Practical Dosimetry for Therapeutic Nuclear Medicine, MIBG

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Making Cancer History®

Pheochromocytomas and Paragangliomas

Rare neuroendocrine tumors originating in the paraganglia (neural crest origin cells)

- pheochromocytoma: adrenal medulla origin
- paraganglioma: extra-adrenal origin

Clinical manifestations

- predisposition to cardiovascular and gastrointestinal disease
- hormonal

Hereditary in greater than 30% of patients

Most present with localized disease curable with surgery

Metastatic presentation: 15 – 20% (100 – 200 new cases annually)

Jimenez C, William Erwin, Chasen B. Targeted radionuclide therapy for patients with metastatic pheochromocytoma and paraganglioma: from low-specific-activity to high-specific-activity iodine-131 metaiodobenzylguanidine. Cancers 2019.

Metaiodobenzylguanidine (MIBG)

substrate of tumor cell membrane norepinephrine transport

- ^{123}I label: diagnostic (pheochromocytoma/paraganglioma, neuroblastoma, cardiac innervation)
- ^{131}I label: therapeutic (pheochromocytoma/paraganglioma, neuroblastoma)

Low-specific-activity ^{131}I label (= a large amount of "cold" MIBG carrier)

- Neuroblastoma therapy (another tumor of neural crest origin)
- investigational (pediatric clinical trial, Jubilant Radiopharma Draximage)

High-specific-activity ^{131}I label (= essentially carrier-free)

- pheochromocytoma/paraganglioma therapy
- FDA-approved (Azedra®, Lantheus Progenics)

Jimenez C, William Erwin, Chasen B. Targeted radionuclide therapy for patients with metastatic pheochromocytoma and paraganglioma: from low-specific-activity to high-specific-activity iodine-131 metaiodobenzylguanidine. Cancers 2019.

Azedra Treatment Regimen

296 MBq/kg (8 mCi/kg) per treatment (patients ≤ 62.5 kg)

otherwise,

18,500 MBq (500 mCi) per treatment (patients > 62.5 kg)

No. of treatments: 2 (nominally spaced 3 months apart)

Pre-requisites

- Adult or child between the ages of 12 and 18 (we have treated one 17 y.o.)
- positive ^{123}I-MIBG scan
- treatment planning (dosimetry of organs at risk)
  - **pre-treatment "tracer" amount of Azedra**
    3.7 MBq (0.1 mCi)/kg (≤ 50 kg); 222 MBq (6 mCi) (> 50 kg)
  - **based on serial planar whole body images**

Azedra Full Prescribing Information (https://www.lantheus.com//assets/AZEDRA-PI-March-2021.pdf)

Azedra Organ Cumulative (two-treatment) Absorbed Dose Limits

Organ	~ 1%-rate: mortality or organ failure associated with disease	Time to death or organ failure	Threshold* absorbed-dose for ~1%-rate mortality or organ failure (Gy)
Red marrow	H-ARS mortality	1-2 months	12
Lungs	Pneumonitis mortality	1-7 months	16.5
Kidneys	Renal failure	>1 year	18
Liver	Hepatomegaly, ascites: possible organ failure	0.5-3 months	31
Small intestine	GI-ARS mortality	6-9 days	40

Only lungs (17.5 Gy), kidneys (23 Gy) and liver (30 Gy) considered at risk in clinical trials

MIBG uptake in heart muscle (wall)

- norepinephrine transport involved in cardiac innervation
- the heart wall is nonetheless not considered an organ at risk for Azedra therapy

Azedra Full Prescribing Information (https://www.lantheus.com//assets/AZEDRA-PI-March-2021.pdf)

Azedra Treatment Planning Dosimetry Guide

Based on guidelines developed for the expanded-access protocol clinical trial

(dosimetry transitioned from central lab to participating clinical sites)

