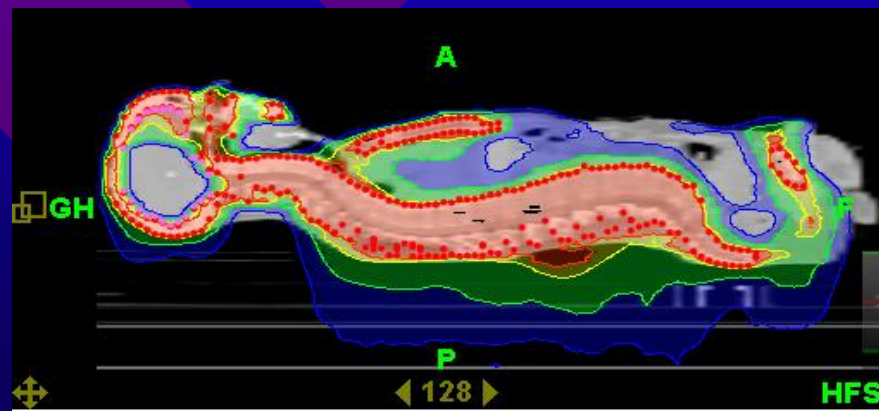
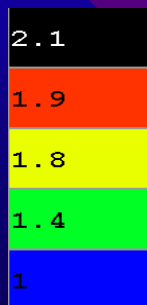
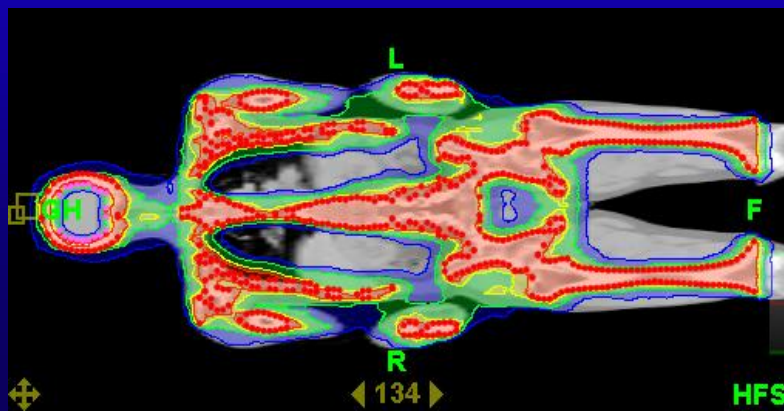


TOTAL MARROW IRRADIATION

Renzo Corvò

National Cancer Research Institute
and University of Genoa



Total Body Irradiation: evolution

| | |
|---------------------|--|
| 1907 | X Ray Bath |
| 1940 - 1950 | Lymphoma/ solid tumors with disseminated disease |
| 1960 | First exploration for bone marrow transplantation |
| 1970- 1980 | TBI with low-dose |
| 1977 | TBI myeloablative TBI sub-myeloablative |
| 2005 → NEW ! | Total Marrow Irradiation (conformal TBI) |

BLOOD STEM CELL TRANSPLANT

Cyclophosphamide
plus

Total Body Irradiation -TBI



“leukemic cell killing”

“immunosuppressive role”

“making space in bone cavities”



ALLOGENEIC TRANSPLANT

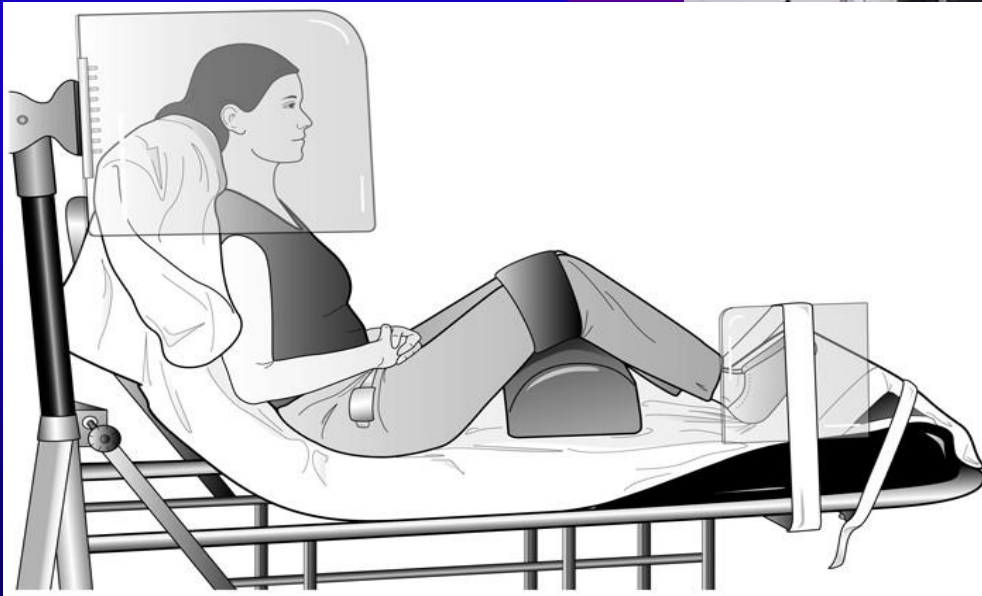
from

matched siblings

unmatched siblings

matched unrelated donors (MUD)

**1977: first TBI
in Genoa**



**more than 2600
patients submitted to
TBI in Genoa**

TBI schedules in Genoa

TBI myeloablative

→ 990 cGy / 3 fractions / 3 days

→ 1200 cGy / 6 fractions / 3 days
(with 6 hour inter-fraction interval)

