

ROLE OF RADIOTHERAPY / PROPHYLACTIC CRANIAL RADIATION IN PAEDIATRIC LEUKEMIAS



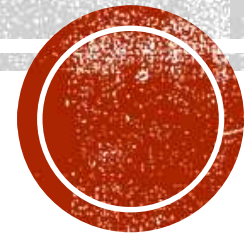
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OVERVIEW

- DEFINITION
- EVOLUTION AND INDICATIONS OF RT
- CAVEATS IN CURE
- VARIOUS PROTOCOLS
- FOCUS ON CRANIAL RT IN ALL/ AML
- RELAPSE RATE
- OUTCOME



DEFINITION

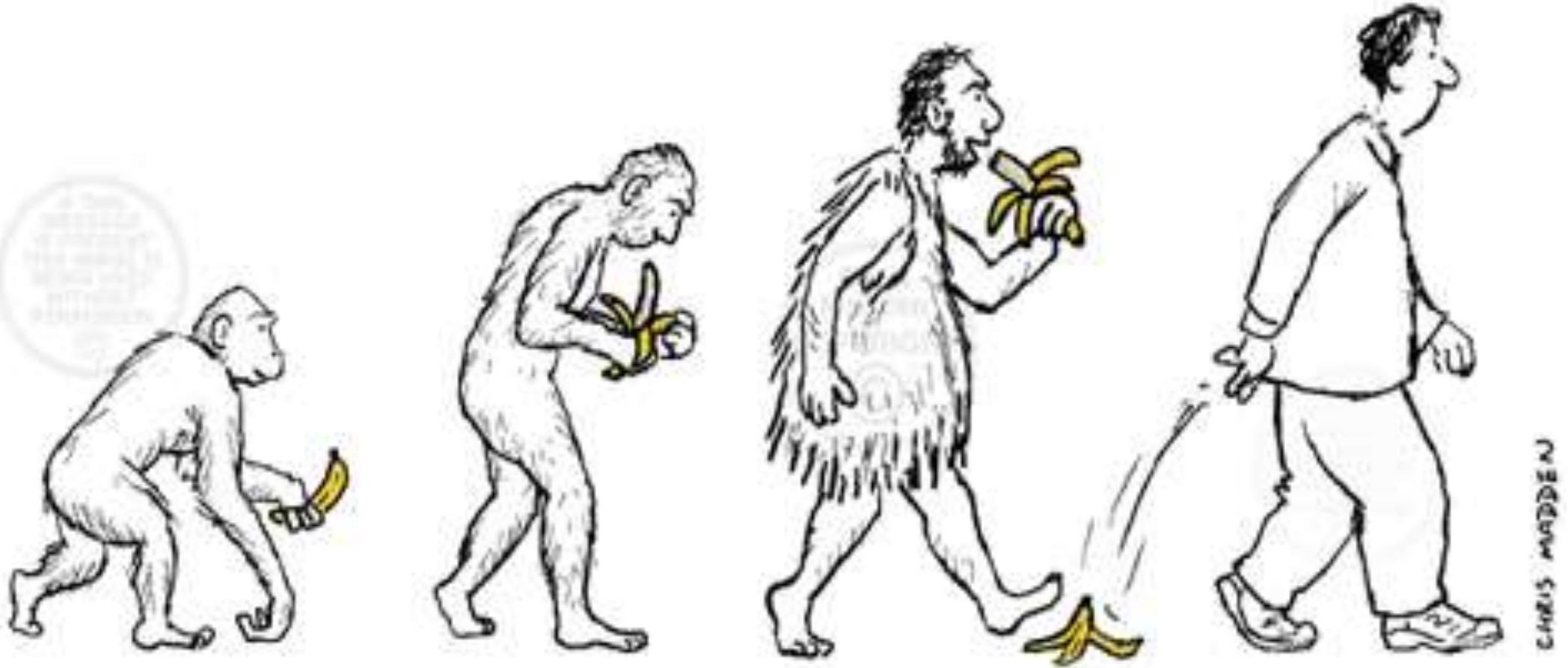
- Malignant disorder in which hematopoietic blast cells proliferate and constitute >30% of the bone marrow

▪ Lymphoblast  Lymphoblastic Leukemia

▪ Myoblasts.  Myeloid Leukemia



THE EVOLUTION OF HUMOUR



EVOLUTION TILL NOW

- Incorporation of risk-adapted strategies with induction and maintenance regimens
- Understanding of disease biology
- Superior supportive care



INDICATION OF RT IN LEUKEMIA

- CNS Prophylaxis
- CNS Relapse
- Pre HSCT
- Testicular Disease
- Mediastinal Disease
- Total Body Irradiation



SANCTUARY

- **Compartment.**
- **Site :**



SANCTUARY SITE.

SANCTUARY:

"protection or a safe place, especially for someone or something being chased or hunted"



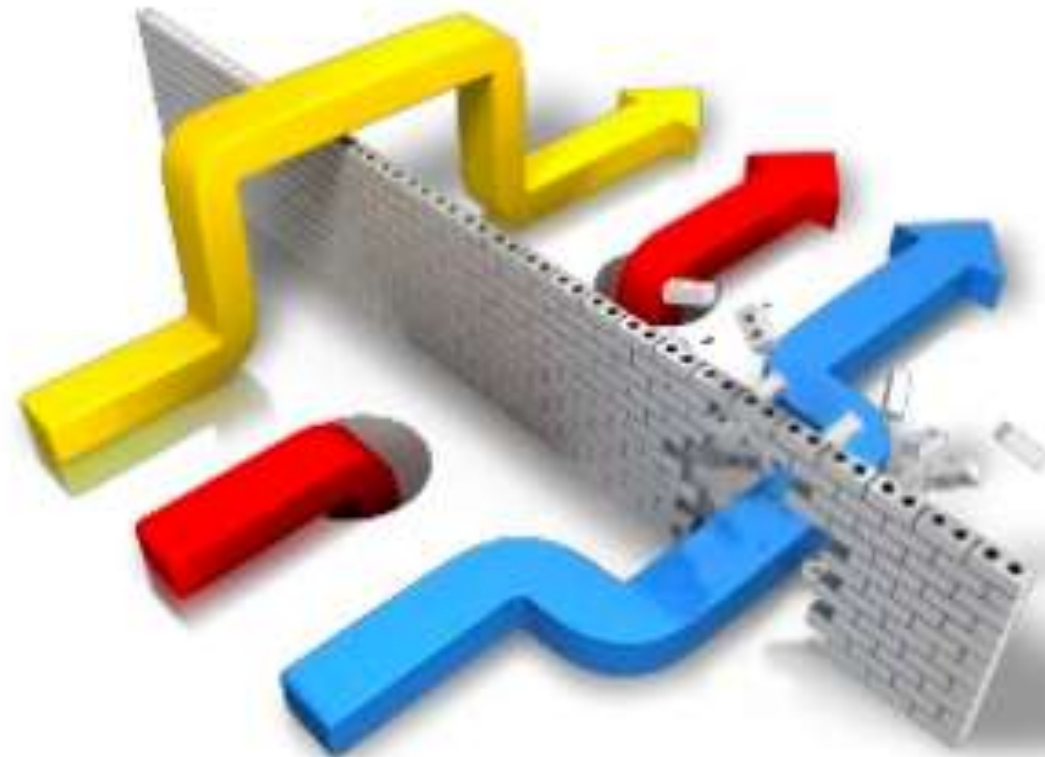
WHAT HAPPENS AT SANCTUARY SITE???

