IRCCS Azienda Ospedaliera Universitaria
San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

Verso nuovi regimi di condizionamento in ambito trapiantologico?

XXI Congresso Nazionale AIRO
Genova 22 Novembre 2011

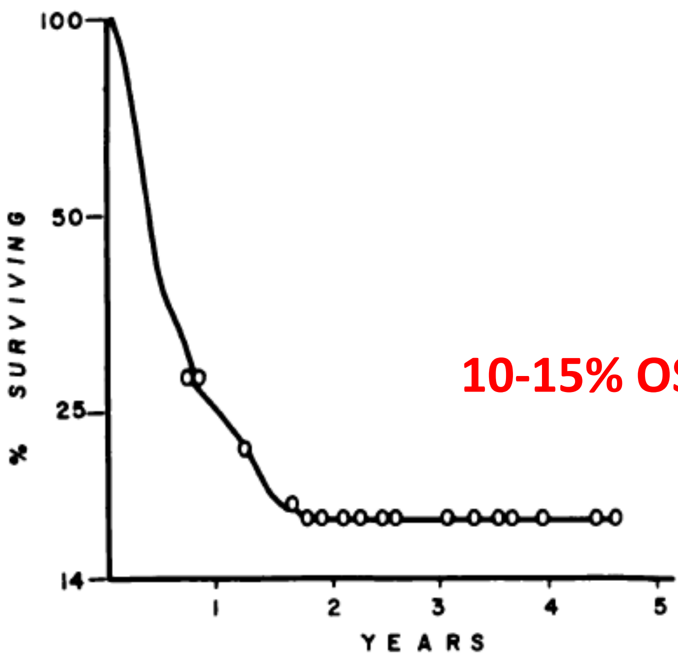
Stefano Vagge

U.O.C. Oncologia Radioterapica

What's changed in the last three decades for advanced leukemia patients?

One Hundred Patients With Acute Leukemia Treated by Chemotherapy, Total Body Irradiation, and Allogeneic Marrow Transplantation

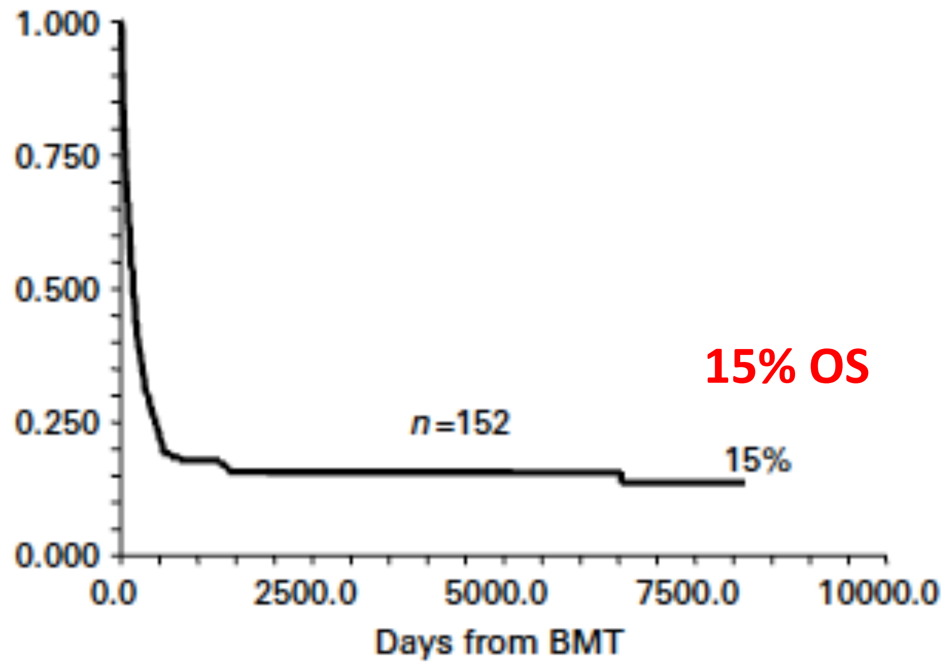
Thomas Blood 1977



10-15% OS

Allogeneic hemopoietic stem cell transplants for patients with relapsed acute leukemia: long-term outcome

Bacigalupo BMT 2007



15% OS

LONG-TERM
outcome of 152 patients
with relapsed acute Leukemia

- The actuarial **20 year** survival is **15%**
- The cumulative incidence of **TRM** is **40%**
- The cumulative incidence of **RRD** is **45%**

THE MOST COMMON CAUSE OF DEATH IS LEUKEMIA RELAPSE

Multivariate analysis between

- Transplant related mortality
- donor related mortality
- disease related mortality

only →

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

Bacigalupo BMT 2007

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**

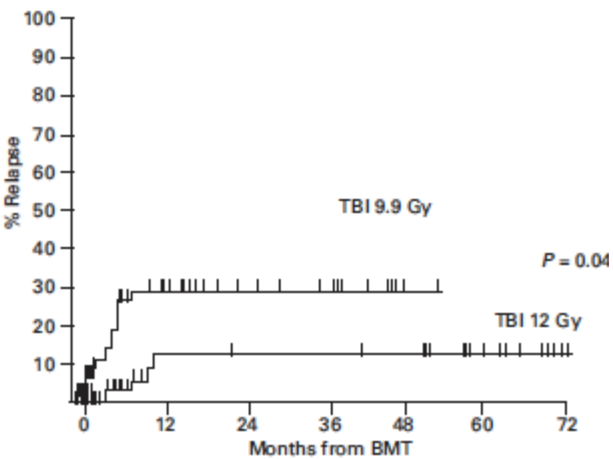
  → **higher disease-free survival**

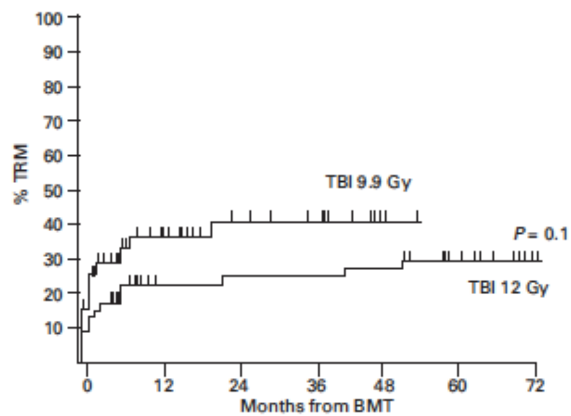
Xu Shi-Xia et al, Leukemia & Lymphoma 51:50-60 2010

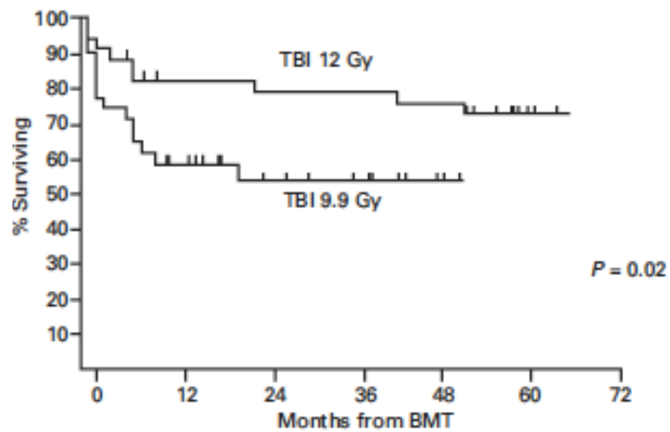
TBI fractionation influence the outcome

Low-dose fractionated total body irradiation (TBI) adversely affects prognosis of patients with leukemia receiving an HLA-matched allogeneic bone marrow transplant from an unrelated donor (UD-BMT)

6 x 2.0 Gy bid vs 3 x 3.3 Gy







Hyper-fractionation allow increasing total dose with less toxicity than single daily fraction

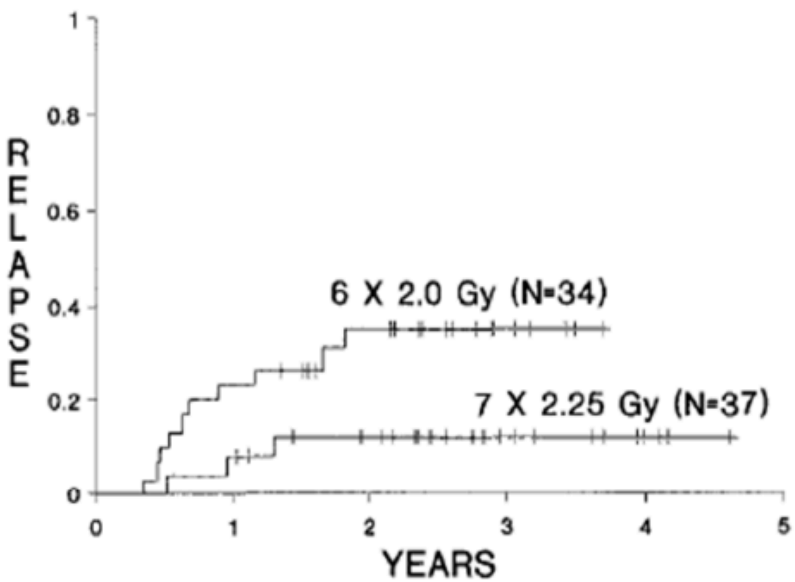
Corvò BMT 2002

THE RADIATION DOSE DILEMMA

Allogeneic Marrow Transplantation in Patients With Acute Myeloid Leukemia in First Remission: A Randomized Trial of Two Irradiation Regimens

By Reginald A. Clift, C. Dean Buckner, Frederick R. Appelbaum, Scott I. Bearman, Finn B. Petersen, Lloyd D. Fisher, Claudio Anasetti, Patrick Beatty, W.I. Bensinger, Kristine Doney, Roger S. Hill, George B. McDonald, Paul Martin, Jean Sanders, Jack Singer, Patricia Stewart, Keith M. Sullivan, Robert Witherspoon, Rainer Storb, John A. Hansen, and E. Donnall Thomas

Blood, Vol 76, No 9 (November 1), 1990: pp 1867-1871



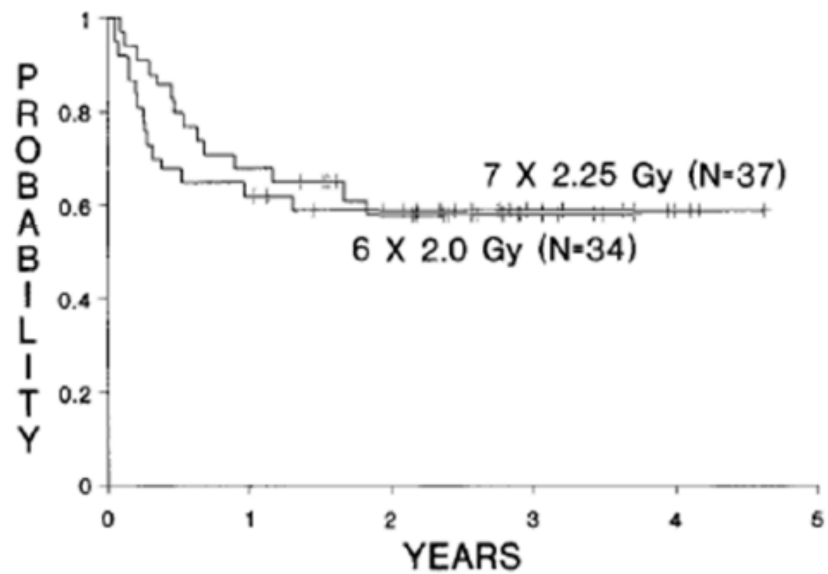


Fig 4. **Probability of surviving relapse-free after transplantation.**

THE RADIATION DOSE DILEMMA

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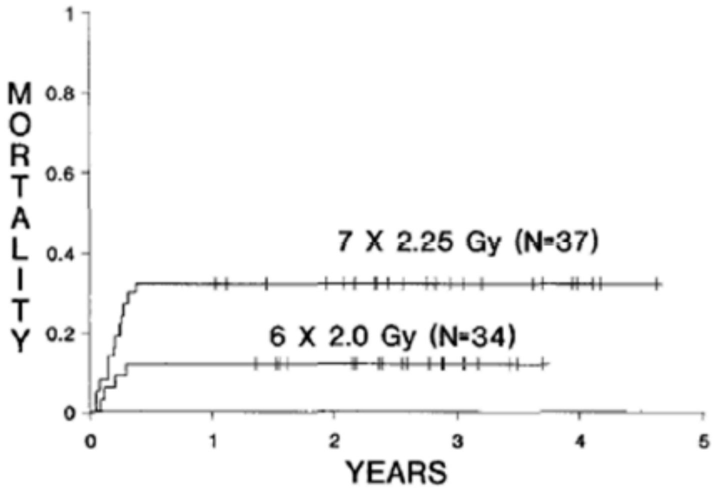
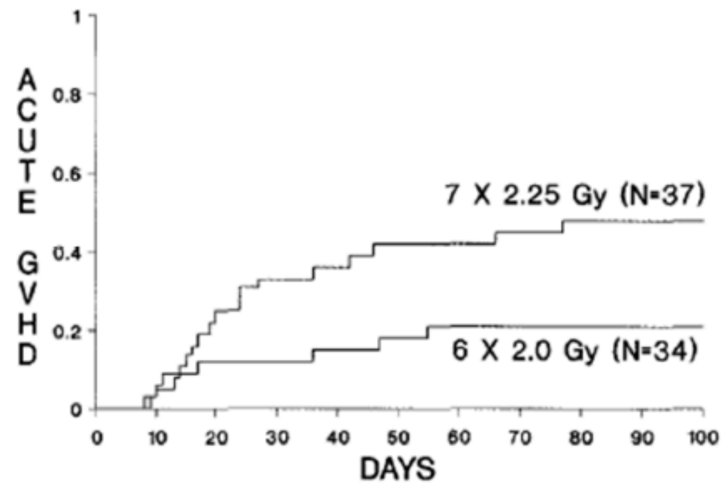
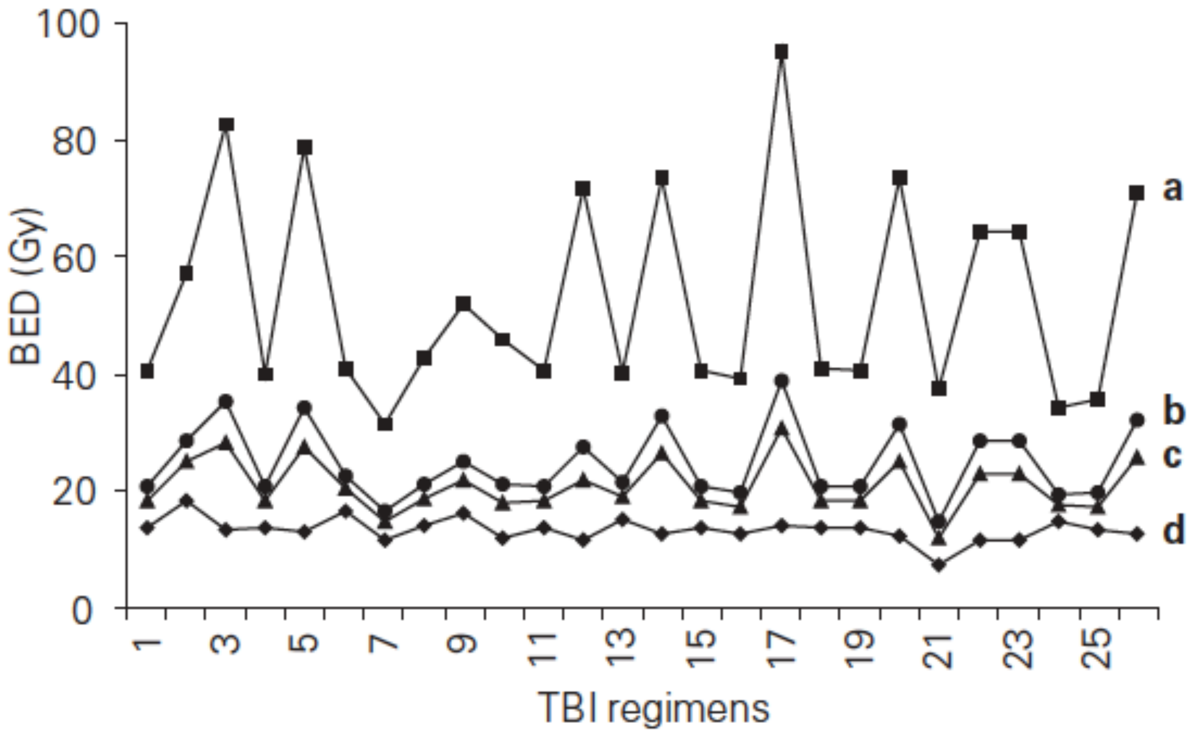




