e-session 574

Frontiers in bone marrow transplantation for acute leukemia: Total Marrow/Lymphoid Irradiation

Expert: **Dr Stefano Vagge**, San Martino Hospital - National Cancer Institute, Genoa, Italy

Discussant: **Prof Benedetto Bruno**, University of Turin, Turin, Italy

Discussant: **Prof Andrea Riccardo Filippi**, Policlinico S. Matteo IRCCS Foundation, Pavia, Italy

Frontiers in bone marrow transplantation for acute leukemia: Total Marrow/Lymphoid Irradiation

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Disclosures

Advisory boards or speakers' fee

- *Astra Zeneca*
- *Accuray International*
- *-Roche*

Radiotherapy helped to win a Nobel prize again…

Seattle doctor's radical idea saves 70,000 people a year

By RUBY DE LUNA · 4 HOURS AGO

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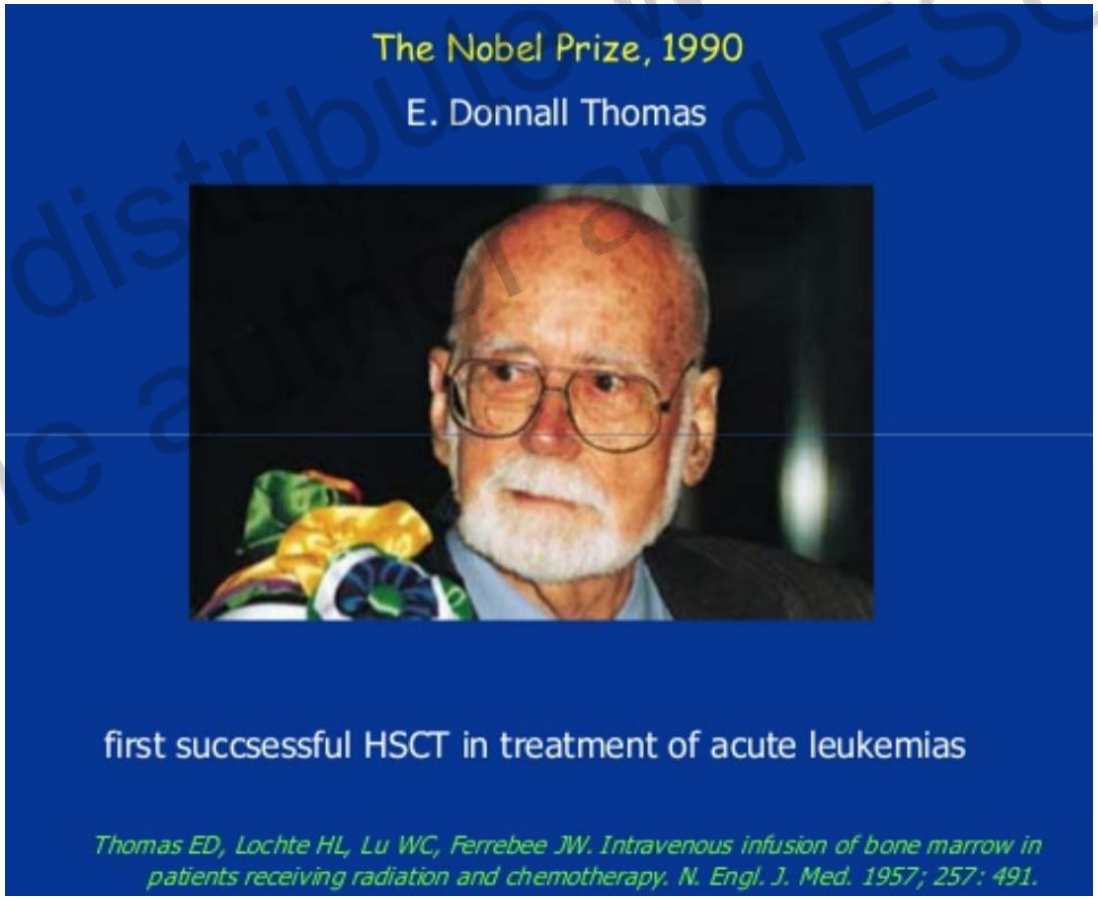
Joe DiMaggio, Dr. E. Donnall Thomas, and patient Darrell Johnson in LAF (laminar airflow) room, 1978



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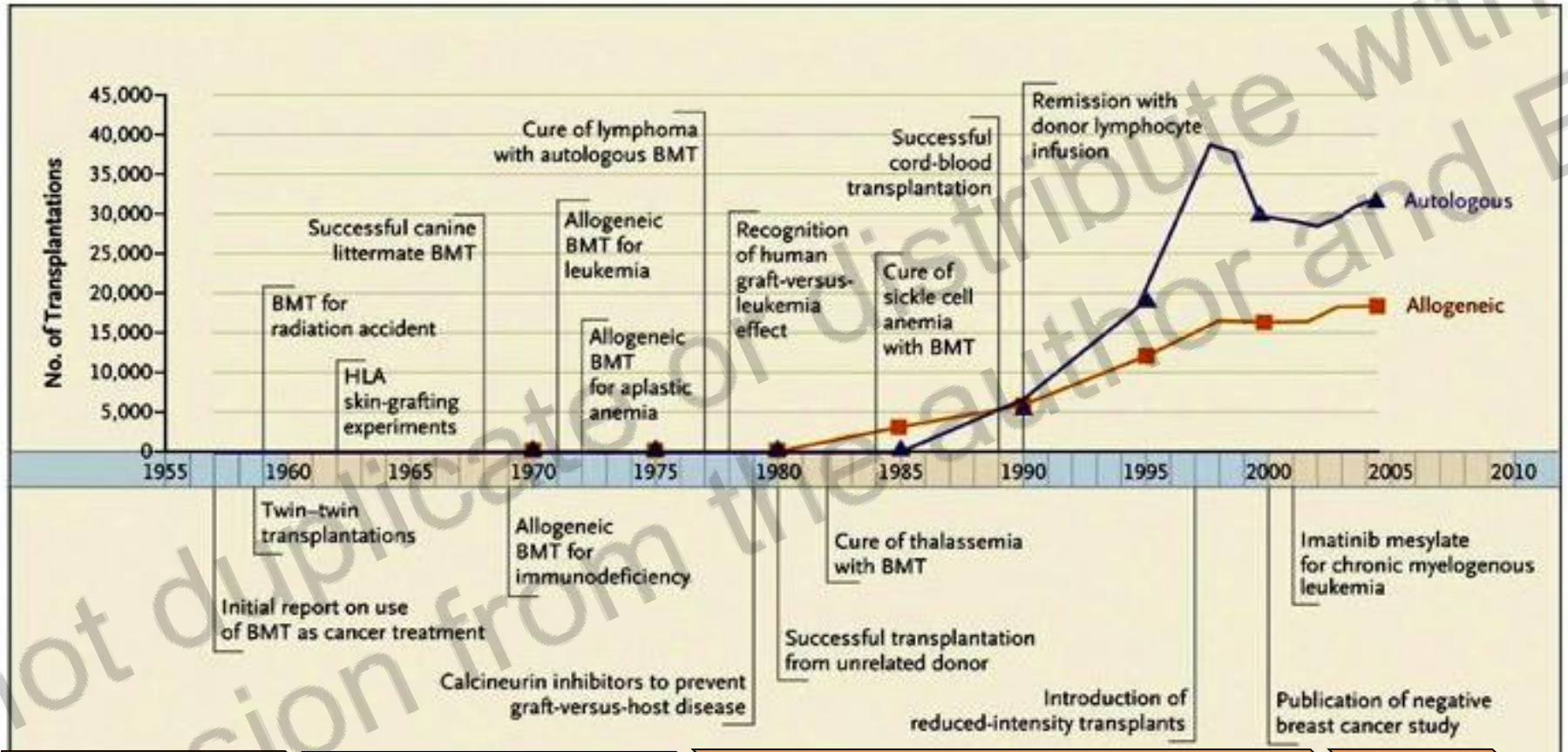
Sistema Sanitario Regione L

Hematopoietic Stem Cell Transplantation

A long-time history



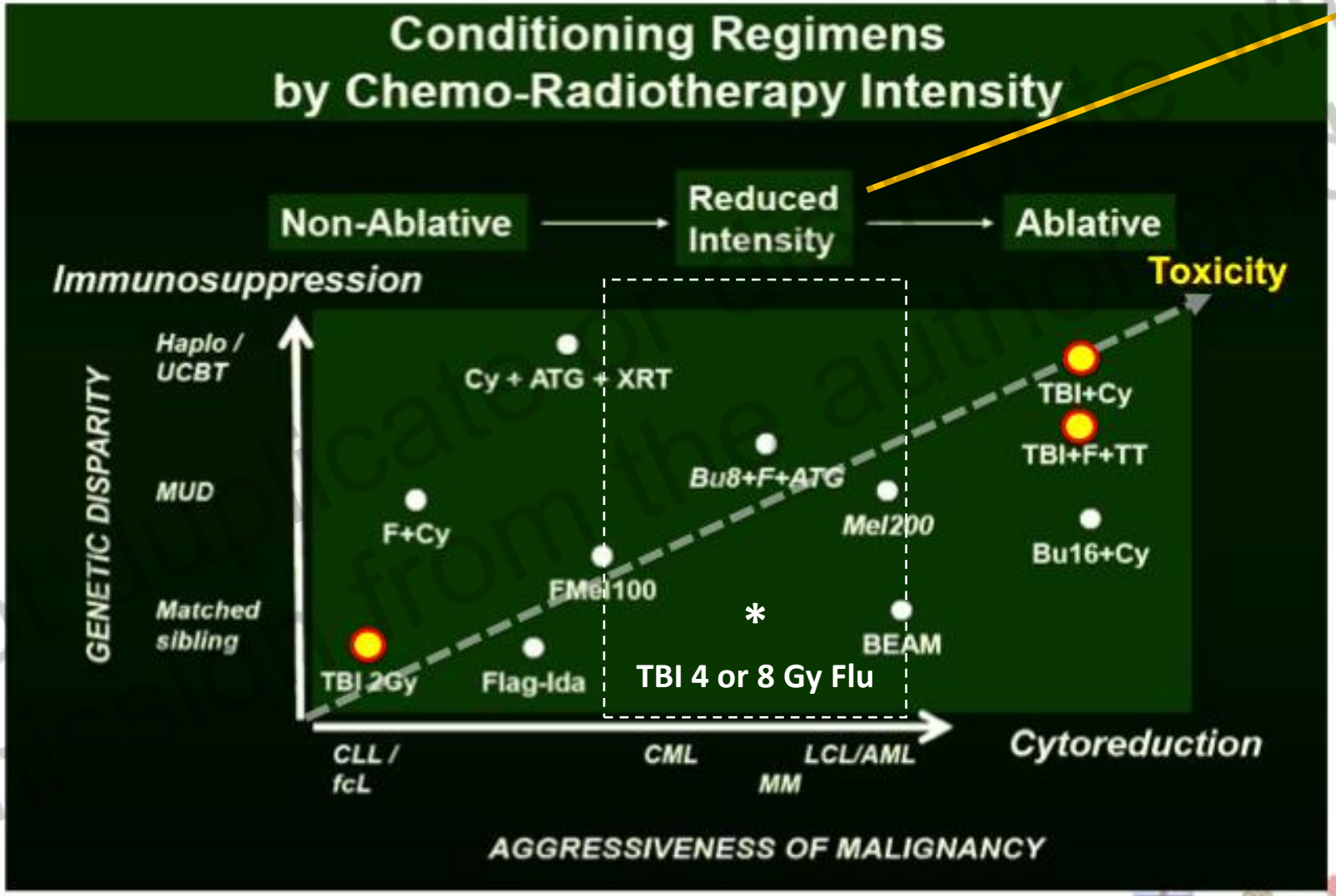
TBI for lymphoma & solid mts → ***TBI with low dose for CLL*** → ***TBI myeloablative & sub-myeloablative*** → ***TMI***

Aims of conditioning

One or more of the following

- Destroy any existing cancer cell or abnormal cells
- Stop the recipient immune system working to reduce risk of the transplant being rejected
- Destroy existing bone marrow cells to make room for the tranplanted tissue

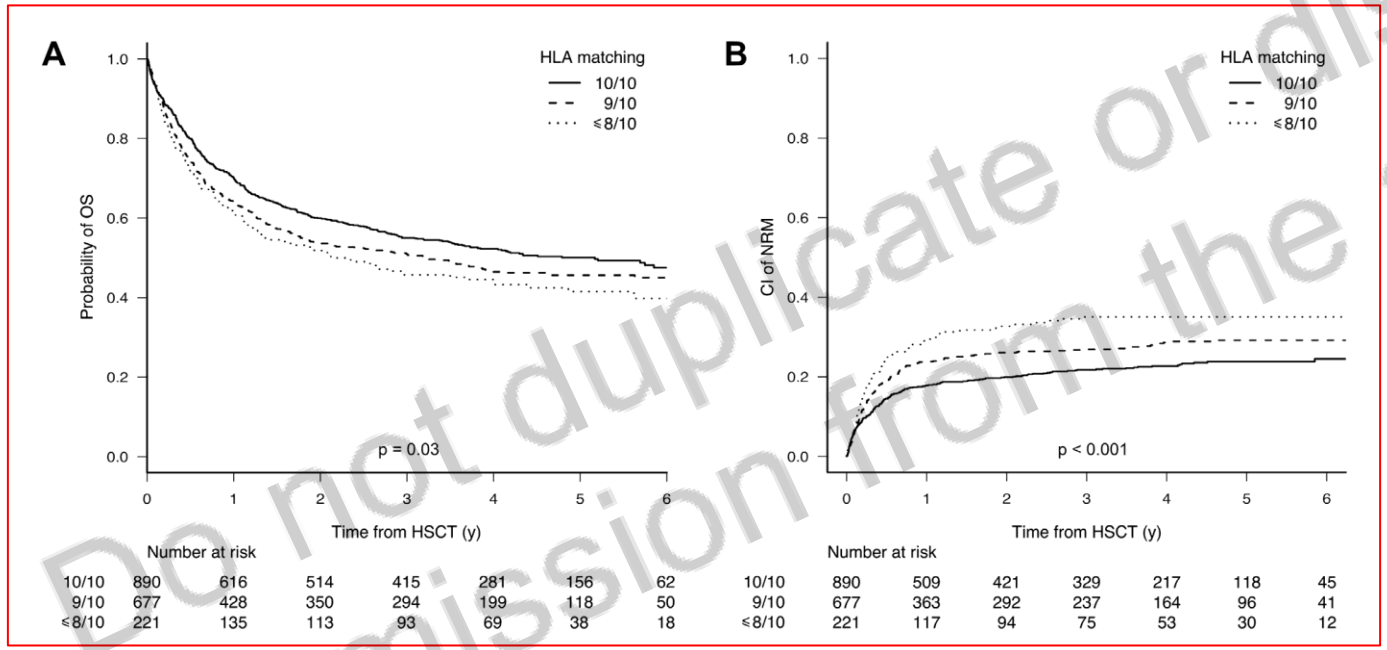
Role of Radiotherapy



Reduction of more than 30% in RT and CT doses

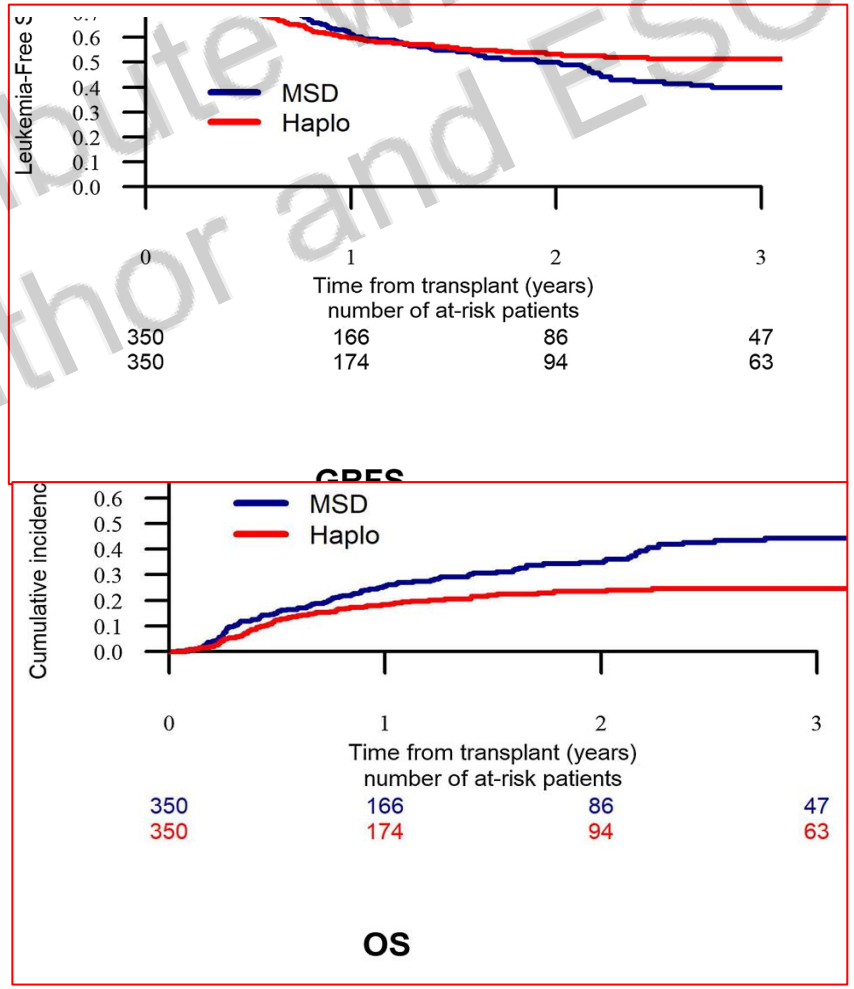
Influence of Donor type

HLA matching for unrelated



Picardi A. et al Transplantation and cellular therapy 2021

APLO vs MSD in ALL



Nagler A. et al Journal of Hemat Oncol 2021

Is not easy to take out TBI clear data in HSCT

Different regimens for alloHSCT

- BuCy2/BuCy4
- BuCyMel
- BuMel
- BuCyEto
- BuFlu
- BuFluThio
- BuFluClo
- TBIEto
- TBI/Cy
- TBI/CyEto
- TBI/Thio
- TLI/ATG
- FLAMSA/TBI
- TBI/Treo
- FluTreoMel
- TreoMel
- FluTreo
- TreoCyEto
- TreoEtoCarbo
- FluTreoThio
- FluCy
- FluMel
- FluThio(Cy)
- Cy (ATG)
- Mel
- no (ATG)
- ……