FIRST CRITICAL PROBLEM

MORE RADIATION DOSE

=

MORE LEUKEMIC CELL KILLING

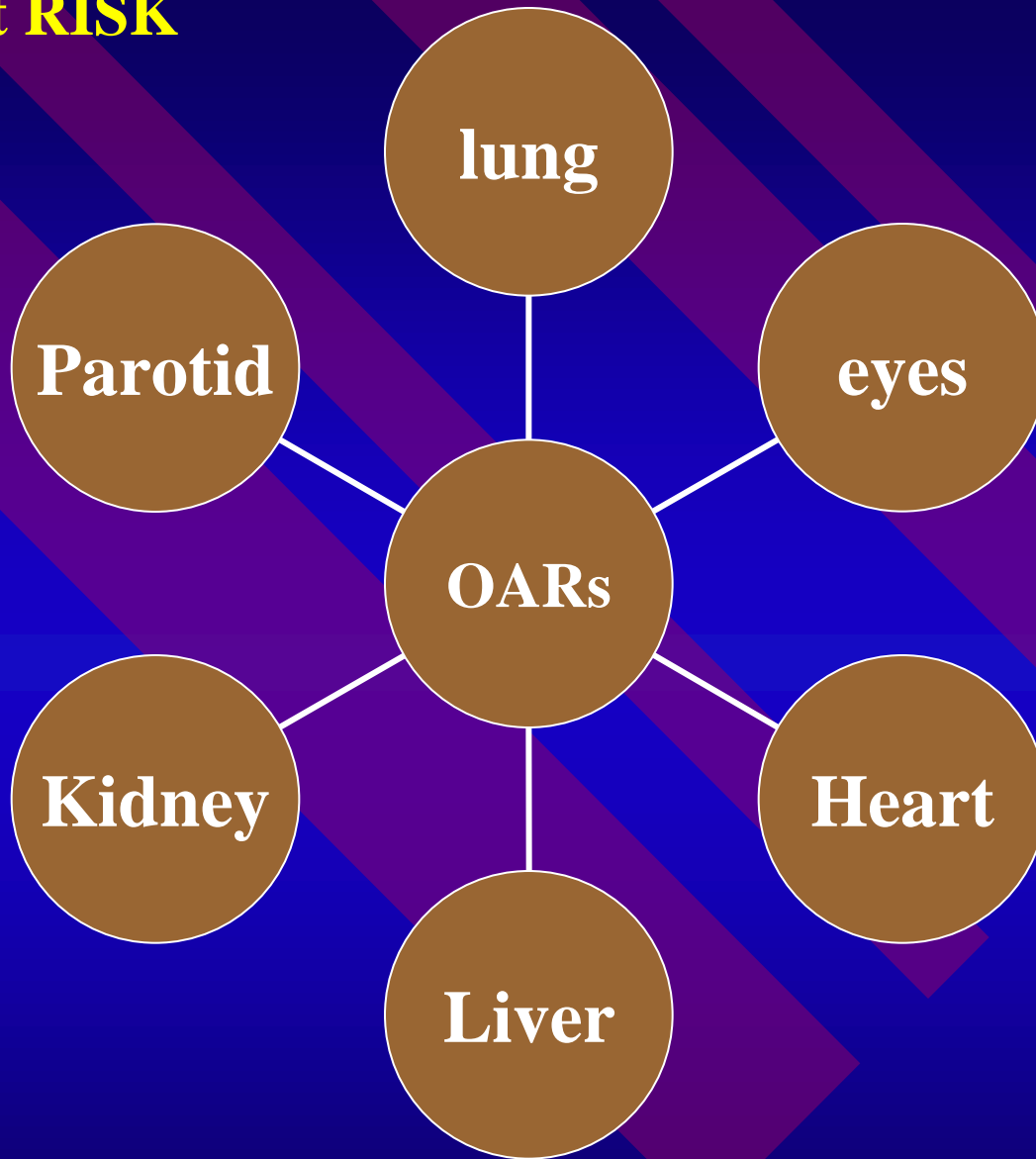
=

**MORE RADIATION INDUCED
EFFECTS**

→

NO IMPROVEMENT IN SURVIVAL

ORGANS at RISK



RISK FOR TOXICITIES

ACUTE AND LATE TBI- INDUCED TOXICITIES

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

Second Critical Issue!

No dose
distribution
in 2010 !

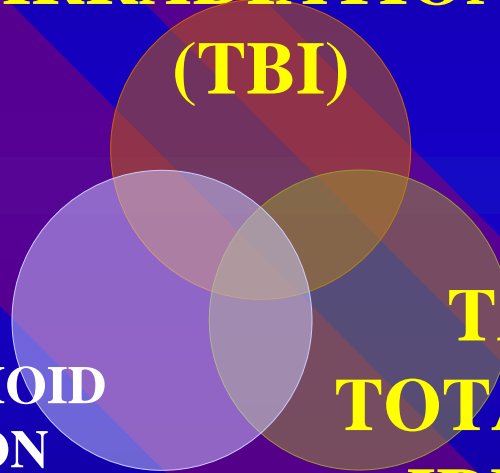


HELICAL TOMOTHERAPY

**TOTAL BODY
IRRADIATION
(TBI)**

**TOTAL LYMPHOID
IRRADIATION
(TLI)**

**TARGETED
TOTAL MARROW
IRRADIATION
(TMI)**



Total Marrow Irradiation Contouring

■ Target

bone marrow sites:

- head (cranium, mandible)
- upper limb girdle
- sternum
- ribs
- vertebrae
- pelvis
- lower limb girdle
- spleen
- (leukemic bulk)

