Experience and Dosimetry Standardization for Total Body Irradiations in Research

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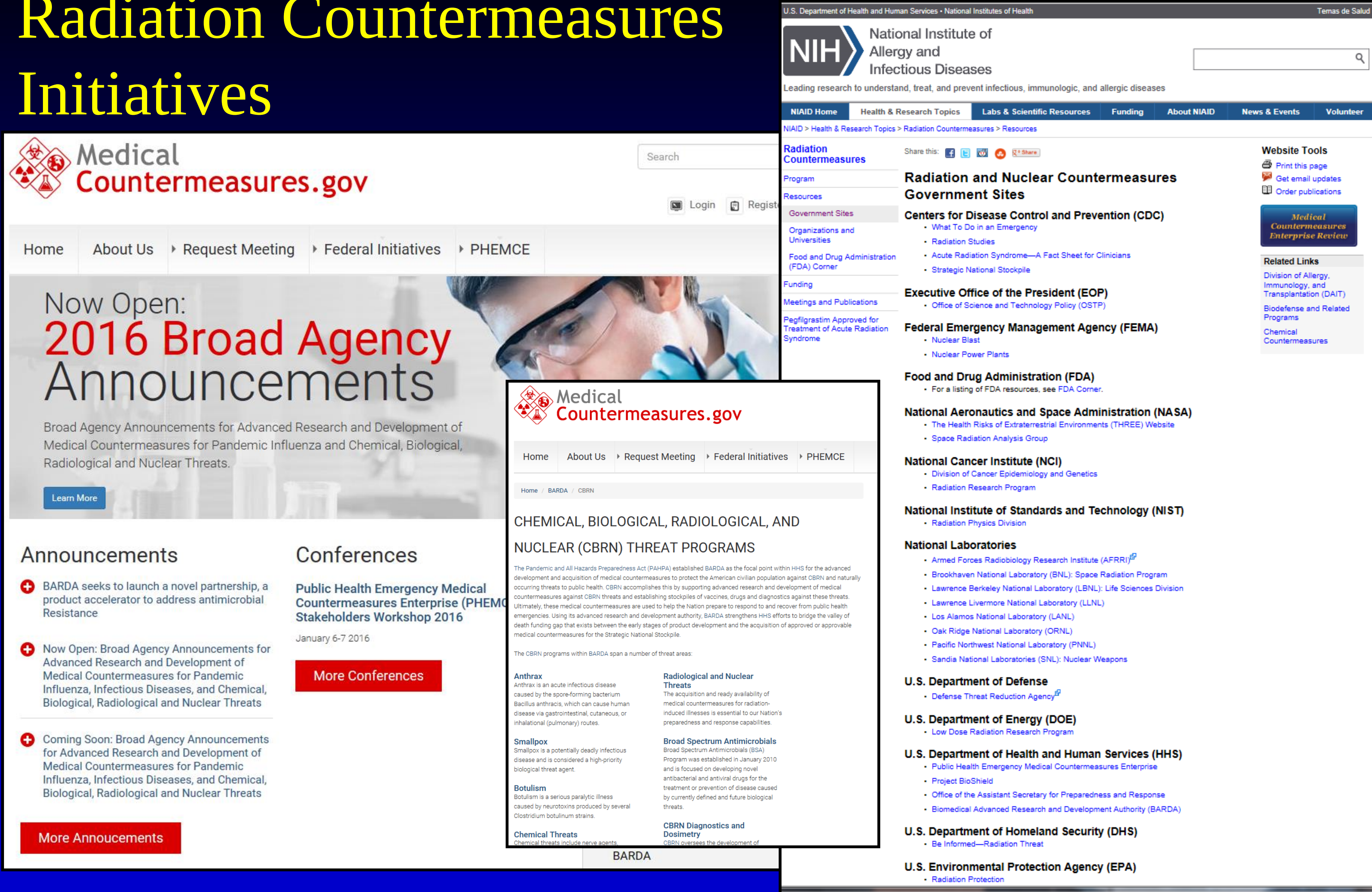
Radiation Countermeasures Initiatives



Radiation: the delivery of energy to a distant point by some mechanism; "effect at a distance"

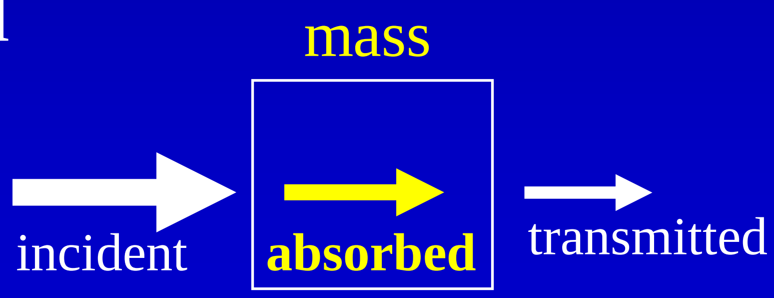
Ionizing Radiation

- That radiation which is capable of ionization
  - Radiation energy must be greater than the binding energy of the atomic electrons, ie, 13.6 eV - ~100 keV
- Radiation may be photons ($E=h\nu$) or particles
  - x rays, γ rays, UV; $E > 13.6$ eV
  - electrons, protons, neutrons, etc

Communication Challenge

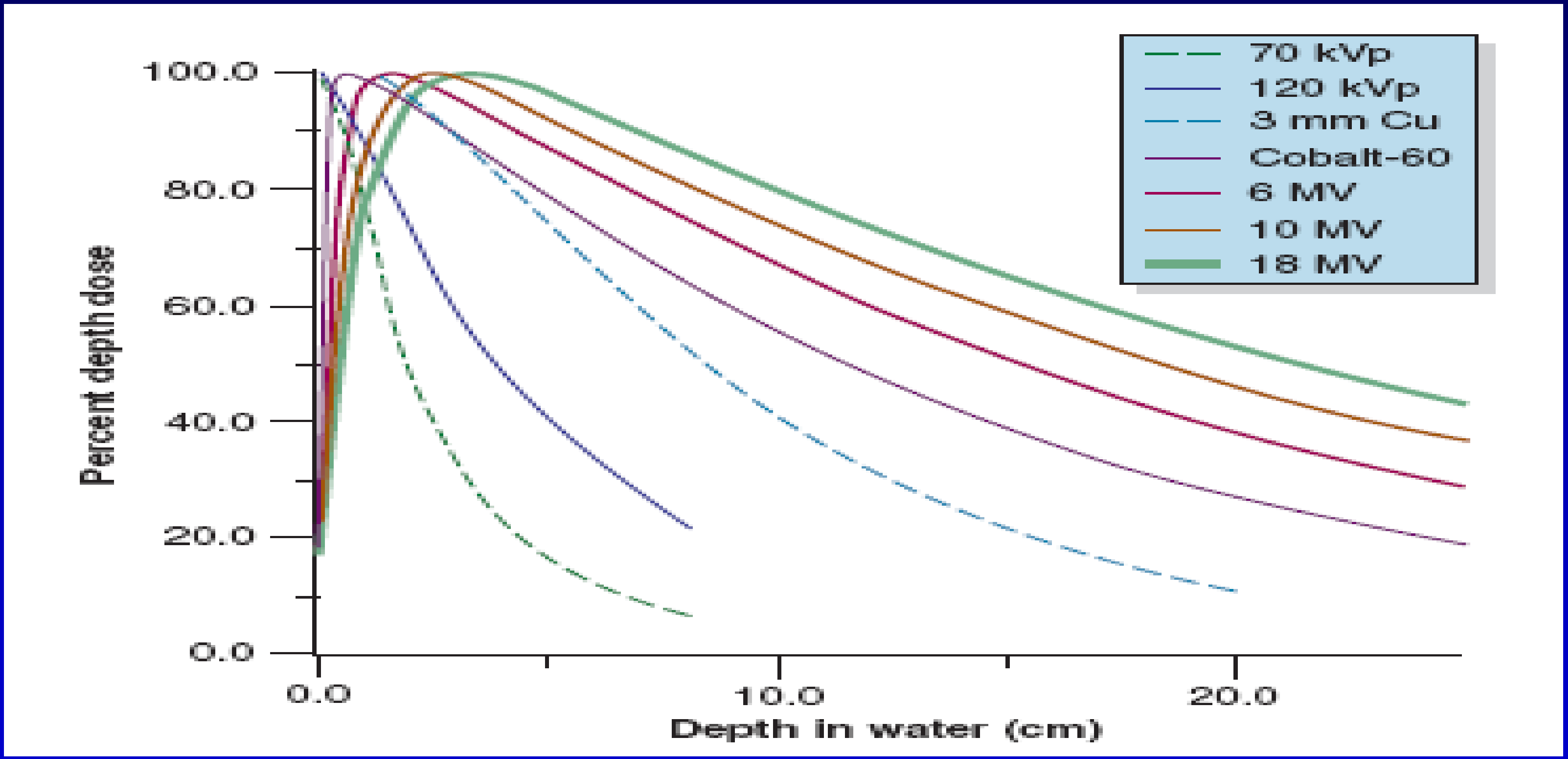
Radiation Dose: E / mass, and Dose Distributions (dose / organ)

- Dose: energy absorbed per unit mass
  - Unit: rad — 1 rad = 100 erg/g
  - SI Unit: Gray — 1 Gy = 1 J/kg
  - Conversion: — 100 rad = 1 Gy
- Measured by ionization, calorimetry, or chemical
- Calibration protocols defined
- Great detail in practice
- See your local physicist



Communication Challenge

MV vs kV Radiation Beam Depth Dose Curves



Communication Challenge
Radiation Response Sequence

Physical

↓

Chemical

↓

Biological

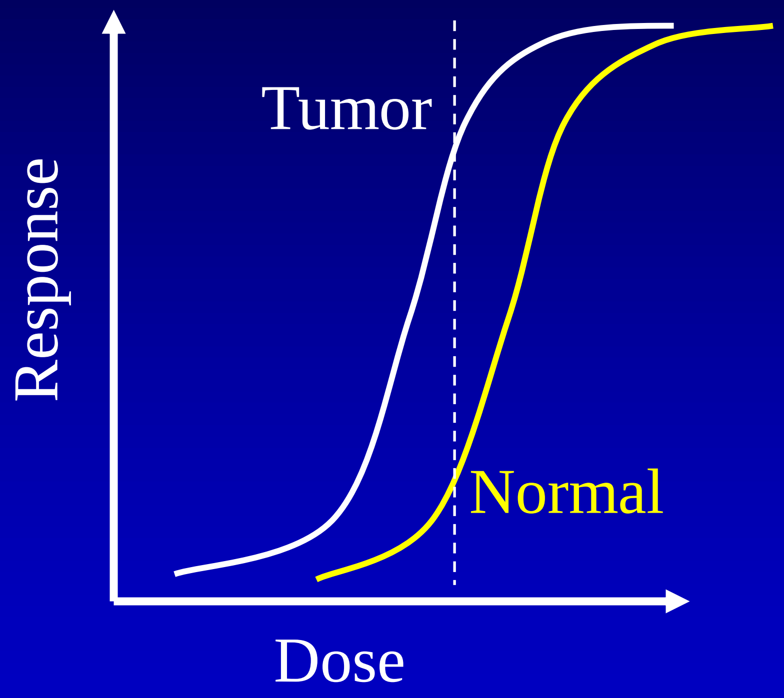
↓

Clinical

(responses, changes, consequences)

Radiation Biology and "Treatment"
Radiobiology of Tumor and Normal Tissues

- Radiation Biology "is complicated"
- Sigmoidal dose-response curve
- Response is dependent on
  - Total radiation dose
  - Fractionation regimen (# of fractions, dose per fraction)
  - Dose rate
  - Radiosensitivity of target
  - Radiosensitivity of nearby normal and/or critical structures, etc



WFU Radiation Survivor Cohort

JM Cline, PI

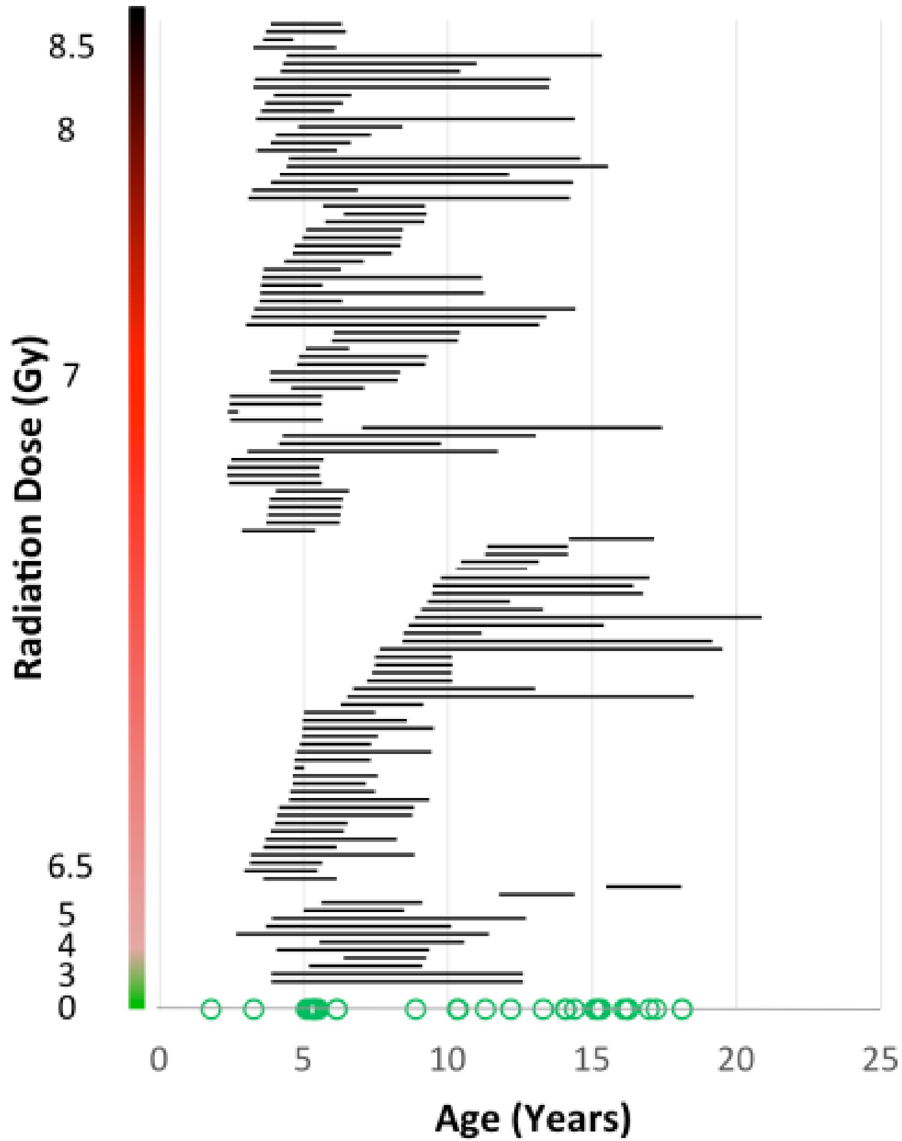


Figure 0.1: Age and dose distribution of the Radiation Survivor Cohort. Each horizontal bar represents a single animal; the left end of the bar is the age at which the animal was irradiated, and the right end of the bar is the animal's current age or age at time of death. Green circles represent the current age of non-irradiated controls. For rhesus monkeys, the typical age a puberty is 3.5 years; typical lifespan is 30 years.

Table 1: Threshold-based determinations of morbidity in the long-term Radiation Survivor Cohort.