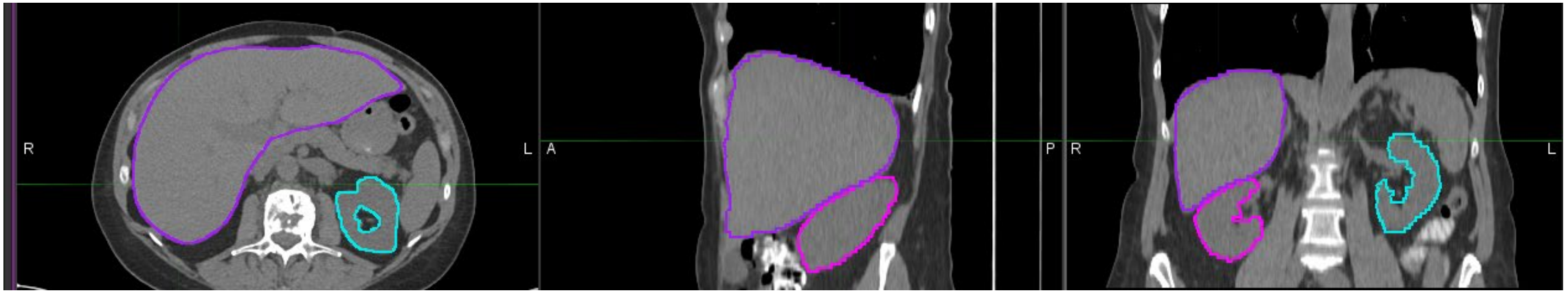
Covers all steps EXCEPT for MIRD dose calculation part (more on this later)

1. organ mass
2. ^{131}I-MIBG whole body scanning (speed, energy window, collimation, imaging time points)
3. organ and whole body region of interest analysis
4. calculation of fraction of injected activity (FIA) vs. time (TAC)
5. TAC fit and residence time (a.k.a. time-integrated activity coefficient, or TIAC) calculation
6. maximum allowable activity calculation

Worked example included

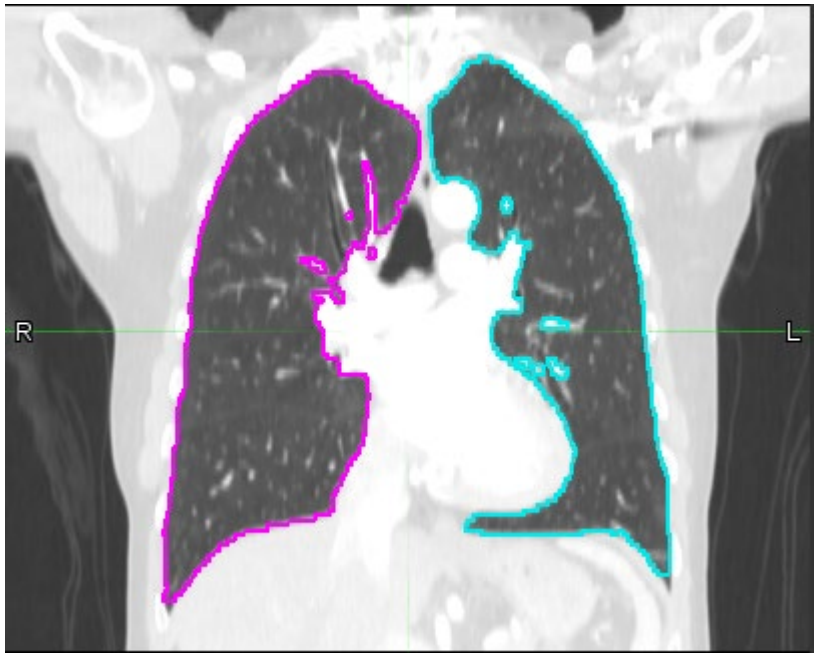
Azedra Dosimetry Guide (https://www.azedra.com/content/pdf/3_Dosimetry_Guide_1019.pdf)

