



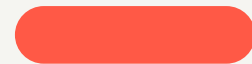
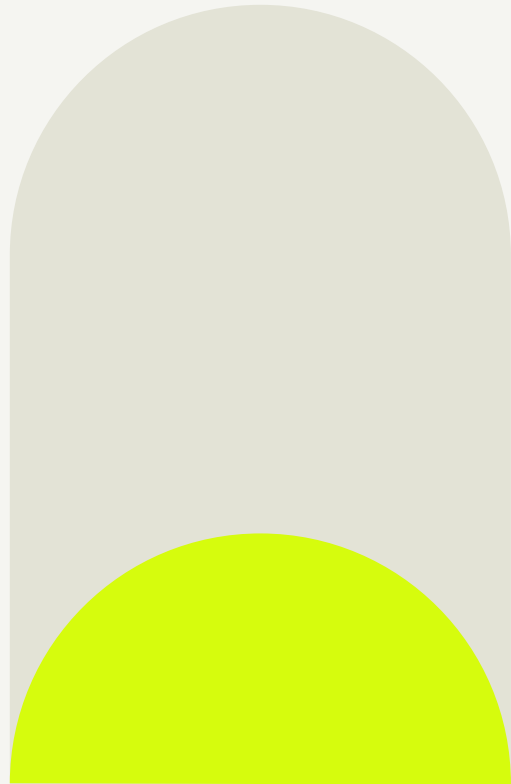
ACCURAY

Developing a World-class TMI Program on the the Radixact[®] System

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Developing a World-class Total Marrow Irradiation (TMI) Program on the Radixact® System

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Accuray Disclaimers and Disclosure

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Safety Statement

Most side effects of radiotherapy, including radiotherapy delivered with Accuray systems, are mild and temporary, often involving fatigue, nausea, and skin irritation. Side effects can be severe, however, leading to pain, alterations in normal body functions (for example, urinary or salivary function), deterioration of quality of life, permanent injury and even death. Side effects can occur during or shortly after radiation treatment or in the months and years following radiation. The nature and severity of side effects depend on many factors, including the size and location of the treated tumor, the treatment technique (for example, the radiation dose), the patient's general medical condition, to name a few. For more details about the side effects of your radiation therapy, and if treatment with an Accuray product is right for you, ask your doctor.

City of Hope Medical Center

- One of the Largest Radiation Oncology Networks In Southern California
 - 22 Linear Accelerators in 1 main campus and 16 community sites
 - 1 TomoTherapy® System, 1 Radixact® System
 - 1 RefleXion X1
 - 1 Viewray MRIdian (go live in Q1 2023)
 - 7 TrueBeam/TrueBeamSTX, 3 Halcyon
 - 8 Varian iX, 23EX, 21EX
 - PET/CT simulator, 3T MR simulator
 - MR Guided Focused Ultrasound
 - Elekta/Varian HDR, XOFT IORT/Skin
- City of Hope Hematopoietic Cell Transplant Program
 - One of the largest programs in the US
 - ~ 800 transplants per year
 - Established in 1975
 - > 17,000 patients since 1975
 - 120-200 TBI patients per year