- Leukemic cells prime a maladapted niche that in turn provides signals capable of sustaining the dormancy of leukemia initiating cells.
- Protects them from toxic chemotherapeutic agents.
- “Leukemia initiating cells” (LICs) share common features with normal hematopoietic stem cells (HSCs),
 - multi-potency,
 - dormancy
 - self-renewal

This implies that leukemia stem cell-like cells have features that make them less responsive to therapy and can lead to cancer relapse.



Ways to get past the Sanctuary sites !!



CNS DISEASE

- ALL  7%

Absence of CNS prophylaxis > 50% relapse

- AML  1% involvement



RISK FACTORS FOR CNS DISEASE

- Increased LDH levels
- Mature B cell-subtype
- High leukemia cell proliferation index
- T-cell immunotype



RT PROTOCOL

DFCI

BFM



Sidney Farber, MD, with a young patient



THE BFM GROUP

- Founded in 1975 in Germany,
- Hansjörg Riehm in **Berlin (B)**, Bernhard Kornhuber in **Frankfurt (F)** and Günther Schellong in **Münster (M)** initiated the first multicentre BFM trial.
- The BFM treatment concept – based on a very intensive chemotherapeutic approach employing eight different drugs – led to a revolutionary increase in survival of children and adolescents with acute lymphoblastic leukaemia (ALL).
- **“BFM treatment backbone”**



DFCI PROTOCOL 95-01

DFCI Consortium protocol: cranial RT 12 Gy indications

- T-cell phenotype,
- CNS-3 status at diagnosis
- residual disease after induction



BFM 95 PROTOCOL DEFINITION OF RISK GROUPS

STANDARD RISK (6 - CRITERIA)

- Prednisone good response (blasts < 1000/miclit of peripheral blood on D-8)
- After a 7 day prednisone prephase wbc < 20000/miclit
- Age > 1-< 6 years
- A complete remission on D33 (M1-MARROW)
- No translocation t (9:22) or BCR/ABL recombination
- No translocation t (4:11) or MLL/AF4 recombination
- No T – immunology



MEDIUM RISK GROUP (4+1) MORE

- Leukemic cells <1000 /mic lit in the peripheral blood on D8 (Prednisone Group)
- Complete remission on D33 (M1- Marrow)
- No translocation t(9:22) or bcl/abl recombination
- No translocation t(4:11) or mll/af4 recombination
- Leucocytes more than 20,000 / mic lit, age less than 1 yr or more than 6 yrs.



HIGH RISK GROUP (EVERY CRITERION)

- More than 1000 / miclit of leukemic cells in peripheral blood on D8
- no complete remission on D33
- Translocation t(9:22) ot bcr/abl recombination
- Translocation t(4:11)or mll/af4 recombination



CNS DISEASE BASED ON CNS EXAMINATION

CNS STATUS 1 (NEGATIVE):

- No clinical evidence of a CNS disease
- No imaging CT/MRI evidence of CNS lesion
- Normal fundoscopic finding
- Blast free CSF



CNS STATUS 2 (NEGATIVE)

- Blasts identified RBC/WBC < 100:1(non traumatic uncontaminated CSF)
- Blasts identified, RBC/WBC > 100:1 (traumatic, blood contaminated CSF)
- Traumatic LP (blood contaminated CSF) ALL IC BFM 2002



CNS STATUS 3 (POSITIVE)

- A mass lesion in the brain and/or meninges on CT/MRI
- Cranial nerve palsy unrelated to the original event even if the CSF is blast free or no circumscribed space occupying lesion on CT/MRI.
- CT pure retinal involvement with blast free CSF and no mass on CT/MRI.
- Non traumatic LP with a CSF cell count of $>5/\text{microlit}$



CNS PROPHYLAXIS

- **ALL-BFM 83-** 12 GY OF PREVENTIVE CRT WAS AS EFFECTIVE AS 18 GY OF HIGH- SRG
- **ALL-BFM 90-** REDUCTON OF LONG TERM MORBIDITY IN PRED-GR PATIENTS BY LIMITING RADIATION DOSE -12 GY TO MR-ALL AND HR
- **ALL -86 TO 90-**IN CRITICAL GROUPS INCIDENCE OF CNS RELAPSE WAS LESS THAN 5 %.ESPECIALLY WITH HD-MTX AND MTX -IT INCIDENCE WAS LESS THAN 3 %
- **ALL-BFM-90-**12 GY INSTEAD OF 18 GY PROVIDED EQUALLY EFFICIENT CNS PROPHYLAXIS IN HIGH RISK GROUPS HAD PGR
- **AMERICAN STUDIES** –MR PATIENTS WITH T-ALL HAD HIGHER INCIDENCE OF SYSTEMIC AND CNS RELAPSE IN NON IRRADIATED PATIENTS



CNS PROPHYLAXIS

- Overt CNS involvement at time of diagnosis
- High risk disease
 - <1 yo, >10 yo
 - WBC > 50,000
 - T-cell ALL
 - Philadelphia chromosome (bcr-abl translocation)



HOW MUCH DOSE ??

COG AALL0232 protocol (High risk B-precursor ALL)

- **Prophylactic 12 Gy cranial RT**
 - Slow early responders (day 15 BMBx shows M2/M3 disease, or day 29 BMBx shows MRD)
 - MLL rearrangement
 - Patients pre-treated with steroids (e.g. for bronchiolitis symptoms)
- **Therapeutic 18 Gy cranial RT**
 - CNS 3 disease
- **Therapeutic 24 Gy testicular RT**
 - Initial testicular involvement, and continued evidence of testicular involvement at the end of Induction



RADIATION THERAPY FOR CNS PROPHYLAXIS

- Unfavoured
- Replaced by Methotrexate and Cytarabine

Adverse effects

- Neuro-cognitive decline
- Endocrinological abnormalities
- Brain necrosis



RELAPSED CNS DISEASE

- Mainly chemotherapy
- Considered after failure of primary protocol.



CNS DIRECTED RT BEFORE ALLOGENIC HCT

- Achieves balance between maximising disease control and minimising toxicity.
- Major risk factor: pretransplant history of CNS involvement.(diag/relapse)
- **Walker et al.**



THERAPEUTIC CRANIAL IRRADIATION

- 5% of those on initial presentation

Dose

- Varies on protocol
- 24 Gy in past, no longer used.
- 18 Gy (standard dose) associated with decreased risk of CNS complications
- 12 Gy has been used more recently in European trials

Fraction size

- Usually 180cGy /#
- Sometimes 160 cGy /#



VOLUMES

Volume

- Cranial radiation only (no spinal irradiation)

Areas to watch

- Cribiform plate (reported site of failure for medulloblastoma)
- Temporal lobes



CRT VS ICT

- **Meta-analysis, 2003** "CNS-directed therapy for childhood acute lymphoblastic leukemia: Childhood ALL Collaborative Group overview of 43 randomized trials." (Clarke M, J Clin Oncol. 2003 May 1;21(9):1798-809.)
- 2848 patients randomly assigned to CNS-directed therapy prior 1993
 - 10-year EFS: RT + IT-chemo 64% vs. high-dose IT-chemo 63% (NS)
 - Conclusion: "Radiotherapy can be replaced by long-term intrathecal therapy.
 - Intravenous methotrexate gives some additional benefit by reducing non-CNS relapses."



