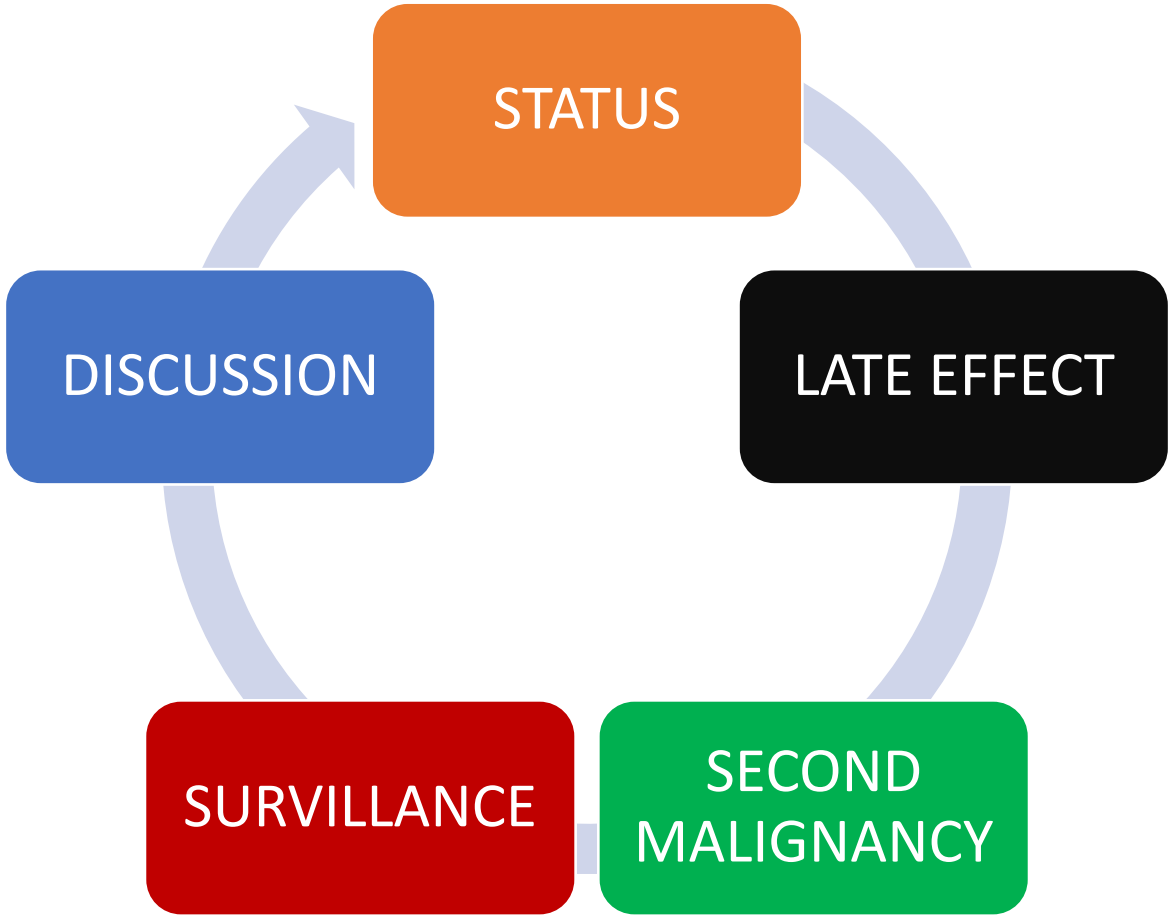
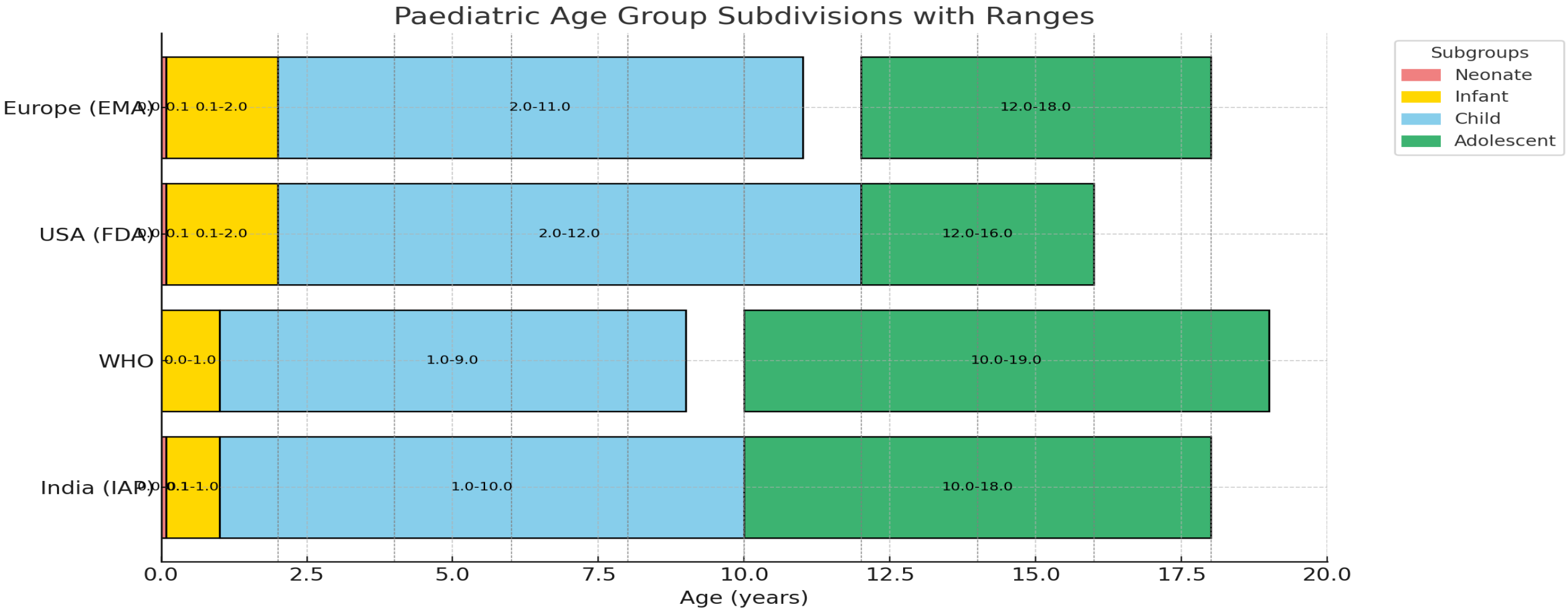
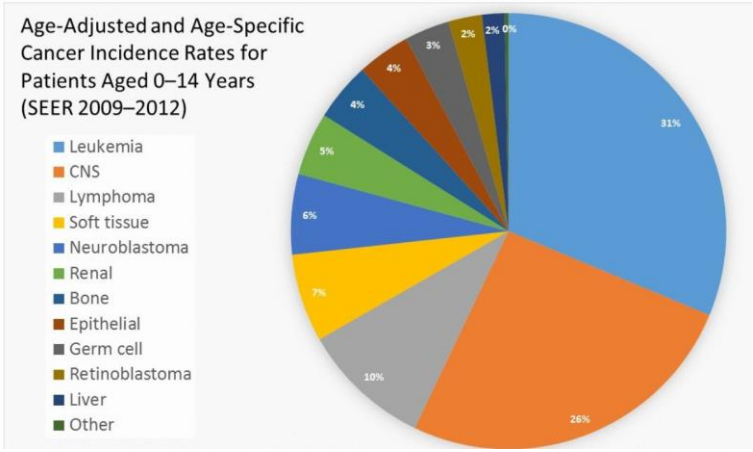
ROAD MAP


STATUS
LATE EFFECT
SECOND MALIGNANCY
SURVILLANCE
DISCUSSION

PAEDIATRIC AGE GROUP:-WHAT AGE



WHAT ARE THE PAEDIATRIC CANCERS WE COME ACROSS



Age-adjusted and age-specific (0–14 years) (SEER) Program cancer incidence rates from 2009 to 2012 by International Classification of Childhood Cancer group.