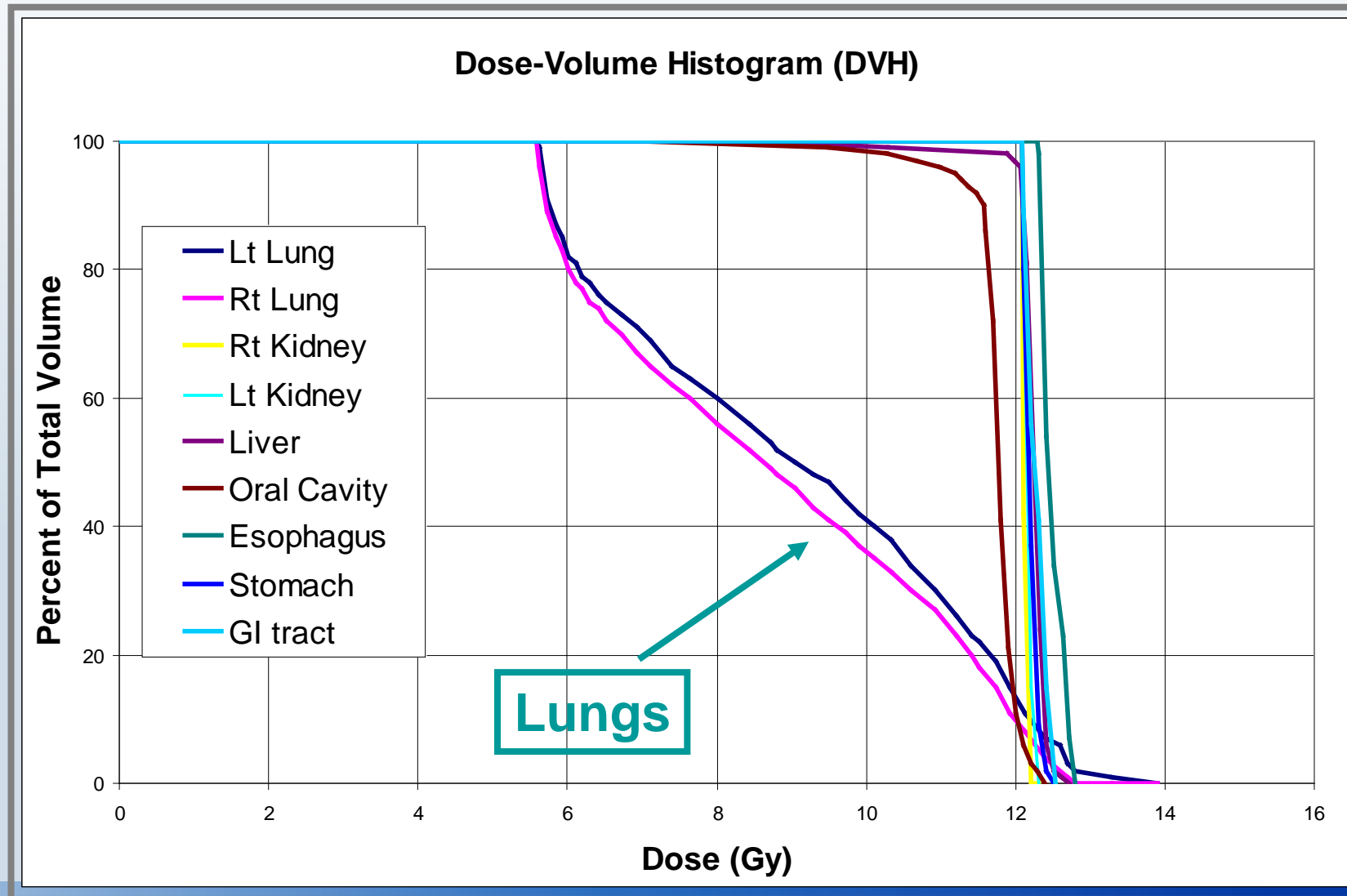
Conventional Total Body Irradiation (TBI)



- Patient standing at extended distance
- TID 1.2Gy/fraction X 10/11
=12Gy/13.2Gy
- 50% transmission lung blocks
- Chest wall boost with 3Gy X 2
- Lead filters used to achieve uniform mid-plane dose

Conventional TBI (12 Gy)

with 50% transmission lung blocks and chest wall electron boost



Outline of TMI on the Radixact[®] System

- Immobilization/Simulation
- Contouring
- Planning
- Physics QA
- Treatment delivery
- Clinical outcome

CT Simulation Immobilization



- Simulated supine, arms at sides
- Accuform molded cushion from neck to shoulders
- S-frame thermoplastic mask for head & shoulder
- Body Vac-lok
- 4D CT to account for respiratory motion or 3 non-contrast scans (5-8 mm slices)
 - Quiet breathing (from top of head to proximal thighs), shallow inspiration (Chest and Abd), shallow expiration (Chest and Abd)
- 4th CT of the legs
- 3 sets of radiopaque BBs, 1 placed proximal thigh to mark lower border of TMI fields for planning