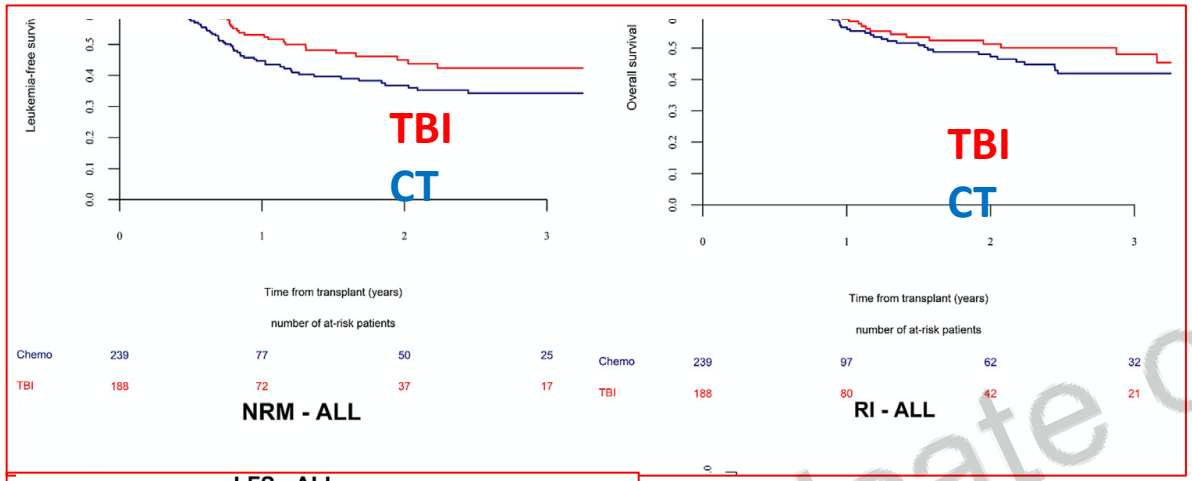
TBI plus Cy vs Bu/Cy a meta-analysis in allo-SCT

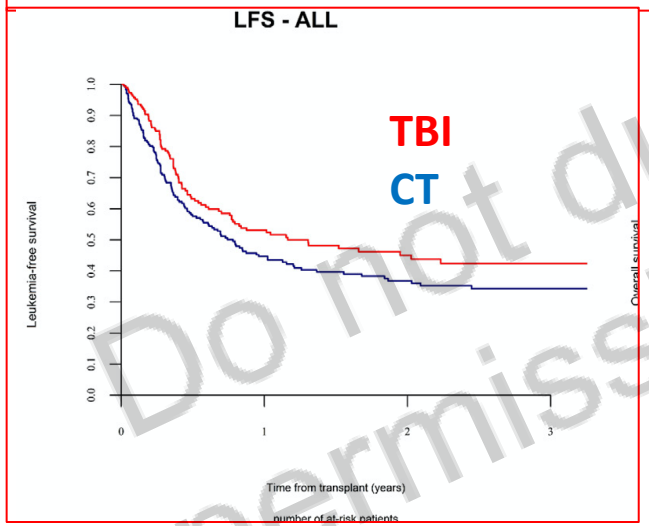
- 18 trials totaling 3172 pts
- TBI/Cy (compared with Bu/Cy)
  - → lower leukemia relapse for ALL, AML, not for CML
  - → lower transplant-related mortality
  - → higher disease-free survival

Xu Shi-Xia et al, Leukemia & Lymphoma 51:50-60 2010

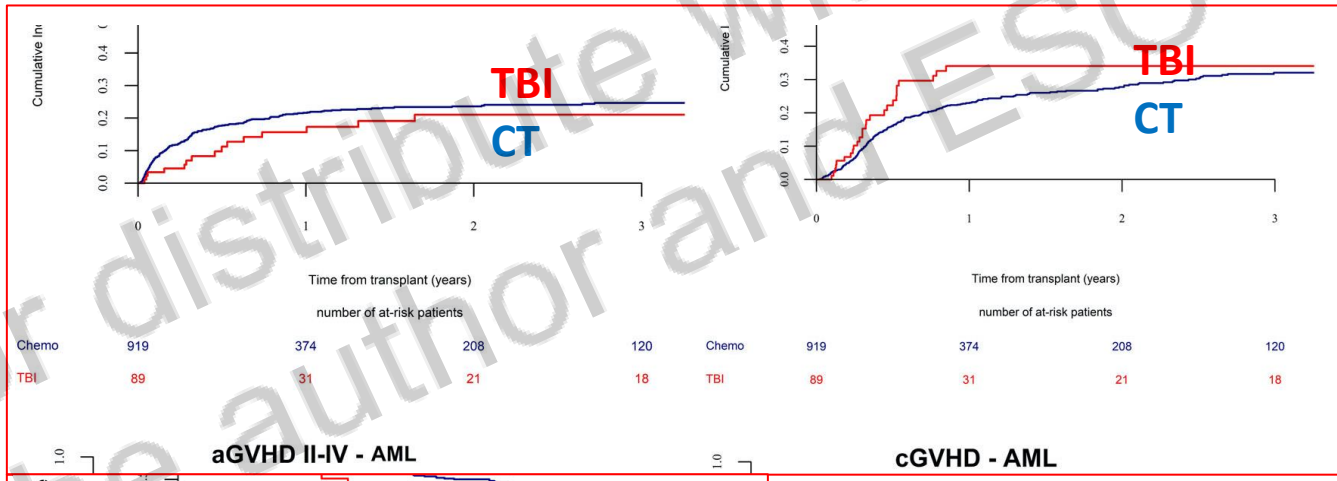
Influence of TBI

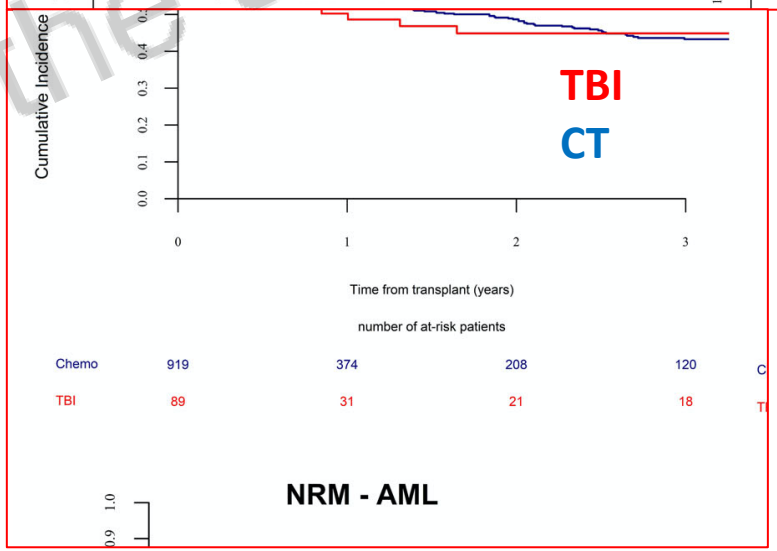
MAC for Aplo in ALL TBI vs CT





MAC for Aplo in AML TBI vs CT



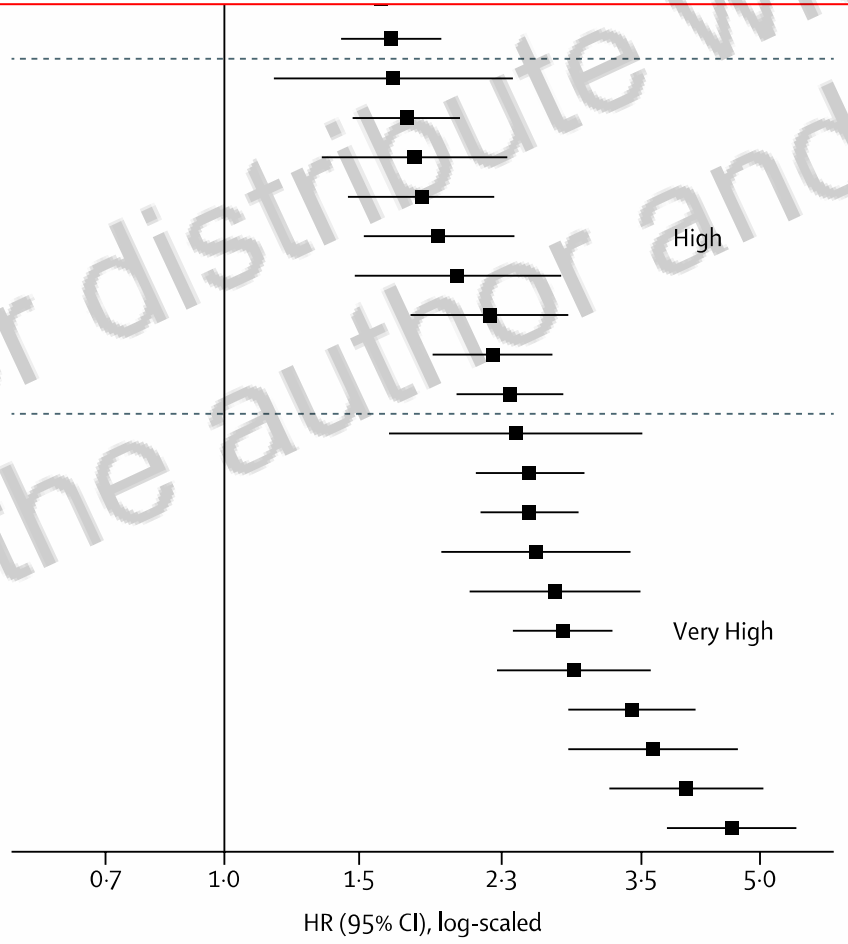


Dholaria et al Transplantation and cellular therapy 2021

Dholaria et al AJH 2020

EBMT DISEASE RISK STRATIFICATION

AML, adverse cytogenetics, first complete remission	343/806	1·65 (1·42–1·92)
Mantle cell lymphoma, partial response	34/75	1·66 (1·16–2·38)
MDS-MPN overlap syndrome	274/574	1·73 (1·47–2·03)
CML, blast crisis	65/154	1·77 (1·34–2·34)
Sec AML, non-adverse cytogenetics, refractory	112/217	1·81 (1·45–2·25)
Sec AML, adverse cytogenetics, complete remission	101/214	1·90 (1·52–2·39)
Hodgkin lymphoma, progressive disease or stable disease	52/129	2·01 (1·48–2·75)
AML, adverse cytogenetics or *FLT3*-ITD, subsequent complete remission	90/173	2·22 (1·75–2·81)
MDS, EB, adverse cytogenetics	187/338	2·24 (1·87–2·68)
ALL, subsequent complete remission	280/684	2·36 (2·01–2·77)
Mantle cell lymphoma, progressive disease or stable disease	31/58	2·40 (1·64–3·51)
AML, non-adverse cytogenetics, refractory	373/708	2·50 (2·16–2·90)
Sec AML, unknown cytogenetics, refractory	271/477	2·50 (2·13–2·95)
MM, progressive disease or stable disease	60/120	2·55 (1·92–3·39)
T-NHL, progressive disease or stable disease	73/141	2·70 (2·09–3·49)
AML, unknown cytogenetics, refractory	370/679	2·77 (2·38–3·21)
B-NHL, aggressive, partial response	93/183	2·86 (2·27–3·60)
AML, adverse cytogenetics, refractory	153/236	3·40 (2·81–4·12)
Sec AML, adverse cytogenetics, refractory	76/120	3·62 (2·81–4·68)
B-NHL, aggressive, progressive disease or stable disease	95/145	4·00 (3·18–5·05)
ALL, refractory	151/234	4·59 (3·78–5·58)

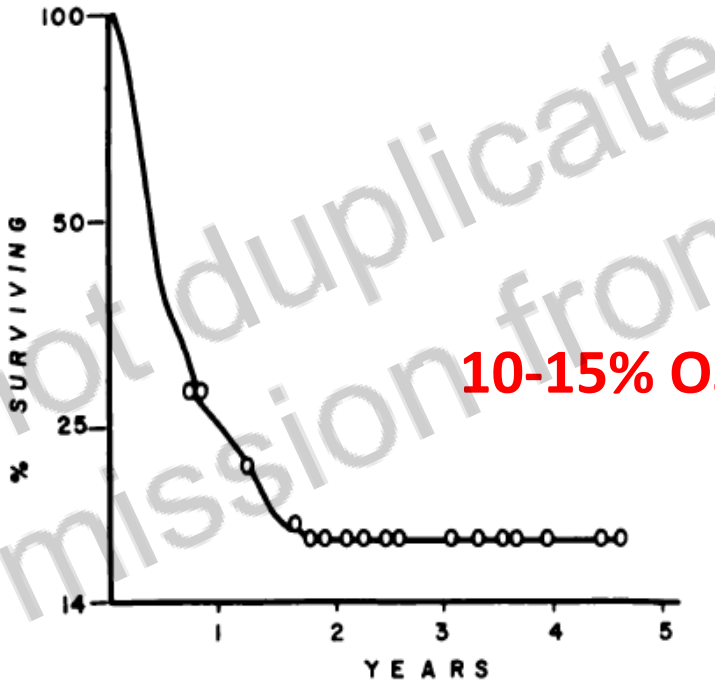


Shouval et al Lancet Haematol 2021

Rationale: TBI dose escalation in advanced acute leukemia…..why?

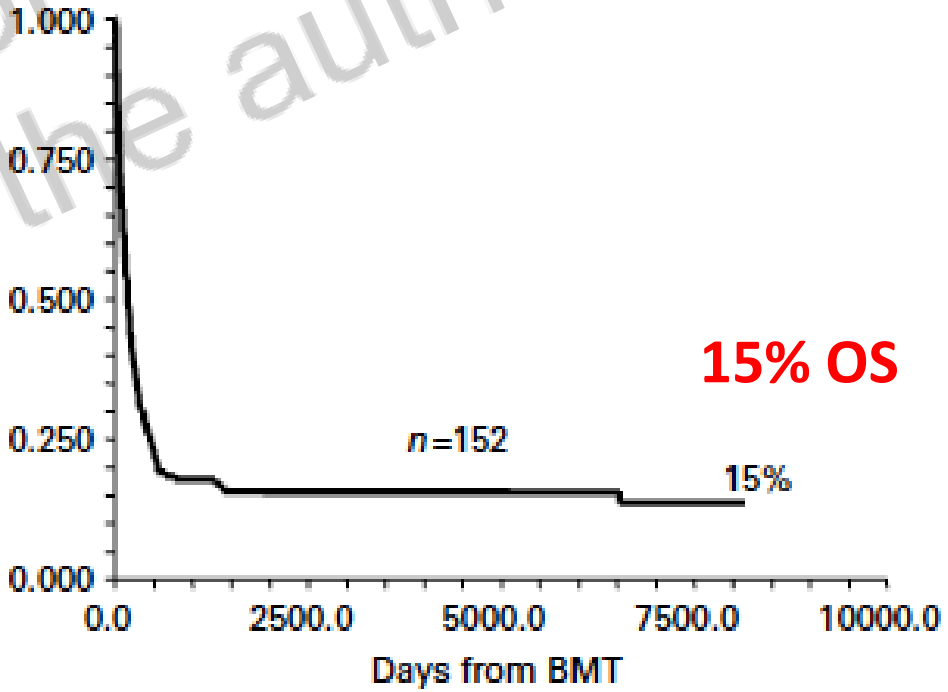
Three decades and small changes for high risk patients

Thomas Blood 1977



10-15% OS

Bacigalupo BMT 2007



15% OS

Rationale: TBI dose escalation in advanced acute leukemia…..why?

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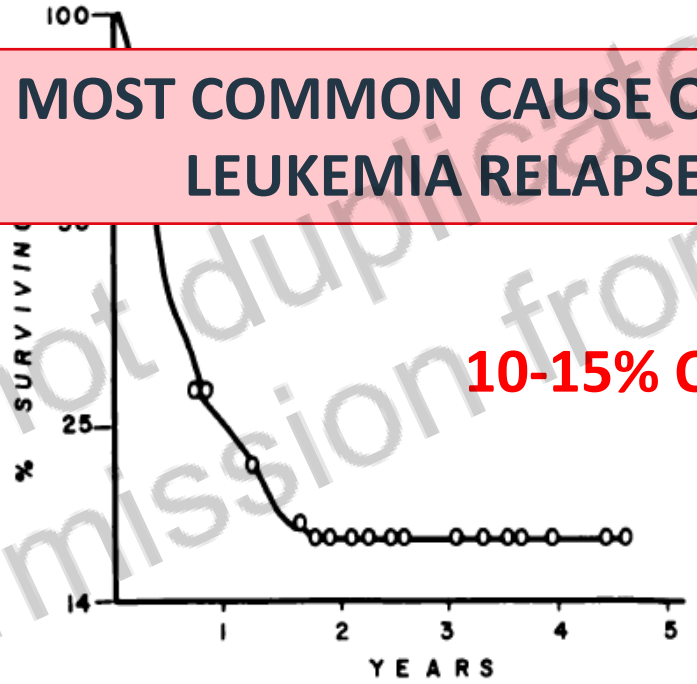
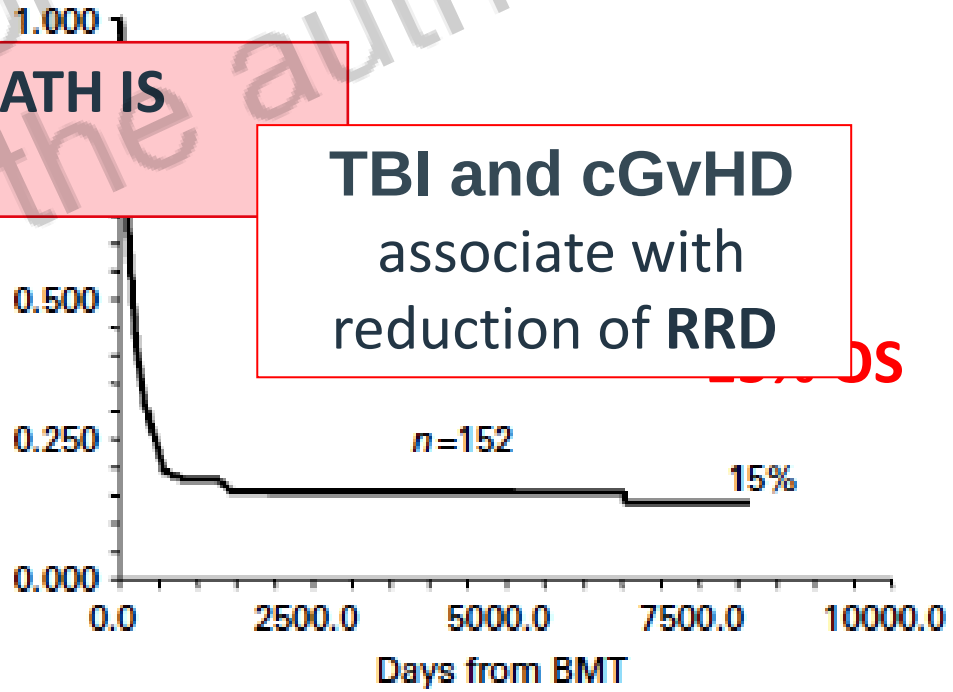


