

USE OF RADIATION THERAPY IN ACUTE LEUKEMIA

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June, 2021

USE OF RADIATION THERAPY IN LEUKEMIA:

- Overview of Treatment Approaches
- TBI: indications and techniques
- Extra-medullary manifestations of leukemia
- CNS leukemia
- Ocular leukemia
- Testicular leukemia

Acute Myeloid Leukemia (AML)

- 19,950 new cases/yr in US
- Median age 68
- Risk stratification:
cytogenetic and molecular
- Induction therapy
(daunorubicin or idarubicin x 3 d
and cytarabine x 7d)
- Consolidation therapy
(high dose Ara-C)
- Allogeneic HCT
 - First remission (CR1) – intermediate and poor risk
 - Induction failure (IF)
 - Second remission (CR2) or subsequent remission
 - Refractory relapse, EM relapse

European Leukemia Net Classification System

Prognostic Group	% age < 60 age ≥ 60	Subsets
Favorable	41% 20%	Inv (16), t(16;16), t(8;21) NC with NPM mutation (NPM+) but no FLT3 ITD (ITD-) NC with mutated CEBPA
Intermediate 1	18% 19%	NPM- ITD – NPM + ITD + NPM – ITD +
Intermediate 2	19% 30%	Cytogenetic abnormalities (including t(9;11) not considered best or worse)
Adverse	22% 31%	3q abnormalities t(6;9), -7, -5, del 5q, abnormal 11 q, abnormal 17p, complex abnormalities

NC = normal cytogenetics; FLT3 = FMS-like tyrosine kinase 3; ITD = internal tandem duplication; NPM = nucleophosmin; CEBPA = CCAAT enhancer binding protein alpha

Acute Myeloid Leukemia (AML)

■ Induction therapy

(daunorubicin or idarubicin x 3 d and cytarabine x 7d)

- Favorable and intermediate risk
 - CR 80% - favorable ; CR 50-60% - intermediate
 - Gemtuzumab ozogomycin (anti-CD33)
 - Midostaurin – TKI active in patients with FLT3 mutations
- Adverse risk
 - CR rate 40% - median survival 12-18 months
 - alloHCT CR 1 or CR 2 – 50% relapse
 - Venetoclax – inhibitor of anti-apoptotic protein BCL2
 - CPX 351 – liposomal formulation of cytarabine and daunorubicin

■ Consolidation therapy

- high dose Ara-C
- allogeneic HCT

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Acute Myeloid Leukemia (AML)

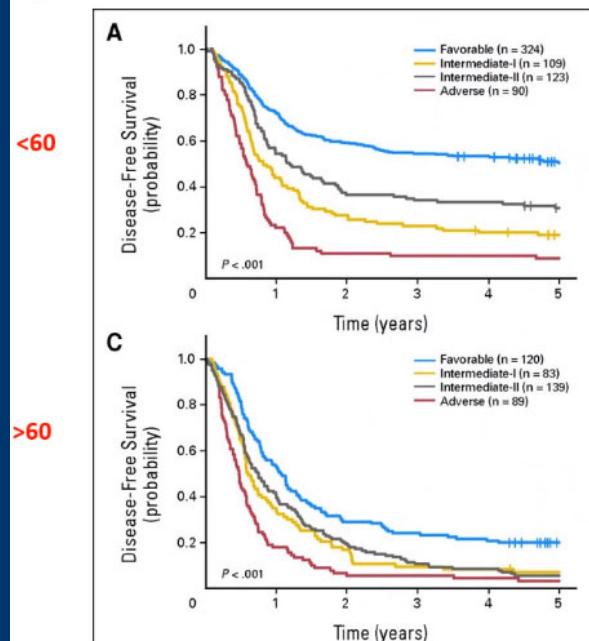
- WHO (2016) – six groups
 - AML with recurrent genetic abnormalities
 - AML with myelodysplasia related changes
 - Therapy-related AML
 - AML NOS
 - Myeloid sarcoma
 - Myeloid proliferations - Down's syndrome
- Overall survival (< 55 years)
(Grimwade, Blood 1998)
 - Favorable risk 64%
 - Intermediate risk 41%
 - Adverse risk 11%

Table 1. Risk Profile Categories as Determined by Molecular and Cytogenetic Abnormalities

Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1;
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
	Mutated NPM1 without FLT3-ITD/low FLT3-ITD
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD(high)
	Wild-type NPM1 without FLT3-ITD/ low FLT3-ITD (normal karyotype)
	t(9;11)(p21.3;q23.3)MLLT3-KMT2A
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); DEK-NUP214
	t(v;11q23.3); KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); GATA2,MECOM(EVI1)
	-5 or del(5q); -7; -17/abn(17p)
	Complex karyotype
	Monosomal karyotype
	Wild-type NPM1 and high FLT3-ITD
	Mutated RUNX1
	Mutated ASXL1
	Mutated TP53

Adapted from Blood 2017 129:424-447

Outcome of Patients with Primary Acute Myeloid Leukemia by Risk Stratification



Krzysztof Mrózek et al. JCO 2012;30:4515-4523

Genetic Group	Subsets
Favorable	t(8;21)(q22;q22); RUNX1-RUNX1T1 inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11 Mutated NPM1 without FLT3-ITD (normal karyotype) Mutated CEBPA (normal karyotype)
Intermediate-I	Mutated NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 and FLT3-ITD (normal karyotype) Wild-type NPM1 without FLT3-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); MLL3-MLL Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1 t(6;9)(p23;q34); DEK-NUP214 t(v;11)(v;q23); MLL rearranged -5 or del(5q) -7 abnl(17p) Complex karyotype*



Factors in the Elderly Associated With Poor Prognosis in AML

Risk Factors:

Higher rates of secondary AML (AML with myelodysplasia-related changes and treatment related AML)

Higher likelihood of unfavorable cytogenetics

Low performance status

Comorbidities, and organ dysfunction

Treatment toxicity from intensive treatments

- Infections
- Prolonged myelosuppression
- Higher treatment related mortality (10-20%)

Acute Lymphoblastic Leukemia (ALL)

- 5,960 new cases/ year in US in 2018
- Median age 15 years
- 75% B-cell ALL, 25% T-cell ALL
- Adults > 55 years old
 - 20 % of ALL cases
 - 51% of ALL deaths
 - More frequent high-risk genetic alterations that confer resistance to chemotherapy
 - Unable to tolerate same intensity regimens as children
- 5 yr overall survival
 - ~ 90% children
 - ~20-25% adults > 50 years old

■ Risk characterization

- Demographic
- Clinical (CNS+, WBC count)
- Immunophenotype
- Cytogenetic abnormalities
- Molecular abnormalities
- Response to therapy

Risk factor	Prognosis association
<i>At presentation</i>	
Age	Continuous variable; adverse outcome with advancing age
CNS involvement	Adverse outcome
Presenting WBC count	Adverse for B-cell phenotype: $>30 \times 10^9/L$ Adverse for T-cell phenotype: $>100 \times 10^9/L$
Immunophenotype	Adverse with CD20 expression
Cytogenetics	Adverse: t(9;22); t(4;11); complex (>5 abnormalities); low hypodiploidy, near tetraploidy Favorable: high hyperdiploid; del 9q
Molecular abnormalities	Adverse: JAK2; IKZF1; PAX5; TLX3; ERG; BAALC Favorable: TLX1
<i>In response to therapy</i>	
Time to initial response	Adverse: failure to attain CR within 4 weeks of induction (variably demonstrated among studies)
Detection of MRD	Adverse: detection at various time-specific points in several studies

Acute Lymphoblastic Leukemia (ALL)

	Favourable factor	Adverse factor
Demographic and clinical features		
Age	1 year to <10 years	<1 year or ≥10 years
Sex	Female	Male
Race and ethnicity	White, Asian	Black, Hispanic
Clinical, biological, or genetic features of leukaemia		
CNS involvement	No	Yes
Blood count at diagnosis	Low blood count; $<50 \times 10^9$ cells per L for B-cell acute lymphoblastic leukaemia and $<100 \times 10^9$ cells per L for T-cell acute lymphoblastic leukaemia	High blood count; $\geq 50 \times 10^9$ per L for B-cell acute lymphoblastic leukaemia and $\geq 100 \times 10^9$ cells per L for T-cell acute lymphoblastic leukaemia
Immunophenotype	B-cell lineage	T-cell lineage
Cytogenetic features	Hyperdiploidy, <i>ETV6-RUNX</i> , <i>TCF3-PBX1</i> , and trisomy of chromosomes 4, 10, or 17	Hypodiploidy, <i>BCR-ABL1</i> Philadelphia chromosome-positive, <i>MLL</i> rearrangements, <i>TCF3-HLF</i> , and complex karyotype (≥ 5 chromosomal abnormalities)
Genomic features	<i>DUX4</i> -rearrangement (<i>ERG</i> deletion)	<i>IKZF1</i> deletions or mutations, Philadelphia chromosome-like, <i>MEF2D</i> -rearrangement
Response to treatment		
Minimal residual disease at specified time points	Low minimal residual disease $<10^{-3}$ nucleated cells or undetectable	Persistence of minimal residual disease $\geq 10^{-3}$ nucleated cells, the higher this value the worse the prognosis

Table 2: Prognostic factors for acute lymphoblastic leukaemia

Lancet Oncology 2020

Acute Lymphoblastic Leukemia (ALL)

- Therapy over 2-3 years
 - Induction therapy
 - Consolidation
 - Intensification
 - Maintenance
 - CNS prophylaxis

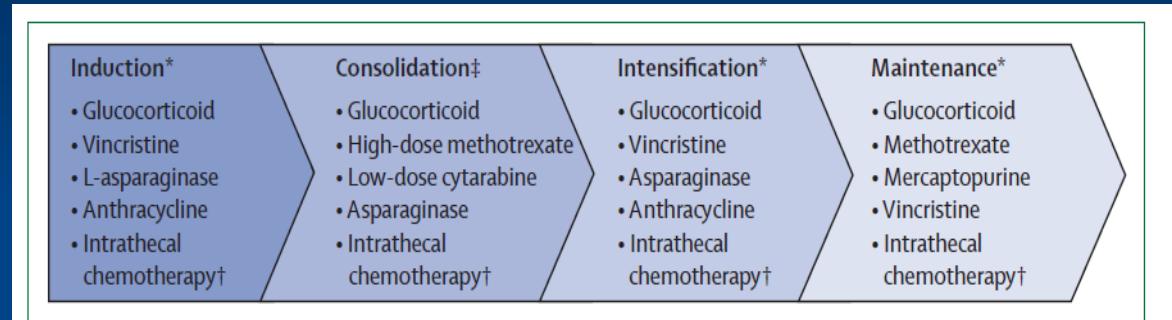


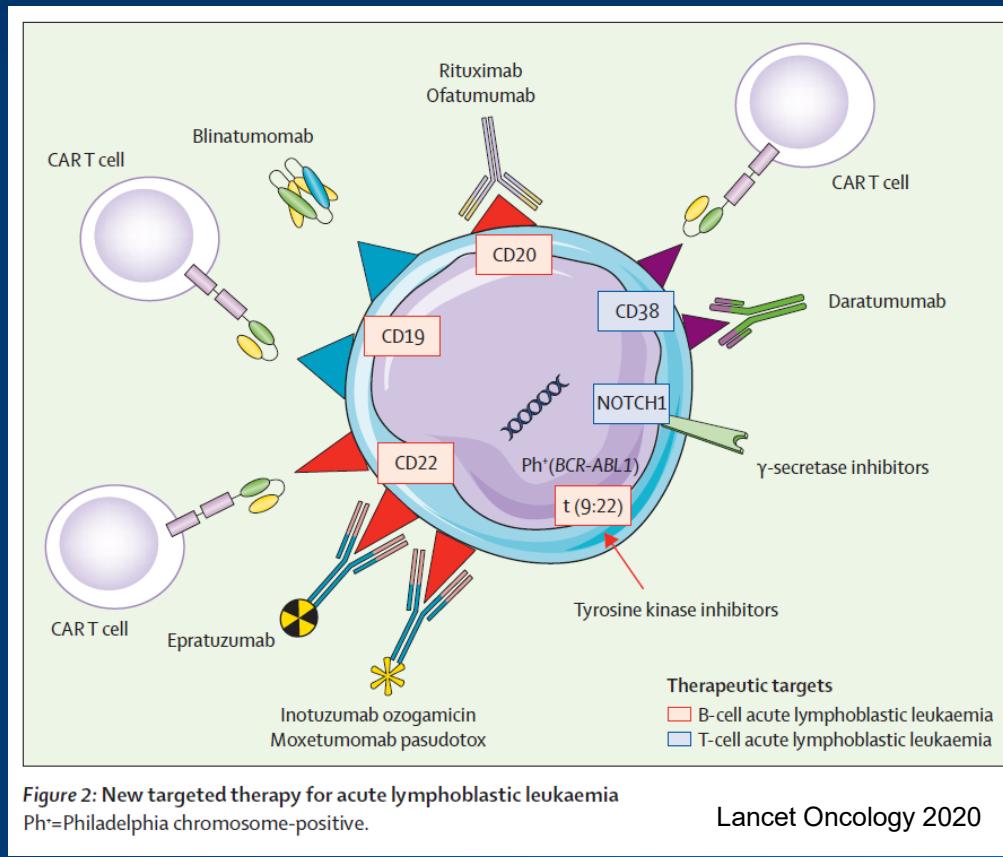
Figure 1: Front-line treatment of acute lymphoblastic leukaemia

*Tyrosine kinase inhibitors are given during each phase of treatment in Philadelphia chromosome-positive acute lymphoblastic leukaemia. †Intrathecal chemotherapy consists of methotrexate alone or combined with cytarabine and hydrocortisone. ‡Allogeneic haemopoietic cell transplantation is optional after consolidation.

Lancet Oncology 2020

- Allogeneic HCT
 - High risk or persistent disease
 - First remission (CR1) – Ph+ or Ph- with high-risk features
 - Primary refractory
 - Second remission (CR2) or subsequent remission
 - Refractory relapse
 - CNS relapse, EM relapse

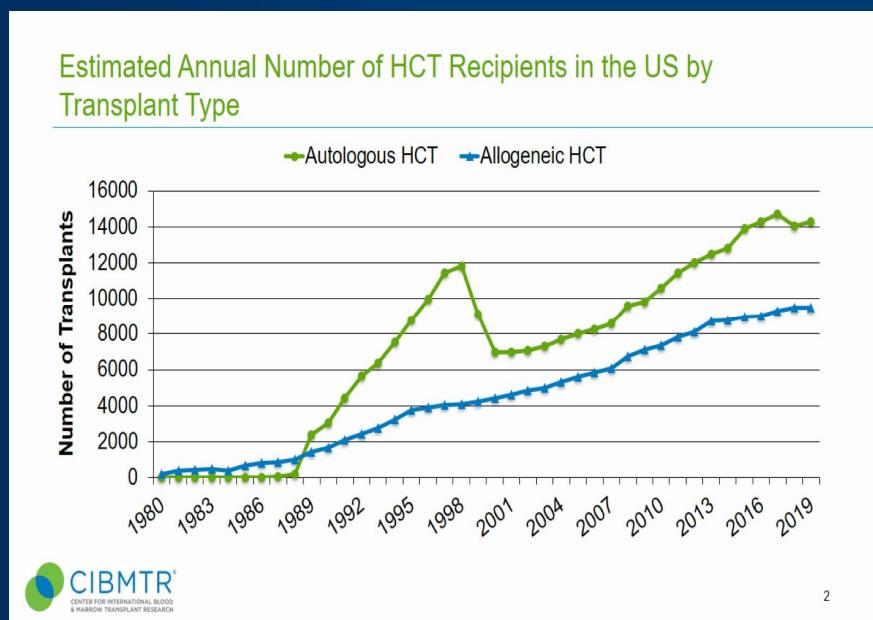
Acute Lymphoblastic Leukemia (ALL)



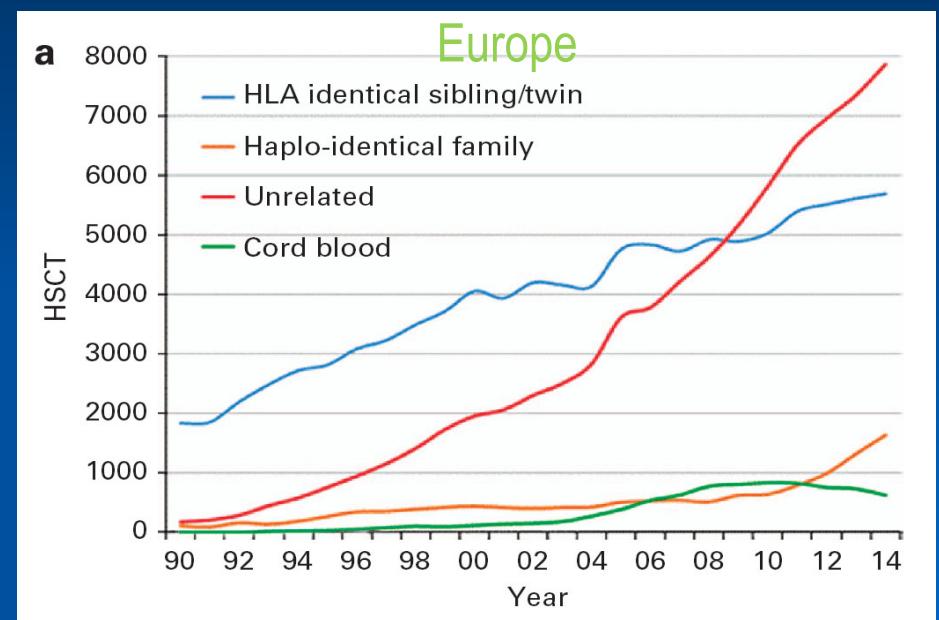
USE OF RADIATION THERAPY IN LEUKEMIA:

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Frequency of Hematopoietic Cell Transplantation (HCT) Increasing Worldwide