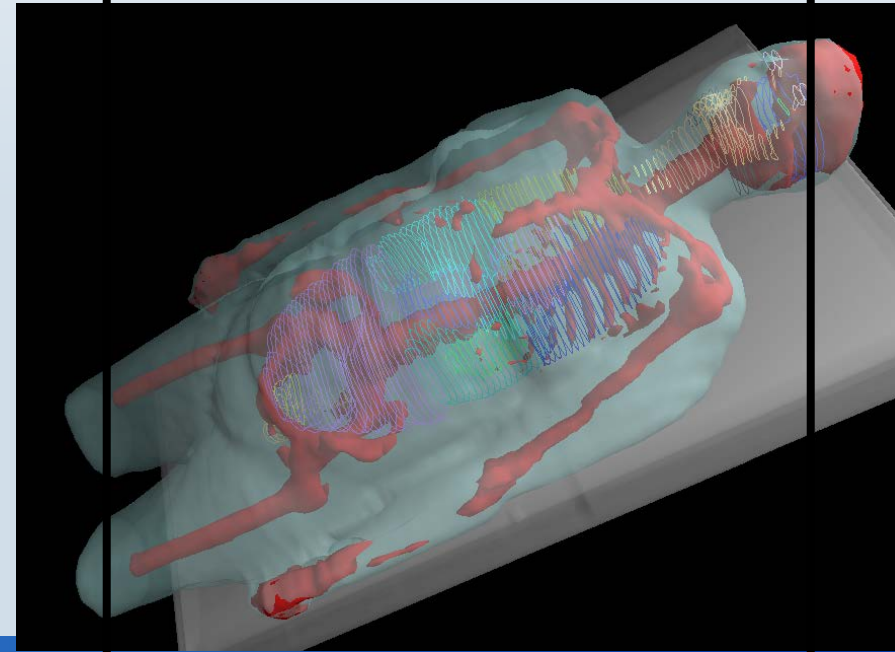
Contours needed for TMI Treatment Plan

Avoidance Structures

- Lungs
- Oral cavity
- Esophagus
- Stomach
- Small intestine
- Rectum
- Heart
- Kidneys
- Liver
- Brain
- Parotid
- Thyroid
- Ovaries
- Breast
- Bladder
- Eyes
- Optic nerves
- Lens
- Testes

Target Structures

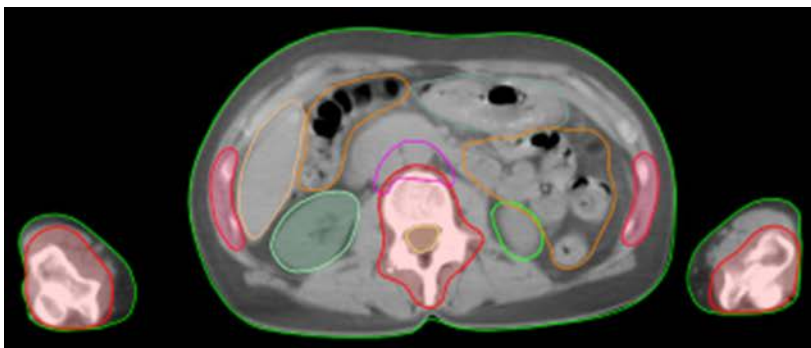
- Bone/marrow
- Lymphnodes



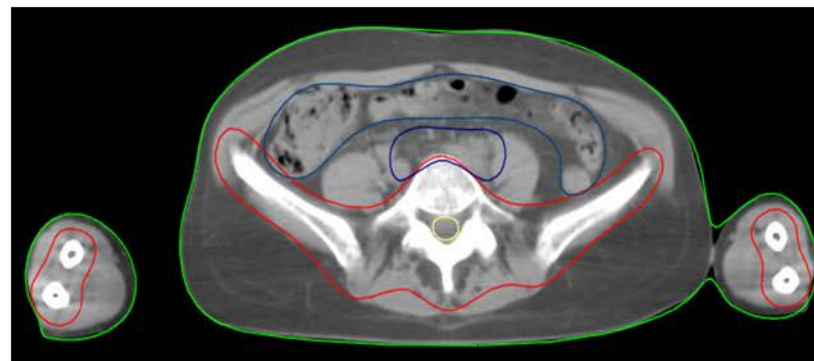
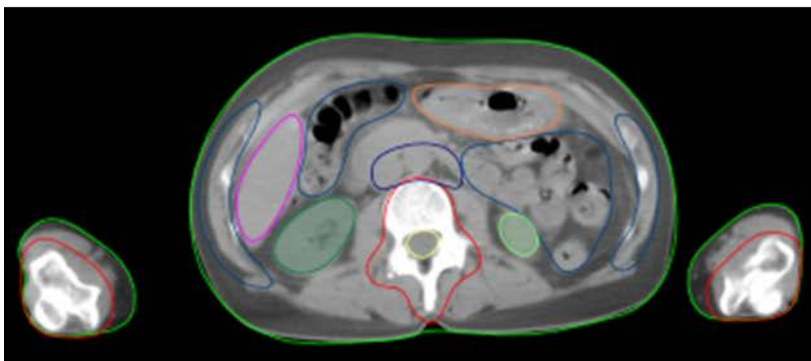
AI Based Auto Segmentation