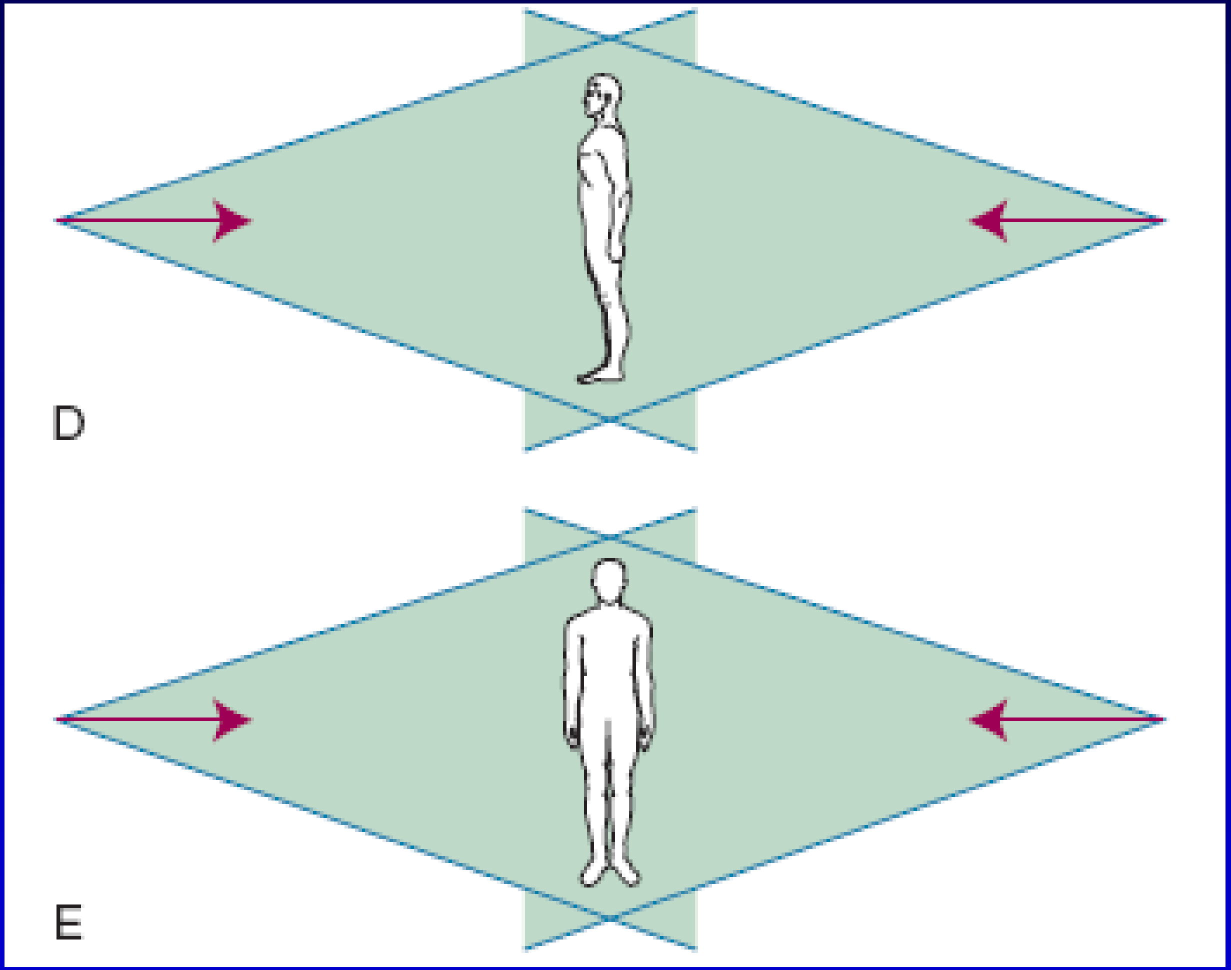
Organ or Disease	Irradiated	Control	Fisher's Exact p value	Criteria for Diagnosis of Abnormality
Body Condition Obese	44.4% (20/45)	60% (9/15)	NSD	Waist Circumference > 45 cm or DEXA Body Fat > 30% after 7 years of age
Body Condition Underweight	15.6% (7/45)	13% (2/15)	NSD	Waist Circumference < 25 cm or DEXA Body Fat < 12.3% after 7 years of age
Bone (osteopenia)	34.10% (15/44)	0% (0/13)	0.0129	DEXA BMC < 274g BMD < 0.373 g/cm^3 after 7 years of age CT: Fracture or other abnormality
Brain	12.50% (12/96)	0% (0/15)	NSD	Any MRI lesion Neurologic abnormality
Cardiovascular	25.30% (21/83)	20% (3/15)	NSD	Murmur/valvular insufficiency on echo Stroke volume <5 mls/stroke Cardiac output <0.5 L/min Hypertension MAP > 120 Other
Diabetes	13.10% (16/122)	0% (0/38)	0.013	HbA1c >6.5 Fasting Blood Glucose > 100 mg/dL x 3 Non Fasted Blood Glucose > 200 mg/dL
Gastrointestinal	6.00% (5/83)	6.70% (1/15)	NSD	Any lesion on endoscopy Chronic diarrhea (severity code >2 for >5 days) Other GI signs
Lung	10.80% (9/83)	13.30% (2/15)	NSD	CT densities (any amount) Emphysema >25% of lung volume Hypoxia under sedation (SPO2 < 80%)
Neoplasia	13.10% (16/122)	0% (0/38)	0.0125	Biopsy with histologic diagnosis
Ocular (cataracts)	21.70% (18/83)	0% (0/15)	NSD	Ophthalmologic exam (slit lamp); lens opacity
Renal	35.60% (31/87)	0% (0/24)	< 0.001	Bun > 30 mg/dl Cr > 1.1 mg/dl Loss of renal volume >50% Urolithiasis
Skin	22.90% (19/83)	6.70% (1/15)	NSD	Biopsy diagnosis of dermatitis Other significant disease (e.g. alopecia, depigmentation)
Testicular atrophy	56.70% (17/30)	6.30% (1/16)	0.0253	<10 ml testis volume after 5 years of age

Abbreviations: BUN = blood urea nitrogen; Cr = serum creatinine; CT = computed tomography; DEXA = dual emission x-ray absorptiometry; HbA1c = hemoglobin A1c; MRI = magnetic resonance imaging; NSD = no significan difference; SP02 = oxygen saturation.

Irradiation Geometry
Total Body Irradiation

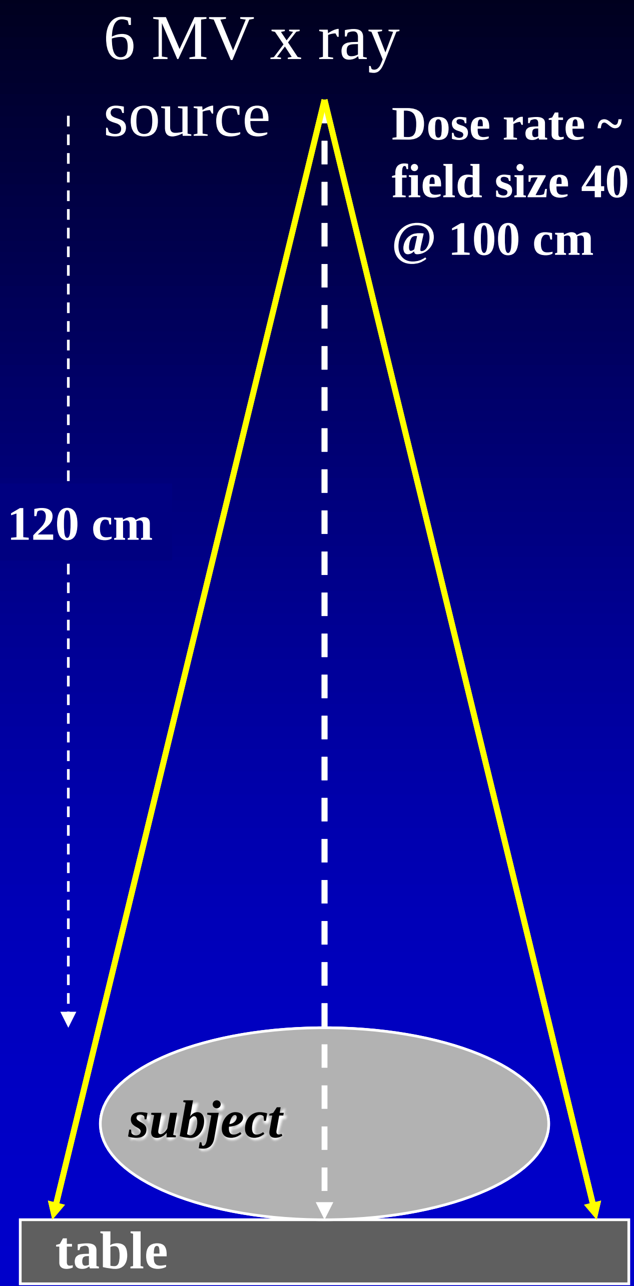
Characteristics

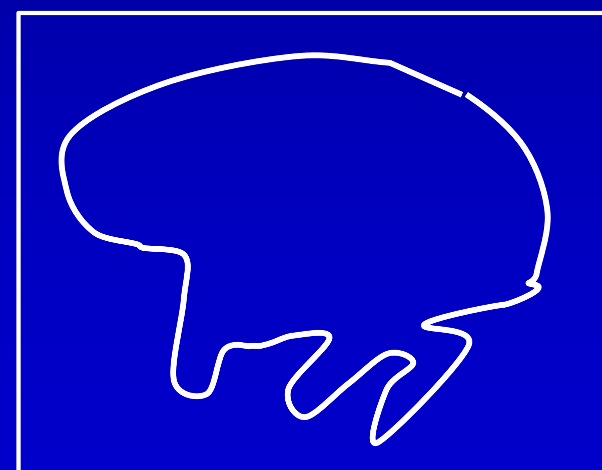
- Extended distance
  - 150 – 500 cm
- Large fields
- Parallel-opposed pairs
  - AP-PA or RT-LT
- Photons, E ≥ 6MV
- Geometry similar to human TBI protocols



TBI Pilot Geometry

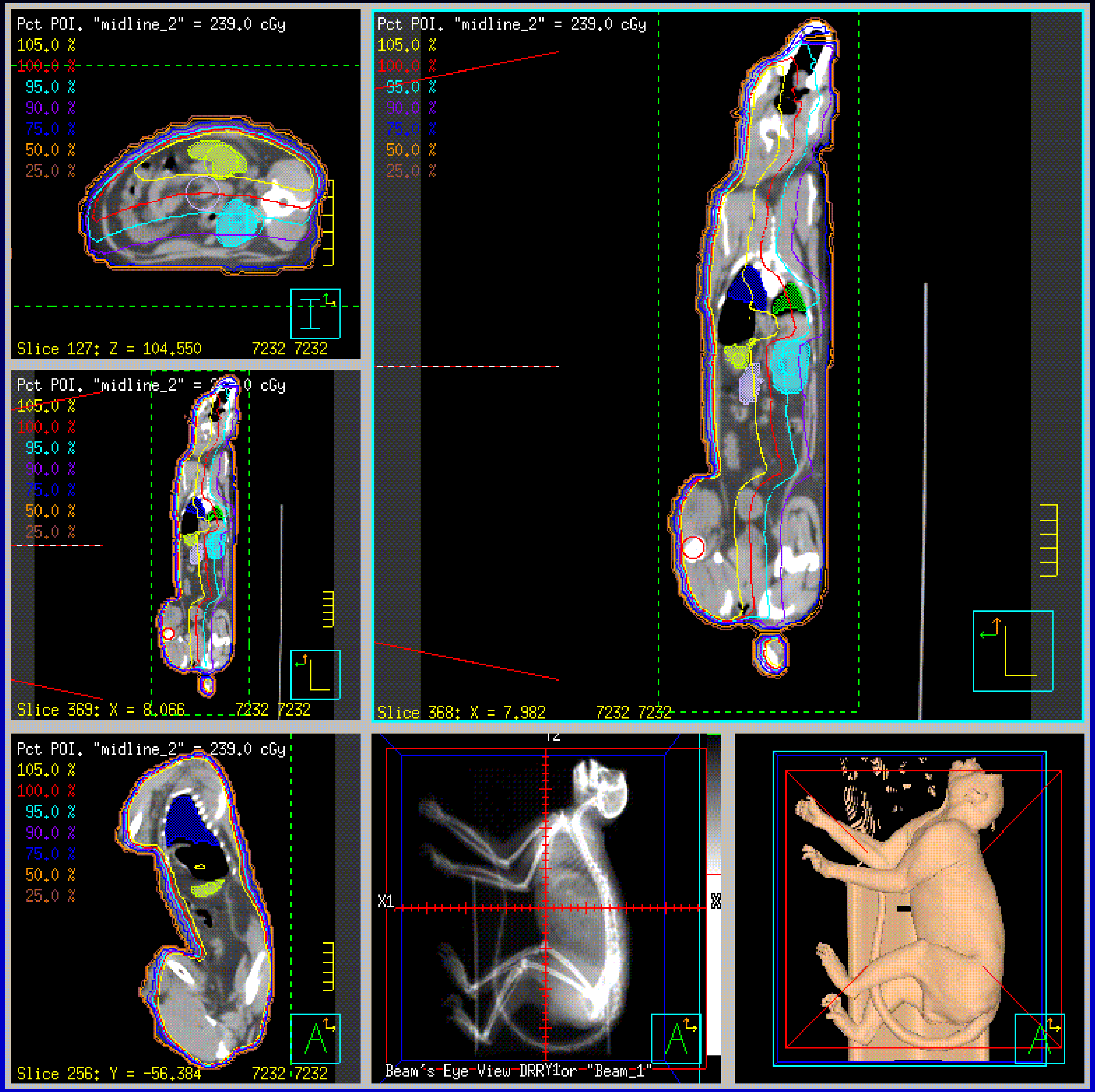
Dose rate ~ 4 Gy/min
field size 40 x 40 cm^2
@ 100 cm





Dose Distribution

- Single Field
- Obtain CT scans in irradiation positions
- Segment (outline) “all” anatomy
- Simulate the radiation geometry
- Calculate dose
- Evaluate dose
- CT scan size a challenge for supine animal

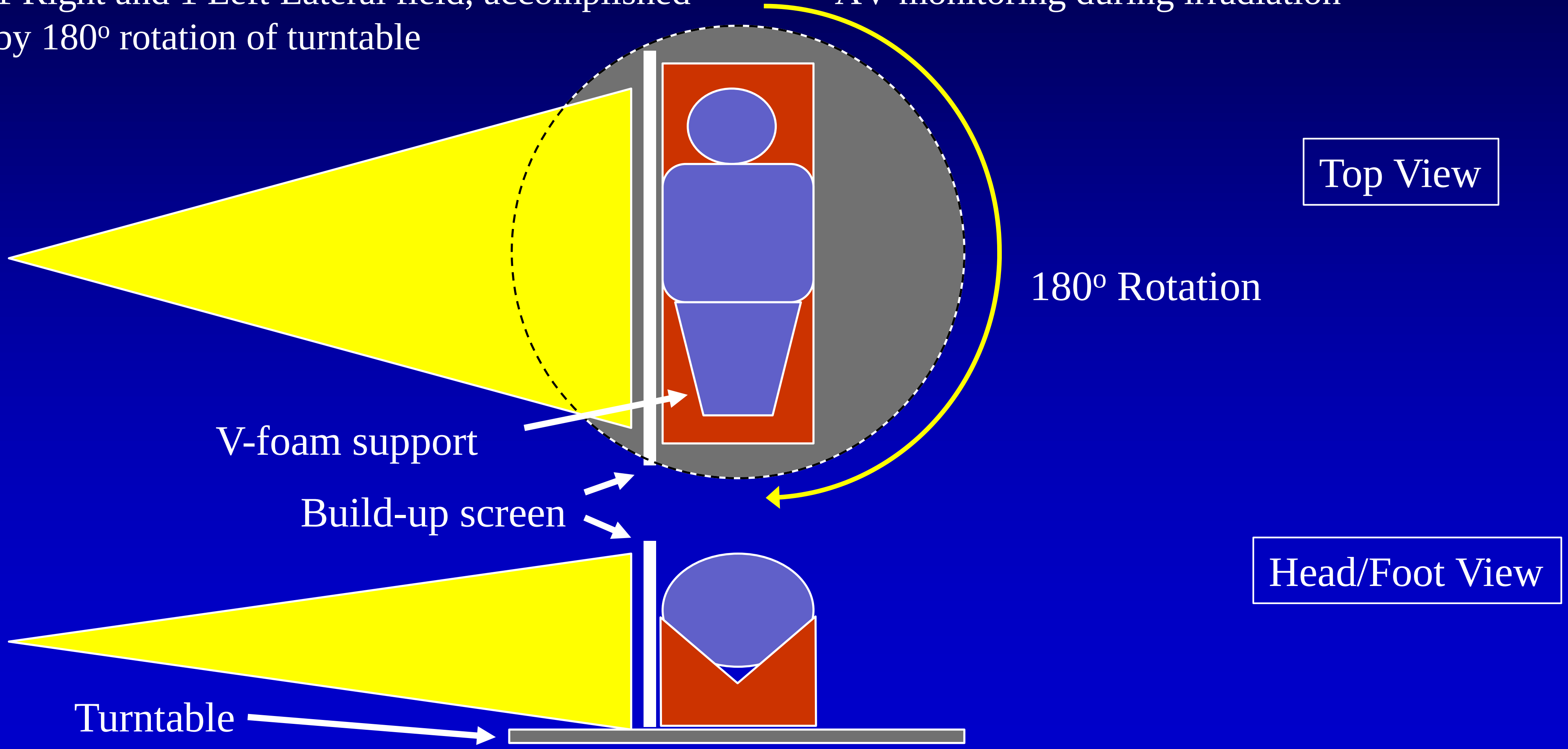


L1 TBI Dose Parameters: NHP

- 6 MV x rays, Opposed Pairs of Fields
  - Left-Right Laterals, with build-up screen
- Extended SSD to include whole body: 1.4 to 1.8m
  - Knees bent/legs retracted; arms at side, wrists at midline
- Dose rate of 0.8 Gy/min at midline
- Dose per protocol, MU calculated to midline, equal weights, no inhomogeneity calculations
- Specific irradiation geometry measured/validated
- Linear accelerator clinically used, QA per natl stds