2020 CIBMTR.org (Center for International Blood and Marrow Transplant Research)



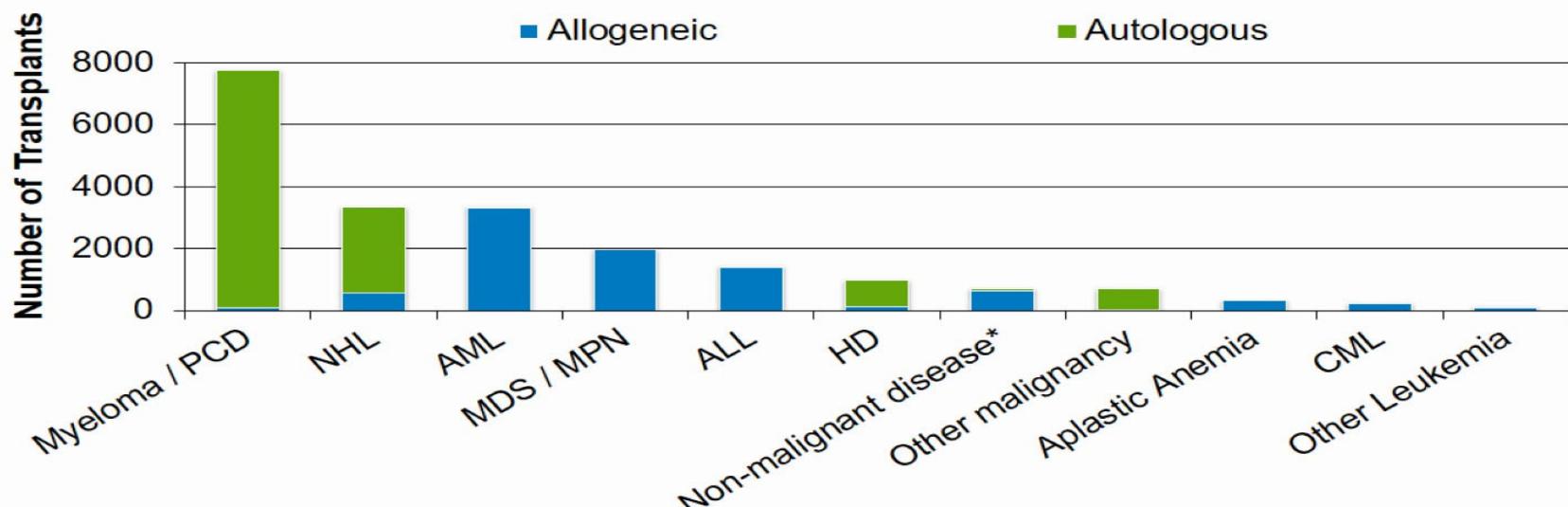
Hematopoietic stem cell transplantation in Europe 2014: more than 40000 transplants annually

Passweg JR et al., BMT (2016) 1-7. (656 teams, 49 countries)

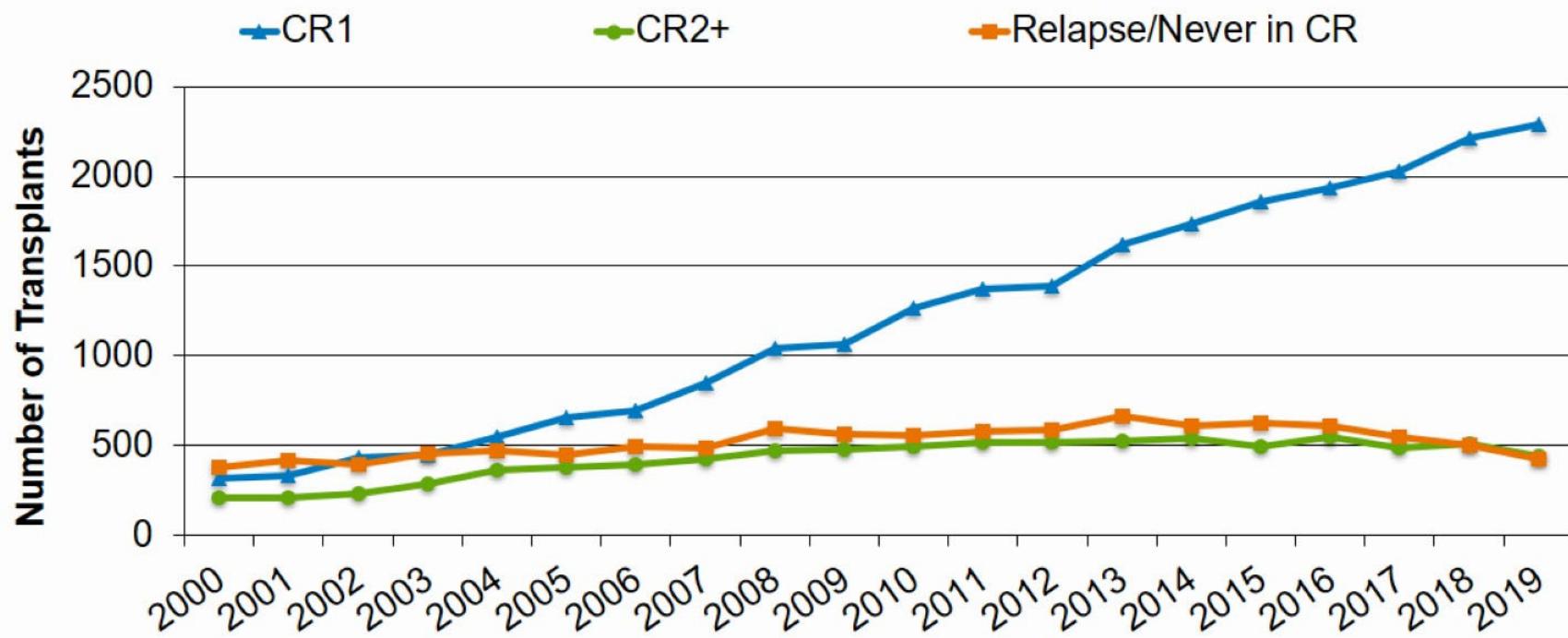
Adult Leukemia: Indications for HCT

- Myelodysplastic syndrome (MDS) – poor risk
- CML - accelerated phase, blast crisis, unresponsive to TKI

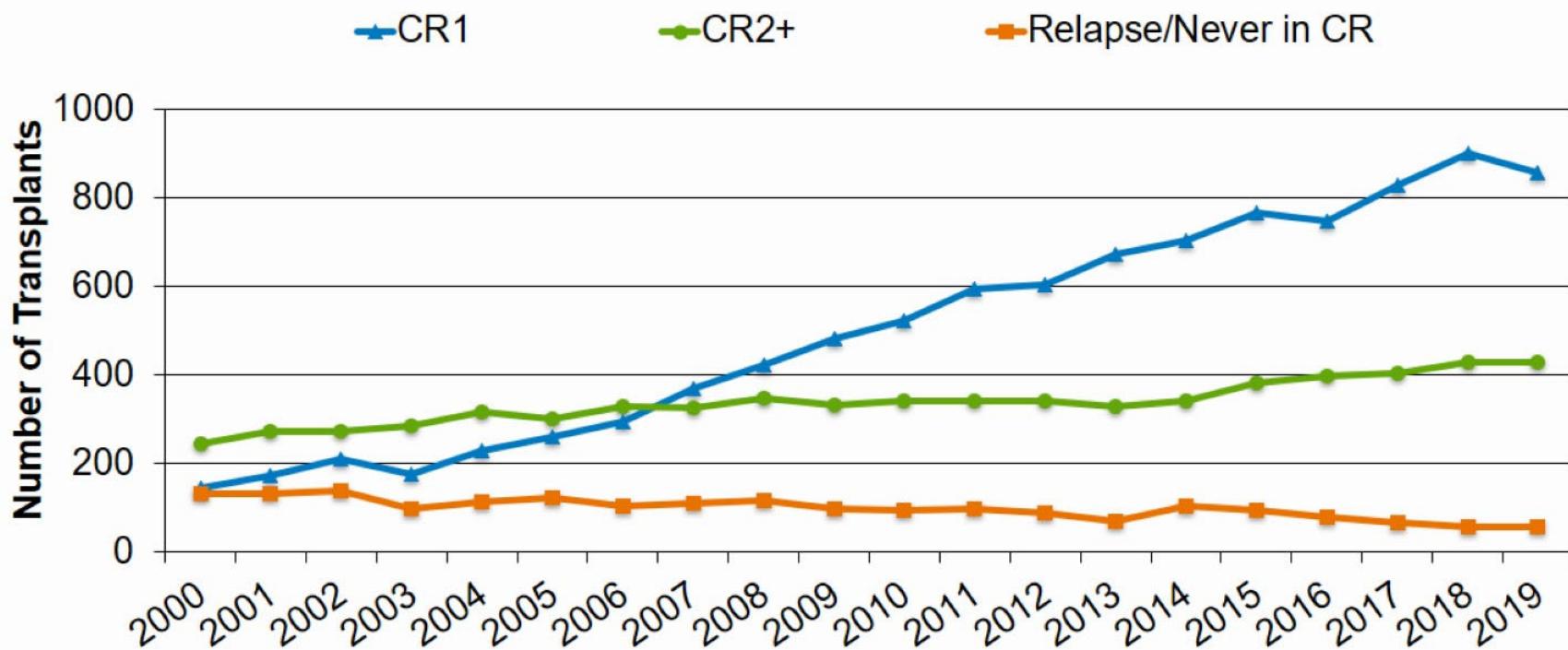
Indications for Hematopoietic Cell Transplant in the US, 2019



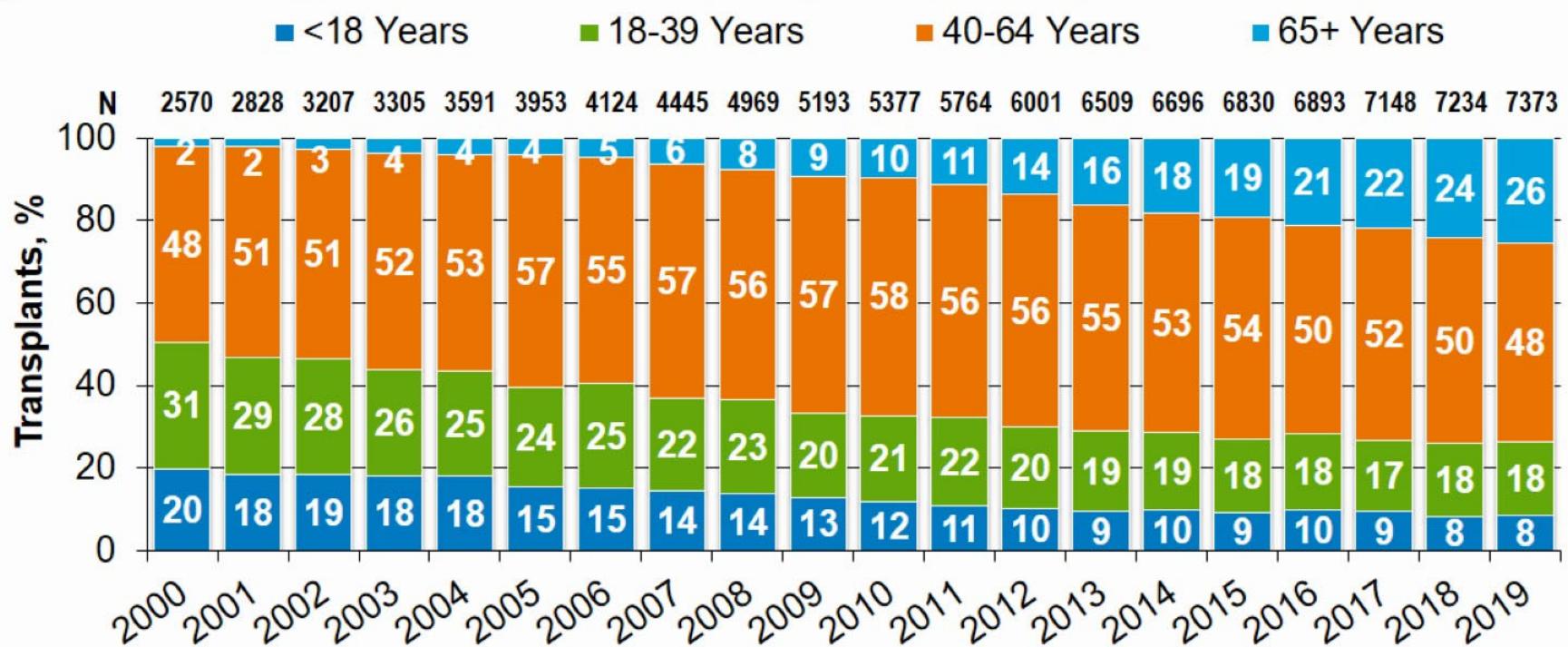
Trends in allogeneic HCT for Acute Myelogenous Leukemia (AML) by Disease Status in the US



Trends in allogeneic HCT for Acute Lymphoblastic Leukemia (ALL) by Disease Status in the US



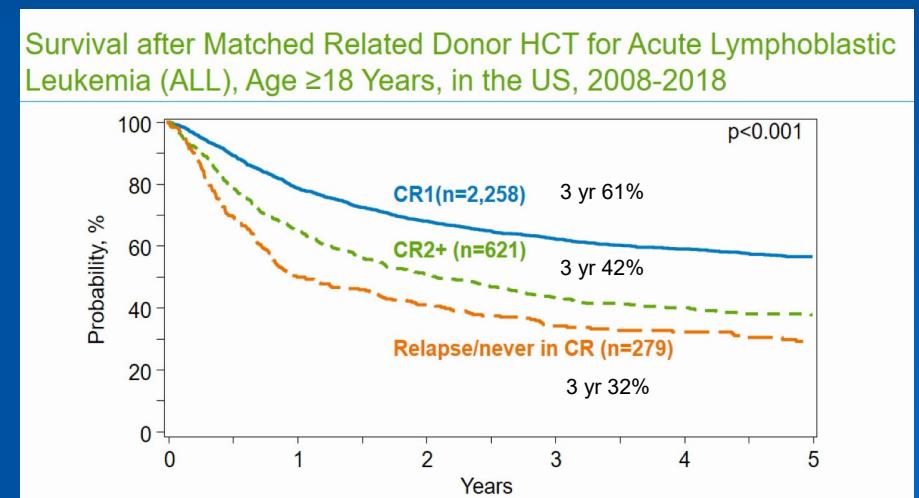
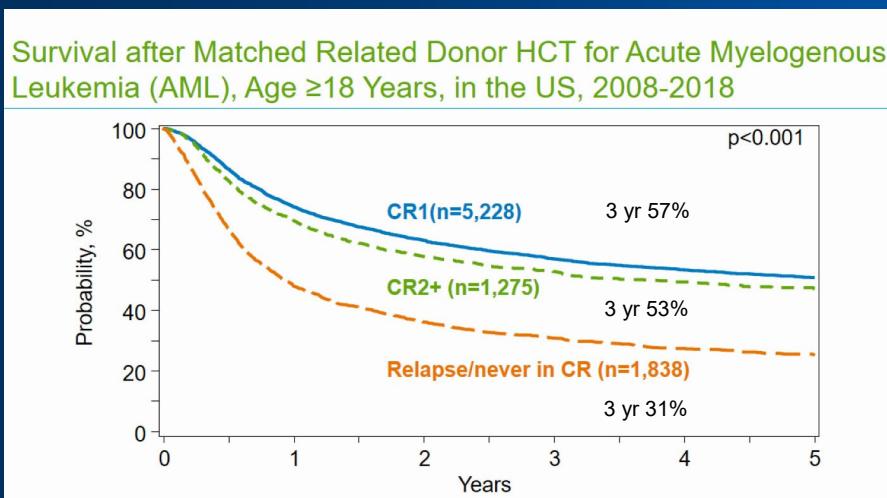
Trends in Allogeneic HCT in the US by Recipient Age[^]



Allogeneic HCT Conditioning Regimens

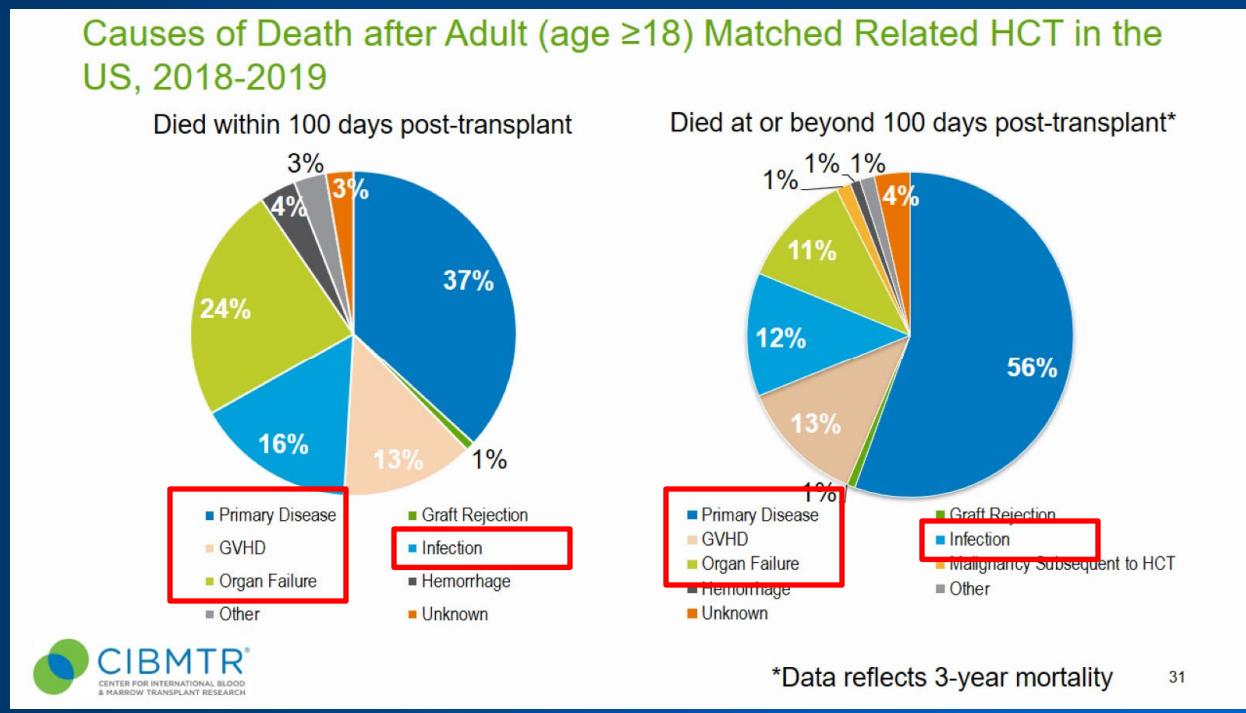
■ Myeloablative conditioning regimens (MAC)