RELAPSE

- 20% of children with ALL experience relapse, despite current modalities.
- Relapse is defined as the reappearance of leukemic cells at any site in the body.
- It may be isolated event at one site (medullary or extramedullary) or may be combined (medullary and extramedullary).
- Most relapsed leukemias retain their original immunophenotype and genotype, but rarely another cell lineage (“lineage switch”) is observed.



CNS RELAPSE

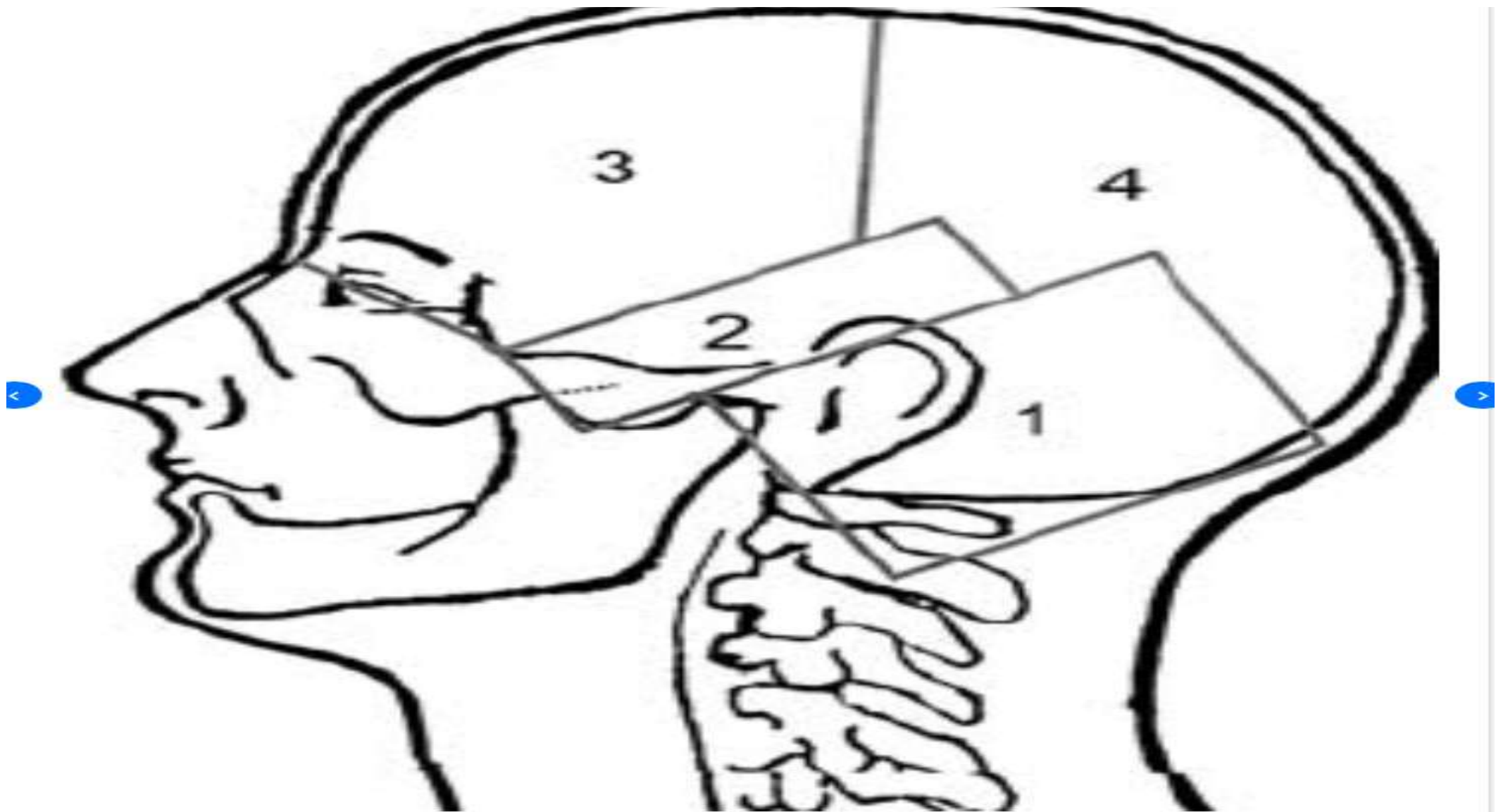
- Less than 5% of children with ALL.
- It occurs more frequently in children with T-ALL or mature B-ALL.
- Intrathecal chemotherapy alone fails to cure CNS leukemia.
- Most regimens include intrathecal chemotherapy until CSF remission, in parallel with a systemic induction therapy, followed by consolidation chemotherapy, craniospinal irradiation (2.400 to 3.000 cGy cranial, and 1.200 to 1.500 cGy spinal) and maintenance intrathecal chemotherapy
- Factors influencing outcome include whether CNS relapse is early or late (EFS 83% and 46%, respectively), and whether the child received prior CNS irradiation. For patients with earlier prophylactic irradiation, long-term secondary remission does not exceed 30%, and these patients are candidates for HSCT



HAS DOSE BEEN ALTERED TO CSI??

- Trials from 1978-83 used 24 Gy cranial + 12 Gy spinal given during consolidation phase along with systemic and intrathecal chemo.
- CNS disease at diagnosis was not an independent prognostic factor, thereby indicating the effectiveness of CNS treatment regimens used.
- CCG trials from 1983-89 used more intensive chemotherapy. **Reduced spinal dose to 6 Gy in those treated with intensive consolidation phase in order to limit hematopoietic toxicity.**
- **CNS disease at diagnosis is not a poor prognostic factor** for children treated with intensive chemo + craniospinal RT + intrathecal chemo. 6 Gy of spinal RT + 24 Gy cranial RT is appropriate.