THE MOST COMMON CAUSE OF DEATH IS LEUKEMIA RELAPSE

10-15% OS

Bacigalupo BMT 2007



TBI and cGvHD associate with reduction of **RRD**

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In myeloablative conditioning with TBI-Cy the higher radiation dose reduce disease relapse

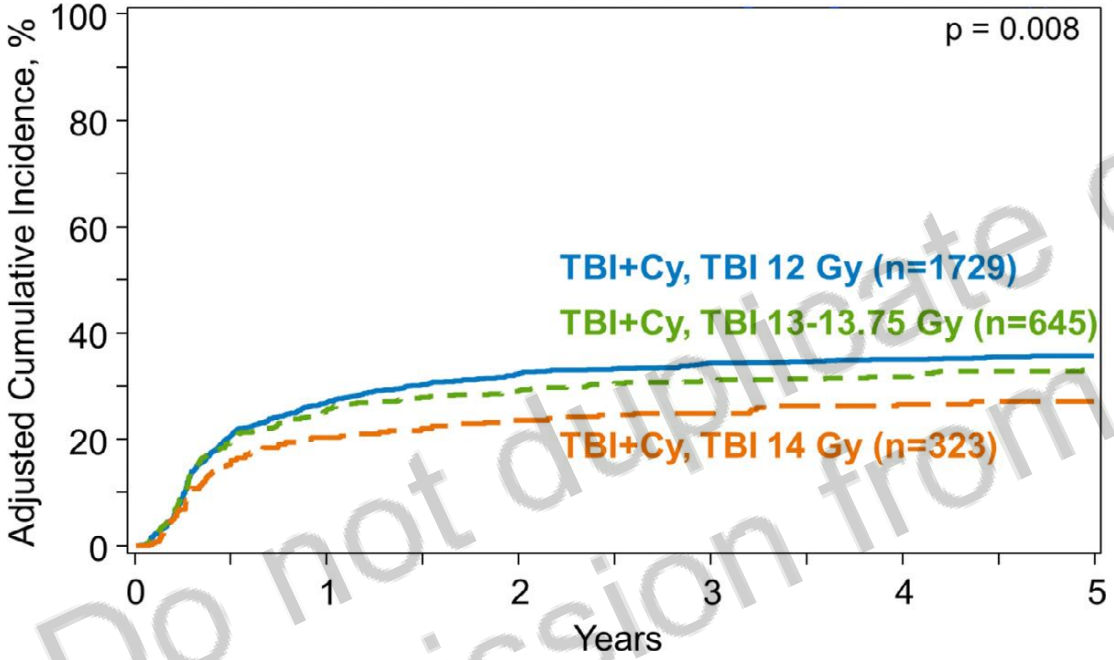

Figure 4. Cumulative incidence function of relapse by dose of TBI.

AML; ALL; CML; MDS

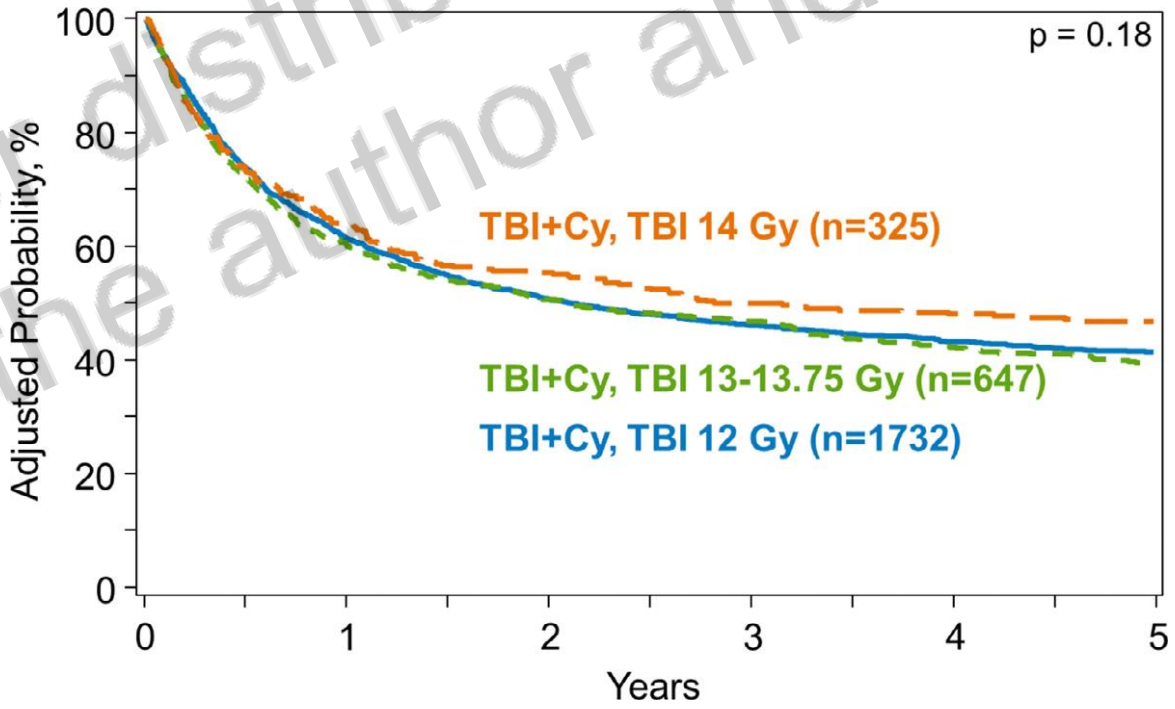

Figure 2. Kaplan-Meier curve of OS by dose of TBI.

Sabloff , Biol of Blood and Marrow Transpl 2019

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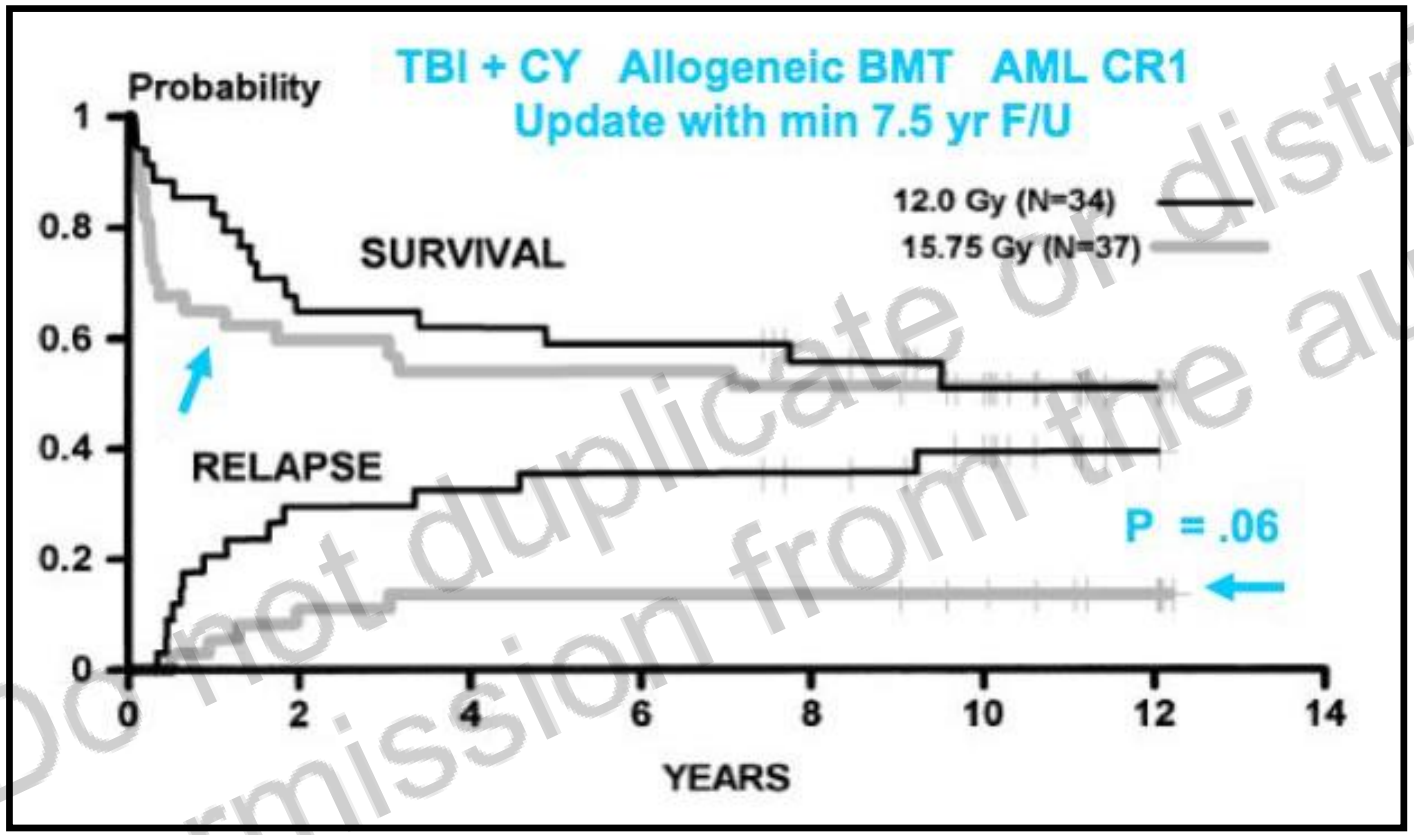
TBI dose escalation: conventional 12 Gy vs 15.75 Gy



Clift et al, Blood 1998

MORE RADIATION DOSE

=

MORE LEUKEMIC CELL KILLING

=

MORE RADIATION-INDUCED EFFECTS

→

NO IMPROVEMENT IN SURVIVAL!

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ACUTE AND LATE TBI- INDUCED TOXICITIES

Biological Effects	Rate (%)
kidney failure	5-15%
intestitial pneumonitis	5-15%
cataract	4-22%
growth delay	40-90%
amenorrea	90%
azoospermia	95%
veno-occlusive disease	<5%
cognitive deficits	<20%
neurological complications	<5%
Hypothyroidism subclinical clinical evident	 25-43% 3-13%

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Original Article

Extreme Heterogeneity of Myeloablative Total Body Irradiation Techniques in Clinical Practice

A Survey of the Acute Leukemia Working Party of the European Group for Blood and Marrow Transplantation

Total Dose, Gy	No. of Fractions (Dose per Fraction, Gy)	Dose Rate in the Axis of the Beam, cGy/Minute	No. of Centers (%)
12	6 (2)	16	3 (5.4)
12	6 (2)	8	2 (3.6)
12	6 (2)	11	2 (3.6)
12	6 (2)	10-15	2 (3.6)
12	6 (2)	20-30	2 (3.6)

Abbreviations: cGy, centigrays; Gy, grays, TBI, total body irradiation.
[a] All other modalities were represented by single centers.

Giebel S. *Cancer* 2014

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Clinical Investigation

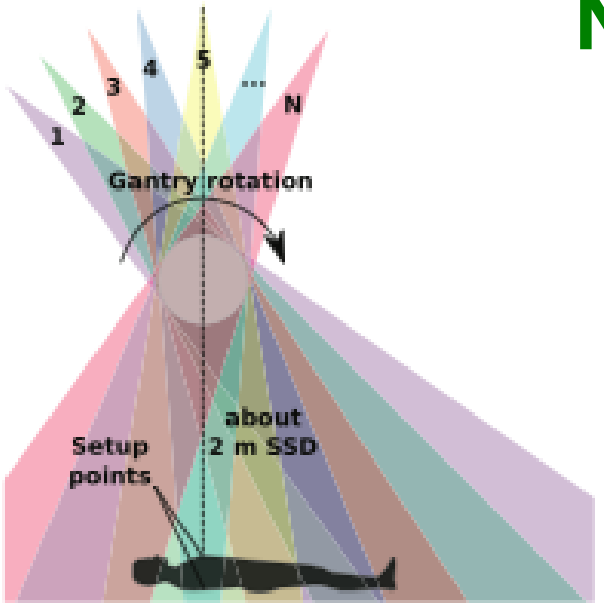
Single-Dose Daily Fractionation Is Not Inferior to Twice-a-Day Fractionated Total-Body Irradiation Before Allogeneic Stem Cell Transplantation for Acute Leukemia: A Useful Practice Simplification Resulting From the SARASIN Study

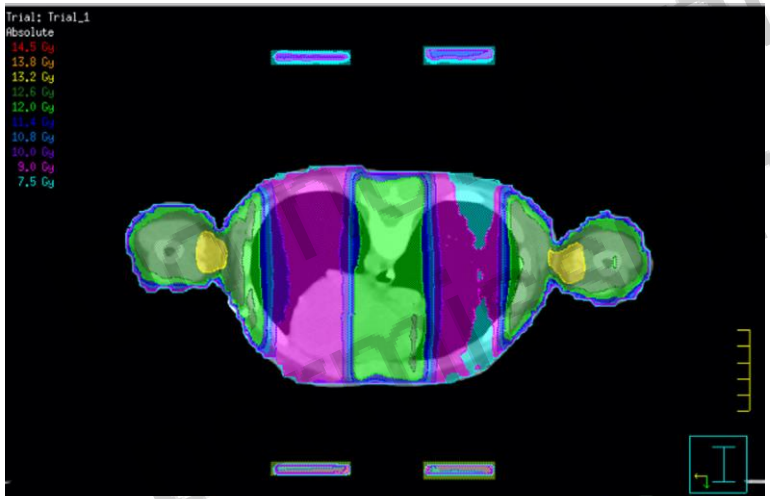
12 Gy in 6 fractions (BID) (2 Gy fraction)
vs
12 Gy in 3 fractions (4 Gy fraction)

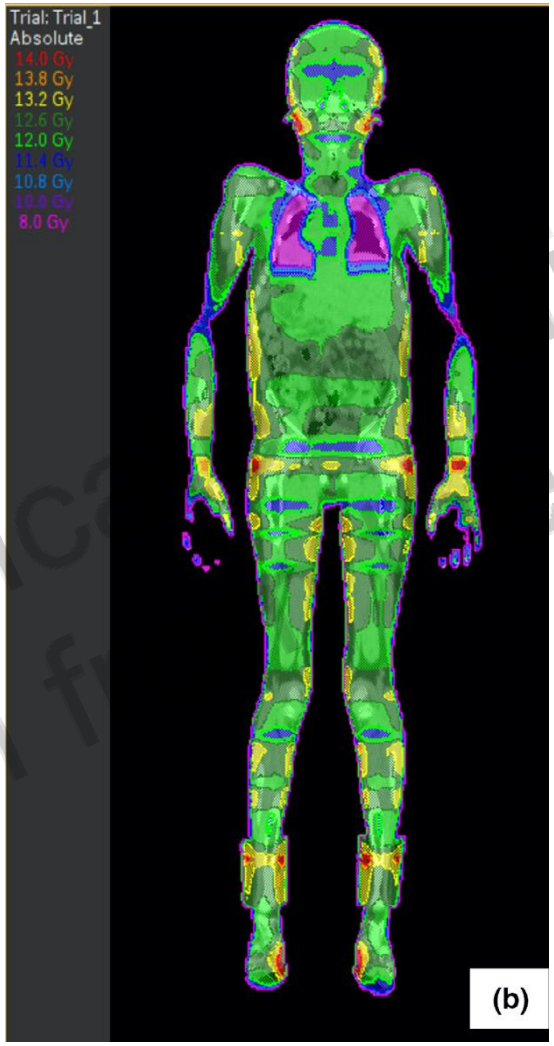
No differences in terms of outcomes and toxicity

Y. Belkacemi IJROBP 2018

Next generation TBI





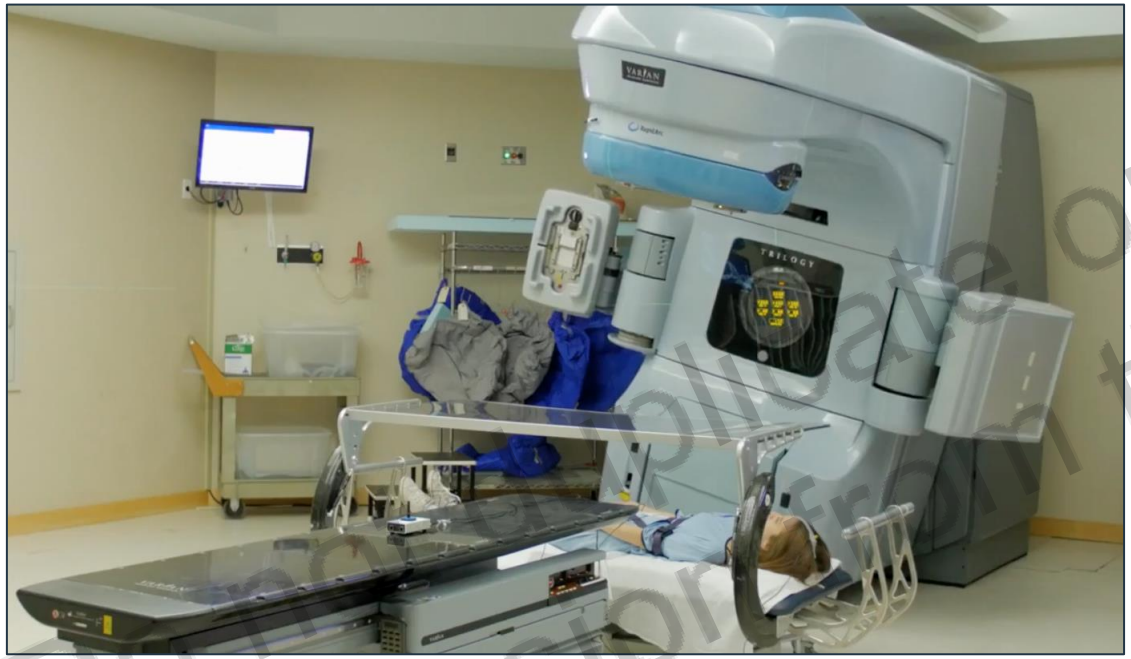


- A more suitable surrogate of conventional TBI
- Low homogeneity of the dose
- No IGRT
- Limited OARs sparing

Kirby N Medical Physics 2012

Effeney B. *2019 JMRS*

Next generation TBI



Pics from Ontario center

Review

Total marrow and total lymphoid irradiation in bone marrow transplantation for acute leukaemia

Jeffrey Y C Wong, Andrea R Filippi*, Marta Scorsetti, Susanta Hui, Ludvig P Muren, Pietro Mancosu**

Blood 2011

Lancet Oncology 2020

• • • TRANSPLANTATION

Comment on Rosenthal et al, page 309

TMLI: a better TBI or more of the same?