■ OARs

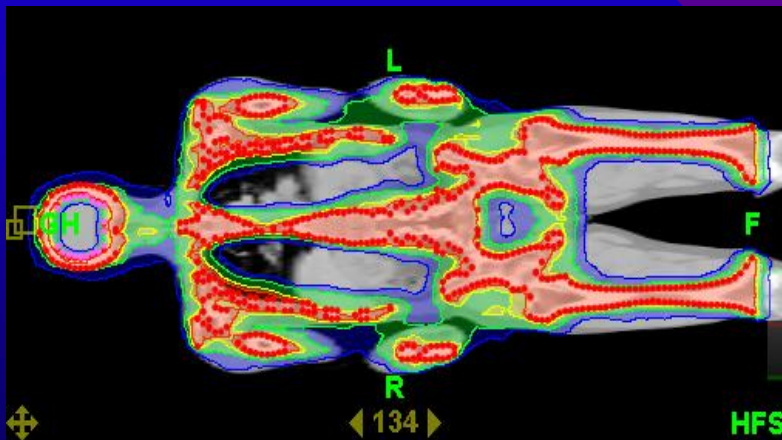
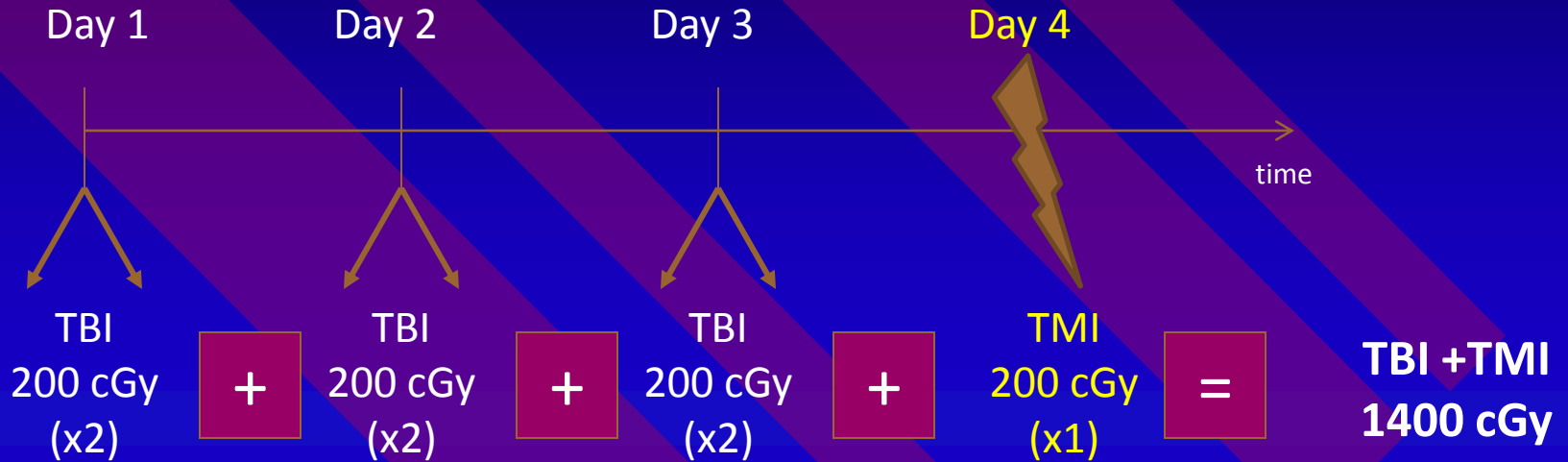
- lungs
- spine
- eyes, larynx, oral mucosa
- heart, breasts, esophagus
- liver
- kidneys
- brain
- testes
- thyroid
- parotids
- bowel / bladder/ rectum

Preliminary clinical experience @ IST Genoa

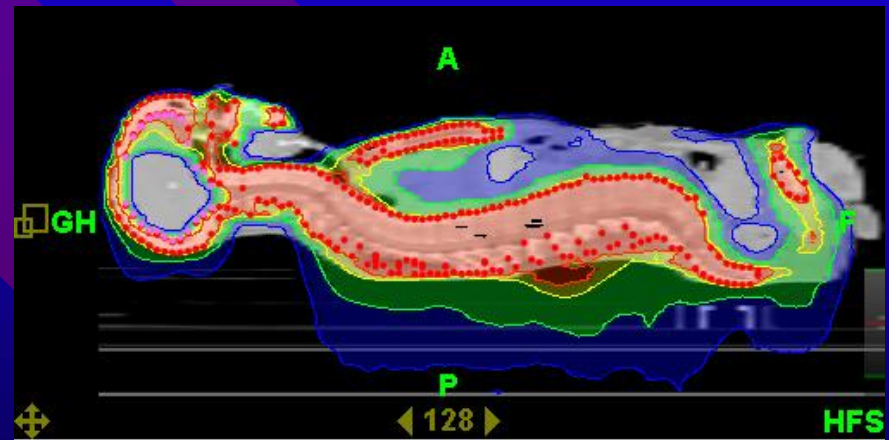
**TOTAL MARROW
IRRADIATION - TMI
with Helical Tomotherapy**