There is a limit for TBI dose

THE LQ MODEL IN TBI



a: Lens

b: Kidneys

c: Lungs

d: **LEUKEMIC CELLS**

No TBI schedule exist with radiobiologically advantages for healty tissue versus leukemic tumor burden

Henk B. Ka l Strahlenther Onkol 2006

HT-TMI

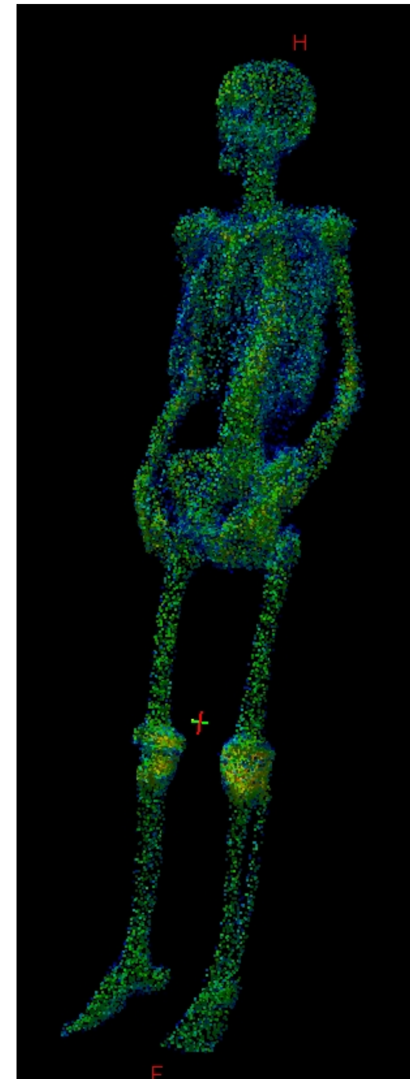
Can we go toward new conditioning regimens in **HSCT** for advanced leukemic patients ?

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



Total Marrow Irradiation as a Boost after TBI in allo-SCT conditioning for relapsed acute leukemia

RATIONALE

▪ **TBI is actually the standard treatment** in the conditioning regimen of advanced leukemia providing good clinical outcome especially in HLA-matched unrelated donors .

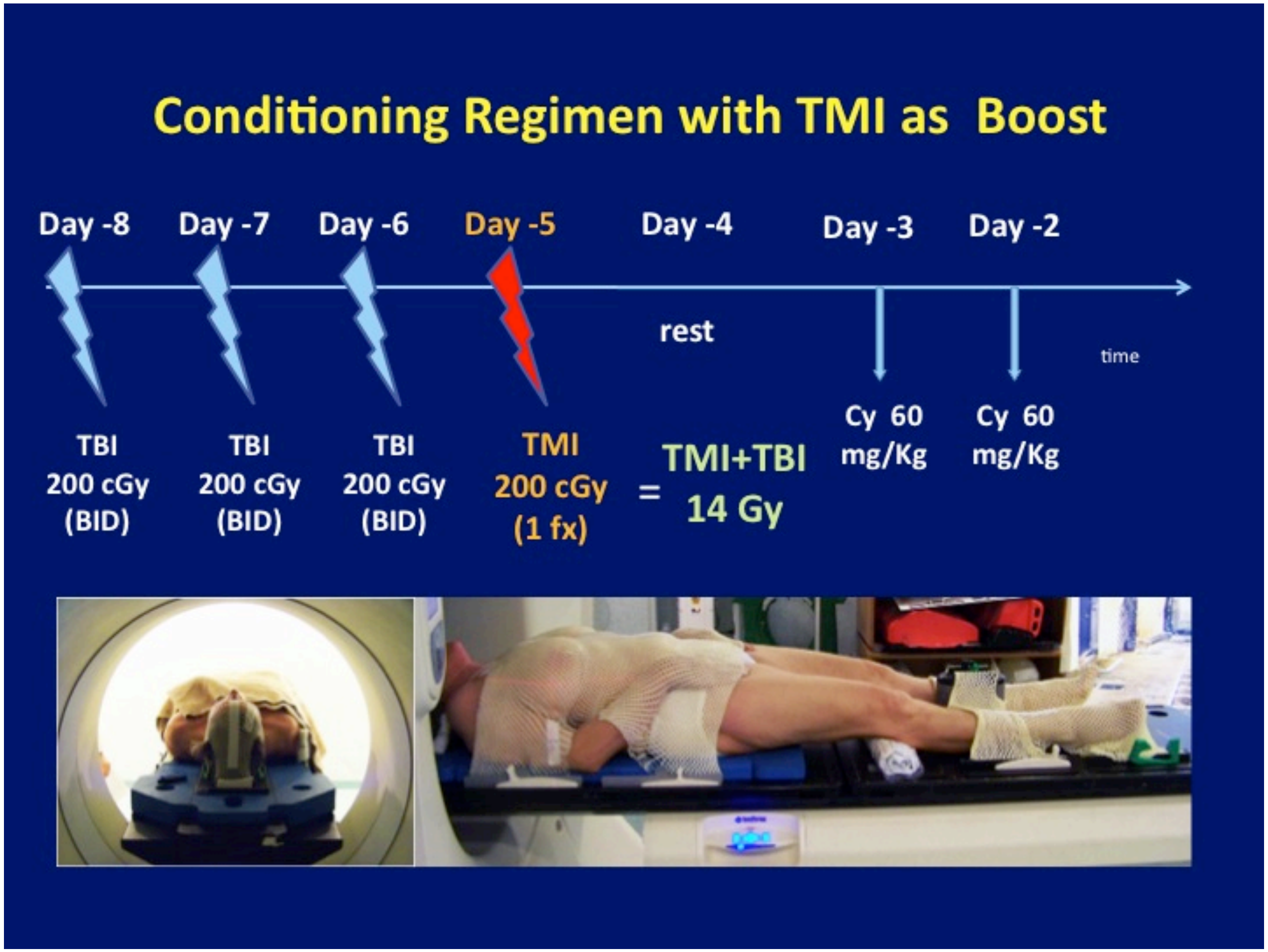
▪**TBI** assures a good coverage of entire body by **avoiding the risk of leukemia relapse in sites such as skin.**

▪ **Increasing the dose of TBI is not advisable** due to the high risk of increased toxicity mainly to the lungs, liver, and kidneys

▪Hypothesis**:** ***total dose of RT*** *can be increased, thus* ***increasing leukemia cell kill****, without increasing overall toxicity of TBI*

Corvò Radiother Oncol 2011

Total Marrow Irradiation as a Boost after TBI in allo-SCT conditioning for relapsed acute leukemia



Corvò Radiother Oncol 2011

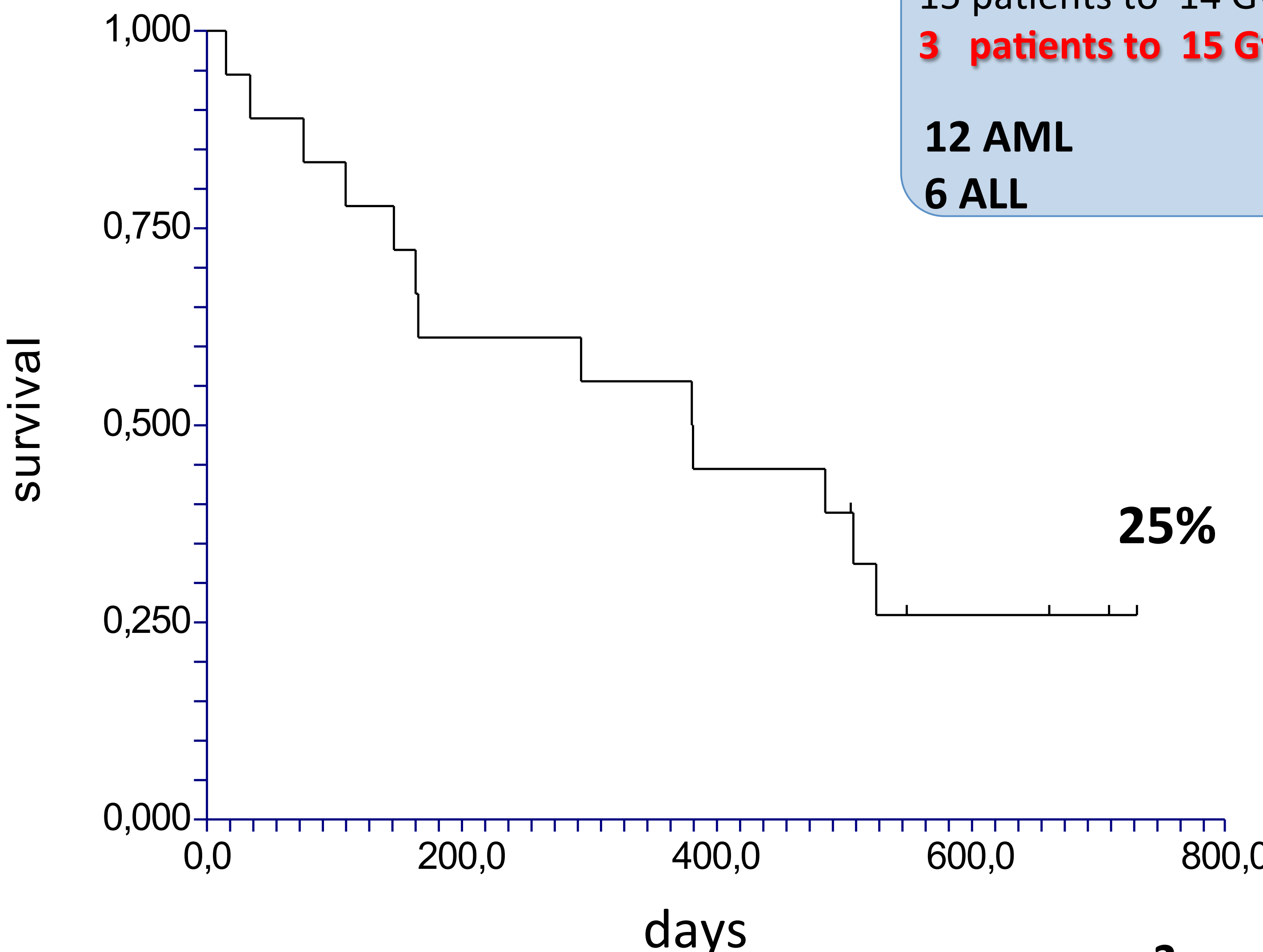
Median organ dose reduction escalating Bone Marrow dose with TMI (1 Gy each step)

	TBI 12 Gy	TBI/TMI basic	TBI/TMI Level 1	TBI/TMI Level 2	TBI/TMI Level 3	TBI/TMI Level 4	TBI/TMI Level 5	TBI/TMI Level 6
Marrow	**12**	**14**	**15**	**16**	**17**	**18**	**19**	**20**
Brain	*10*	*11*	*11.5*	*12*	*12.5*	*13*	*13.5*	*14*
Eye	**10**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**
Spinal Cord	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Oral mucosa	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Thyroid	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Oesophagous	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Lung	**10**	**11**	**11.5**	**12**	**12.5**	**13**	**13.5**	**14**
Heart	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Breast	*10*	*11*	*11.5*	*12*	*12.5*	*13*	*13.5*	*14*
Liver	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Bowel	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Kidney	**12**	**13**	**13.5**	**14**	**14.5**	**15**	**15.5**	**16**
Bladder	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Rectum	*12*	*13*	*13.5*	*14*	*14.5*	*15*	*15.5*	*16*
Testes	*12*	*12.2*	*12.4*	*12.6*	*12.8*	*13*	*13.2*	*13.4*

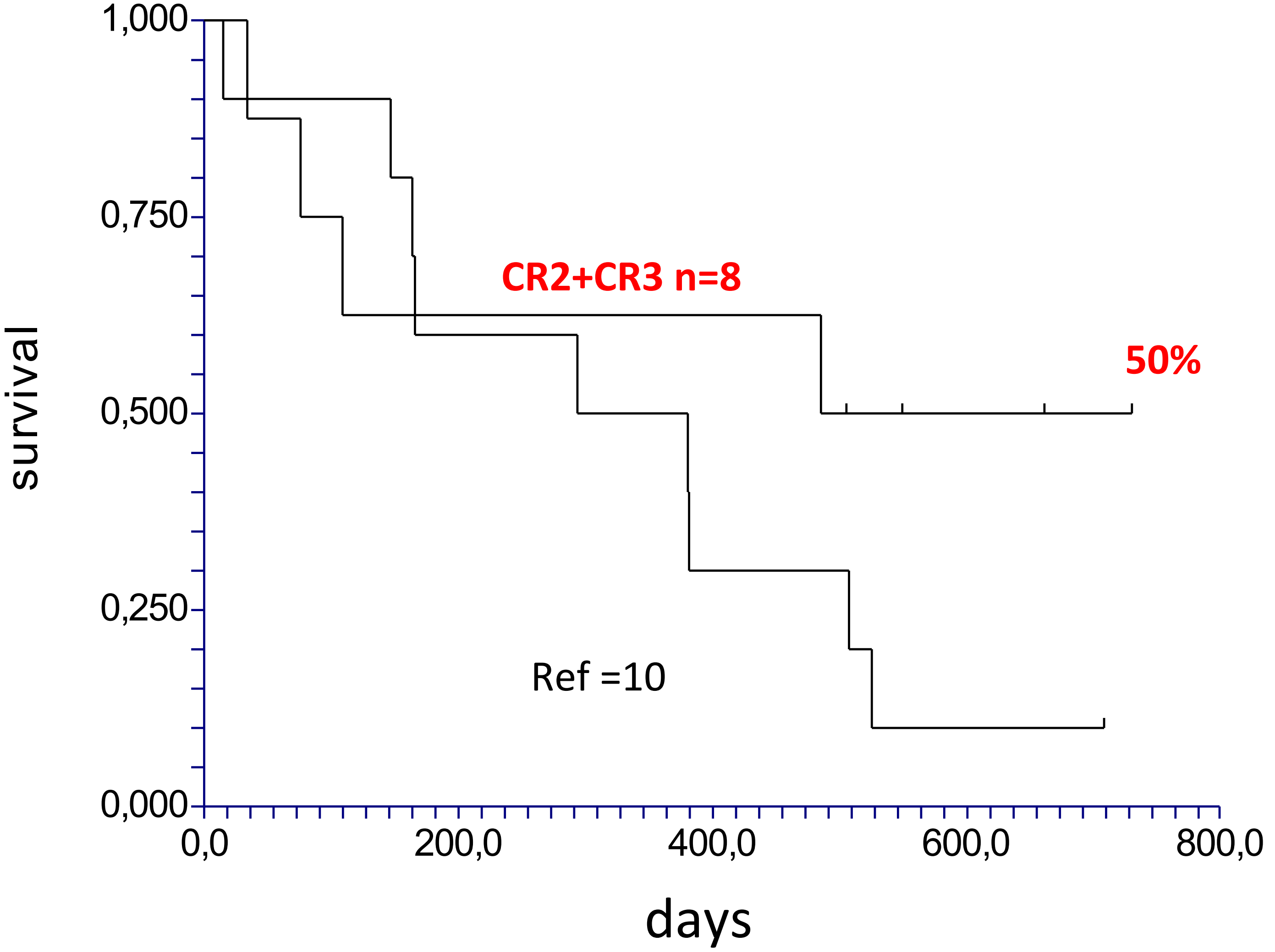
TMI : 18 patients; 10 with refractory dis; 8 second allo