L1 Irradiation Geometry: 2007

- 6MV x rays, 161cm SSD, $40x20^2$ @ 100cm, diameter of 10-13cm, depth of 5-6.5cm
- DR of 200 MU/min → 0.8 Gy/min at midline
- 1 Right and 1 Left Lateral field, accomplished by 180° rotation of turntable
- 1 Build-up Screen
- Average midline depth, adjust for outliers
- Dose measurement prior in phantom
- AV monitoring during irradiation



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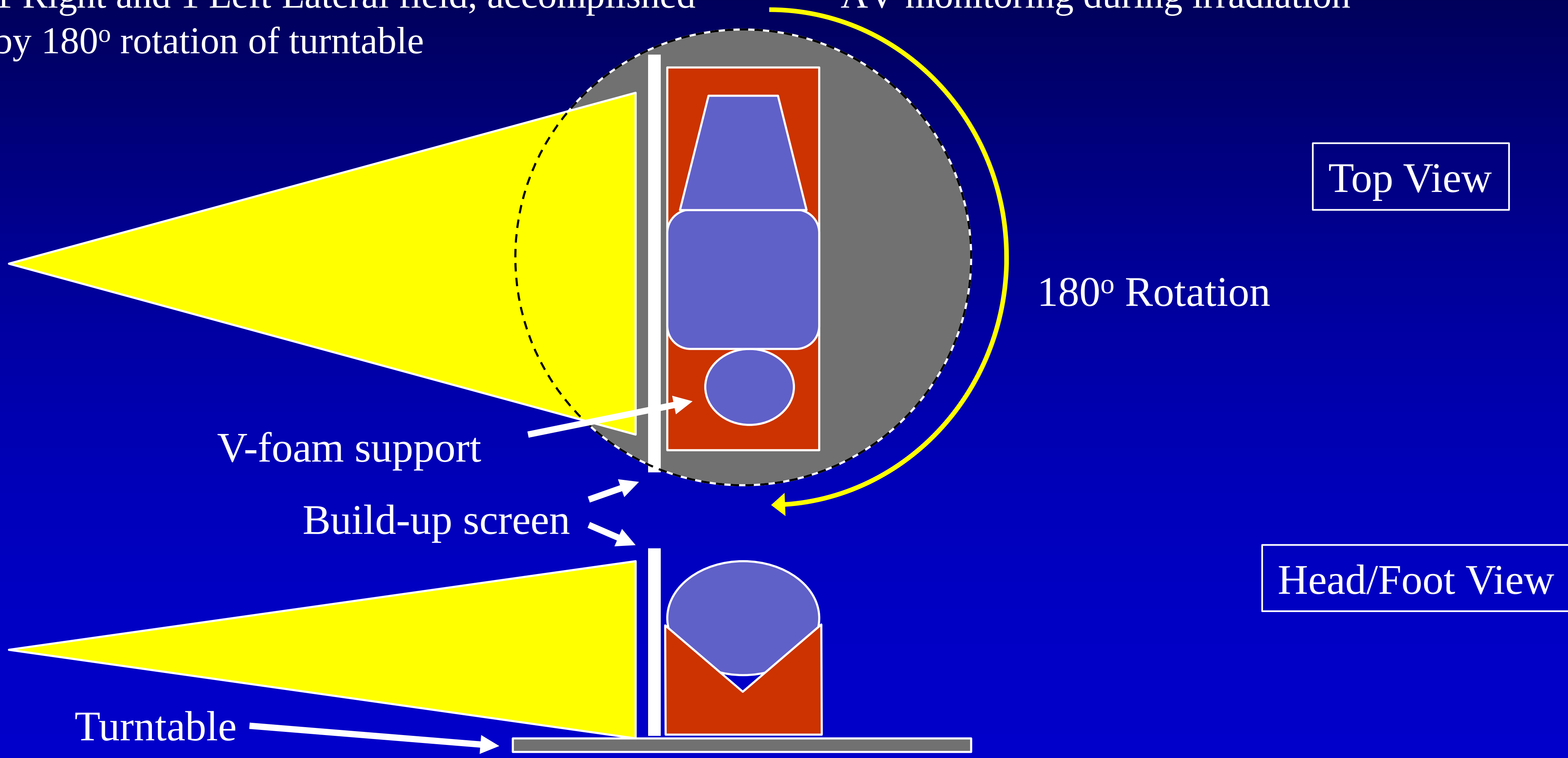

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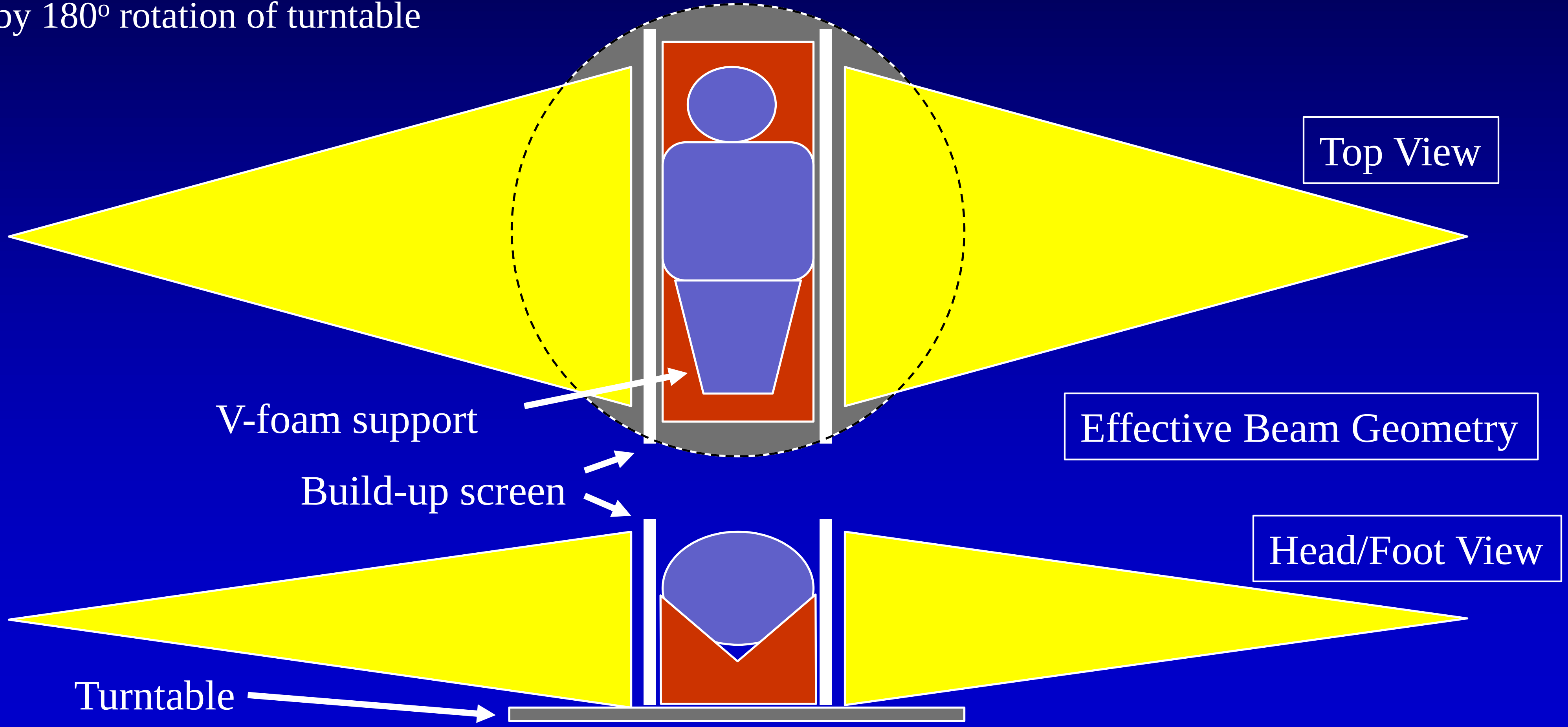
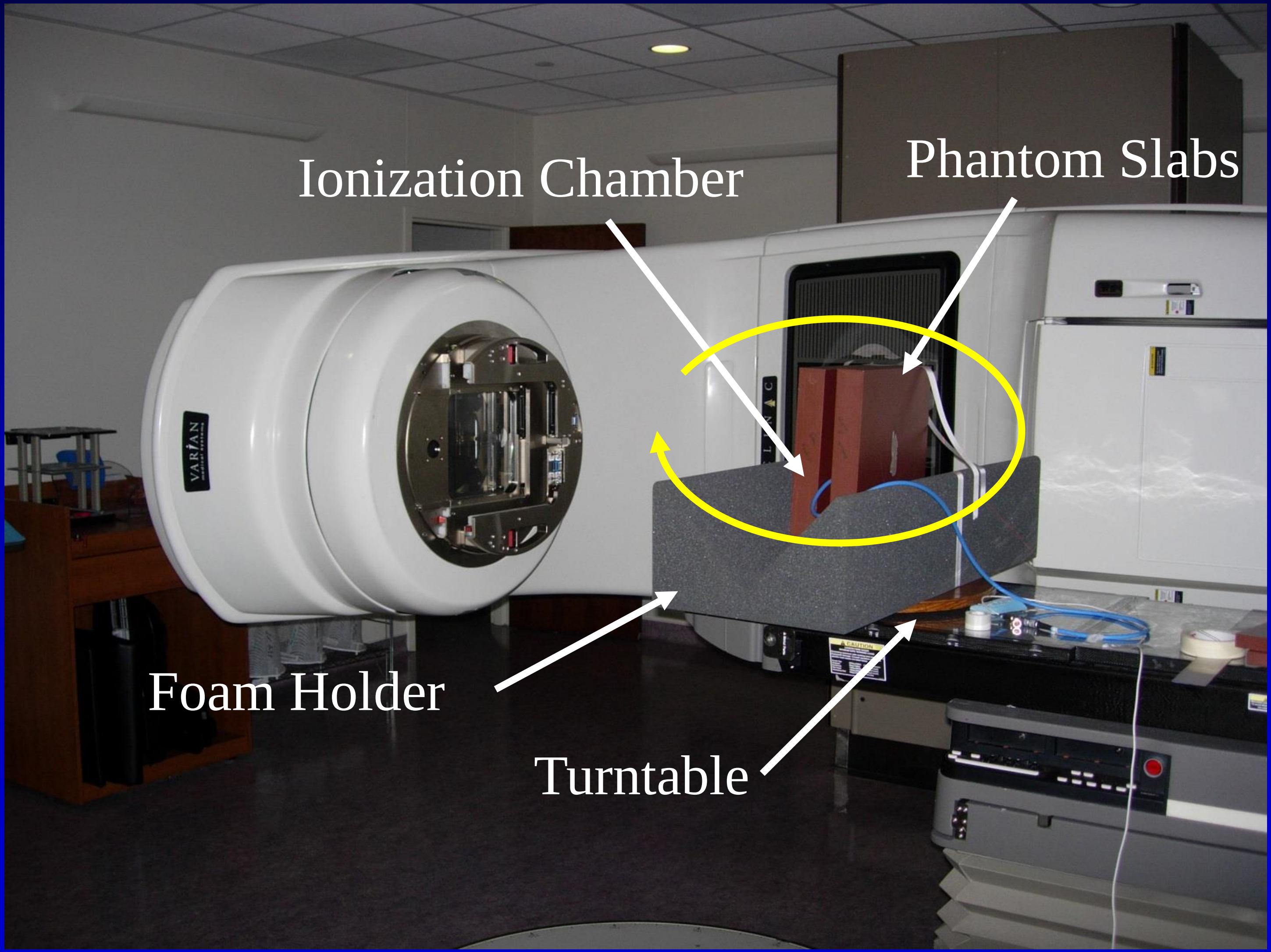