PAEDIATRIC MALIGNANCY

OPENION OF PANELIST HAVE ANY EXPERIENCE ON LATE TOXICITY/SECOND MALIGNANCY

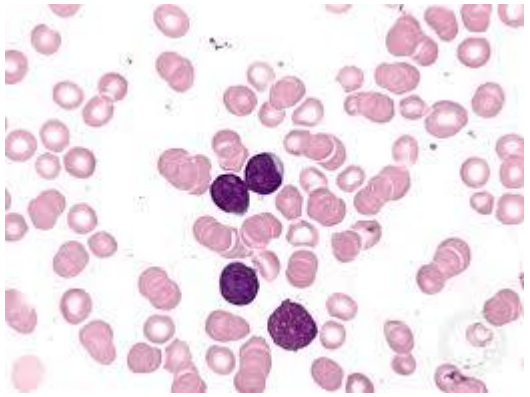
LATE TOXICITY

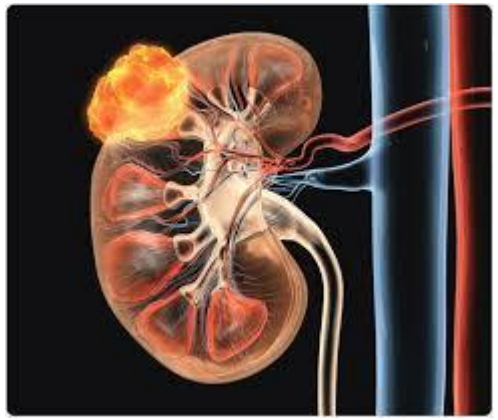
SECOND MA;PGNANCY

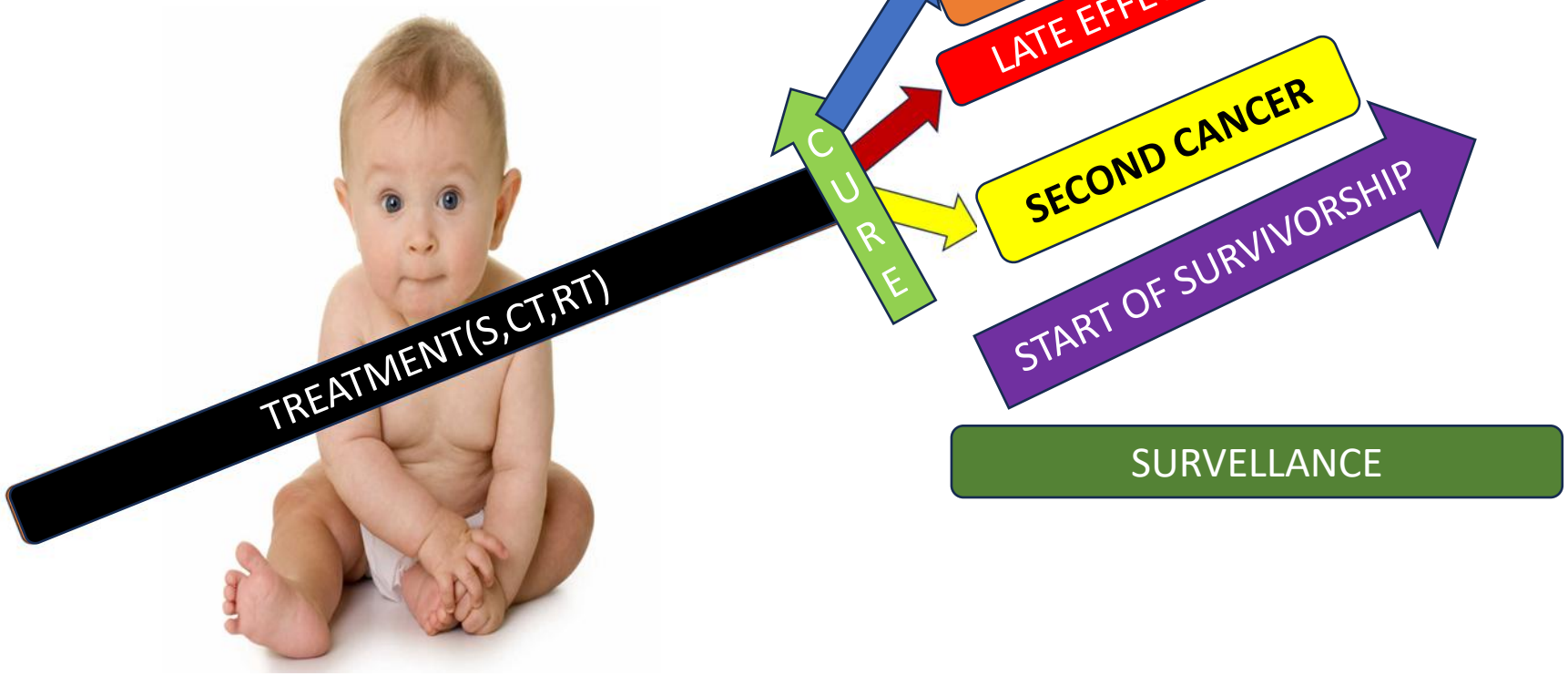
SURVILLANCE

WHAT IS OBSERVATION VS SURVILANCE

JOURNEY OF PAEDIATRIC CANCER PATIENTS







IS THERE ANY DIFFERENCE IN SURVIVAL IN PAEDIATRIC MALIGNANCY IN DEVELOPED VS DEVELOPING COUNTRY

CANCER TYPE	DEVELOPED COUNTRIES (HICS)	Developing Countries (LMICs)
ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)	>85–90% SURVIVAL; STANDARDIZED PROTOCOLS; MRD-BASED RISK STRATIFICATION; LATE EFFECTS: NEUROCOGNITIVE, OBESITY, METABOLIC SYNDROME.	40–60% SURVIVAL; TREATMENT ABANDONMENT, INFECTIONS; LIMITED MRD TESTING; HIGHER RELAPSE; LATE EFFECTS UNDER-DIAGNOSED.
HODGKIN LYMPHOMA	>90% CURE; RISK-ADAPTED THERAPY; LATE EFFECTS: SECONDARY BREAST CANCER, HYPOTHYROIDISM, CARDIAC DISEASE.	50–70% SURVIVAL; LIMITED PET STAGING & RT; HIGHER TOXICITY; POOR SURVEILLANCE FOR SECOND MALIGNANCY.
NON-HODGKIN LYMPHOMA	>80% CURE; INTENSIVE CHEMO; LATE EFFECTS: CARDIOTOXICITY, INFERTILITY, NEUROCOGNITION.	30–50% CURE; DELAYED DIAGNOSIS, POOR SUPPORTIVE CARE; HIGHER ABANDONMENT; MINIMAL LATE EFFECTS MONITORING.
WILMS' TUMOR	>85–90% CURE; NEPHRECTOMY + CHEMO; LATE EFFECTS: RENAL DYSFUNCTION, HYPERTENSION.	50–70% CURE; LATE PRESENTATION; LIMITED RT ACCESS; HIGHER SURGICAL MORBIDITY; CKD UNDER-MONITORED.
RETINOBLASTOMA	>95% SURVIVAL; ENUCLEATION + FOCAL THERAPY; LATE EFFECTS: SECONDARY SARCOMA, PSYCHOSOCIAL ISSUES.	<50% SURVIVAL; LATE PRESENTATION; GLOBE SALVAGE RARE; MORTALITY DUE TO EXTRAOCULAR DISEASE; PSYCHOSOCIAL STIGMA HIGH.
CNS TUMORS	70–80% SURVIVAL; PROTON THERAPY REDUCES NEUROCOGNITIVE DECLINE; LONG-TERM: ENDOCRINE, LEARNING ISSUES.	20–40% SURVIVAL; LATE DIAGNOSIS; LACK OF NEUROSURGERY/RT; HIGH MORTALITY; SURVIVORS: SEVERE DISABILITY.
OSTEOSARCOMA / EWING'S SARCOMA	60–70% SURVIVAL; LIMB-SALVAGE; LATE EFFECTS: PROSTHESIS, CARDIOTOXICITY, INFERTILITY.	20–40% SURVIVAL; LATE DIAGNOSIS; HIGH AMPUTATION RATES; POOR ACCESS TO CHEMO; PHYSICAL DISABILITY, STIGMA.
NEUROBLASTOMA	>70% SURVIVAL IN LOW–INTERMEDIATE RISK; TRANSPLANT & IMMUNOTHERAPY; LATE EFFECTS: HEARING LOSS, GROWTH/ENDOCRINE.	<30% SURVIVAL; MOST PRESENT ADVANCED STAGE; LACK OF TRANSPLANT/IMMUNOTHERAPY; SURVIVORS RARE.

WHAT ARE THE LATE COMPLICATIONS

NEUROCOGNITIVE – DEFICITS AFTER CRANIAL RT OR METHOTREXATE

PULMONARY FIBROSIS

RENAL/OTOTOXICITY

FERTILITY: PREMATURE OVARIAN FAILURE, AZOOSPERMIA

ENDOCRINE – GROWTH HORMONE DEFICIENCY, HYPOTHYROIDISM,GONADAL FAILURE

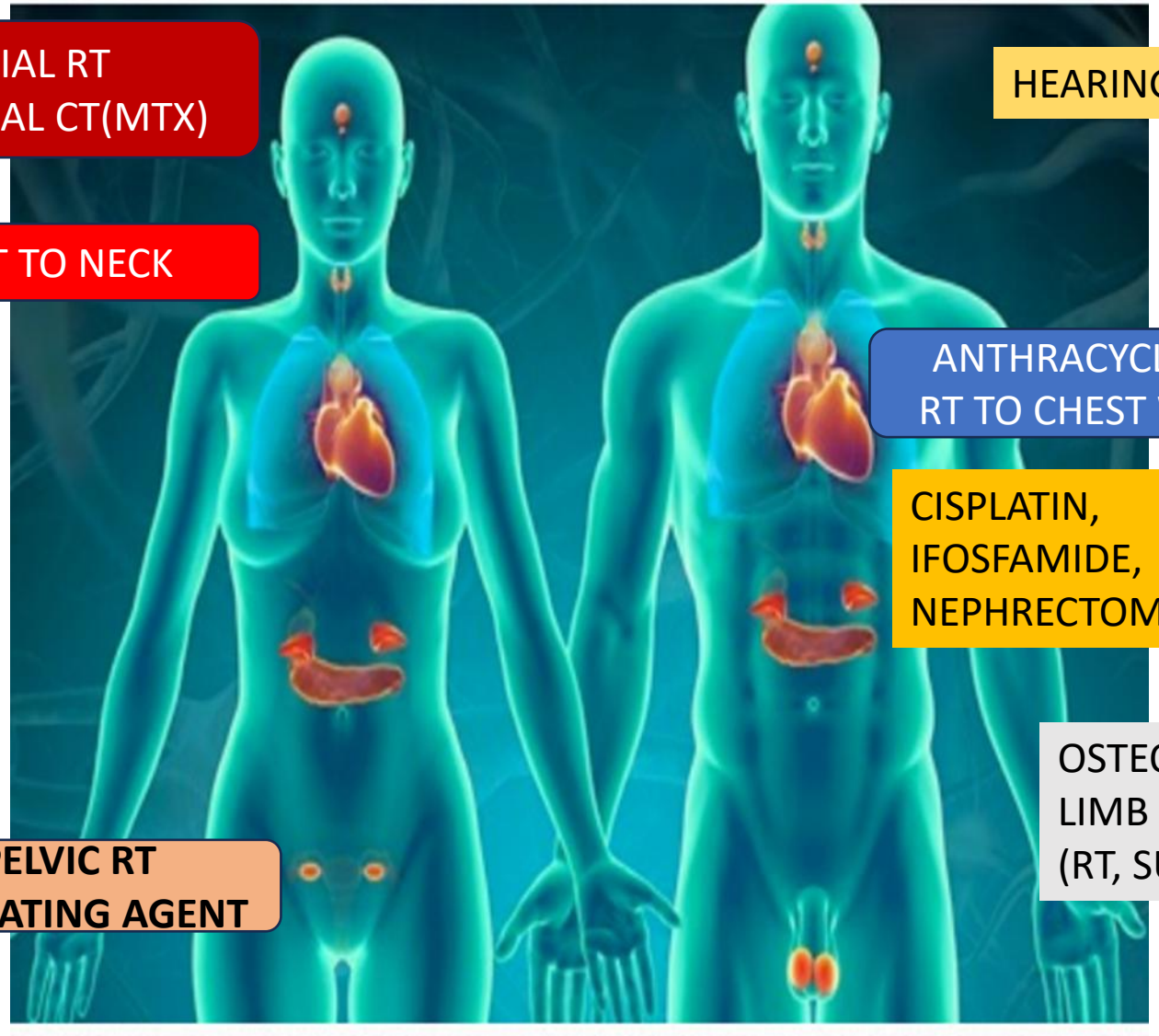
CARDIAC –CARDIOMYOPATHY, CORONARY ARTERY DISEASE

MUSCULOSKELETAL – OSTEONECROSIS, STUNTED GROWTH

WHY THERE IS LATE COMPLICATION

CRANIAL RT
INTRATHECAL CT(MTX)

RT TO NECK



HEARING: (CISPLATIN).

