Radiation Therapy for Leukemia

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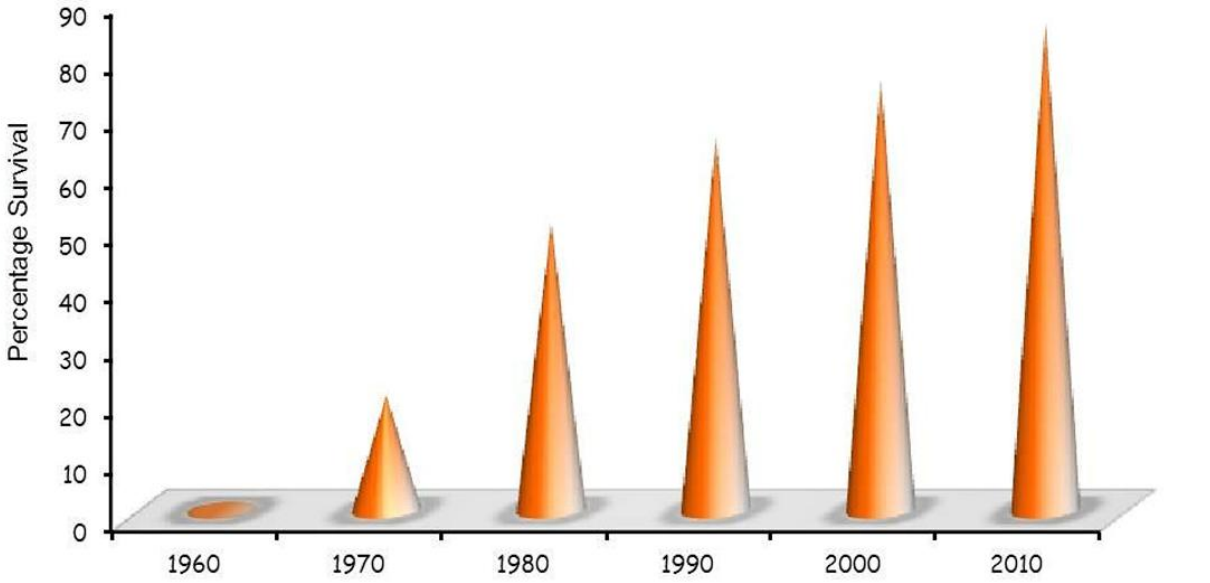
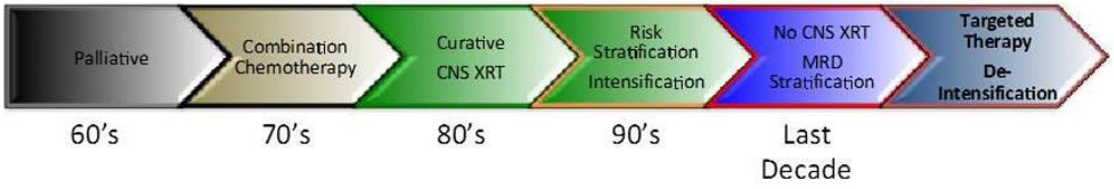
INTRODUCTION

- Leukemias (>95% of which are acute) constitute the most common diagnostic group of childhood cancers worldwide, and in India.
- Acute Lymphoblastic Leukaemia (ALL) is the most common cancer of childhood worldwide with the exception of Sub-Saharan Africa. It is estimated that over 10,000 cases of childhood ALL occur in India every year





In the west, outcomes have improved from near certain failure in the 1960's to more than 80% being cured in the modern era with the use of same drugsby adopting

✓ Risk stratification

✓ Intensifying therapy.