15 patients to 14 Gy (12 +2)
3   patients to 15 Gy (12+3)

12 AML
6 ALL

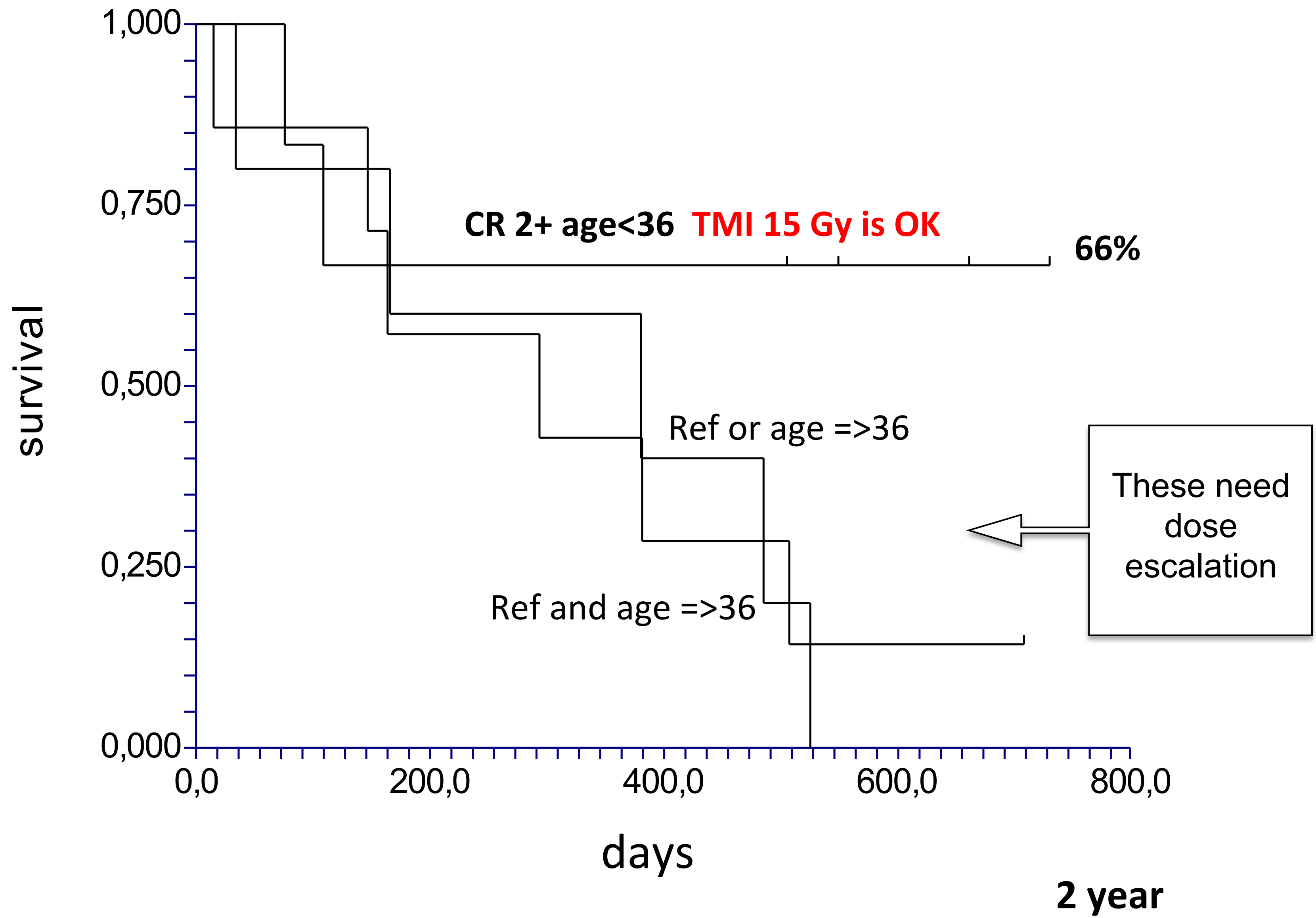


2 year



1,000
0,750
0,500
0,250
0,000
survival
CR2+CR3 n=8
50%
Ref =10
0,0
200,0
400,0
600,0
800,0
days

2 year



1,000
0,750
0,500
0,250
0,000
survival
0,0
200,0
400,0
600,0
800,0
days
CR 2+ age<36 TMI 15 Gy is OK
66%
Ref or age =>36
Ref and age =>36
These need dose escalation
2 year

Is there a new role for TBI and ASCT in leukemic patients?

Role of TBI in ASCT for Leukemia

Bu-Cy Vs TBI-CTX
EBMT survey in 661 AML autografted pts

Ringden O Br J Haematol. 1996; 93:637-645.

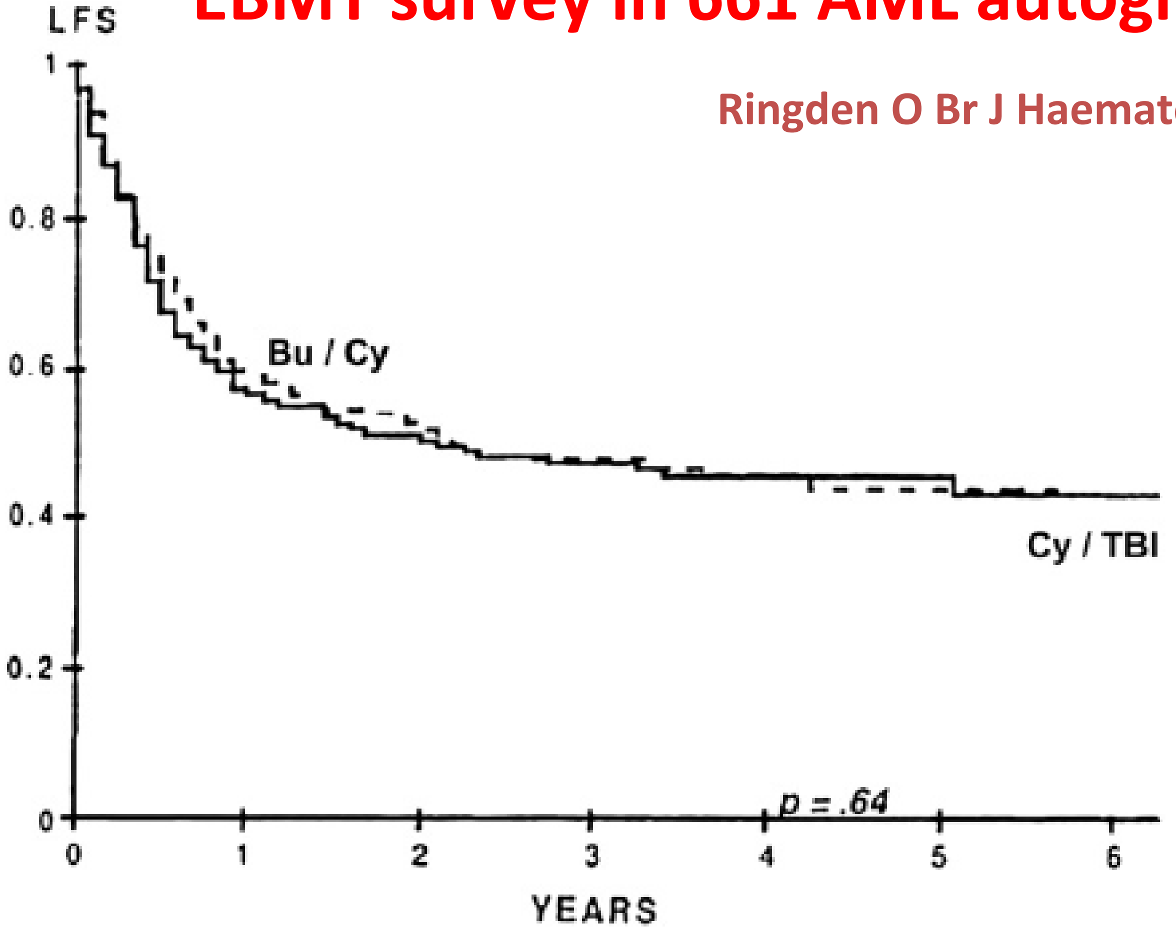
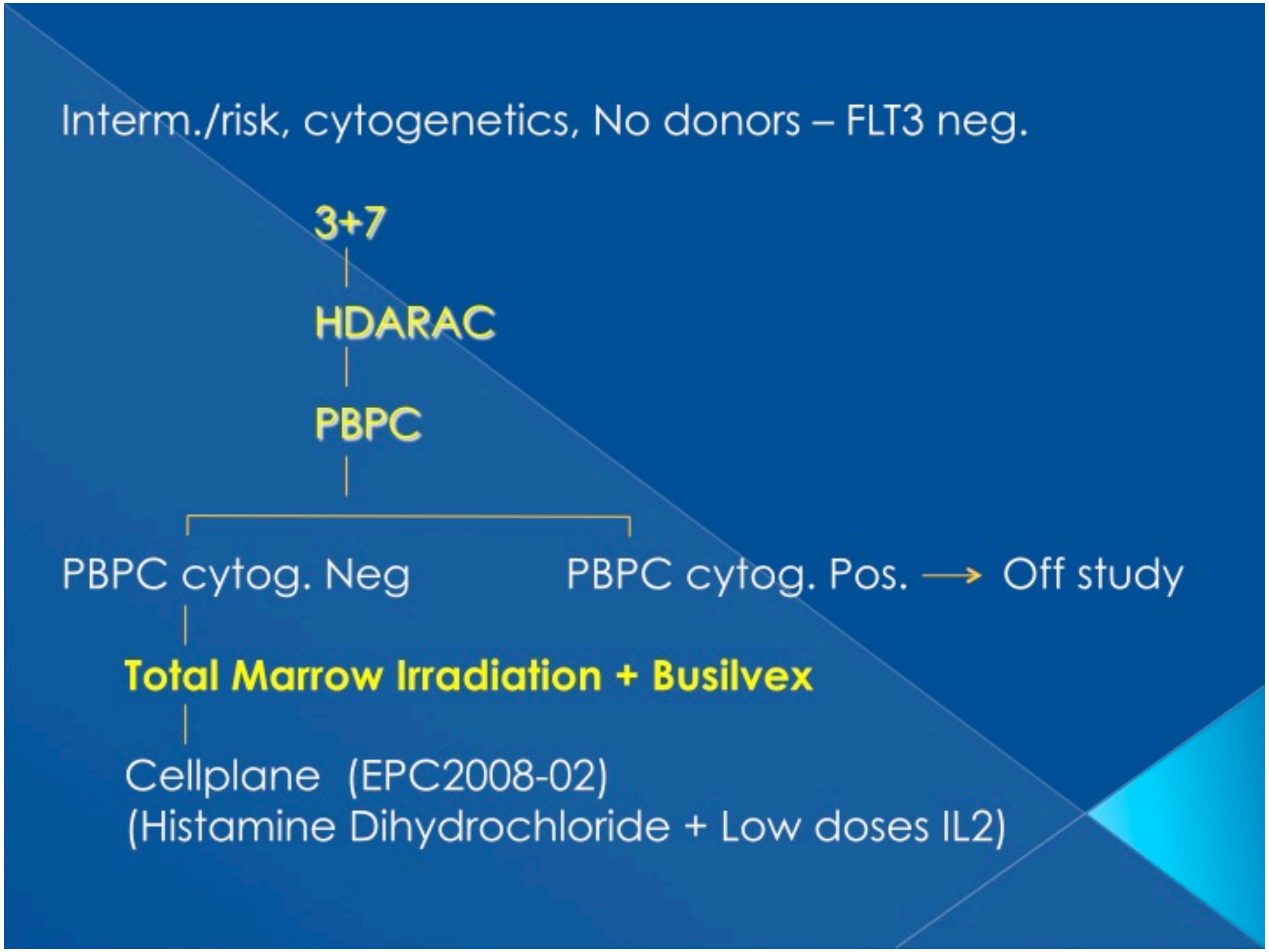
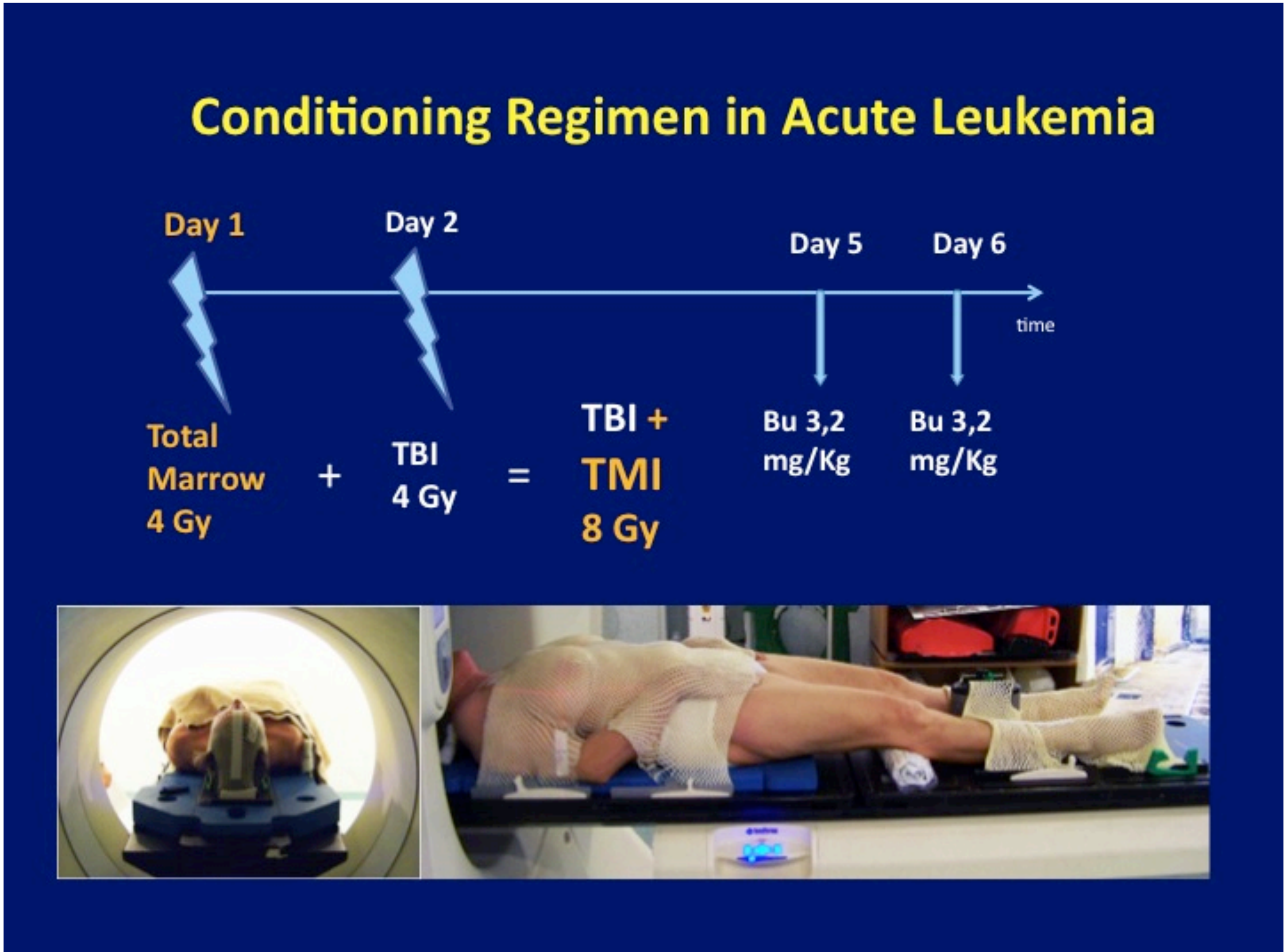