- Eradicate malignant cells
- Immuno-suppression to facilitate engraftment
- Delivered in the week prior to HCT
- FTBI 10-16 Gy + chemotherapy (CT) (e.g. cyclophosphamide (Cy))
- Chemotherapy alone (e.g. busulfan (BU) and cyclophosphamide (Cy))



Allogeneic HCT Conditioning Regimens

- Myeloablative conditioning regimens (MAC)
 - Treatment related mortality (TRM) or non-relapse mortality (NRM) about 15-25%
 - Not used in older patients (> 60 years old) or those with co-morbidities



Allogeneic HCT Conditioning Regimens

- Reduced intensity conditioning regimens (RIC)
 - Reduced CT and RT doses
 - Fractionated TBI \leq 8 Gy
 - or single fraction TBI \leq 5 Gy
 - BU \leq 9 mg/kg, Melphalan $<$ 140 mg/m²
 - e.g. fludarabine (Flu) + melphalan (Mel)
 - Prolonged pancytopenia and HCT required
- Non-myeloablative regimens (NMA)
 - Sufficient immunosuppression for engraftment
 - Reversible pancytopenia
 - Low dose TBI (< 2 Gy) alone +/- Fludarabine
 - Flu + Cy +/- rituximab

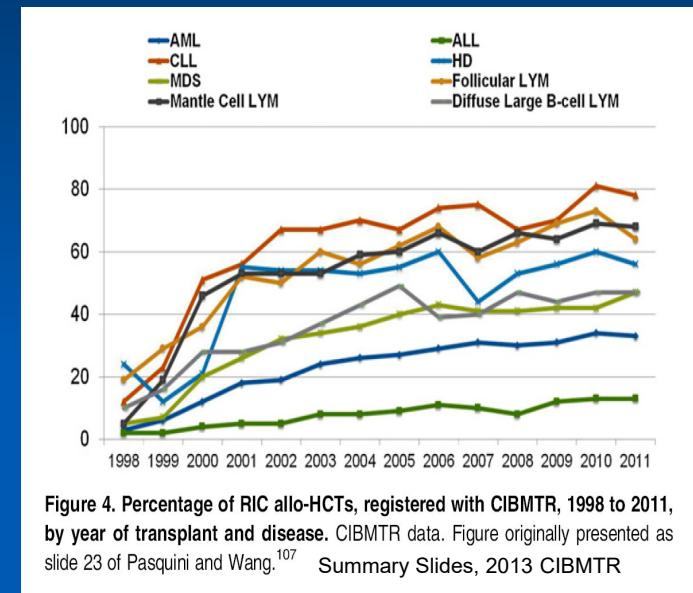
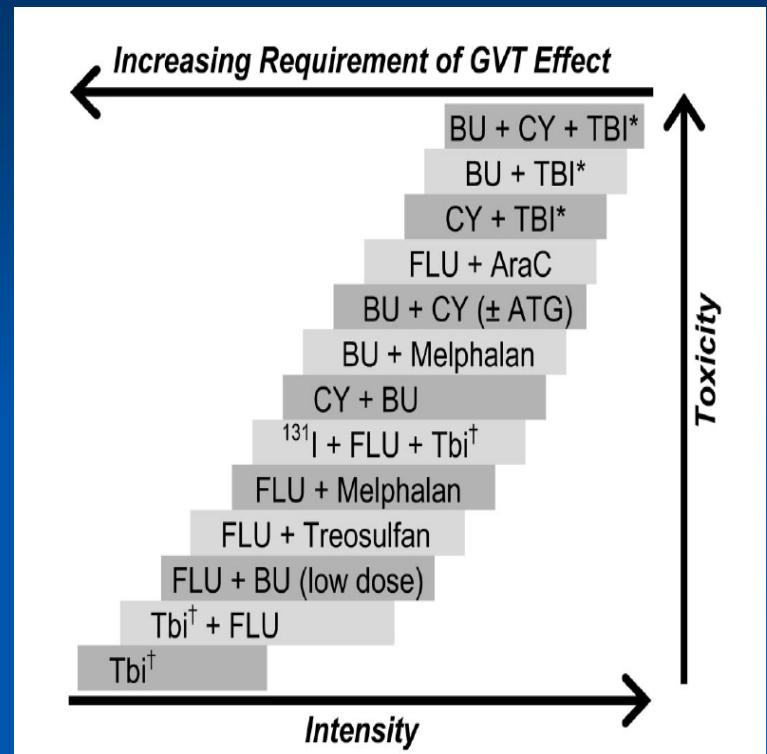


Figure 4. Percentage of RIC allo-HCTs, registered with CIBMTR, 1998 to 2011, by year of transplant and disease. CIBMTR data. Figure originally presented as slide 23 of Pasquini and Wang.¹⁰⁷ Summary Slides, 2013 CIBMTR

RIC and NMA Conditioning Regimens

- Better tolerated, reduced toxicities
- Offer HCT to more patients
 - Older (> age 55-60)
 - Co-morbidities, poor KPS
- Less myeloablative
- Greater reliance on graft versus tumor effects (GVT) for leukemia control
- ? Increased relapse rates



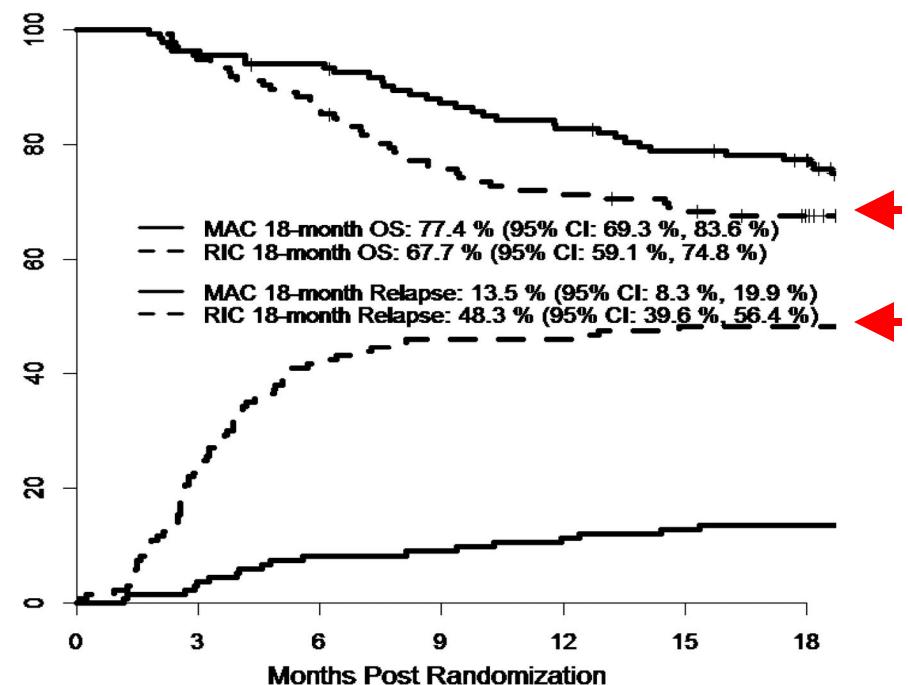
From Deeg and Sandmaier Blood 116: 4762-4770, 2010

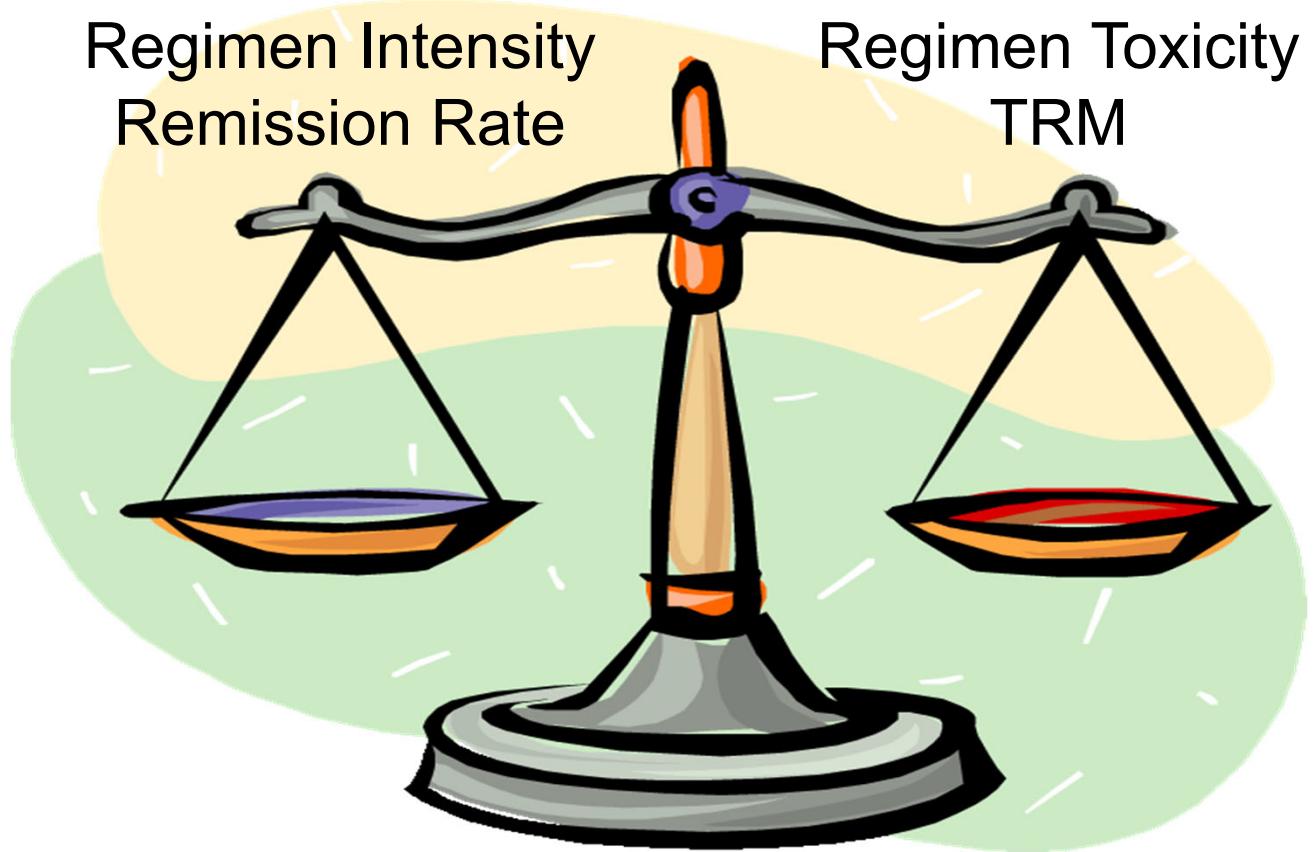
Phase III Randomized, Multi-Center Study of Allogeneic Stem Cell Transplantation after High (MAC) Versus Reduced Intensity Conditioning (RIC) in Patients with Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML): Blood and Marrow Transplant Clinical Trials Network (BMT CTN) 0901

- 272 patients AML (218), MDS (54)
- 18-65 yrs old
- CR1 (< 5 % marrow myeloblasts)

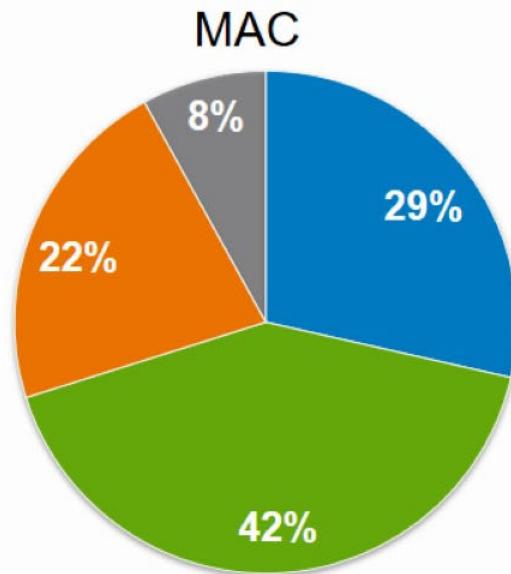
	MAC	RIC	P value
Regimen (n)	Bu/Cy (40) Bu/Flu (87) Cy/TBI (8)	Flu/Bu (110) Flu/Mel (27)	
TRM (95% CI)	15.8 (10.2-22.6)	4.4 (1.8-8.9)	0.02
Relapse (95% CI)	13.5 (8.3-19.9)	48.3 (39.6-56.4)	< 0.01
RFS (95% CI)	67.7 (59.0-74.9)	47.3 (38.7-55.4)	<0.01
OS at 18 months (95% CI)	77.4 (69.3-83.6)	67.7 (59.1-74.8)	0.07

OS and Relapse by Treatment Arm

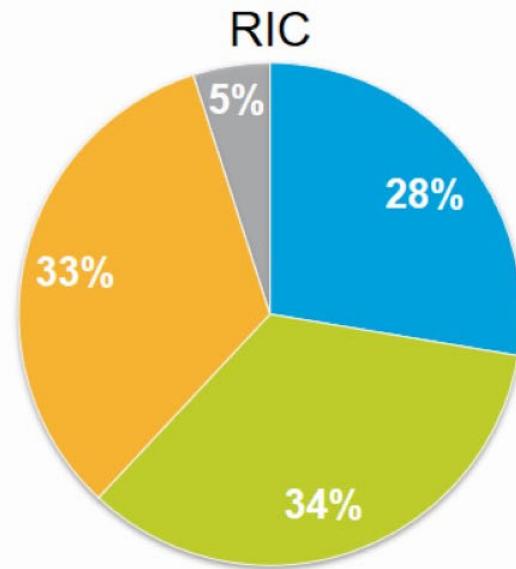




Common Conditioning Regimens in Acute Myelogenous Leukemia (AML) or Myelodysplastic Syndrome (MDS) Allogeneic HCT in the US, 2009-2019

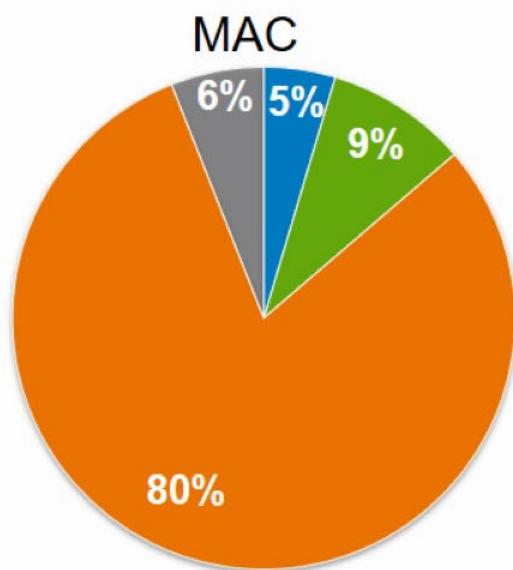


- MAC Bu+Cy+/-others
- MAC Bu+Flu+/-others
- MAC TBI+/-others
- MAC Others

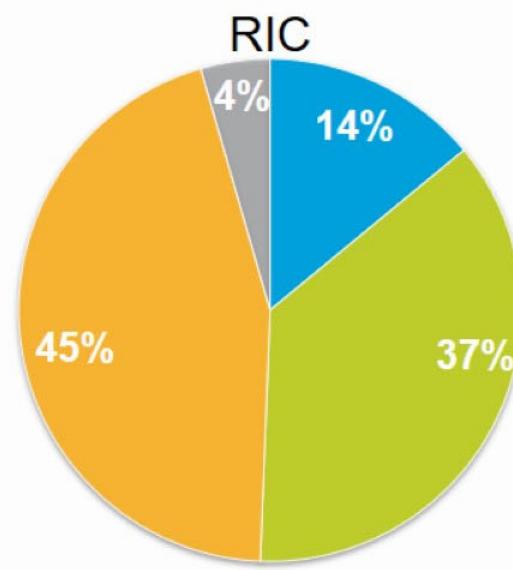


- RIC Bu+Flu+/-others
- RIC Flu+Mel+/-others
- RIC TBI+/-others
- RIC Others

Common Conditioning Regimens in Acute Lymphoblastic Leukemia (ALL) Allogeneic HCT in the US, 2009-2019



- MAC Bu+Cy+/-others
- MAC Bu+Flu+/-others
- MAC TBI+/-others
- MAC Others

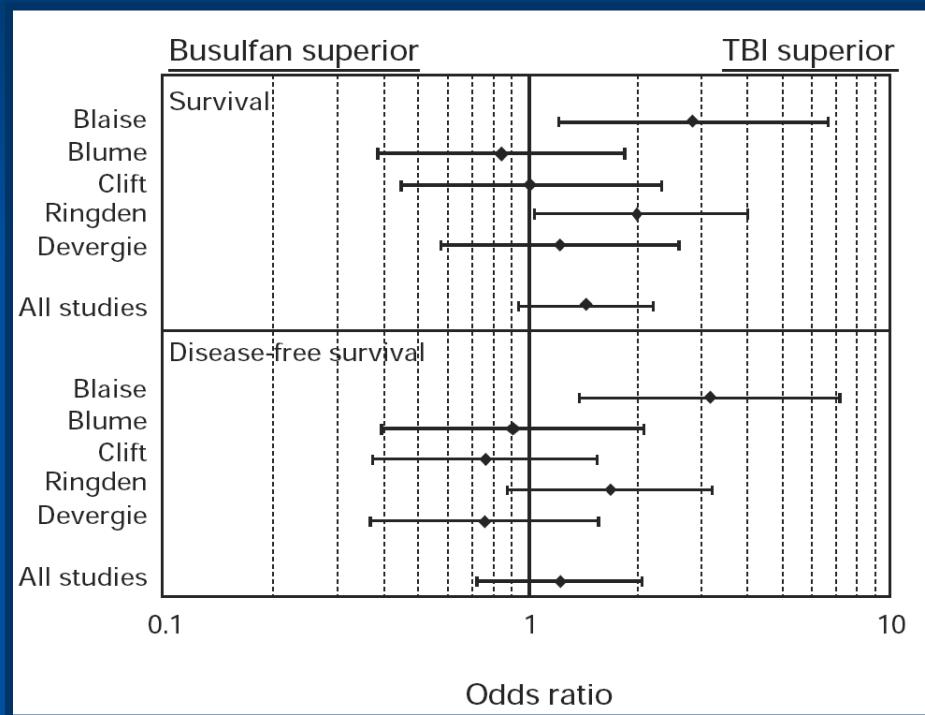


- RIC Bu+Flu+/-others
- RIC Flu+Mel+/-others
- RIC TBI+/-others
- RIC Others

TBI Remains an Important Part of AlloHCT Regimens

Meta-analysis of 5 RCT:
CY-TBI or VP16-TBI vs. BuCy

- Anti-leukemic effects
- Immunosuppressive effects
- Sanctuary sites
- Chemo-refractory disease
- Some early RCT suggest TBI-containing regimens are superior to chemotherapy in acute leukemia