B cell ALL

Standard Risk (SR)	Intermediate Risk (IR)	High Risk (HR)
• Age >1 and <10 years • Non T-cell • Prednisolone Good Responder • No high risk cytogenetics • WBC <50,000/mm3 • MRD <10-4 after induction • Complete Remission after induction • No CNS disease.	• Good risk features but age ≥10 years. • Good risk features but WBC ≥50,000/mm3. • Good risk features but bulky lymph nodes (≥5 cm in peripheral region and in chest >5 cm on • CT scan or occupying ≥1/3rd diameter on chest x-ray) and/or bulky liver/spleen reaching • beyond umbilicus and/or presence of testicular disease. • MRD <10-4 after induction . • No High Risk criteria	• All prednisolone poor responders, irrespective of age and presenting WBC count. • High risk cytogenetics. • CNS disease (as defined below) . • MRD ≥10-4 after induction

T-cell ALL

- All T- Cell ALL are treated uniformly.
- Prednisolone Response:
  a) Good: <1000 blasts/l in peripheral blood after 1 week of prophase
  b) Poor: Presence of ≥1000 blasts/l in peripheral blood after 1 week of prophase
- Measured as a percentage of blasts of the absolute leukocyte count.
- Those who do not have blasts in the peripheral smear at diagnosis, will be treated as good/intermediate risk, UNLESS
  1. Other features suggest that they should be treated as high risk
  2. Peripheral blast count on day 8 is ≥1000/mm3

RISK ASSESSMENT

Prednisolone Response

- Good: No blasts after 1 week of prophase
- Poor: Presence of blasts after 1 week of prophase.
- Those who do not have blasts on peripheral smear would be treated as good risk

Cytogenetics

- Karyotyping and FISH used
- B-cell precursor ALL (BCP-ALL) into two risk groups.
  - Standard Risk disease
    - ❖ High hyperdiploidy (modal chromosome number 51 – 67)
    - ❖ ETV6/RUNX1 fusion translocation [t(12;21)(p13; q22)]
  - High risk disease
    - ❖ MLL gene rearrangement,
    - ❖ Ph+ ALL [t(9;22) (q34; q11); BCR/ABL1]
    - ❖ Intrachromosomal amplification of chromosome 21 (iAMP21)
    - ❖ Hypodiploidy (less than 45 chromosomes)
    - ❖ E2A/HLF fusion translocation [t(17;19)(q22;p13)]

RISK ASSESSMENT continued..

CNS status

- To be done on Cerebrospinal fluid studies (Day 8, diagnostic)
- CNS 1:Absence of blasts in CSF on cytospin
- CNS 2:

2a: <10 RBCs; <5 WBC and cytospin positive for blasts.

2b: ≥10 RBCs; <5 WBCs and cytospin positive for blasts

2c: ≥10 RBCs; ≥ 5 WBCs and cytospin positive for blasts

- CNS 3:

3a. ≥5 WBCs; <10 RBCs, with blasts in the CSF (with or without clinical signs) .

3b. Clinical evidence of CNS disease alone (facial nerve palsy, brain, eye involvement, hypothalamic syndrome) with no accompanying CSF findings

- If ratio of WBC/ RBC in CSF > 2 x Blood WBC/RBC with blasts then the patient qualifies as CNS 3.

Marrow

To be done at end of Induction (Day 35)

- <5% blasts = in remission
- 5-25% blasts = M2 marrow
- >25% blasts = M3 marrow

- Minimal residual disease (MRD) will be estimated by flow cytometry at the end of induction, and those who have MRD ≥10-4 will be treated as high risk post induction

B Cell ALL

Sl no	Protocol name
1	Berlin- Frankfurt- Munster (ALL BFM-95)
2	Children's Oncology group
3	Dana Farber cancer institute consortium (DFCI 95-01)
4	St. Jude Children's research hospital (TOTXV)
5	UK ALL2003
6	MCP841
7	ICiCLe ALL-14

ROLE OF RADIATION THERAPY IN LEUKEMIA

- CRANIAL IRRADIATION
- TESTICULAR IRRADIATION
- MEDIASTINAL IRRADIATION
- TOTAL BODY IRRADIATION – BMT CONDITIONING

CRANIAL IRRADIATION

- CSF formation in brain ventricles by choroid plexus, ivf-cerebral aqueduct to 4th ventricle communicates with sub arachnoid space-csf resorbtion by arachnoid villi in the dural sinuses.
- It therapy theoretically under treats ventricular spaces and cerebral and cerebellar Sulci and gross disease extending to brain Substance.

