ROLE OF RADIATION IN PAEDIATRIC LEUKAEMIA

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LEUKAEMIAS IN CHILDREN

- Leukaemias- most common cancer types in children
- Nearly 30% of all childhood cancers in North America

ALL

- 80% of childhood Leukaemias
- 24% of all cancers in children
- Prototype childhood cancer that documented importance of combined modality therapy incorporating irradiation for “sanctuary sites”
- Early success in Leukaemia control attributed to introduction of CNS irradiation

ALL

- Clonal expansion of dysregulated, immature lymphoid cells
- B-precursor Leukaemias -85% of all ALL in children
  - Early pre- B cell lines-55% (cIg negative)
  - pre-B cell lines-25% (cIg positive)
  - Mature B-cell differentiation with surface Ig-2-3%
- T-precursor ALL- 15% of childhood ALL
- **B-cell ALL** in **young children**- wide range of clinical manifestation and initial WBC counts
- **T-cell ALL** in **older children** (above 10 years, extramedullary involvement (mediastinal lymph nodes & CNS), high presenting WBC

ALL

Clinical Presentation

- Median age at presentation- 4 yrs
- Peak occurrence- ages 2 & 4 years
- Boys more commonly affected (notable in T cell ALL)
- Common presenting symptoms-fever, bleeding & bone pain
- Findings at diagnosis- ecchymoses or petechiae, signs of LN enlargement, hepatosplenomegaly
- Less often- clinical signs or symptoms of extramedullary involvement of CNS, testis or kidney
- CBC- presence of immature lymphoblasts in peripheral blood or elevated WBC (WBC <10,000/ml in 50%, 10-50,000/ml in 30% and >50,000/ml in 15-20% at diagnosis)

ALL

Clinical Presentation

- **Systemic disease**-usually involving bone marrow diffusely & associated with lymphoblastic infiltration, microscopic or overt in organ systems, e.g. lymph nodes, liver, spleen etc.
- **CNS leukaemia** usually asymptomatic
  Extensive leptomeningial involvement - irritability, headache, vomiting or sometimes weight gain ("hypothalamic syndrome"), cranial nerve palsies(VII, less often VI, III), or seizures.
  Advanced disease - papilloedema and diffuse retinal infiltration

AML

- 20% of childhood Leukaemias
- Over half of Leukaemic deaths in US children
- Throughout Paediatric age range-greater frequency in newborns and adolescence.
- **Presenting symptoms:**

  Pallor
  Fatigue
  Bleeding
  Infection and Fever
  Leukostasis
  Organomegaly at diagnosis- less common than in ALL
  Localized extramedullary tumour deposits (**chloromas** and **granulocytic sarcomas**) - can present as symptomatic masses- head & neck, spinal cord, brain

AML

- African American, older age (>2 and increasing age) and overweight habitus- poorer outcome
- CNS disease at presentation- 5-15% cases- high peripheral WBC, age <2 years, favorable cytogenetic characteristic
- Mainstay of treatment- induction with Daunorubicin (or Idarubicin) in conjunction with Cytarabine and Etoposide
- Post-induction- intensified consolidation CT or the use of matched sibling or matched unrelated stem cell transplant
- Role of Radiation therapy remains poorly identified
- AML- more common indications for BMT in children- impact of TBI in this setting significant
- Transplant regimens continue to evolve- increasing indications for radiation immunosuppression

ALL

Staging: Risk Categories for ALL

- NIH sponsored Consensus Conference 1995 Clinical criteria:
- **Low Risk** (45-50% cases**):**
  B-precursor ALL in children 1-10 years
  WBC < 50,000/mL
  DNA index of >1.16 or presence of TEL-AMLI fusion
- **Intermediate Risk** (40-45% cases)**:**
  Infants <1year, children 10 years or older
  B-cell lineage with WBC >50,000/mL
  all with T-cell lineage
  cases with t(1:19)/E2A-PBX1 fusion
- **High Risk** (8-10% cases)**:**
  those with t(9:22)/BRC-ABL fusion (Ph^+ ALL)

ALL

Staging: Risk Categories for ALL

- Important predictors of outcome::
  - Clinical features
  - Biological features
  - Early response to induction chemotherapy
- **Standard risk (rather than Low Risk):**
  - MRD quantitatively defined by immunohistochemistry
  - **or** PCR blasts defined as ≥1% on day 19 of induction
  - **or** 0.1-0,99% at completion of 6 week of induction
- **High Risk**
  - those with ≥ 1% at completion of 6 week of induction