Hartman et al, BMT 1998; 22: 439-43

Prospective cohort study comparing intravenous busulfan to total body irradiation in hematopoietic cell transplantation

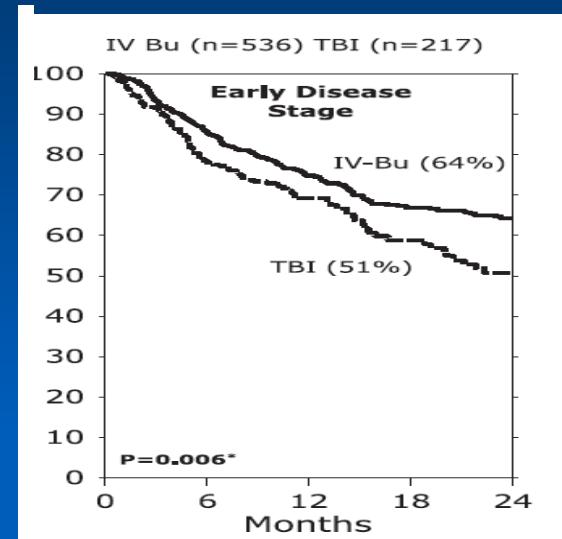
Blood 122: 3871-3878, 2013

Christopher Bredeson,¹ Jennifer LeRademacher,² Kazunobu Kato,³ John F. DiPersio,⁴ Edward Agura,⁵ Steven M. Devine,⁶ Frederick R. Appelbaum,⁷ Marcie R. Tomblyn,⁸ Ginna G. Laport,⁹ Xiaochun Zhu,² Philip L. McCarthy,¹⁰ Vincent T. Ho,¹¹ Kenneth R. Cooke,¹² Elizabeth Armstrong,³ Angela Smith,³ J. Douglas Rizzo,² Jeanne M. Burkart,² and Marcelo C. Pasquini²

- CIBMTR 120 center study
- 1483 patients, 2009-2011 (AML, CML, MDS)

	IV - BU	TBI
Patient No.	1025	458
AML (%)	68%	78%
2 yr OS	56%* (53-60%) *P = .019	48% (43-54%)
2 yr OS AML	57%* (53-61%) *P = .003	46% (40-52%)
100 day cum. incidence SOS	5%* (4-6%) *P < .001	1% (4-7%)
100 day cum. incidence IP	4% (2-5%)	6% (4-8%)
100 day cum. incidence renal failure requiring dialysis	6% (4-7%)	7% (5-10%)
2 yr cum. Incidence TRM	18% (16-21%)	19% (15-23%)

95 % confidence interval in parentheses



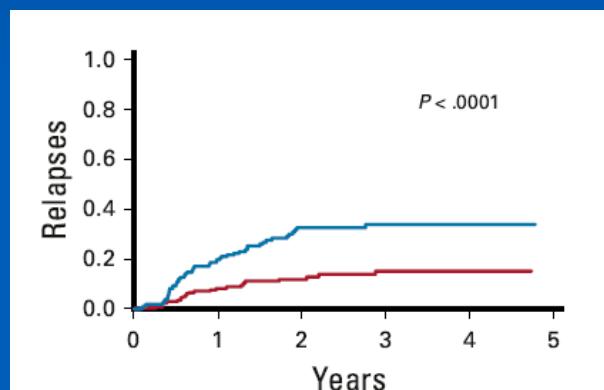
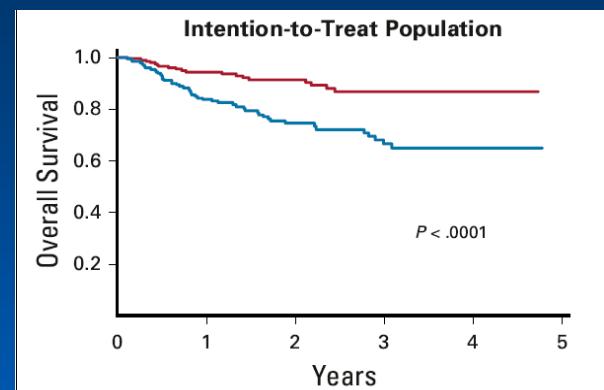
No survival differences in intermediate or advanced stage AML, CML, MDS

Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomized, Noninferiority Phase III Study

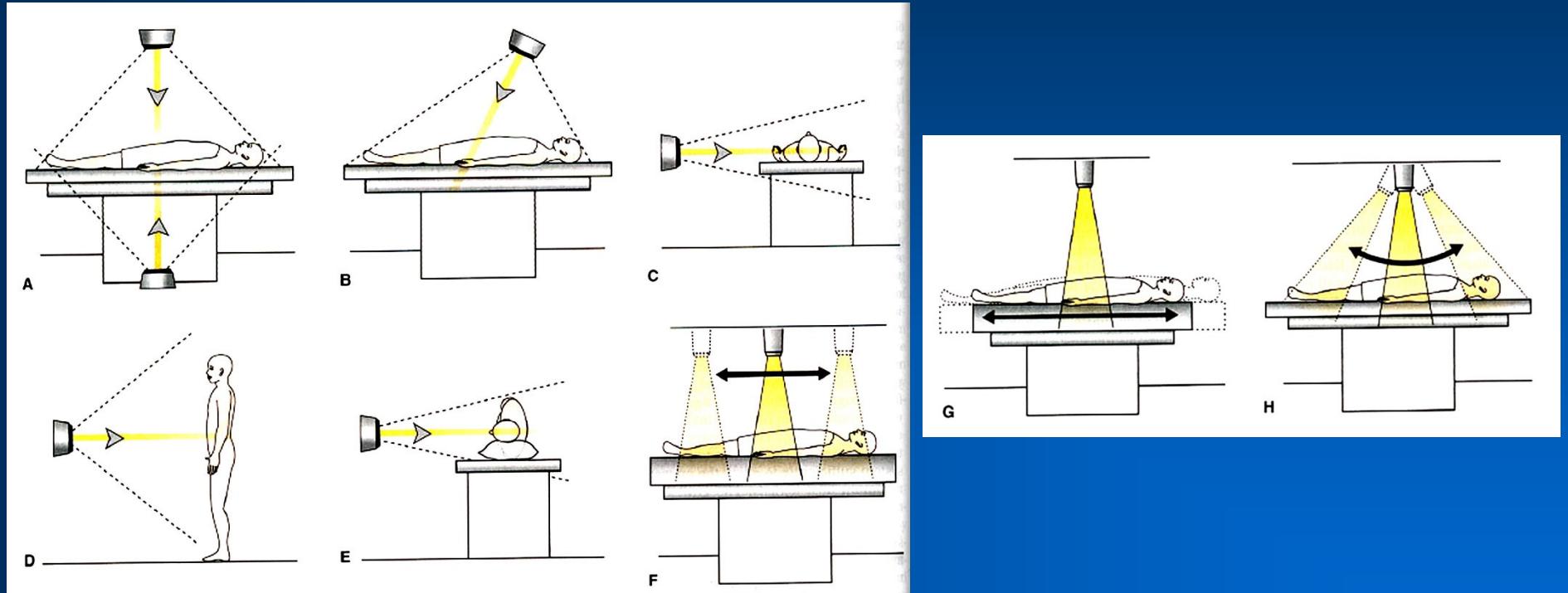
Check up

Peters et al., JCO 2020

- FORUM – phase III RCT multi-center, non-inferiority
- Patients with high risk ALL \leq 18 years at diagnosis (4-21 at HCT) in CR and with matched related or unrelated donor
- Randomized to either
 - 12 Gy TBI + etoposide
 - Fludarabine, thiotapec, and either busulfan or treosulfan
- Median follow-up 2.1 years
- Significant increase in 2 year OS with TBI (0.91 vs 0.75)
- Significant decrease in cumulative incidence of relapse (0.12 vs 0.33)
- No difference in treatment related mortality (TRM)

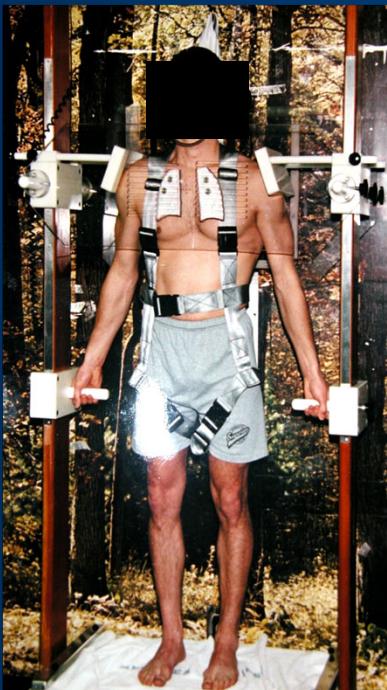


Total Body Irradiation (TBI)



Total Body Irradiation: Guidelines from
the International Lymphoma Radiation
Oncology Group (ILROG)

Vol. 101, Issue 3
Published online: May 2, 2018
[Full-Text HTML](#) | [PDF](#)



Total Body Irradiation (TBI)

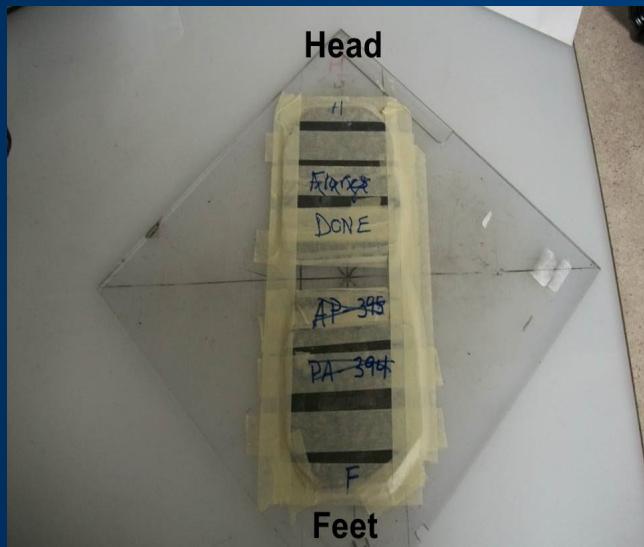
- Patient standing or lying
- Usually extended distance
- Usually between 6 and 10 MV
- Fractionated 10 – 16 Gy
 - 1.2 -1.35 Gy TID
 - 1.5 - 2 Gy BID
 - 3 - 4 Gy QD
- 5 - 6 hours between fractions
- Dose-rate 5 - 30 cGy/minute
- Single field, collimator rotated 45 degrees
- Lung shielding (8-10 Gy)
- Electron chest wall boost
- Some centers shield kidneys, liver, and/or previously irradiated sites
- 4 Gy testicular boost (used less especially pediatrics)
- Compensator for dose uniformity at midplane
- 1 inch Plexiglass spoiler to decrease skin sparing

Total Body Irradiation (TBI)



Patient on TBI stand relative to linear accelerator. A Plexiglas beam spoiler on a rolling stand (arrow) is positioned in front of the patient during treatment.

Total Body Irradiation (TBI)

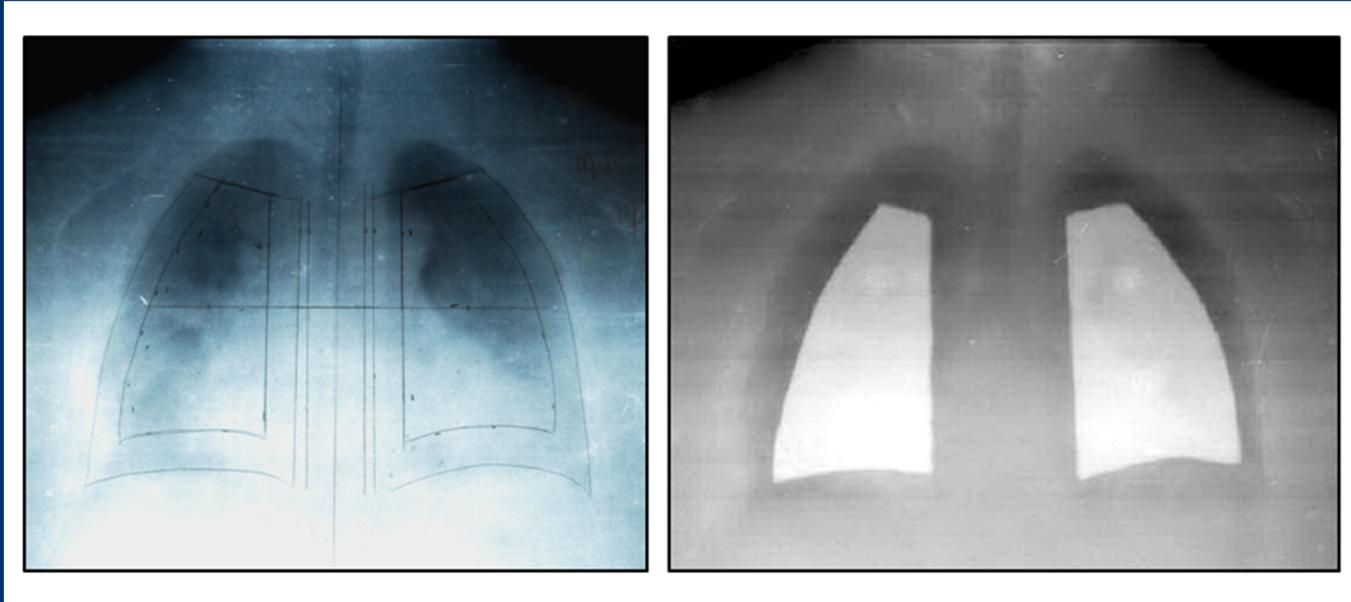


Measurements for planning purposes measure the thickness, distance from soles of the feet, and distance from central axis at the following anatomic points: top of head, forehead, chin, suprasternal notch, xiphoid, umbilicus, central axis, pelvis, thigh, knees, calf, ankle, and toes. Differences in separation along the patient's length can result in dose heterogeneity that can exceed 10-20%.

Construct a patient specific compensating filter constructed of thin lead sheets on a Plexiglas® which is inserted in the beam's path.

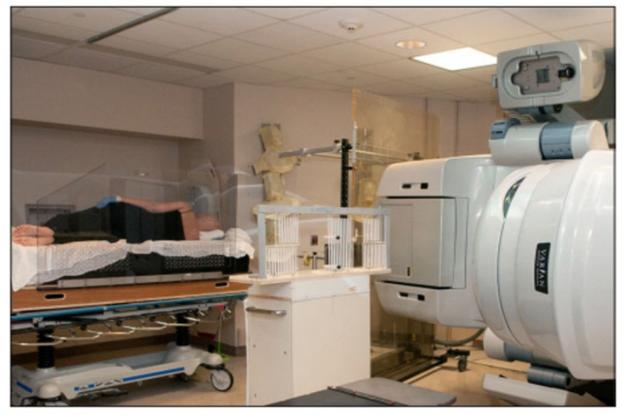
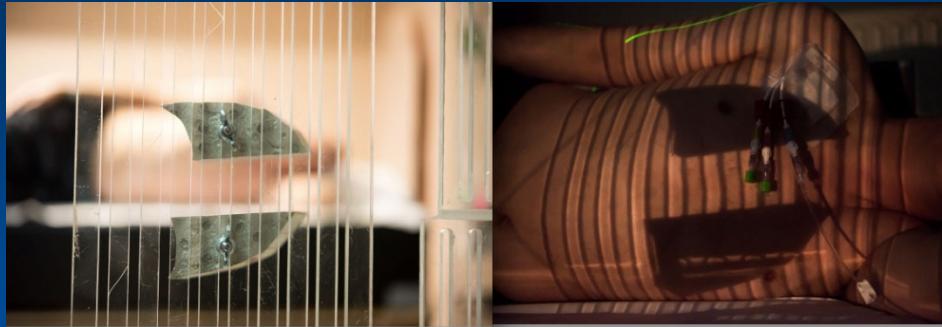
In vivo dosimetry should be performed to measure dose at several points on the patient's body with the goal of achieving a uniform dose within $\pm 5\%$.

Total Body Irradiation (TBI)



Lung blocks from planar images in the standing position. Typical margins used are 2 cm from the diaphragm and vertebral edge, 1.5 cm from the rib cage, and at the bottom edge of the clavicle. Lung blocks can be modified depending on the clinical circumstances. Left is the image used for block design. Right is a portal image for block placement verification.

Total Body Irradiation (TBI)



TBI delivery with the patient treated in the lying position on a gurney. Lung blocks and its reflections on skin

Toxicities - HCT Conditioning Regimens

Short-term Toxicities

- Nausea
- Vomiting
- Mucositis
- Esophagitis
- Enteritis
- Xerostomia
- Parotiditis

Long-term Toxicities

- Interstitial pneumonitis (IP)
- Sinusoidal obstruction syndrome (SOS)
(veno-occlusive disease of the liver)
- Nephrotoxicity
- Infertility
- Second malignancies
- Hypothyroidism and other endocrinopathies
- Short stature
- Cataract formation

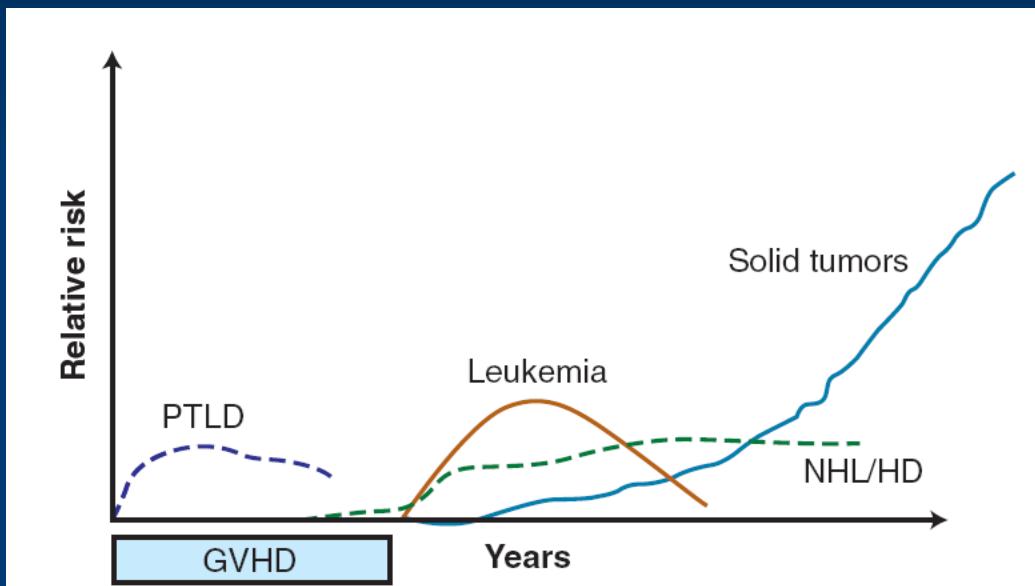


Figure 18-5 Relative risk and chronology of second malignant tumors after allogeneic hematopoietic stem cell transplant (HSCT). *GVHD*, Graft-versus-host disease; *HD*, Hodgkin disease; *NHL*, non-Hodgkin lymphoma.