Radiation Dose Scheduling



TMI - coronal view



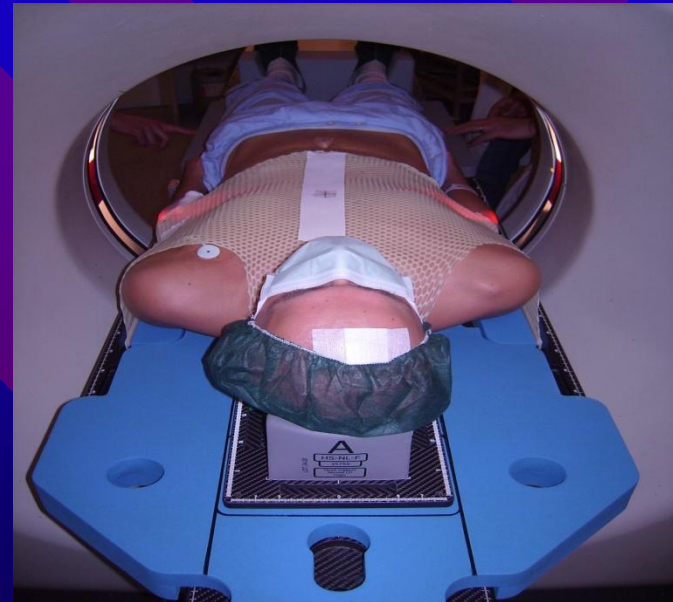
TMI - sagittal view

Sequence TBI → TMI

- **TBI for allograft:** excellent results in acute leukemia in early stage of disease with low toxicity
- **TMI:** in advanced leukemia may be the best way to increase the TBI dose without increasing radiation-induced toxicity

Steps for TMI delivery

- **Patient set-up** (immobilization systems, field junction between upper TMI e lower TMI)
- **CT scan from vertex to feet**
- **Contouring** CTVs, OARs e VOIs
- **Dosimetric Planning** (CTV → PTV = 5 mm)
- **Physical dose verify**
- **Patient set-up verify with IGRT-MV**
- **TMI delivery** (upper e lower) con **IMRT**



No Photo



Plan: Plan_01
Plan status: Unapproved
DQA plan:
Patient position: HFS



What's Next

Verify Optimization

- Click **Resume**, and then click **Get Full Dose** to complete the optimization, OR
- Adjust constraints as necessary, then click **Resume** to continue optimizing

User Name: Michele Zeverino

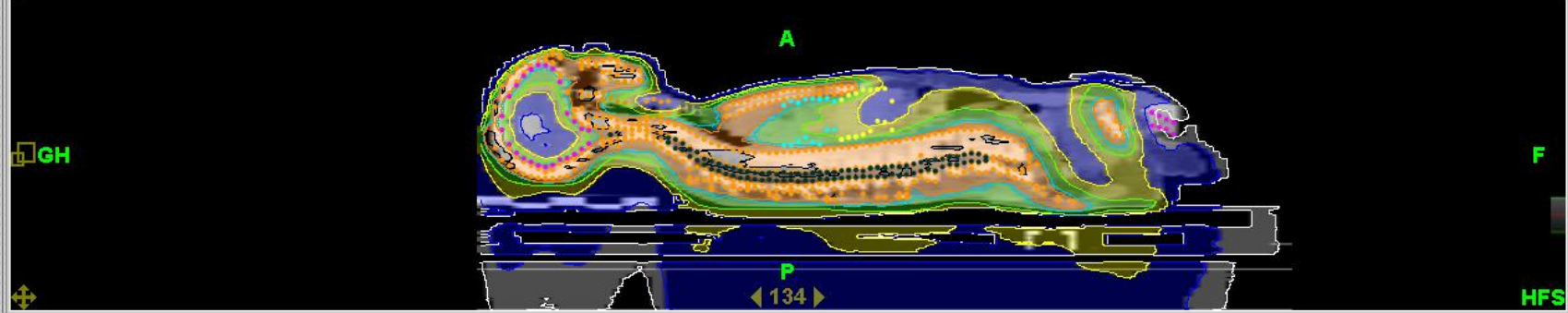
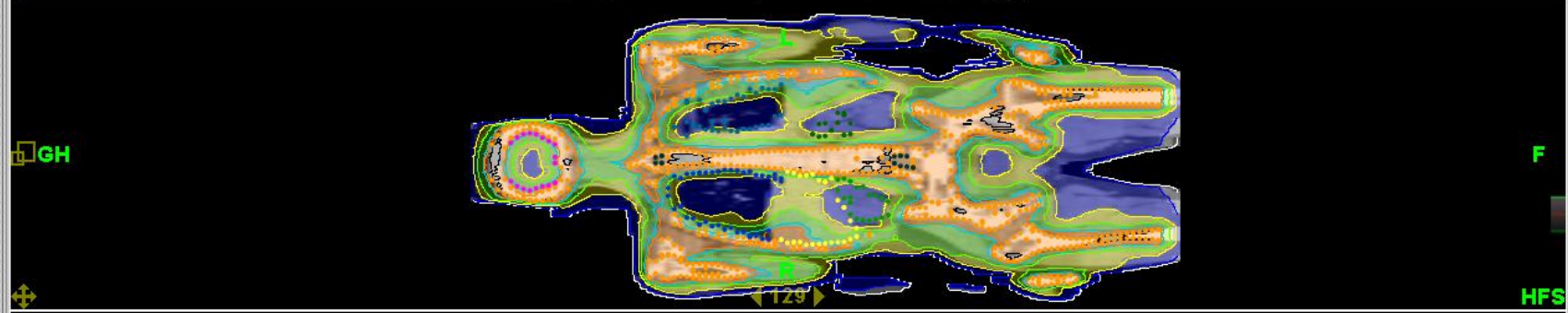
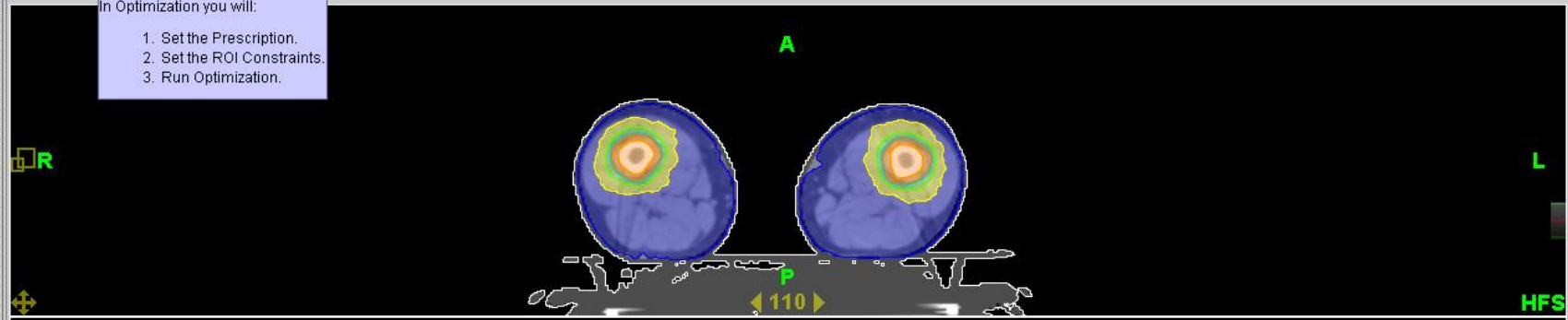