Human



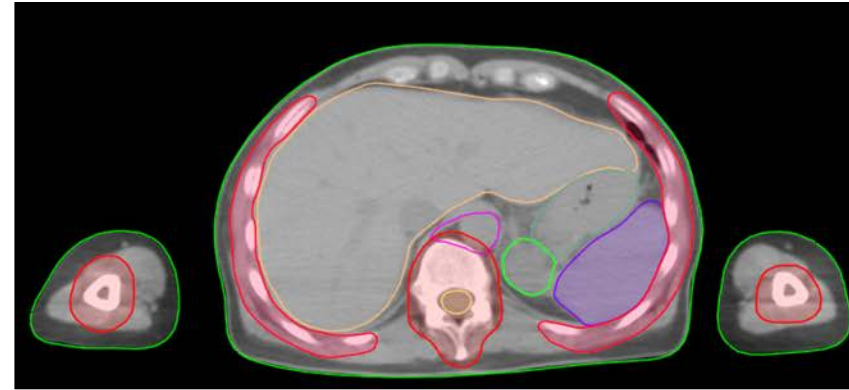
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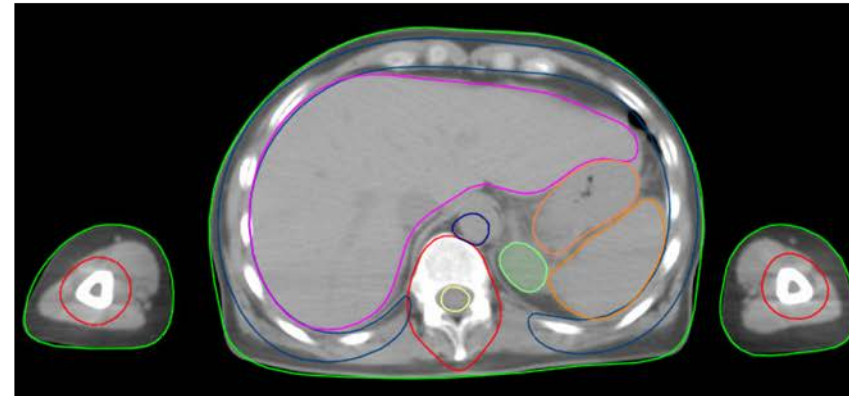
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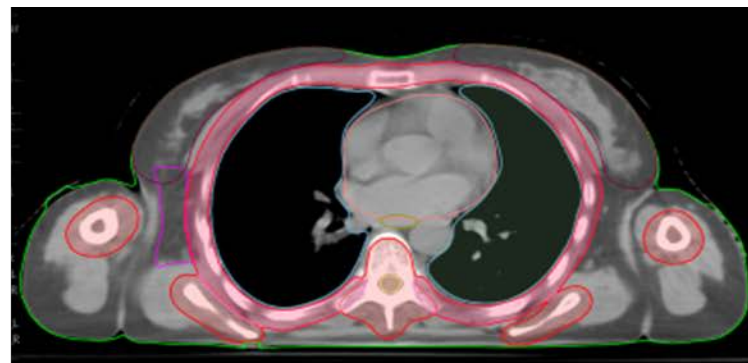
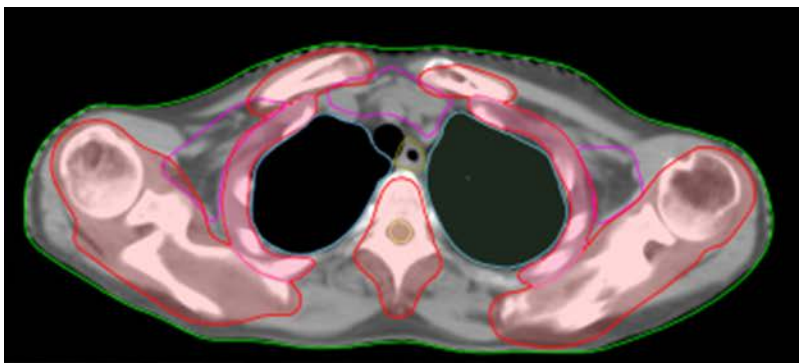
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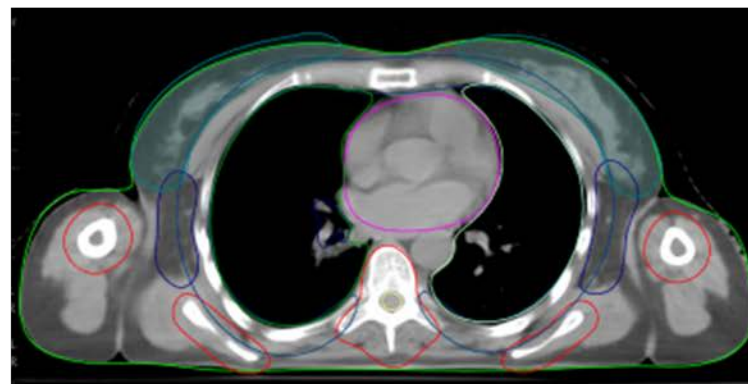
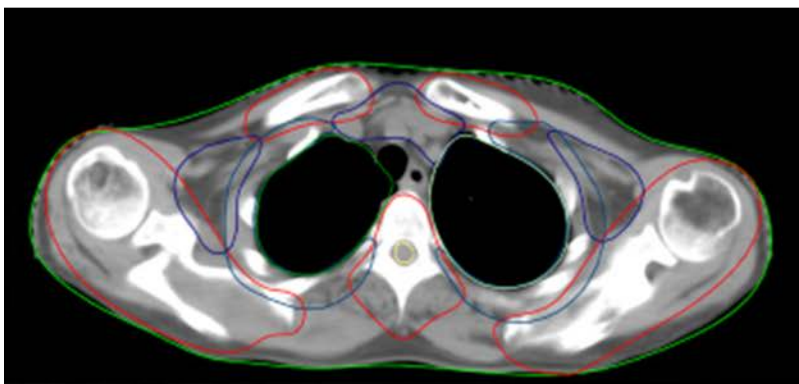
AI Based Auto Segmentation