Figure 6. Actuarial LFS in autograft recipients with AML in CR1 treated with Bu/Cy (broken line) (n = 330) or Cy/TBI (solid line)

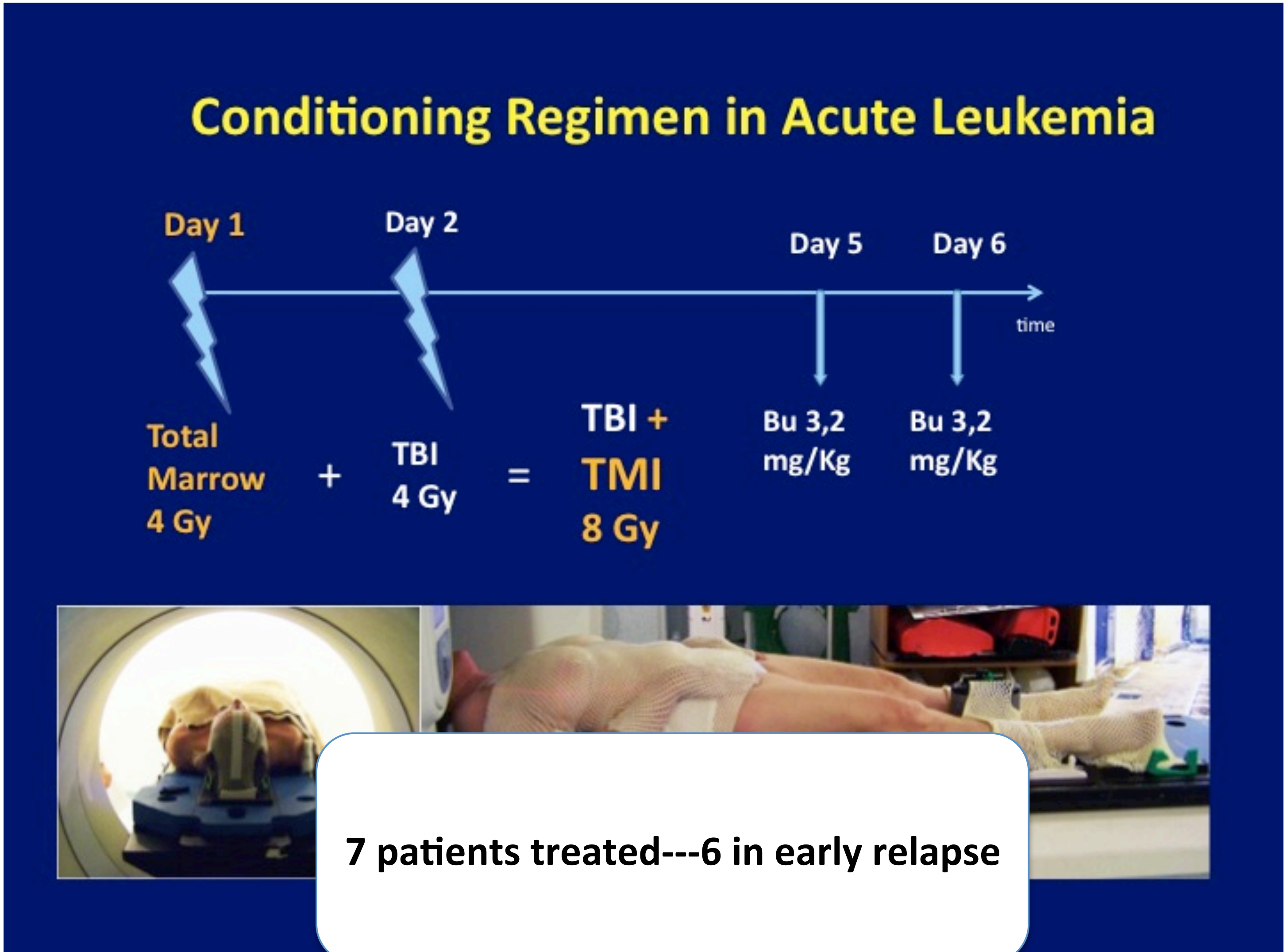
Tandem TMI-TBI in ASCT for AML



Tandem TMI-TBI in ASCT for AML

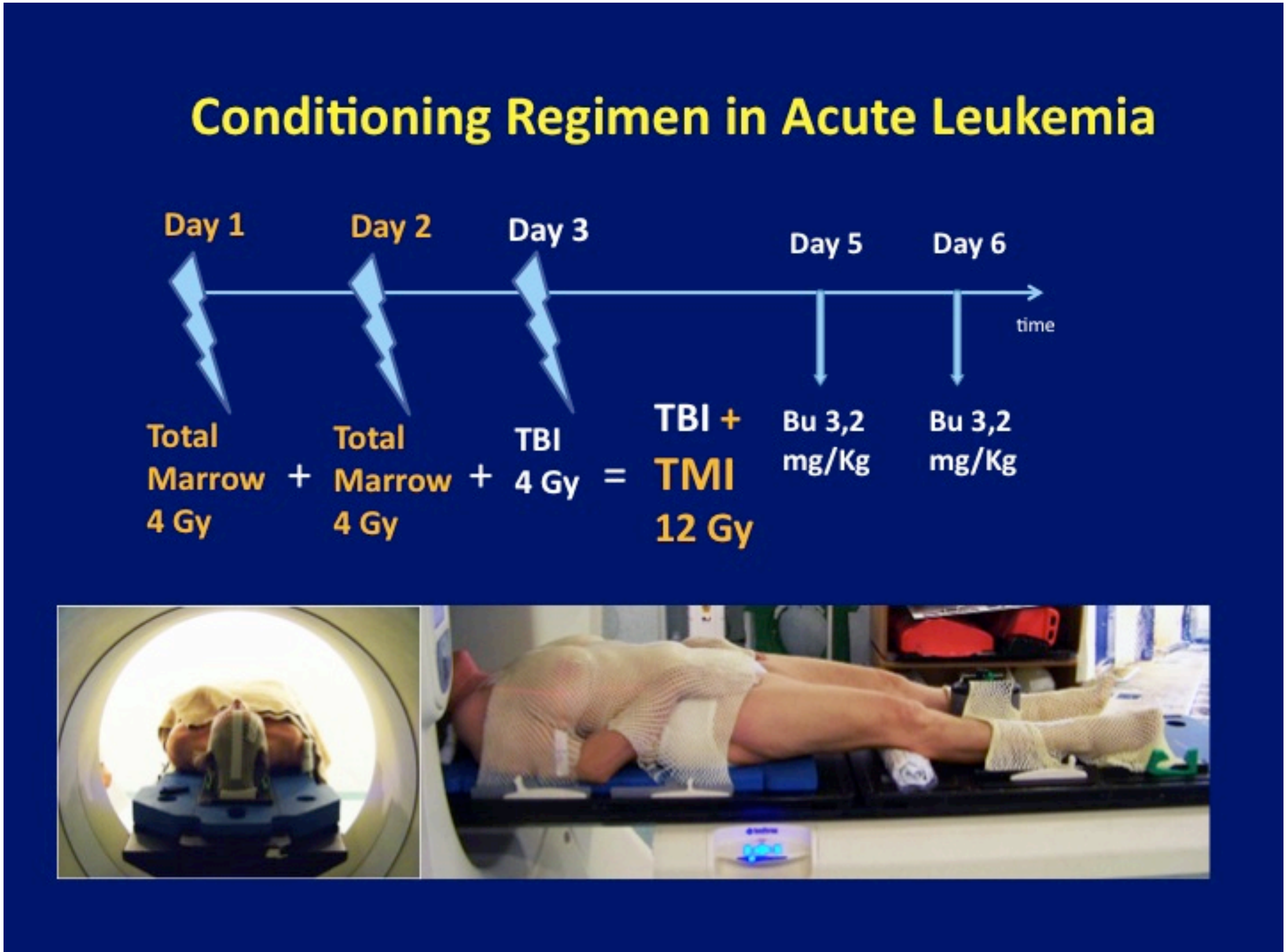


Tandem TMI-TBI in ASCT for AML



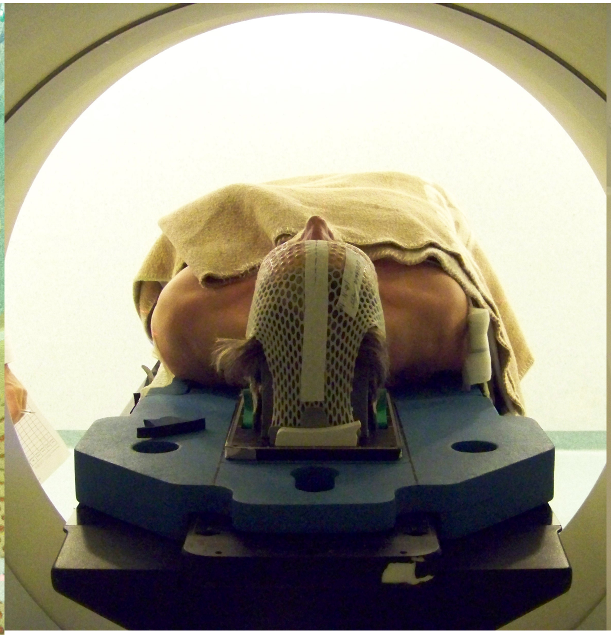
7 patients treated---6 in early relapse

Tandem TMI-TBI in ASCT for AML



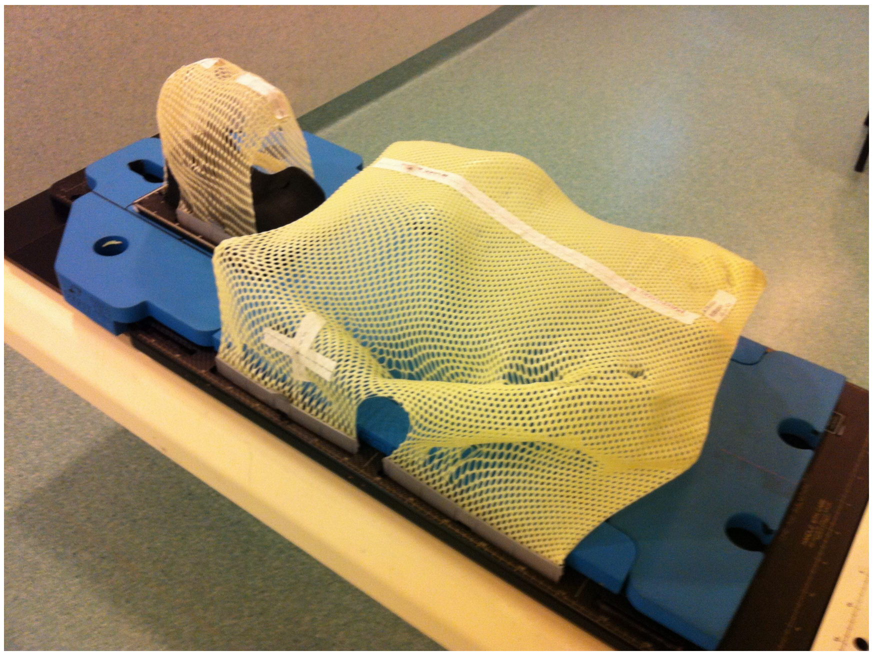
Educational GITMO 2011

Performing SET- UP for TMI-TLI



1 h

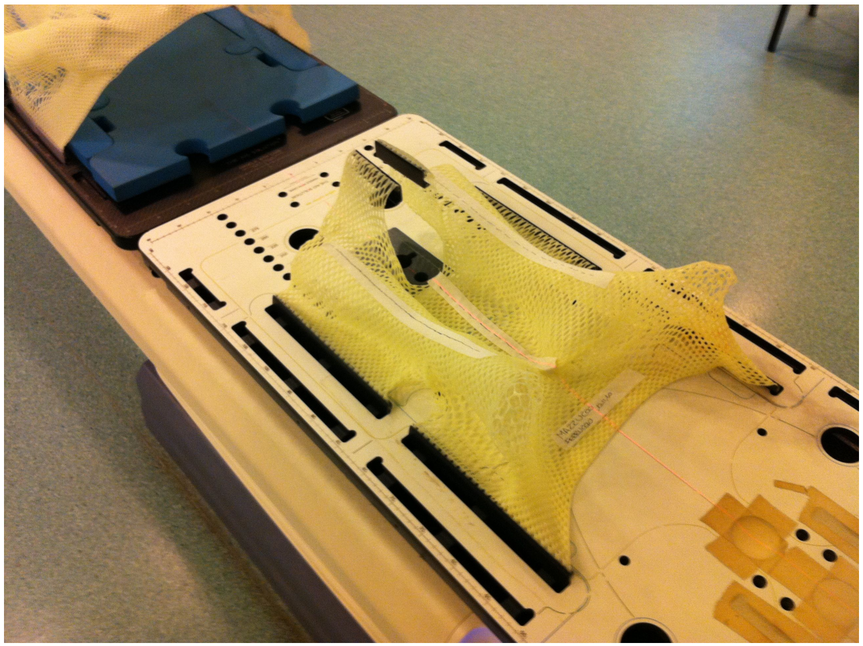
Simulation TC (kV)

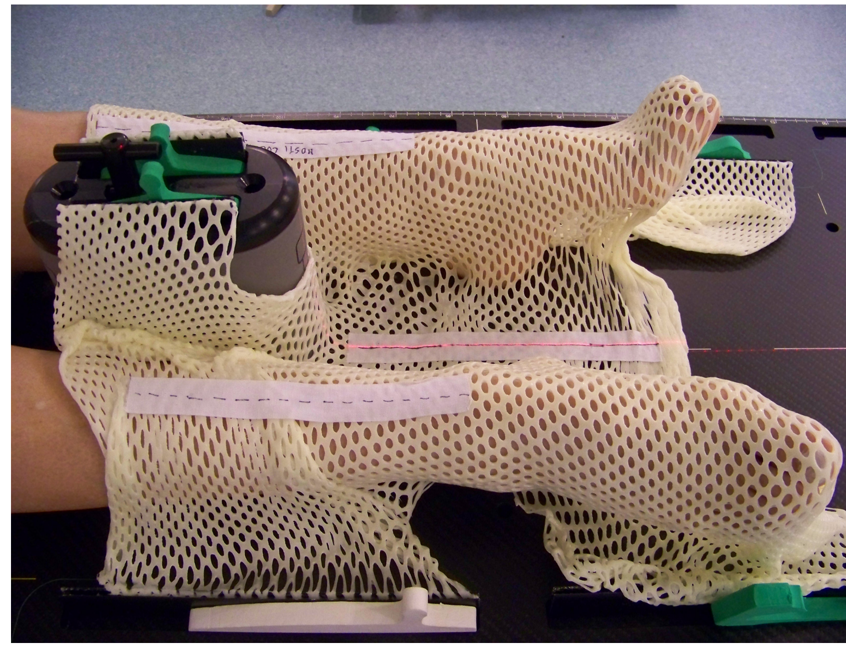


Upper- body

(from vertex to kneecap)