Data from Ades L, Guardiola P, Socie G: Second malignancies after allogeneic hematopoietic stem cell transplantation. New insight and current problems. Blood Rev 16(2):135–146, 2002; Figure 1, © 2005, Elsevier, with permission from Elsevier.

Solid cancers after allogeneic hematopoietic cell transplantation

J. Douglas Rizzo,¹ Rochelle E. Curtis,² Gérard Socié,³ Kathleen A. Sobocinski,¹ Ethel Gilbert,² Ola Landgren,² Lois B. Travis,⁴ William D. Travis,⁵ Mary E. D. Flowers,⁶ Debra L. Friedman,⁶ Mary M. Horowitz,¹ John R. Wingard,⁷ and H. Joachim Deeg⁶

- Blood 113: 1175-1183, 2009;
- 28,874 alloHCT patients. Retrospective analysis CIBMTR and Seattle
- 67% received TBI

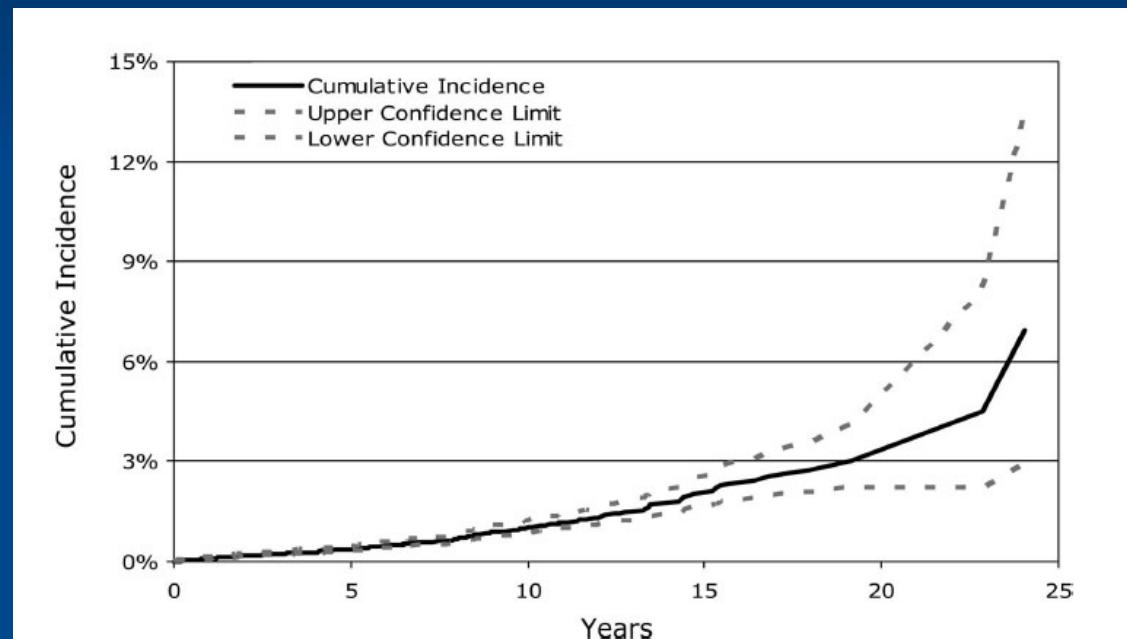


Figure 1. Cumulative incidence of second solid malignancies after allogeneic HCT.

Randomized Trials: Single Fraction vs. Fractionated

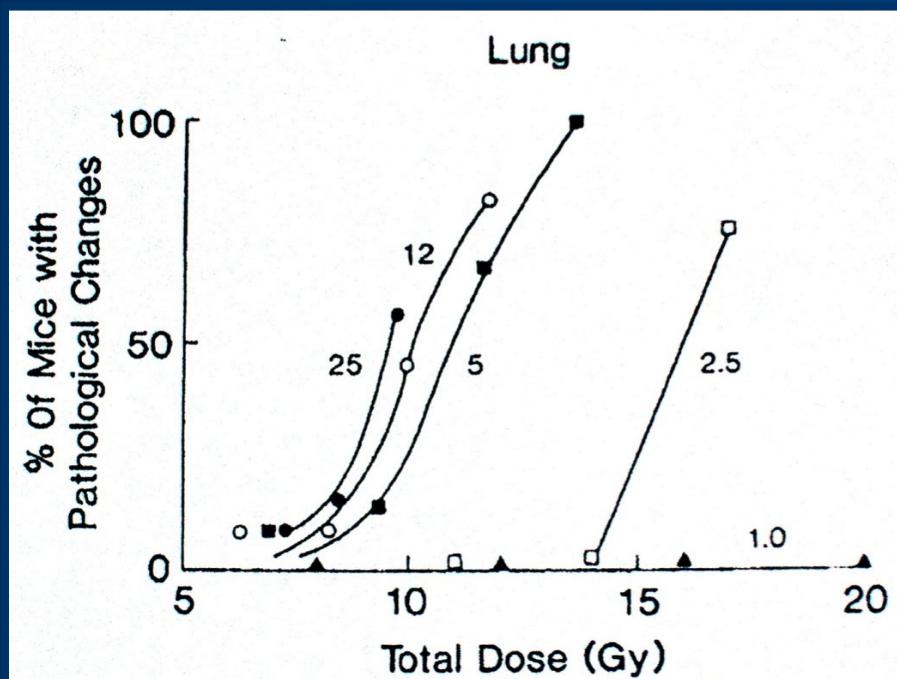
Study	Patient No.	Randomization	Survival	IP	SOS
Deeg, 1986 Seattle	53 AML CR1 1978-1980	<u>CY-TBI</u> <u>(no lung shielding)</u> 1. 10 Gy x 1	<u>5 yr OS (+ 95% CI)</u> <u>33 ± 31%</u>	11%	52%
		2. 12 Gy (2 Gy QD)	<u>54 ± 26% (p=0.04)</u>	4% (NS)	19% (p=0.02)
Girinsky 2000 France	147 ALL, AML, CML, LY, MM 1986-1994	<u>TBI-Cy or TBI-Mel</u> 1. 10 Gy x 1 (lung dose 8 Gy) 2. 14.85 Gy /1.35 TID (lung dose 9 Gy)	<u>8 yr OS / CSS</u> <u>38% / 63.5%</u> <u>45% / 77% (NS)</u>	19%	14%
				14% (NS)	4% (p=0.04)

Lung Shielding and Interstitial Pneumonitis (IP)

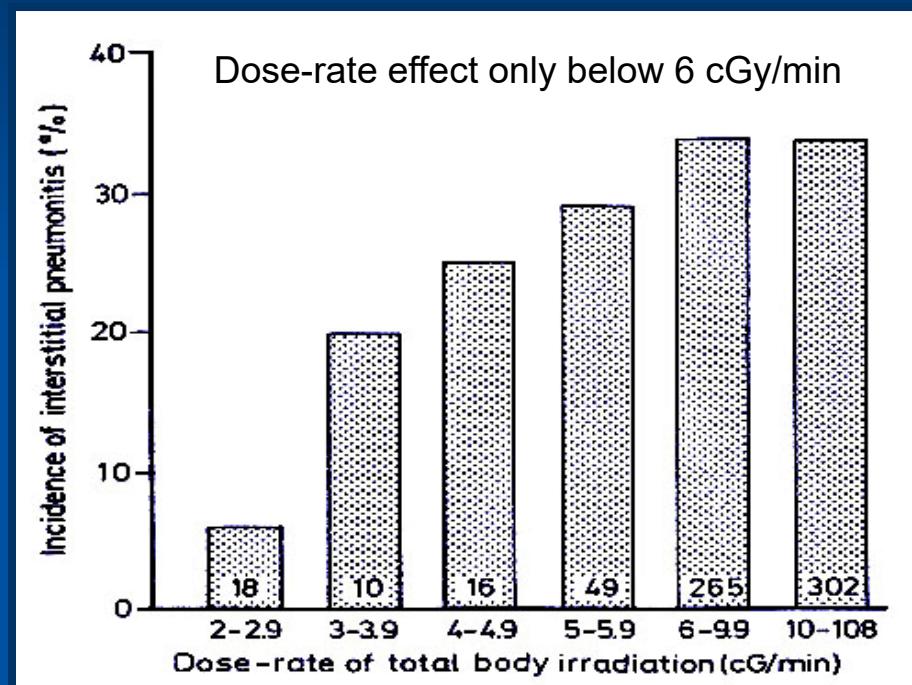
Study	No.	Comparison Groups	Survival	IP
Labar 1992 Croatia	64 AML, ALL, CML	<p><u>Randomized trial:</u> Cy-TBI 12 Gy (4 Gy QD)</p> <p>1. No lung shielding (33) (median lung dose 13.9 Gy)</p> <p>2. Lung shielding (31) (median lung dose 10 Gy)</p>	<p><u>3 year leukemia free survival</u></p> <p>54 ± 18%</p> <p>51 ± 18% (NS)</p>	<p>15 ± 14%</p> <p>5 ± 5% (NS)</p>
Shank 1983 MSKCC	96 AML ALL	<p><u>Historical control comparison</u></p> <p>1. Cy-TBI 8-10 Gy (single fx) No lung shielding (76 pts)</p> <p>2. TBI-Cy 13.2 Gy (1.2 TID) Lung shielding (~ 9 Gy) (20 pts)</p>	<p><u>AML 1 year OS</u></p> <p>17%</p> <p>61% (p<0.01)</p>	<p>70 %</p> <p>24%</p>

Dose-rate Effects

TBI at 1 – 25 cGy/minute



CIBMTR: N=932, 1978-83



Travis et al. Radiother Oncol 1985; 4: 341-351

Weiner et al, Ann Int Med 1986; 104: 168-75

Fractionation Reduces Dose-rate Effect

Mice - Upper Hemibody Irradiation
 $LD_{50/30-180}$ (95% CI)

Schedule	HDR 80 cGy/min	LDR 5 cGy/min
Single Fx	1299 (1263-1336)	2247 (2191-2307)
200 BID	2410 (2343-2477)	2842 (2783-2910)
120 TID	2817 (2713-2974)	2860 (2788-2939)

Tarbell et al., IJROBP, 13:1065, 1987

TBI + Cyclophosphamide: Radiation Pneumonitis

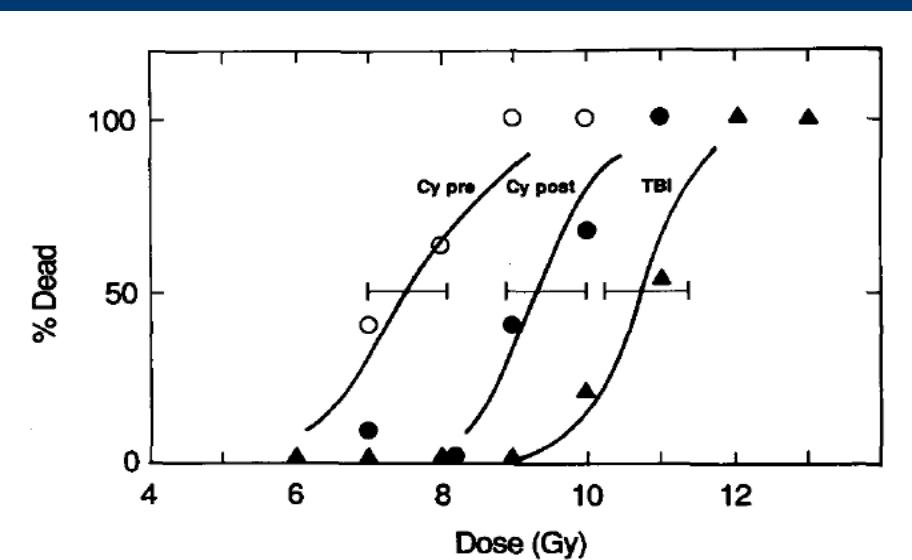
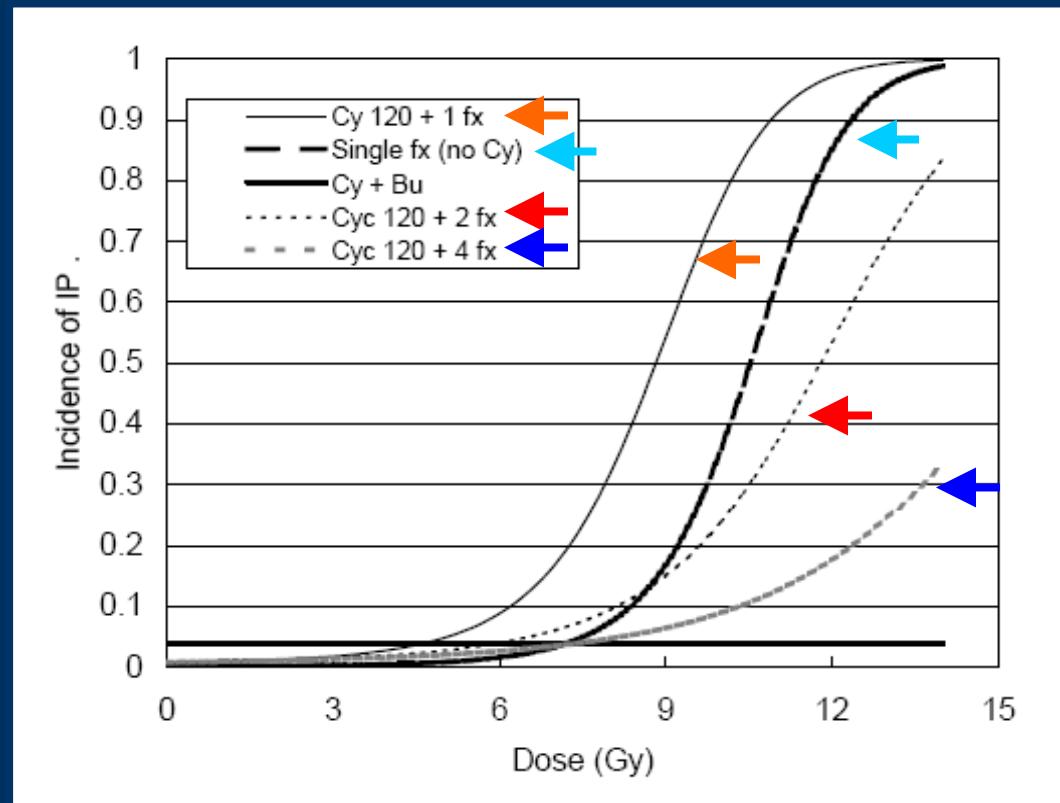


Fig. 3. Percent of animals dead from radiation pneumonitis as a function of single doses of total body irradiation (TBI) alone (\blacktriangle) or in combination with 180 mg/kg cyclophosphamide given either 24 h before irradiation (\circ), or 24 h after irradiation (\bullet). The curves were fitted by logit analysis. Error bars at the $LD_{50/30}$ s are 95% confidence limits.