DoseVerification
Prior to Research Procedures

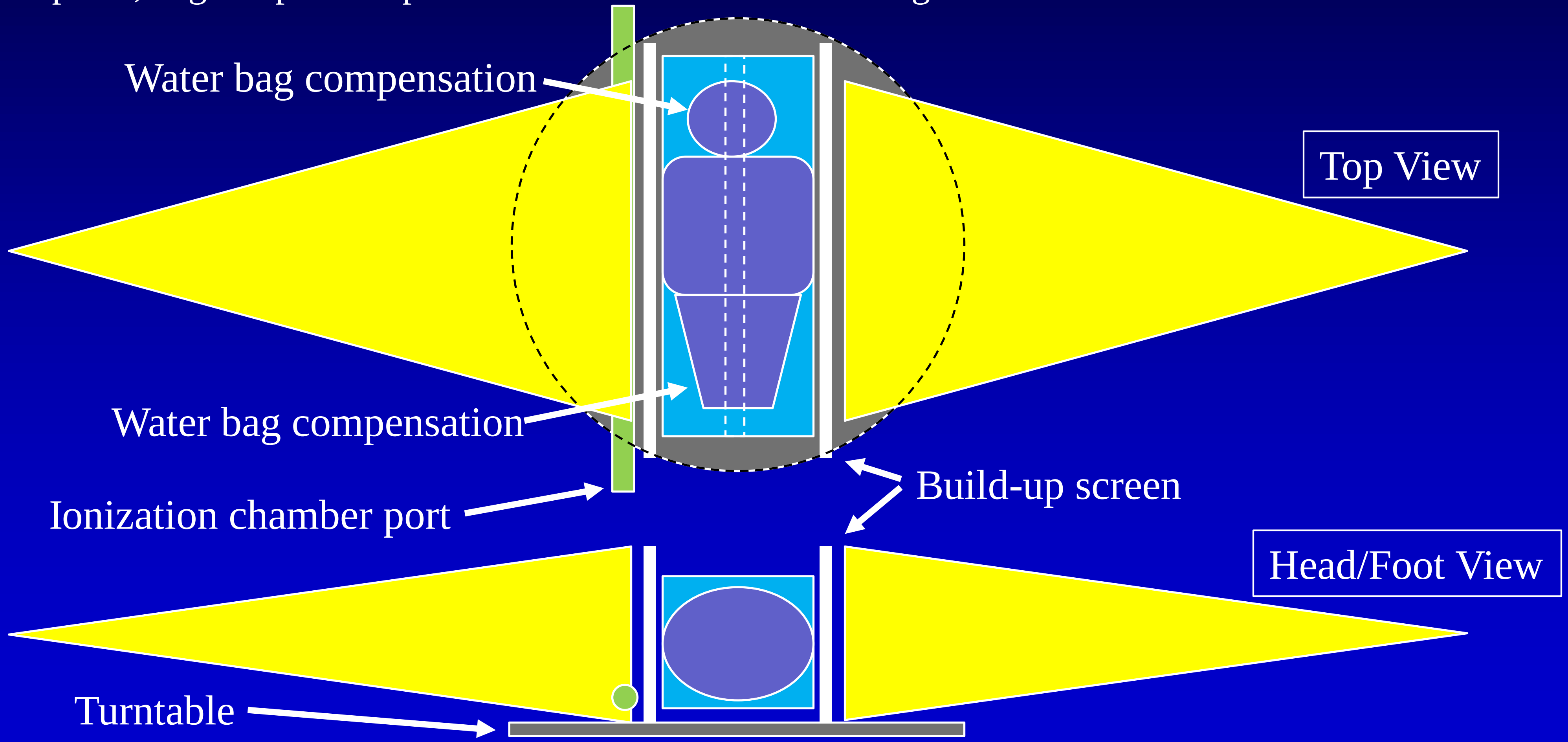


Irradiation Record

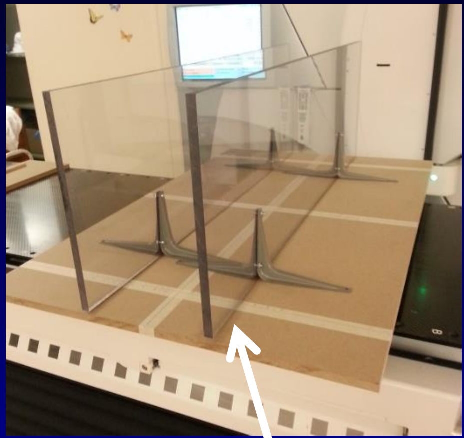
Animal #	Time In / Out (AM)	MU Rt	MU Lt	SSD	Field Size 40x20 @ 100 cm	Nominal Diameter (cm)	Mid-Plane Depth (cm)	Bolus Screen	Weight (kg)	Comment
7487 C1	8:10 / 8:55	291	291	161.3	Y	13	6.5	N / Y	6.3	First animal for set-up. Tail radius limited. Adjusted nominal SSD to 161.3 cm. Screen on Lt side only. DRlow on Rt side and 168/291 of Lt side. Animal awoke.
7492 C2	9:15 / 9:21	291	291	(163.1)	Y	(13)	(6.5)	Y	7.0	T = 1.46 min per side
7495 C2	9:24 / 9:32	291	291	(163.1)	Y	(13)	(6.5)	Y	5.5	T = 1.46 min per side
7499 C3	9:49 / 9:55	291	291	(163.1)	Y	(13)	(6.5)	Y	6.1	T = 1.46 min per side
7493 C3	10:00 / 10:07	291	291	(163.1)	Y	(13)	(6.5)	Y	6.8	T = 1.46 min per side
7494 C4	10:23 / 10:29	291	291	(163.1)	Y	(13)	(6.5)	Y	6.8	
7501 C4	10:32 / 10:40	281	281	162.8	Y	10	5.0	Y	4.2	Pee Wee – Revised MU for size
7486 C5	11:00 / 11:07	291	291	(163.1)	Y	(13)	(6.5)	Y	6.55	
7489 C5	11:09 / 11:16	291	291	(163.1)	Y	(13)	(6.5)	Y	6.0	
7498 C5	11:19 / 11:25	286	286	162	Y	11.5	5.8	Y	5.3	Revised MU for size. Lt side at DRhigh

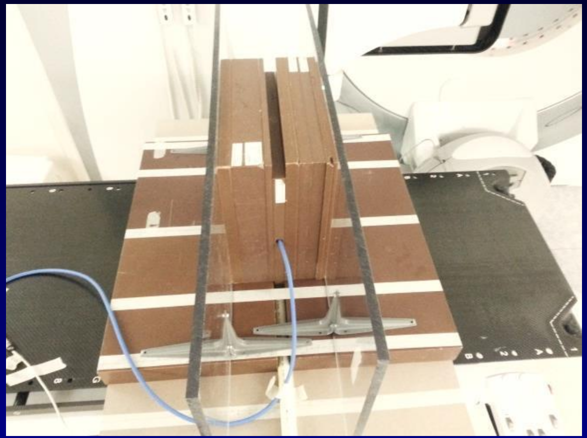
WFU L2A Irradiation Geometry

- Lazy Susan, 2 Build-up Screens
- Dose measurement prior in phantom
- 174 cm SSD, 6MV x rays, 80 cGy/min @ midplane, avg midplane depth of 11cm
- Dose measurement during irradiation at an exit reference point, all fields
- Water bag compensation for head, ankles
- 1 Right and 1 Left Lateral field



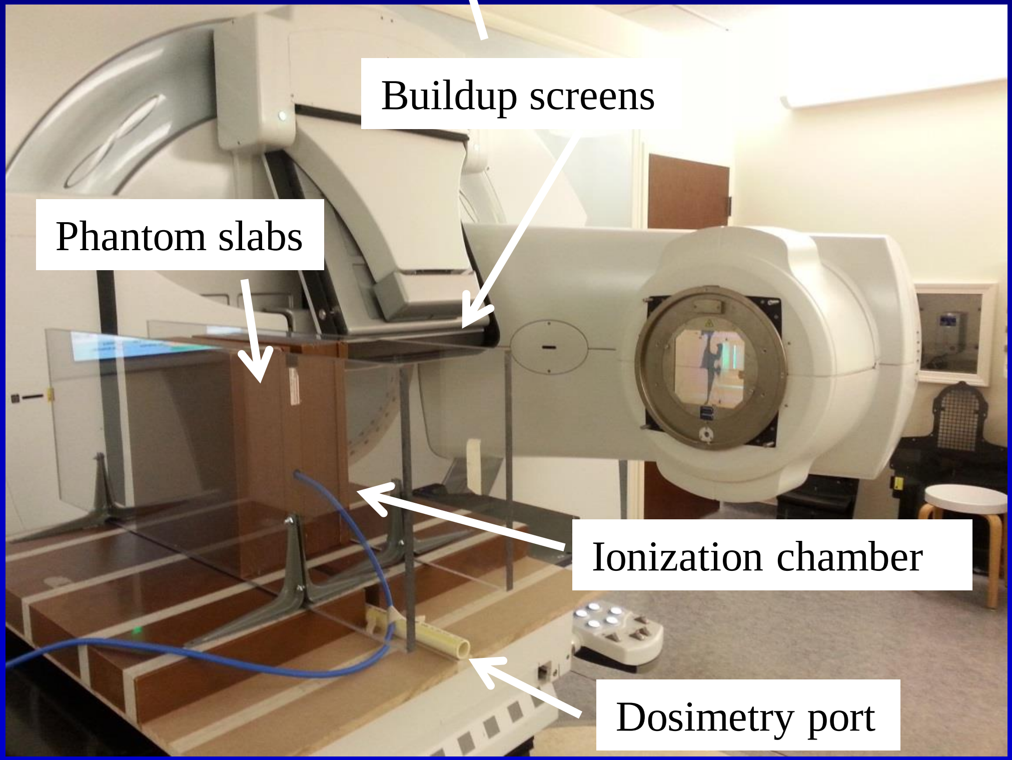
L2A Irradiation Geometry: 2015

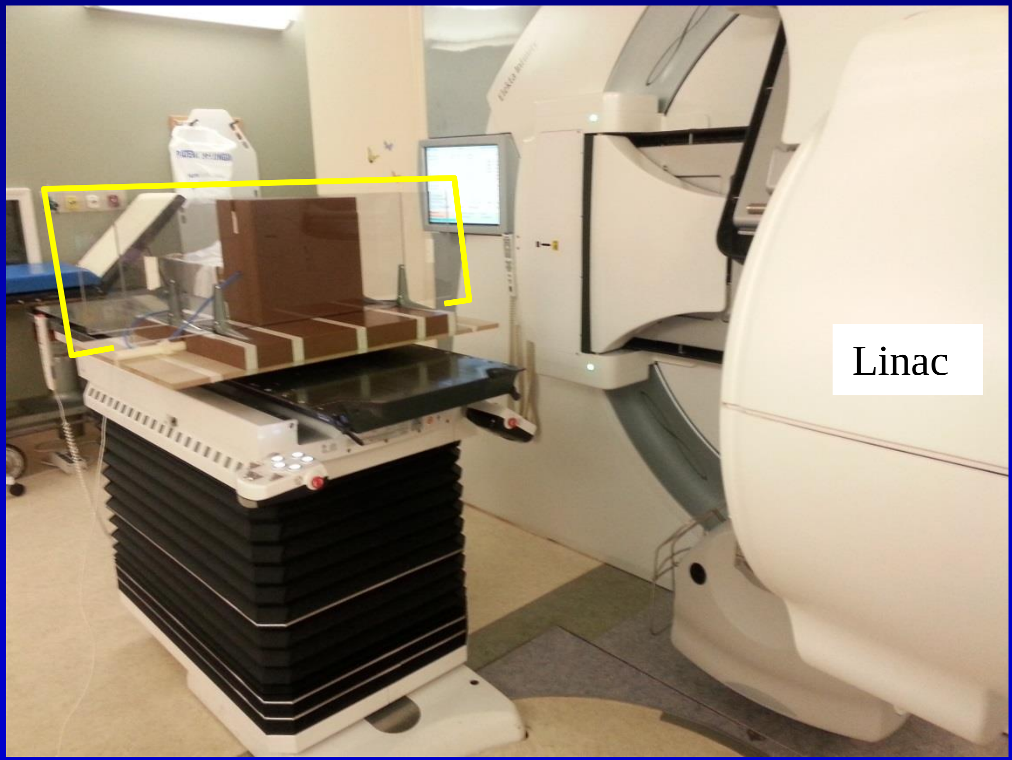




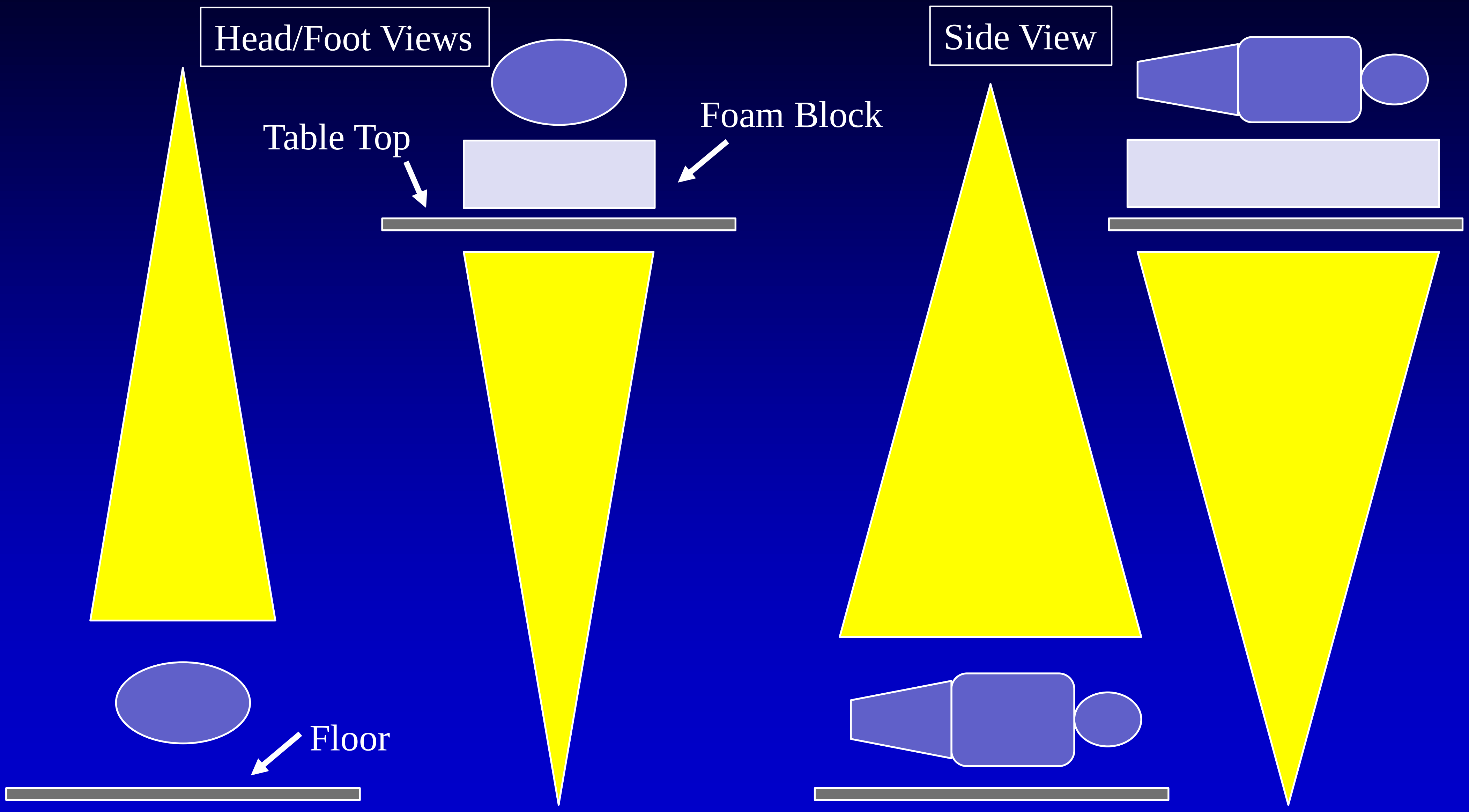
In vivo Dose Results

592.34	620.06	-0.01	**1732**
579.97	616.45	-0.03	**1763**
579.33	615.77	-0.03	**1765**
578.99	630.50	-0.04	**1784**
585.37	613.12	-0.02	**1788**
583.17	615.82	-0.03	**1790**
583.20	**618.62**	**-0.03**	