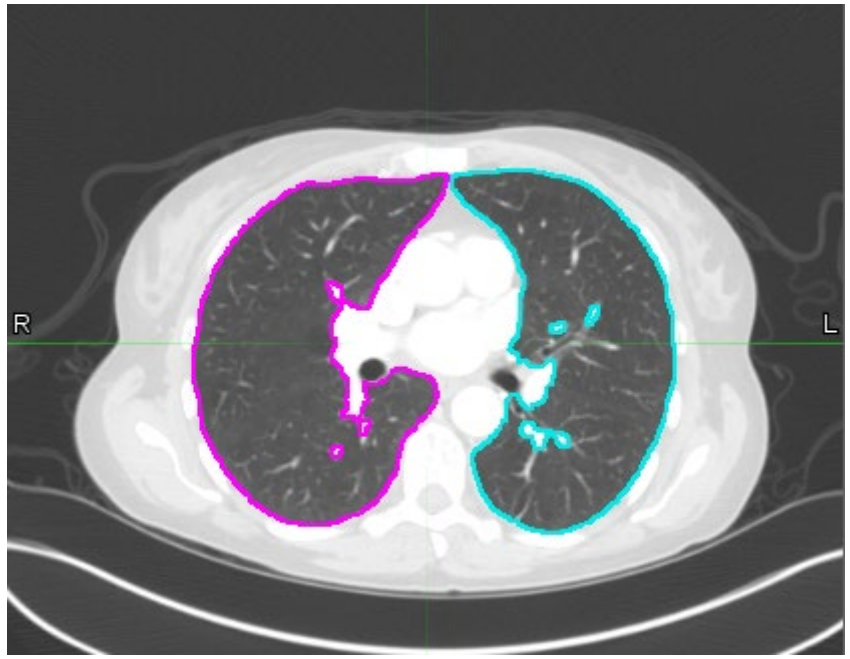
CT-based Liver and Kidney(s) Mass Estimation



Azedra Dosimetry Guidelines: mass = volume × 1.03 g/cc

CT-based Lung(s) Mass Estimation





Azedra Dosimetry Guidelines: volume × 0.25 g/cc

volume estimate varies based on scan technique (breath-hold, free-breathing, respiratory-gated)

Busse method (technique-independent): volume × 1.04 g/cc × $\frac{\text{Lung mean HU} - \text{Air mean HU}}{\text{Tissue mean HU} - \text{Air mean HU}}$

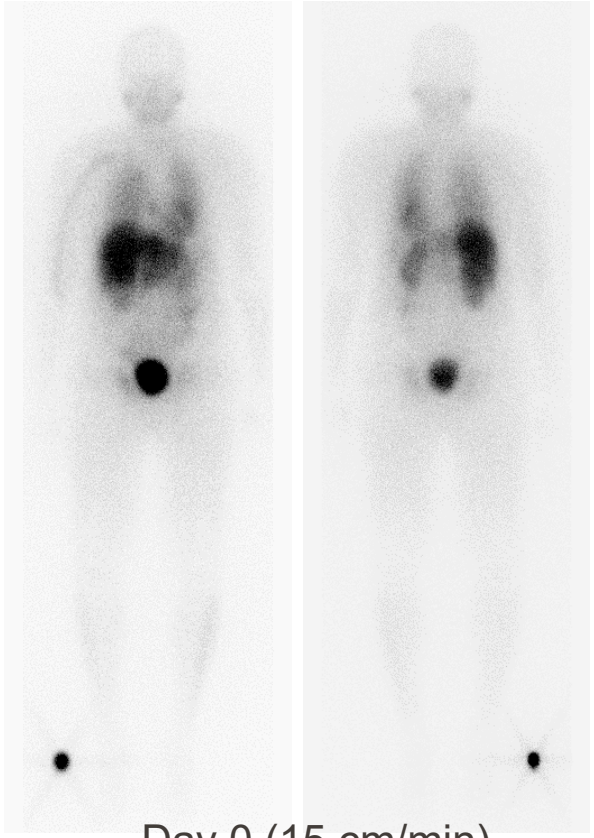
Busse N et al. Evaluation of a semiautomated lung mass calculation technique for internal dosimetry applications. Med Phys 2013;40(12)