ROIs Optimization Fractionation Delivery QA Setup Delivery QA Analysis

Patient Images

In Optimization you will:

1. Set the Prescription.
2. Set the ROI Constraints.
3. Run Optimization.



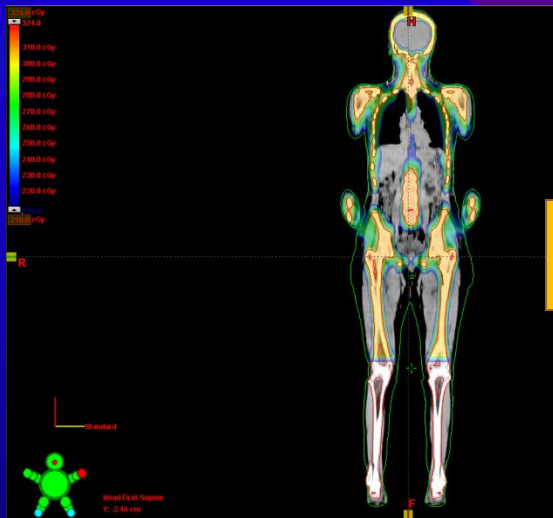
Iteration 484 received

Wednesday, June 3, 2009

18:22:41

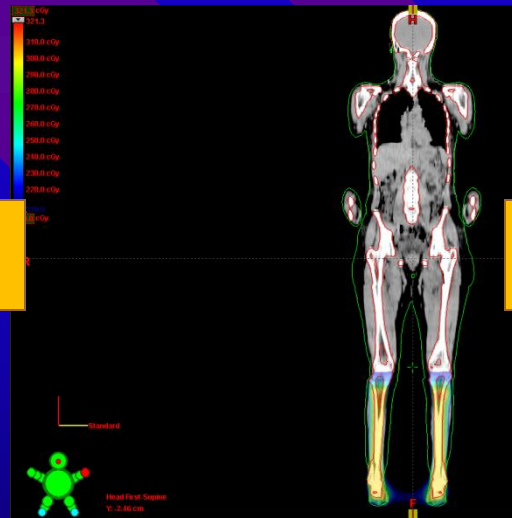
Treatment technique

- **Upper body TMI (UTMI)** = from vertex to knees
- **Lower body TMI (LTMI)** = from knees to tip of the feet
- **UTMI and LTMI** plans are properly matched in terms of dose uniformity