Yan et al., Radiother. Oncol. 21:149, 1991

Pneumonitis: Dose, Chemotherapy, and Fractionation Effects

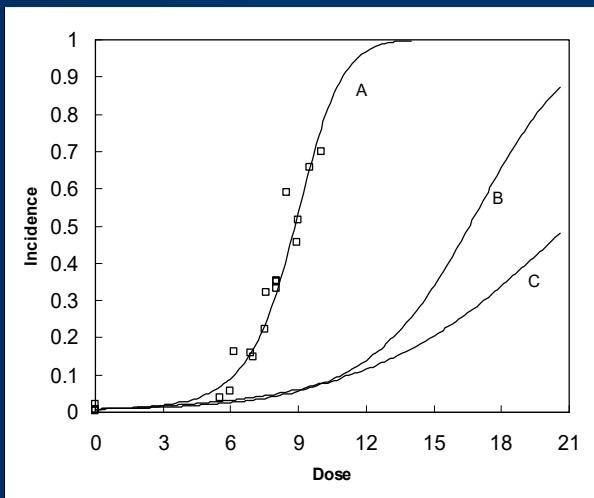


Sampath et al., IJROBP 63:876-884, 2006

- Retrospective review
 - 20 articles
 - 1090 patients
 - Multivariate logistic regression analysis
- Single or daily fraction TBI
 - Dose-response
 - Cyclophosphamide
 - No. of fractions
- No dose response for hyperfractionated TBI
- No dose-rate effect (3-41 cGy/min)

TBI Dose Response - Toxicities

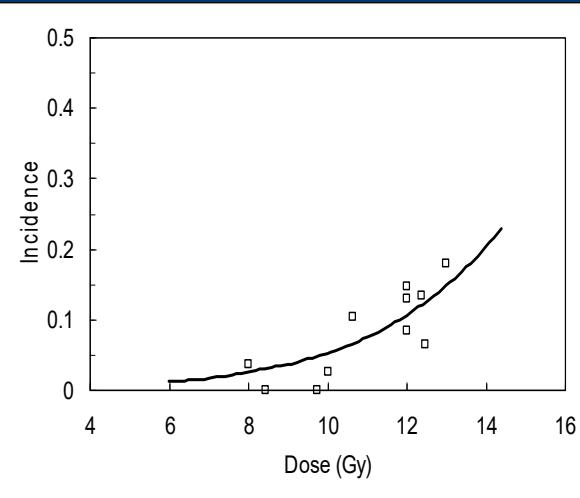
Pneumonitis



A) 1 fraction; B) 5 fractions; C)
2 Gy/ fraction

18 TBI regimens, 1090 patients,
multivariate logistic regression analysis
Sampath et al., IJROBP 63:876-884, 2006

Nephritis

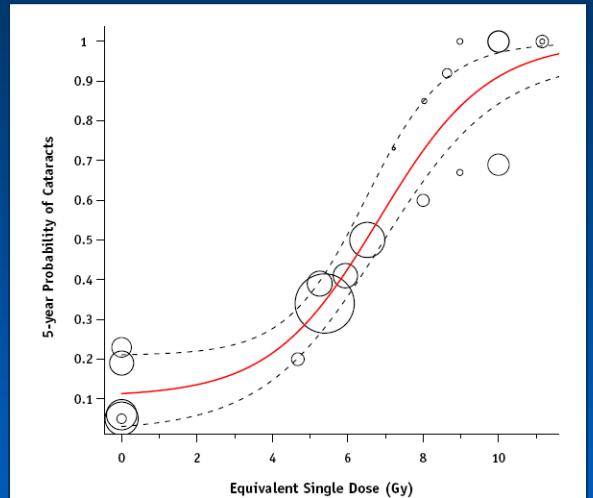


Equivalent dose in 2-Gy fractions

24 TBI regimens, 1108 patients,
multivariate logistic regression analysis

Cheng et al., IJROBP 71:1436-1443, 2008

Cataracts



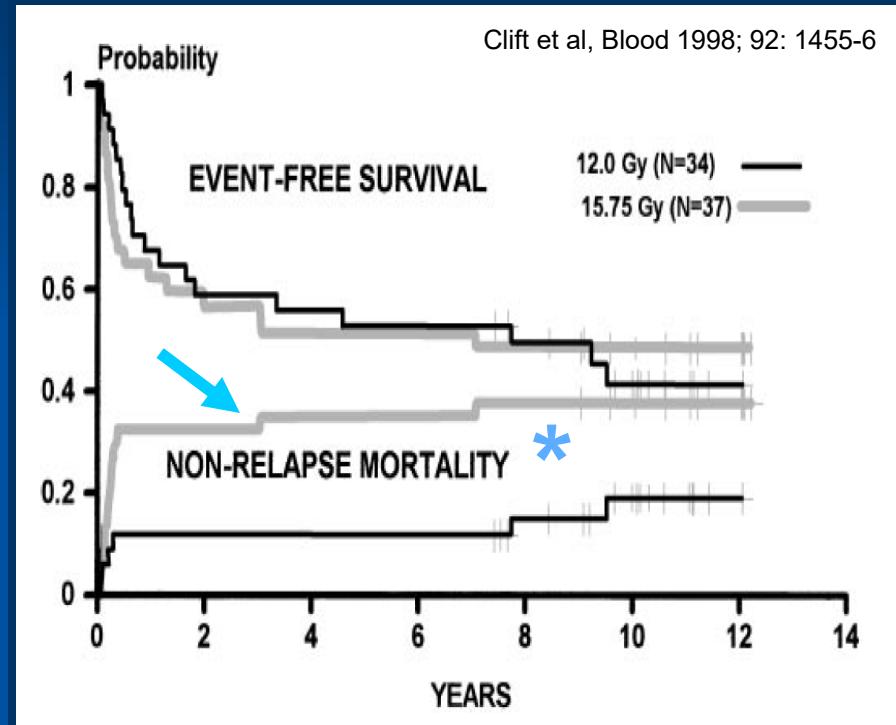
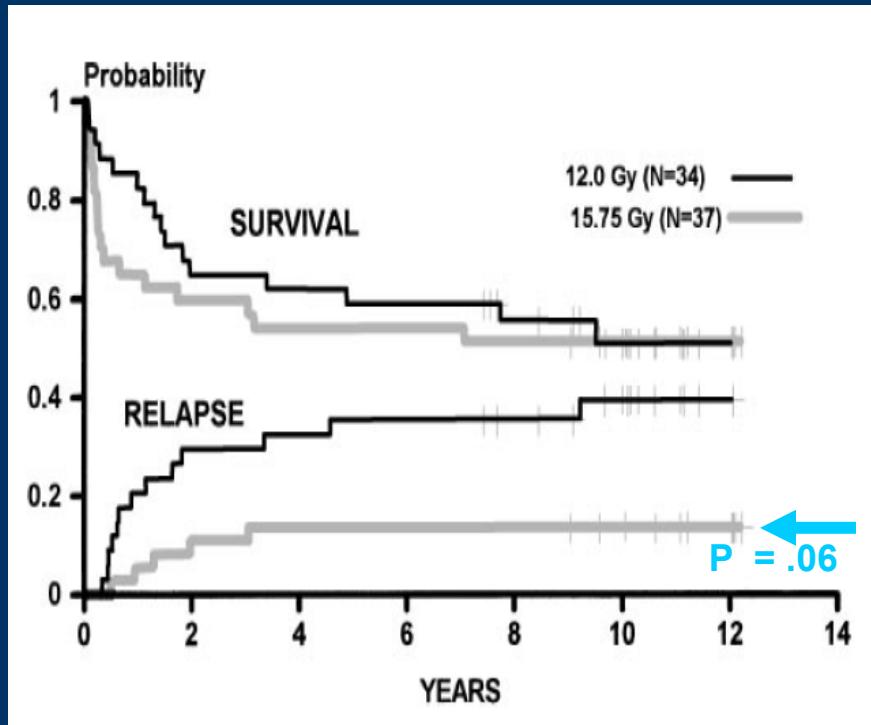
Single fraction. 5 year incidence.

13 TBI regimens, 1386 patients,
multivariate logistic regression analysis

Hall et al., IJROBP 91: 22-29, 2015

TBI Dose Response -1200 cGy vs. 1575 cGy

TBI (Dual Co⁶⁰ - no lung shielding) + CY AML CR1 (min 7.5 yr F/U)



* Increase in lung, liver and mucous membrane toxicities (Transplantation 54, 829, 1992)

Targeted TBI: Rationale

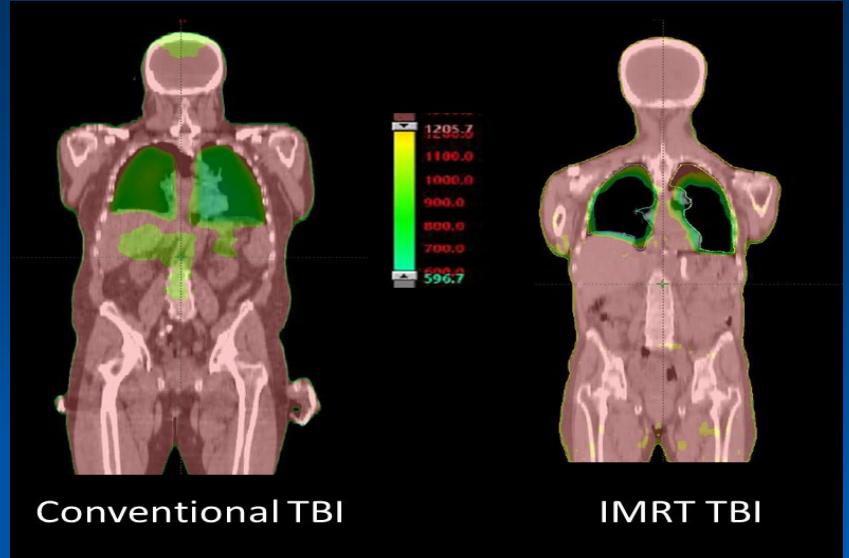
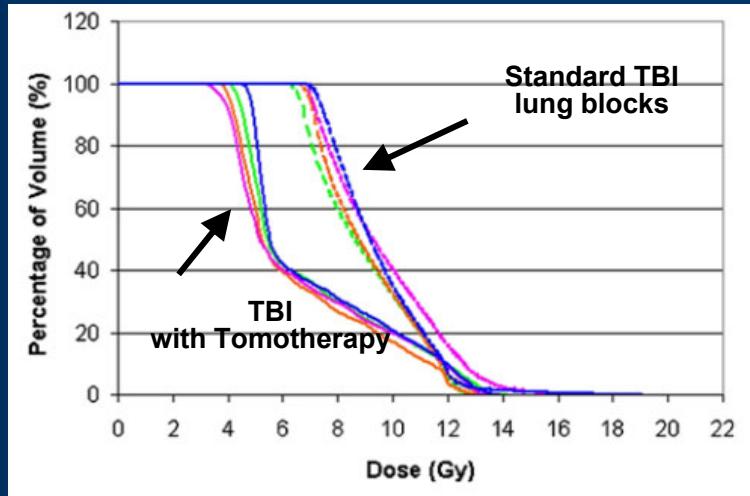
- Reduce acute and late toxicities
- Add myeloablative RT doses to established chemotherapy only regimens to potentially improve outcomes (MAC and RIC)
- Broader spectrum of patients unable to tolerate standard TBI regimens
 - Older patients, co-morbidities, poor performance status
 - Advanced refractory or relapsed disease where standard of care HCT options are unavailable or suboptimal
- Dose escalate to potentially reduce relapse rates without increasing toxicities
- Two approaches
 - Image guided – IMRT based (total marrow irradiation or TMI)
 - Biologically guided (radioimmunotherapy or RIT)

TMI: City of Hope

- Over 430 patients to date (first patient June 2005)
- Up to 2-3 patients/week
- 7 trials completed, 5 trials ongoing, 1-2 planned
- Multiple myeloma (high risk, progressive) in earlier trials
- Acute leukemia patient populations studied (> 390 acute leukemia)
 - Advanced relapsed/refractory acute leukemia (AML and ALL)
 - AML CR1 and CR 2 included in recent trials
 - Haplo-identical alloHCT
- Clinical regimens
 - TMLI containing myeloablative (MAC) regimens – younger patients (\leq 60 years)
 - TMLI added to established reduced intensity (RIC) – patients older 60 years or with co-morbidities
 - IMRT TBI to replace conventional TBI with lung and organ sparing (no dose escalation)

Institution NCT Trial No.	Type of Trial	Type of HCT	Disease Type	Targets	TMI Dose (Gy)	Fraction and Schedule	Chemo therapy
City of Hope (40) 00540995 IRB 05013	Phase I	allogeneic	AML relapsed or refractory with active disease Not eligible for standard HCT	bone, nodes, testes, spleen, 12 Gy liver, brain	12, 13.5	1.5 BID	BU 4800 uM*min VP16 30 mg/kg
City of Hope (18) 02446964 IRB 05021	Phase I	allogeneic	AML, ALL relapsed or refractory with active disease Not eligible for standard HCT	bone, nodes, testes, spleen, 12 Gy liver, brain	12, 13.5, 15, 16, 17, 18, 19, 20	1.5-2 Gy BID	Cy 100 mg/kg VP16 60 mg/kg
City of Hope 02094794 IRB 14012	Phase II	allogeneic	AML or ALL, IF, relapsed or > CR2	bone, spleen, node, 12 Gy liver, brain	20	2 Gy BID	Cy 100 mg/kg VP16 60 mg/kg
City of Hope 03467386 IRB 17423	Phase I	allogeneic	AML CR1 or CR2	bone, spleen, node, 12 Gy liver, brain	18, 20	2 Gy BID	Cy 50 mg/m ² /d x 2
City of Hope 02446964 IRB 14106	Phase I	allogeneic haplo- identical	AML, ALL, MDS CR1 high risk, CR2, CR3, refractory	bone, spleen nodes 12 Gy liver, spleen 16 Gy testes ALL 12 Gy brain ALL	12, 14, 16, 18 20	1.5-2 Gy BID	Flu 25 mg/m ² /d x 5 Cy 14.5 mg/kg/d x 2 ptCy 50 mg/kg/d x 2
City of Hope 04262843 IRB 19518	Phase II	allogeneic haplo- identical	AML: CR1 intermediate or poor risk In CR2 or CR3, with chemosensitive active disease; MDS int. and high risk categories	Bone, spleen, nodes, testes 20 Gy Liver, brain 12 Gy	20 Gy	2 Gy BID	Flu 30 mg/m ² /d x 3 (prior to TMLI) ptCy 50 mg/d x 2
City of Hope 00544466 IRB 04199	Pilot	allogeneic	Advanced disease > 50 yrs old or co-morbidities ineligible for standard myeloablative regimens	bone, nodes, spleen, ALL testes, brain	12	1.5 Gy BID	Flu 25 mg/m ² /d x 4 Mel 140 mg/m ²
City of Hope 03490569 IRB 17505	Phase I	allogeneic matched	AML, ALL, MDS > 55 yrs old or co-morbidities ineligible for standard myeloablative regimens	bone, spleen nodes 12 Gy spleen 16 Gy testes ALL	12, 14, 16, 18 20	1.5-2 Gy BID	Flu 30 mg/m ² /d x 3 Mel 100 mg/m ²
City of Hope 03490569 IRB 17505	Phase I	allogeneic haplo- identical	AML, ALL, MDS > 55 yrs old or co-morbidities ineligible for standard myeloablative regimens	bone, spleen nodes 12 Gy spleen 16 Gy testes ALL	12, 14, 16, 18 20	1.5-2 Gy BID	Flu 30 mg/m ² /d x 3 Mel 100 mg/m ² ptCy 50 mg/d x 2

IMRT TBI



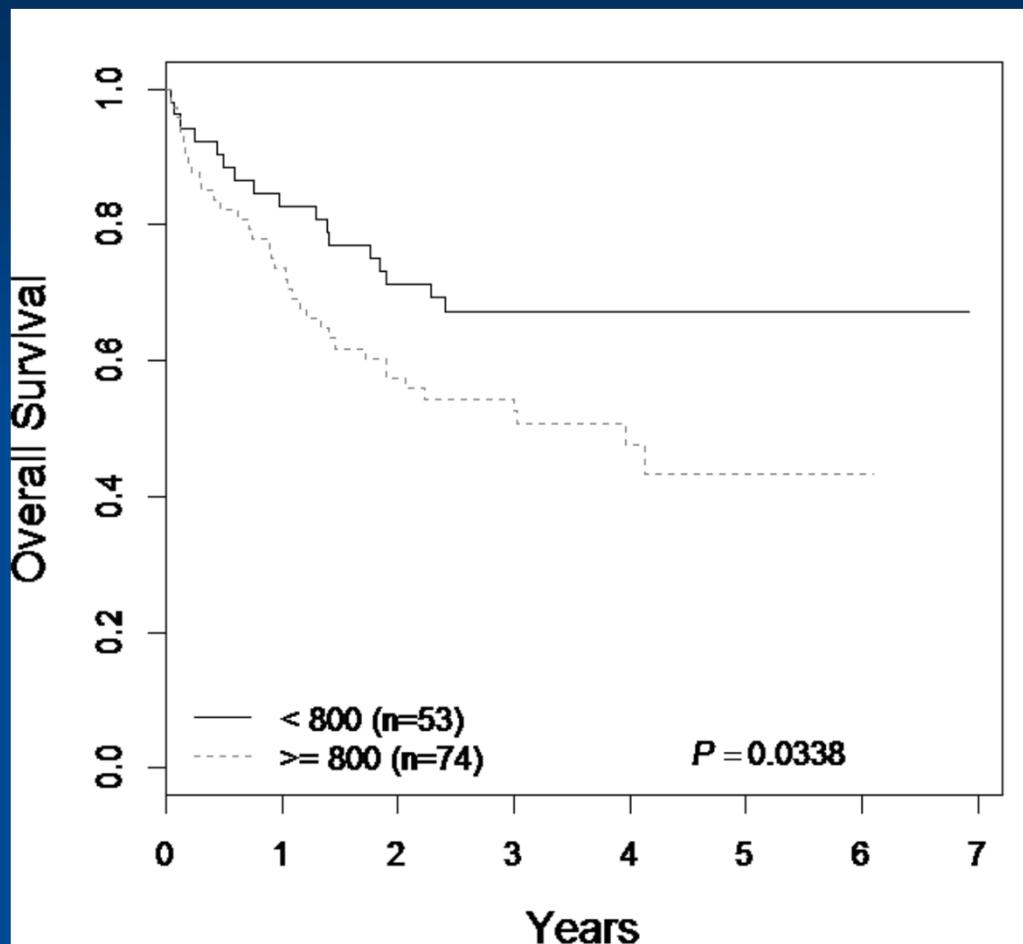
	Median Lung Dose (Gy) (n=4)
TBI 12 Gy with Tomo	5.40 ± 0.12
Standard TBI 12 Gy; lung blocks (1 HVL); eboost 6 Gy	8.95 ± 0.13 ($p < 0.002$)

Zhuang et al. IJROBP, 2009

Lancet Oncology October 2020

- Improved lung sparing
- Improved dose uniformity
- Patients with prior RT
- Patients unable to stand
- Increasing number of centers

Esiashvili, N., et al. (2015). "Association of higher lung dose received during total body irradiation for allogeneic hematopoietic stem cell transplantation in children with acute lymphoblastic leukemia with inferior progression-free and overall survival: A report from the Children's Oncology Group." Journal of Clinical Oncology 33(15_suppl): 10030-10030.