Organ Mass Estimation

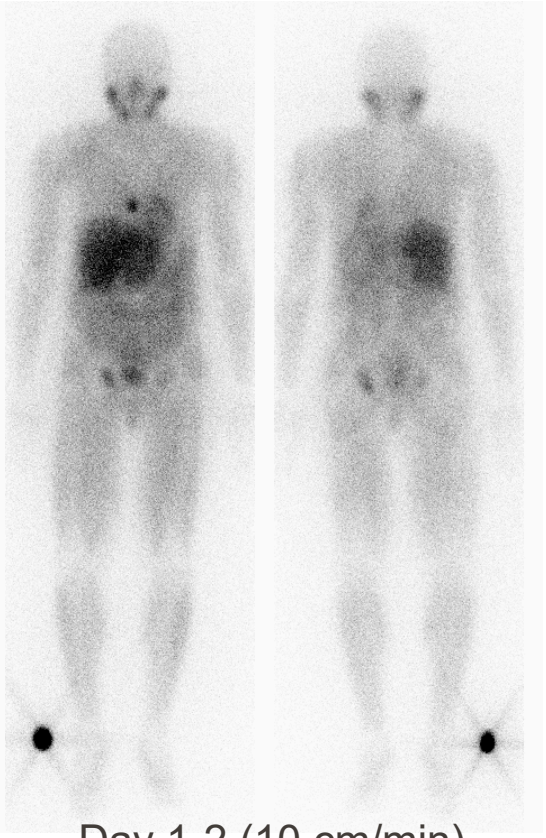
Number of kidneys =		**2**	**kidney(s)**				
Kidney vol (cc)	**335.9**	**345.9**	**gram**	Rt Kidney cc	**177.0**	Lt Kidney cc	**158.9**
Liver vol (cc)	**1771.2**	**1824.3**	**gram**				
	cc	**Average HU**	**Air HU**	**Tissue HU**			
Left Lung	**2072.5**	**-766.9**	**-1001.9**	**52.1**		Fixed Lung	
Right Lung	**2525.9**	**-775.6**				Density = 0.25	
Total Lung Mass		**1044.9**	**gram**	Busse method		1149.6	gram
NOTE: If single kidney ROI used and TWO kidneys present, must scale %IA for total kidney %IA							
Patient Total Body Mass		**60.8**	**kg**	**Use Adult Female Phantom for calculations**			
NOTES:							
Right kidney overlapped by liver so its ROI counts not accurate.							
Scale left kidney %IA to estimate total kidney %IA (using mass ratios).							
Extrapolation factor = (g/ g) =			**2.11**				

1. **If there are two kidneys but left only is used for analysis, scale FIA by (M_{right} + M_{left}) / M_{left}**
   (assumes equivalent physiologic function per unit mass between the two kidneys)
2. **patient-specific lung and kidney masses crucial when the patient has only one of either!**
   (we have treated one patient with one kidney and one patient with one lung)