Sergio Giralt MEMORIAL SLOAN-KETTERING CANCER CENTER

Total body irradiation (TBI) has been an integral component of allogeneic hematopoietic stem cell transplantation since this treatment modality was pioneered by Dr E. Donald Thomas in the 1970s.[1] Although higher TBI doses are associated with better disease control in patients with myeloid leukemias, the increased risk of TBI-related toxicities negate any potential survival advantage.[2-4]

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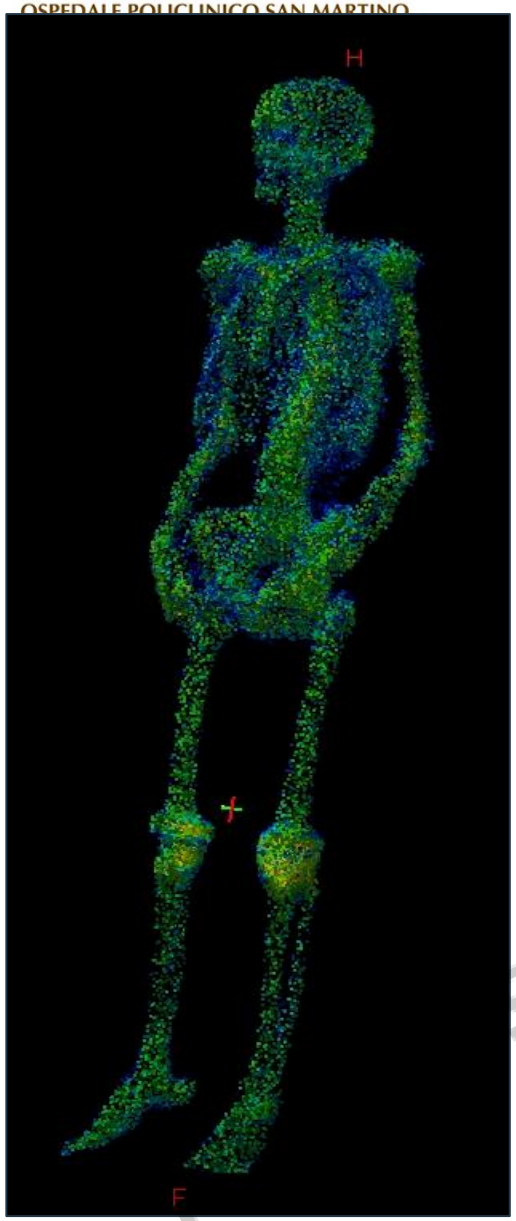
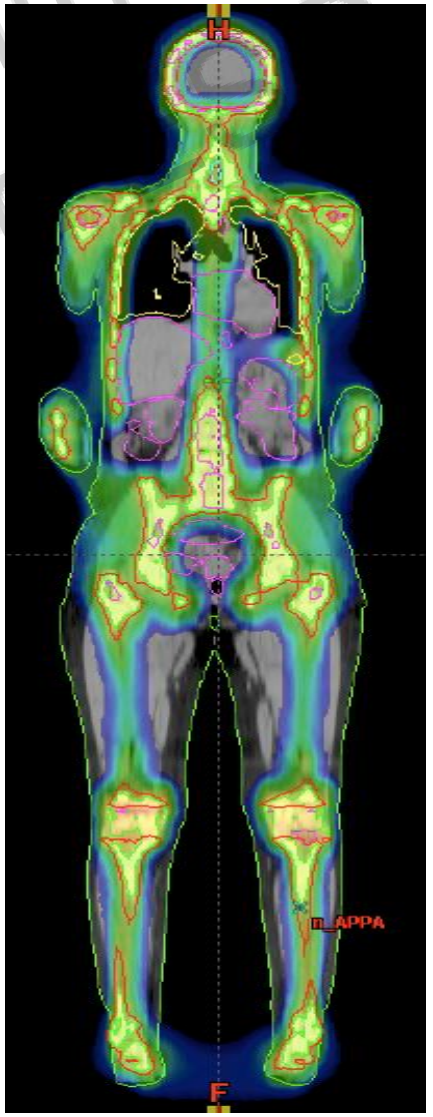
We can spare better and cover homogeniously



Organ	Median Dose reduction (%)	Range (%)
Brain	**48.1**	41.0 – 60.0
Parotid gland	**29.3**	15.0 – 43.5
Eye	**52.0**	30.2 – 60.4
Oral mucosa	**42.1**	20.5 – 50.0
Larynx	**54.5**	43.0 – 61.7
Thyroid	**48.4**	27.5 – 51.0
Lung	**48.8**	41.0 – 53.0
Breast	**61.0**	45.1 – 68.2
Heart	**46.7**	43.0 – 52.5
Liver	**52.3**	43.5 – 60.0
Bowel	**53.7**	47.7 – 59.5
Kidneys	**63.0**	47.0 – 73.0
Bladder	**62.1**	50.2 – 69.3
Rectum	**58.4**	48.2 – 65.2
Uterus	**64.7**	58.0 – 76.2

PTV		
Value	Mean (%)	Range (%)
D95	93.3	91.9 – 94.2
D90	95.7	94.1 – 96.7
D5	102.9	101.7 – 103.8

from 40% to 60 % for major organs



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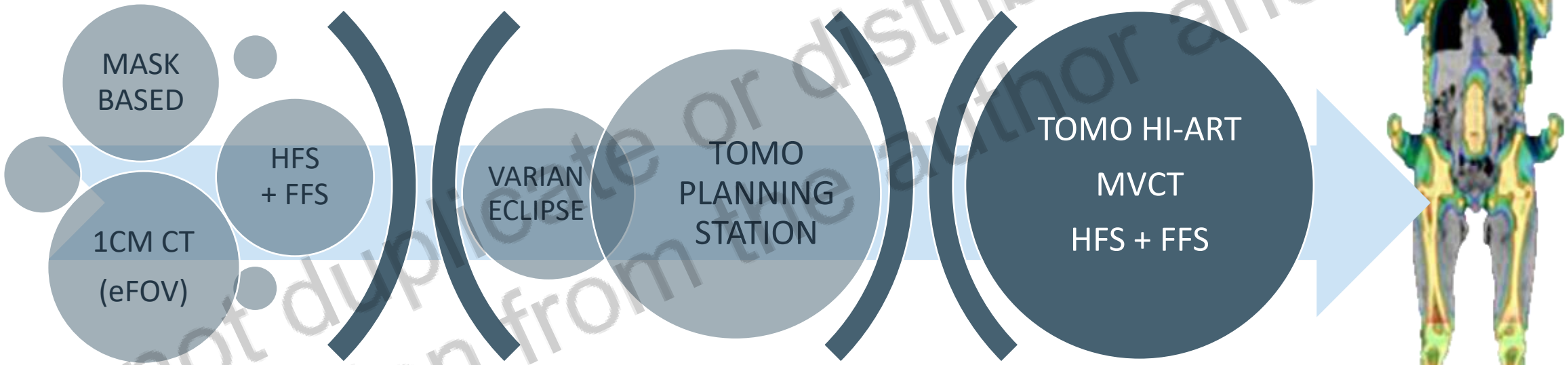
OVERVIEW



SETUP

PLANNING

IGRT & DELIVERY (FULL TOMO)

TOMO HI-ART 7 blades cluster

1 h

1-2 d + 3-4 d

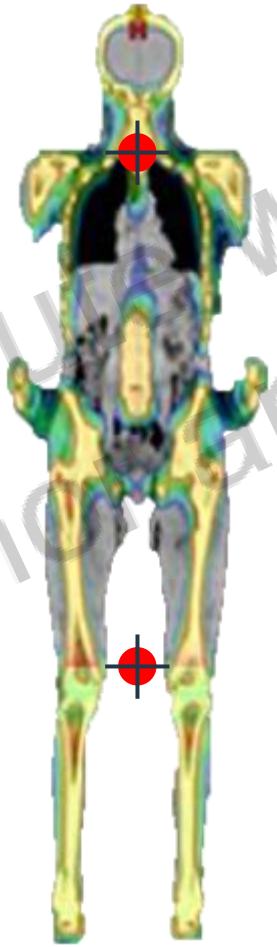
~1.5-2 h @ 4 Gy

(2 w in busy clinic)

TMI ON TOMO

12 FULL ARCS

VMAT + LEGS AP/PA



5 cm FW
MF = 2.4 - 2.8
Pitch = 0.287

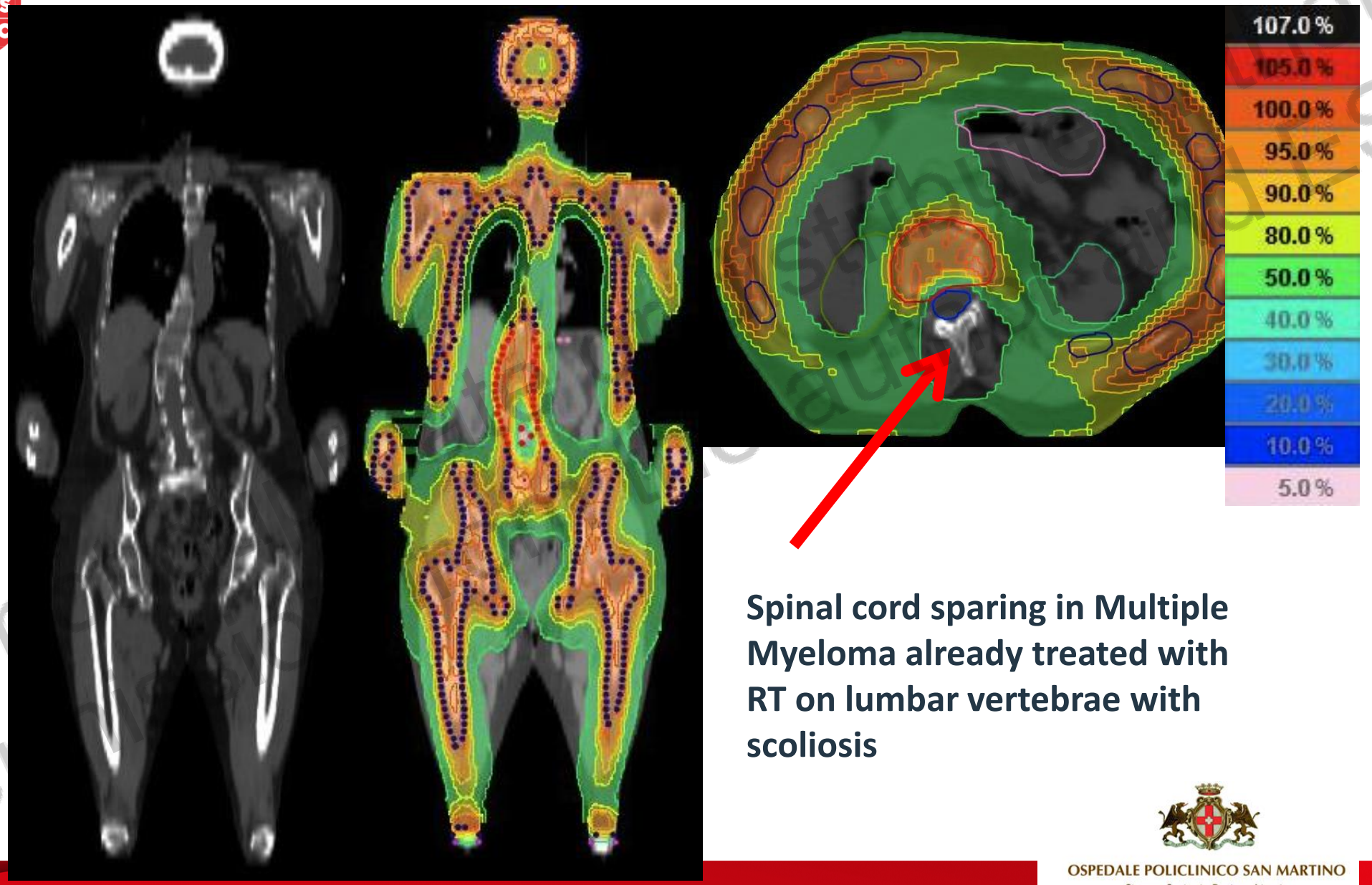
5 cm FW
MF = 1.8 - 2.6
Pitch = 0.287

FULL TOMO

FOR EMERGENCY SITUATIONS
LEGS CAN BE TREATED w LINAC AP/PA

The James
The Ohio State University
Wexner Medical Center

Importance of IGRT for accuracy in TMI/TLI



Spinal cord sparing in Multiple Myeloma already treated with RT on lumbar vertebrae with scoliosis

Radiother Oncol. 2019 Aug 14. pii: S0167-8140(19)33000-2. doi: 10.1016/j.radonc.2019.07.010.

Contents lists available at ScienceDirect

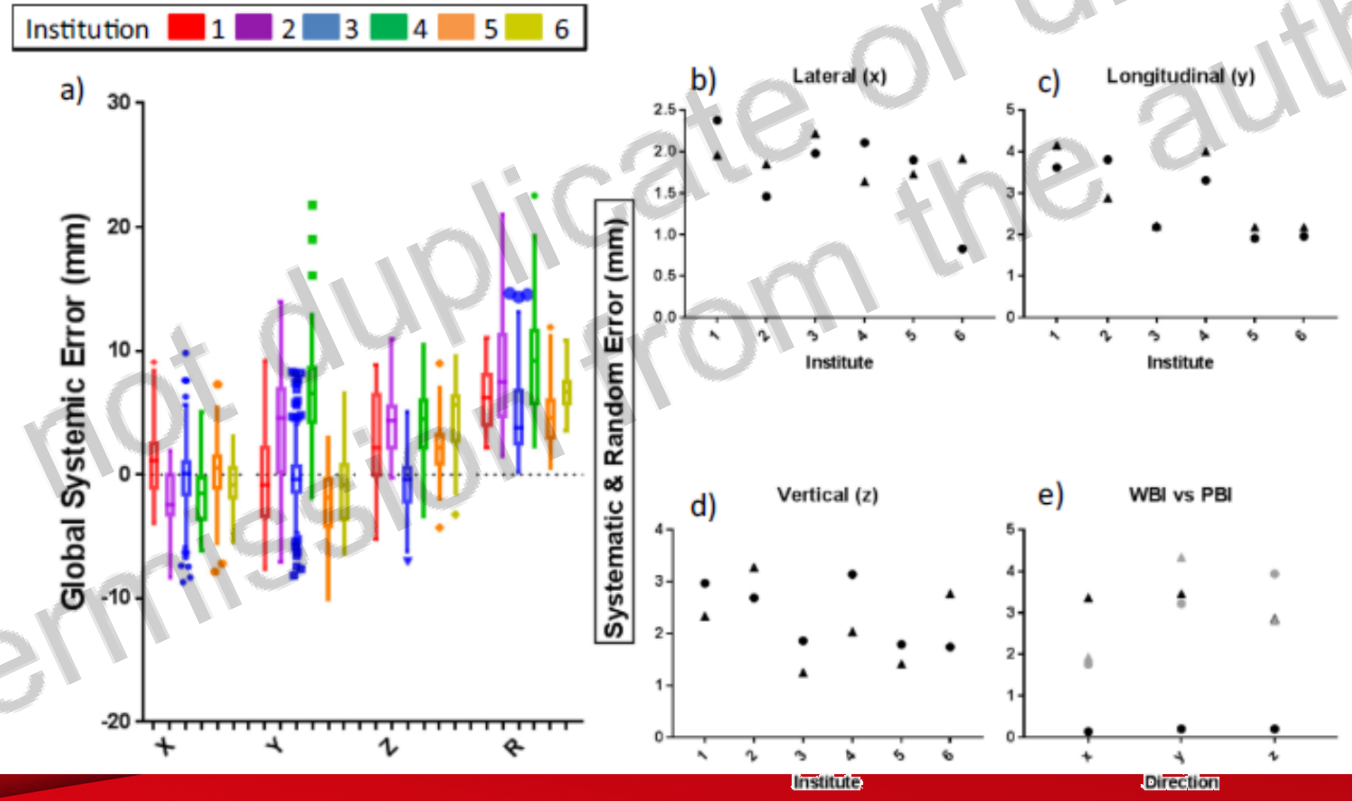
Radiotherapy and Oncology

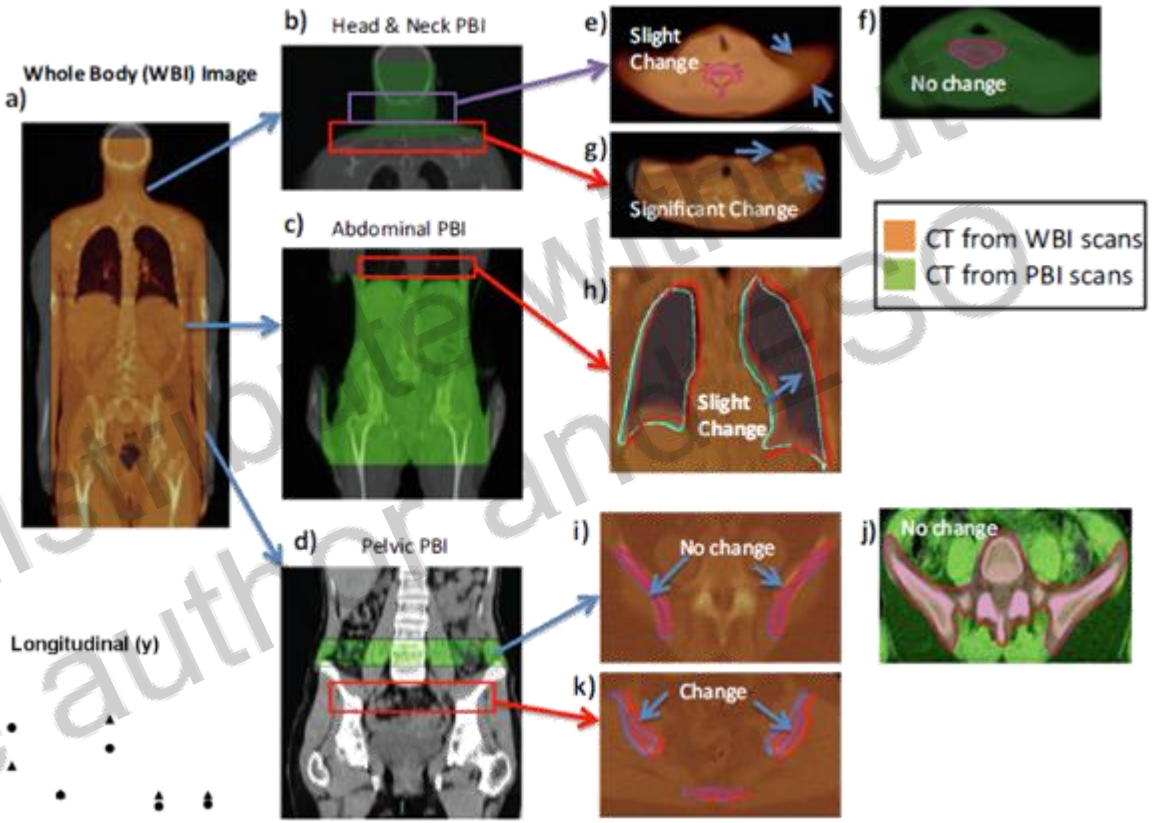
journal homepage: www.thegreenjournal.com

Original Article

Multi-institutional evaluation of MVCT guided patient registration and dosimetric precision in total marrow irradiation: A global health initiative by the international consortium of total marrow irradiation

Darren Zuro [a,b], Stefano Vagge [c], Sara Broggi [d], Stefano Agostinelli [c], Yutaka Takahashi [e], Jamison Brooks [a], Paulina Leszcynska [f], An Liu [a], Claudio Zucchetti [g], Simonetta Saldi [h], Chunhui Han [a], Mauro Cattaneo [d], Sebastian Giebel [f], Marc Andre Mahe [h], James F. Sanchez [a], Parham Alaei [b], Chiara Anna [d], Kathryn Dusenbery [b], Antonio Pierini [i], Guy Storme [j], Cynthia Aristei [h], Jeffrey Y.C. Wong [a], Susanta Hui [a,*]





WBI MVCT is the recommended IGRT for TMI

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TMI
Can we go toward a new Reduced Toxcity Conditioning in HSCT?