ALL

Staging: CNS involvement in ALL

- Diagnosis of CNS disease in Leukaemia standardized by Rome Workshop:
  - Presence of ≥ 5 WBC/μL in CSF
  - Cranial nerve palsies believed related to CNS infilt.
- **Present Classification** (based on disease control in ALL studies through 1990s)
  - **CNS 1 -** no blasts
  - **CNS 2 -** (varies between 5% and 10-30%) - blasts with <5 WBC/ μL
  - **CNS 3 - (3-5% cases) -** as above: ≥5 WBC**/** μL and cytologic biologic evidence of blasts in CSF
- **SJCRH study** - Traumatic lumbar puncture early in diagnosis/ therapy equivalent to CNS 2 disease

AML

CNS Disease in AML

- CNS disease at presentation - 5-15% cases- high peripheral WBC, age <2 years, favorable cytogenetic characteristic
- Incidence of CNS disease at diagnosis exceeds that seen with ALL
- CNS disease at diagnosis with other extramedullary disease and WBC> 100000/ml related to high frequency of relapse
- Preventive CrI – not utilized in North American AML trials over past 2 decades

AML

CNS Disease in AML

- BFM group studied impact of CrI in AML-BFM-87 - without CNS disease- 18 Gy CrI or enhanced systemic CT- randomization stopped early as no excess CNS relapse in non-RT group- final analyses higher CNS and systemic relapse in those without CrI
- Subsequent BFM studies- CrI for children >1 year old
- Other studies without CrI- no excessive CNS failure in AML
- CNS relapse in AML- intensified IT ara-C ±MTX
- T/t of focal infiltrates ("chloromas")-symptom control or consolidation
- AML sensitive to RT- symptomatic and measureable response apparent after 12-15 Gy
- Consolidative therapy effective at 18 Gy
- Lesions with incomplete response to CT- 21-27Gy

ALL

Treatment: CNS Preventive Therapy

Evolution-

- Initial concept from Mouse L1210 Leukaemia model
- SJCRH- application of exp. model to children in 1960s.
- Early studies- 5-12 Gy CSI- CNS relapse dominant event once CT prolonged “haematologic remission”>6-12 months.
- CSI or CrI (CrI+IT-MTX) to 24Gy reduced incidence of CNS relapse from >60% to <5-10%.
- Children in haematologic remission - preventive CSI (24Gy) Vs therapeutic CSI (24Gy) at time of overt CNS relapse- HIgher EFS & OS with preventive therapy.- cure following CNS relapse significantly greater functional deficits

ALL

Treatment: CNS Preventive Therapy

Evolution-

- Later trials- equivalence of 18Gy (1.5-1.8 Gy/#) and 24Gy
- Other approaches in 1970s- high dose systemic MTX and increased IT Chemotherapy
- Trials over past 10-15 years have limited use of prev. CrI-defined cohorts at higher risk of for CNS relapse likely to benefit-balancing efficacy vs. RT related toxicity with added CNS exposure to IT and systemic MTX
- Trials-
  Dana Farber Can. Inst. Childhood ALL Consort. Prot. 95-01
  German-Austrian-Swiss ALL-BFM-95 study
  St. Jude Total XII, XIII, XV trials

ALL

Treatment: CNS Preventive Therapy

Evolution-

In Summary

- Standard risk ALL can be treated without CrI
- Group for which CrI may be beneficial:
  cohort with T-cell ALL & with WBC >100,000/μL
  Appr. 20% children with T-cell ALL(2% of all children with ALL) present with high WBC count
- HD-MTX & IT-MTX have neurologic sequelae- interest in considering CrI dose reduction (12 Gy/8# in recent BFM studies)