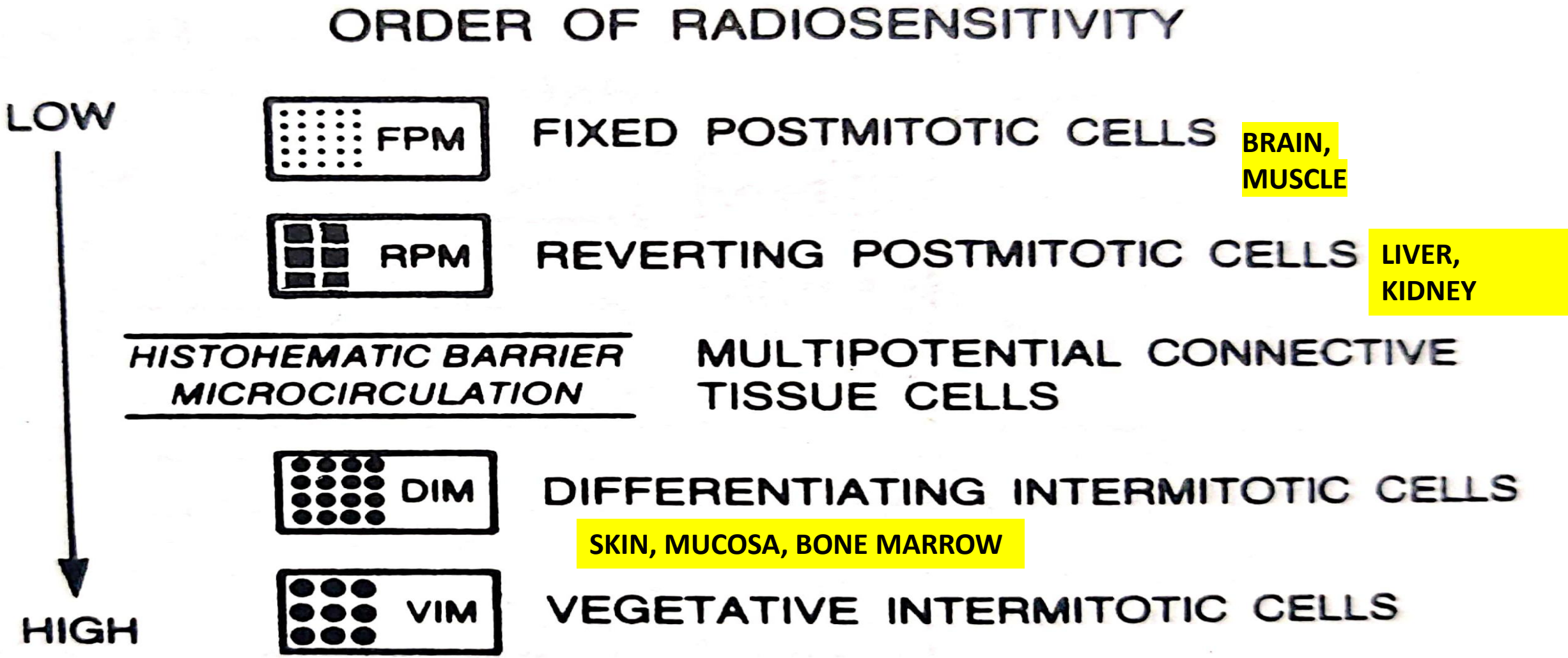
ANTHRACYCLINE,
RT TO CHEST WALL

CISPLATIN,
IFOSFAMIDE,
NEPHRECTOMY).

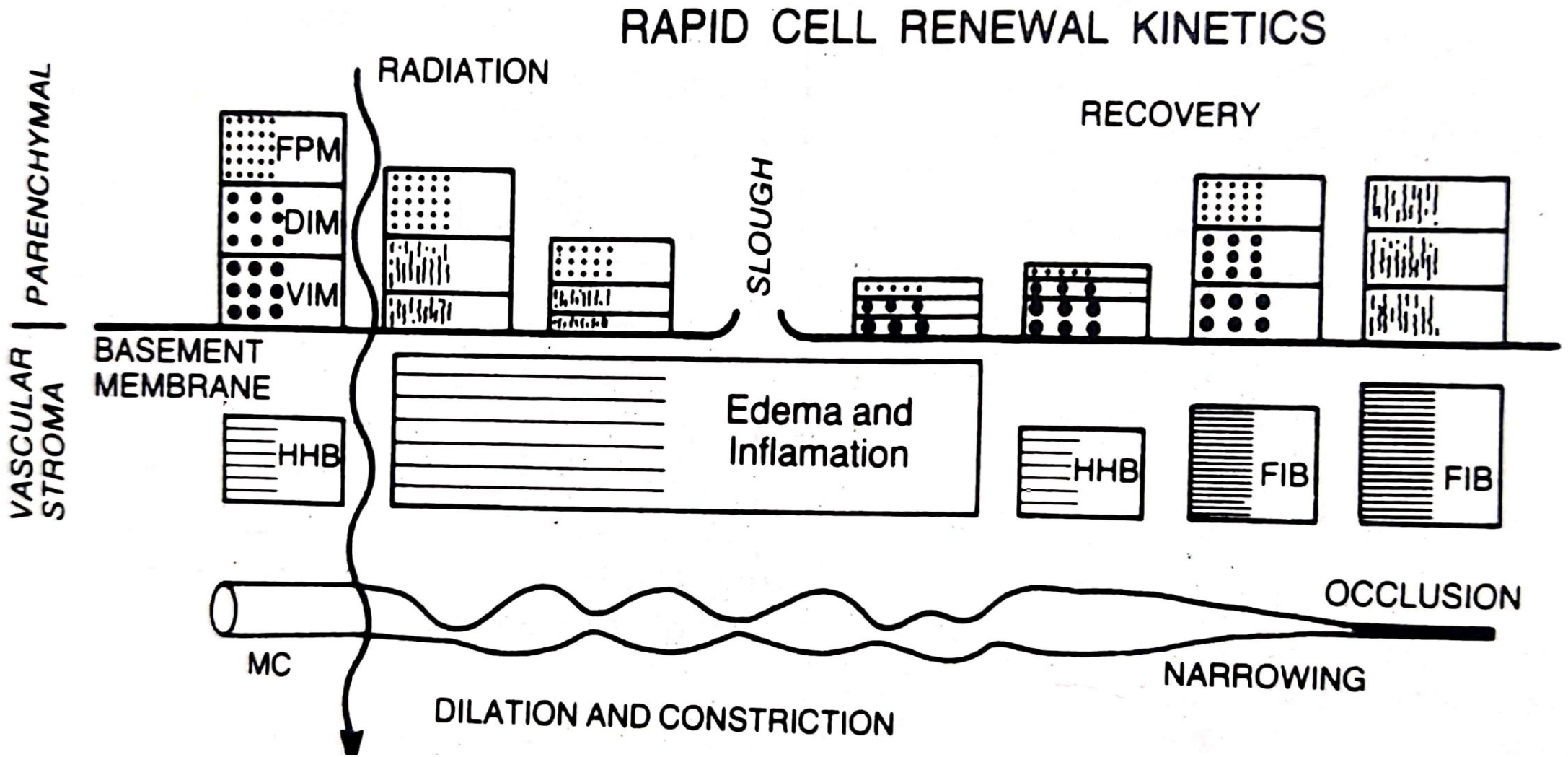
OSTEONECROSIS (STEROIDS),
LIMB LENGTH DISCREPANCIES
(RT, SURGERY).

PELVIC RT
ALKYLATING AGENT

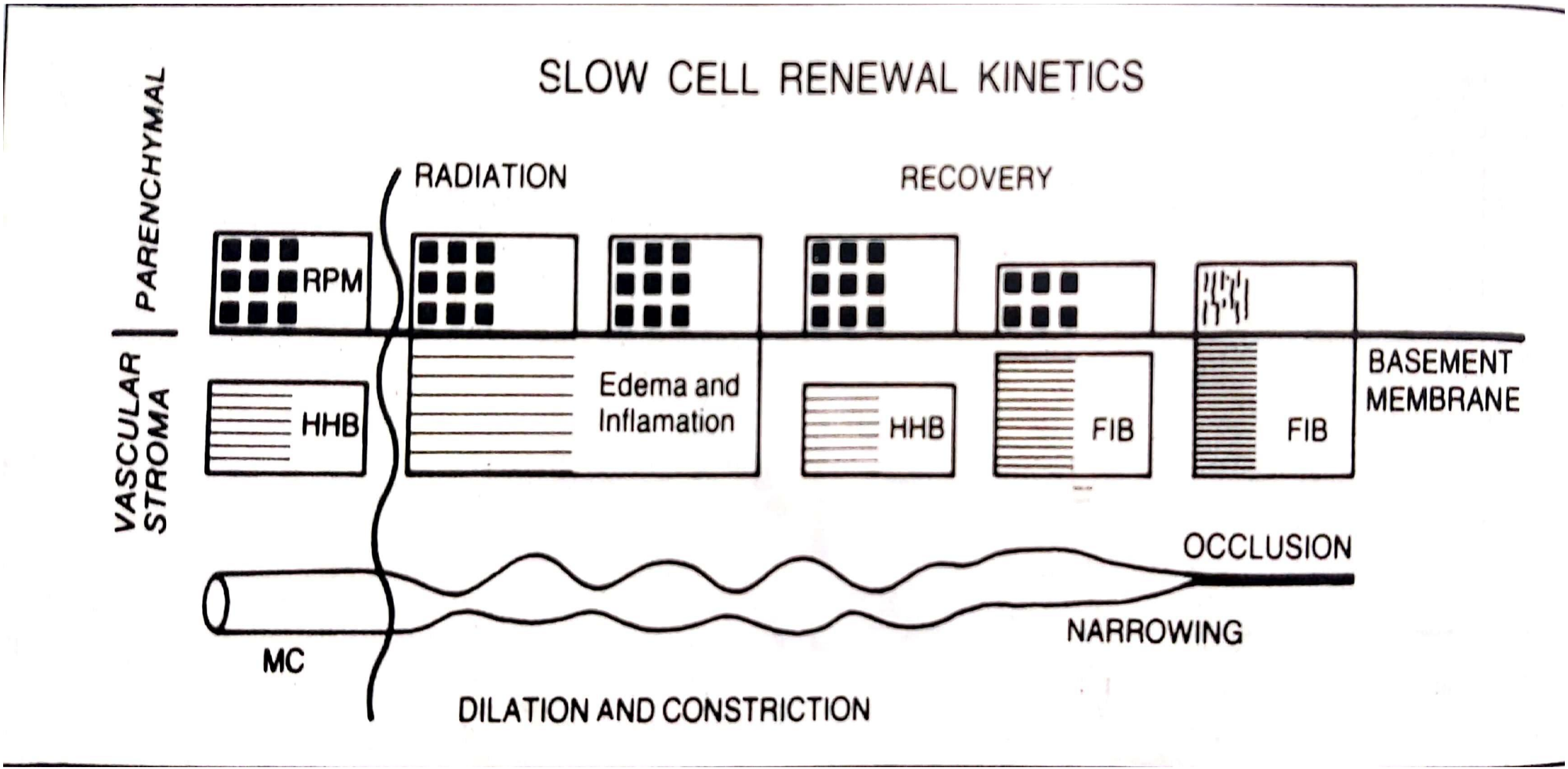
PHILOSOPHY BEHIND THE COMPLICATIONS IN RELATION TO CELL RADIOSENSITIVITY(cowdery etal)