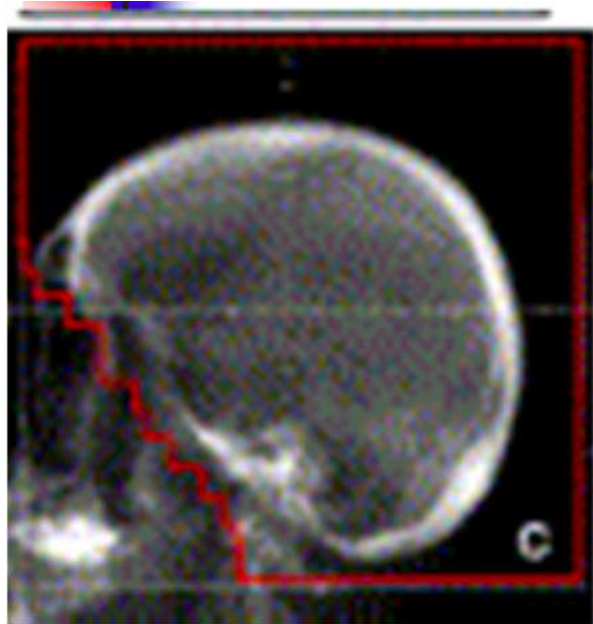




Division of the brain for regional dose estimation. 1, posterior fossa; 2, temporal; 3, frontal; 4, parieto-occipital.



QUICK RECAP



- **High voltage conditions with Co -60 or LA**
- **Photon energies of 6MV or less**
- **Photon energies more than 6 MV should not be used so that the build up region at initial depth is superficial to the meninges.**
- **Daily set up-mask technique**
- **Irradiation volume-**
 - **Whole neurocranium with both upper vertebra (c2),**
 - **Retrobulbar tissue and**
 - **Complete cranial base with its middle cranial groove.**



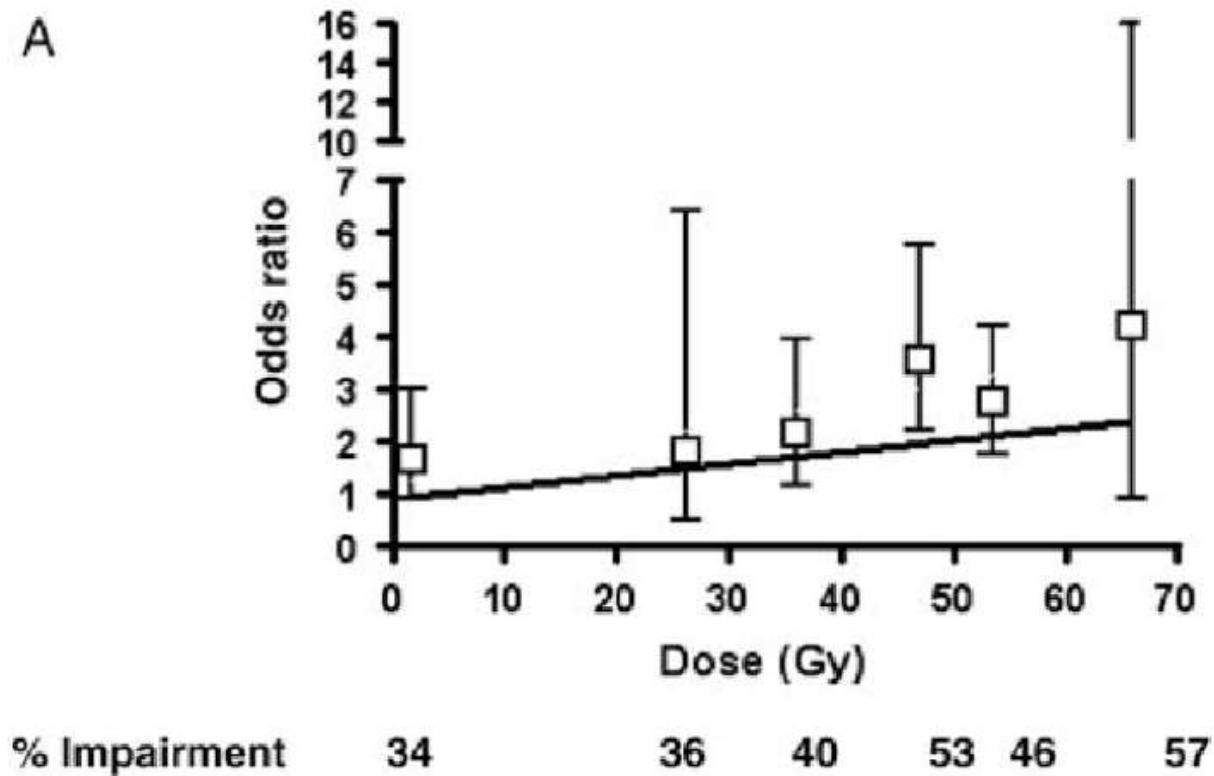
EVERY FIELD SHOULD BE TREATED IN EVERY SESSIONS

DAILY SINGLE DOSE IS 1.5 GY .THIS IS ADMINISTERED IN 5 SESSIONS PER WEEK UNTIL THE TOTAL DOSE HAS BEEN APPLIED

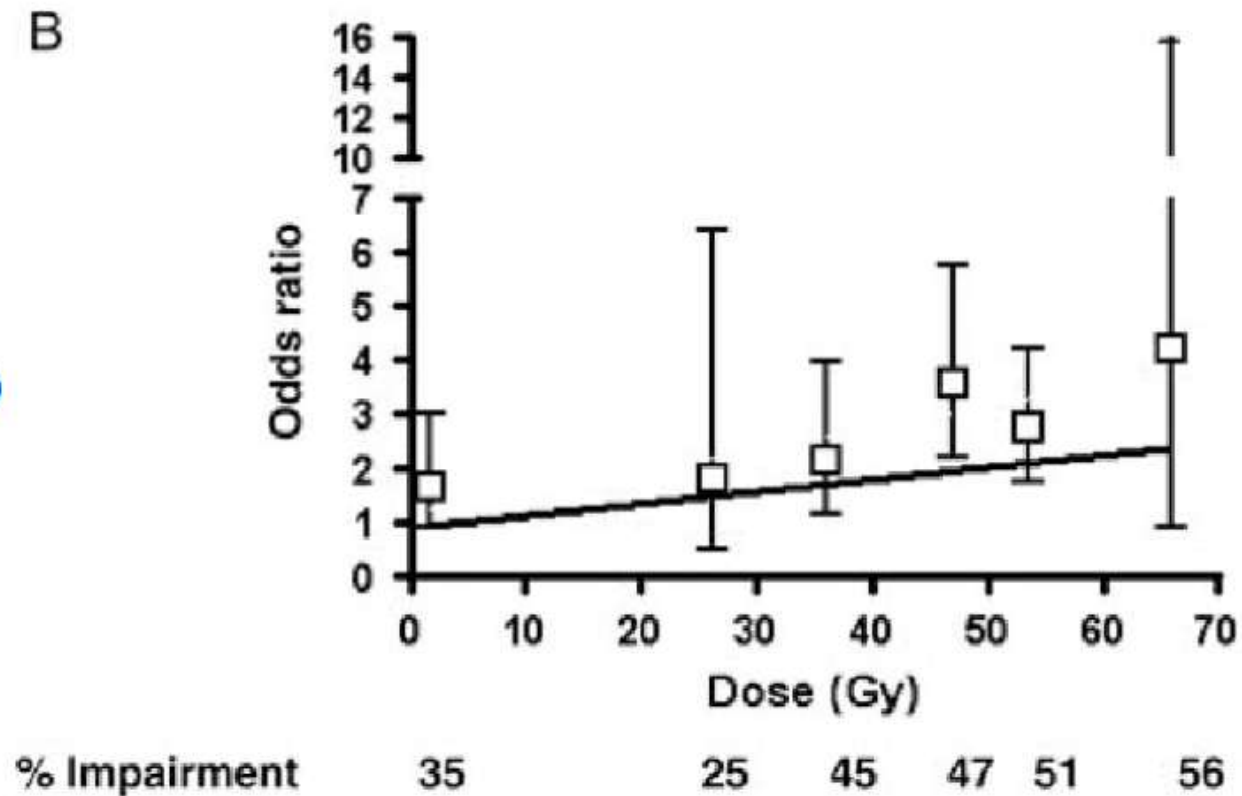
ANGULATION OF THE BEAM (3-5 DEG POSTERIOR),HALF BEAM- TO AVOID OPHTHALMOLOGICAL COMPLICATIONS