Simulation TC (kV)





Lower- body

(from kneecap to feet)

10 min

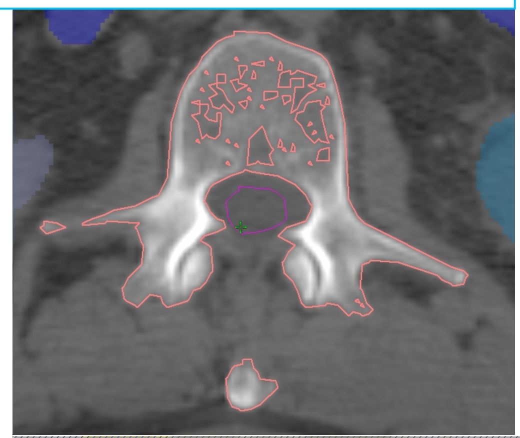
Contouring

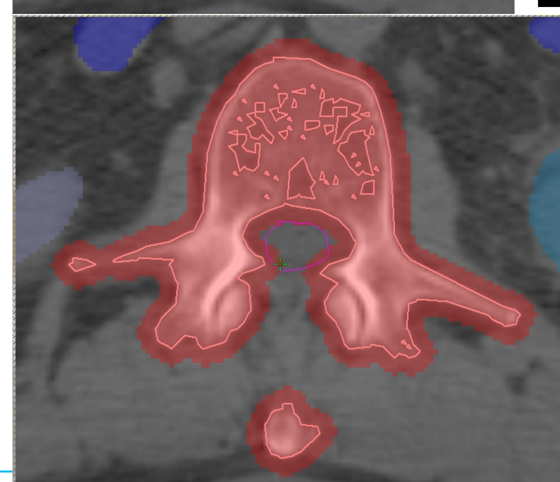
Target volumes *(automatic contours)*

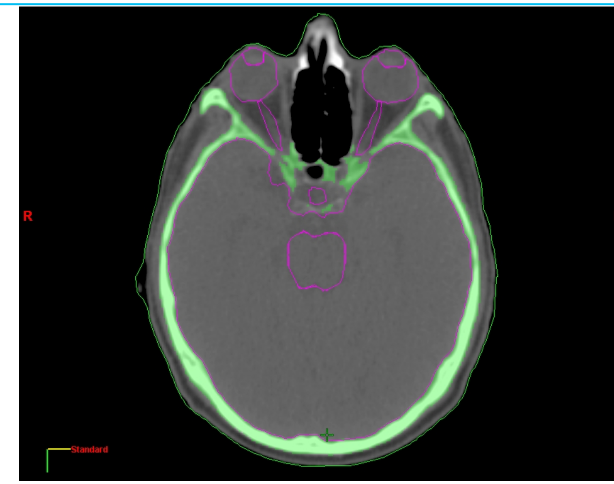
TARGET:
Bone marrow

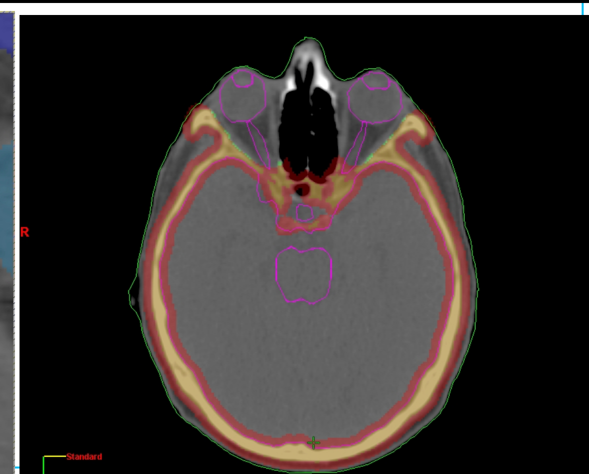
Clinical **T**arget **V**olume:
Bone
Drawn on two CT series (normal breathing and inspiration)

Planning **T**arget **V**olume:
CTV + 4 mm isotropic

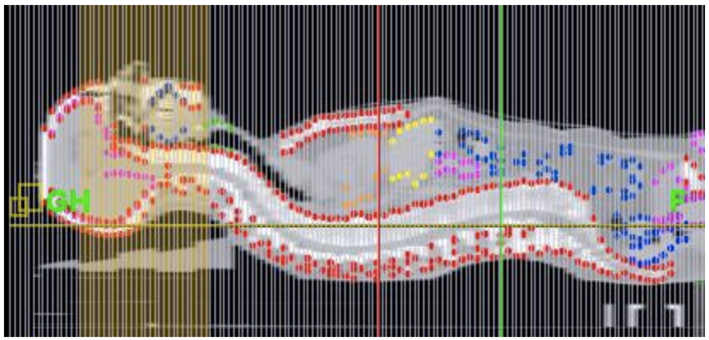




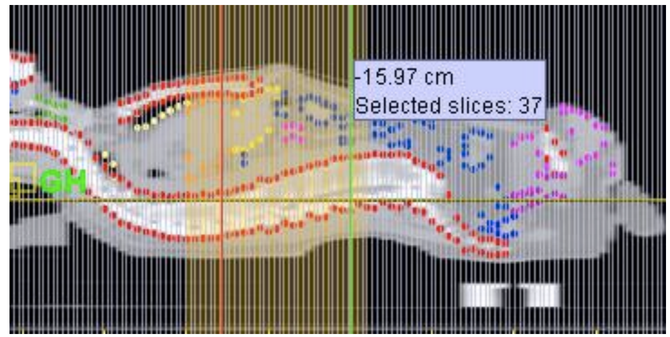




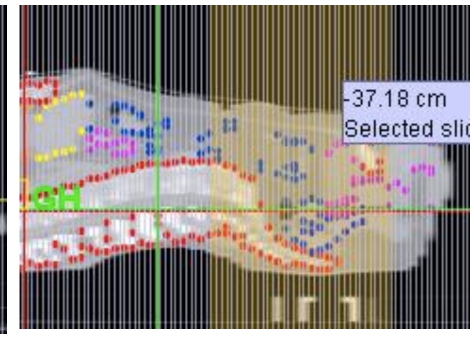
Set-up and verification



Head and neck region

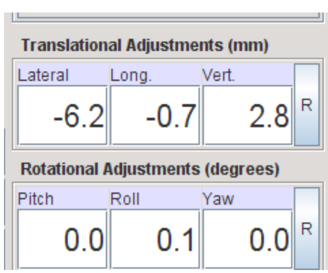


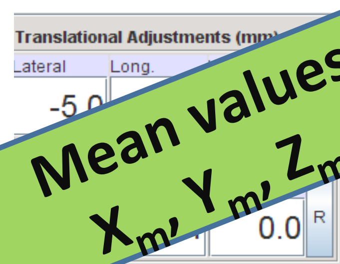
Thoracic region



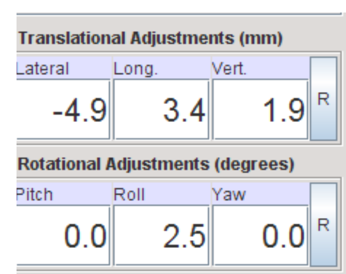
Abdominal region

Matching kVCT vs MVCT



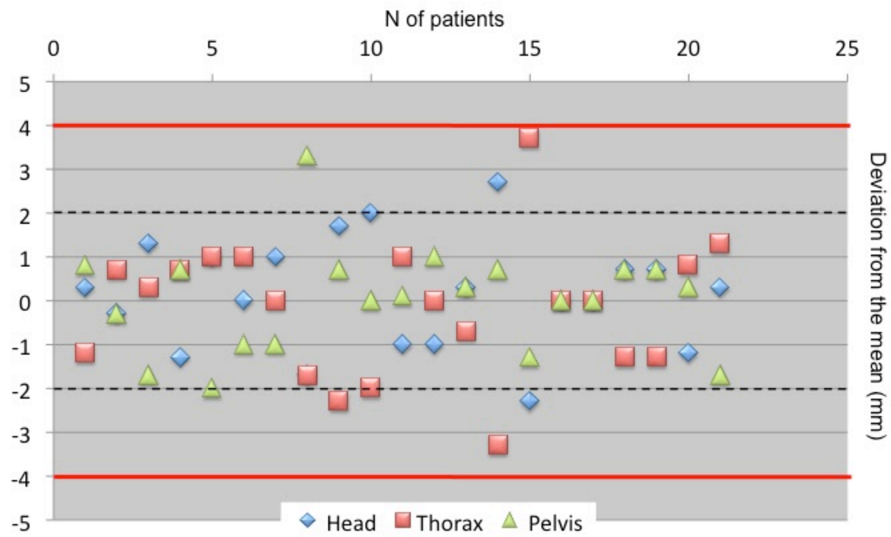


Mean values X_m, Y_m, Z_m

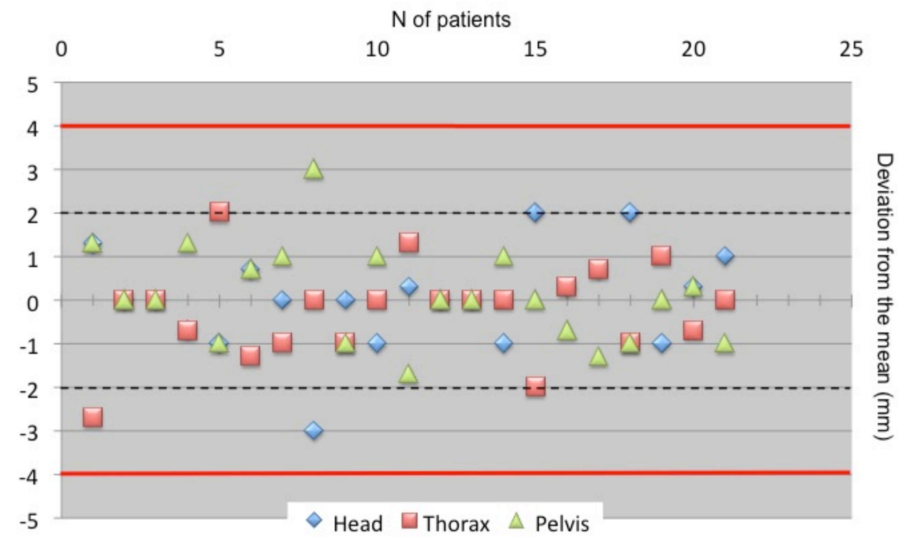


Set-Up accuracy

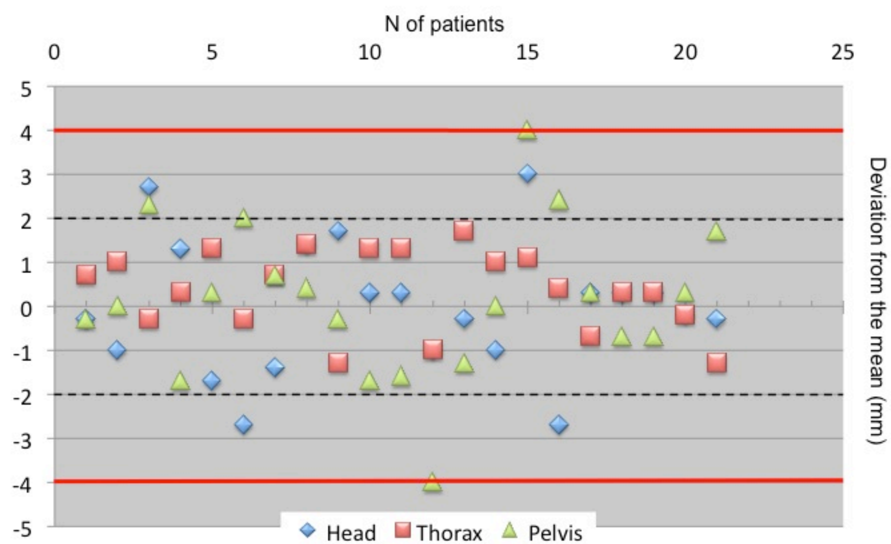
Lateral shift



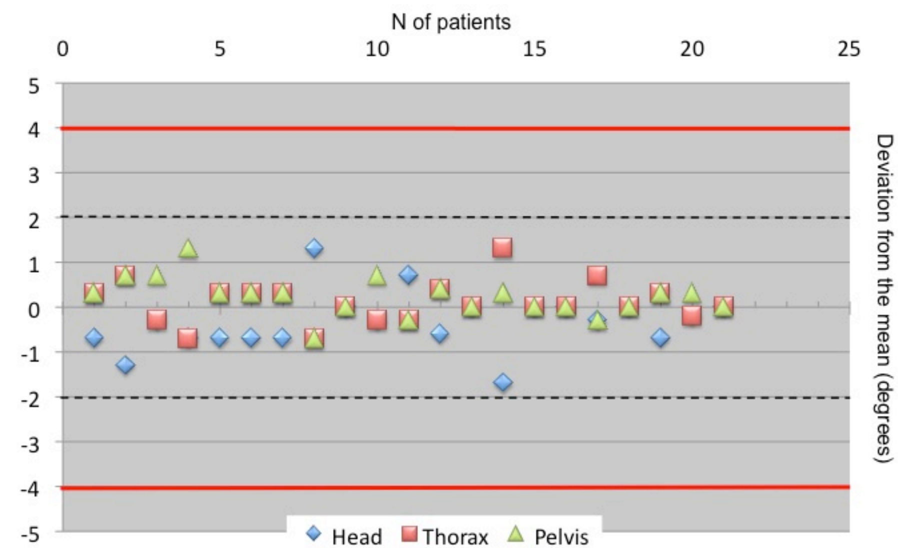
Longitudinal shift



Vertical shift



Rotational shift



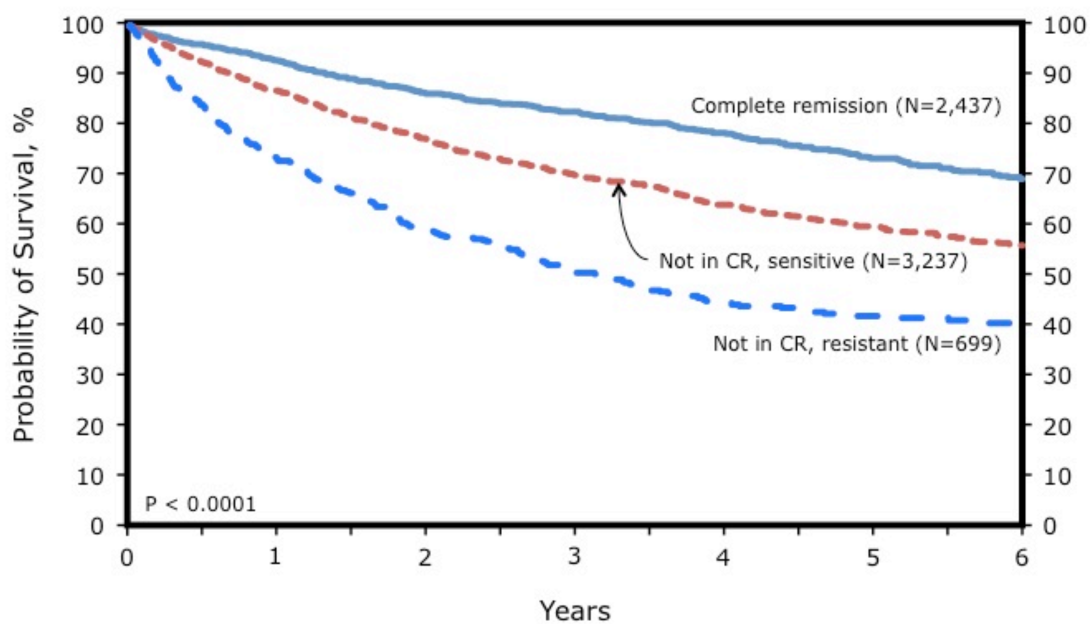
IMRT-TLI
a new look to an old method for
HSCT