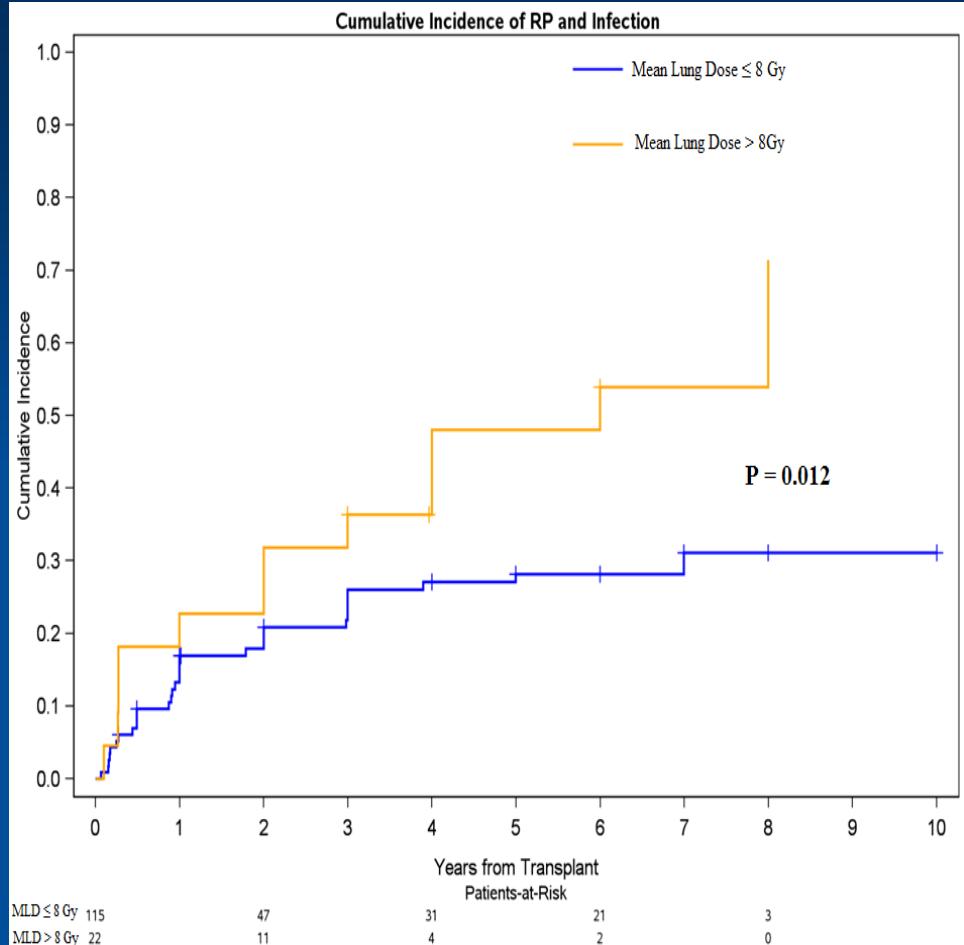


Prospective analysis of TMI/TMLI toxicity. Shinde et al, IJROBP 2020

A total of 142 patients were identified, with 74.6% being treated with allogeneic HCT, mostly for leukemia diagnoses. Median TM(L)I dose was 14 Gy (range 10-19 Gy).

Median follow-up was 2 years for all patients, 5.5 years for alive patients. Incidence of radiation pneumonitis (RP) was 1/142 (0.7%). Cumulative incidence (CI) of infection or RP (I/RP) was 22.7% at 2 years post TM(L)I.

Mean lung dose (MLD) < 8 Gy was identified as a parameter predicting for lower rates of I/RP (2-year CI 20.8% vs 31.8% if MLD ≥ 8 Gy, p=0.012).



TMI/TMLI - Summary

- Feasible with different technology platforms
- Pilot, Phase I, and Phase II trials (adult leukemia, multiple myeloma)
- Incidence of toxicities less than TBI (Shinde et al., IJROBP, 2020)
- No engraftment failure reported to date
- No increase in EM relapse compared to TBI (Kim et al. IJROBP, 2014)
- Higher dose-rate and organ sparing appear not to be adverse factors
- Myeloablative TMLI (12 Gy) added to RIC in older patients is feasible
- Dose escalation to 20 Gy safe and feasible with Cy/VP16 or Flu/Cy in younger patients
- Phase II results superior to published reports for R/R AML and ALL
- Number of centers involved increasing

Radioimmunotherapy: Acute Leukemia

Target	Disease	Expressed by
CD33	Myeloid leukemia	Promyelocytes to mature myeloid cells AML blasts (not ALL blasts) Not hematopoietic stem cells or ALL blasts
CD45	AML, ALL	Virtually all hematopoietic stem cells except plasma cells 90% of AML and ALL
CD66	AML, ALL	Mature myeloid and monocytic cells Not on AML blasts (relies on cross-fire effect)
CD22	ALL	B-cell acute lymphoblastic leukemia

Radionuclide	Particles emitted	Half life	Energy (MeV)	Path length	Comments
Iodine-131 (¹³¹ I)	β , γ	8.1 days	0.6	0.8 mm	dehalogenation
Yttrium-90 (⁹⁰ Y)	β	2.7 days	2.3	2.7 mm	goes to bone, liver
Rhenium-188 (¹⁸⁸ Re)	β , γ	17 hours	2.1	2.4 mm	goes to kidney
Bismuth-213 (²¹³ Bi)	α , γ	46 min	6.0	84 um	requires fast targeting
Actinium-225 (²²⁵ Ac)	α , γ	10 days	8	50-80 um	difficult to generate

Select HCT Trials Combining RIT with MAC or RIC

Author year	Antibody (target)	No.	Disease	HCT	Marrow dose (Gy)	Response	Toxicities
Burke 2003 Phase I	¹³¹ I-M195, Hu195 (CD33)	31	AML relapsed AML refractory CML-AP MDS advanced	Bu/Cy	2.72 - 14.7	3 CR 59+, 87+, and 90+ months	TRM 65%
Pagel 2006 Phase I/II	¹³¹ I-BC8 (CD45)	46	AML CR1	Bu/Cy	5.3 - 19 Mean 11.3	3 yr DFS 61%	3 yr TRM 21%
Pagel 2009 Phase I	¹³¹ I-BC8 (CD45)	58	AML advanced MDS high risk Age > 50	RIC: Flu+TBI (2Gy)	6.3 - 46.9 At MTD 36	1 yr OS 41%	1 yr TRM 22%
Mawad 2014 Phase I	¹³¹ I-BC8 (CD45)	58	AML advanced MDS high risk Age < 50	RIC: Flu+TBI (2Gy)	12 - 43.3 Mean 27	1 yr OS 73% 1 yr RFS 67%	1 yr TRM 0%
Koenecke 2008 Phase I/II	¹⁸⁸ Re-BW 250/183 (CD66)	21	AML high risk MDS advanced	Bu/Cy or RIC	4.95 – 21.3 Mean 10.9	DFS 43% median follow-up 42 months	1 yr TRM 28.6%
Ringhoffer 2005 Phase I/II	¹⁸⁸ Re- or ⁹⁰ Y-BW 250/183 (CD66)	20	AML, MDS Age 55-65	Flu + ATG or Mel	21.9 +/- 8.4	1 yr OS 70% 2 yr OS 52%	Cumulative TRM 25%
Lauter 2010 Phase II	¹⁸⁸ Re-BW 250/183 (CD66)	22	AML advanced Age > 54	RIC: Flu/Bu/ campath		2 yr OS 40% 2 yr DFS 41%	2 yr TRM 23%

Select HCT Trials Combining RIT and TBI (12 Gy)

Author year	Antibody (target)	No.	Disease	HCT	Marrow dose (Gy)	Response	Toxicities
Matthews 1999 Phase I	¹³¹ I-BC8 (CD45)	44	AML, ALL beyond first remission	CY/TBI (12 Gy)	4 – 31 24 at MTD	AML: 7/25 (28% NED 15-89 months ALL: 3/9 NED at 23, 58, 70 months	One engraftment failure at 31 Gy RIT + 12 Gy TBI
Bunjes 2002 Phase I/II	¹⁸⁸ Re-BW 250/183 (CD66)	57	High risk AML and MDS ≤ 25% marrow blasts	CY/TBI (12 Gy) TBI/Cy/TT By/Cy	15.5 +/- 5.1	DFS 54% ≤ 15% blasts DFS 64% (n=44) > 15% blasts DFS 8% (n=13)	14% late renal toxicity Radiation nephropathy in 6 4/6 > 12 Gy 26 month TRM 30%

Extra-Medullary Manifestations of Leukemia

Extra-medullary (EM) Manifestations of Leukemia

- Chloroma (granulocytic sarcoma or myeloid sarcoma)
 - EM immature myeloid leukemia cells in ~ 10% AML or CML-AP
 - Predates AML infrequently but will progress to BM involvement in months to a year after presentation.
 - Soft tissue, bone, nodes, gingiva, others
- Leukemia cutis

AML - Dose Response Effects

- Chloroma – (granulocytic sarcoma or myeloid sarcoma)
 - Extramedullary tumors consisting of immature myeloid cells
 - ~ 5% of AML patients usually with marrow involvement, CML, MDS
 - Indications for RT: poorly responding, progression, or relapse after chemotherapy; palliation of symptoms
- Chak et al. IJROBP 9: 1173, 1983
 - 33 patients, 54 courses RT
 - Recommend 30 Gy at 2 Gy/d
- Bakst et al. IJROBP 82:1816, 2012
 - 22 chloroma patients, 33 courses RT
 - Only 1 local failure (6 Gy)
 - Recommend at least 20 Gy at 2 Gy/fx and propose 24 Gy at 2 Gy/d

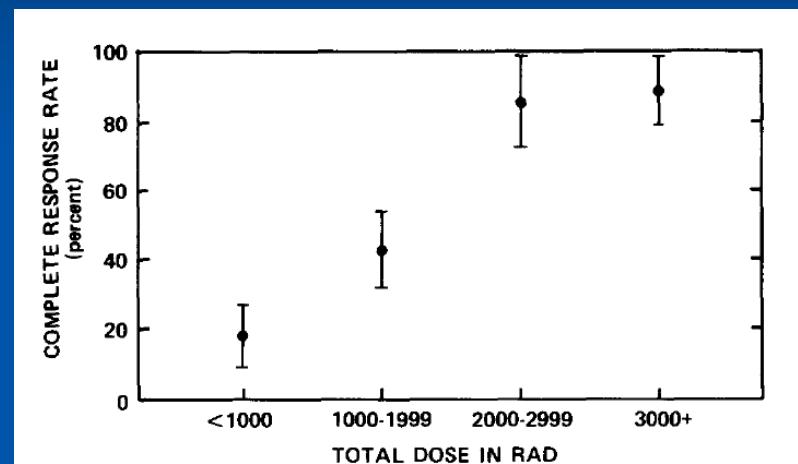


Fig. 2. Correlation of complete response rate to total dose of irradiation in extramedullary leukemic lesions. Error bars represent one standard deviation.

Extra-medullary (EM) Manifestations of Leukemia

- Indications for radiotherapy
 - Palliation of symptoms
 - Chemo-refractory disease
 - Disease reduction and control prior to transplant, including TBI regimens (12-14 Gy)
- Recommended dose 24 Gy at 2 Gy per fraction
 - Lower doses (2-20 Gy) can provide palliation if deliver of additional dose is limited

Extra-medullary (EM) Manifestations of Leukemia

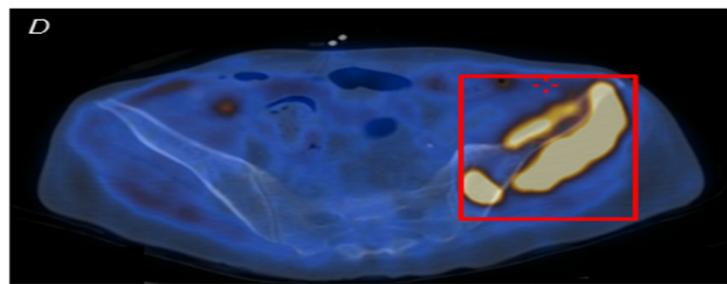
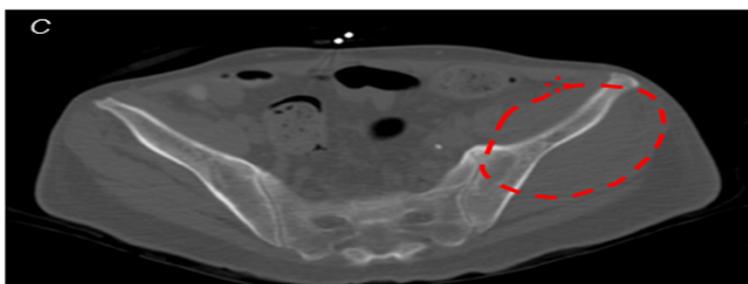


Figure 1. Clinical and radiographic appearance of chloroma. Chloroma in the oral cavity (A) and in the vulva (B). Chloroma in the left hemipelvis on (C) axial computed tomography imaging (dashed line) and (D) positron emission tomography.

Extra-medullary (EM) Manifestations of Leukemia

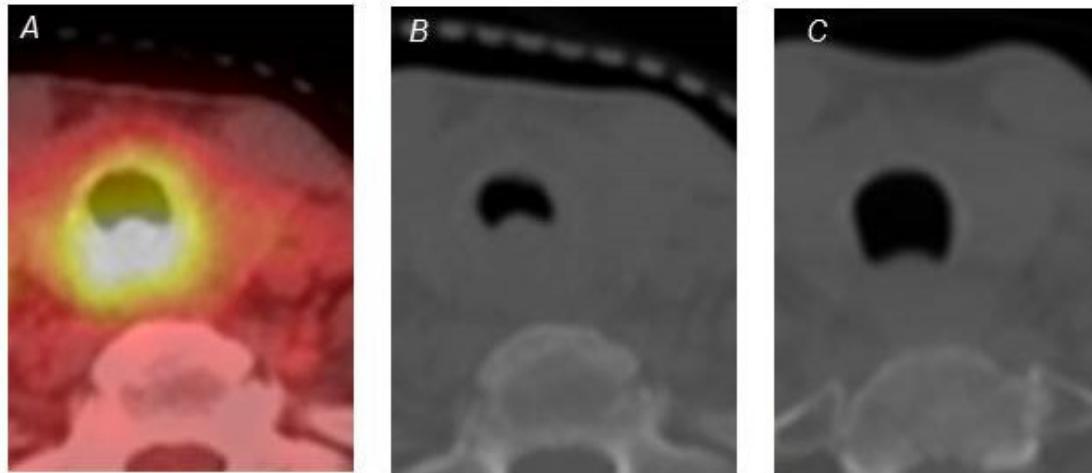


Figure 2. Rapid Response to Radiation. Clinical appearance of chloroma on PET (A) and CT (B) who was symptomatic with stridor who underwent 24 Gy with rapid symptomatic relief and radiographic response immediately following completion of radiation (C).

Extra-medullary (EM) Manifestations of Leukemia

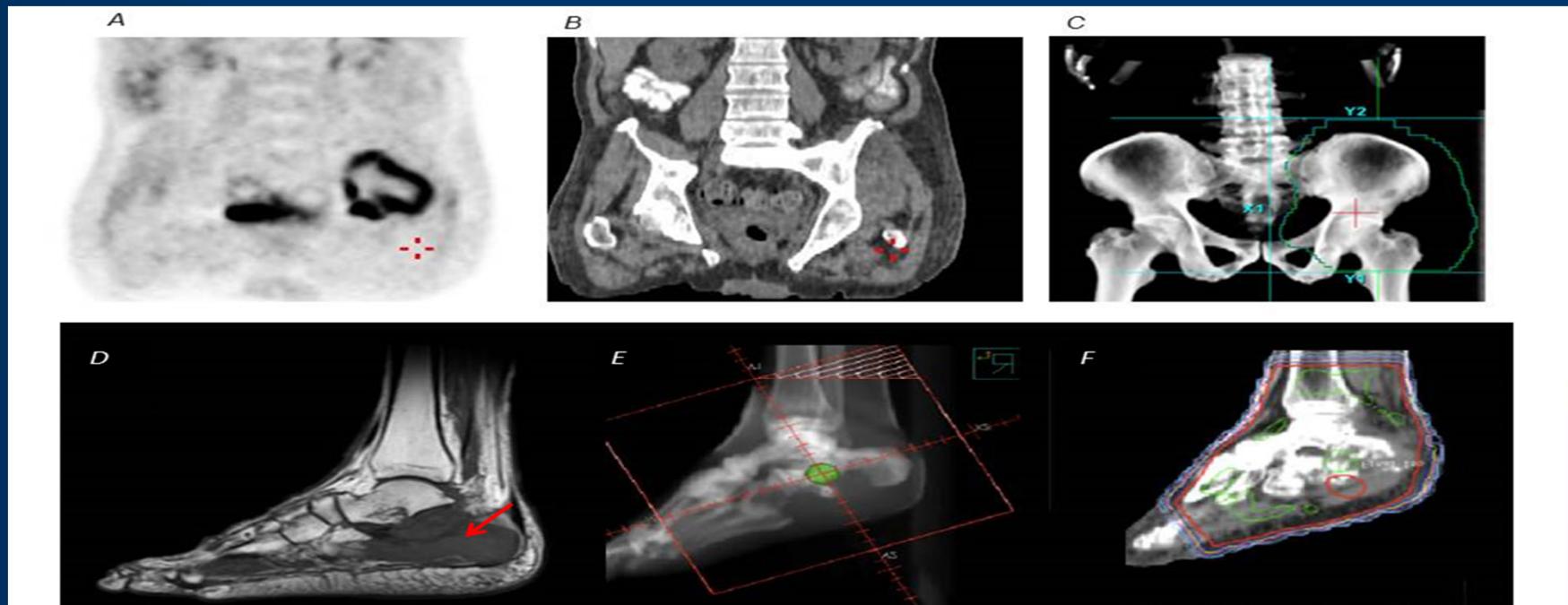


Figure 3. Radiation treatment field design. (A) Chloroma in the left pelvis on positron emission tomography and (D) coronal computed tomography imaging. (C) Radiation treatment field. (D) Chloroma in the calcaneus as seen on a T1 MRI (arrow). (E) Radiation treatment fields. (F) Dose distribution, red line represents 20 Gy isodose line.

Extra-medullary (EM) Manifestations of Leukemia

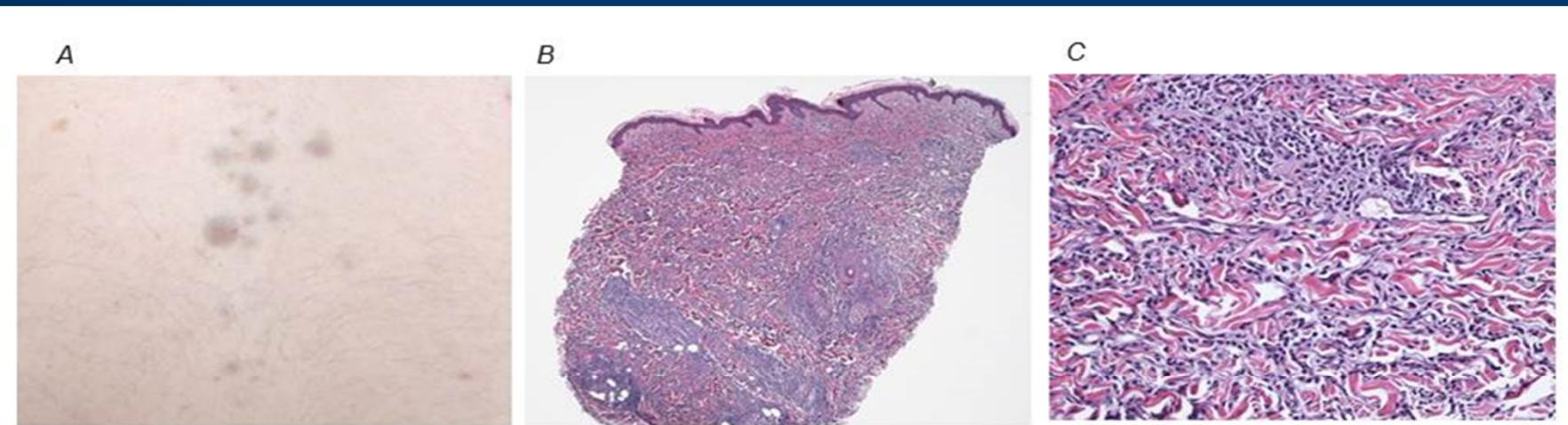


Figure 4. Leukemia cutis. (A) Clinical appearance of LC consisting of clustered indurated papules on the back of a patient with acute leukemia. (B) Hematoxylin and eosin staining of a skin biopsy demonstrating a dense monomorphic infiltrate involving the dermis on low power with sheets of atypical myeloid cell percolating between collagen bundles on high-power (C) consistent with LC.