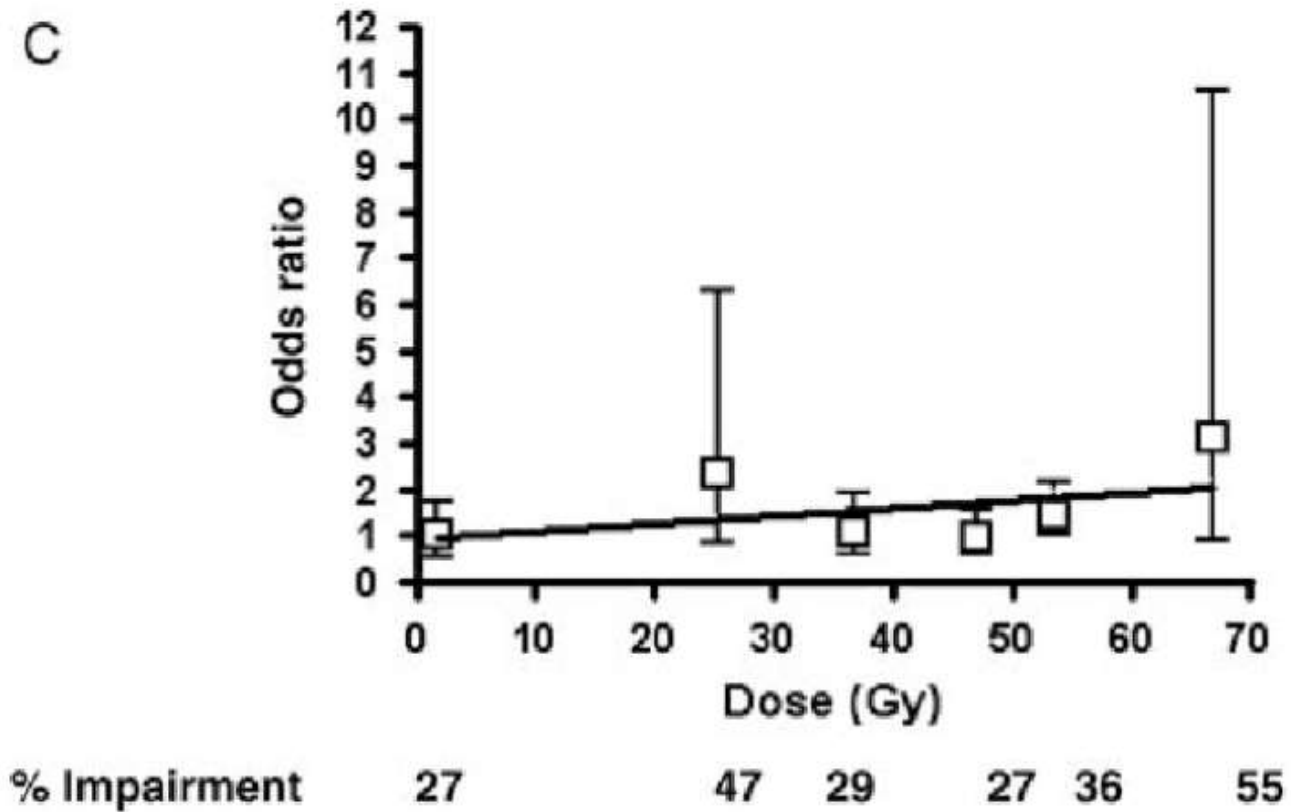
MEMORY IMPAIRMENT



TASK-EFFICIENCY IMPAIRMENT



SOCIAL-FUNCTION IMPAIRMENT



RECURRENCE AFTER PROPHYLAXIS

Central Nervous System
Recurrence Rate in Adult
Acute Lymphoblastic
Leukemia- Cancer May 15,
2010

| PROTOCOL | CNS RELAPSE | PROPHYLAXIS |
|-----------|----------------|-------------|
| HYPERCVAD | 4% | NO RT |
| BFM | 1% | 18GY |
| AUG BFM | 1% | 18GY |
| CALGB | 11% | 24GY |



SUMMARY IN ALL

- **ROLE OF RT IN ALL:**
 - CRANIAL PROPHYLAXIS(MRG-T CELL ALL,HRG)
 - CRANIAL TREATMENT (ALL CNS INVOLVEMENT)
 - CRANIOSPINAL IRRADIATION (OVERT CNS INVOLVEMENT IN ADULT ALL,ISOLATED CNS RELAPSE)



OTHER SITES WHICH NEED RT

- TESTICULAR IRRADIATION (RESIDUAL,RELAPSE)
- MEDIASTINAL IRRADIATION (RESIDUAL,T CELL ALL,RELAPSE)
- TOTAL BODY IRRADIATION (SECOND REMISSION AFTER EARLY RELAPSE,HIGH RISK WITH FIRST REMISSION)



AML

- CNS involvement- rare
- More prevalent in (M4 myelomonocytic/ M5 monocytic) subtypes.
- Risk factors include

High lactate dehydrogenase (LDH),

Young age,

High-risk cytogenetics,

Hyperleukocytosis,

African American ethnicity].

The CSF accounts for approximately 19% of extramedullary relapse (skin and soft tissue are most common)



OTHER SIGNS OF CNS INVOLVEMENT

- altered mental status,
- headache,
- visual disturbances,

Routine LP??

Important message: It has been postulated that CNS prophylaxis for AML can improve survival, but this strategy is currently not used given the relatively low incidence of CNS involvement.



CSI IN AML SUPPORTIVE EVIDENCE?????