ALL

Treatment: Current Recommendations for Preventive CNS Therapy

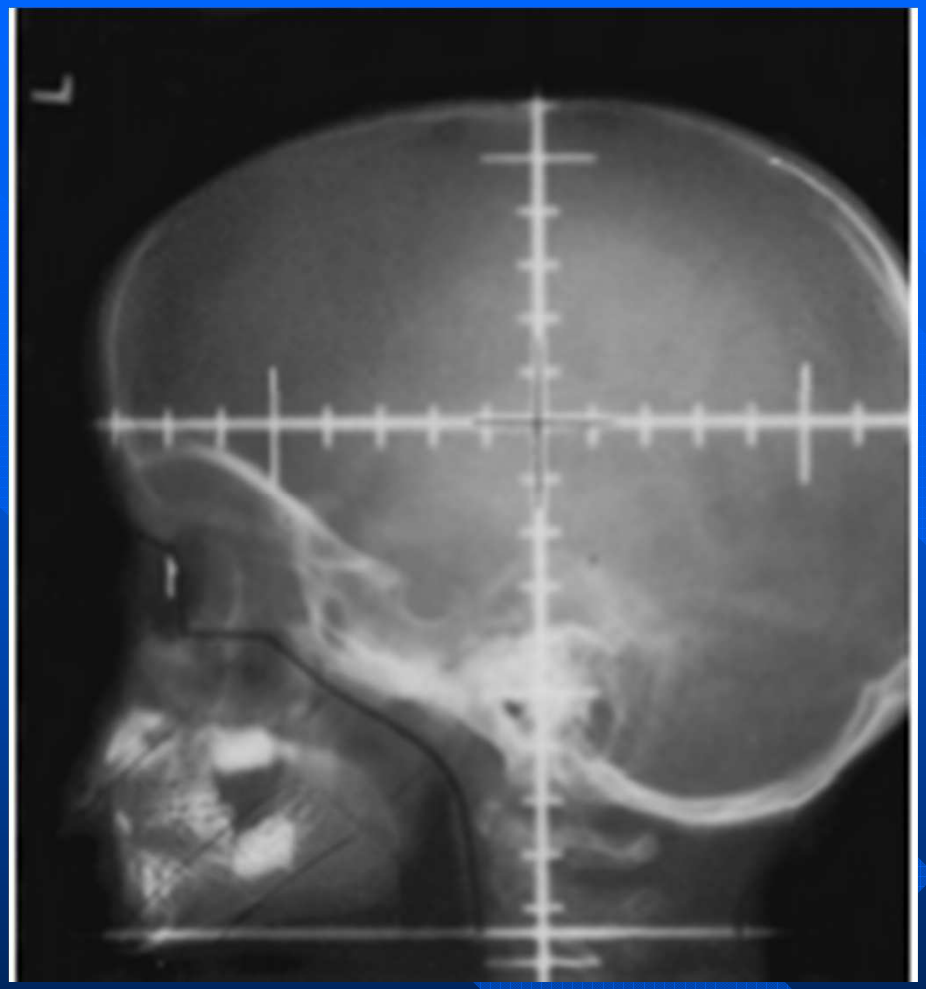
- Contemporary regimens- preventive CrI in 2-20% children
- Cohorts where risk of CNS relapse exceeds 10% - where use of 18(or 12Gy) preventive or therapeutic CrI offers superior disease control with acceptable balance regarding known late toxicities:
  - T-Cell disease and high WBC
  - Ph^+ [t(9:22)] presentations
  - CNS 3 (possibly CNS 2)
  - B-Cell precursor ALL with t(1:19)

ALL

CNS Preventive Treatment- Radiotherapy:

Volume:

- Proph. CNS therapy- entire intracranial subarachnoid space
- Key Margins at skull base:
  - -Cribriform plate- (lowest point of anterior cranial fossa- in midline at level typically below orbital roof)
  - -Lower limit of temporal fossa
- Lower border at Inferior margin of 2nd cervical vertebra
- Incl. of post. retina & orbital apex, subtending extension of subarach. space around optic nerves- stand. requirement - retinal involv. late manifestation of CNS leukaemia
- Include post. orbit and globe – spare ant. globe and lens
- Accept dose appr. 20% to lens to cover cribriform plate
- Custom block improve T/t compared to MLC



Cranial irradiation field . Treatment encompasses entire cranial subarachnoid space. Radio-opaque markers outline anterior aspect of bony orbit to demarcate inclusion of posterior aspect of eye within treatment filed

ALL

CNS Preventive Treatment- Radiotherapy:

Dose:

- Dose Range- 12-18 Gy
- Fractionation- 150-180cGy daily
- Study at DFCI, Boston- no difference in efficacy or toxicity between conventional RT (180cGyX10) and Hyperfractionated CrI (90 cGy twice daily to 18Gy)

ALL

Treatment of Established CNS Leukaemia

CNS Leukaemia at Diagnosis

- In 3-5% of children
- Earlier trials-CNS Leukaemia at diagnosis associated with negative outcome
- More intensive systemic and IT CT- successfully eliminated CNS relapse in children with CNS 2 disease
- Therapeutic CrI or CSI used in most series for CNS 3 disease
- Most current protocols- consolidative CrI after intensification therapy for children with CNS 3 disease at diagnosis
- Recom. dosage of CrI 18Gy,- 150-180 cGy fractions daily

ALL

Treatment of Established CNS Leukaemia

CNS Relapse

- Despite CNS preventive therapy, 1-8% children isolated CNS relapse
- Asymptomatic at diagnosis (detected by routine surveillance LP) in 75% cases
- Symptoms and signs in 25% children- headache with or without vomiting, papilloedema, cranial nerve palsies (VI, VII & V), hyperphagia and CNS haemorrhage

ALL

Treatment of Established CNS Leukaemia

CNS Relapse

- Therapy for isolated CNS relapse-
  - -Systemic CT for reinduction
  - - IT CT (MTX ± Cytarabine & Hydrocortisone)
- CNS control following neuraxis irradiation- overall control in 50-70% children after isolated CNS relapse
- Serial trials in POG- benefit of initial systemic and IT CT for isolated CNS relapse
- Early CNS relapse (<18months post diagnosis) more aggressive- secondary 4 year EFS 46% Vs. 83% for relapse after 18 months
- NCI high risk group- 4 times greater likelihood of relapse after isolated CNS relapse