Does **T**otal **L**ymphoid **I**rradiation *play a role in HDT/ASCT for refractory/relapse HL ?*

- **HDT/ASCT** has become the **standard salvage program** for patients who failed chemotherapy alone or combined CT/RT modality

- although approximately **50% of patients remain refractory or relapse shortly after BMT**

- dangerous escalating doses of current combinations to increase tumoricidal effect



Probability of survival after HDT/ASCT for Hodgkin disease, 1998-2008 *CIBMTR 2010*

Total **L**ymphoid **I**rradiation

in HDT/ASCT for refractory/relapse HL

	Nº pts	**TLI dose (Gy)**	**IF dose (Gy)**	**HDCT**	**5-yy EFS**	**5-yy OS**	**TRM**	**OTT days**
Yahalom JCO 1993	47	**20.04** over 4 days 1.63 tri	**15** over 5 days 1.5 bid or 3 daily	VP-16 + Cy	**50%**	___	17%	30
Evans Ann Oncol 2007	48	**15** over 10 days 1.5 daily (a.m)	**15** concomitant over 10 days 1.5 daily (p.m)	VP-16+Cy + Carboplatin	**63%**	61%	___	10
Moskowitz BJH 2010	105	**18** over 5 days 1.8 bid	**18** over 5 days 1.8 bid	CBU or BEAM or VP-16+Cy	**68%**	81%	3.6%	10
		Range **15-20 Gy**	Range (TLI+IF) **30-45 Gy**					

Rationale for **T**otal **L**ymphoid **I**rradiation
in HDT/ASCT for refractory/relapse HL

Target Total Lymphoid chain

- frequently patients who come to salvage therapy have multiple sites of involvement
- pattern of relapse is "mostly nodal"

IFRT to areas of residual or recurrent disease

- for the involved nodal sites the relapse risk is higher

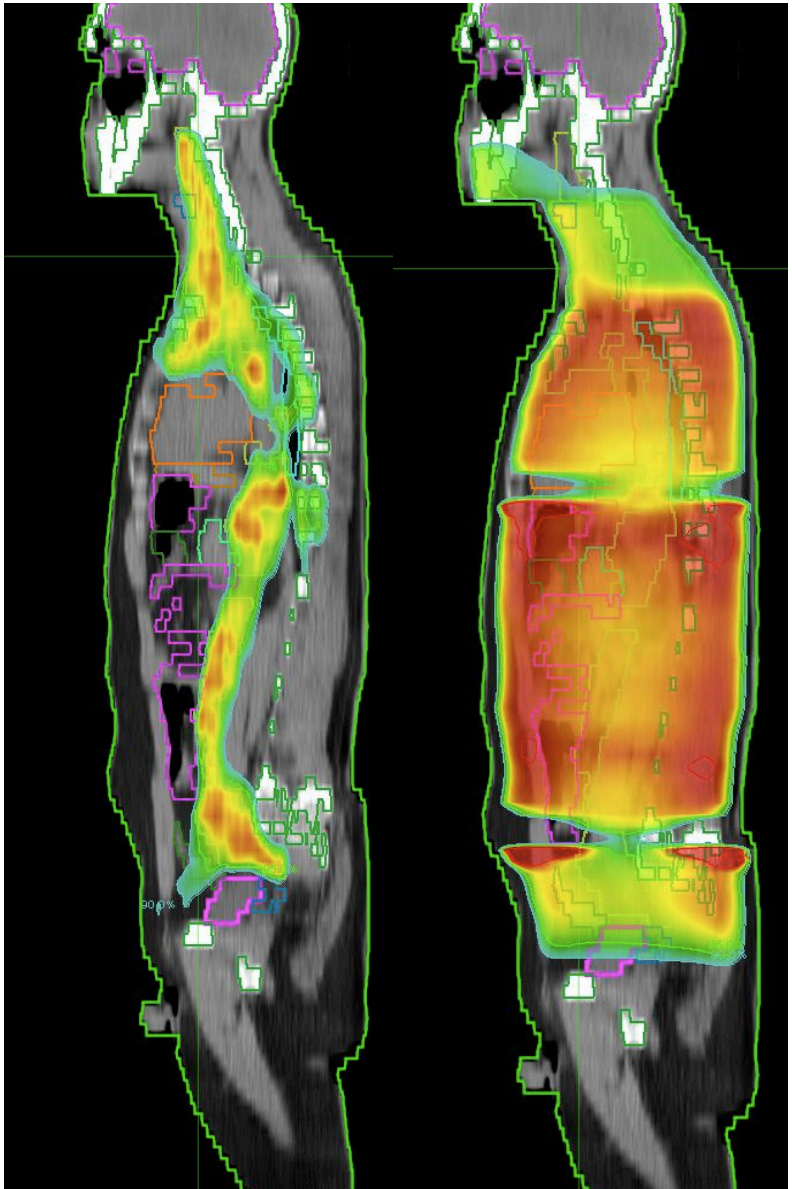
Accelerate treatment TLI and IFRT before ASCT

- might prevent tumor repopulation
- minimizing the period of marrow aplasia before engraphment
- reduce pulmonary toxicity induced by radiation in combination with HDT

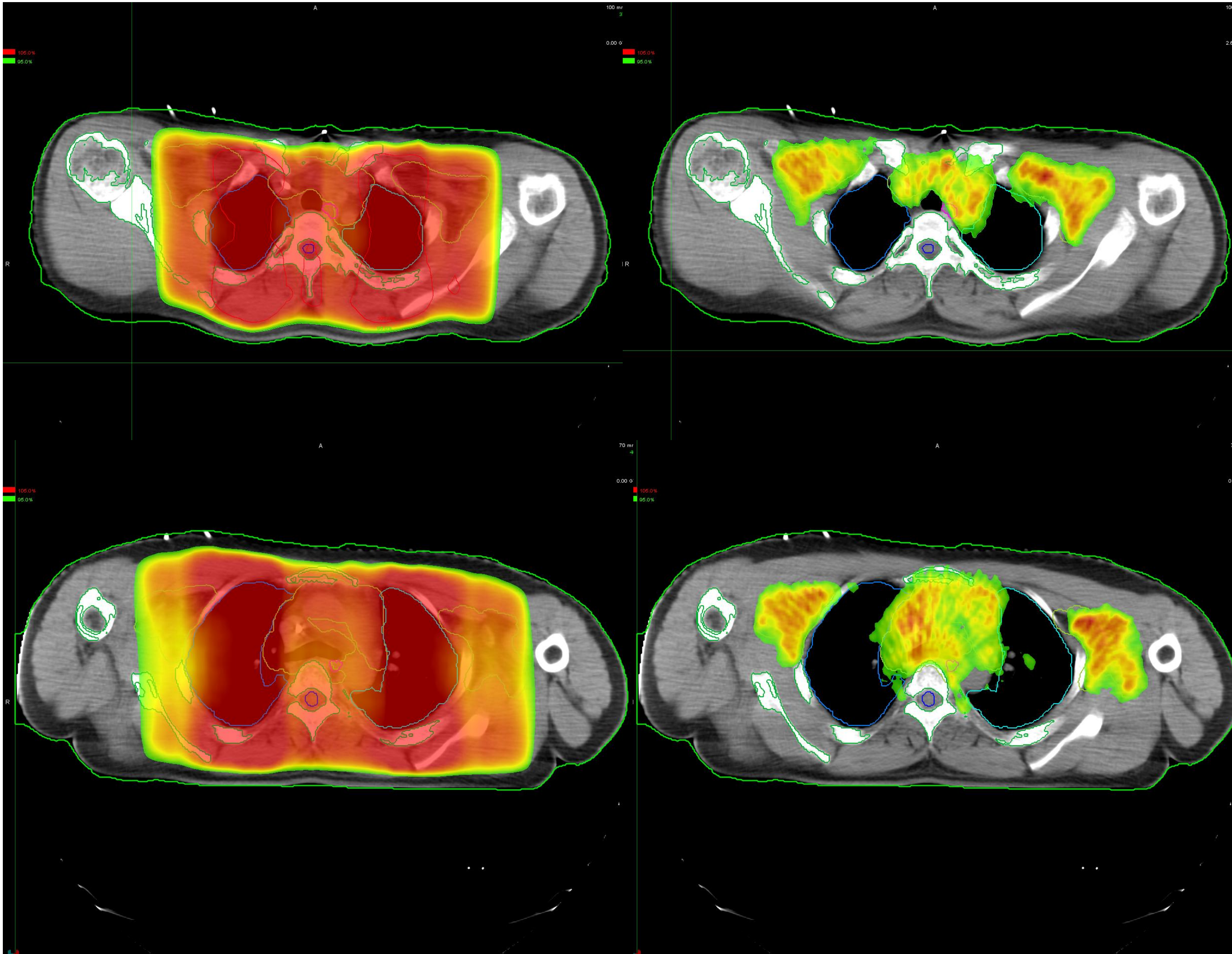
IMRT – TLI improove

in HDT/ASCT for refractory/relapse HL

HT- IMRT



3D RT


A
R
P
105.0%
95.0%

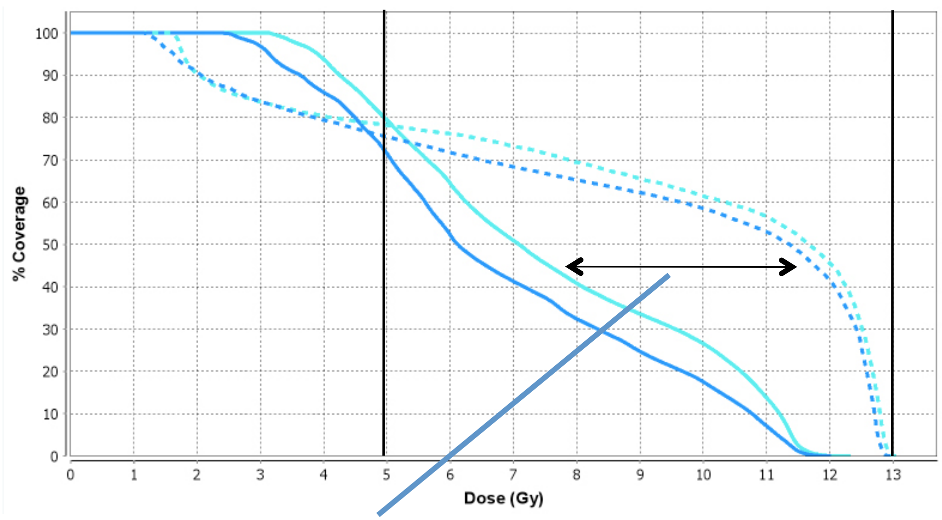
Healthy tissues dose reduction of HT-IMRT compared with 3D for TLI

OARs	% difference of D_{mean}
Lungs	**-33%**
Kidney L	**-7%**
Kidney R	***+100%***
Spinal Cord	**- 61% (D_{max})**
Parotids	**-22%**
Sub Mandibular Glands	**-25%**
Stomach	**-48%**
Liver	***+25%***
Small Bowel	**-23%**
Oral Cavity	**-70%**
Thyroid	**-23%**
Larynx	**-34%**
Heart	**-40%**

- generalized dose reduction to OARs in favour of HT-IMRT
- allow increasing the dose

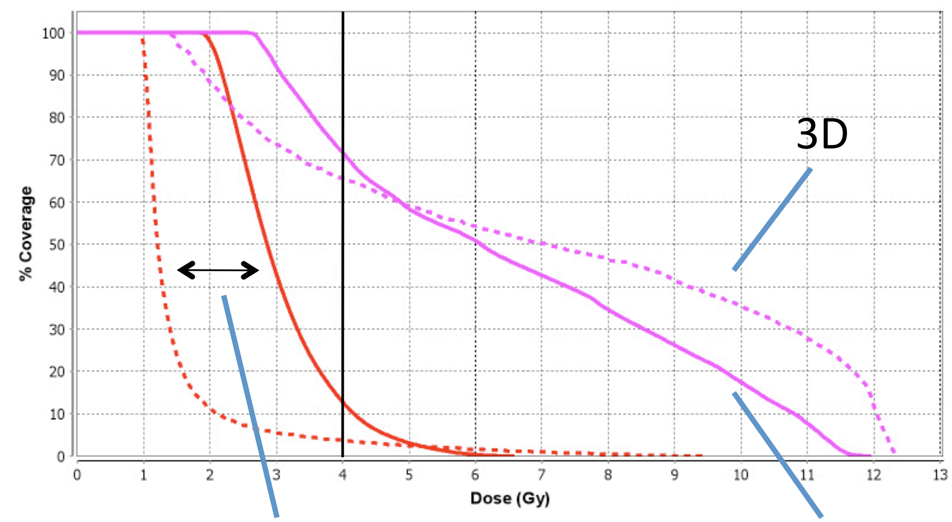
Healthy tissue dose reduction of HT-IMRT compared with 3D for TLI

Lungs



Range of higher doses

Kidney R

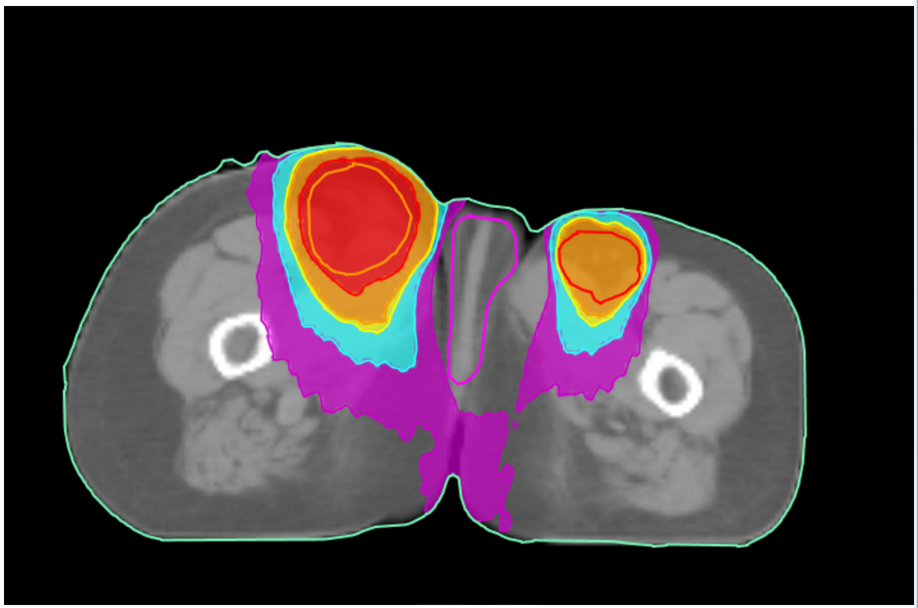


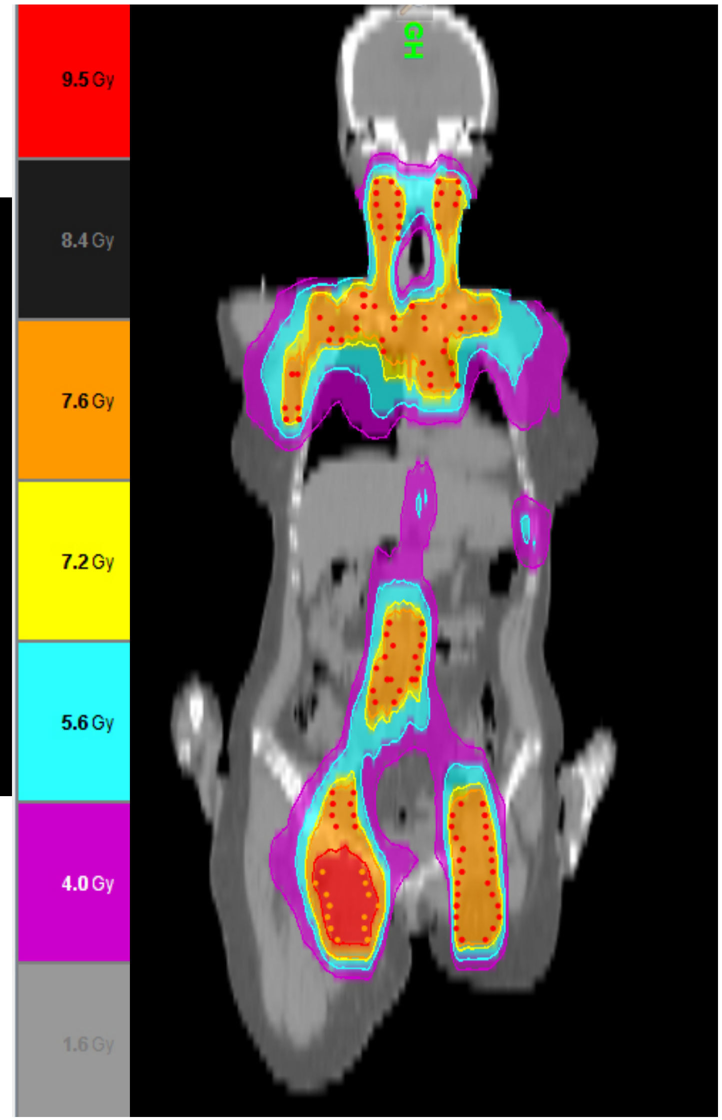
Range of lower doses

HT

HT-IMRT is unfavorable only for Low doses in limited organs but the major gains are in the range of higher and toxic doses