- Initial involvement of the central nervous system (CNS) in AML occurs in less than 5% of patients.²⁶⁵

Various regimes to tackle CNS infiltration

- 40 to 50 mg of cytarabine should be administered intrathecally, 2 to 3 times per week until clearance of blasts, followed by 3 further injections with the same dosage.
- Alternatively, liposomal cytarabine (50 mg every other week) may be given for approximately 6 cycles.
- For prevention of arachnoiditis, dexamethasone (4 mg three times a day [tid] p.o.) may be considered on the days of intrathecal application.
- Craniospinal irradiation with or without intrathecal chemotherapy has also been shown to be effective; however, its impact on long-term outcome is unknown.²⁶⁷



ROLE OF CSI IN AML

- Role of cranial radiotherapy 250cGy in 2 fraction-
Blood Vol No:2 1982
- CRT doesn't impact survival -AJH 2007
- No role of RT –Cancer 2008



GRANULOCYTIC SARCOMA

- Isolated extramedullary form of AML
- Common with M4,M5
- Symptomatic areas-Orbit, spinal cord
- Dose 4 GY to 30Gy in 2 to 15 fractions with 2-3 cm margins depends upon the size of the tumor

Cancer 1981



CNS PROPHYLAXIS

- Dose > 3Years 18Gy
1-3 Years 15 Gy
Less than 1 year No radiation
- With or without CNS involvement after complete remission
- Mandatory for all with high counts 70,000/microL with or without initial CNS involvement

Leukemia (2005) 19, 2030–2042



TOTAL BODY IRRADIATION

- Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia in First Complete Remission: Systematic Review and Meta-analysis of Prospective Clinical Trials
- Ablative conditioning regimen 10-14 Gy of TBI

JAMA. 2009;301(22):2349-2361



TESTICULAR IRRADIATION



MANAGEMENT-IN THE CASE OF TESTICULAR INVOLVEMENT NO UNILATERAL OR BILATERAL ORCHIDECTOMY IS PLANNED.

IF THE TESTICLE SIZE NORMALIZES COMPLETELY AFTER THE PROTOCOL AT THE LATEST ACCORDING TO TACTILE AND SONOGRAPHIC FINDINGS THERE IS NO EXTRA TESTICULAR IRRADIATION.

IF AFTER THE PROTOCOL A DOUBTFUL CLINICAL FINDINGS REMAINS,BIOPSY IS REQUIRED AND IN CASE OF INVOLVEMENT LOCAL IRRADIATION MUST BE APPLIED.

ALL IC BFM 2002



- UNILATERAL IRRADIATION OR ORCHIDECTOMY AS LOCAL MANAGEMENT WAS FELT TO BE ASSOCIATED WITH A SIGNIFICANT RISK OF CONTRALATERAL DISEASE JUSTIFYING TREATMENT DIRECTED AT BOTH TESTIS FOR LEUKEMIA MANAGEMENT.
- 24 TO 30 GY OVER 2 TO 3 WKS(200CGY-300CGY/#) (ALL BFM 95)
- 18 GY IN 10 FRACTIONS OVER TWO WEEKS –(ALL IC 2002)



Secondary manifestations of leukemia in brain

Cerebrovascular complications (may be due to leukemia or induced by chemotherapy)

- Hemorrhage

- Infarction

- Dural sinus thrombosis

Infections (may be due to leukemia or induced by chemotherapy)

- Parenchymal

- Meningitis

Drug-induced neurotoxicity

- Meningitis

- Leucoencephalopathy

Posterior reversible encephalopathy syndrome (PRES)

Radiotherapy-induced complications

- Leucoencephalopathy

- Mineralizing microangiopathy

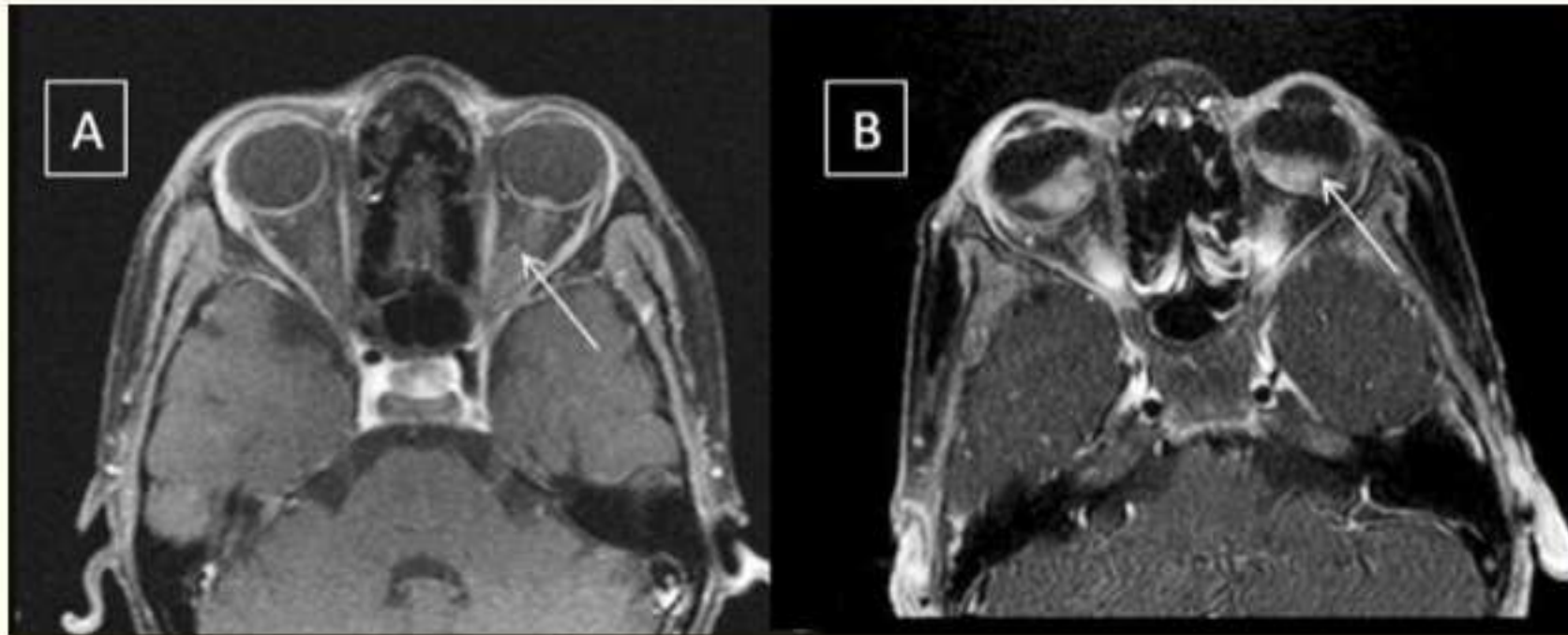
- Radiation-induced cryptic malformations

Parenchymal atrophy (due to leukemia or induced by therapy)