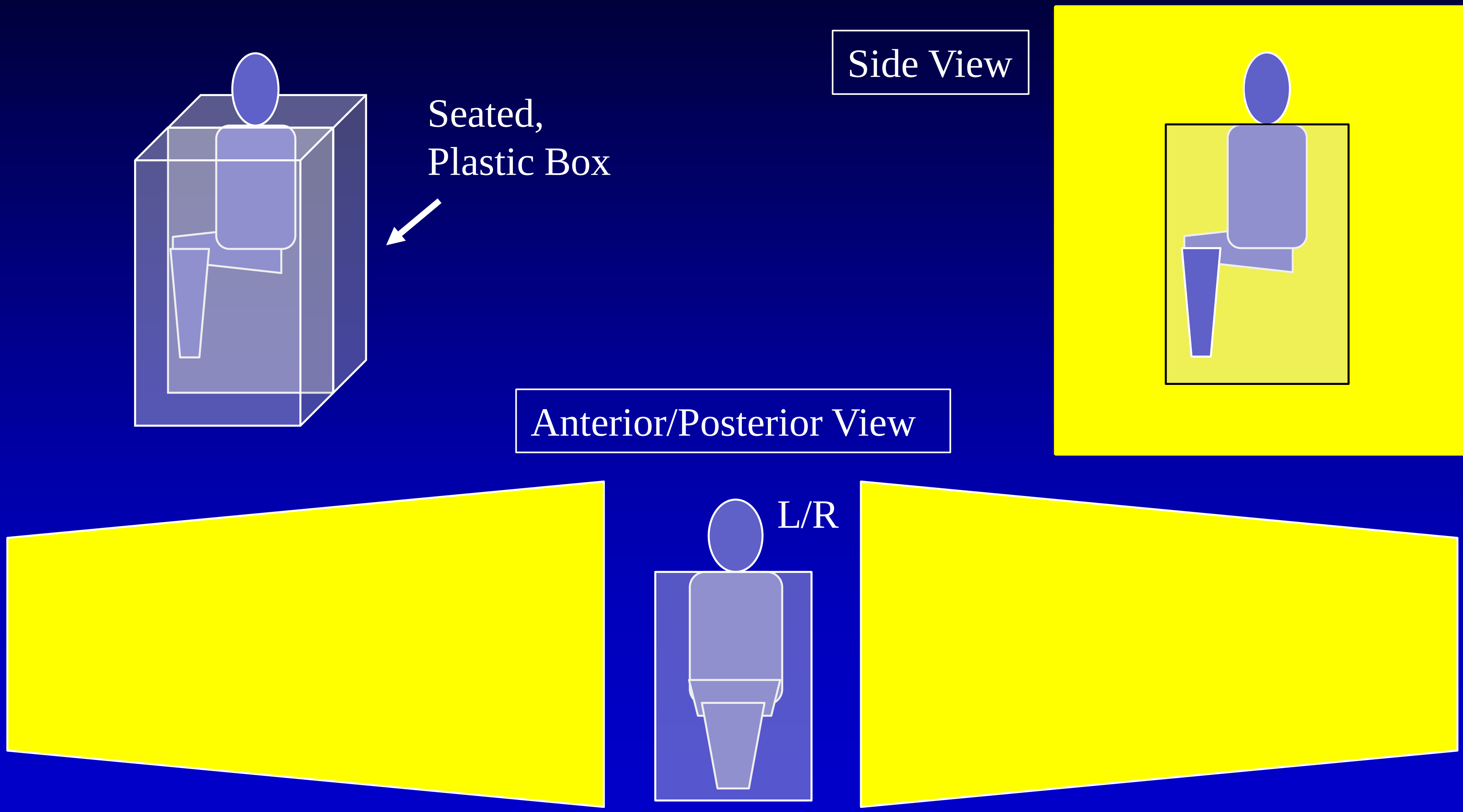




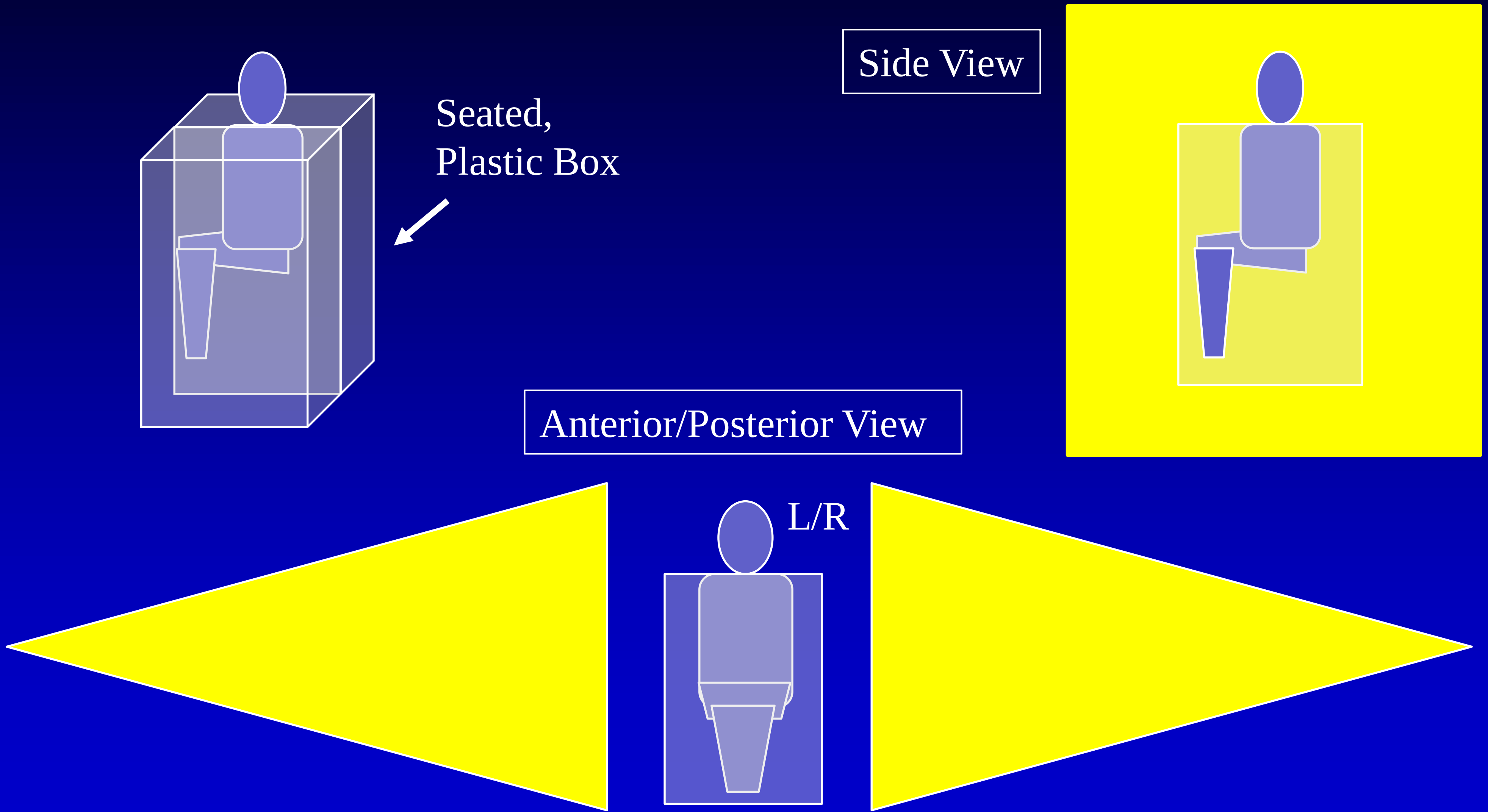
Irradiation Geometry: Site 1: 6 MV X Rays



Irradiation Geometry: Site 2: Cobalt-60 Flood

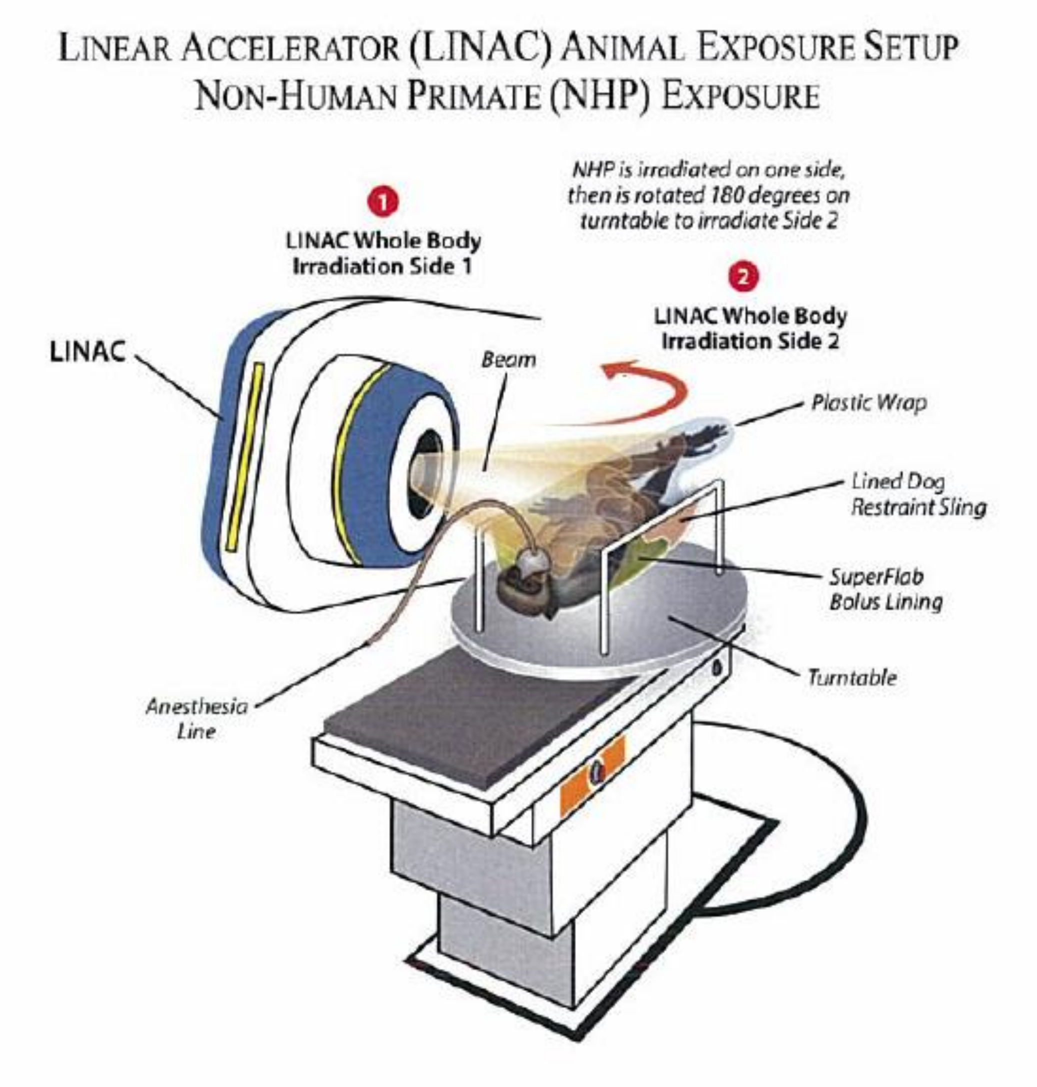


Irradiation Geometry: Site 3: 6 MV X Rays

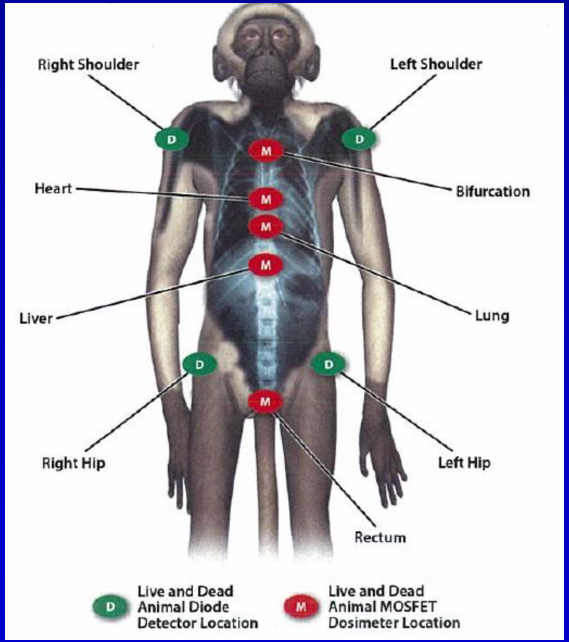


Comparison of Dosimetry Techniques in Rhesus Macaques

Dunstana Melo[1], Waylon Weber[1], Daniel Sandoval[2],
Melanie Doyle-Eisele[1], A. Matchett[1], J. Bayardo[1], Philip Heintz[2], Ray Guilmette[1]
Lovelace Respiratory Research Institute, Albuquerque, NM; [2]University of New Mexico, Albuquerque, NM



Animal	Average ± SD % planned dose diode detectors (range)	Average % planned dose measured with MOSFET dosimeters				
		Bifurcation of trachea	Heart	Lung	Liver	Rectum
Live	99 ± 1 (98 – 101)	98 ± 5 (93 – 105)	108 ± 6 (102 – 115)	105 ± 4 (100 – 109)	104 ± 2 (102 – 107)	105 ± 2 (102 – 108)
Dead	100 ± 2 (98 – 102)	100 ± 4 (96 – 106)	104 ± 1 (103 – 105)	104 ± 2 (101 – 105)	101 ± 2 (98 – 105)	103 ± 2 (102 – 104)



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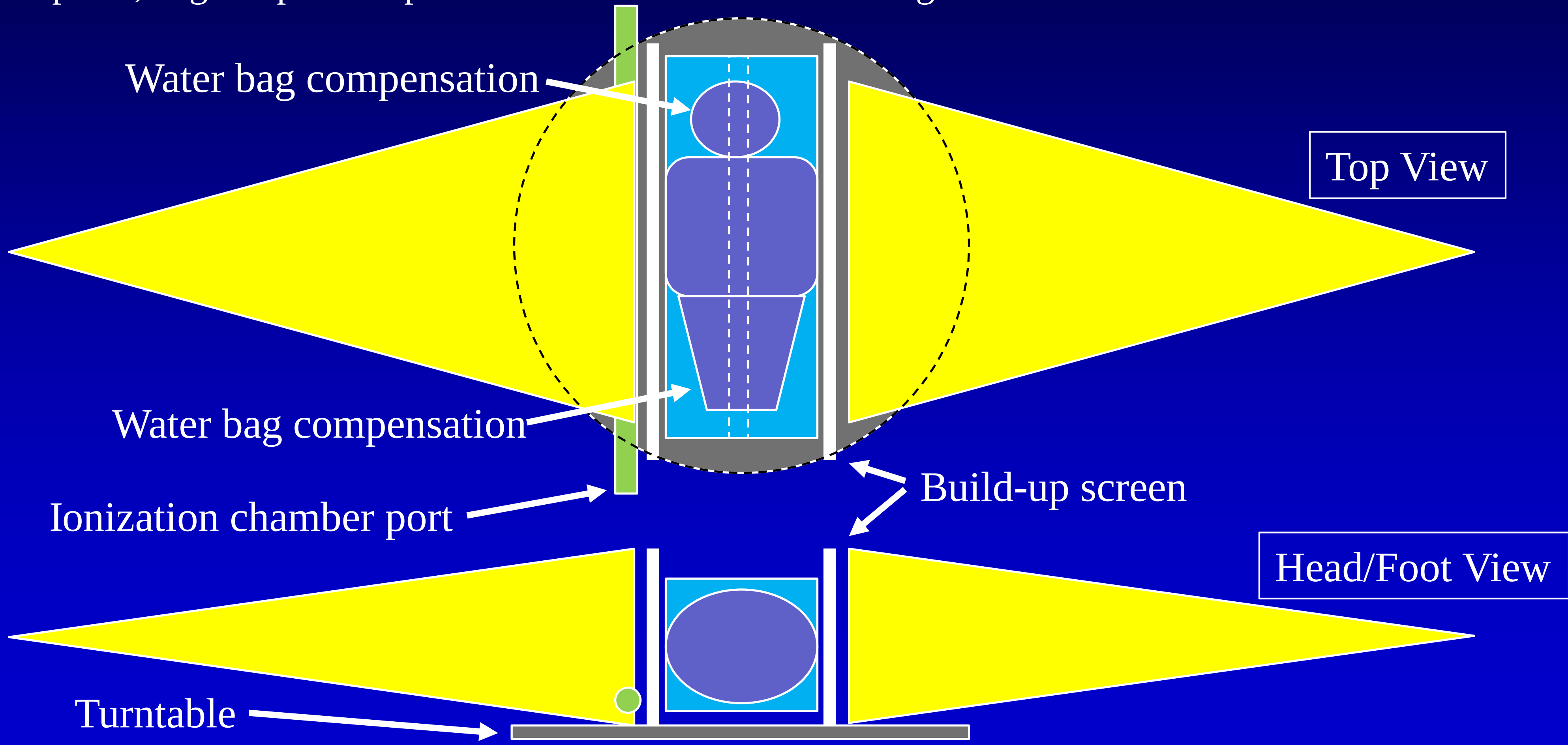
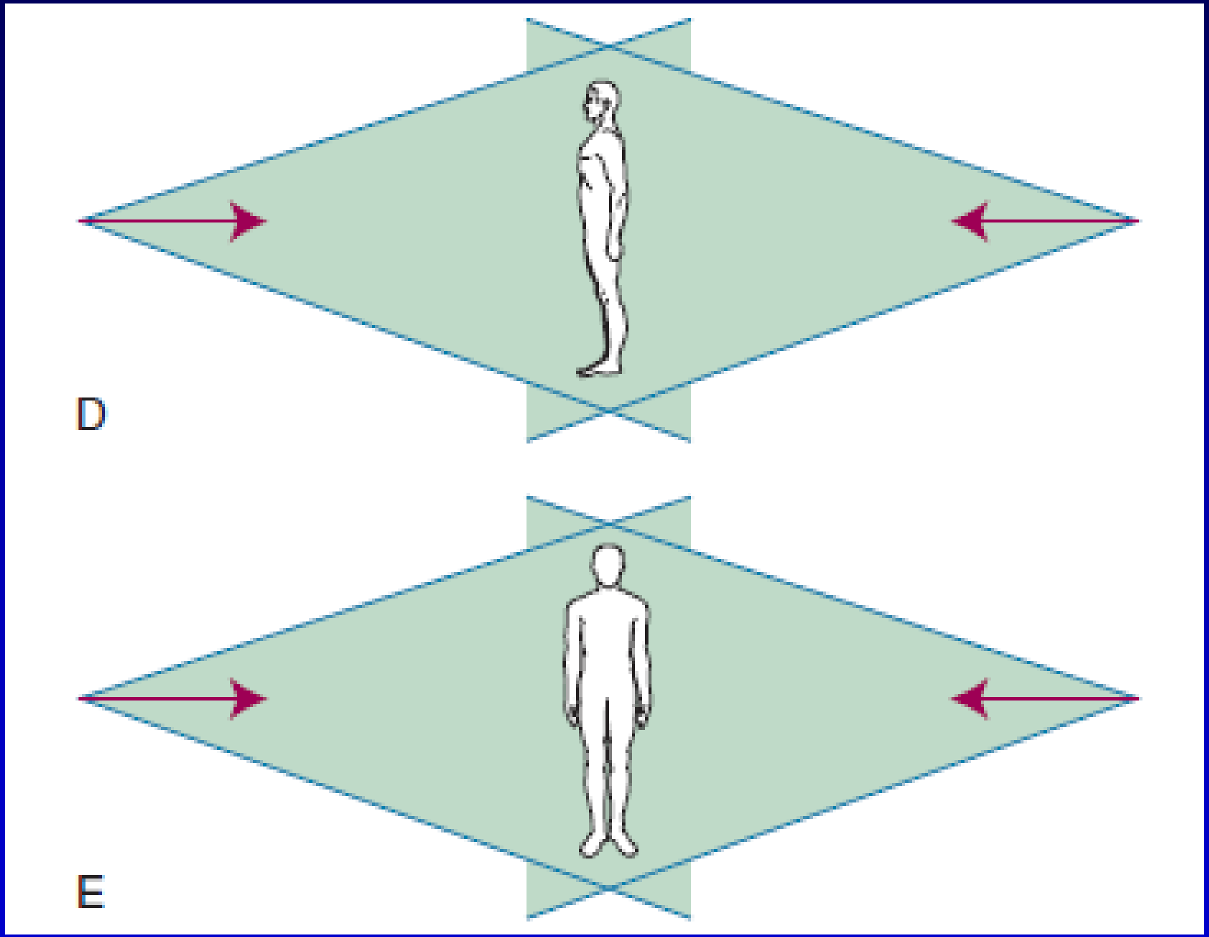