PROPHYLAXIS

- **ALL-BFM 83-** 12 Gy of preventive CRT was as effective as 18 Gy of high- SRG
- **ALL-BFM-90**-12 Gy instead of 18Gy provided equally efficient CNS prophylaxis in high risk groups had PGR
- **ALL-BFM 90-** Reducton of long term morbidity in pred-gr patients by limiting radiation dose -12 Gy to MR-ALL and HR group.

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Treatment of Childhood Acute Lymphoblastic Leukemia Without Prophylactic Cranial Irradiation

Ching-Hon Pui, M.D., Dario Campana, M.D., Ph.D., Deqing Pei, M.S., W. Paul Bowman, M.D.,

With effective risk-adjusted chemotherapy, prophylactic cranial irradiation can be safely omitted in the treatment of childhood acute lymphoblastic leukemia.

CRANIAL IRRADIATION conti..

- In ICiCLe ALL-14 protocol which is followed in many centres across India
- **Indications:**

a) Age ≥3 years and CNS Status 3 at day 8

b) the presence of cranial nerve palsies believed to be related to CNS infiltration.

- **Timing:**

Cranial RT will be administered following completion of the delayed phase of intensification prior to commencement of the first cycle of maintenance.

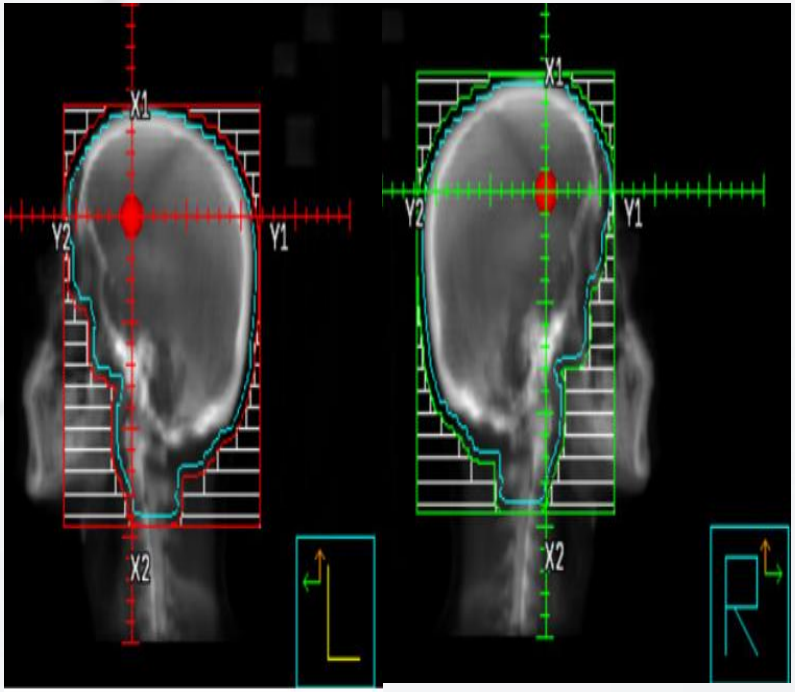
- **Clinical target volume (CTV):** Entire intracranial subarachnoid space

a)at the skull base: the cribriform plate (lowest point of the anterior cranial fossa, located in the midline at a level that is typically below the orbital roof) and the lower limit of the temporal fossa

b)Retrobulbar tissue

c)Till C2 vertebra level

CRANIAL IRRADIATION conti..