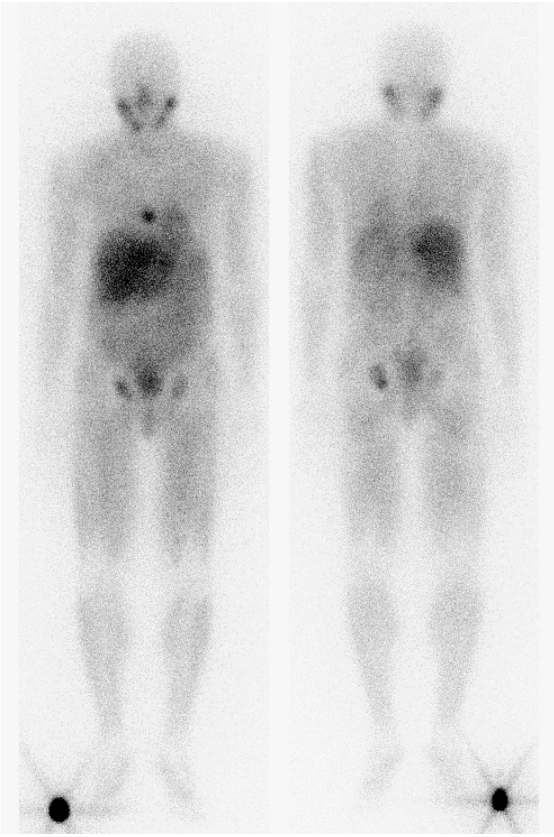
Azedra Whole Body Imaging



Day 0 (15 cm/min)



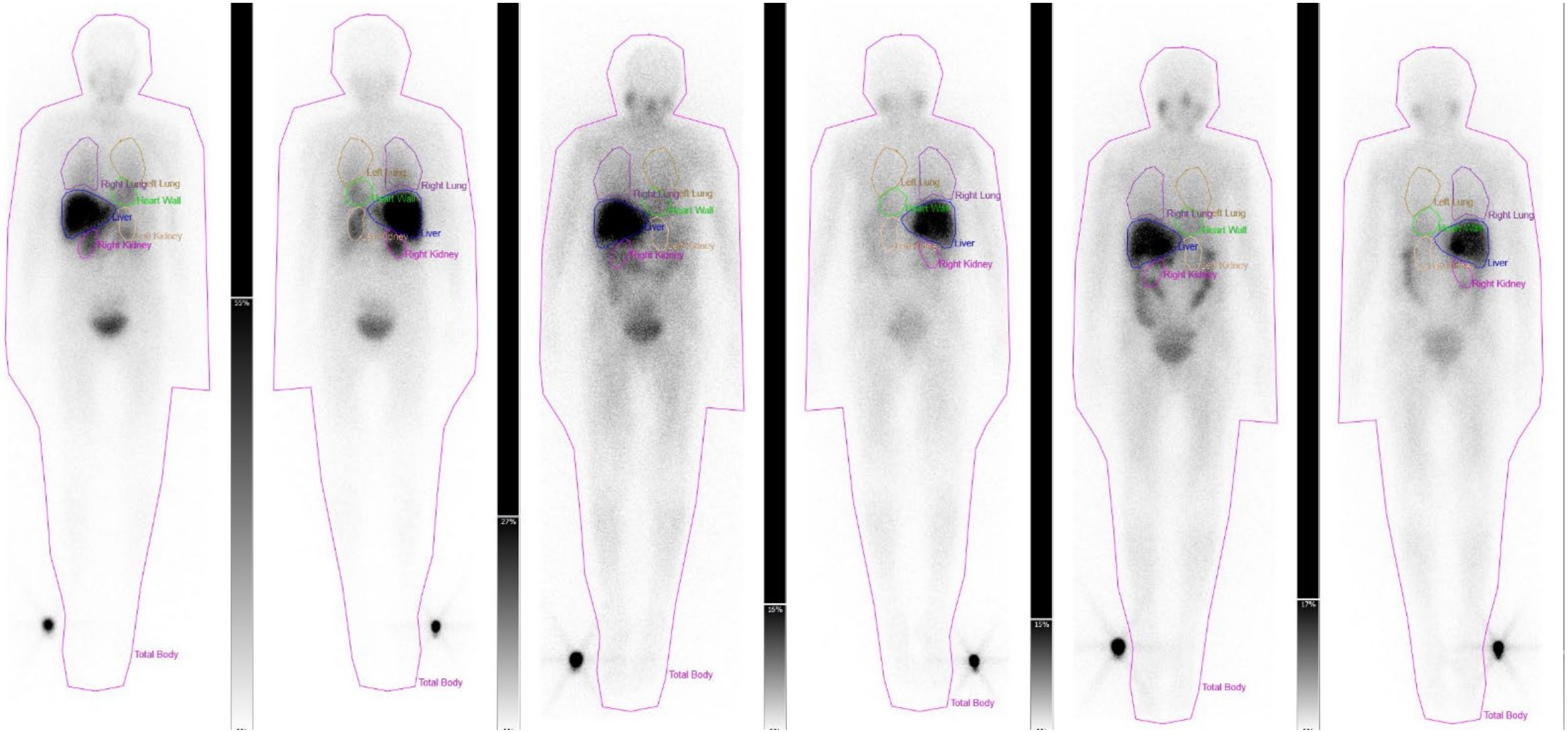
Day 1-2 (10 cm/min)