Physics Challenge

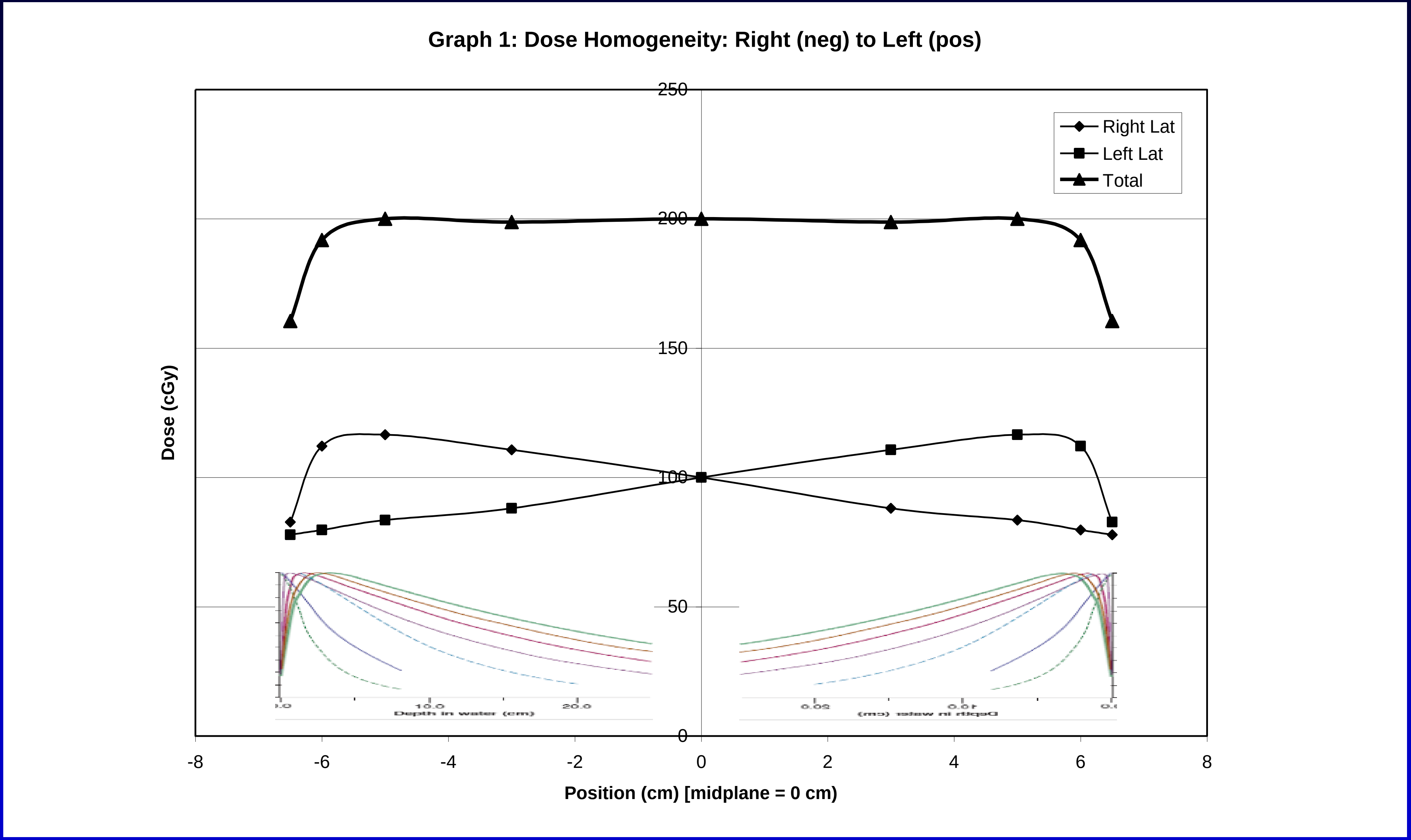
Whole Body Irradiation Geometry

Two Most Commonly Used Geometries

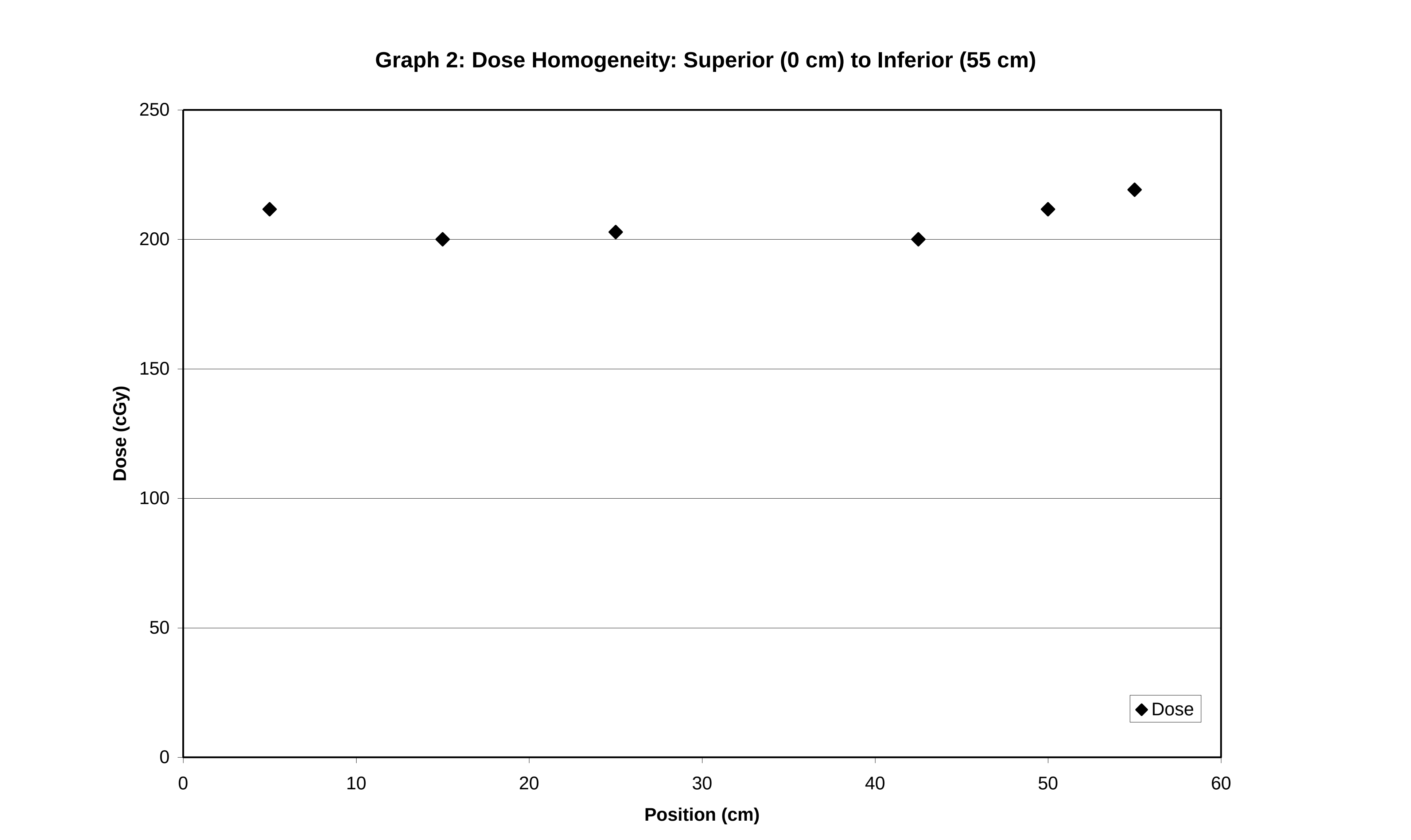
- Which technique best?
- Animal species in use?
- Photon energy?
- Dose calc point?
- Dose rate?
- Y/N Buildup?
- Y/N Compensation?
- Overall dose homogeneity?
- Dose monitoring?
- **Shall we standardize TBI?**



Dose Homogeneity: 14cm diameter



Dose Homogeneity: S-I Level



Measurements for Dose Calculations

AP, RL Diameters, Length, Weight

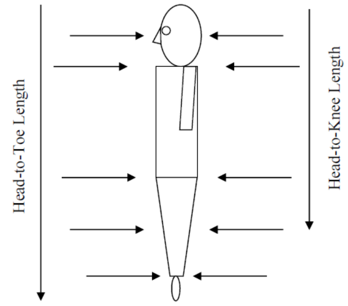
				Anterior-Posterior Diameters														
Animal ID#	Gender (M/F)	Body Weight (kg)		Head To Toe Length (cm)		Head To Knee Length (cm)		Head (cm)		Shoulders (cm)		Pelvis (cm)		Knees (cm)		Ankles (cm)		Total %Diff
8410	F	3.9	8.5%	74	-0.5%	51	1.4%	11	1.4%	9.3	0.4%	7.7	15.7%	3.2	-10.7%	3.1	0.9%	17.5%
8411	F	3.95	9.9%	77	3.5%	53	5.4%	11.3	4.2%	9	-2.8%	6.3	-5.3%	3.4	-5.1%	3.5	13.9%	-4.0%
8412	F	3.75	4.3%	75	0.9%	51	1.4%	10.9	0.5%	9.9	6.9%	8.3	24.7%	3.8	6.1%	3.3	7.4%	32.1%
8413	F	3.5	-2.7%	74	-0.5%	49	-2.5%	10.5	-3.2%	9.4	1.5%	5.8	-12.8%	3.6	0.5%	3.2	4.1%	-14.6%
8414	F	3.2	-11.0%	72	-3.2%	48	-4.5%	10.5	-3.2%	8.4	-9.3%	6.6	-0.8%	3.3	-7.9%	2.7	-12.1%	-13.3%
8415	F	3.2	-11.0%	71	-4.5%	47	-6.5%	11.5	6.0%	10.7	15.5%	6.8	2.2%	3.6	0.5%	3	-2.4%	23.7%
8416	F	3.55	-1.3%	78	4.9%	53	5.4%	11.1	2.3%	8.8	-5.0%	6.1	-8.3%	4.2	17.3%	2.7	-12.1%	-11.0%
8417	F	3.9	8.5%	78	4.9%	54	7.4%	11.3	4.2%	9.4	1.5%	6.6	-0.8%	4.2	17.3%	3.2	4.1%	4.8%
8418	F	4.65	29.3%	76	2.2%	53	5.4%	10.9	0.5%	9.7	4.7%	7.6	14.2%	3.8	6.1%	3.4	10.7%	19.4%
8419	F	3.05	-15.2%	71	-4.5%	47	-6.5%	10	-7.8%	8.2	-11.5%	6.1	-8.3%	3.7	3.3%	3.1	0.9%	-27.6%
8420	F	2.9	-19.3%	72	-3.2%	47	-6.5%	10.3	-5.0%	9.1	-1.8%	5.3	-20.4%	2.6	-27.4%	2.6	-15.4%	-27.2%
		3.6		74.4		50.3		10.8		9.3		6.7		3.6		3.1		
Cohort 1	F	3.9	8.9%	76.3	2.6%	52.7	4.8%	11.2	3.3%	9.2	-0.3%	6.9	3.2%	3.6	0.5%	3.3	6.3%	6.1%
Cohort 2	F	3.9	7.5%	74.0	-0.5%	50.3	0.1%	11.1	2.3%	10.1	9.0%	7.6	13.7%	3.7	4.2%	3.2	5.2%	25.1%
Cohort 3	F	3.4	-5.0%	74.7	0.4%	50.0	-0.5%	10.7	-1.3%	8.9	0.0	6.2	-7.3%	3.7	3.3%	2.9	-6.7%	-13.0%
Donors	F	3.0	-17.3%	71.5	-3.9%	47.0	-6.5%	10.2	-6.4%	8.7	-6.6%	5.7	-14.3%	3.2	-12.1%	2.9	-7.2%	-27.4%
8421	M	5.3	-16.2%	76	-6.6%	52	-5.1%	12.2	-3.9%	13.1	6.5%	9.5	-12.8%	4	-9.3%	2.9	-12.8%	-10.2%
8422	M	5.2	-17.8%	80	-1.7%	54	-1.5%	11.9	-6.2%	14.3	16.3%	10.5	-3.7%	4.5	2.1%	3.6	8.2%	6.4%
8423	M	5.5	-13.8%	79	-2.9%	53	-3.3%	12.2	-3.9%	11.1	-9.8%	10.7	-1.8%	4.2	-4.7%	2.8	-15.8%	-15.5%
8424	M	5.8	-8.3%	80	-1.7%	54	-1.5%	12.8	0.9%	10.2	-17.1%	11	0.9%	4.9	11.1%	3.4	2.2%	-15.3%
8425	M	6.8	6.8%	84	3.2%	57	4.0%	13.2	4.0%	12.9	4.9%	8.3	-23.9%	4.3	-2.5%	3.2	-3.8%	-15.0%
8426	M	7.9	24.9%	83	2.0%	55	0.3%	14	10.3%	12.7	3.3%	11.5	5.5%	4.5	2.1%	3.1	-6.8%	19.1%
8427	M	8.2	28.9%	87	6.9%	57	4.0%	13.4	5.6%	12.6	2.4%	9.6	-11.9%	5.3	20.2%	3.4	2.2%	-3.9%
8428	M	7.6	20.2%	80	-1.7%	54	-1.5%	13.2	4.0%	12.3	0.0%	13.4	22.9%	3.8	-13.8%	3.6	8.2%	26.9%
8429	M	5.5	-13.8%	84	3.2%	56	2.2%	11.5	-9.4%	14.3	16.3%	10.5	-3.7%	4.5	2.1%	3.4	2.2%	3.2%
8430	M	5.6	-12.2%	80	-1.7%	55	0.3%	12.1	-4.7%	11.4	-7.3%	11.8	8.3%	4.6	4.3%	3.4	2.2%	-3.7%
8431	M	6.4	1.2%	82	0.8%	56	2.2%	13.1	3.2%	10.4	-15.4%	13.1	20.2%	3.9	-11.5%	3.8	14.2%	8.0%
		6.3		81.4		54.8		12.7		12.3		10.9		4.4		3.3		
Cohort 1	M	6.3	0.2%	81.0	-0.4%	54.7	-0.3%	12.6	-1.0%	12.4	0.5%	10.3	-5.5%	4.6	5.1%	3.2	-2.8%	-5.9%
Cohort 2	M	5.7	-10.1%	82.0	0.8%	55.3	0.9%	12.2	-4.1%	13.0	5.7%	11.4	4.3%	4.3	-2.5%	3.6	8.2%	5.8%
Cohort 3	M	6.0	-5.1%	81.0	-0.4%	54.7	-0.3%	12.7	0.3%	11.4	-7.3%	10.0	-8.3%	4.5	1.3%	3.1	-5.8%	-15.2%
Donors	M	7.8	22.6%	81.5	0.2%	54.5	-0.6%	13.6	7.2%	12.5	1.6%	12.5	14.2%	4.2	-5.9%	3.4	0.7%	23.0%