Human



AI



TMI Methodology (City of Hope)

- Target CTV's and organs contoured
 - 5-10 mm margin on portions of CTV with set-up variability (shoulder, extremities, spinous process)
- The skull volume and rib bone volume are contoured separately to ensure adequate dose coverage.
- Kidney, ribs, lung, liver and spleen contours modified to account for respiratory motion
- PTV min. 85% prescribed dose
- Mobius, film exposure and ion chamber exposure performed for patient Q/A
- Approximately 1 week from CT sim to TMI start

TMI Treatment Planning

Objectives

- Maximize the normal organ sparing
- Minimize target non-uniformity
- Reasonable treatment time

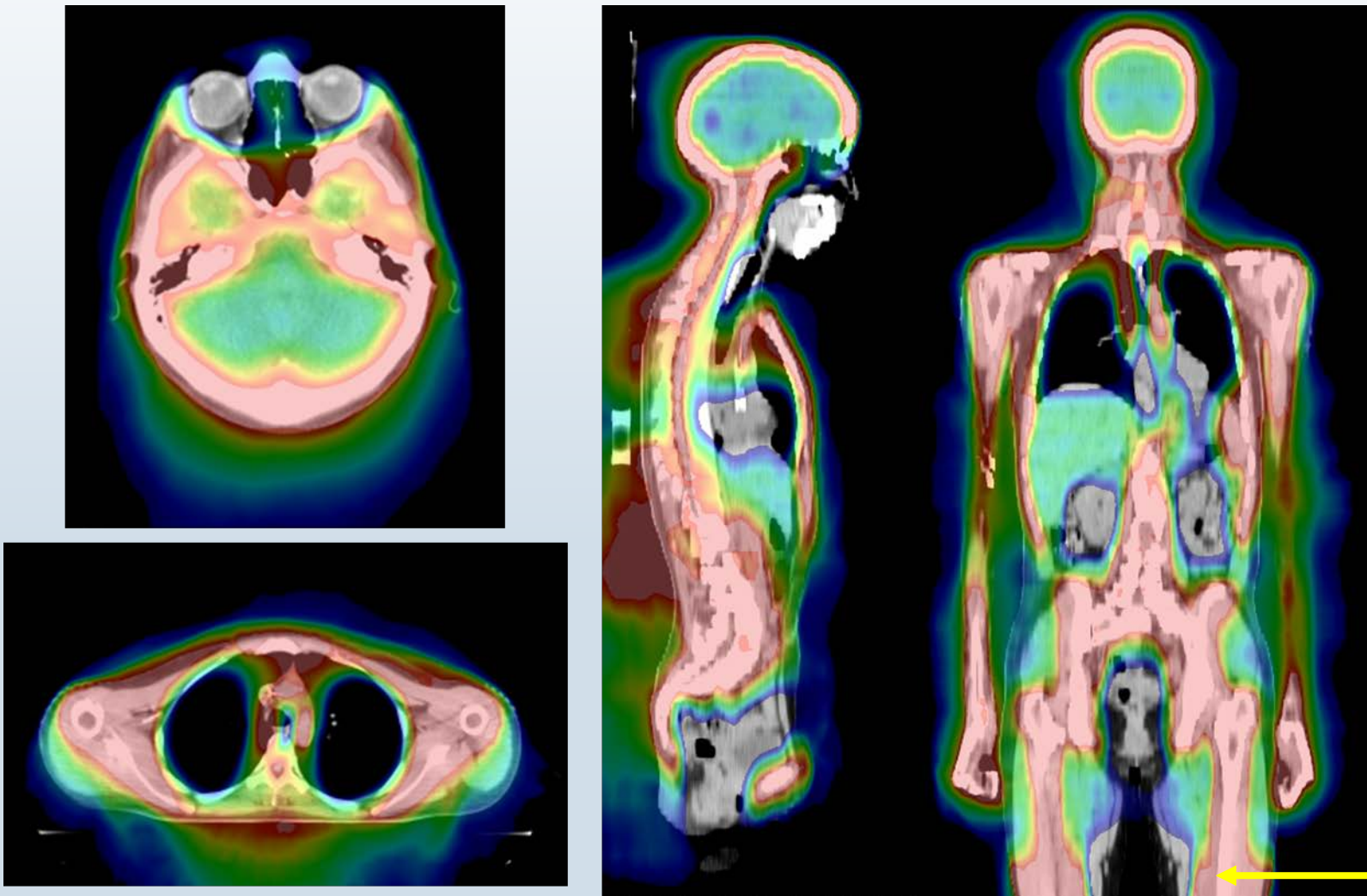
Treatment Planning

- Prescriptions (weightings)
- Jaw size (1.0cm, 2.5cm, 5.0cm)
- Modulation factor (~2.5)
- Pitch (0.287-0.444)

TMI Treatment Planning Template

Organ	Importance	Max Dose	Max Penalty
Lungs	30	10	10
Esophagus	30	10	1
Stomach	10	10	10
Oral Cavity	10	10	1
Intestine (Bowel)	5	7.2	1
Brain	3	12	1
Kidneys	3	12	1
Liver	3	12	1
Bladder	1	12	1
Breasts	1	12	1
Eyes	1	12	1
Parotids	1	11.2	1
Rectum	1	10	1
Thyroid	1	10	1
Heart	1	9.6	1
Lens	1	2.5	100