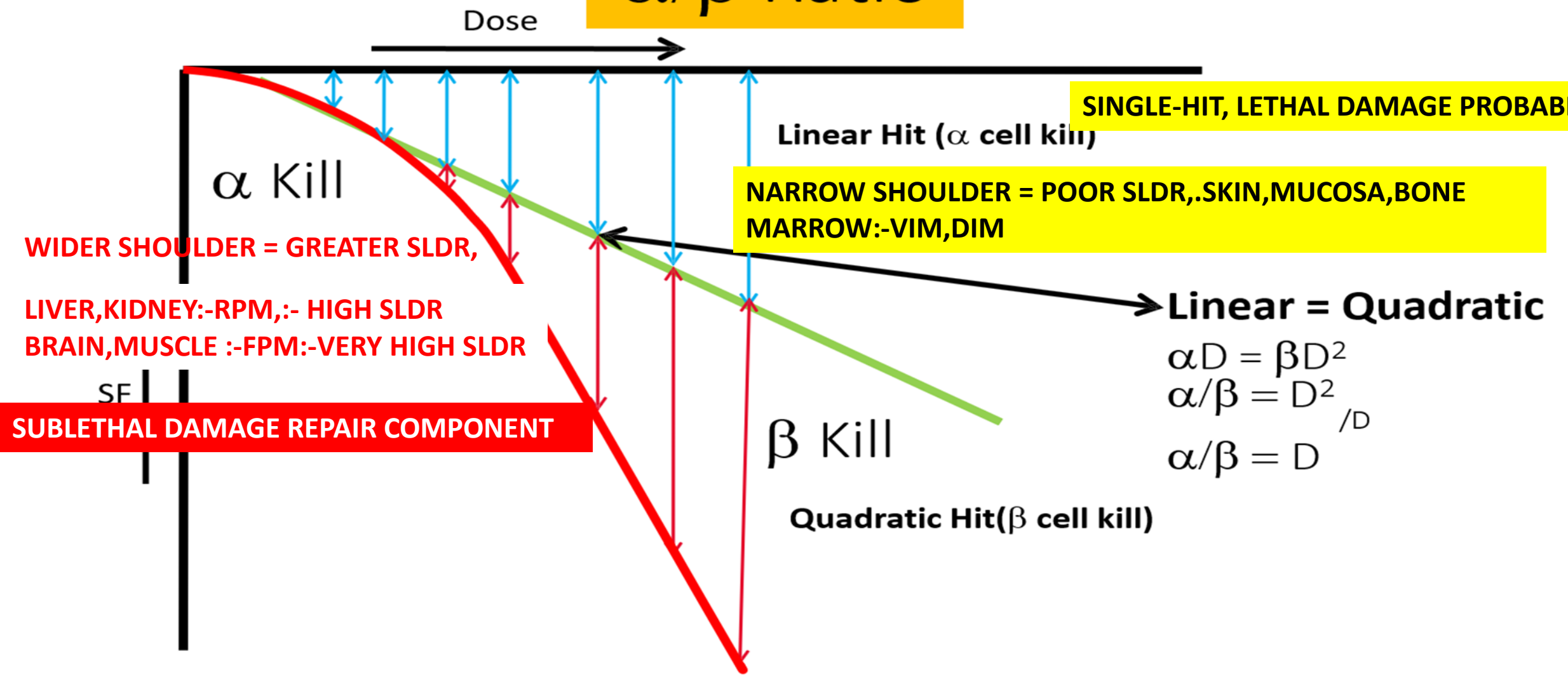
RAPIDLY PROLIFERATING TISSUE,ACUTE TOXICITY



SLOW RENEWAL KINETICS,LATE TOXICITY



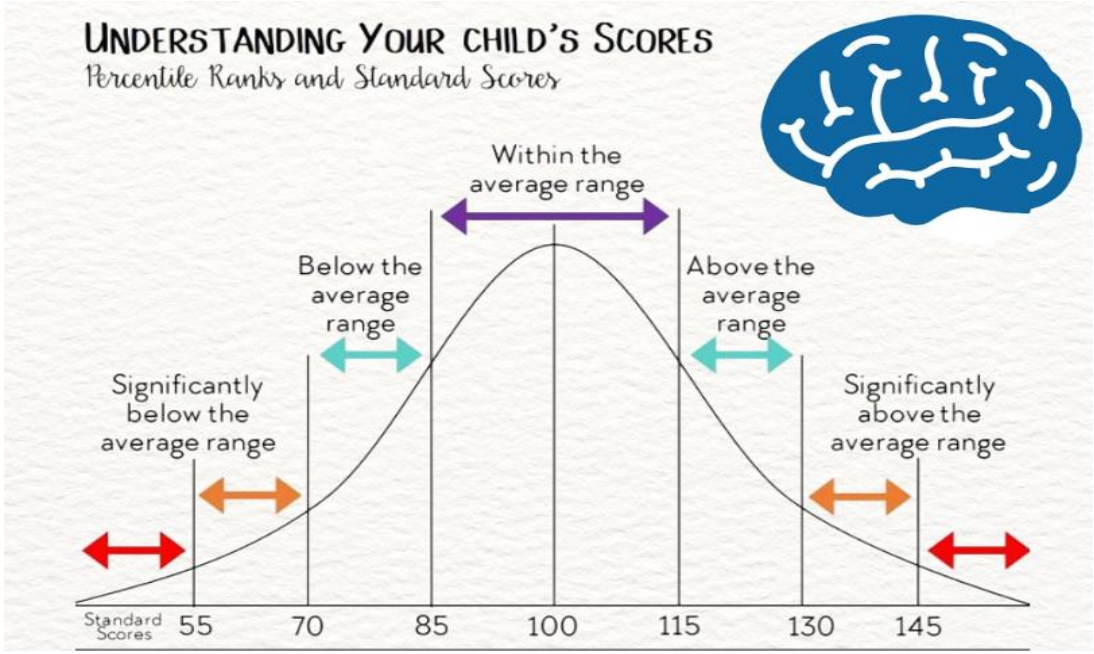
α/β Ratio

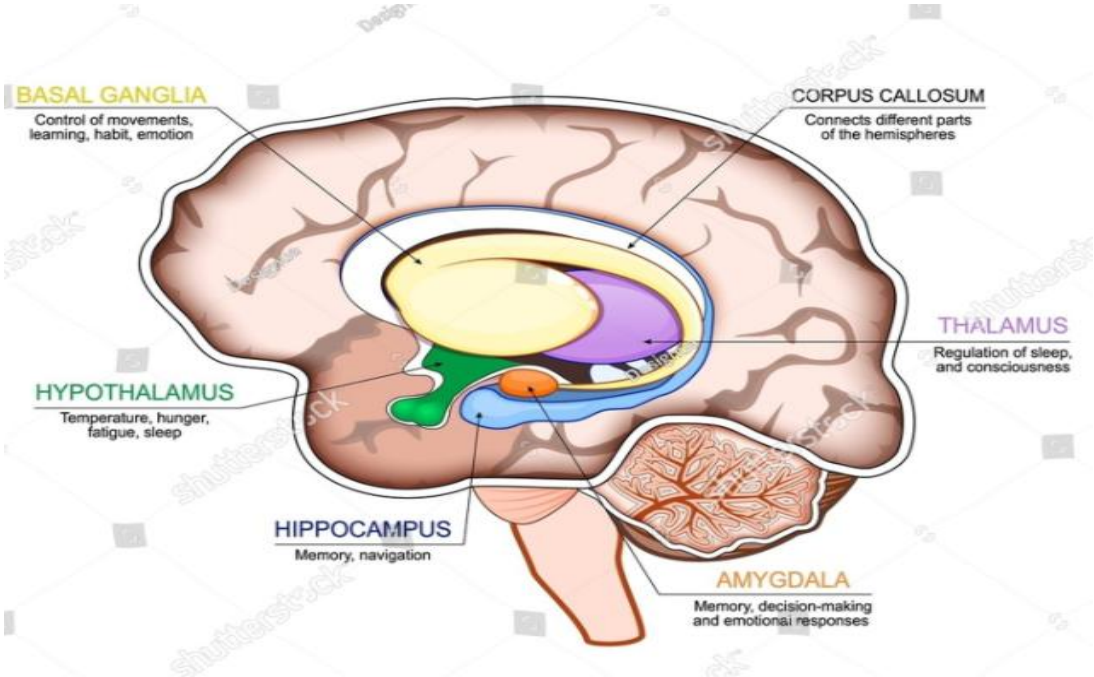


➢So α/β can be defined as the dose at which contribution by single hit (Linear) kill becomes equal to double hit (Quadratic) kill.

CASE CAPSULE :-1

- *A 14-year-old boy Now has poor school performance, attention deficit, and growth <3rd percentile.*
- *Past History:- treated at age 4 for ALL with MCP-841 WITH prophylactic cranial RT 18 Gy to the whole brain..*





WHAT LATE EFFECTS ARE EXPECTED AFTER PROPHYLACTIC CRANIAL IRRADIATION (PCI) IN CHILDHOOD ALL?
Answer :
•**Neurocognitive:** ↓processing speed, attention/executive deficits, working memory decline; younger age at RT and ≥18 Gy increase risk.
•**Endocrine:** GH deficiency (earliest/most common), ± gonadotropin, TSH, ACTH deficits over time; growth failure common.
•**Others:** Secondary neoplasms (long-term), cerebrovascular disease, psychosocial/education impact.