The Bone Marrow as Target

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First three phases of myeloablative approach to allografting

Components	Purpose
1. Myeloablative conditioning pretransplant	Host immunosuppression Eradication of underlying disease Creation of Marrow Space
2. Stem Cell Graft	Rescue from myelosuppression Establishment of normal hematopoiesis Graft-versus-tumor
3. Postgrafting immunosuppression	Prevent rejection Control of GVHD

 # Which mechanism regulate BM radiation injury

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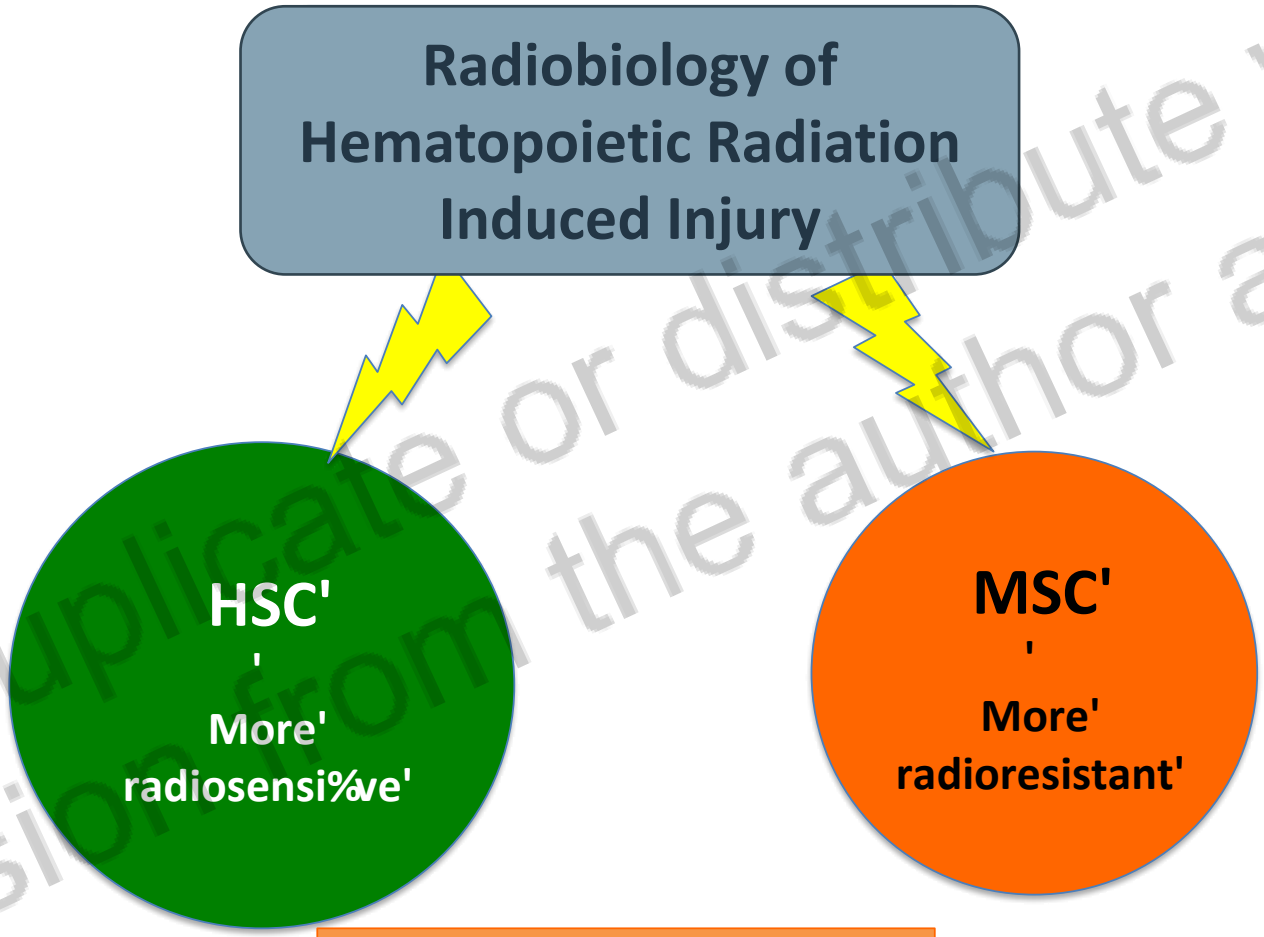
Key players of myelosuppression rescue



Stem Cells with different mechanism of response

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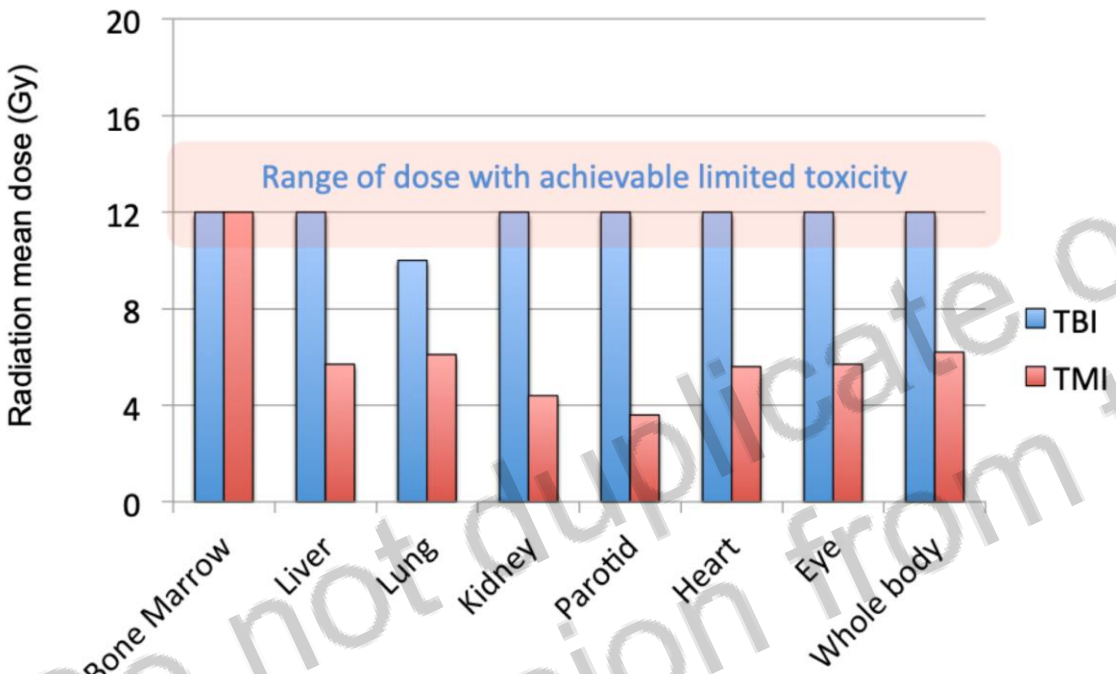

Is 20 Gy feasible ?

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Clinical reports on TMI

	Trial phase	NCT trial number*	Number of patients	Eligibility criteria	Targets	TMI dose (fractionation)	Chemotherapy	NRM and survival data
Stein et al (2017)[33]	Phase 1	02446964	51	AML, ALL relapsed or refractory	Bone, lymph nodes, testes, spleen; 12 Gy liver and brain	12–20 Gy (1·5–2·0 twice a day)	Cyclophosphamide (100 mg/kg); etoposide (60 mg/kg)	100-day NRM 3·9%, 1-year NRM 8·1%; 1-year PFS 40%; 1-year OS 55·5%; 2-year OS 41·5%
Wong et al (2013)[34]	Phase 1	00540995	20	AML relapsed or refractory	Bone, lymph nodes, testes, spleen; 12 Gy liver and brain	12 Gy, 13·5 Gy (1·5 twice a day)	Busulfan (4800 μM × min); etoposide (30 mg/kg)	NRM eight (40%) of 20; five (25%) of 20 complete remission at 20·8–49·4 months
Stein et al (2017; 2019)[35,36]	Phase 2	02094794	57	AML or ALL, induction failure, relapsed or >CR2	Bone, spleen, lymph nodes; 12 Gy liver and brain	20 Gy (2·0 twice a day)	Cyclophosphamide (100 mg/kg); etoposide (60 mg/kg)	100-day NRM 4%, 1-year NRM 6%; 1-year PFS 48%; 1-year OS 67%
Patel et al (2014)[37]	Phase 1	00988013	14	Refractory or relapse AML, ALL, MDS, MM, CML	Bone	3–12 Gy (1·5 twice a day)	Fludarabine (40 mg/m² per day for 4 days); busulfan (4800 μM × min)	NRM 29%; RFS 43%; OS 50%
Hui et al (2017)[38]	Phase 1	00686556	12	High risk ALL, AML, CR2, CR3, relapse, induction failure	Bone	15 Gy, 18 Gy (3·0 twice a day)	Fludarabine (25 mg/m² per day for 3 days); cyclophosphamide (60 mg/m² per day for 2 days)	1-year NRM 42%; relapse rate 36%; 1-year DFS 22%; 1-year OS 42%
Rosenthal et al (2011; 2018)[39,40]	Pilot	00544466	61	AML, ALL, >50 years or comorbidities	Bone, lymph nodes, spleen, ALL testes, brain	12 Gy (1·5 twice a day)	Fludarabine (25 mg/m² per day for 4 days); melphalan (140 mg/m²)	2-year NRM 30%, 5-year NRM 33%; 2-year EFS 49%, 5-year EFS 41%; 2-year OS 50%, 5-year OS 42%
Welliver et al (2018)[41]	Pilot	02122081	15	High-risk AML, ALL, MDS, >50 years or comorbidities unable to undergo TBI-based regimens	Bone, brain, testes	12 Gy (2·0 twice a day)	Cyclophosphamide	NRM four (25%) of 16; median OS 313 days
Al Malki et al (2019);[42] Arslan and Al Malki (2020)[43]	Phase 1	02446964	29	AML, ALL, MDS CR1 high risk, CR2, CR3, refractory, haploidentical	Bone, spleen, lymph nodes; 12 Gy liver and spleen; 16 Gy testes ALL; 12 Gy brain ALL	12–20 Gy (1·5-2·0 twice a day)	Fludarabine (25 mg/m² per day for 5 days); cyclophosphamide (14·5 mg/kg per day for 2 days); post-transplant cyclophosphamide (50 mg/kg per day for 2 days);	1-year NRM 9·3%; 1-year OS 83%; 1-year relapse rate 24%
Aristei et al (2020)[44]	Phase 2	03977103	20	AML in CR1, CR2, PR, haploidentical donor	Bone; 11·7 Gy lymph nodes	13·5 Gy (1·5 twice a day)	Thiotepa (2·5 mg/kg per day for 2 days); fludarabine (30 mg/kg per day for 5 days); cyclophosphamide (15 mg/kg per day for 2 days); T-cell manipulated graft	NRM six (30%) of 20; 14 (70%) of 20 alive and relapse-free; no chronic graft versus host disease

Wong et al Lancet Oncol 2020

Phase II Study of Total Marrow and Lymphoid Irradiation (TMLI) in Combination with Cyclophosphamide and Etoposide in Patients with Poor-Risk Acute Leukemia

Methods

- Relapsed or refractory AML or ALL: induction failure, in relapse or beyond 2nd remission with active disease
- Ages 18-60
- TMLI target structures bone, lymph nodes, and spleen to 20 Gy (2 Gy BID) and liver and brain to 12 Gy (1.2 Gy BID) over 5 days (days -9 through -5)
- The primary endpoint was progression free survival (PFS), and secondary endpoints included overall survival (OS), non-relapse mortality (NRM), and toxicities.

*Adjusted body weight **Ideal body weight
***Window of 1-2 d allowed for stem cell availability

City of Hope

Results

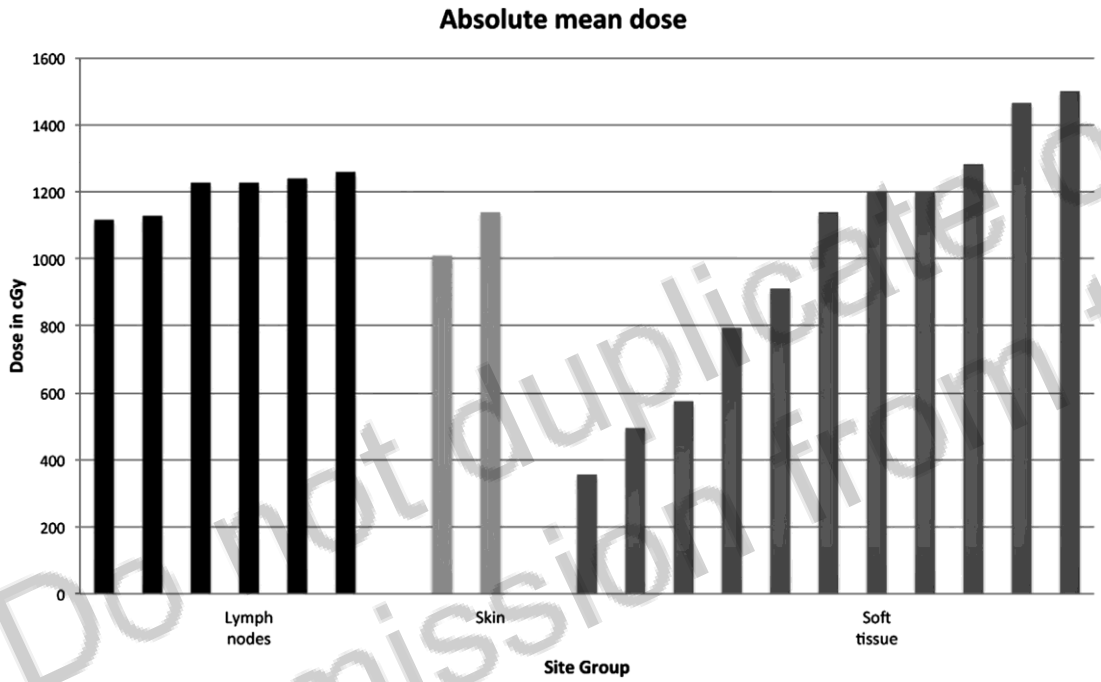
- Median follow-up 21.8 months (1.1 - 48.3)
- All patients engrafted.
- Complete response rate at day + 30 was 100% (N=56)
- 2- year progression free survival (PFS): 33% (95%CI: 21-45).
- 2-year overall survival (OS): 48% (95%CI: 35-61)
- Disease relapse/progression at 2 years: 58% (95%CI: 47-73).
- NRM at 100 days and 2 years were 4% (95%CI: 1-14) and 9% (95%CI: 4-21), respectively.
- Stomatitis (Bearman Gr 2 n=14, Gr 3 n=5) most frequent toxicity
- No significant differences in OS/PFS/RP/NRM between AML and ALL

City of Hope

Courtesy by J Wong

Extramedullary Relapse Following Total Marrow and Lymphoid Irradiation in Patients Undergoing Allogeneic Hematopoietic Cell Transplantation