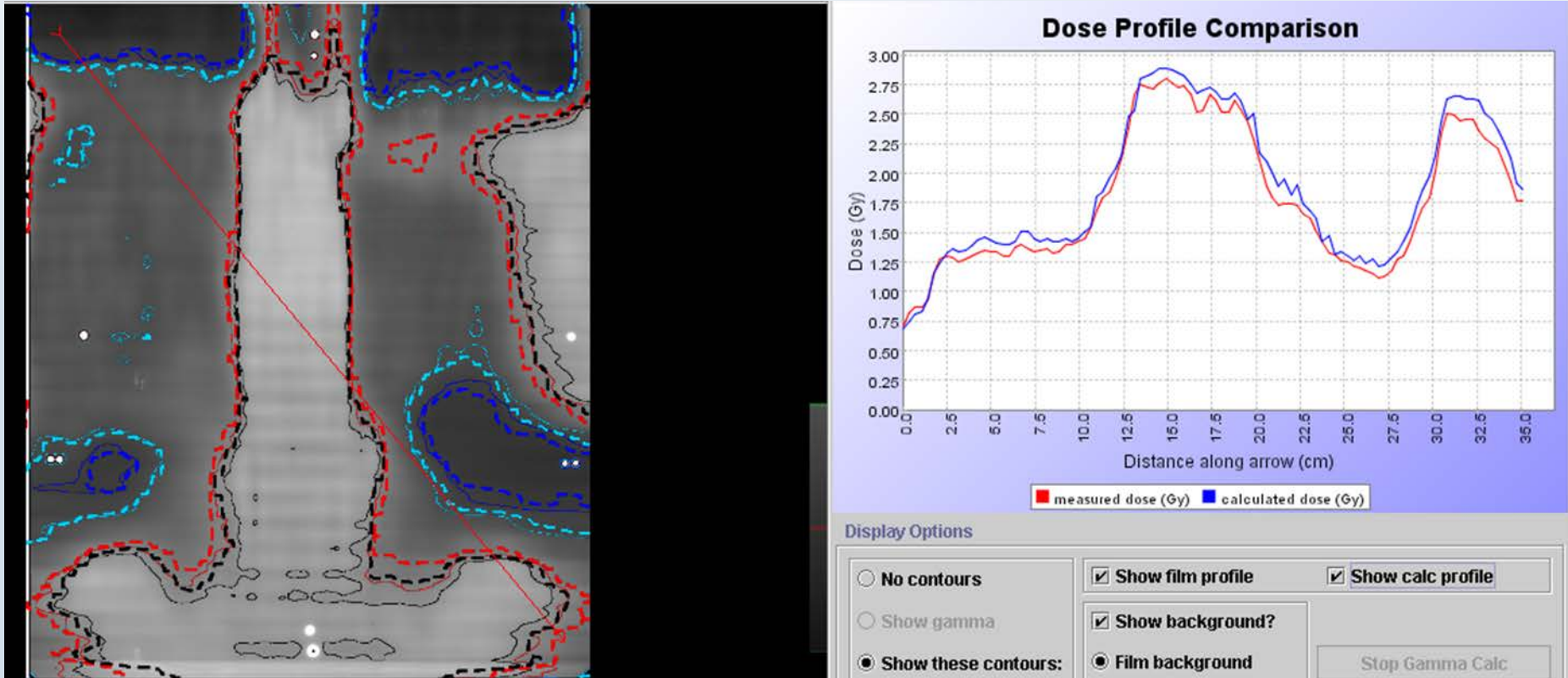
Total Marrow Irradiation



TomoDirect™ abutted
to TomoTherapy®
Helical plan 50%
isodose line to treat
lower extremities

Patient Specific QA