2) WHICH COGNITIVE DOMAINS ARE MOST AFFECTED, AND HOW SHOULD WE TEST?
ANSWER:
•**Most affected:** attention, processing speed, working memory; often > global IQ.
•**Testing:** comprehensive pediatric battery—**WISC-V** (indexes), **CPT-3/TOVA** (attention), **Trail Making**, **Digit Span/Working Memory**, **Children's Memory Scale**, school reports.

3) Why is his height <3rd percentile—what endocrine axes are at risk after 18 Gy?
Answer:
•**GH axis is most radiosensitive** → **GH deficiency** → growth failure; later risk to **gonadotropin**, **TSH**, **ACTH**.
•**Dose-time effect:** even **18 Gy** can cause progressive pituitary dysfunction over years

4) What are current strategies to reduce late effects in ALL?
Answer:
•**Eliminate CRT** (except rare CNS-3/high-risk scenarios), optimize **IT schedules**, leucovorin rescue with MTX, risk-adapted systemic therapy, **MRD-guided** intensity.
•Structured **survivorship programs** and early neurocognitive/endo screening.
Evidence: COG, **St. Jude**, **UKALL** contemporary protocols showing maintained survival with **no PCI**.

- **Children's Oncology Group (COG) protocols (e.g., AALL0331, AALL0232, AALL1131):**
- CRT eliminated for standard- and intermediate-risk patients.
- Reserved only for **very high-risk or CNS3 disease**.
- Today, <2–3% of children with ALL in the U.S. receive CRT.

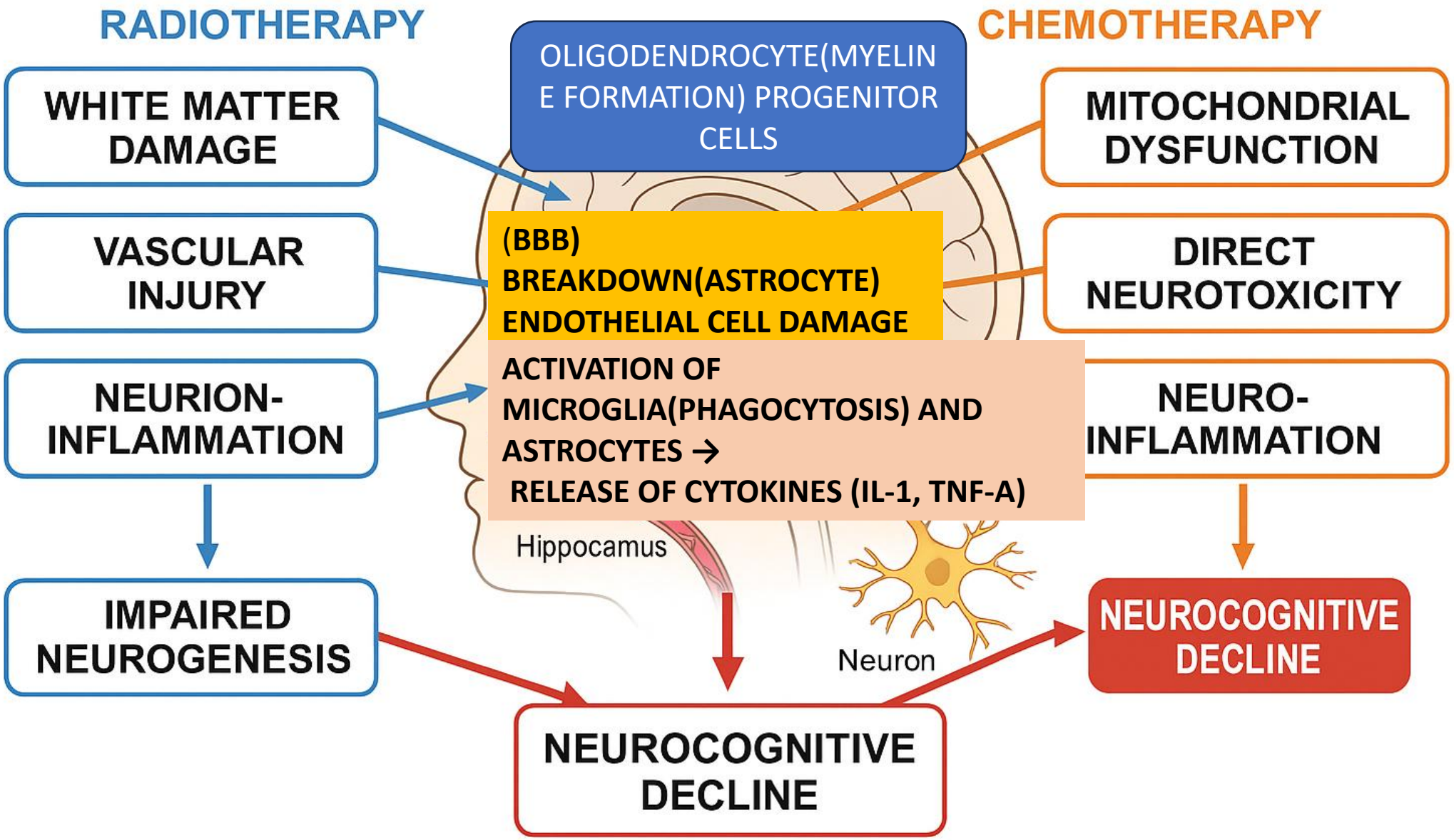
Risk Categories in Childhood ALL

Risk Category	Criteria	CRT (Past)	CRT (Now)
Standard Risk	Age 1–9 y, WBC <50k, CNS1	18 Gy	0 Gy
High Risk	≥10 y or WBC ≥50k, T-ALL, MRD+, CNS2	18 Gy	0 Gy (chemo only)
Very High Risk	CNS3, relapse, induction failure, adverse genetics	24 Gy	18–24 Gy (only if overt CNS disease)

4) Imaging and labs you'd order today—what and why?
Answer:
•**MRI brain** (WM changes/leukoencephalopathy, hippocampal volume if available).
•**Endo panel:** IGF-1/IGFBP-3, TSH/Free T4, AM cortisol ± ACTH, LH/FSH + sex steroids; **bone age**; fasting glucose/lipids (metabolic risk).

11) What rehabilitation/academic supports are effective now?
Answer:
•**Neuropsychologic rehab** (attention/working memory training), **school IEPs**, extra time, assistive tech, behavioral therapy (ADHD strategies), sleep hygiene, exercise.
•Consider **methylphenidate** in selected attention-deficit phenotypes (specialist guided).
Evidence: Survivorship intervention studies within **CCSS/COG**, small RCTs on stimulant use for cognitive deficits in survivors.

Mechanisms of Neurocognitive Decline After Chemotherapy and Radiotherapy to Brain



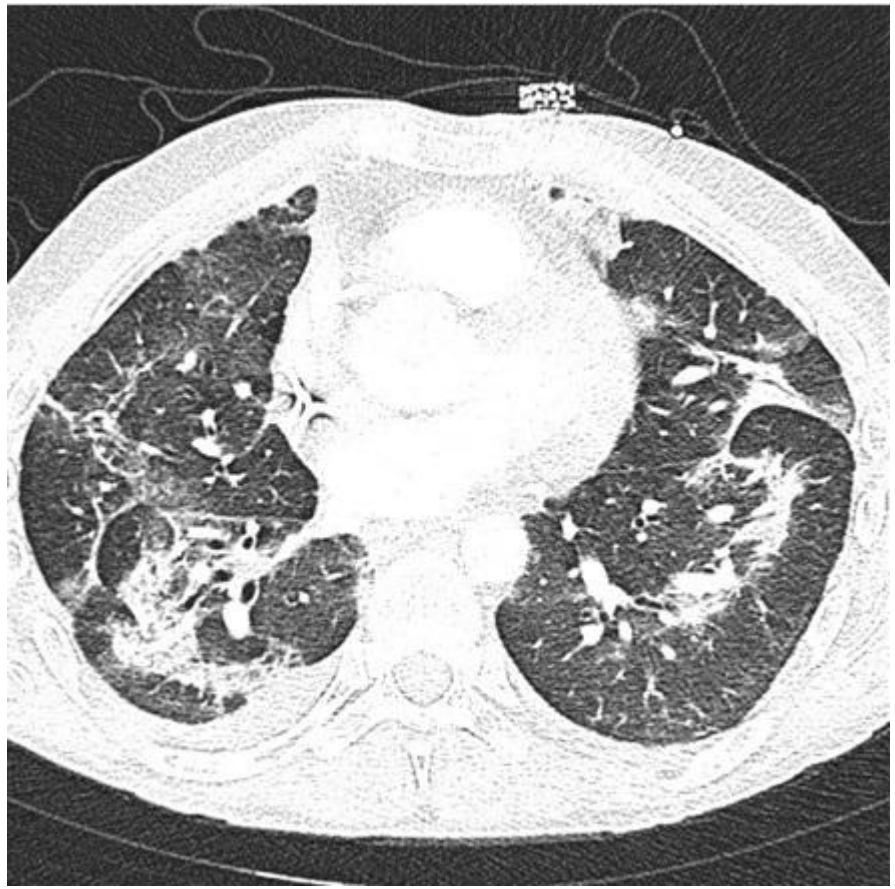
CASE CAPSULE:-2

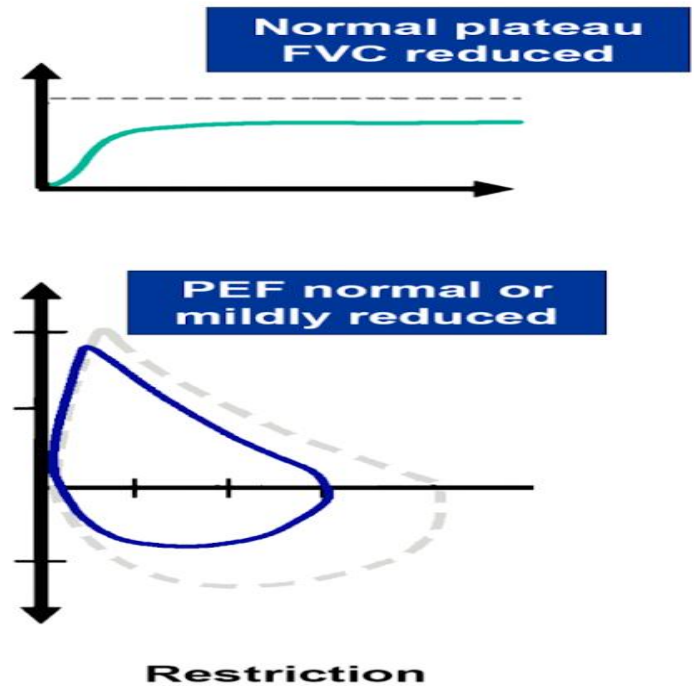
- **A 16-year-old female child clinically presented with chronic cough and dyspnoea on exertion for last 2 months.**
- **Past history:-Patient was diagnosed as a case of Hodgkins disease and was treated with 6 cycle of ABVD chemotherapy 6 yrs back**
- **O/E:-Tachypnoea, exercise intolerance, clubbing.**
- **Chest exam: Reduced expansion, end-inspiratory fine crackles ("Velcro rales"), shallow rapid breathing.**
- **Signs of pulmonary hypertension/cor pulmonale.**
- **PFT shows restrictive pattern.**
- **CE CT:-Bilateral basal reticular changes + traction bronchiectasis ± honeycombing**

.