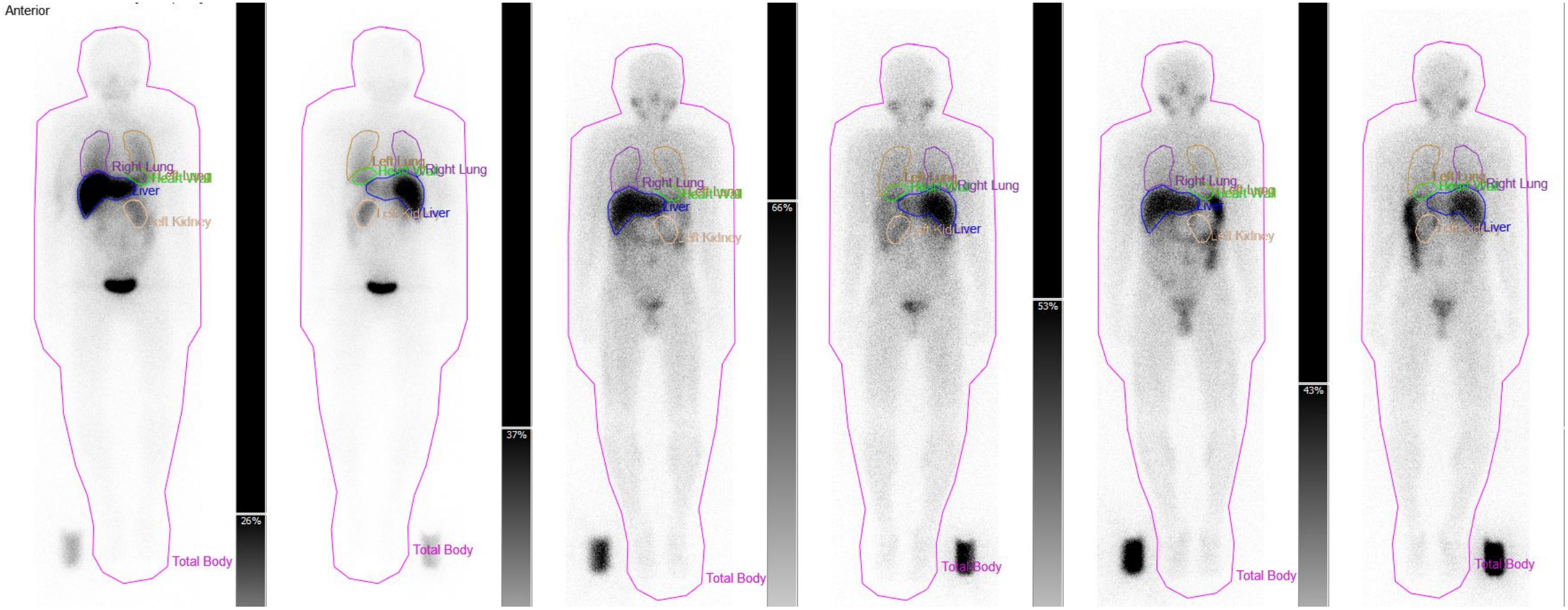
Day 2-5 (5 cm/min)