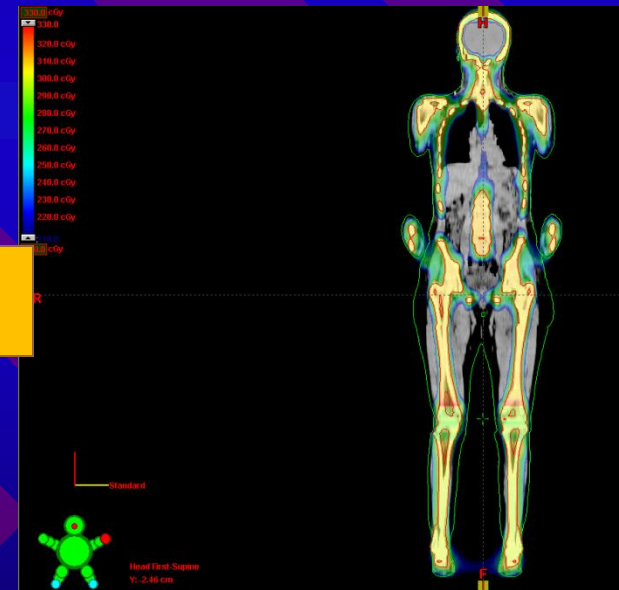
UTMI dose distribution

+



LTMI dose distribution

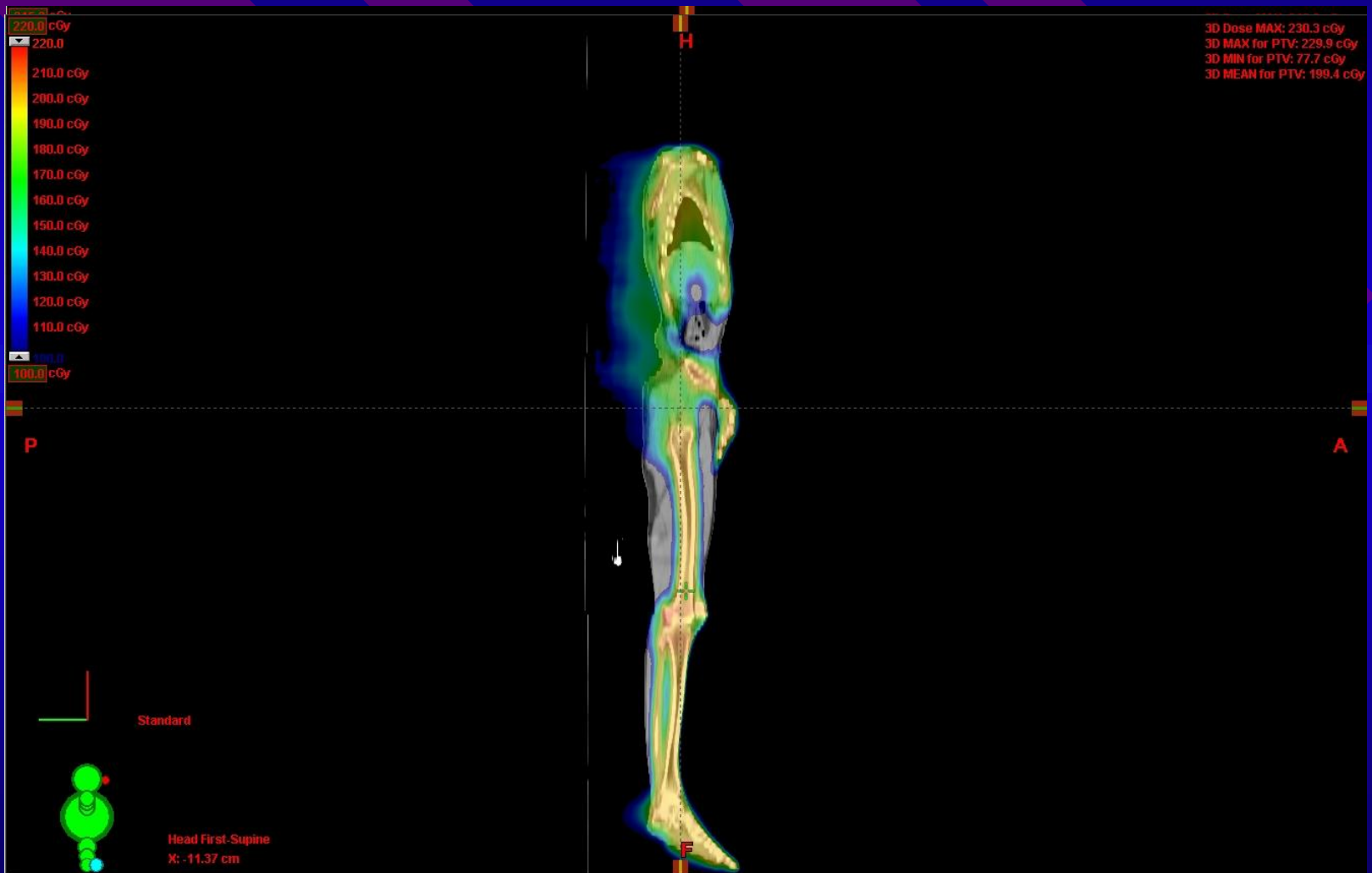
=



TMI dose distribution

Full Helical TMI Dose


UTMI and tLTMI plans can be summed on the same CT data set



TMI-DVH - dose 200 cGy

Tomotherapy Planning Station -- IST - Genova

No Photo



Plan: Plan_01
Plan status: **Approved**
DQA plan:
Patient position: HFS

What's Next

Adjust Fractionization Schedule

- Modify the fraction count or adjust details for each fraction as necessary.
- Run **Final Dose**.

When you are satisfied with the plan, click Final Accept.

User Name: Michele Zeverino

ROIs Optimization Fractionation Delivery QA Setup Delivery QA Analysis

Fraction Count: 1

The plan has 1 fractions defined for a planned delivery of 2.0 Gy. 60.0% of the PTV volume receives at least 2.0 Gy for the current plan. Modulation factor for this tomotherapy IMRT plan is 1.183

Unlock All Fractions

Dose Display

Isodose

2.1
1.9
1.8
1.4
1
0.4

| Fraction | Locked | Fraction Date | Fraction | Locked | Fraction Date |
|----------|--------------------------|---------------|----------|--------------------------|---------------|
| 1 | <input type="checkbox"/> | June 05, 2009 | 2 | <input type="checkbox"/> | |

Finalize

Final Dose
Final Accept
Plan Report

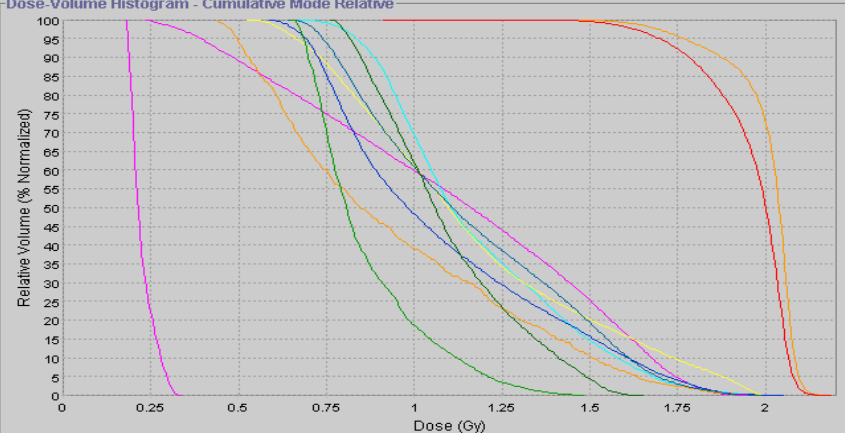
Tumor Settings

| Name | Display | Color |
|-------------|-------------------------------------|-------|
| PTV | <input checked="" type="checkbox"/> | |
| PTV alunzio | <input type="checkbox"/> | |