ALL

Treatment of Established CNS Leukaemia

CNS Relapse- Volume and Dose

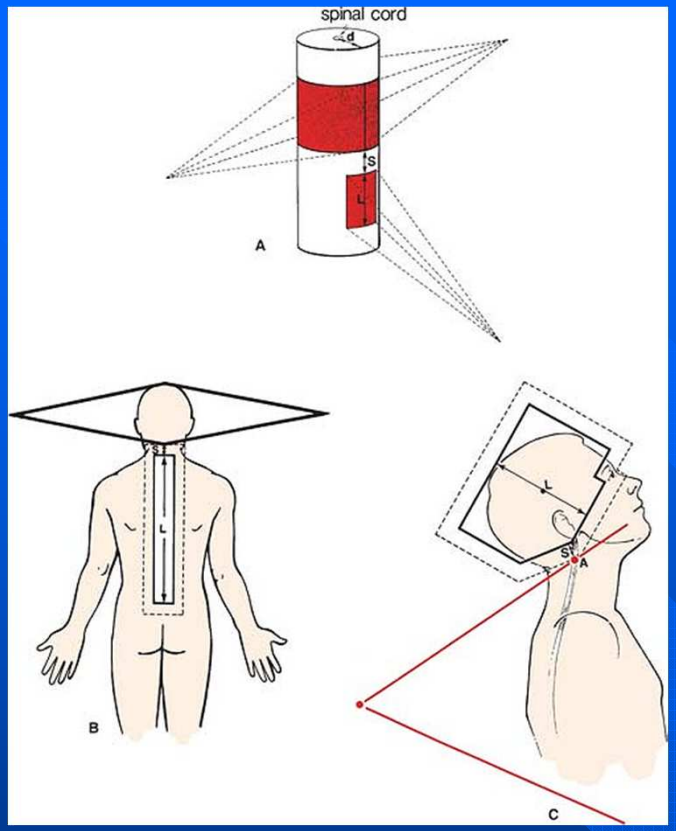
- **CrI**- adequate **for CNS relapse beyond 18 months**
- Current standard- 18 Gy (at 150 Cgy once daily)
- Ongoing assessment-reduction of Cranial dose to 12Gy in late relapsing CNS Leukaemia- premature to use as standard treatment
- **Early relapse-CSI standard**-24 Gy to cranium and 15Gy spine
- Ongoing trial- testing 18Gy in later setting yet inconclusive

Craniospinal Irradiation

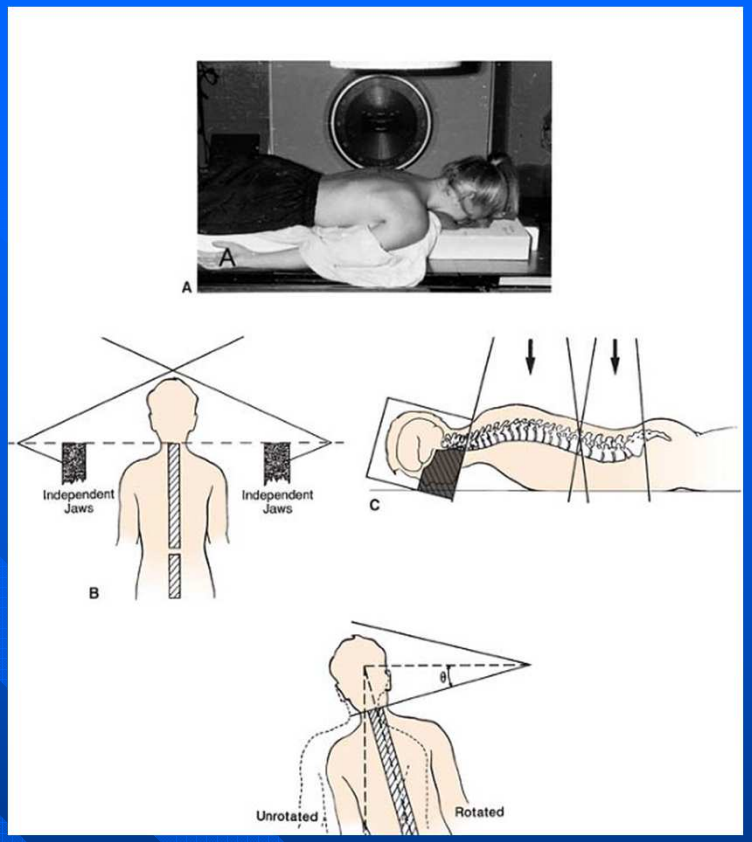
- CTV for CSI - an irregular shape- whole brain, spinal cord and their overlying meninges.
- Standard Techniques- lower borders of lateral whole-brain fields matched to cephalad border of posterior spine field
- Moving junction between brain and spine fields to minimize risk of underdose or overdose in cervical spinal cord.
- Compensators to achieve dose homogeneity throughout target volume.