- **364 keV/15% energy window, ME or HE (preferred), constant scan length between scans**
- **Day 0 (within 1st-hour): pre-void, Day 1-2 (24 – 48 h) and Day 2-5 (48 – 120 h): post-void**

Azedra Regions of Interest (both kidneys)



Azedra Regions of Interest (Left Kidney Only)



Azedra Organ ROI FIA vs. Time Calculation (geometric mean)

Azedra Dosimetry Guidelines

$$FIA_{organ}(t) = \frac{\sqrt{C_{organAnt}(t) \times C_{organPost}(t)}}{\sqrt{C_{wholebodyAnt}(0) \times C_{wholebodyPost}(0)}} \times \frac{\sqrt{C_{standardAnt}(0) \times C_{standardPost}(0)}}{\sqrt{C_{standardAnt}(t) \times C_{standardPost}(t)}}$$

Day 0 whole body pre-void activity assumed to be FIA = 1, i.e., an attenuated standard

Caution: decaying reference standard normalizes for scan speed, but also corrects for physical decay, resulting in biologic FIA vs. time. Apply $e^{-\lambda_{I\text{-}131} \times t}$ to obtain ^{131}I effective FIA vs. time.

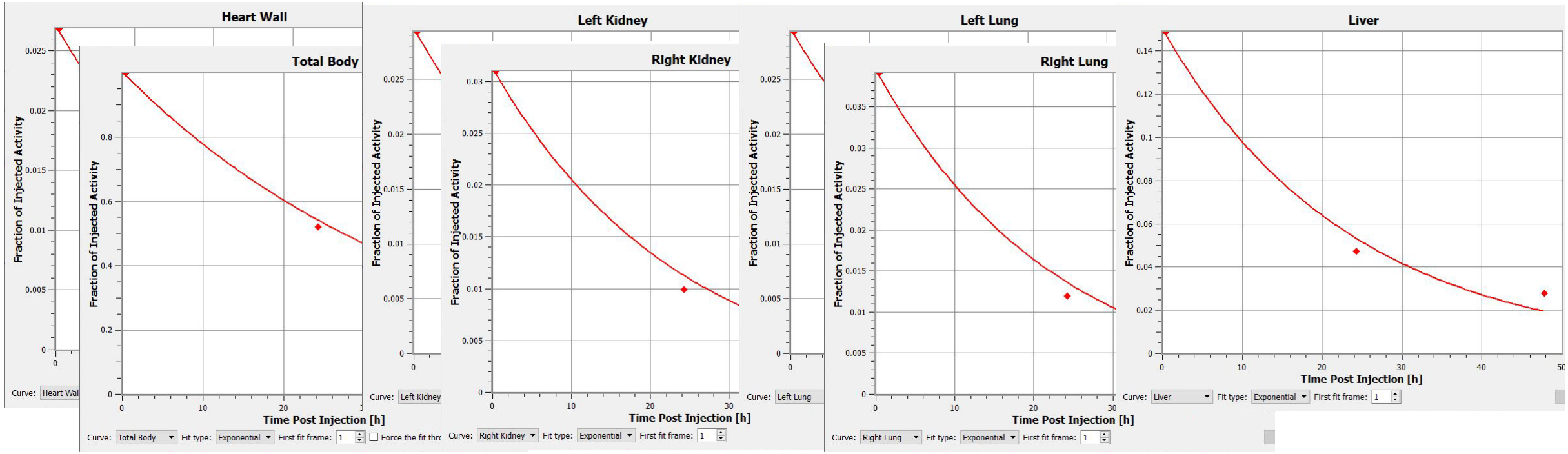
A simpler, more reliable and exact way (in the presenter's opinion)

$$FIA_{organ}(t) = \frac{\sqrt{C_{organAnt}(t) \times C_{organPost}(t)}}{\sqrt{C_{wholebodyAnt}(0) \times C_{wholebodyPost}(0)}} \times \frac{X\ cm/min}{15\ cm/min}$$

where *X* = scan speed at time *t* (=15 for Day 0, 10 for Day 1–2, and 5 for Day 2–5)