International Journal of Radiation Oncology biology • physics
www.redjournal.org

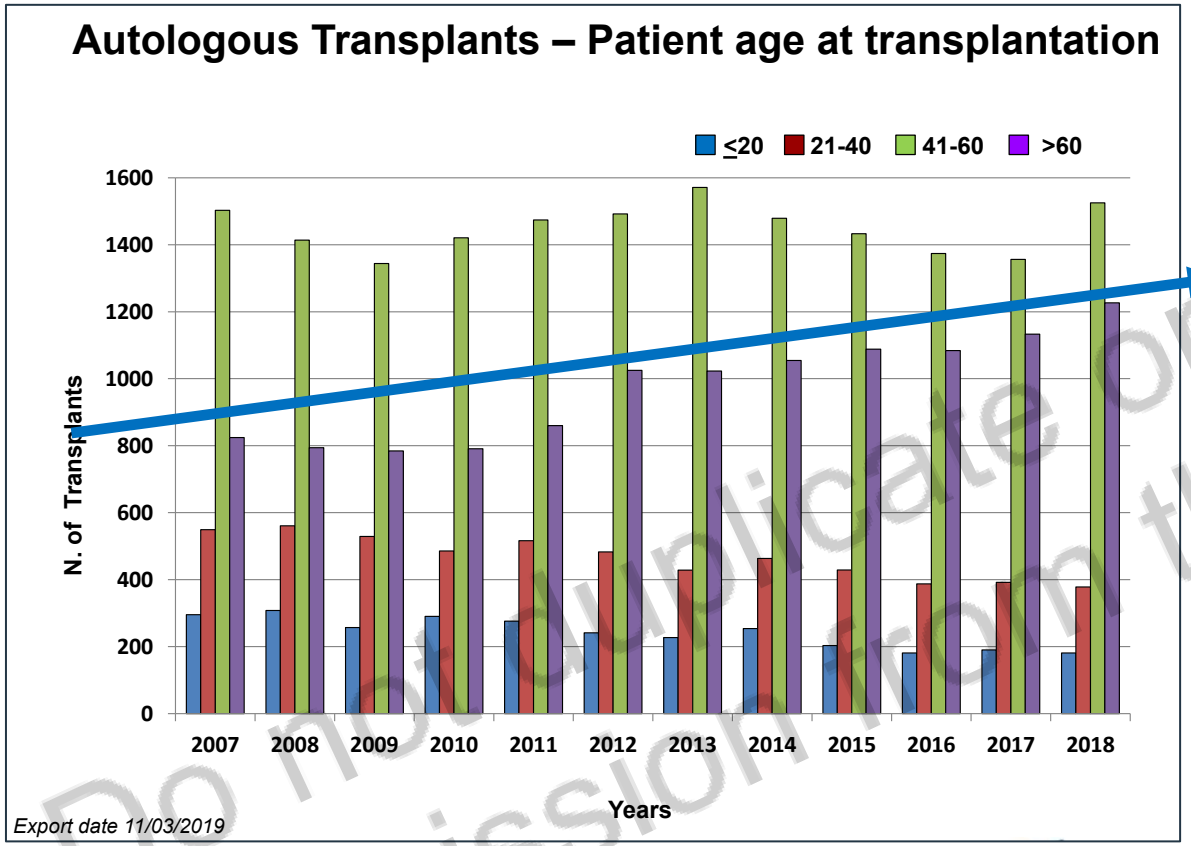


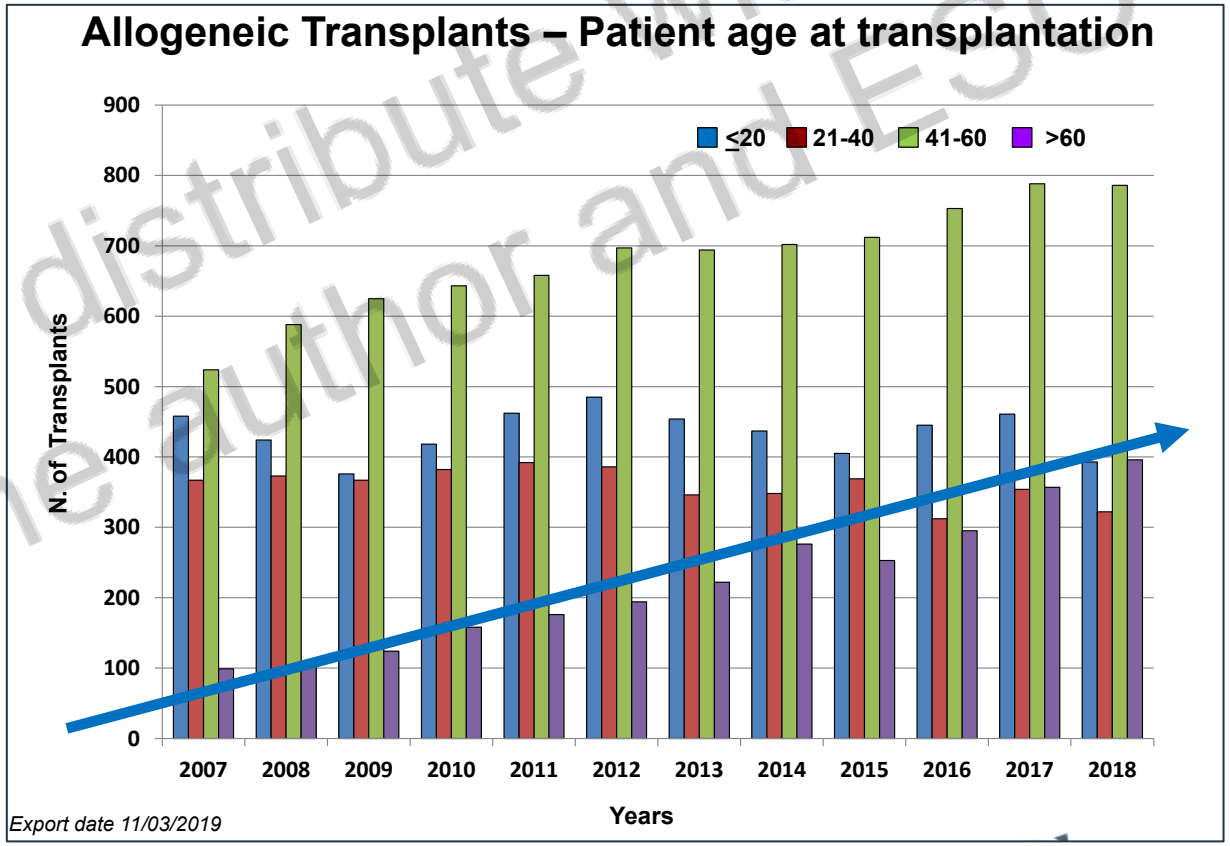
- 101 patients treated between 2006-2012 (AML,ALL,CML,MDS)
- median f.u. 12. months
- 12.9% patients EM relapse
  - 4 patients with BM relapse
  - 9 only EM relapse
  - 7 patients with EM relapse prior TMI
- pre-transplant EM disease only predictor for EM relapse
- **cumulative incidence of EM relapse 4% at 1 year and 11.4% at 2 year (similar to EM relapse with TBI)**

No increase incidence of EM relapse with TMLI

Kim JH 2014

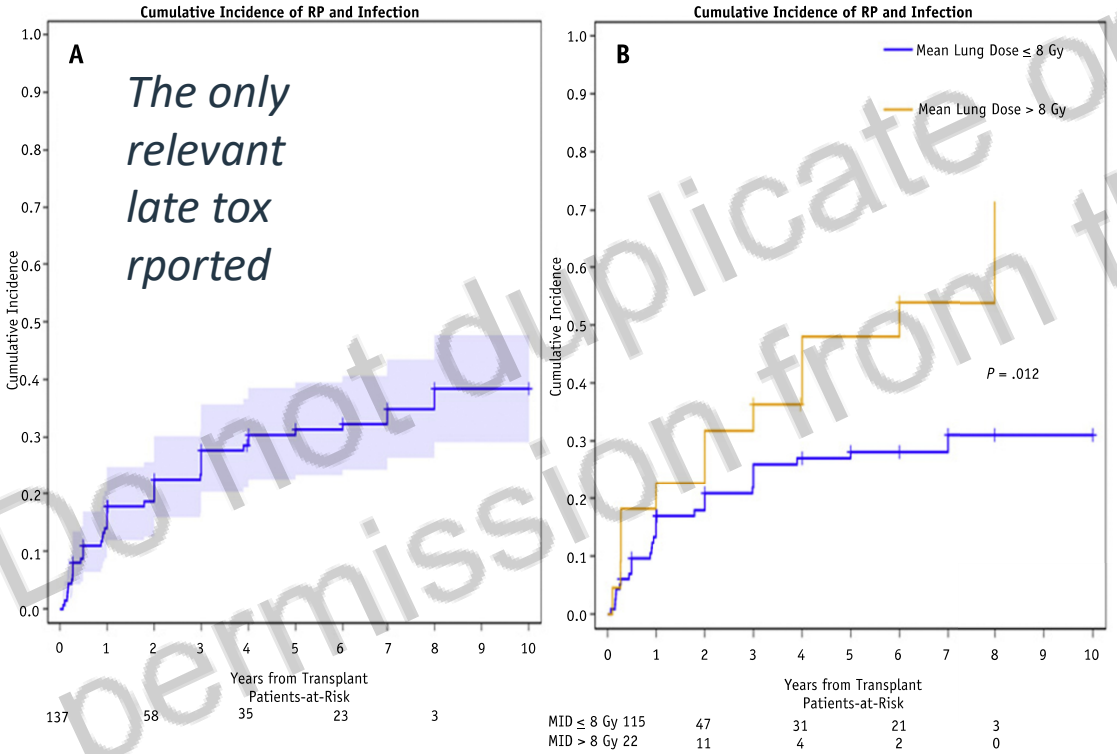
Age is really not a problem?





RIC with Fludarabine Melphalan and Total Marrow and Lymphoid Irradiation

12 Gy (1.5 Gy x 8 bid) TMLI



- 61 patients with Advanced leukemia
- median age 55 (9-70)
- median follow-up 7.4 years
- aGVHD II IV 69%
- cGVHD 74%
- 5 yy OS 42%
- 5 yy RFS 41%
- 5 yy CRI 26%
- 5 yy NRM 33%

Shinde 2019 IJROBP

Jensen 2018 Bio Blood Marrow Transplant

The «ULTIMATE»

Haplo for elderly with high risk leukemia

Haplo-HSCT for the elderly with high risk AL

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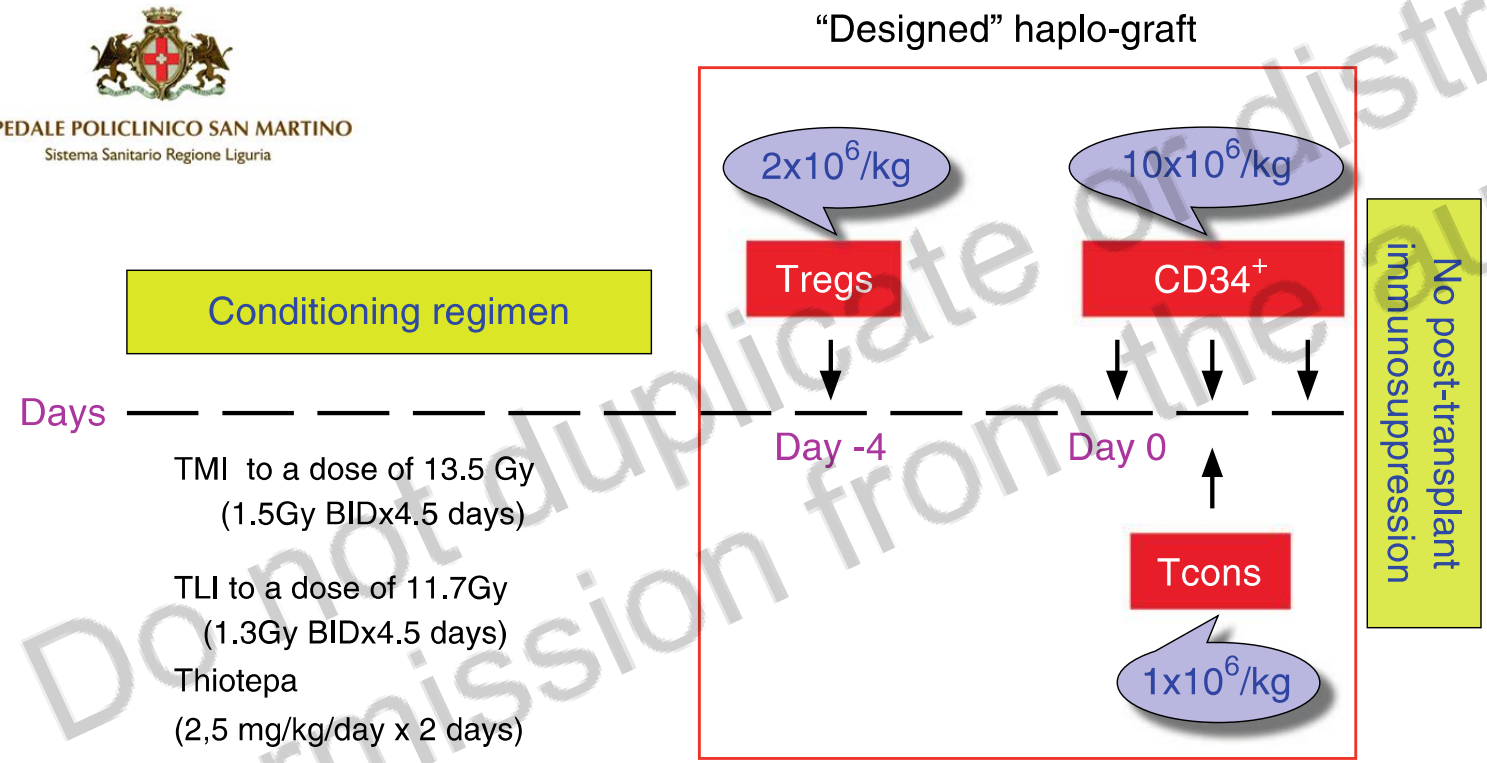
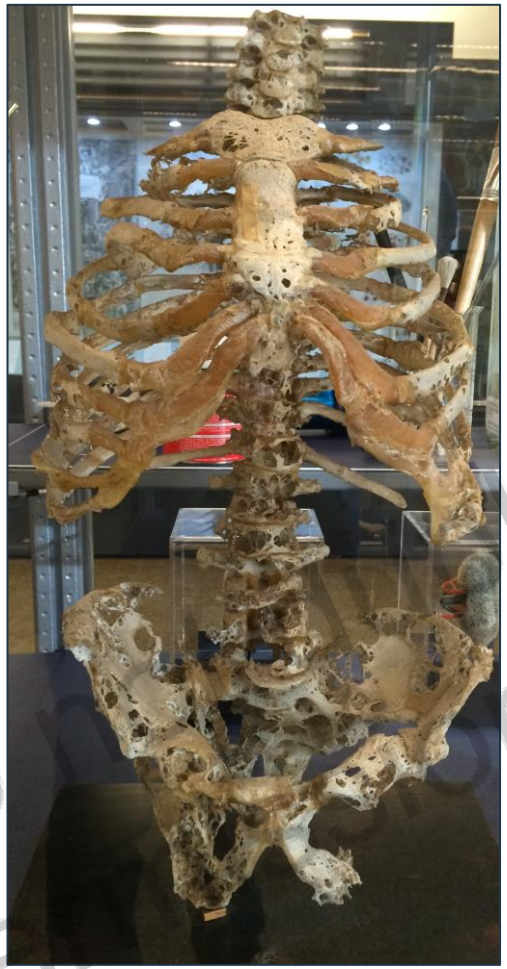


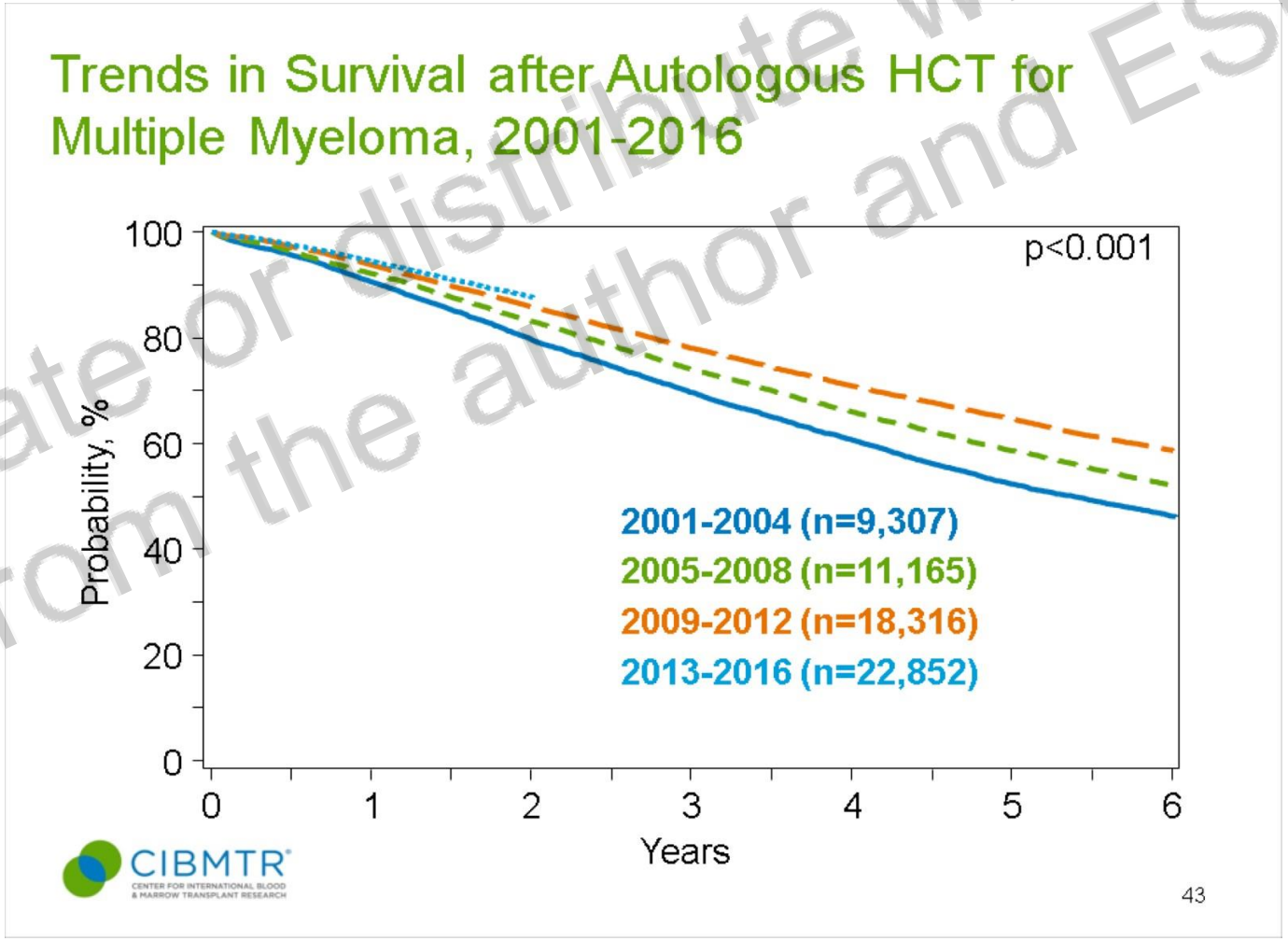
The Perugia Group

- **T cell depleted**
- **TMLI dose tailored**
- **median age 62 (55-68)**
- **AML high risk**
- **aGVHD II-IV** 43%
- **cGVHD** *none*
- **NRM** 29%
- **2 yy RFS** 71%

Pierini BMT 2019

Multiple myeloma

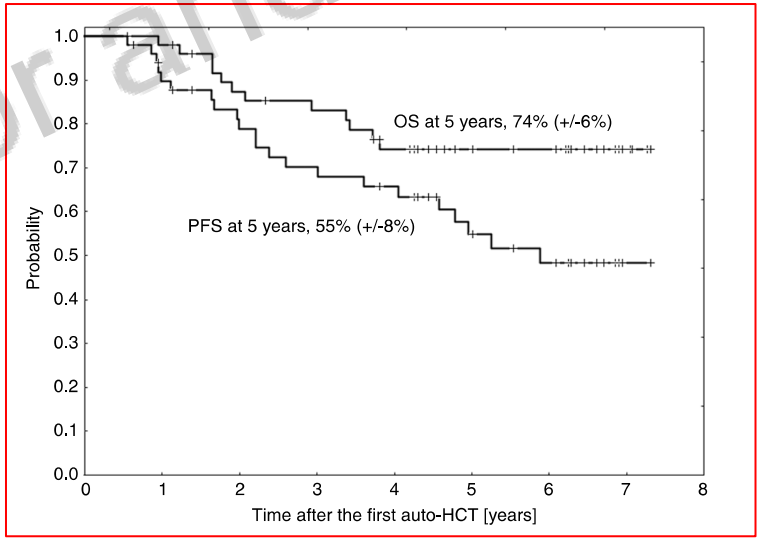




Tandem autologous hematopoietic cell transplantation with sequential use of total marrow irradiation and high dose melphalan in multiple myeloma