- Dose:18 Gy 10 fractions over 2wks
- Dose constraints:

  Lens-10 to 15% of prescribed dose

  Bilateral Parotids
- Technique:3DCRT/ IMRT.
- Treatment interruptions : Radiation treatment need not be withheld due to cytopenia unless the patient is symptomatic or unwell. But desired to have hemoglobin >10gm/dl.
- Role of CRANIO SPINAL IRRADIATION is not much explored and very limited role.

CRANIAL IRRADIATION conti..

- Toxicities:

1. Usually CNS related like Somlonence syndrome, Pituitary dysfunction, Cognitive function defects, leukoenchephalopathy.
2. Development of Cataract in later part of life
3. Loss of Parotid gland function of about 5%/ 1 Gy of mean dose has been reported, suggesting that higher mean doses could cause significant impact to salivary function leading to Xerostomia and there by affect QOL.

Retrospective study done at Kidwai during 2019 to 2020 a total of 33 patients of ALL were treated, the dosimetry showed

Each gland receives- a mean dose of 11.63±4.64 Gy.

Around 92.97±11.42 percentage of gland receives 15Gy.

4. Secondary malignancies

TESTICULAR RADIATION

- **Indication:**

Patients with testicular enlargement that persists after completion of the consolidation phase of chemotherapy.

- **Timming**:

✓ After completion of the delayed phase of intensification prior to first cycle of maintenance chemotherapy.

✓can be delivered concurrently with cranial irradiation in patients who require both.

- **Technique:**

a) Supine position, both hands above the head

b) Penis may be shielded or strapped away from the radiation field.

c) During daily positioning to ensure complete descent of testes into the scrotum during treatment.

TESTICULAR RADIATION conti..

- **Clinical target volume (CTV):**

  Both testes and spermatic cord to the level of the deep inguinal ring.

- **Dose**:

  24 Gy 12 fractions over 2.5 weeks , 90% of the prescribed dose should cover the posterior aspect of testis.

- **Technique:**

  a) Single Anterior Electron beam using 9 to 12MeV Electrons with Lead block is used to support testis and shield the perineum

  b) Photons of 6MV ca also be used. To achieve dose homogenicity 0.5 to 1 cm of bolus over the entire scrotal area may be required. Exist dose will be very high leading to skin recations.

- **Treatment interruptions** :

  Radiation treatment need not be withheld due to cytopenias unless the patient is symptomatic