Date: ______________

Animal: ______________

Weight: ______________

Head-to-Toe Length (cm): ______
Head-to-Knee Length (cm): ______



Anterior-Posterior Diameter (cm)

Head: __________

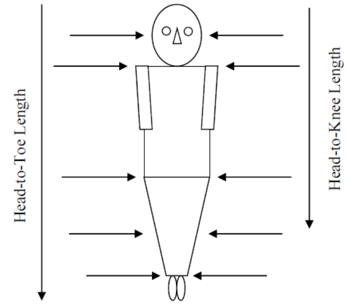
Shoulders: _______

Pelvis: __________

Knees: __________

Ankles (both): ____

Head-to-Toe Length (cm): ______
Head-to-Knee Length (cm): ______



Left-Right Diameter (cm)

Head: __________

Shoulders: _______

Pelvis: __________

Knees: __________

Ankles (both): ____

Initials: __________

Monitor Unit (Time) Calculations

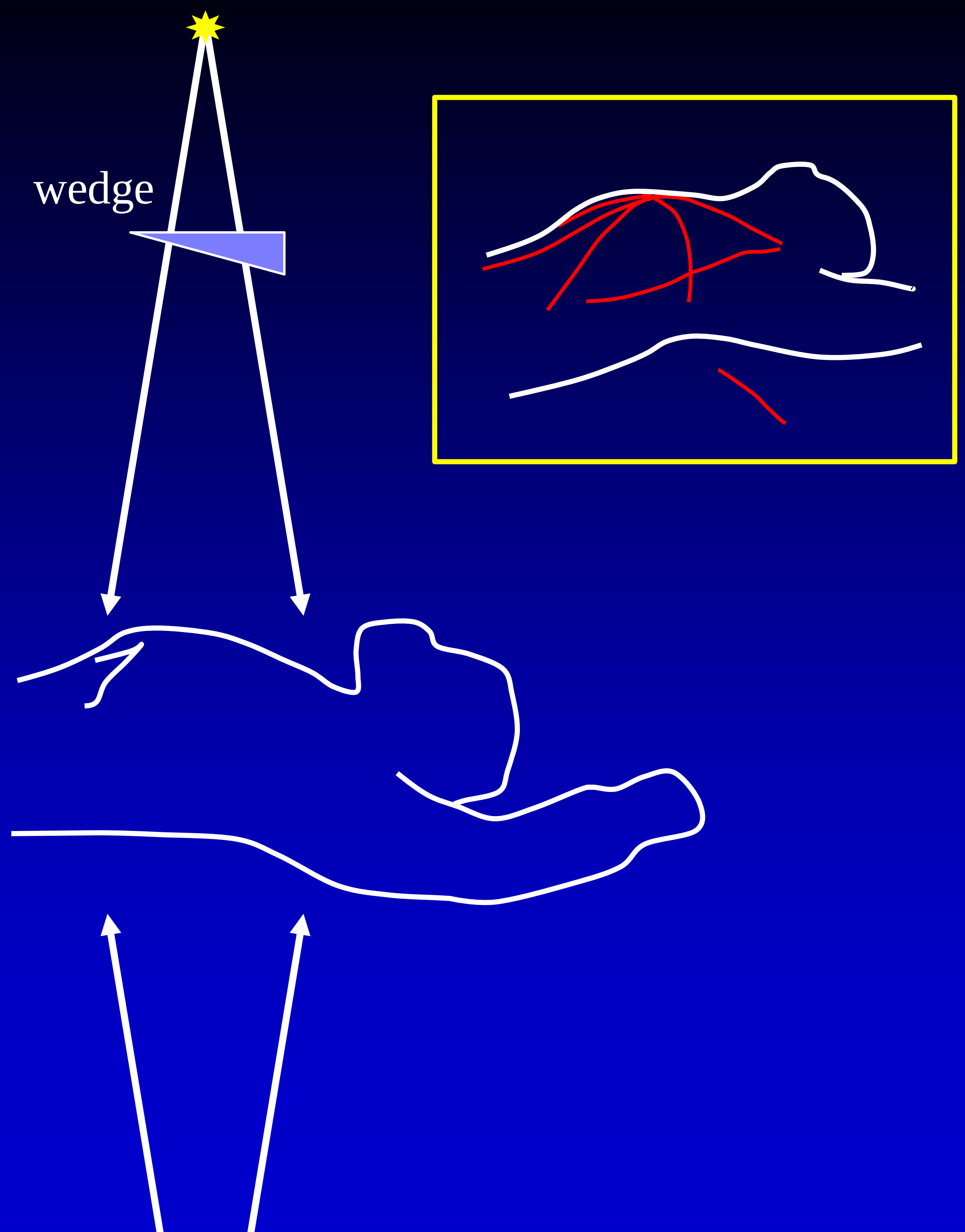
- NHP measurements, dose, and geometry parameters used to calculate monitor unit (timer) settings for the linear accelerator
- Validated with specific experiment measurements

$$MU = \frac{TD}{D_o \cdot \left[\frac{(SAD + dm)}{(SSD + d)}\right]^2 \cdot Sc \cdot Sp \cdot TMR \cdot OAF \cdot WF \cdot TF \cdot OF}$$

L2B: Irradiation Geometry

Partial Body: Lungs

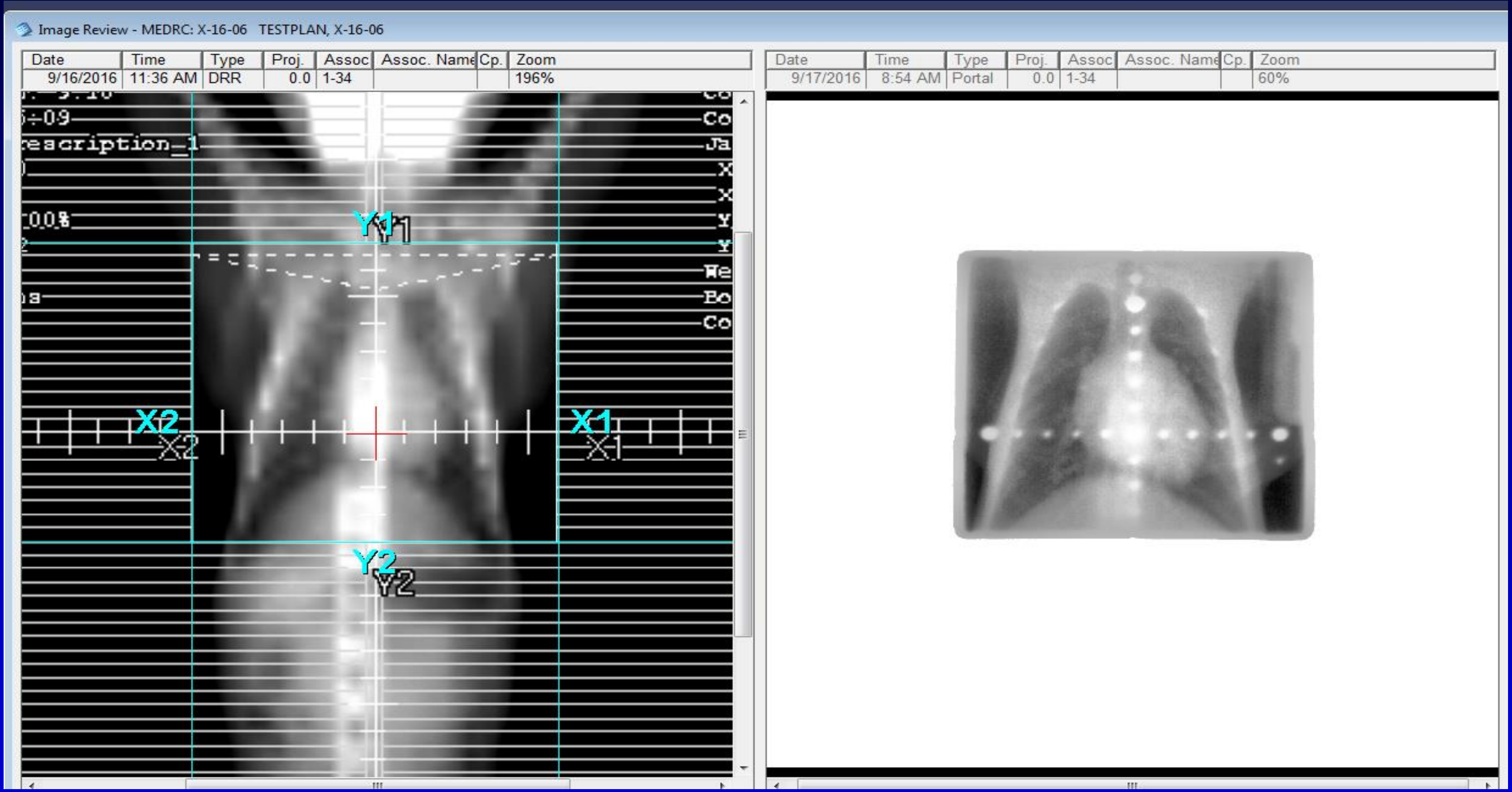
- AP-PA, 6 MV x rays
- 96 cm SSD (average)
- FS: 10.0 x [5.0, 7.5] cm^2
- 1 cm bolus, AP field
- Table + post tissue, PA
- Calculated to midplane, no lung corrections
- Non-ketamine anesthesia – aid for flexibility of positioning without rigidity



AP-1934

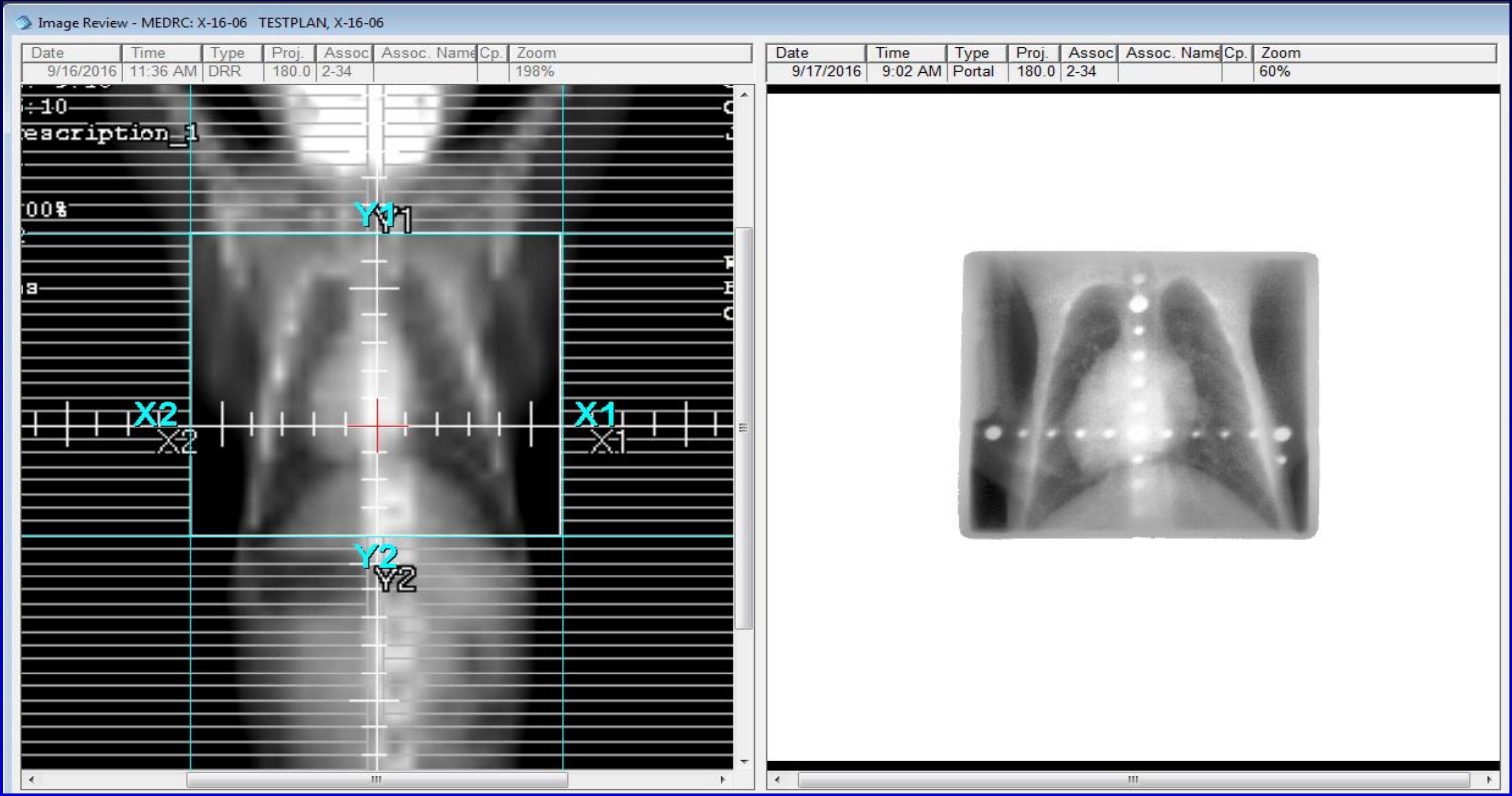
DRR-Planned

Port-Delivered



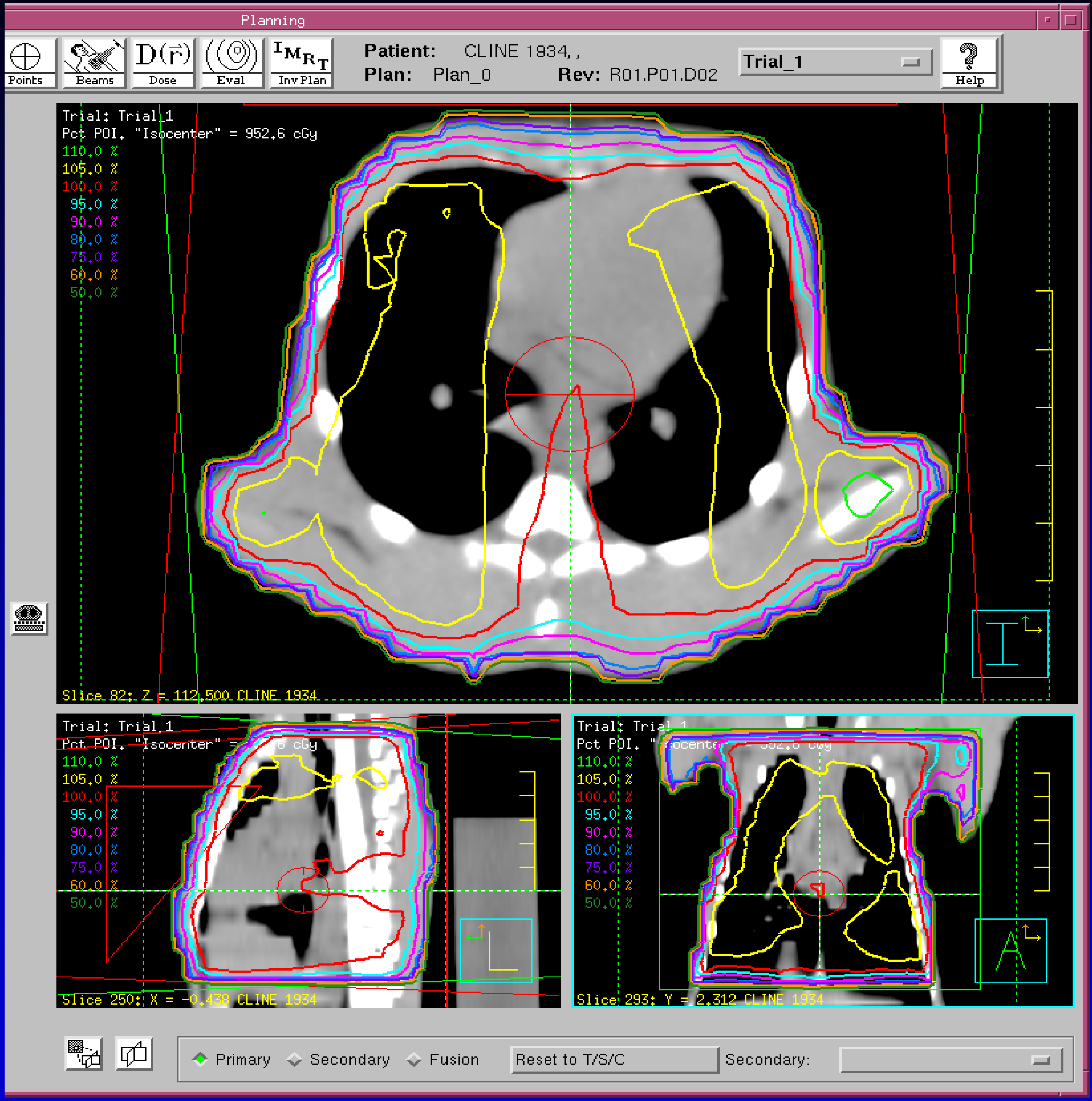
PA-1934

DRR-Planned | Port-Delivered



Radiation Plan - 1934

- 10 Gy @ 105% of dose at isocenter
- Isocenter dose of 9.5 Gy
- Lung dose of 10 Gy
- 12 deg wedge Ant
- 55:45 AP:PA beam weights