N	50
Median age, years (range)	58 (41–64)
Age > 60 years	18 (36%)
Sex: male/female	25 (50%)/25
Paraprotein isotype	
IgG	35 (70%)
IgA	6 (12%)
Light chain	6 (12%)
Non-secretory	3 (6%)
Stage at initial diagnosis[a]	
I	4 (11%)
II	12 (34%)
III	19 (54%)
No data	15
International scoring system	
I	15 (41%)
II	11 (30%)
III	11 (30%)
No data	13
Lines of preceding therapy, median (range)	1 (1–5)
1	37 (74%)
2	12 (24%)
3	1 (2%)

	First auto-HCT (TMI)				Second auto-HCT (melphalan)				TMI vs. melphalan Grade 2–4 AEs
Adverse event	Grade 2	Grade 3	Grade 4	Grade 2–4	Grade 2	Grade 3	Grade 4	Grade 2–4	*P* value
Febrile neutropenia[a]	–	10 (20%)	–	10 (20%)	–	14 (28%)	–	14 (28%)	0.48
Infections	2 (4%)	12 (24%)	1 (2%)	15 (30%)	2 (4%)	12 (24%)	–	14 (28%)	1.0
Nausea	11 (22%)	1 (2%)	–	12 (24%)	17 (34%)	10 (20%)	–	27 (54%)	0.008
Vomiting	2 (4%)	–	–	2 (4%)	6 (12%)	2 (4%)	–	8 (16%)	0.09
Diarrhea	3 (6%)	1 (2%)	–	4 (8%)	7 (14%)	1 (2%)	–	8 (16%)	0.38
Mucositis	–	1 (2%)	–	1 (2%)	3 (6%)	4 (8%)	–	7 (14%)	0.06
Hypokalemia	1 (2%)	1 (2%)	–	2 (4%)	4 (8%)	–	–	4 (8%)	0.68
Hyponatremia	–	1 (2%)	–	1 (2%)	–	–	–	–	1.0
Elevated liver enzymes/ bilirubin	2 (4%)	–	–	2 (4%)	–	1 (2%)	–	1 (2%)	1.0
Hemorrhagic cystitis	1 (2%)	–	–	1 (2%)	–	–	–	–	1.0
Cardiac insufficiency/ hypotensia	–	–	–	–	1 (2%)	–	–	1 (2%)	1.0



4 Gy x 3 fx

Giebel S el al Bone marrow Transplant 2020

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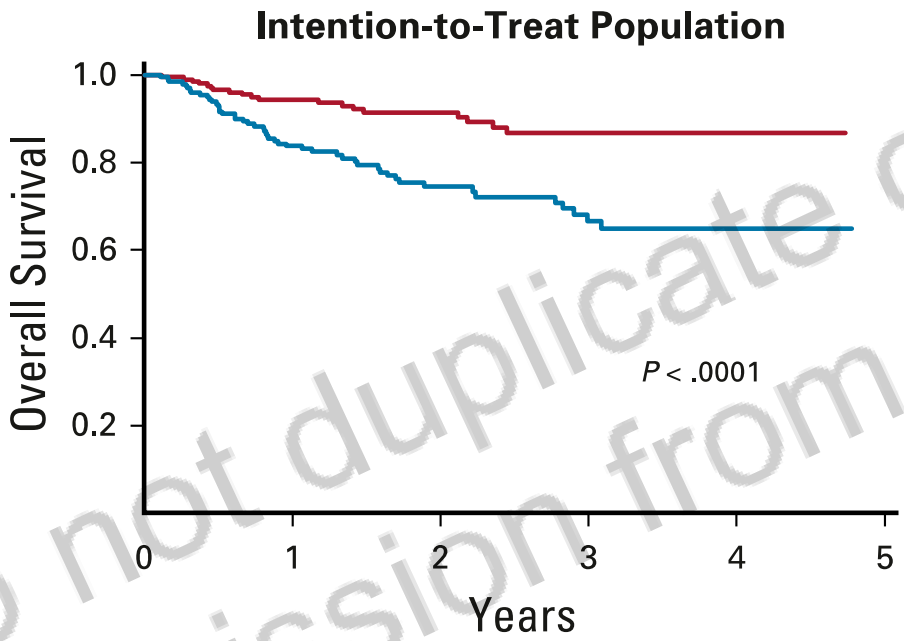
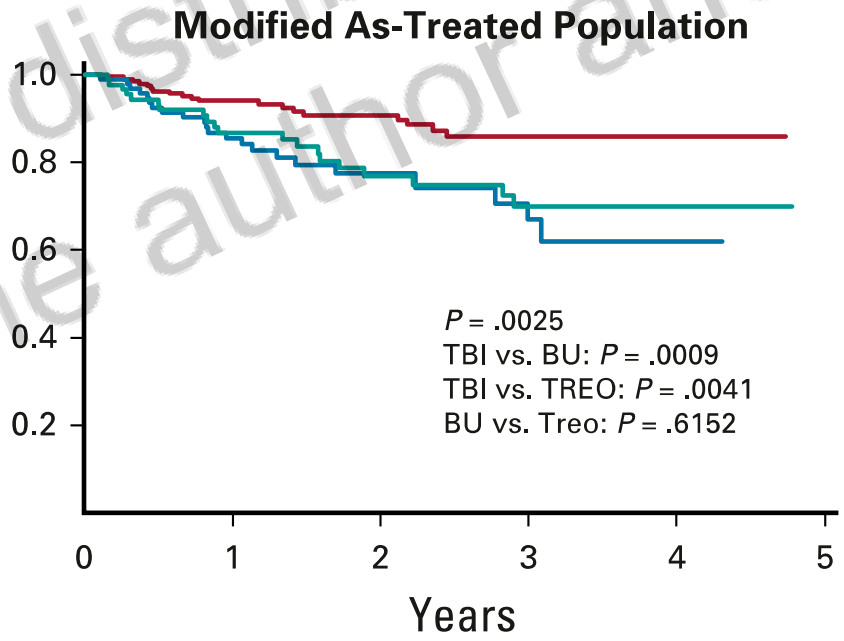
TMI potential advantages in pediatric patients

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





Peters C et al JCO 2020

POTENTIAL OF TMI IN PEDIATRIC PATIENTS

TMI in pediatric patients …
a new challenge to manage different toxicity from adults

Identical twins at 26 year of age After pediatric allo TBI

Diller L. et al N Engl J Med 2011

In which **acute** toxicities TBI can be a risk factor?

✓ ***salivary acute dysfunction***, with transitory bilateral enlargement of parotids

✓ ***Acute hemorrhagic cystitis*** (from 10% to 60% of patients) 48 to 72 h from transplantation

✓ ***VOD*** liver pain and icterus in 8.9% of allo-HSCT and 3.1% in auto-HSCT

✓ ***DAH*** diffuse hemorrhagic alveolitis from 2,5% to 10% of patients (mortality of 50-80 %)

✓ ***Acute mucositis***

Pediatric patients

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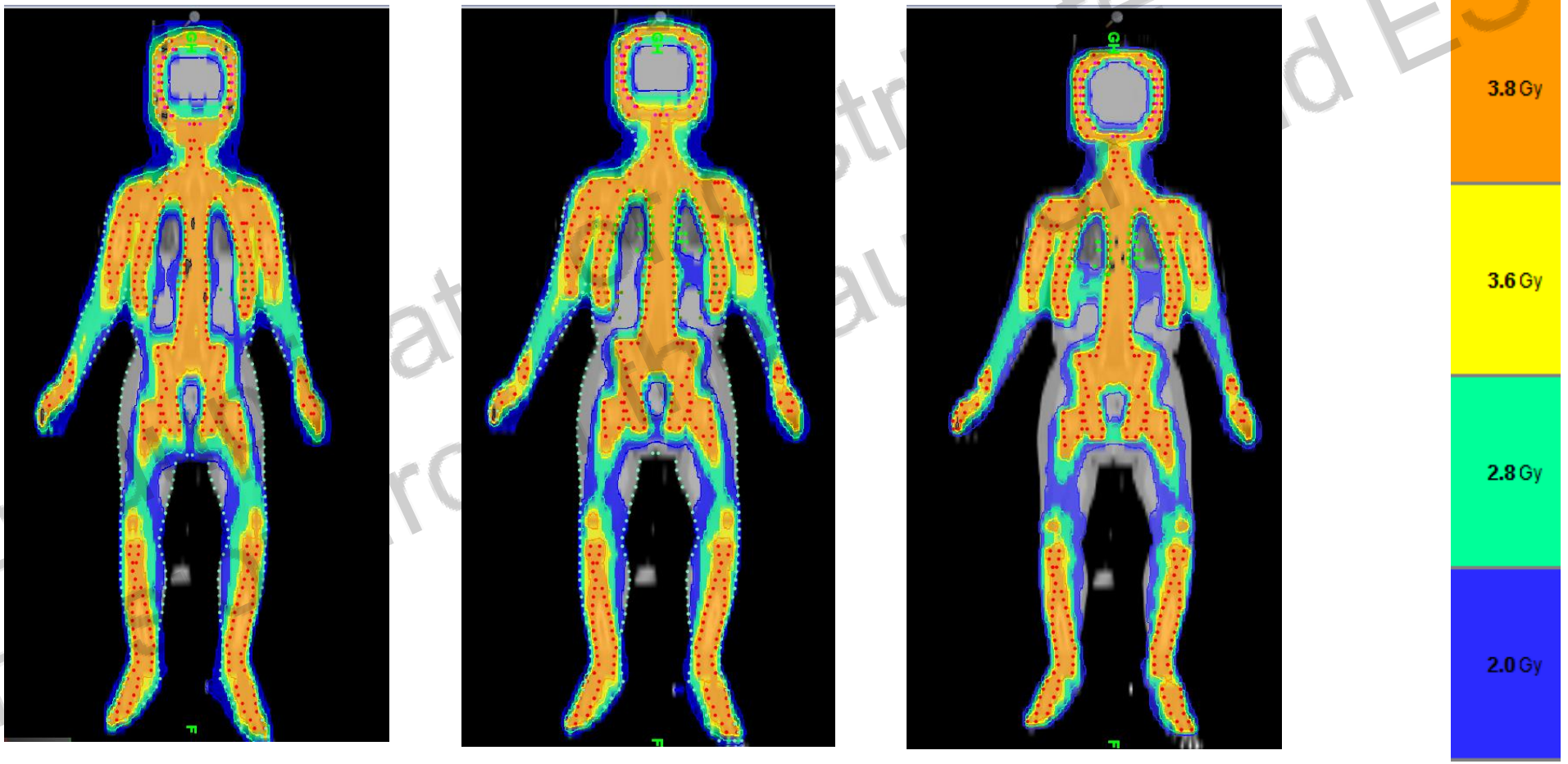

5 cm

2.5 cm

1 cm

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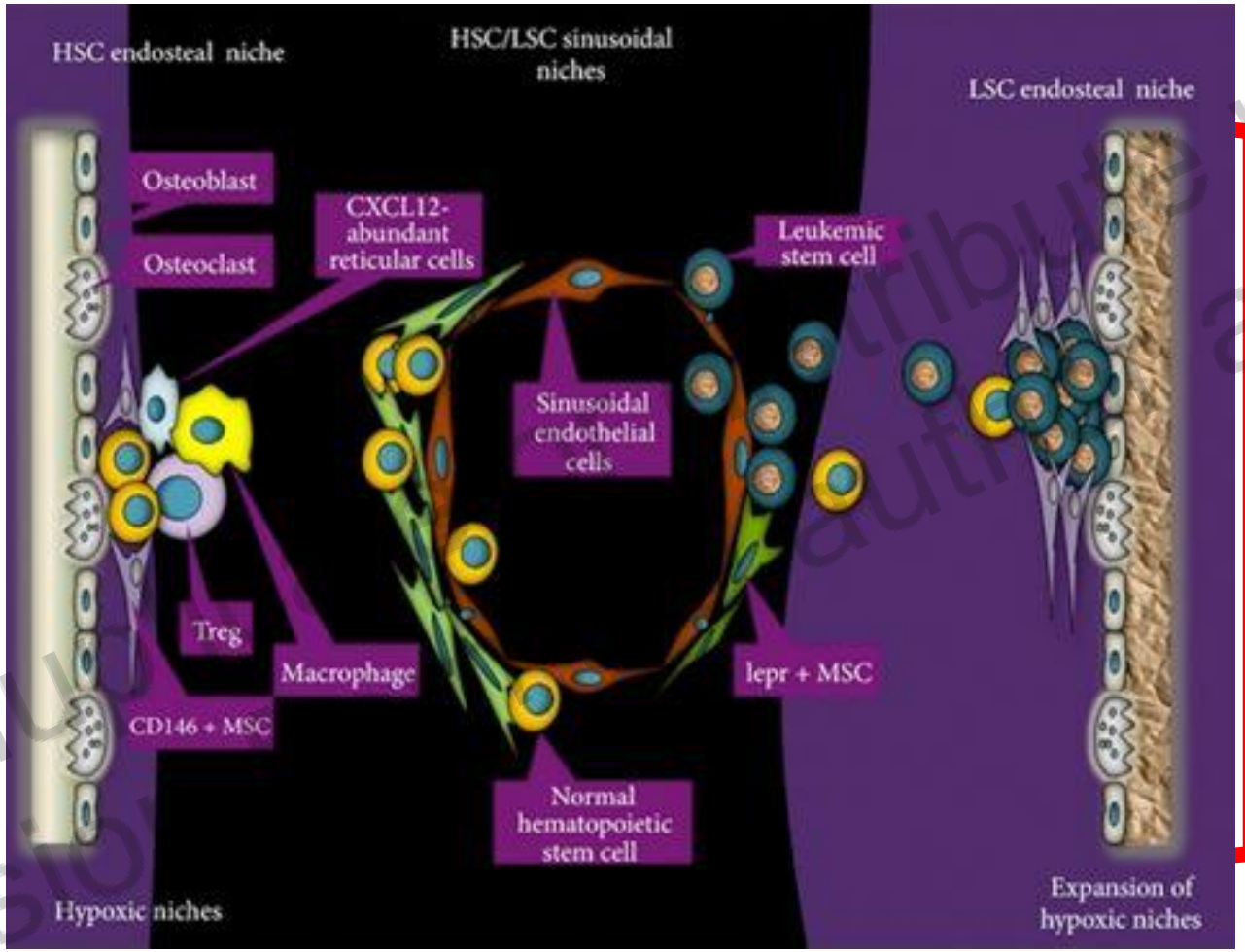
Technology meets biology: Imaging to target TMI

Leukemic Stem Cells



Larger hypoxic endosteal niche:
- **More radioresitant**
- **Detectable?**

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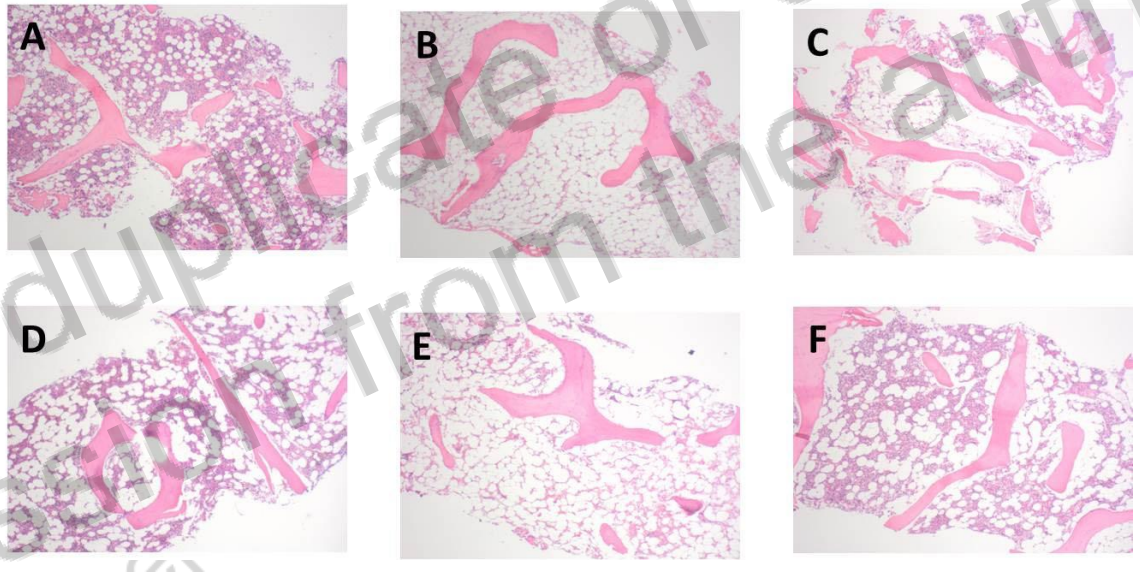
Precision allow to measure correctly the biological response

Marrow damage and hematopoietic recovery following allogeneic bone marrow transplantation for acute leukemias: effect of radiation dose and conditioning regimen



MAC

RIC

Bone marrow cellularity
Before and after 21 day from transplantation and at 1 Y

Wike C et al. ***Radiother & Oncol*** *2016*

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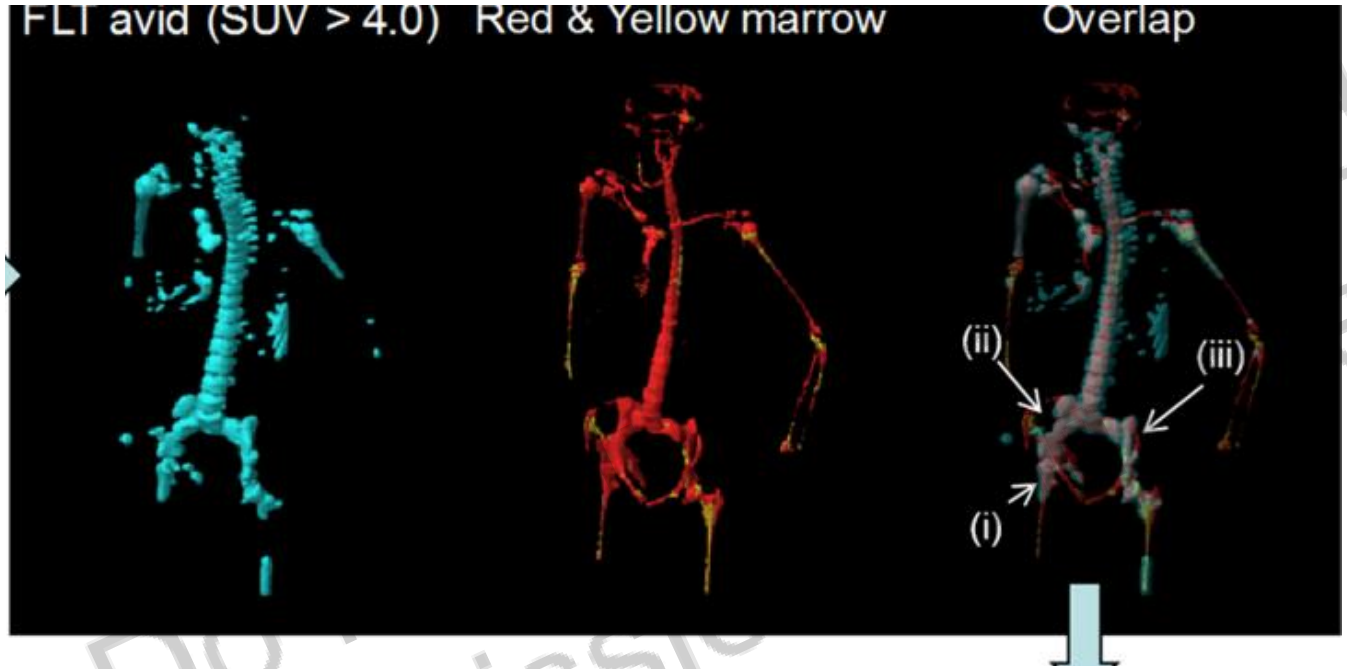
Whole-Body Distribution of Leukemia and Functional Total Marrow Irradiation Based on FLT-PET and Dual-Energy CT