- **Toxicities:**

  Sterility, Leydig cell dysfunction, dermatological reactions

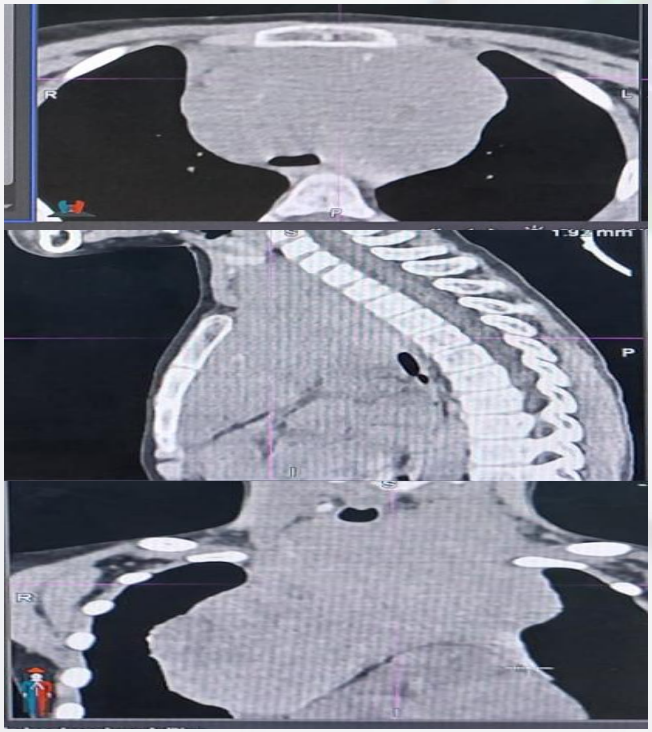
MEDIASTINAL RADIATION

- Most commonly seen in T-ALL patients.
- With mediastinal enlargement, volumetric measurement of tumor mass should be made as soon after presentation preferably by CT scan. Followed by assessment for reduction in tumor volume on day 35.
- > 35% regression of mass- In remission, Patient continues treatment on the same arm and moves to Consolidation phase.
- IF >30% Residual tumor remains in the CT /MRI after a induction therapy it can be considered for resection.
- If any vital structures infiltration present, to consider for Mediastinal Irradiation.
- **Position:** Supine, both the hands above the head, Vacloc or thermoplastic cast for immobilization.
- **Motion management techniques** like Breath hold techniques to be adopted if patient is cooperative.
- If breath hold techniques not possible to consider for **4DCT scan** and plan by generating ITV

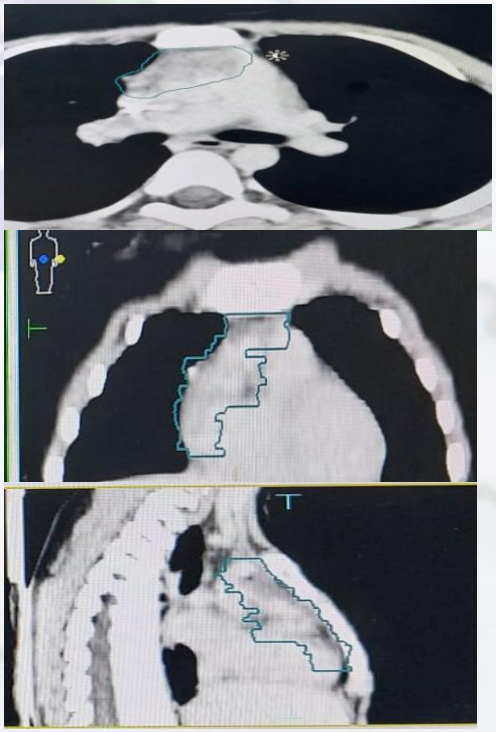
MEDIASTINAL RADIATION conti..

- **Technique:** IMRT/IGRT.
- **Dose:** 30 to 40 Gy with 2Gy/ fraction over 3 to 4 weeks.
- **Dose Constraints:** Lung, Heart, Esophagus, Trachea and Spinal cord to be given.
- **Treatment interruptions** : Radiation treatment need not be withheld due to cytopenia unless the patient is symptomatic.

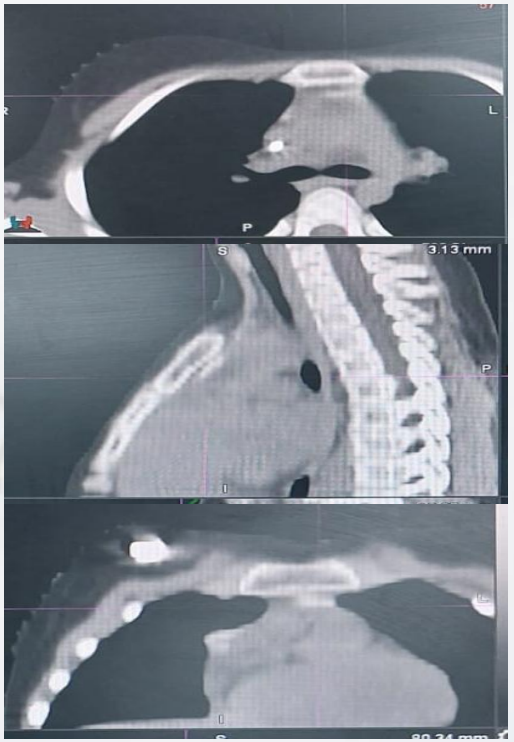
Pre Chemotherapy



Post Chemotherapy



Post Treatment



Total Body Irradiation

- Both Cytotoxic and Immunosuppresive agent.