Secondary brain tumors



CHLOROMA



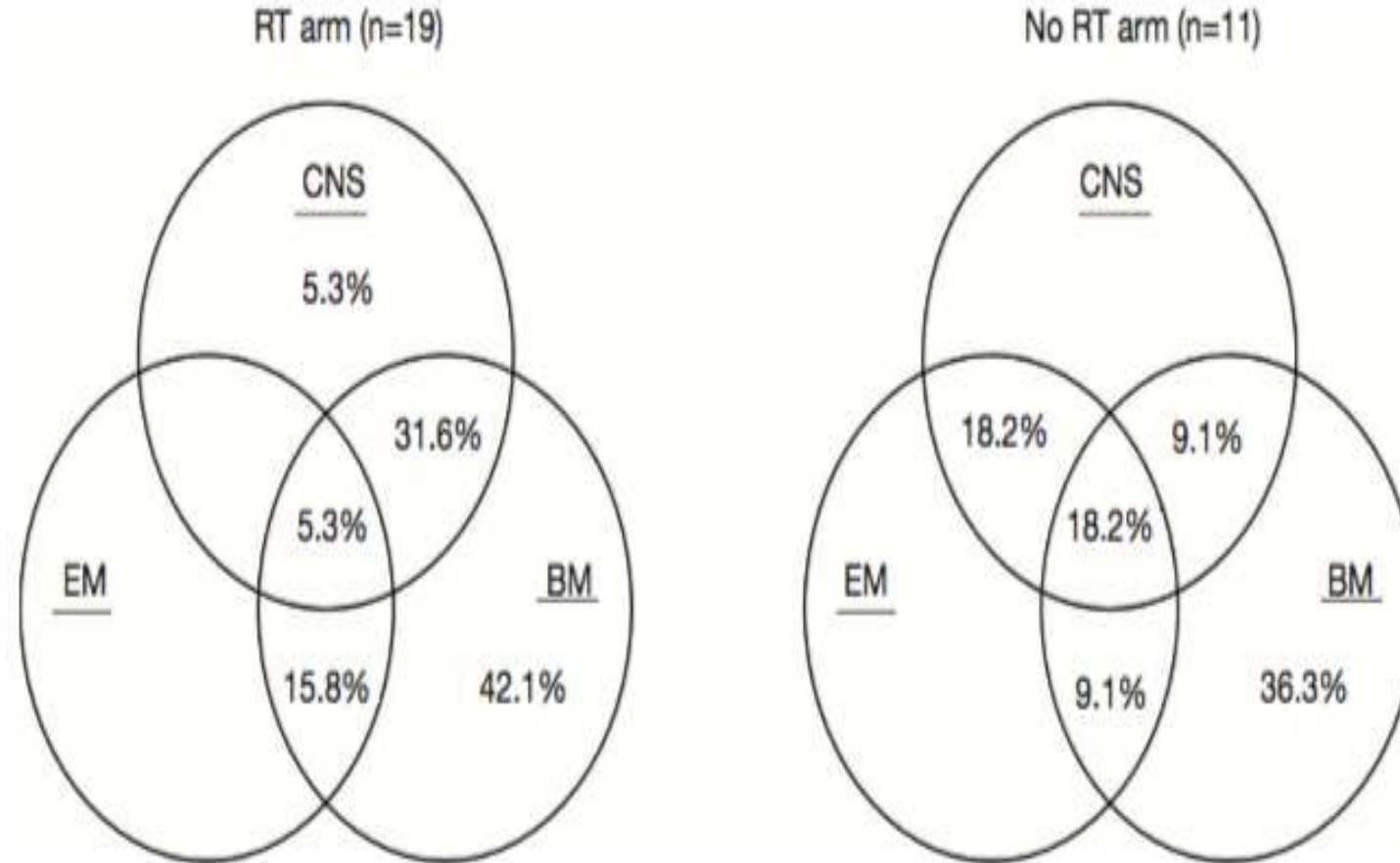


Figure 4 Relapse pattern after transplantation: RT group and no RT group. CNS, central nervous system; EM, extra-medullary site; BM, bone marrow; RT, radiation therapy.



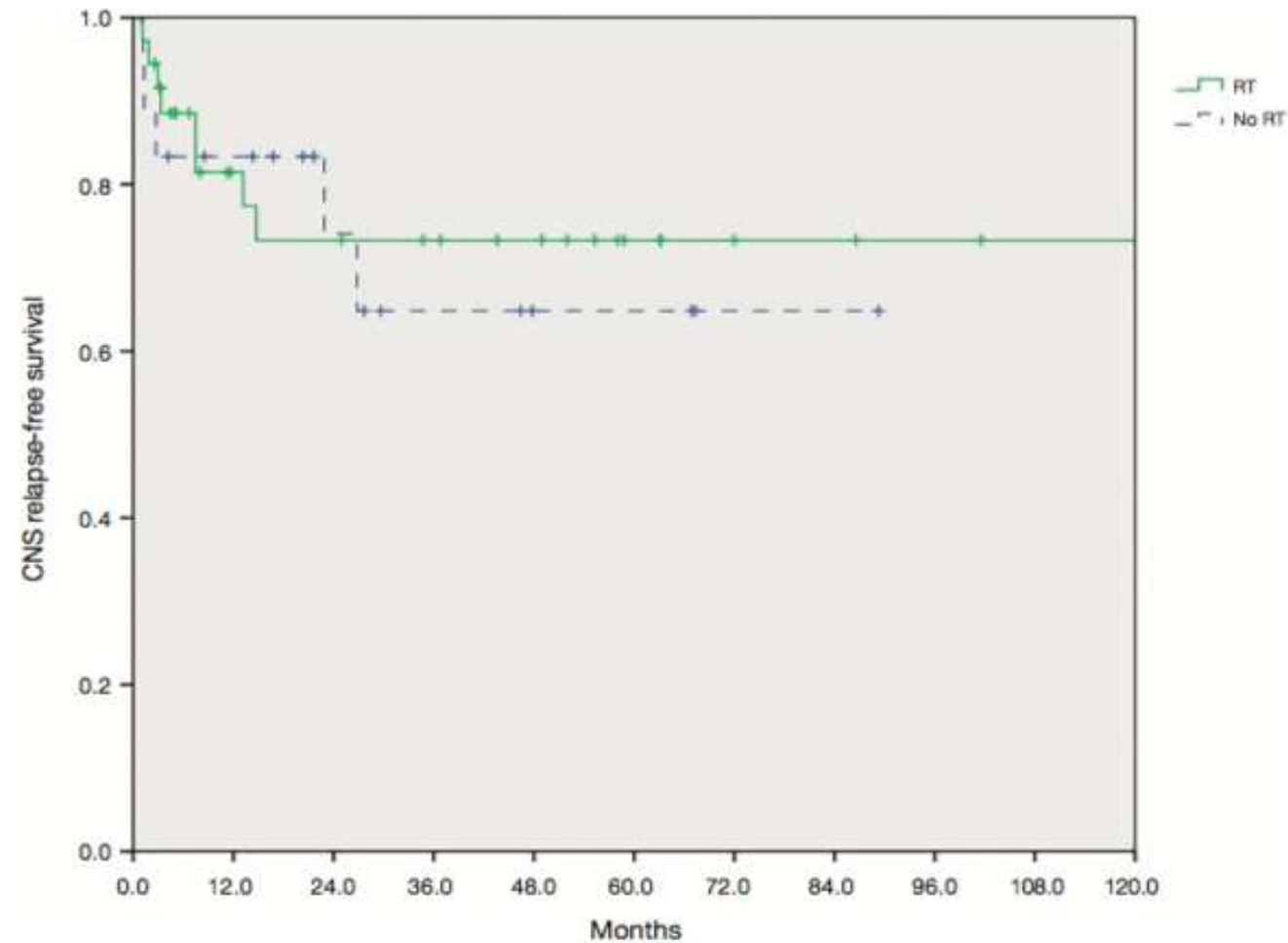


Figure 3 CNS relapse-free survival according to radiotherapy treatment groups ($P=0.742$). CNS, central nervous system; RT, radiation therapy.