Patient Positioning and Immobilization

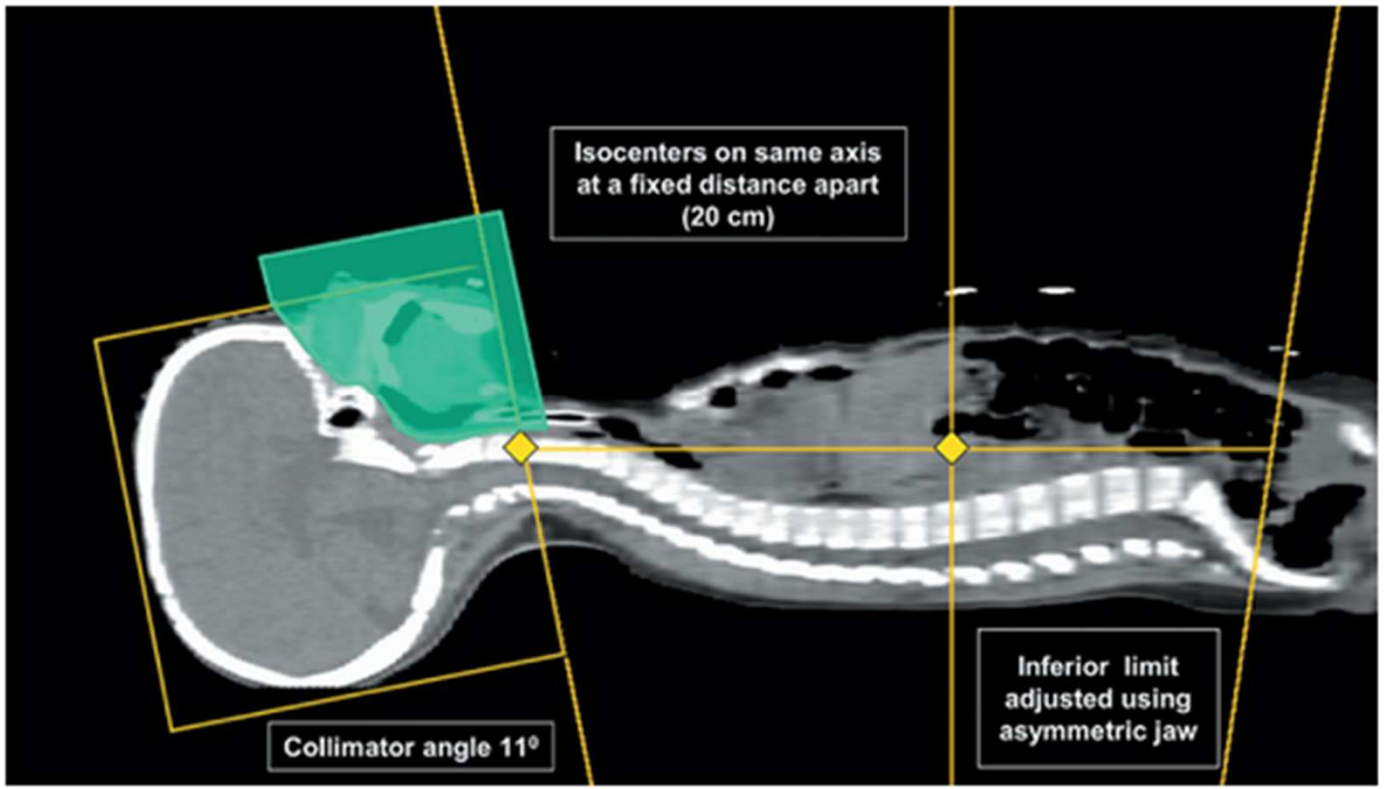
- Traditionally in prone position,
- Modern technology - safe treatment in supine position - more comfortable , if anaesthesia required, better control of airway.
- Head shell or full-body immobilization.



A: A general diagram showing the separation of orthogonal fields. B: Orthogonal fields used for craniospinal irradiation. C: Lateral view of B, illustrating the geometry of orthogonal field separation.



Craniospinal irradiation. A: Patient setup showing Styrofoam blocks and Alpha Cradle mould for stable position for abdomen, chest, and head. B: : Elimination of cranial field divergence by using an independent jaw as a beam splitter. C. Lateral view of fields showing cranial field rotated to align with the diverging border of spinal field. D: Couch rotated for match between spinal field and diverging border of cranial field.. Technique B gives alternative to couch rotation in D.