Logistics: Irradiation Procedures

Research Study Design

- IACUC-approved protocols
- Linear accelerator QA: TG-51, other
- Validation of research geometry dosimetry

Irradiation Day

- Warm up linear accelerator, verify in-vivo dosimetry
- Set up specific geometry (previous evening)
- Verify anesthesia unit
- Animal transport of 1, then 2 at a time after 1st setup
- Verify animal ID, verify positioning
- Verify anesthesia: Anesthesia time < 45 min
- Recording form for MUs, dose, time in, time out
- Radiation On time 3-10 min; Total In-room time < 15 min
- Linac operator at control console, Linac personnel for positioning
- Animal handlers at housing and irradiation locations
- Backup plan – next day

Bone Marrow Distribution
Average of Fe-59 and Tc-99m

10.9%	skull, mandible, maxilla
0.6%	2 clavicles
9.9%	all ribs, sternum, 2 scapulae
3.1%	2 ulnae, 2 radii
0.6%	2 hands, 2 wrists
0.9%	2 patellae
6.5%	2 tibiae, 2 fibulae
0.9%	2 ankles, 2 feet

cervical vert	2.2%
Thoracic vert	12.1%
2 humeri	8.8%
lumbar vert	17.5%
2 hips, sacral vert	13.7%
2 femurs	13.3%

Summary

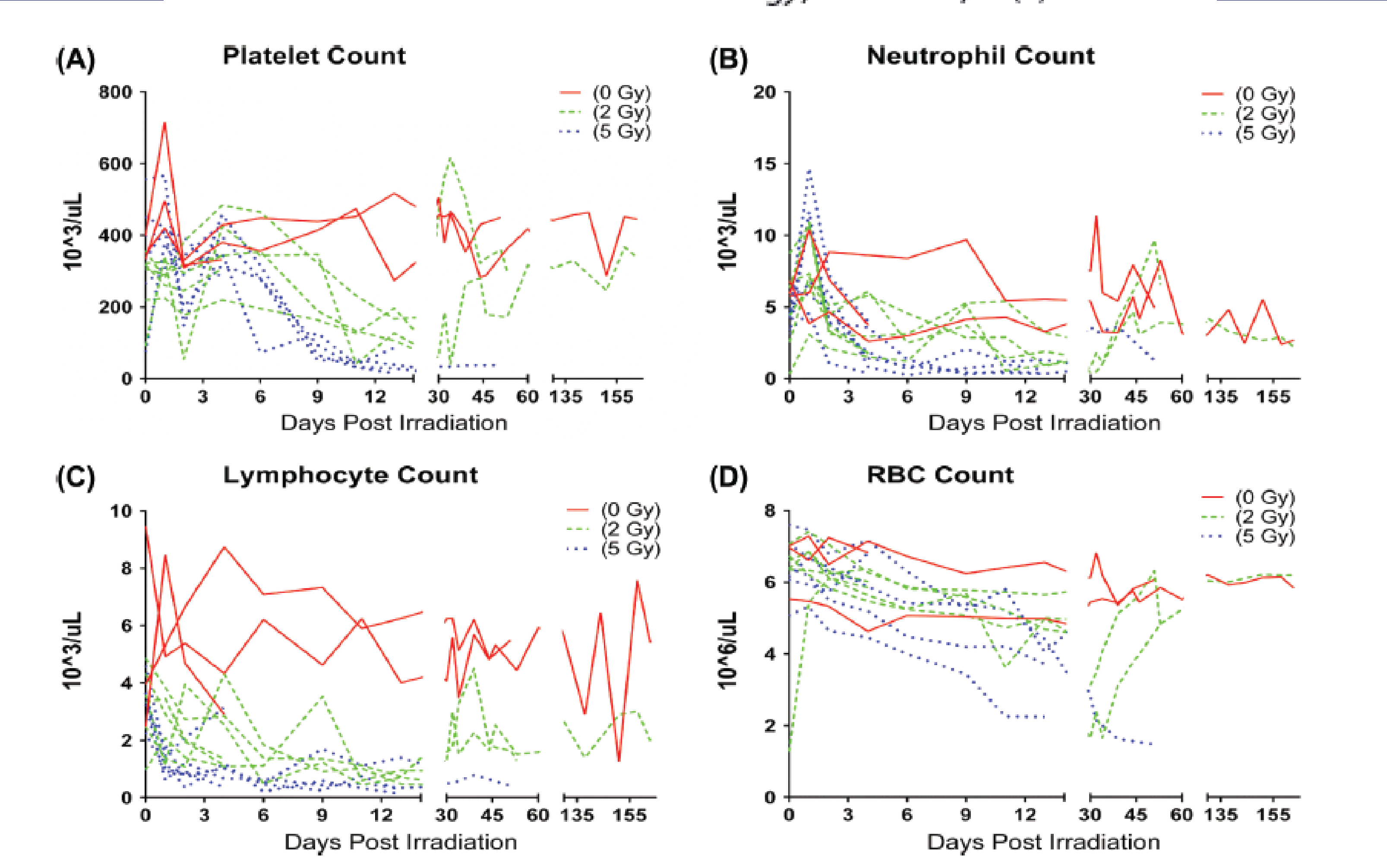
11%	skull, mandible, maxilla
13%	arms
22%	legs
54%	trunk: c-spine thru pelvis

References: Drawing © of Jay H. Matternes. Data from Taketa et al., Life Sciences 9:Part II:169-174, 1970.

Molecular and cellular profiling of acute responses to total body radiation exposure in ovariectomized female cynomolgus macaques

Ryne J. DeBo[1], Thomas C. Register[1], David L. Caudell[1], Gregory D. Sempowski[2,3,4], Gregory Dugan[1], Shauna Gray[1], Kouros Owzar[5], Chen Jiang[6], J. Daniel Bourland[7], Nelson J. Chao[8] & J. Mark Cline[1]

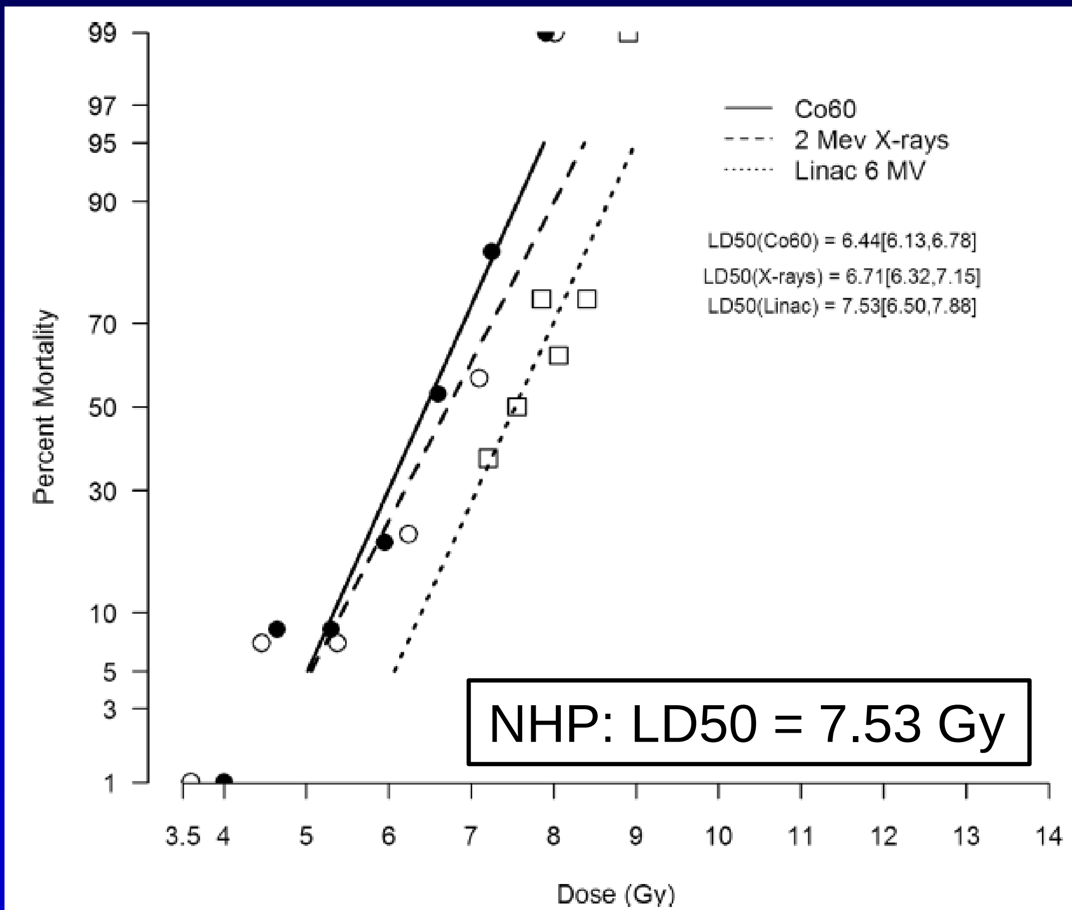
International Journal of Radiation Biology, June 2015; 91(6): 510–518



A Nonhuman Primate Model of the Hematopoietic Acute Radiation Syndrome Plus Medical Management

A.M. Farese*, **M.V. Cohen**†, **B. P. Katz**‡, **C. P. Smith***, **W. Jackson III**§, **D. M. Cohen***, and **T.J. MacVittie***

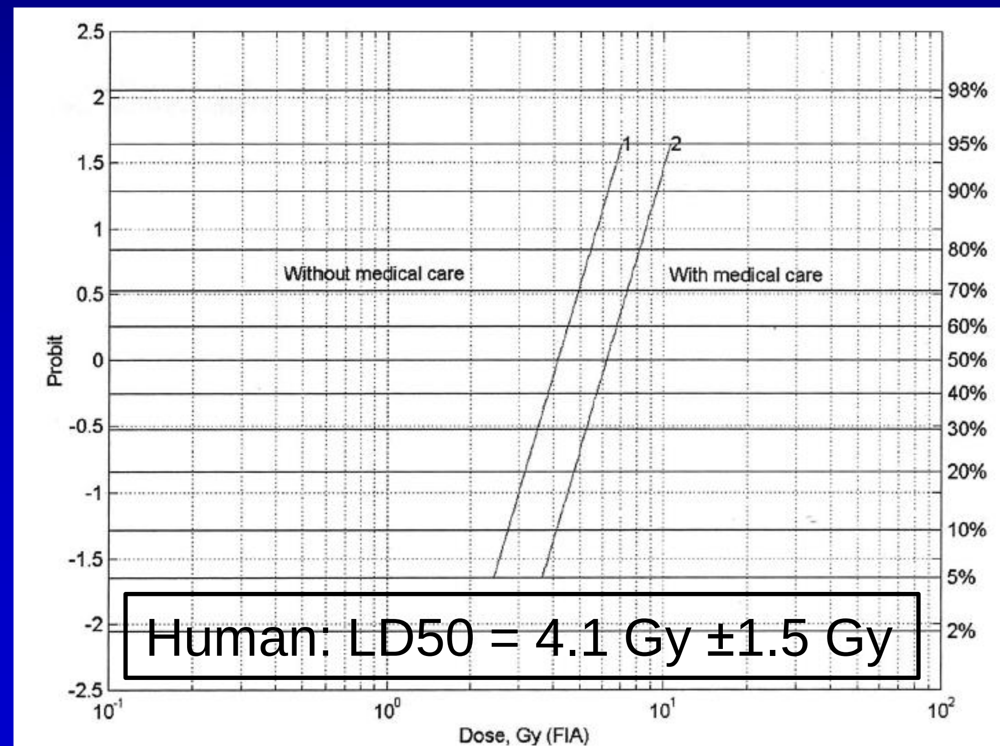
Health Phys. 2012 October ; 103(4): . doi:10.1097/HP.0b013e31825f75a7.



DOSE RESPONSE RELATIONSHIPS FOR ACUTE IONIZING-RADIATION LETHALITY

Health Physics May 2003, Volume 84, Number 5

G. H. Anno,* R. W. Young,† R. M. Bloom,* and J. R. Mercier‡



QUANTEC Papers

"Quantitative Analysis of Normal Tissue Effects in the Clinic"

- ASTRO and AAPM: This series of papers offers focused summaries of the dose/volume/outcome data for many of the organs potentially impacted by radiation treatment and gives physicians and treatment planners excellent resources to assist in determining acceptable dose/volume constraints.
- **Topics**: [**Science**: Accumulation of dose, Scientific issues, Biomarkers, Imaging for assessment, Improving complication models]; [**Organs**: Brainstem, Penile bulb, Rectum, Brain, Esophagus, Heart, Larynx/pharynx, Lug, Spinal cord, Stomach/SB, Optic nerve/chiasm, Bladder, Hearing, Kidney, Liver, Salivary gland]; [**Guidance**: Users Guide, Model use in the clinic]
- IJROBP, Vol 7, No. 3, Supplement, 2010 – publically available at:
- https://www.astro.org/Clinical-Practice/Quantec/QUANTEC.aspx

CMCR TBI Parameter Survey

1. Institution name
2. Radiation source: Cobalt-60 or Linear accelerator
3. Radiation source energy
4. Radiation beam geometry and techniques
   a. 1 field at a time or 2 fields at a time
   b. Anatomical pose: supine, prone, decubitus, seated, other
   c. Anterior-posterior or lateral or other
   d. Distance to mid-plane of animal
   e. Field size at mid-plane of animal
   f. Use of build-up material and/or compensation material - describe
   g. Nominal dose rate setting on the radiation device – at the control console: cGy/min or MU/min
   h. Dose rate at mid-plane of animal
   i. Radiation dose prescription
   j. Irradiation time per field
   k. Elapsed irradiation time to deliver prescribed dose
   l. Elapsed time for anesthesia and/or sedation
5. Dose computation algorithm or methods
6. Radiation source calibration protocol: TG-51 or TG-21 or other
7. Instrumentation used for in-vivo dose confirmation
8. Medical supportive care provided in the peri-irradiation phase

Experience and Dosimetry Standardization for Total Body Irradiations in Research

Summary

- Physics integral to RCM work
- Multi-disciplinary communications imperative
- TBI parameters vary and specific to available resources
- Validation, quality assurance and constancy are keys
- Analysis of techniques and standardization for reporting of results necessary
- Standardization, inter-comparison of techniques are important opportunities

Physics → Chemistry → Biology → Clinical

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