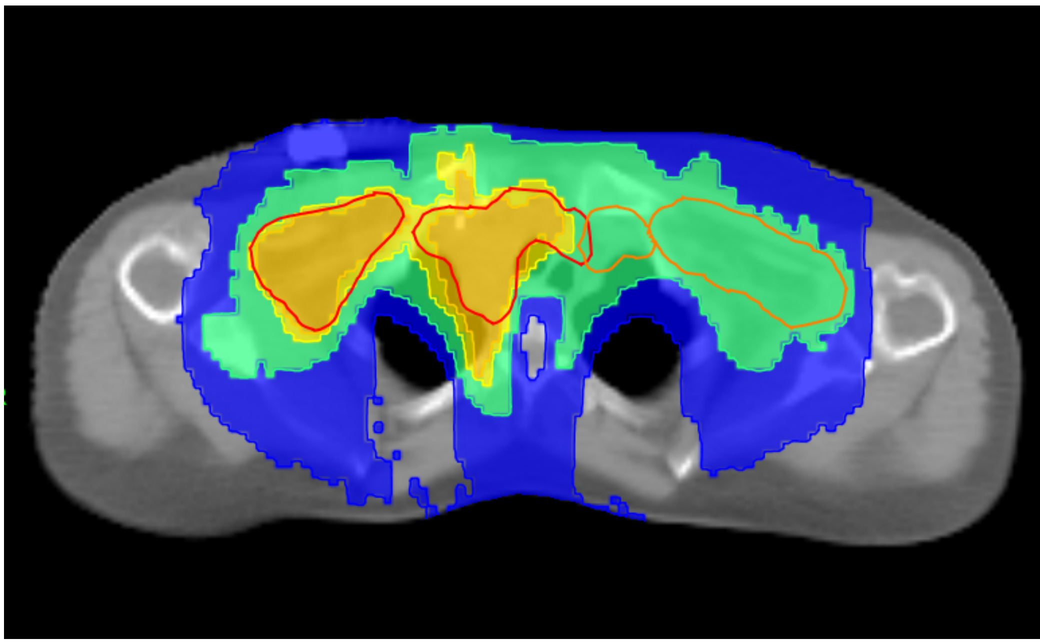
HT-IMRT
Delivery Simultaneous Integrated Boost compared with IFRT

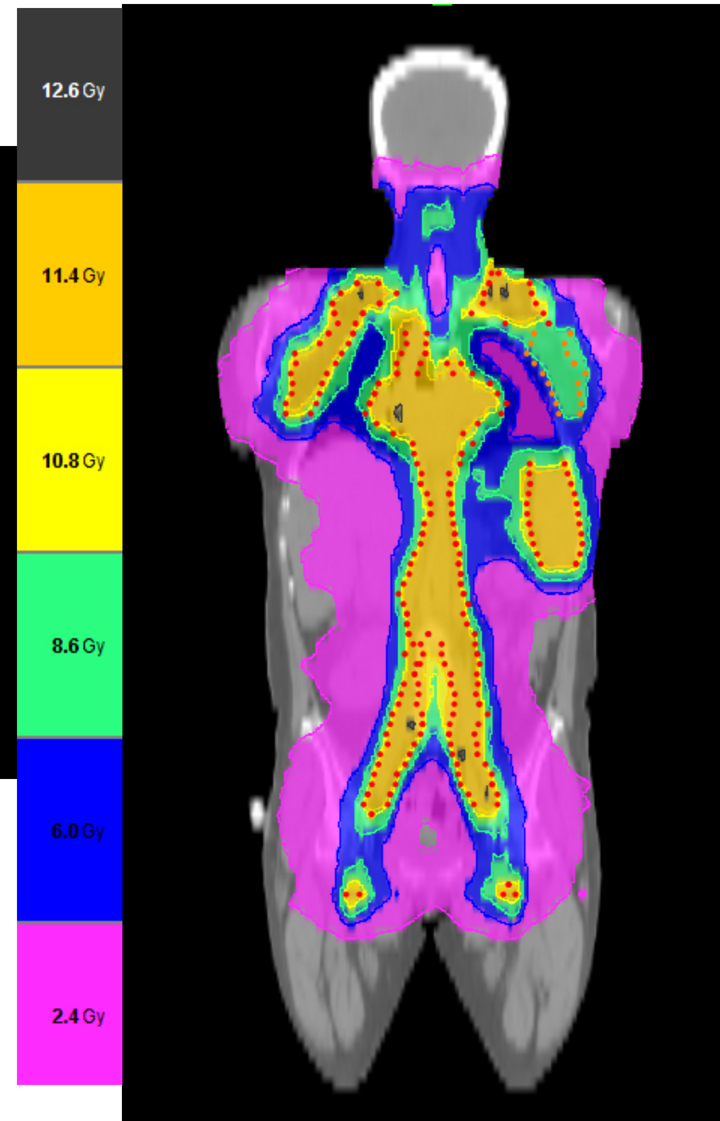




Inguinal bulky

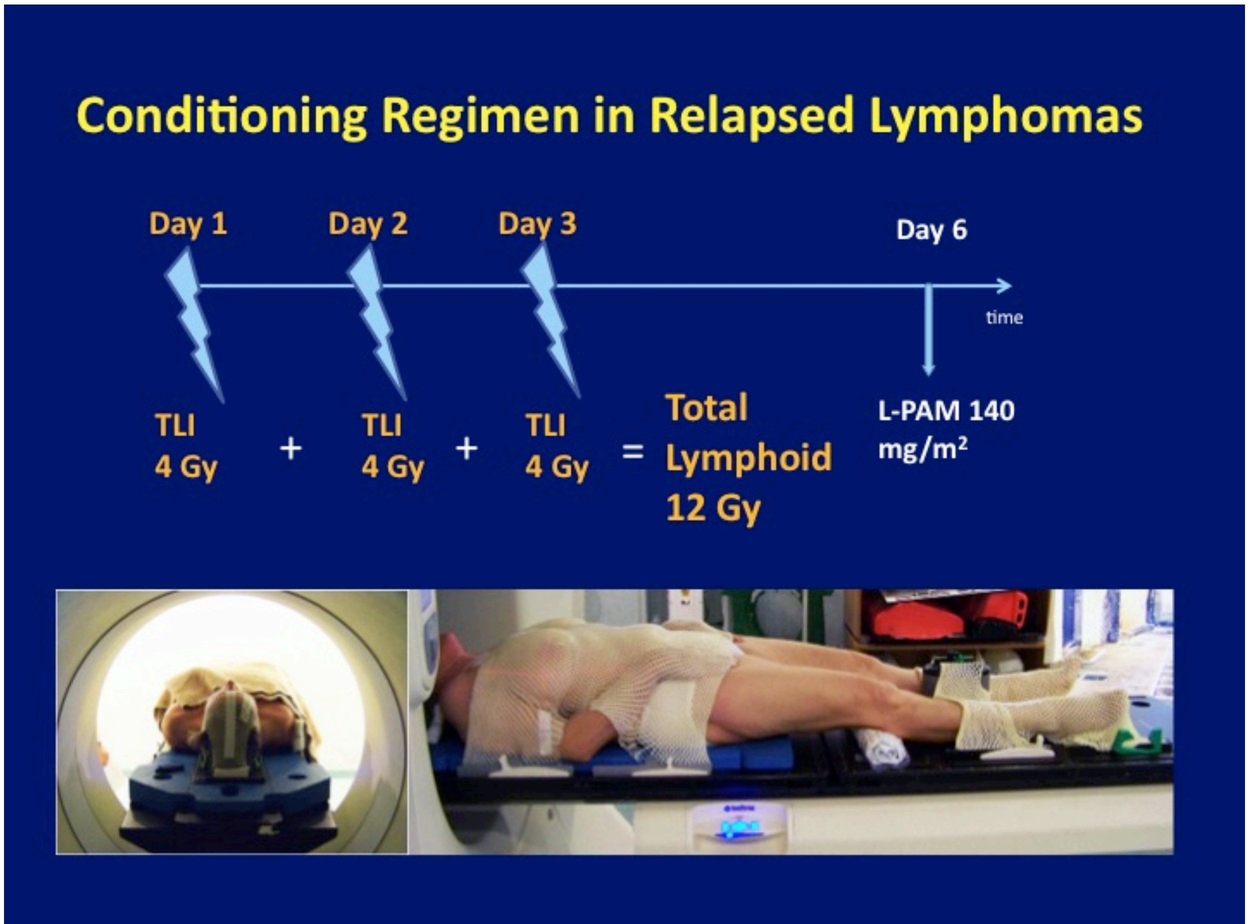
HT-IMRT
dose reduction to previously irradiated sites





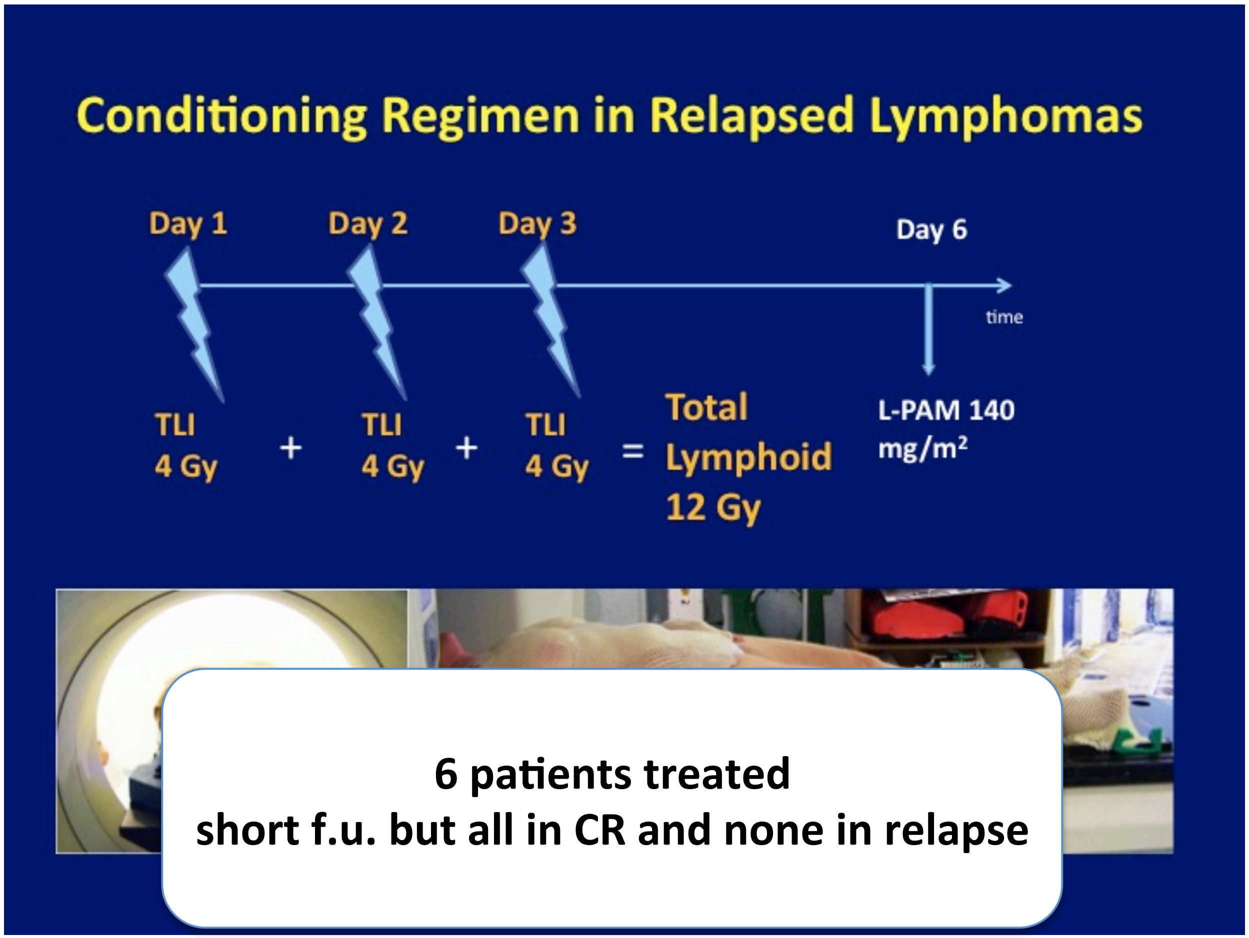
previously IFRT on left axilla

Total Lymphoid Irradiation Plus Chemotherapy As a Conditioning for Autologous Stem Cell Transplantation



GITMO 2011

Total Lymphoid Irradiation Plus Chemotherapy As a Conditioning for Autologous Stem Cell Transplantation



GITMO 2011

Conclusions

- Technology improvement open to new therapeutic choice (CT combinations or RIC regimens with higher radiation doses, restyle of old promising but to toxic combinations)

- New radiobiological aspects should be investigate as dose rate effect and role of circulating clonogenic cells

- Treatment accuracy as much achievable is also mandatory to perform translational research

Genoa-----------Minneapolis

TOTAL BODY AND TOTAL MARROW IRRADIATION:
the effect on marrow microenvironment

IRCCS Azienda Ospedaliera Universitaria
San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro

Acknowledgments

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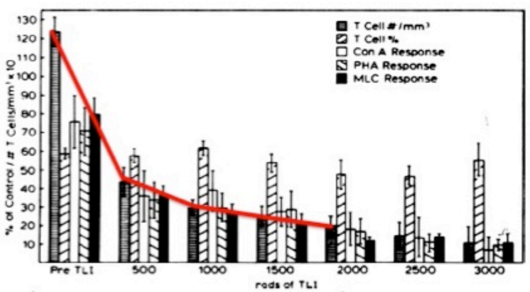
- *Michele Zeverino*
- *Stefano Agostinelli*
- *Gianni Taccini*