Lateral opposed fields used to treat the brain and direct posterior filed is used to cover spinal axis. Field junction over cervical cord at a level that avoids inclusion of teeth in exit of spinal field and is usually moved weekly (“feathered”) to avoid over or under-dosage

Craniospinal Irradiation

Target Volume Definition

- CT simulation to ensure adequate coverage of CTV in subfrontal region at the cribriform plate.
- Blocks in lateral fields to shield facial structures and lenses.
- In most- impossible to adequately irradiate cribriform plate & shield lenses- adequate PTV coverage takes precedence.
- CT simulation- identifying lateral aspect of CTV for spine field- includes extensions of meninges along nerve roots to lateral aspects of spinal ganglia.
- Lower CTV limit for the spine field best determined by MRI.
- Traditionally, lower border of spine field at lower border of 2nd sacral foramen- lower border of thecal sac can be as high as L5 or as low as S3- individualized as per MRI findings.

Craniospinal Irradiation

Treatment Planning and Delivery

- Many issues need to be addressed in designing a CSI technique
- Many of the different solutions add further complexity.
- Using modern tools for treatment planning and delivery-possible to greatly simplify the technique and substantially reduce planning and delivery times.
- Photons in the 6- to 10-MV range provide satisfactory coverage of the PTV.
- Variation of dose along spinal axis of >10% will require use of dose compensation achieved using multileaf collimation.

ALL

Treatment of Testicular Leukaemia

- T/t of ALL in 1980s - significant risk of testicular relapse
- 5-10% boys presented with overt testicular leukemia-10-20% of all failures
- Testicular relapse - a late event- at median of 3yrs post diagnosis
- Related to high risk features- T-cell phenotype, high WBC at diagnosis
- Most instances-clinical or histological evidence of bilateral infiltration
- Enhanced systemic disease control- high dose MTX in prolonged intensification regimen- largely eliminated occurrence of testicular relapse since 1990

ALL

Treatment of Testicular Leukaemia

- Systemic chemotherapy
- Preliminary data using CT alone- orchiectomy reserved for local disease control where no prompt histologically verified disease control
- Testicular irradiation no longer as prophylactic treatment
- Systematic testicular irradiation eliminated from current treatment regimen
- Irradiation reserved for documented residual testicular infiltration after reinduction chemotherapy
- COG trial-radiation reserved for disease persistent after high dose MTX and induction CT
- Dutch Late Effects Study Group- management of testicular relapse without local irradiation

ALL

Treatment of Testicular Leukaemia

- When indicated- irradiation directed to both testes
- Dose 24Gy/12 #- sometimes persistent disease with this
- For those with testicular disease-part of current high risk COG trial-given during consolidation at 24 Gy/12 #.
- Most often- single AP field- set to smallest filed
- If Photon- angled in Sup.-Inf. Direction-treat tangentially
- If Electron- set up *en face* to testis directly
- Penis taped to abdomen-out of treatment field
- Frog leg position
- Testis centered in field and bolus applied to bring centre of testis to depth of max. dose

ALL

Treatment of Testicular Leukaemia

- Attention to daily positioning- ensure descent of testes into scrotum during therapy
- Field may be reduced as testicular mass decreases in size- electron energy chosen to minimize dose beyond target
- Energy calculated to deliver 90% dose to posterior aspect of testes
- Dose- 20-24 Gy, usually 200cGy/ fraction
- Interest in limiting RT- sterility and Leydig Cell hypofunction following irradiation

ALL

Other Extramedullary Disease

- Other extramedullary relapse uncommon- <2% of failures
- Anterior chamber of Eye- Disease confined to this- unusual - unlike diffuse retinal involvement
- En-face electrons- superficially irradiates eye- 12Gy/6#
- Others- Lymph nodes, ovaries, uterus, bone
- Local irradiation either as consolidation after intensification CT or in conjunction with BMT when:
  - fails to respond to reinduction CT
  - truly sizeable local disease

ALL

Local recurrence or site related disease

- Whether nodal or otherwise, is site specific
- Individual sites treated with simple AP/PA technique with appropriate blocks for critical structures
- If spinal column in the field entire width of vertebral body to be included

TBI

- Role- destroy recipient's bone marrow and tumor cells- immuno-suppress patient sufficiently to avoid rejection of donor bone marrow transplant- part of allogenic but not autologous transplantation
- TBI with megavoltage photon beams- part of preparatory conditioning regimen for bone marrow transplantation- in various conditions including Leukaemia
- Addition of TBI is considered beneficial for certain diseases and clinical conditions

  :a) TBI allows almost homogeneous dose (within 10%) to the entire body including "sanctuary areas"

  b) Selected parts of the body (e.g., lungs, kidneys, and head) partially or fully shielded,

TBI

- Originally given alone- more effective when CT also employed
- Fractionated regimens generally used with or without lung shielding and electron boosts to chest wall
- Dose prescribed to mid plane, typically **level of umbilicus**
- Compensators or bolus used to maintain dose uniformity of better than ±10%
- Variety of treatment techniques

TBI

Choice of a particular technique depends on:

Available equipment,
Photon beam energy,
Maximum possible field size,
Treatment distance,
Dose rate,
Patient dimensions,
Need to shield selectively certain body structures.