Eliminate residual leukemia and equally effective in medullary and extramedullary region.

- Indication: allogenic transplant-all in second remission after an early relapse, high risk all (ph +) after first remission.
- Dose: 2gy given in bid with 6hours apart, 3 days continuously to a total dose of 12gy.
- In HR patients CNS positive disease cranial boost- 12 Gy, Testicular boost in case of involvement 18Gy a week preceding the TBI

AML

1. **GRANULOCYTIC SARCOM**:

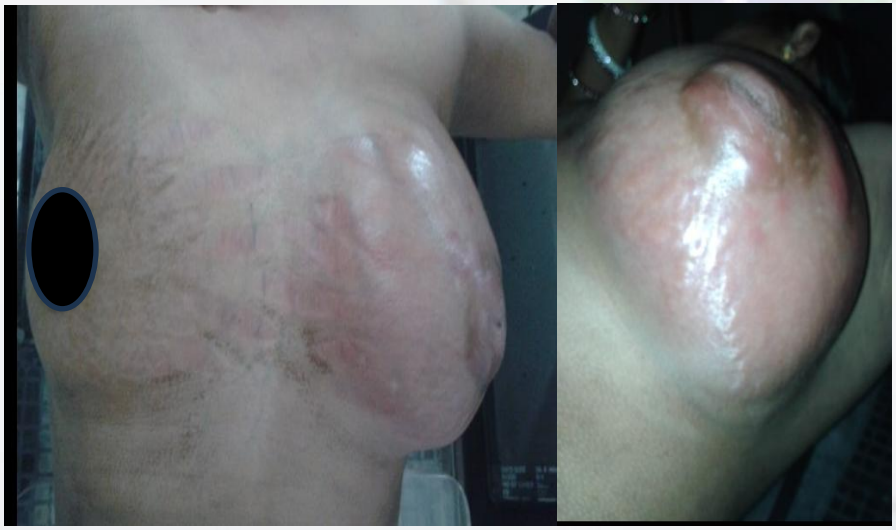
Isolated extramedullary form of AML, commonly seen in M4 and M5 type.

- Dose of 10 to 30 Gy in 5 to 15 fractions, based on the adjacent critical structures.

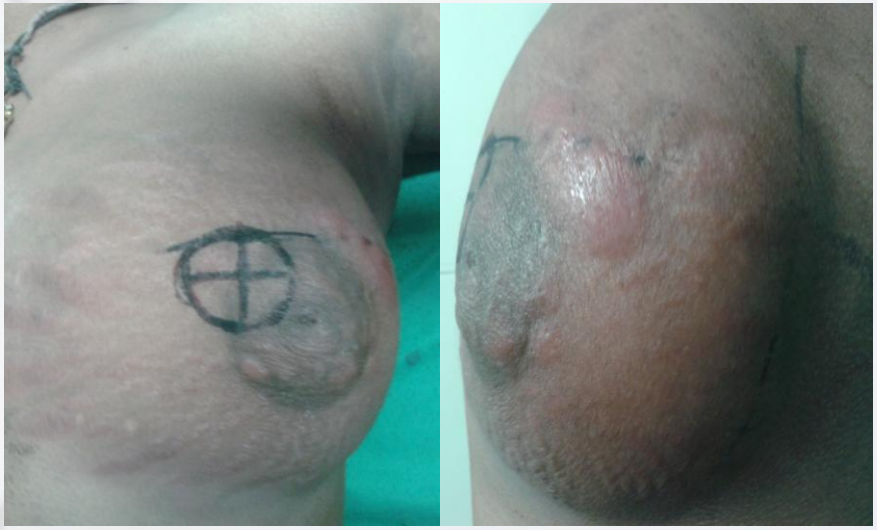
2. **Cranial Radiation**: No role of Prophylaxis. Only therapeutic in isolated Relapses

3. **TBI**: used as conditioning regimen.

Pre Radiation therapy



Post 5# Radiation therapy



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THANK YOU