- Naranjo's scale
- **(Bleomycin pulmonary fibrosis Hodgkin's survivor)**

- Q1: Yes, well reported (+1)
- Q2: Symptoms after drug exposure (+2)
- Q3: Improved after stopping bleomycin (NA, but usually yes) (+1)
- Q4: Rechallenge not done (0)
- Q5: Alternative causes? Unlikely (0)
- Q6: Placebo? (0)
- Q7: No toxic level test (0)
- Q8: Dose–response? Yes, higher cumulative doses ↑ risk (+1)
- Q9: Prior reaction? No (0)
- Q10: Objective evidence (HRCT/PFT) (+1)
- **Total ≈ 6 → Probable ADR**




Normal plateau
FVC reduced
PEF normal or
mildly reduced
Restriction

WHAT IS THE MOST LIKELY DIAGNOSIS IN THIS CASE?

Answer:

- Bleomycin-induced **pulmonary fibrosis** (late toxicity), with secondary pulmonary hypertension/cor pulmonale.
- Supported by history of ABVD (Bleomycin), restrictive PFT, basal fibrosis, and honeycombing on CT.

What are the risk factors for bleomycin lung toxicity?

Answer:

- **Cumulative dose > 400 units**.
- **Older age at treatment**, prior chest radiation, high O_2 exposure, renal dysfunction.
- Even at moderate doses in children, late fibrosis can occur.

How do we differentiate bleomycin pulmonary toxicity from relapse of Hodgkin's disease?

Answer:

- **Bleomycin fibrosis**: diffuse basal reticular/ground-glass pattern, volume loss, no new nodes.
- **Relapse**: nodal mass, mediastinal widening, focal consolidation.

What are the management options for bleomycin-induced pulmonary fibrosis?

Answer:

- Supportive care: oxygen cautiously, pulmonary rehab.
- Avoid re-exposure to bleomycin, minimize high O_2.
- Corticosteroids sometimes tried in early pneumonitis (limited role in established fibrosis).
- Advanced: transplant referral.

How do guidelines recommend surveillance for this patient population?
Answer:
- **History & exam annually** for respiratory symptoms.
- **PFT with DLCO** if symptomatic or if abnormal baseline.
- **Chest imaging** if progressive symptoms.
- Cardiac echo every 2–5 years for anthracycline exposure

What other late toxicities should we consider in Hodgkin's survivors after ABVD?
Answer:
- **Cardiac**: Anthracycline-induced cardiomyopathy.
- **Endocrine**: Thyroid dysfunction (if chest/neck RT).
- **Secondary cancers**: Breast, lung, GI, thyroid.

Mechanism of Bleomycin Pulmonary Toxicity

Bleomycin

BLEOMYCIN–FE^{2+} COMPLEX.

Free Radical Formation

REACTIVE OXYGEN SPECIES (ROS) (SUPEROXIDE, HYDROXYL RADICALS).

DNA STRAND BREAKS

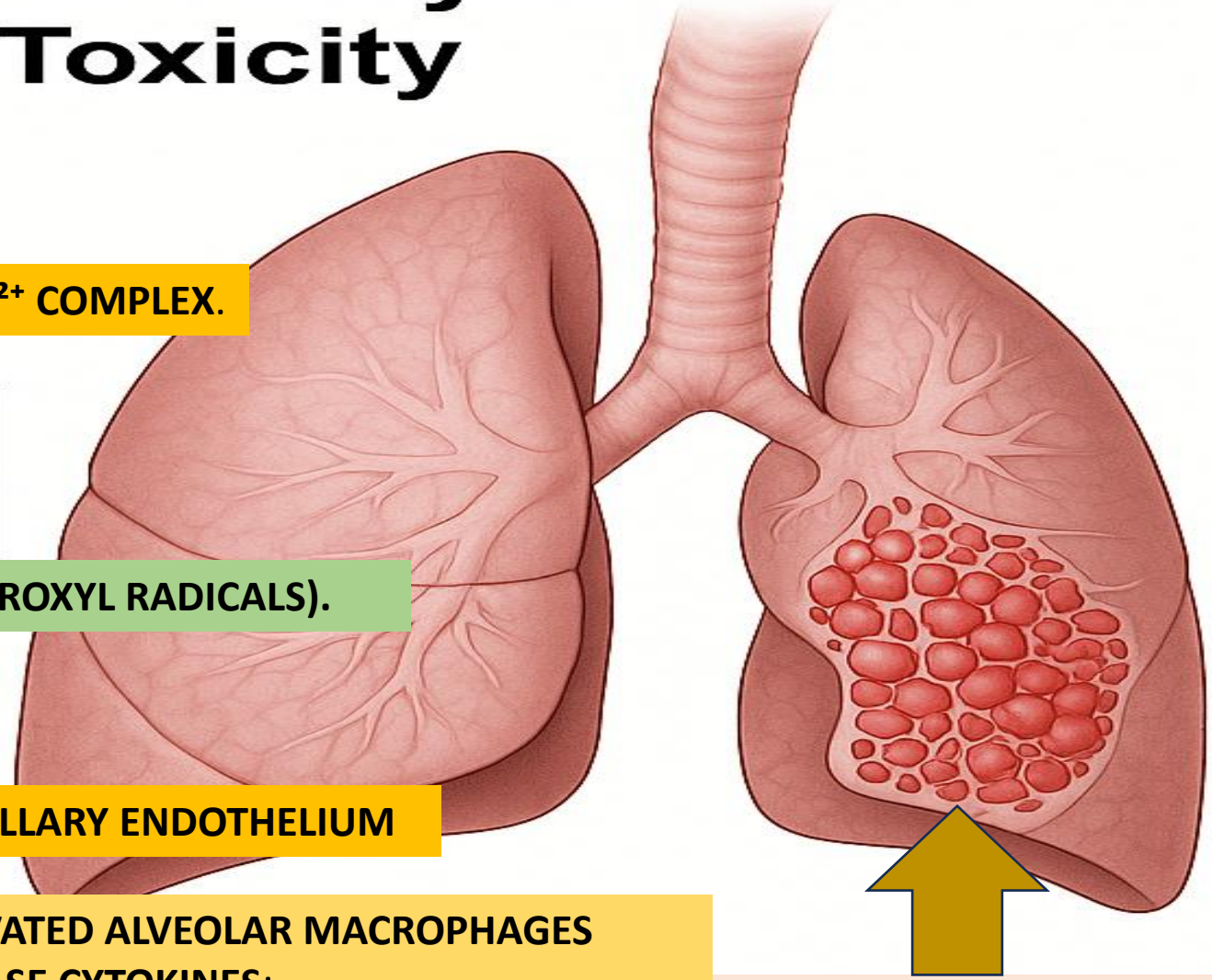
Alveolitis

ALVEOLAR EPITHELIAL CELLS AND **PULMONARY CAPILLARY ENDOTHELIUM**

Cytokine Release

ACTIVATED ALVEOLAR MACROPHAGES RELEASE CYTOKINES:
•TNF-α, IL-1, IL-6, PDGF, TGF-β.

Pulmonary Fibrosis



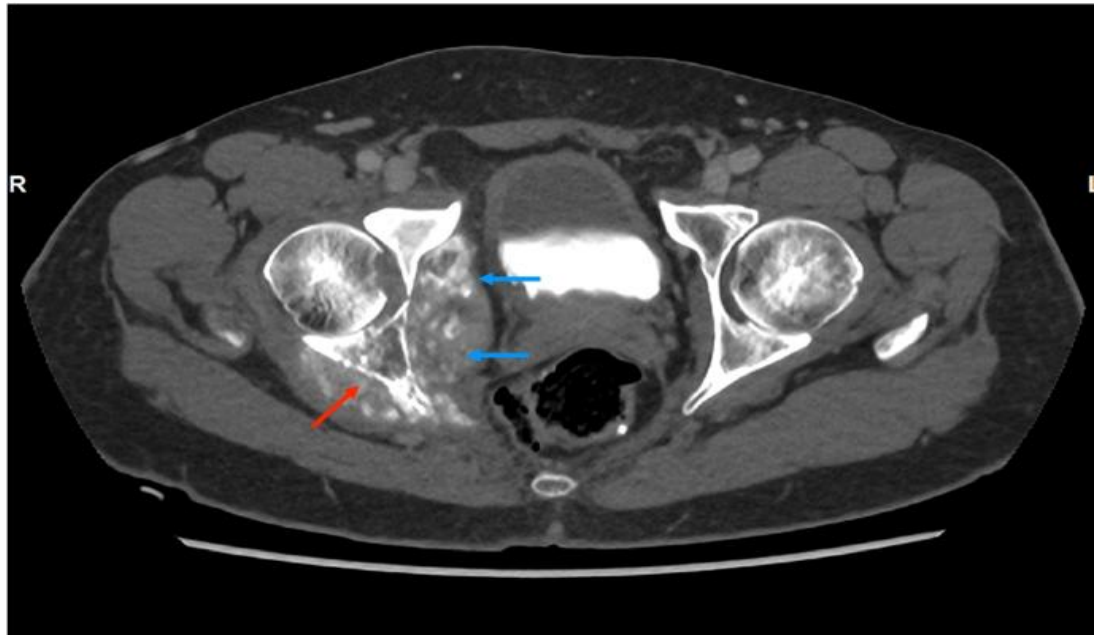
BLEOMYCIN HYDROLASE IS DEFICIENT IN THE LUNG AND SKIN, MAKING THEM MORE SUSCEPTIBLE TO TOXICITY.