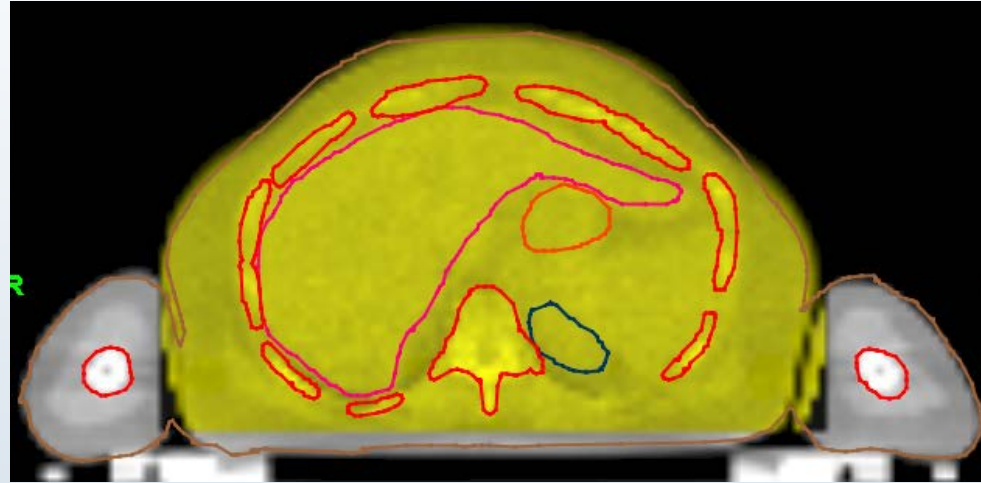
- Mobius
- Ion chamber
- Film



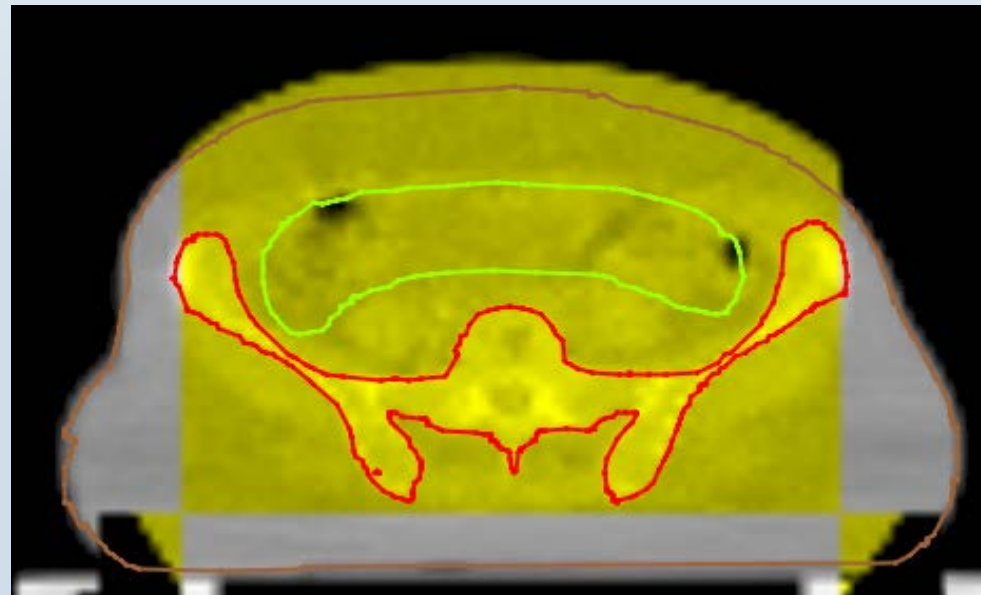
Treatment setup with kvCT



Head & Neck



**Chest &
Abdomen**



Pelvis

TMI (City of Hope)