DUAL energy CT registered different Hounsfield unit for each voxel and estimates are used to infer basis material composition

BONE MARROW

1) Trabeculae-rich osseous matrix
2) hematopoietic active RED marrow
3) fat-reach YELLOW marrow (potential hypoxic sanctuary for LSC)

H_2O and K_2HPO_4

Magome T. IJRBOP 2016

Magome T. molecular imaging 2017

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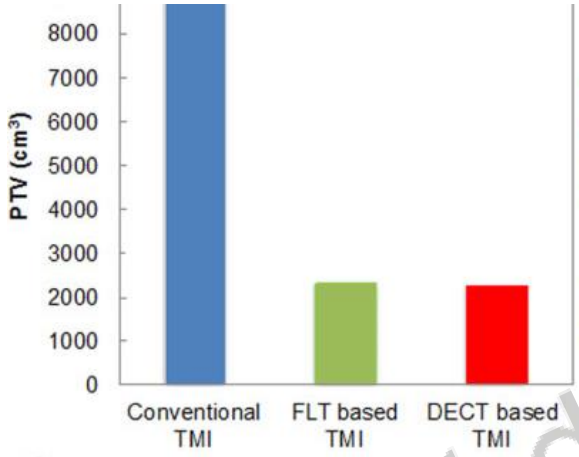
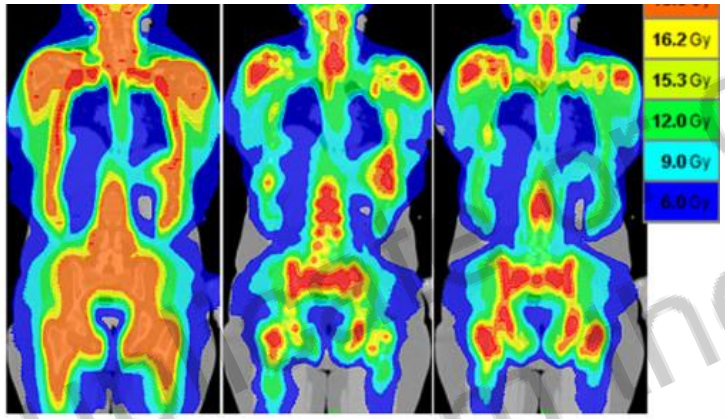
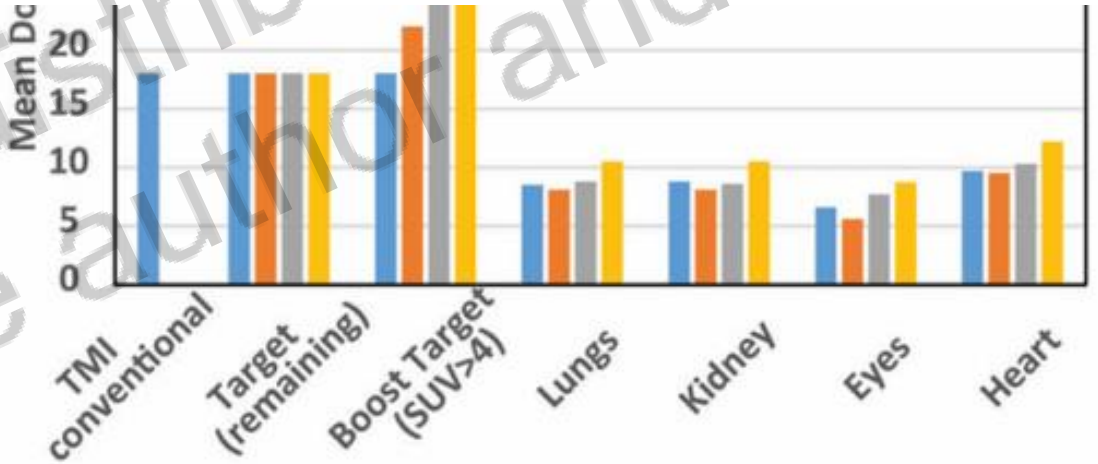
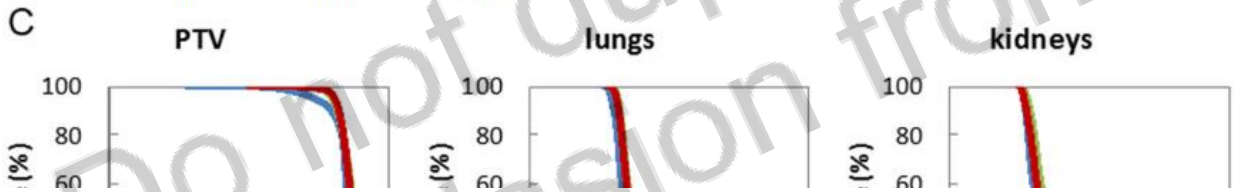
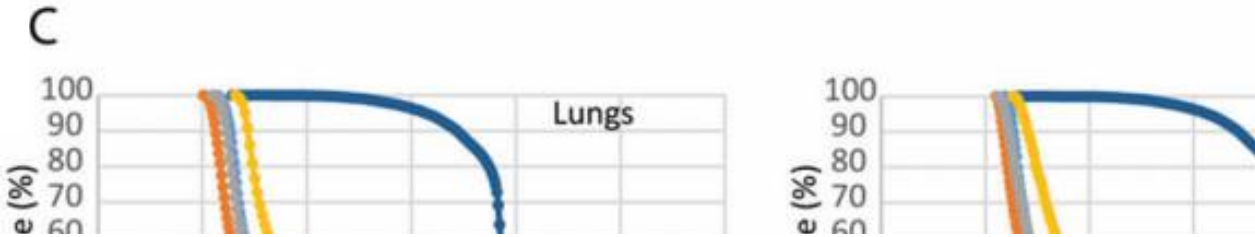
Whole-Body Distribution of Leukemia and Functional Total Marrow Irradiation Based on FLT-PET and Dual-Energy CT











Magome T. molecular imaging 2017

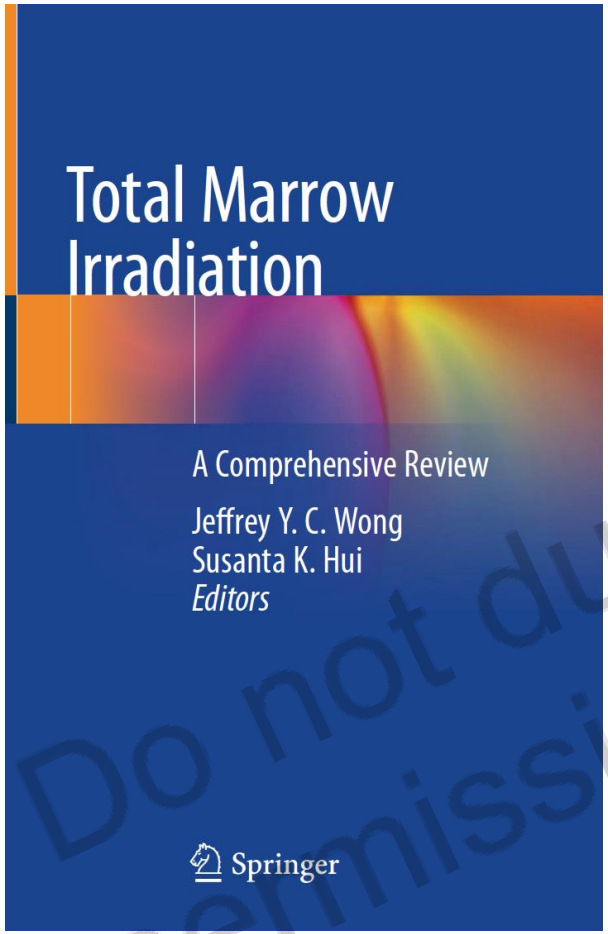
Worldwide ongoing trials

Institution NCT Trial No.	Type of Trial	Type of HCT	Disease Type	Targets	TMI Dose (Gy)	Fraction and Schedule	Chemo therapy
City of Hope NCT00540865 BB 03013	Phase I	allogeneic	AML relapsed or refractory with active disease Not eligible for standard HCT	bone, nodes, testes, spleen, brain	12, 13.5	1-5 BID	BU 4800 uM*min VP16 30 mg/kg
City of Hope NCT02469864 BB 05021	Phase I	allogeneic	AML, ALL relapsed or refractory with active disease Not eligible for standard HCT	bone, nodes, testes, spleen, 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 NCT02284T94 BB 14012	Phase II	allogeneic	AML or ALL IF, relapsed or > CR2	bone, spleen, nodes, 12 Gy liver, brain	20	2 Gy BID	Cy 100 mg/kg VP16 60 mg/kg
City of Hope NCT01467306 BB 11423	Phase I	allogeneic	AML CR1 or CR2	bone, spleen, nodes, 12 Gy liver, brain	18, 20	2 Gy BID	Cy 50 mg/m²/d x 2
City of Hope NCT02469864 BB 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/m²/d x 5 Cy 14.5 mg/kg/d x 2 ptCy 50 mg/kg/d x 2
City of Hope RB 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 Advanced disease > 2yr 1st CR	Bone, spleen, nodes, testes 20 Gy bone, nodes, spleen, ALL testes, brain	20 Gy 12	2 Gy BID 1.5 Gy BID	Flu 30 mg/m²/d x 3 (prior to TMI) ptCy 50 mg/d x 2 Flu 25 mg/m²/d x 4 Mel 140 mg/m²
City of Hope NCT04044496 BB 04199	Pilot	allogeneic	odd or co-morbidities ineligible for standard myeloablative regimens				
City of Hope NCT04080869 BB 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 Gy brain ALL	12, 14, 16, 18 20	1.5-2 Gy BID	Flu 30 mg/m²/d x 3 Mel 100 mg/m²
City of Hope NCT04080869 BB 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 Gy brain ALL	12, 14, 16, 18 20	1.5-2 Gy BID	Flu 30 mg/m²/d x 3 Mel 100 mg/m² ptCy 30 mg/d x 2

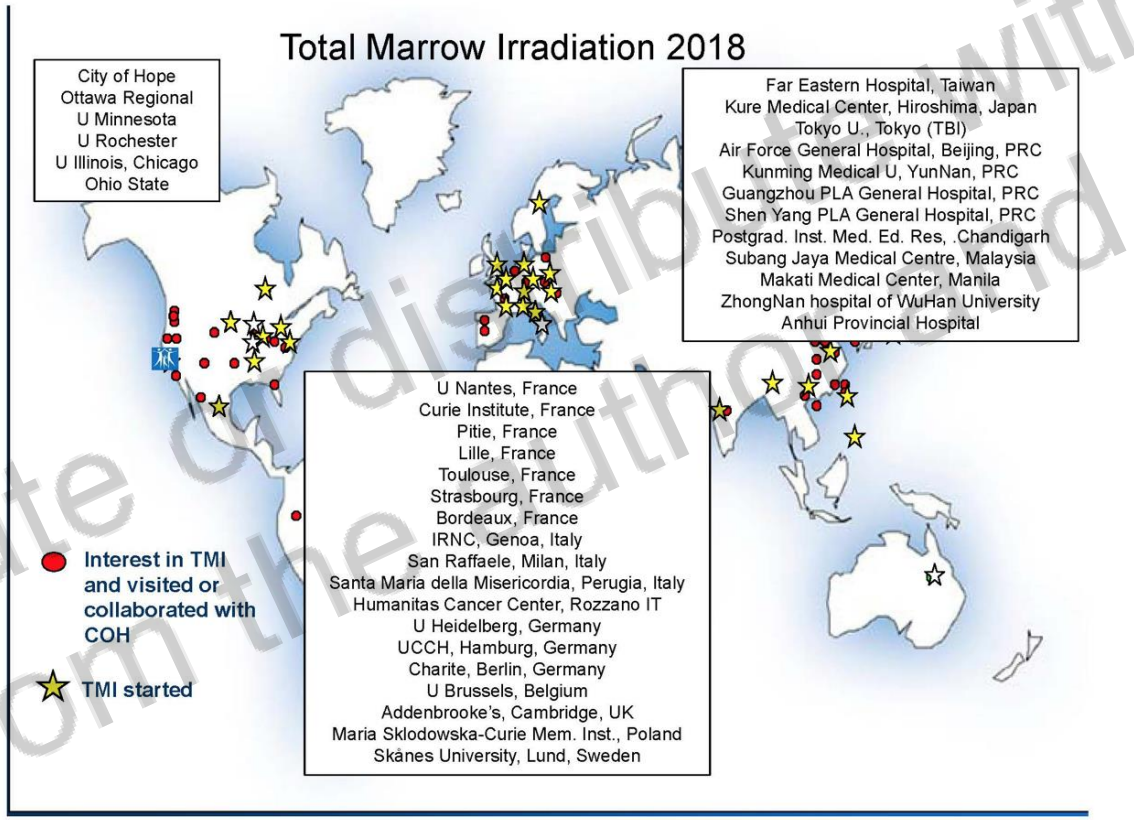
Institution NCT Trial No.*	Type of Trial	Type of HCT	Disease Type	Targets	TMI Dose (Gy)	Fractionation and Schedule	Chemotherapy
U. Illinois, Chicago 09938013	Phase I	Allogeneic	Refractory or relapse AML, ALL, MDS, MMM, CML	bone	3 to 12	1.5 Gy BID	Flu 40 mg/m²/d x 4 BU 4800 uM*min
U. Illinois, Chicago 03120104	Phase II	Allogeneic	Poor risk, refractory or relapse AML, MDS	bone	9	1.5 Gy BID	Flu 40 mg/m2/d x 4 BU 4800 uM*min
U. Illinois, Chicago 02333162	Phase I	Allogeneic	recurrent AML, ALL, MDS undergoing second HCT	bone	NS	BID over 2-5 days	Flu, Mel
Case Comprehensive Cancer Center 02129582	Phase I	Allogeneic	High risk AML, ALL, NHL, HL, MM, MDS, CLL, CML ineligible for full myeloablative regimen	bone	NS	BID over 4 days	Flu, Bu
U. Minnesota 00688566	Phase I	Allogeneic	High risk ALL, AML CR2, CR3, Relapse, IF	bone	15, 18	3 Gy QD	Flu 25 mg/m²/d x 3 Cy 60 mg/m/kg x 2
Ohio State 02122081	Pilot	Allogeneic	High risk AML, ALL, MDS > 50 yrs old or comorbidities unable to undergo TBI based regimens	bone, brain testes	12	2 Gy BID	Cy
U. Perugia 03977103	Phase II	Allogeneic haplo-identical	AML in CR1, CR2, PR	bone nodes 11.7 Gy	13.5 Gy TMI	1.5 Gy BID 1.3 Gy BID	TT 2.5 mg/kg/d x 2 Flu 30 mg/kg/d x 5 Cy 15 mg/kg/d x 2 T-cell manipulated graft
Indiana U. 03696537	Phase I/II	Allogeneic	Relapsed/refractory ALL, AML, MDS, CML ages 18-65	bone	NS	BID over 10 days	Flu 30 mg/m²/d x 5
Beijing 307 Hospital 03049223	Phase I	Allogeneic	High risk AML, ALL (1F, relapse > CR2)	bone, lymph nodes	12 - 20	4 Gy QD	Cy 60 mg/kg/d x 2
Beijing 307 Hospital 03402210	Pilot	Allogeneic	AML, ALL in CR1 or CR2	bone, lymph nodes	12	4 Gy QD	Cy 60 mg/kg/d x 2
University Hospitals of Geneva 03262220	Pilot	Allogeneic	Hematologic malignancy CR1, CR2 or CR3 Age 40 – 80 yrs old	bone	12 (13.5 to active BM)	4 Gy QD with 4.5 Gy QD boost to active BM	

Institution NCT Trial No.	Type of Trial	Type of HCT	Disease Type	Target	TMI Dose Levels (Gy)	Fraction and Schedule	Chemotherapy
City of Hope 00112827	Phase I	autologous (tandem)	stage I-II responding or stable	bone	10,12,14,16,18	2 Gy QD-BID	Mel 200 mg/m² first auto-HCT
City of Hope 00112827	Phase II	autologous (tandem)	stage I-II responding or stable	bone	16	2 Gy BID	Mel 200 mg/m² first auto-HCT
City of Hope 01163237	Phase I	allogeneic	refractory, relapsed prior auto HCT allowed	bone	12, then de-escalated to 9	1.5 Gy BID	Flu 25 mg/m² x 2 Mel 140 mg/m² Bortezomib 0.5 mg/m²
France Multi-Center 01794572	Phase III	autologous	first relapse	bone	8, 10, 12, 14, 16	1-2 Gy BID	Mel 140 mg/m²
Ottawa Regional 00800039	Phase I/II	autologous	relapsed	bone	14, 16, 18 completed plan to go to 28	2 Gy BID	none
Marie Sklodowska-Curie Cancer Center, Poland 01655014	Pilot	autologous (tandem)	CR, VGRR, or PR	bone	12 Gy	4 Gy QD	Mel 200 mg/m² second auto HCT
U. Illinois at Chicago 02024860	Phase I	autologous	high or intermediate risk of progression	bone	3, 6, 9, and 12	3 Gy QD	Mel 200 mg/m²
U. Illinois at Chicago 02043947	Phase I	autologous	relapsed or refractory	bone	3, 6, and 9	3 Gy QD	Mel 200 mg/m²
U Rochester 01182233	Phase I	autologous	MM	bone	10 to 20	2-4 Gy QD	Mel 200 mg/m²

Courtesy by J Wong



International Consortium of Total Marrow Irradiation (ICTMI) (2009)



Thanks