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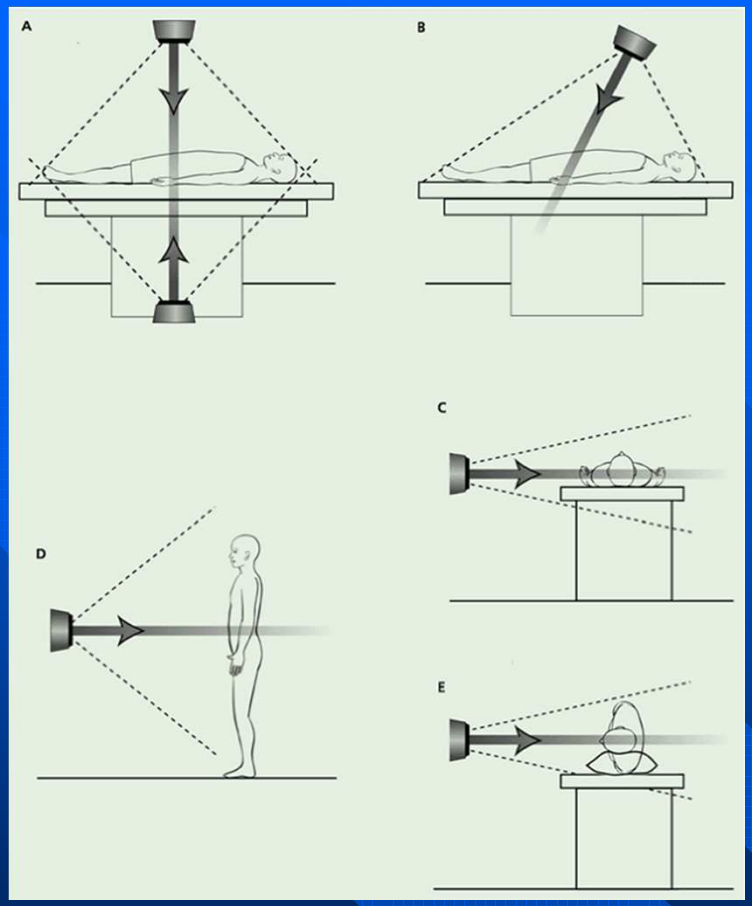


Illustration of some of the current large-field TBI techniques in which patient and beams are stationary. A: Two vertical beams. B: One vertical beam. C: One horizontal beam, patient in supine position. D: One horizontal beam, patient standing or sitting. E: One horizontal beam; patient in lateral decubitus position.