. SECOND MALIGNANCIES

•**Risk factors**:
•**Radiotherapy** → Sarcoma, meningioma, breast cancer (esp. in females irradiated before age 30).
•**Chemotherapy** → Alkylators (leukemia/MDS), etoposide/topoisomerase II inhibitors (AML with 11q23).
•**Genetic predisposition**: Li-Fraumeni, RB1 mutation.
•**Common types**:
•**Solid tumors**: Breast, brain (glioma, meningioma), thyroid, sarcomas.
•**Hematological**: Therapy-related AML/MDS.
•**Latency**:
•Leukemia/MDS: 2–7 years.
•Solid tumors: 10–20+ years.

CASE CAPSULE:-3

- 30-year-old male,Presented with pelvic pain and mass for 6 mo
- Past History:-At the age of 12 yrs
  - •**Ewing's sarcoma**:
  - •Treated with RCT2 PROTOCOL(IE,VAC) WTTH **Pelvic RT dose** often 50 Gy
- **CT Pelvis:**Irregular, destructive, expansile bone lesion in **previously irradiated pelvic bones**.
- Biopsy = **radiation-induced osteosarcoma (RIOS)**.
- Immunohistochemistry (IHC):Osteocalcin, SATB2 → support osteoblastic differentiation.Negative for EWSR1 translocation (rules out recurrent Ewing's).



Q1. What are the diagnostic criteria for radiation-induced sarcoma?

- Sarcoma arises within a **previously irradiated field**.
- **Latency period ≥10 years** after RT.
- **Histology distinct** from the primary tumor.
- **Patient received adequate RT dose** (>30–40 Gy in most cases).
  📖 **Reference:** Cahan's criteria (Cahan et al., 1948; modified by Murray et al., 1999).

- **Murray's Criteria (1999)**
- To diagnose **radiation-induced sarcoma**, the following must be fulfilled:
- **Prior history of radiotherapy**
  – Patient must have received therapeutic RT.
- **Sarcoma arises within the irradiated field**
  – Tumor develops in the previously treated area.
- **Histology must be distinct from the original neoplasm**
  – The secondary sarcoma should not be recurrence or progression of the initial cancer.
- **Latency period must be ≥ 5 years** (shorter in some pediatric reports).

How common is secondary sarcoma in long-term survivors of pediatric cancer?

- Incidence: **0.5–3%** at 20–30 years post-RT.
- Risk factors: high RT dose, young age, alkylating chemotherapy.

Q6. What are the treatment challenges in pelvic RIOS?

✅ **Answer**

- **Surgery is the cornerstone** (wide resection).
- Pelvic resections → morbidity, poor margins.
- **Chemotherapy response is poor** compared to de novo osteosarcoma.
- Role of re-irradiation is limited.

CASE CAPSULE:-4

- **Age:** 15 years,Male
- **Disease:** Classical Hodgkin Lymphoma, advanced stage
- **Treatment:** Received 6 cycles of ABVD
- Had **complete remission**

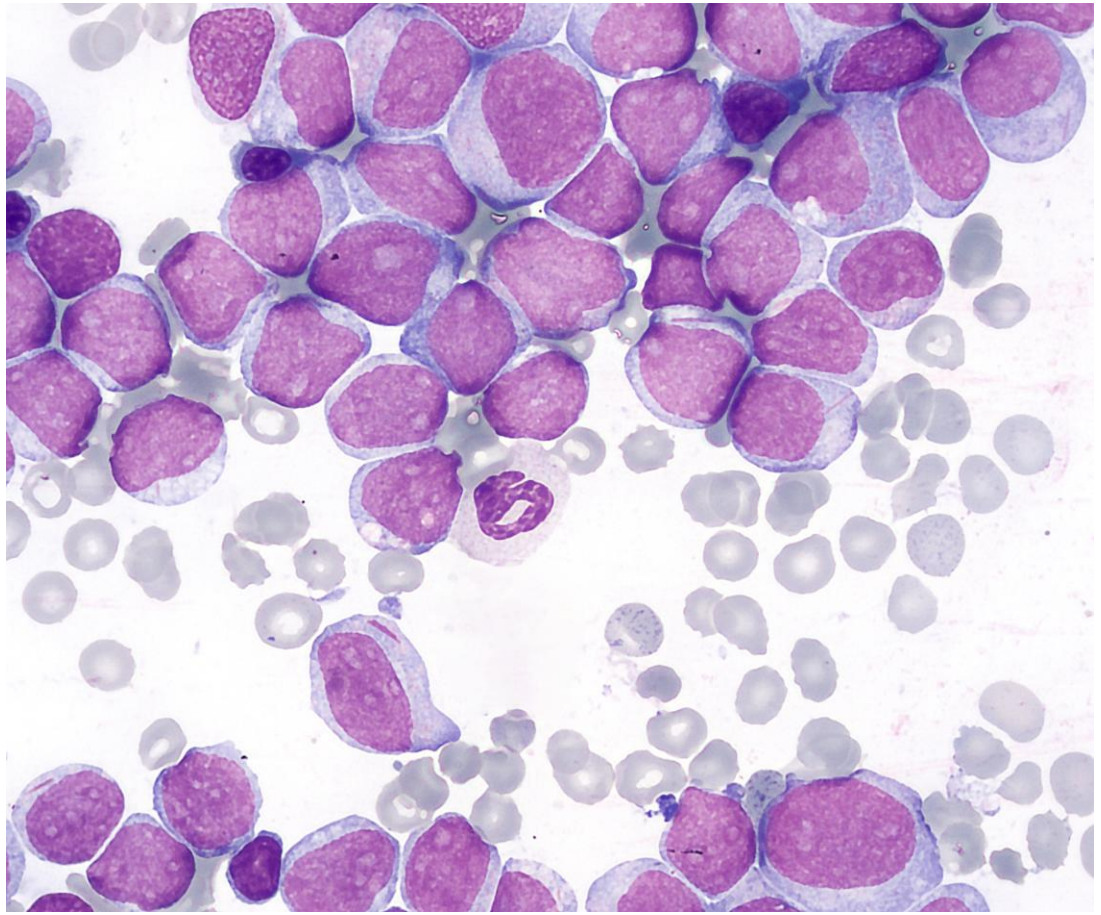
(Age 28)

Symptoms: Fatigue, recurrent infections, easy bruising

Investigations: Pancytopenia on CBC

Bone marrow biopsy: Hypercellular marrow with blasts → AML

Cytogenetics: Complex karyotype with −5q/−7q,
consistent with **therapy-related AML (t-AML)**



Prognosis vs de novo AML?

•t-AML prognosis worse

- Median OS: <12 mo (standard chemo)
- 5-yr OS <20%

📖 *SEER database; CPX-351 trial, Lancet Haematol 2018*

Current treatment strategies?

•Allogeneic SCT = only curative option

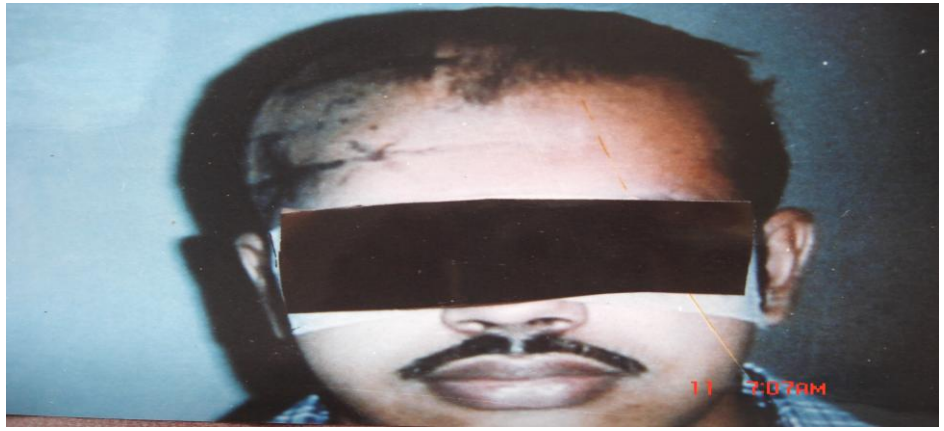
•CPX-351 (liposomal daunorubicin + cytarabine)

- OS: **9.6 mo vs 5.9 mo** (vs 7+3)
- Better CR & transplant outcomes

📖 *Lancet Haematol 2018; Phase 3 trial*

CASE NO :- 5

- 28 yr male presented with features of raised ICT in March 1990
- Pt had clinically controlled disease up to 1990
- Developed forgetfulness,irritability and continuous biting of nail.
- CT Scan:-Oval Iso to Mixed density contrast enhanced lesion at Right frontal lobe with associated Perifocal edema.
- Was diagnosed as ALL in 1978 for which pt was treated with Induction,Consolidation and Maintenance Chemotherapy followed by Prophylactic Cranial Radiation of 24 Gy to the whole brain from 17.3.78 to 4.4.78



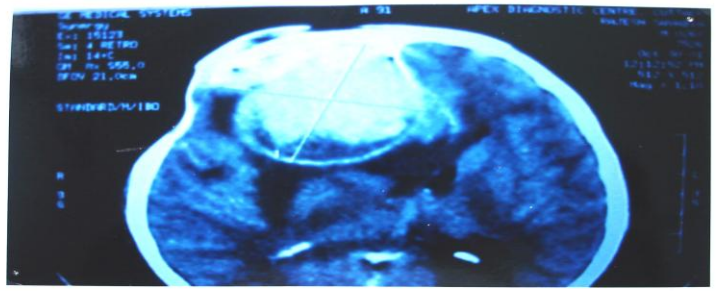


Fig.1 Contrast CT scan of brain showing mass lesion at right frontal lobe with mass effect.