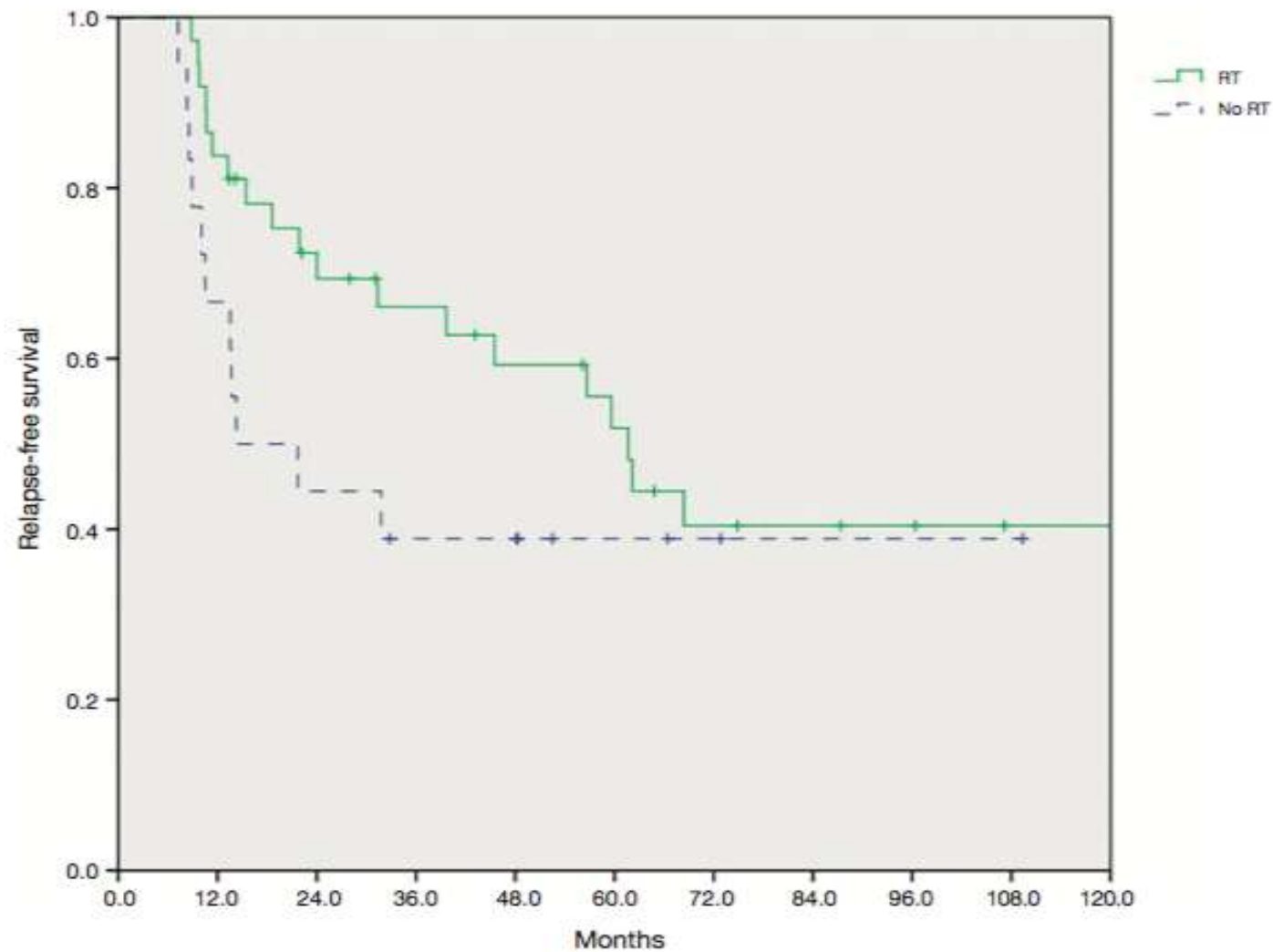


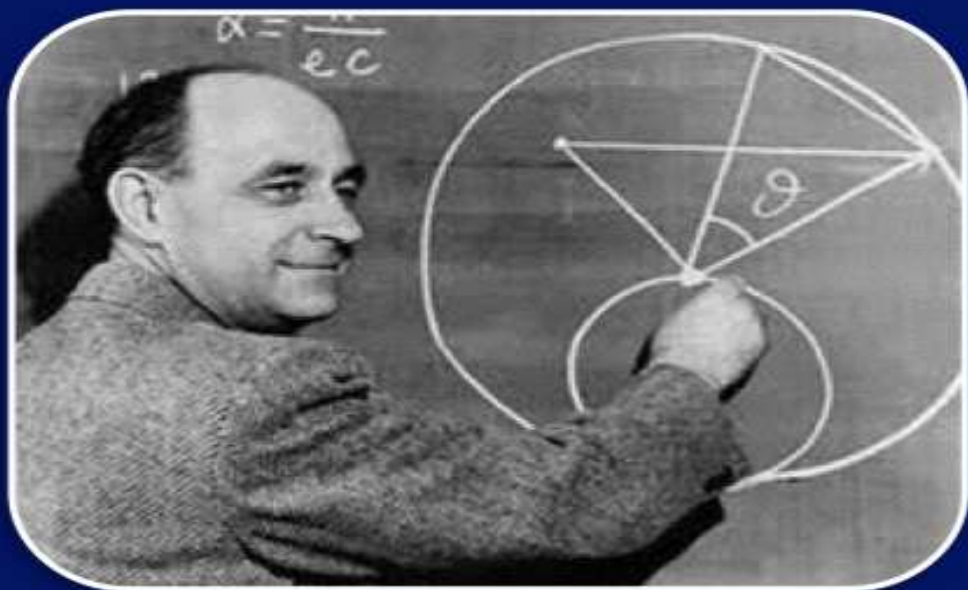
Figure 2 Relapse-free survival according to radiotherapy treatment groups ($P=0.164$). RT, radiation therapy.



SUMMARY OF AML

- CNS involvement is rare/ under exploited field.
- Extramedullary involvement by AML is rare,
- Chemotherapy forms an integral part in the management
- AML with inv(16)(p13.1q22) is known to be associated with extramedullary myeloid sarcoma, whereas AML with t(9;11)(p22q23) has been shown to have association with soft tissue infiltration (gingiva and skin).
- Risk factors and cytogenetic abnormalities that predispose a patient to develop CNS involvement have not been extensively explored.
- This area is deserving of interest due to increased difficulties with treatment and the potential for highly morbid associated sequela, such as blindness.





**BEFORE I CAME HERE I WAS CONFUSED
ABOUT THIS SUBJECT**

**NOW HAVING LISTENED TO YOUR LECTURE,
I AM STILL CONFUSED, BUT AT A HIGHER
LEVEL**