Total **L**ymphoid **I**rradiation
high immunosuppressive effect



most significant drop of **T cell** depletion curve

NAJARIAN Ann. Surg. 1982

hystorically employed for

•*organ transplantation*

•*autoimmune disease*

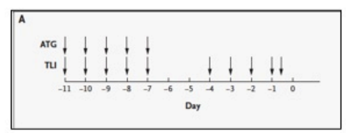
• *early stage HL*

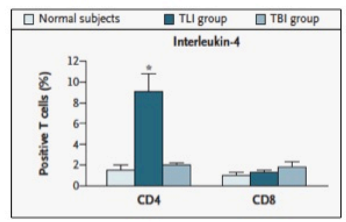
• *aplastic anemia*

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 29, 2005 VOL. 353 NO. 13

Protective Conditioning for Acute Graft-versus-Host Disease





•ATG + TLI 8 Gy over 10 fractions

• predominance of CD4 NK 1.1 after TLI + ATG

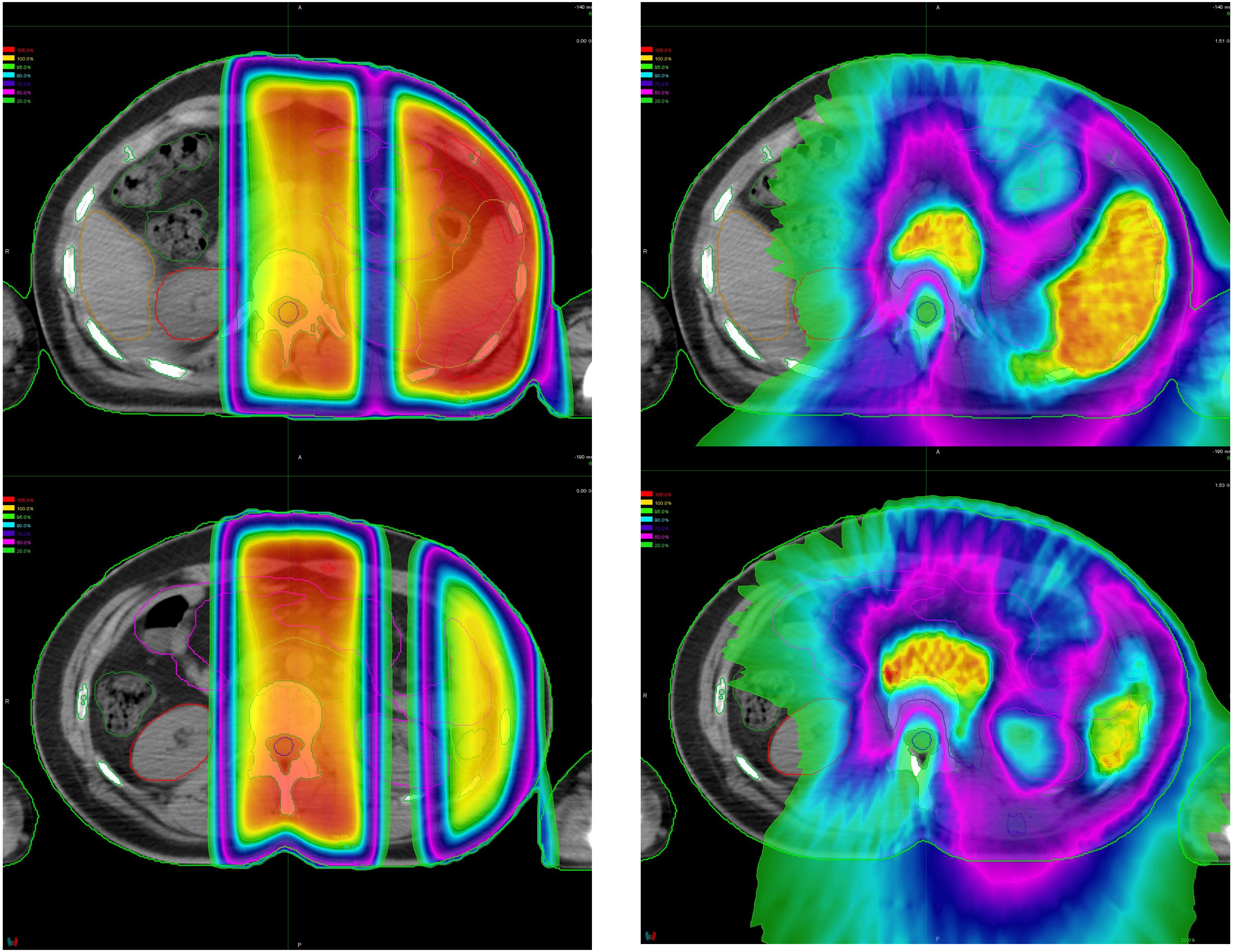
• donor T cells polarized toward Th2

• ↑ IL-4 and ↓ IL-2 , IFNγ

⇩

GvHD protection in RIC regimens for Leukemia and Lymphomas

Lowsky R. et al


105.0%
100.0%
95.0%
90.0%
70.0%
50.0%
20.0%
A
R
P

Tandem TMI-TBI in ASCT for AML

Transplantation

	median (range)
CD34+ cells x 10^6/kg	4,2 (2,0 -10,0)
Engraftment (day)	14 (11-21)
Transfusion support	
PRBC	1-2
Platelet apheresis	2-3

Advers event

- fever of undetermined origin > 5 pts
- grade 3/4 mucositis > 4 pts

	median (range)
FUO (day)	3 (1-6)
i.v. antibiotics therapy (day)	9 (4-13)
total parenteral nutrition (day)	6 (4-8)
Hospitalization (day)	23 (19-29)

IMRT – TLI improove

in HDT/ASCT for refractory/relapse HL

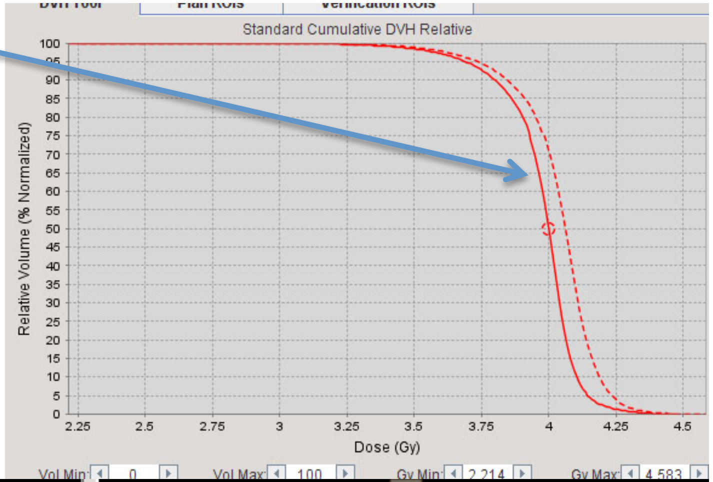
Total Lymphoid 3D → HT

IFRT→ SIB to areas of residual or recurrent disease

Accelerate (Hyperfractionate) → **Hypofractionate TLI**

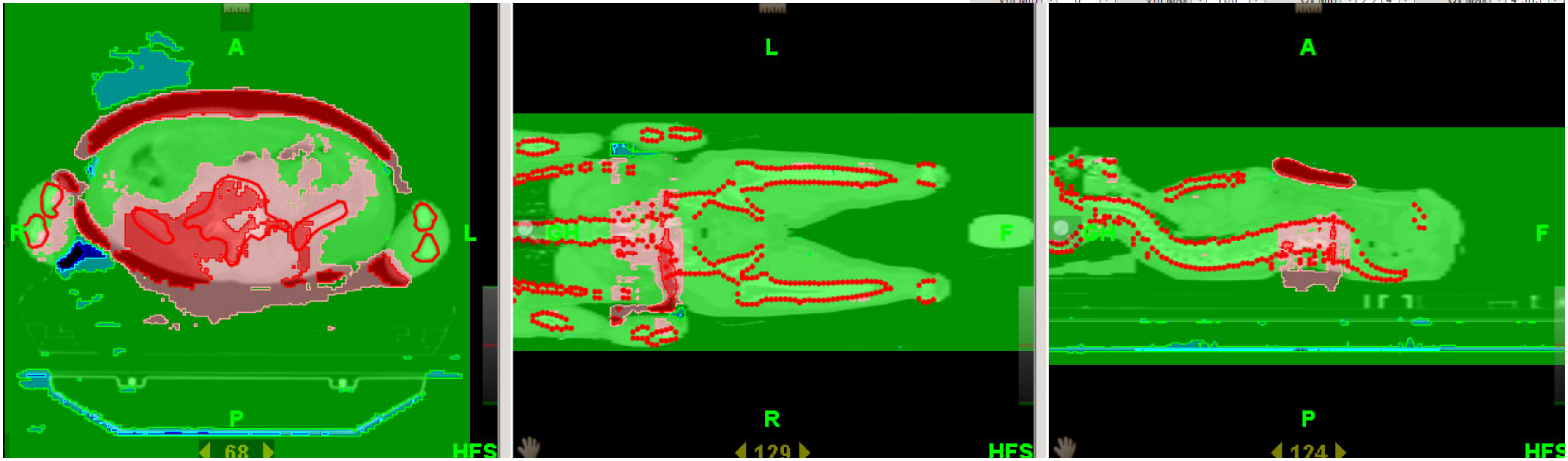
Importance of set-up accuracy

+ 5% of prescribed dose

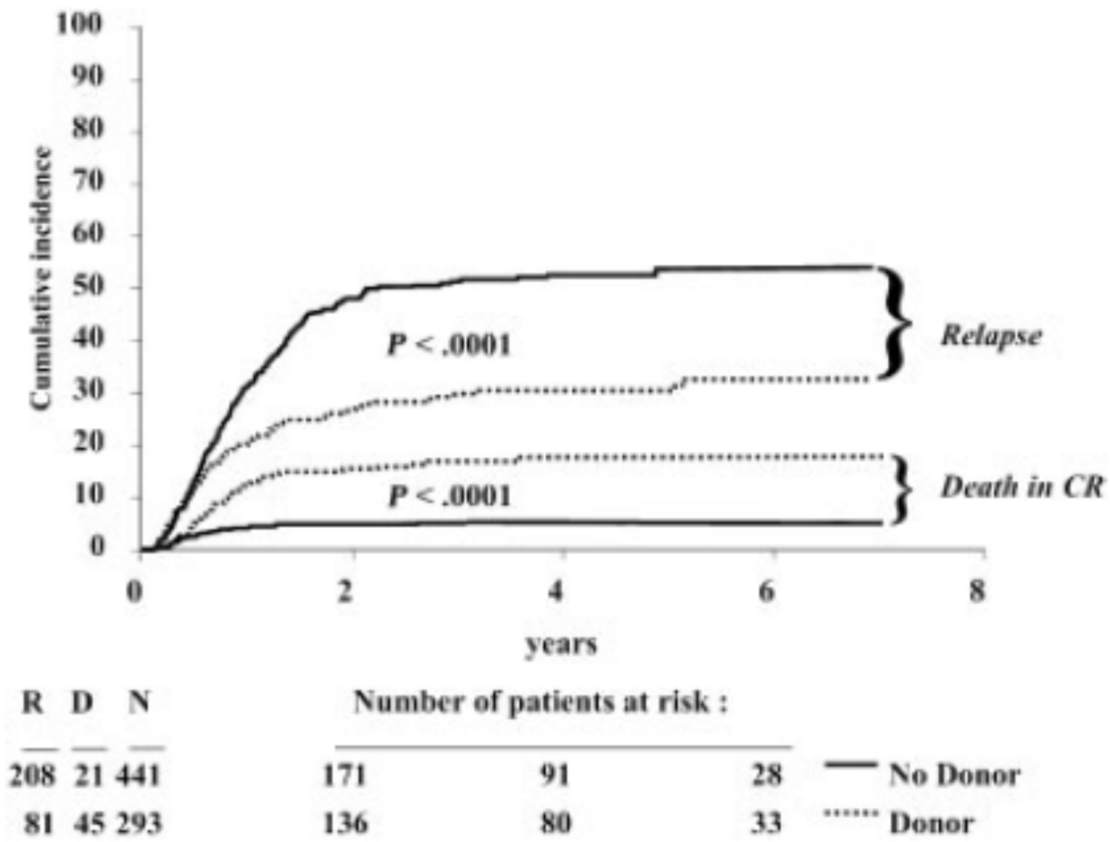


Lateral	Longitudinal	Vertical	Rotational
-1	-3	+ 4.5	0.5

Mean of shifts



Allogeneic compared with autologous stem cell transplantation in the treatment of patients younger than 46 years with acute myeloid leukemia (AML) in first complete remission (CR1): an intention-to-treat analysis of the EORTC/GIMEMA AML-10 trial



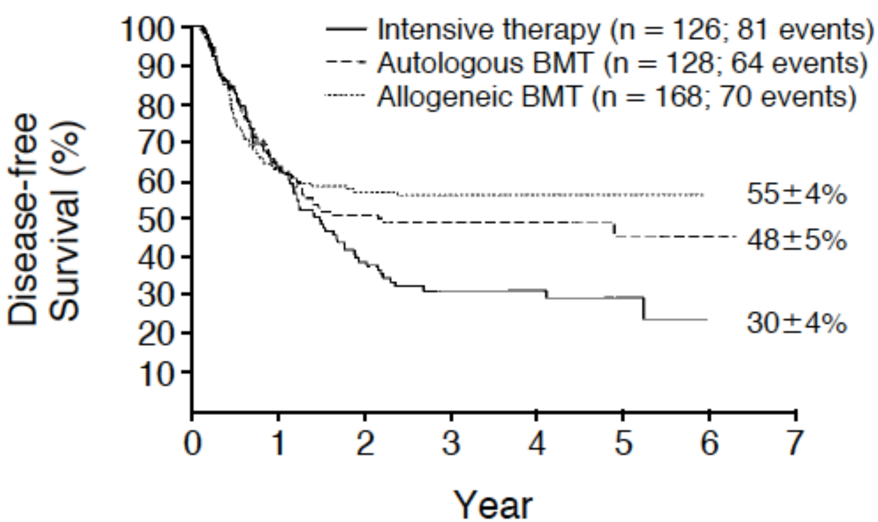
Despite a strong efficacy of allogenic Autologous shown weak evidence vs CT but it might be usefull in CR patients

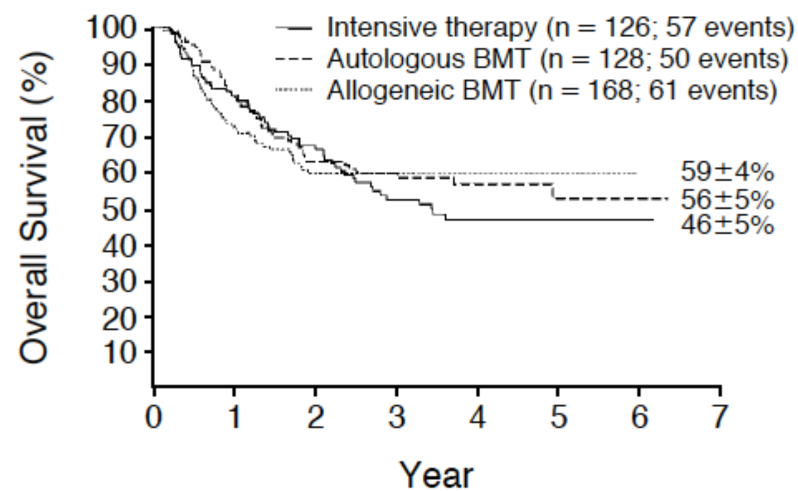
Suciu et al. Blood 2003

HSTC in Leukemia

AUTOLOGOUS OR ALLOGENEIC BONE MARROW TRANSPLANTATION COMPARED WITH INTENSIVE CHEMOTHERAPY IN ACUTE MYELOGENOUS LEUKEMIA

Zittoun R. and GIMEMA group N Engl J Med 1995





HSCT is better than CT