CASE NO:-5

- Dec 1990:-excission-Transitional Meningioma
- April 2001:-excission – Transitional Meningioma
- Nov 2001:- excission – Atypical Meningioma

- ***WHAT TO DO NOW ?????***

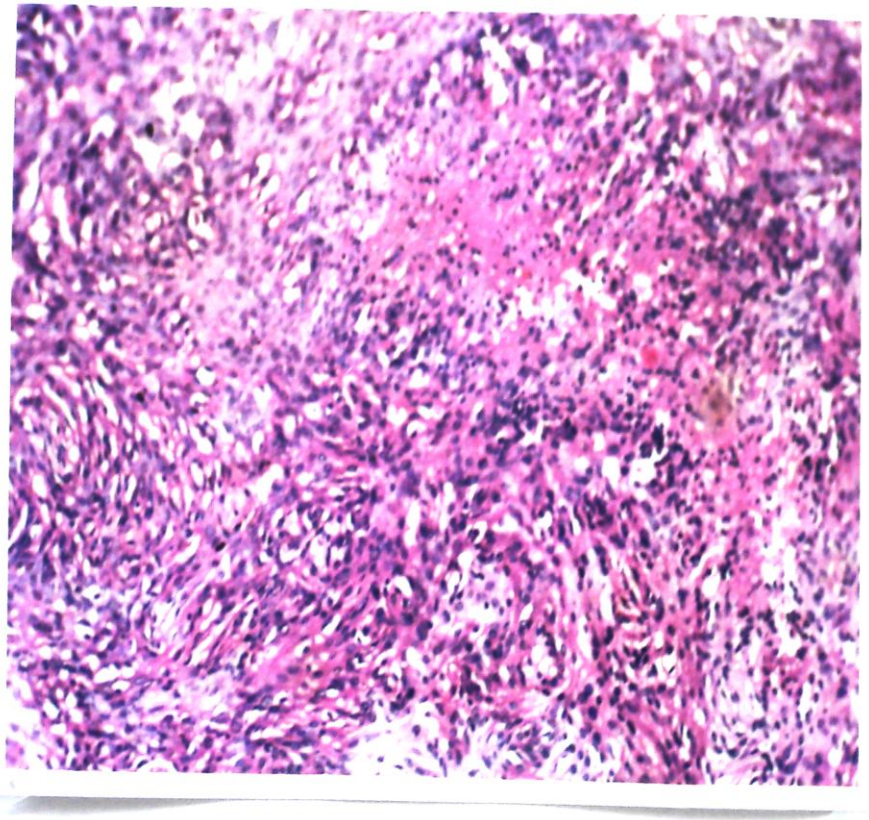


Fig.2 Low power view revealing meningothelial whorls, nuclear pleomorphism and patternless areas suggestive of atypical meningioma(H & E x 50).

11 7:06AM

- Ext beam Radiation:-12th Dec 2001
- Increased right eye proptosis,pain,raised ICT :- Reoperated in Aug 2002
- H.P anaplastic Meningioma with muscle invasion
- Pt was planned for CT but progressively detoriated and died.

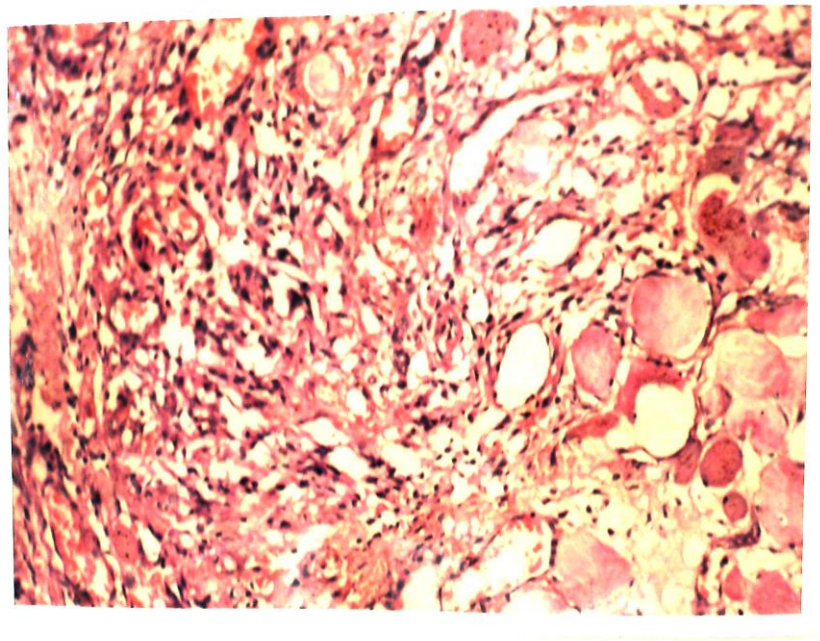


Fig.3 Photomicrograph of recurrent tumor showing invasion of orbital muscle(H & E x 50).

日放腫会誌 J Jpn Soc Ther Radiol Oncol 16: 183-185, 2004

A CASE OF SECONDARY MENINGIOMA FOLLOWING TREATMENT OF ACUTE LYMPHOBLASTIC LEUKEMIA IN CHILDHOOD

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Abstract: Second intracranial neoplasm is one of the late complication of long term survivors of childhood acute lymphoblastic leukemia. The clinical, radiological and pathological features in a 28 year old patient who developed meningioma 13 years after the completion of treatment of acute lymphoblastic leukaemia (ALL) is described here.

The above meningioma may be attributed to prophylactic cranial radiation commonly used in treatment of ALL. This case is reported due to it's rarity.

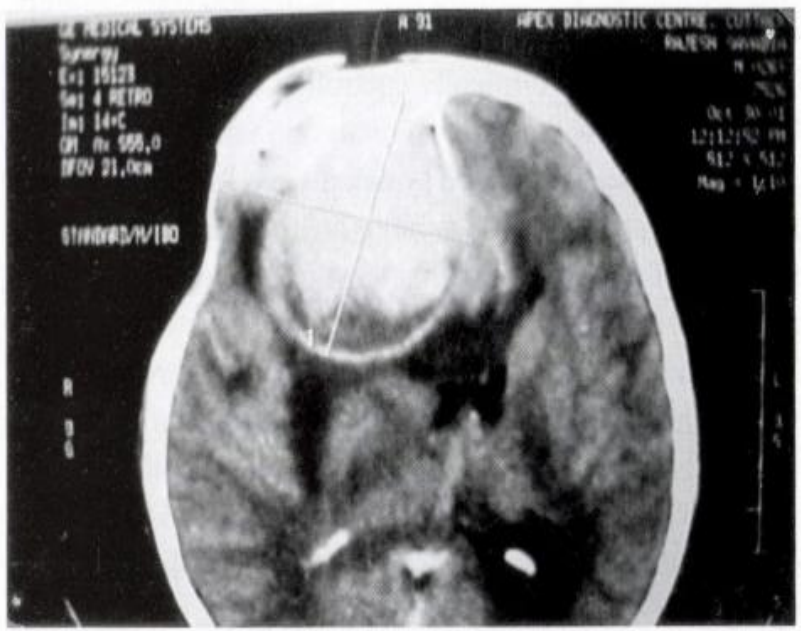


Fig. 1 Contrast CT scan of brain showing mass lesion at right frontal lobe with mass effect.

Fig. 2 Low power view revealing meningothelial whorls, nuclear pleomorphism and patternless areas suggestive of atypical

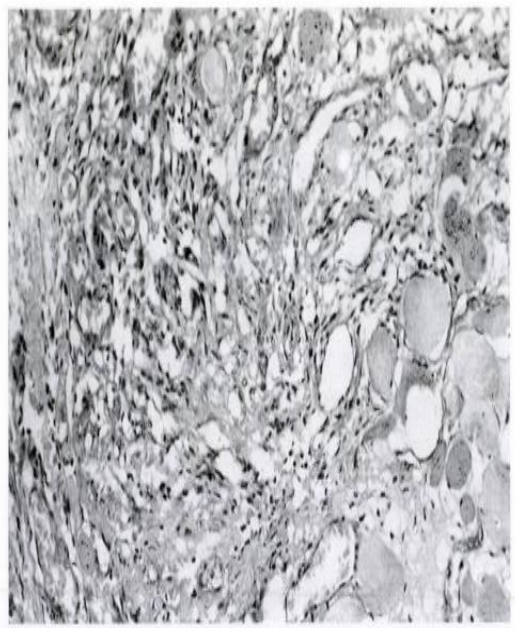


Fig. 3 Photomicrograph of recurrent tumor showing invasion orbtital muscle (H & E×50).

How does radiation-induced meningioma differ from sporadic meningioma?

✅ More often **multiple**, **atypical/malignant histology**, **younger onset**, and **higher recurrence**.

What is the management strategy?

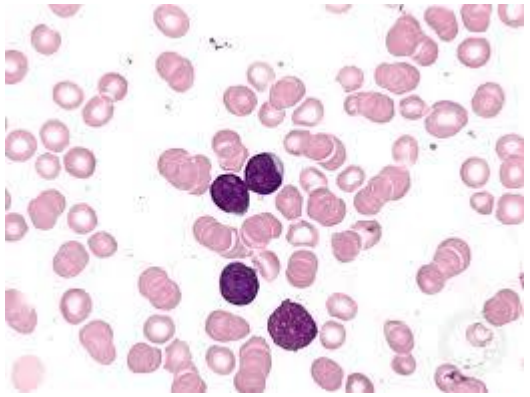
✅ **Symptomatic or growing lesions** → Surgical resection is primary.

- Radiosurgery reserved for selected cases (but caution: already irradiated brain).
- Lifelong surveillance imaging recommended.

Surveillance Strategies

- **General**: Lifelong follow-up in survivorship clinics.
- **Cardiac**: Echocardiography every 1–2 years if anthracycline/RT exposure.
- **Endocrine**: Annual thyroid function tests, growth/ puberty assessment.
- **Fertility**: Hormone profile, menstrual/sexual health evaluation.
- **Second cancers**:
- **Breast**: MRI/mammography from age 25 or 8 years after chest RT (whichever later).
- **Thyroid**: Annual exam ± USG if neck RT.
- **Skin**: Regular dermatology review (RT fields).
- **Colon**: Screening earlier if abdominal/pelvic RT.
- **Vaccination**: Catch-up immunization, avoid live vaccines until immune recovery.
- **Lifestyle**: Counseling on smoking cessation, diet, exercise

TAKE HOME MESSAGE



CURE ,NORMAL LIFE

LATE EFFECT

START OF SURVIVORSHIP

SURVELLANCE

WE CURE THE FIRST CANCER, BUT THE THERAPIES THEMSELVES CAN PLANT SEEDS FOR THE NEXT. THAT IS WHY SURVEILLANCE IS CRITICAL."OUR DUTY IS TO NOT ONLY CURE, BUT ALSO CARE FOR LIFE-LONG HEALTH, DIGNITY, AND QUALITY OF LIFE."

- CURE IS … CANCER CARE—IT IS THE BEGINNING OF SURVIVORSHIP.
- LAT… …ULTI-SYSTEM AND REQUIRE MULTIDISCIPLINARY FOLLOW-UP.
- SEC… …ERS ARE REAL, WITH PREDICTABLE RISKS.
- SURV… …NCE GUIDELINES MUST BE LIFELONG, STRUCTURED, AND INDIVIDUALIZED