Sensitive Structure Settings

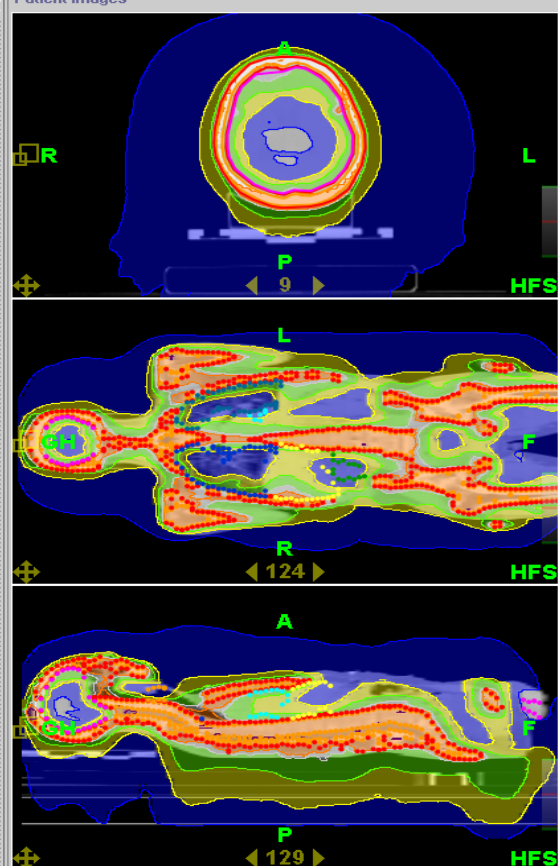
| Name | Displ... | Color |
|-------------|-------------------------------------|-------|
| CTV - Bone | <input checked="" type="checkbox"/> | |
| brain | <input checked="" type="checkbox"/> | |
| cuore | <input checked="" type="checkbox"/> | |
| fedato | <input checked="" type="checkbox"/> | |
| laringe oar | <input checked="" type="checkbox"/> | |
| polmone d | <input checked="" type="checkbox"/> | |
| polmone s | <input checked="" type="checkbox"/> | |
| rene dx | <input checked="" type="checkbox"/> | |
| rene sx | <input checked="" type="checkbox"/> | |
| testicoli | <input checked="" type="checkbox"/> | |

Dose-Volume Histogram - Cumulative Mode Relative



Vol Min < 0.0 > Vol Max Gy Min < 0.0 > Gy Max < 2.2 >

Patient Images



Thursday, June 4, 2009 12:54:38

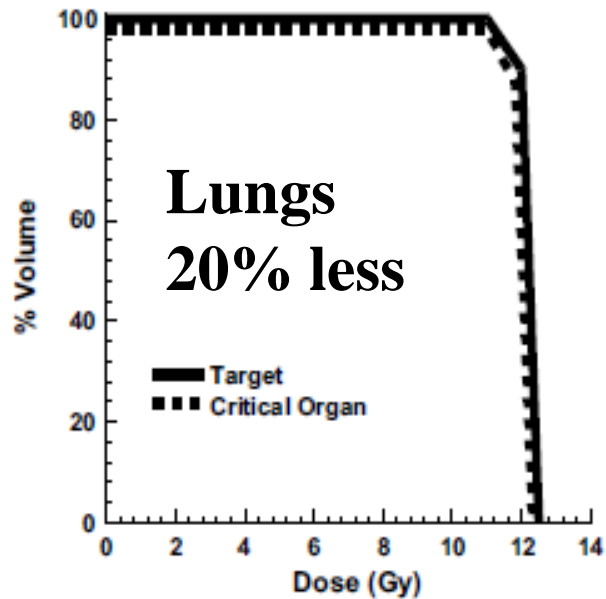
Start Tomotherapy Plannin... CRS Admin Console (tom... Calculator Ganglia Cluster Toolkit:...

12:54 PM

Dose Volume Histograms – TBI plus TMI

TBI

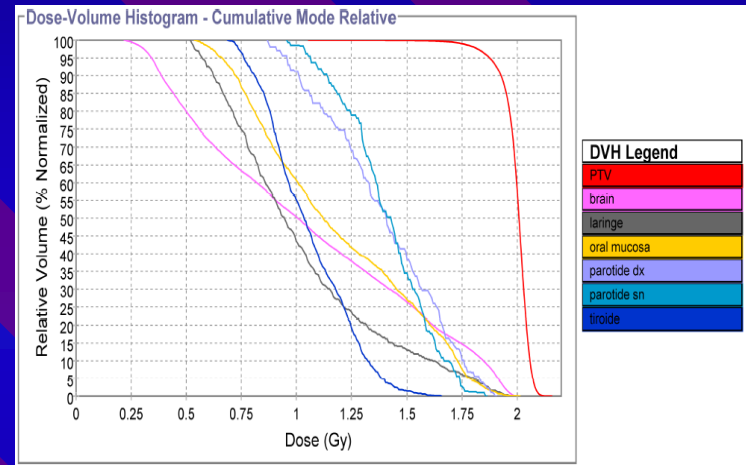
Entire Target Receives Full Dose
Critical Organ Receives Full Dose