CNS Leukemia

CNS Leukemia

- CNS involvement with AML uncommon (< 5%)
- Acute lymphoblastic leukemia
 - CNS involvement at diagnosis in 3-7%
 - Over 50% relapse in CNS if no CNS prophylaxis given
 - Systemic Ara-C and MTX and IT MTX effective at preventing CNS relapse
- Radiotherapy (18 Gy) no longer used routinely for CNS prophylaxis in patients with a negative history of CNS involvement

CNS Leukemia

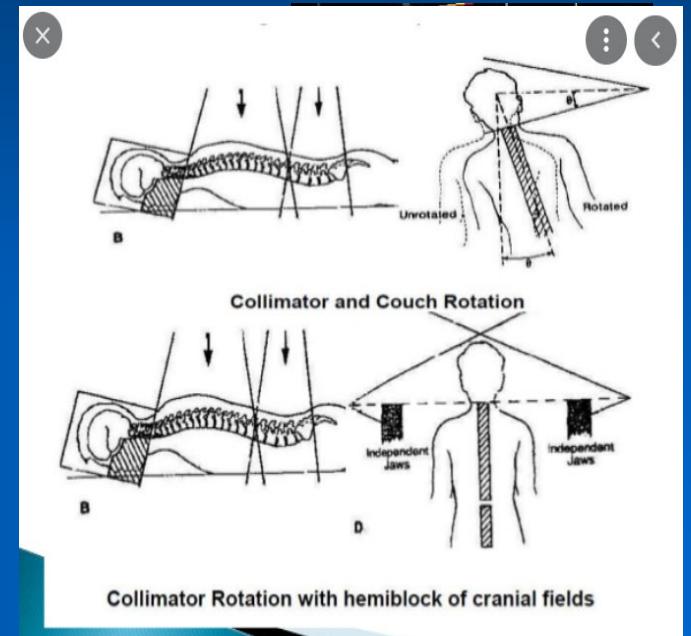
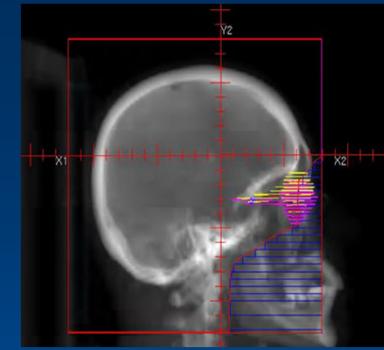
- Radiation therapy considered
 - CNS leukemia at diagnosis
 - CNS leukemia at relapse with systemic relapse
 - CNS leukemia isolated relapse with no systemic disease
 - Especially when other CNS directed therapy has failed.
 - Macroscopic disease on MRI
- For patients undergoing allogeneic HCT, radiation therapy to the CNS is indicated for patients with ALL or AML who have a history of CNS involvement
- Palliation of symptoms

CNS Leukemia

- WBRT 24 Gy
- CSI in select cases (18-24 Gy)
 - Concerns of disease control of chemo-refractory disease
 - CNS relapse and no myeloablative transplant planned
 - isolated CNS relapse
 - Higher tumor burden along spinal axis (MRI visible or symptomatic disease)
- Usually combined with systemic and IT chemotherapy
- Recommend a minimum interval of 48-72 hours (longer if possible) between the last IV or IT administration of methotrexate or Ara-C and initiation of CNS directed RT
- If FTBI to follow, subtract FTBI dose from total planned dose

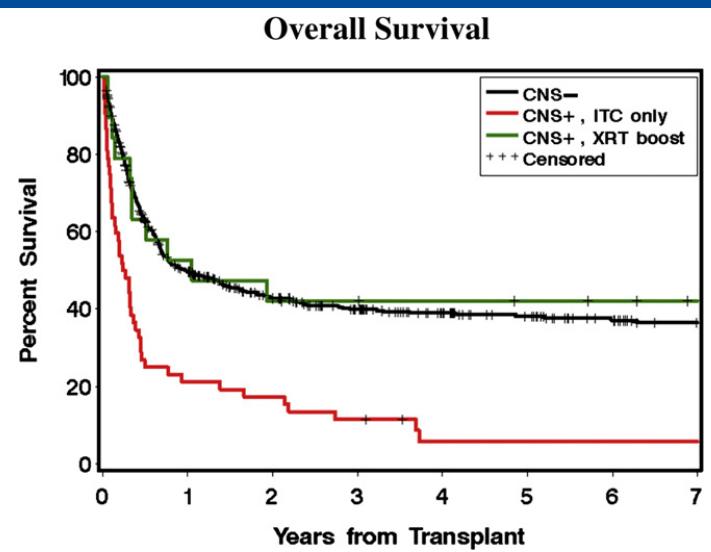
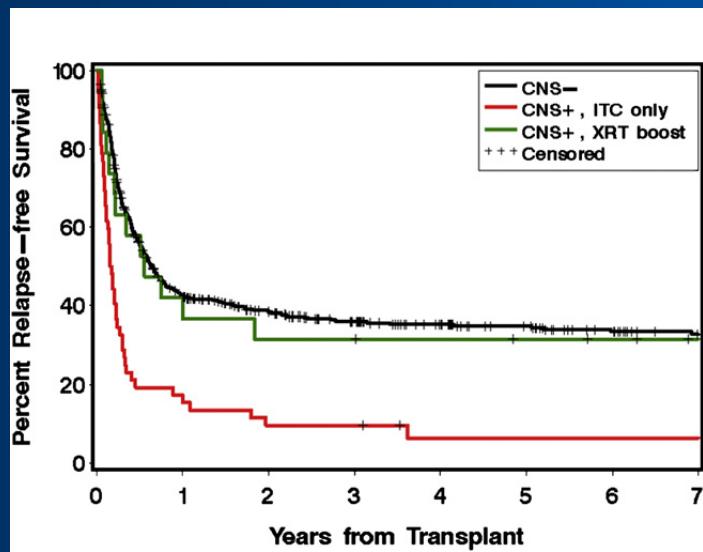
CNS Leukemia

- Cover posterior orbits
- Cover cribriform plate
- Match at bottom of C2
- Correct for beam divergence
- Non-diverging edge at bottom of brain fields
- Collimator rotation of brain fields to match divergence of PA spine field
- Gap to a point anterior to the spinal cord
- Prone to minimize neck curvature at match point
- Feather junction at least 2-3 times during course



IMPACT OF CRANIAL IRRADIATION ADDED TO INTRATHECAL CONDITIONING IN HEMATOPOIETIC CELL TRANSPLANTATION IN ADULT ACUTE MYELOID LEUKEMIA WITH CENTRAL NERVOUS SYSTEM INVOLVEMENT

- Mayadev et al. IJROBP 80: 193-198, 2011 Seattle retrospective study
- 648 adult AML undergoing HCT: TBI 58% CNS – and 86% CNS +)
- 577 CNS -, 52 CNS + ITC, 19 CNS + ITC and RT



Comprehensive Craniospinal Radiation for Controlling Central Nervous System Leukemia

- Walker et al. IJROBP 90: 1119-1125, 2014 MDAH retrospective study
- 163 patients with CNS leukemia (ALL, AML, CML, CLL)
- RT BOS (29%) WBRT (41%) CSI (29%). IT chemotherapy in 88%

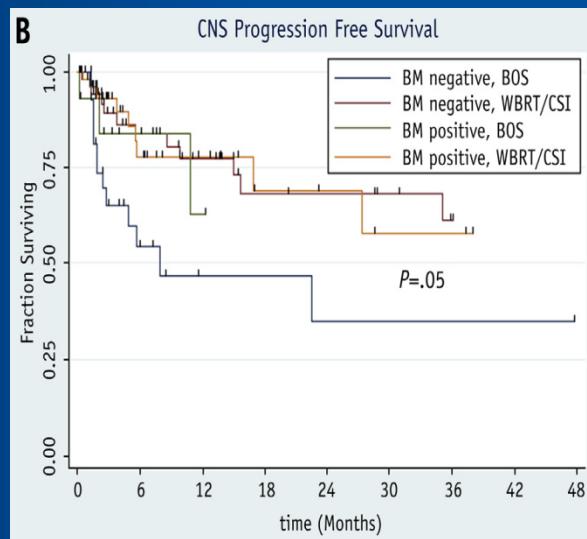
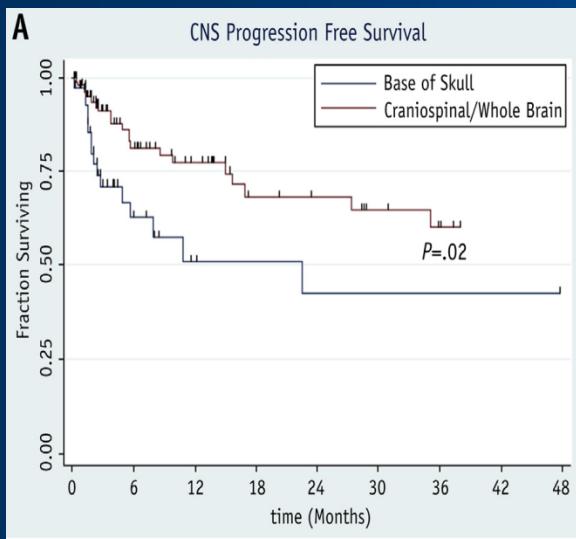
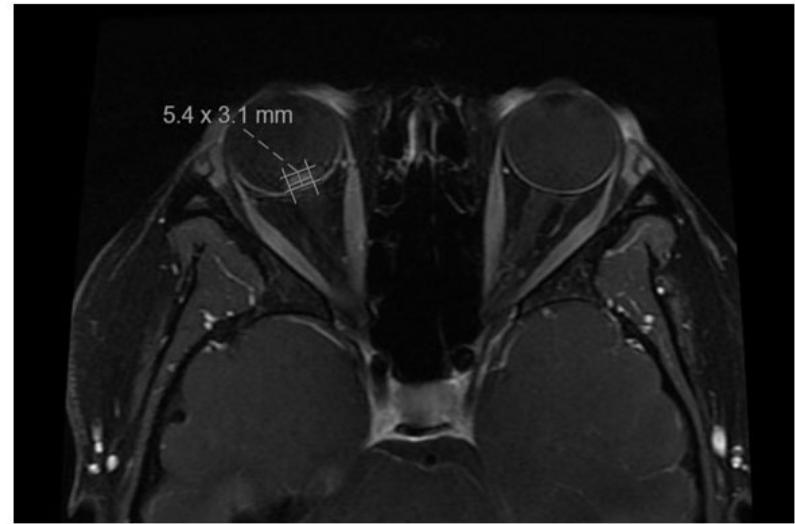
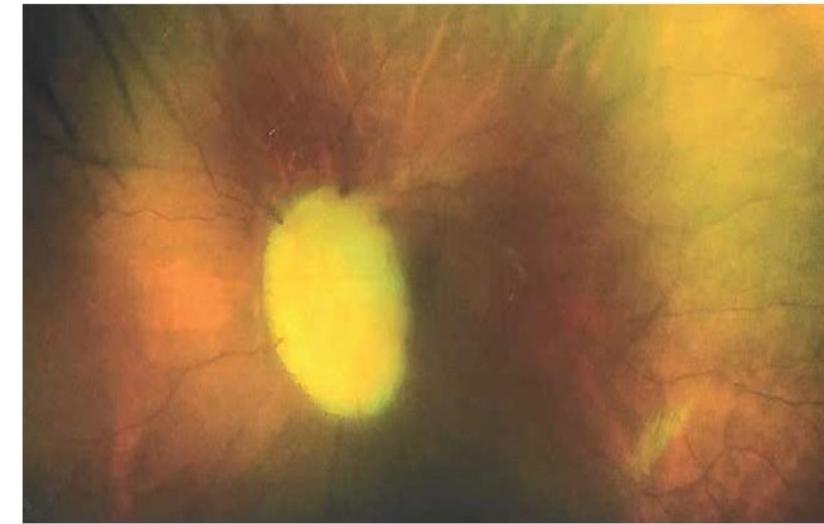


Table 4 Results of Cox multivariate analysis with central nervous system progression-free survival as endpoint (N = 163)

Therapy	HR	95% CI	P
Stem cell transplantation after radiation therapy			
Yes	1		
No	3.89	1.85-8.17	<.001
Radiation type			
CS	1		
WB	1.12	0.48-2.62	.80
BOS	2.84	1.22-6.60	.02

Abbreviations: BOS = base of skull radiation therapy; CI = confidence interval; CS = craniospinal radiation therapy; HR = hazard ratio; WB = whole brain radiation therapy.

Ocular Manifestations of Leukemia



24-year-old female with pre-B cell ALL, CSF negative at diagnosis. Post induction, consolidation, MRD-. Right eye central feld blind spot. Repeat BM biopsy and CSF sampling negative. Plans transition to alloHCT with FTBI.

Ocular Manifestations of Leukemia

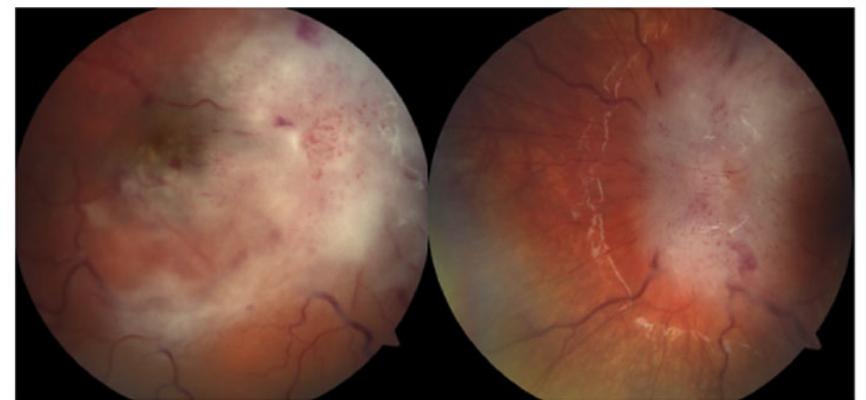


Fig. 1. Initial presentation fundus photographs. Right eye, Left eye respectively. Note optic nerve and retina infiltration, right more than left eye.

7 year old with T-cell ALL. Bilateral optic nerve and retinal involvement right > left. Improvement after 9 Gy orbital RT, systemic and IT chemotherapy and FTBI 12 Gy. Am. J Ophthalmology, 2020



Fig. 4. Serial fundus photographs. From top to bottom, images denote the right and left eye respectively 3 weeks following presentation, one month following bone marrow transplant and 3 months following bone marrow transplant. Note the improvement in perivasculär involvement throughout follow up.

Ocular Manifestations of Leukemia

- Optic nerves and orbits are sanctuary sites
- Leukemia can present as pathology in the adnexae, conjunctiva, sclera, cornea, anterior chamber, iris, lens, vitreous, retina, choroid, and optic nerve.
- If loss of vision should be treated as an urgent / emergency case
- Ophthalmologic exam, CSF sampling, BM Bx, MRI orbits and brain
- RT guidelines: limited data, case reports
 - Dose 1800-2400 cGy (180-200 per fraction)
 - Fields
 - Bilateral orbits and optic nerves (optic chiasm)
 - Brain
 - Anterior orbit
 - Fields and dose dependent on plans for FTBI

Testicular Manifestations of Leukemia

- Testes is a sanctuary site
- 4 Gy testes boost from MSKCC: 4/28 testes recurrence without boost vs 0/300 with boost. (Shanks Rad Onc, 1990)
- As with brain, HD MTX now routine and testes relapse without RT low
- Testes boost 4 Gy with FTBI
 - Optional if no history of testicular involvement, especially for pediatric cases
 - Boost if history of testicular involvement
- Testicular relapse
 - 24 Gy bilateral testes
 - Consider only for patients with residual disease after chemotherapy

Table 1 Key studies on the efficacy of addition of high-dose MTX to intensive chemotherapy on testicular recurrence in ALL

Publication	Study sample	n	Study highlights
Quaranta et al ²	Male children with AML or ALL who underwent HCT with either TBI and testicular RT, TBI only, or chemotherapy only (which included high-dose MTX)	131	<ul style="list-style-type: none">• No testicular relapse noted in chemotherapy-only arm.
van der Werff et al ⁵	Children with ALL in EORTC 58881 trial administered high-dose MTX with or without IV 6-mercaptopurine	601	<ul style="list-style-type: none">• Testicular relapse: 2% in arm A and 2.7% in arm B
Barredo et al ⁴	Patients with B-cell ALL experiencing isolated testicular relapse after 18 months of first clinical remission and receipt of intensive chemotherapy (n = 29) or testicular RT (n = 11)	40	<ul style="list-style-type: none">• No secondary testicular relapse for those with testicular RT, but 20% seen in intensive chemotherapy cohort• Improved 5-year EFS with testicular RT (72.7% vs 62.1%, $P = .64$)• 5-year OS comparable between irradiated and nonirradiated patients (72.7% vs 72.6%, $P = .85$).

Abbreviations: ALL = acute lymphoid leukemia; AML = acute myeloid leukemia; EFS = event-free survival; HCT = hematopoietic stem cell transplantation; IV = intravenous; MTX = methotrexate; OS = overall survival; RT = radiation therapy; TBI = total body irradiation.