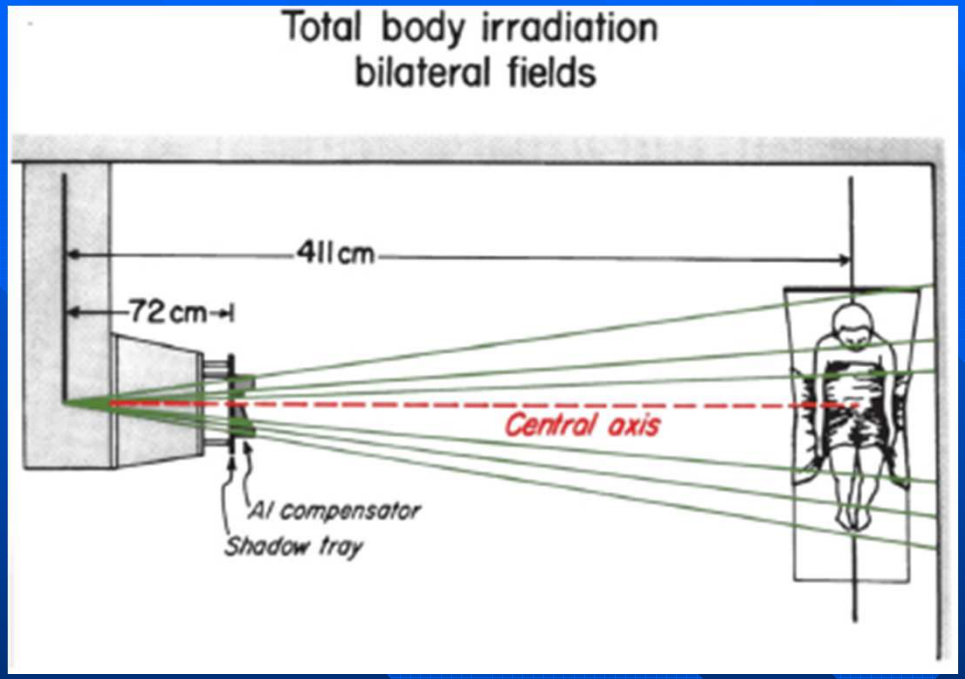
TBI

- Compensators- achieve dose uniformity along body axis to within ±10%-extremities-some noncritical structures may exceed this specification.
- Beam energy: choice of photon beam energy dictated by
  Patient thickness,
  Variation along axis of patient,
  Specification of dose homogeneity
- Initial dose build up: Dose build up data obtained at normal SSD (e.g., 100 cm) do not apply accurately at TBI distances
- TBI protocols-skin sparing not required- bolus or beam spoiler- surface dose- at least 90% of prescribed TBI dose.
- Patient support/positioning devices-to implement a given treatment technique.

TBI

Bilateral TBI technique:

- Bilateral fields (left & right lateral opposing fields)-
- Comfortable if patient seated/supine on TBI couch,
- Greater variation in body thickness along beam path
- Patient seated on couch in semi-fetal position.
- Lateral body thickness varies-compensators needed for head and neck, lungs, and legs- dose uniformity within approx. ±10% along sagittal axis of body.
- Dose prescription- midpoint of body cross section at level of umbilicus.
- Reference thickness for compensation is lateral diameter of body at level of umbilicus



Schematic diagram illustrating patient setup geometry for the Bilateral TBI Technique.

TBI

AP/PA TBI technique:

- Irradiated in standing position at TBI distance
- Better dose uniformity along the longitudinal body axis
- Positioning, other than standing upright-pose problem
- Standing allows- shielding of critical organs from excessive photon dose
- Boosting to superficial tissues in shadow of blocks with electrons.
- Also be adopted for treating small children in reclining position

Pediatric patient in reclining TBI position on the floor. Legs placed in “frog-legged” position to cover entire patient in radiation field. Brain sparing shielding block placed on top of acrylic tray to shadow central part of skull with head turned sideways.

SEQUELAE OF RADIOTHERAPY

Somnolence Syndrome

- Appr. 1 month after CrI- 40% to 50% of patients- lethargy, irritability, anorexia, and even fevers.
- EEG changes and CSF pleocytosis.
- Self-limited and typically reverses within 1 to 3 weeks. Glucocorticoids in acute management- helpful.
- Incidence reduced if patients receive steroids during CrI

Pituitary Dysfunction

- Endocrine function affected- dose and age dependant manner.
- Growth hormone (GH) deficiency most common abnormality.
- Age <5 years at the time of RT- particular susceptibility.
- Higher RT doses & young age- increased incidence GH def.
- More common after 24 Gy than 18 Gy.
- Precocious puberty- dose to hypothalamic-pituitary region-18 Gy

SEQUELAE OF RADIOTHERAPY

Cognitive Dysfunction

- Intellectual and psychological impairments
- RT to blame- studies for lowering dose or eliminating it
- CT may also be causing similar effect.
- Result of white matter injury- deficits in speed of information processing.
- In children <5 years - most pronounced in those <3 years

Leukoencephalopathy

- Early PCI studies-significant incidence months after RT
- Highest with cranial RT as low as 24 Gy + IV MTX.
- Demyelinating condition initiated by endothelial damage & subsequent cytokine cascade with ischaemic microinfarct
- Rare after doses of <20 Gy.

SEQUELAE OF RADIOTHERAPY

Secondary Malignancies

- SJCRH-1962 and 1998-cumulative incidence - 4.2% and 10.9% at 15 and 30 years, respectively.
- Those after 20 yrs-lower-gr. malig. - meningiomas & BCC
- Other secondary cancers - gliomas, parotid gland tumors, thyroid cancers, and sarcomas (bone and soft tissue).
- Secondary brain tumours - evenly split between meningiomas and high-grade gliomas.

SEQUELAE OF RADIOTHERAPY

Testicular Effects from RT

- Gonadal dysfunction -rare from cranial RT unless patients undergo re-treatment - high cumulative doses.
- Direct effects from testicular irradiation- very common.
- Doses as low as 1 Gy, even from scattered dose from adjacent external-beam fields-transient oligospermia or azoospermia.
- Higher doses-those used in TBI or therapeutic testicular radiation- expected to cause permanent infertility.
- Leydig cell function-more radioresistent- Low serum testosterone levels or delayed puberty unusual with doses <29 Gy to the testes.


THANK YOU