Typical TBI Dose
Volume Histogram

TMI

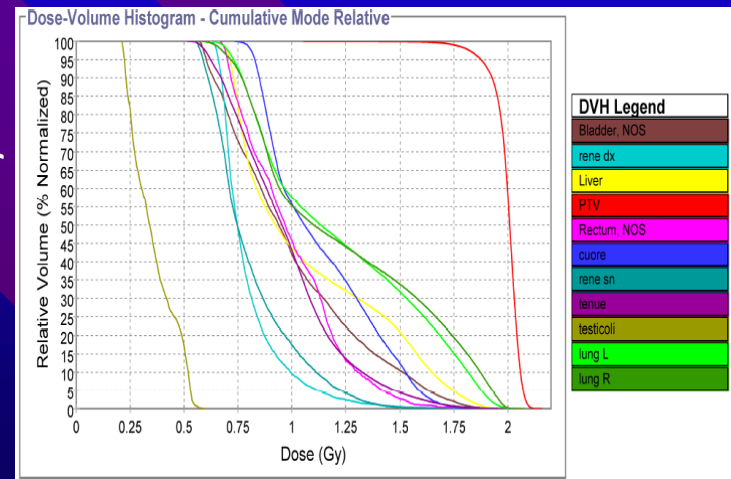
Entire target STILL receives full dose
Critical Organ receives LESS dose



TMI – H&N

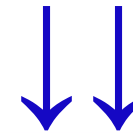
VS

TMI – Body



Organ sparing and marrow coverage

- Organ sparing is achievable in terms of **median dose reduction** (i.e. dose delivered to 50% of organ volume)
- Amount of dose reduction is independent from fractionation
- Small organs are penalized because of technical parameters of treatment
- Optimal PTV coverage and homogeneity



| Organ | Median Dose reduction | Standard Deviation |
|---------------|-----------------------|--------------------|
| Brain | 45,5% | 4,6% |
| Left Parotid | 30,3% | 11,5% |
| Right Parotid | 29,6% | 10,3% |
| Oral Mucosa | 35,8% | 9,2% |
| Larynx | 56,4% | 4,9% |
| Thyroid | 43,3% | 9,6% |
| Left Lung | 44,3% | 2,7% |
| Right Lung | 47,5% | 4,3% |
| Heart | 45,1% | 2,1% |
| Liver | 47,0% | 4,1% |
| Left Kidney | 56,8% | 5,2% |
| Right Kidney | 60,5% | 2,1% |
| Bowel | 52,2% | 3,4% |
| Male Gonads | 80,7% | 12,3% |

| Bone Marrow -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 |

Legenda:

- D95 = dose received by 95 % of Planned Target Volume (PTV)
- D90 = dose received by 90 % of PTV volume
- D5 = dose received by 5 % of PTV volume

TMI- DVH OARs – dose 200 cGy

■ Median doses to OARs:

| | | |
|----------|---------|---------|
| lungs | 100 cGy | (- 50%) |
| liver | 110 cGy | (- 45%) |
| kidneys | 81 cGy | (- 60%) |
| brain | 117 cGy | (- 42%) |
| parotids | 165 cGy | (- 18%) |

TMI-DVH OARs – dose 200 cGy

■ Median doses to OARs:

- heart 111 cGy (- 45%)
- thyroid 144 cGy (- 28%)
- bowel 96 cGy (- 52%)
- larynx 85 cGy (- 57.5%)
- testes 40 cGy (- 80%)

→ Dose to Body (by excluding OARs):

→ **157 cGy (- 22%)**

Delivery Time for upper TMI

According to parameters optimization
(Field Width, Pitch e Modulation Factor):



we can obtain an overall treatment time of
19.5 min for delivery 200 cGy.

Total body irradiation (TBI) and total marrow irradiation (TMI) for patients with advanced hematologic malignancies undergoing an allogeneic stem cell transplant (HSCT) : a pilot study

R Corvo', S. Agostinelli, M. Zeverino, S. Barra, MT Van Lint, F Frassoni, T Lamparelli, G. Taccini, A. Bacigalupo

Divisione Ematologia e Trapianto di Midollo Osseo, Ospedale San Martino ;Istituto Nazionale per la Ricerca sul Cancro- Genova

Presented at EBMT Group – Vienna- 2010

Presented at ESTRO – Barcellona- 2010

Presented at ASTRO – San Diego - 2010

Submitted to Radiotherapy & Oncology- 2010

Submitted to Int J Radiat Oncol Biol - 2010

The Genoa experience in allogeneic stem cell transplantation

- From June 2009 to August 2010
- **15** patients with relapsed acute leukemia
- TBI 12 Gy/ 6 fx → TMI 2 Gy/ 1 fx: **14 Gy/7 fx**
- Median follow-up: 210 days (80-385 days)
- All patients reached Complete Remission
- 3 (20%) deaths for GvHD (2) and infection (1)
- **2 (15%) relapses (in 2 previous autografted pts)**
- **10 (67%) alive in remission**

CONCLUSIONS

Early encouraging outcomes also in patients with very advanced disease, having failed a first allogeneic or autologous transplant.

- Early tolerance is excellent with TBI/TMI **14 Gy**
- **Allogeneic Transplant:**
 - → dose finding study?
- **Autologous Transplant:**
 - → new trial design

TMI: potentials

- TMI as upfront (hard task!)
- TMI *boost* for escalating-dose after TBI in patients with advanced leukemia:

TBI 2 Gy/ 6 fr/ 3 days + TMI with dose escalation:

1° step → 16 Gy/ 8 fr/ 4 days (6 pts)

2° step → 18 Gy/ 8 fr/ 4 days (6 pts)

3° step → 20 Gy/ 8 fr/ 4 days (6 pts)

Ringraziamenti

- **Andrea Bacigalupo, Francesco Frassoni**
(A.O.U. San Martino, Genoa)
- **Salvina Barra, Stefano Vagge (IST)**
- **Personale TSRM (IST)**
- **S.C. Fisica Medica –IST:**
S.Agostinelli, M.Zeverino, G.Taccini

MEETING IN GENOA
on TMI in autograft
19 January 2011