- CT sim: 60 mins appointment
- Contouring: ~1 hours (6-8 hours without auto contouring)
- Planning optimization: 2-4 hours
- QA: 1 hour
- Upper body
 - Imaging: 1.5 mins (KVCT) vs 6-10 mins (MVCT)
 - Treatment: ~20 minutes (Radixact[®]) vs 25 minutes (TomoTherapy[®])
- Legs
 - Imaging: 1.5 mins (KVCT) vs 6-10 mins (MVCT)
 - Treatment: ~6-8 minutes (Radixact[®]) vs 8-10 minutes (TomoTherapy[®])
- Total time on couch: ~70 minutes

TMI: City of Hope

- Over 500 patients to date (first patient June 2005). Almost all on clinical trials
- 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 (> 450 acute leukemia)
- Advanced relapsed/refractory acute leukemia (AML and ALL)
 - AML complete 1st or 2nd remission (CR1 and CR 2) in recent trials
- Clinical regimens
 - TMLI added to established reduced intensity (RIC) – patients 60 or older or with co-morbidities
 - TMLI dose escalated myeloablative (MAC) regimens – patients younger than 60
 - TMLI added to haplo-identical allogeneic HCT regimens with GVHD reduction strategies (post-transplant cyclophosphamide)
 - TMLI dose escalated in AML in first remission
 - IMRT TBI to replace conventional TBI as a method to better spare lung (no dose escalation)

City of Hope TMI Program



- **Relapsed and refractory (R/R) acute leukemia**
 - Challenges: poor prognosis, no standard of care HCT option; unmet need
 - TMLI (total marrow and lymphoid irradiation) added to a reduced intensity regimen (fludarabine and melphalan)
 - ≥ 60 years old
 - Pilot (completed, 12 Gy) \rightarrow Phase I (ongoing, 12 – 20 Gy)
 - TMLI 20 Gy + cyclophosphamide (Cy) + etoposide (VP-16)
 - < 60 years old
 - Phase I completed) \rightarrow Phase II (near completion)
 - \rightarrow multi-center phase II (planned)



≥ 60 years old

12 Gy to bone, LNs,
and spleen



< 60 years old

20 Gy to bone, LNs and spleen
12 Gy to liver and brain

City of Hope TMI Program



TMLI experience at City of Hope in R/R acute leukemia

- Low incidence of pulmonary, renal, thyroid and cataract toxicities which compares favorably to published TBI results ¹
- All patients have engrafted
- No increase in extramedullary relapses compared to published TBI results ²
- In patients \geq 60 years old TMLI 12 Gy can be added to an established chemo only reduce intensity regimen of fludarabine and melphalan. 5-year OS 42%, EFS 41%, and NRM rate 33%^{3,4}
- In patients < 60 years old, escalation of TMLI dose to 20 Gy with VP-16 + Cy in advanced R/R acute leukemia: safe, feasible, acceptable toxicities and encouraging 2-year OS 48%, PFS 33% and NRM rate 9% ⁵

1. Shinde A, et al. Radiation related toxicities using organ sparing total marrow irradiation transplant conditioning regimens. *Int J Radiat Oncol Biol Phys.* 2019;105(5):1025-33.
2. Kim JH, Extramedullary relapse following total marrow and lymphoid irradiation in patients undergoing allogeneic hematopoietic cell transplantation. *Int J Radiat Oncol Biol Phys.* 2014;89(1):75-81.
3. Stein A, et al. Total marrow and lymphoid irradiation (TMLI) in combination with Cyclophosphamide and Etoposide improves the outcome of patients with poor-risk acute leukemia. *European Society for Blood and Marrow Transplantation, Madrid, Spain, March 22-25, 2020.* 2020.
4. Wong JYC, et al. Total marrow and total lymphoid irradiation in bone marrow transplantation for acute leukaemia. *Lancet Oncol.* 2020;21:e477-e87.
5. Jensen LJ, et al. Total marrow lymphoid irradiation/Fludarabine/Melphalan conditioning for allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant.* 2018;24:301-7.

THANK YOU!