Azedra Organ ROI TAC Fit and Residence Time (TIAC) Calculation

Fit 3-point FIA(t) with any function (as long as it is $FIA_0e^{-\lambda t}$!)



$$TIAC = \int_0^{\infty} FIA_0e^{-\lambda_{eff}t}\,dt \text{ (simply } FIA_0 / \lambda_{eff}\text{, } \lambda_{eff} = \lambda_{biol} + \lambda_{I\text{-}131})$$

Azedra Organ Dose Calculation (Gy/mCi)

$$\mathbf{d_k = (37/1000) \times [\ \Sigma_h\ TIAC_h \times S(k \leftarrow h) + TIAC_{RB} \times S(k \leftarrow RB)\ ]}$$

k = target organ, h = source organ, RB = remainder of body

S = dose factor (mGy/MBq-h); 37 MBq/mCi; 1/1000 Gy/mGy

Organ self-dose factor mass correction (kidneys, liver, lungs)

$$S(k \leftarrow k)_{corr} = S(k \leftarrow k)_{\beta} \times (m_{ref}/m_{pat}) + S(k \leftarrow k)_{photon} \times (m_{ref}/m_{pat})^{2/3}$$

Remainder of Body dose factor

$$S(k \leftarrow RB) = (m_{TB}/m_{RB}) \times S(k \leftarrow TB) - \Sigma_h\ (m_h/m_{RB}) \times S(k \leftarrow h)$$

TB = total body; $m_{RB} = m_{TB} - \Sigma_h\ m_h$

Azedra Cumulative Therapy Activity Calculation (mCi)

The smallest among:

Planned	$8\ \text{mCi/kg} \times M_{\text{TotalBody}} \times 2$
Red Marrow Dose-Limiting	$12\ \text{Gy} / d_{\text{RM}}$
Lungs Dose-Limiting	$16.5\ \text{Gy} / d_{\text{Lungs}}$
Kidneys Dose-Limiting	$18\ \text{Gy} / d_{\text{Kidneys}}$
Liver Dose-Limiting	$31\ \text{Gy} / d_{\text{Liver}}$
Small Intestine Dose-Limiting	$40\ \text{Gy} / d_{\text{SI}}$

1. In our experience, kidneys have been most likely to limit the prescribed activity
2. RM and SI targets only, i.e., not quantified sources, so extremely unlikely to be dose-limiting

Example Azedra Cumulative Therapy Activity

Organ	Gy/mCi
Adrenals	5.48E-03
Brain	3.60E-03
Breasts	3.69E-03
Gallbladder Wall	5.59E-03
LLI Wall	4.44E-03
Small Intestine	4.44E-03
Stomach Wall	4.70E-03
ULI Wall	4.77E-03
Heart Wall	1.47E-02
Kidneys	2.13E-02
Liver	1.18E-02
Lungs	8.70E-03
Muscle	4.00E-03
Ovaries	4.51E-03
Pancreas	5.37E-03
Red Marrow	3.59E-03
Osteogenic Cells	3.60E-03
Skin	3.30E-03
Spleen	4.77E-03
Thymus	4.40E-03
Thyroid	3.81E-03
Urinary Bladder Wall	4.03E-03
Uterus	4.48E-03
Total Body	4.51E-03

Therapy Radiation Doses & Limits on Dose/Administered Activity

Proposed Activity (mCi)->	486.4	972.8	(60.8 kg total body mass)			
	Gy	**Gy**	**Limiting Dose**		**Limiting Activity**	
Kidneys	10.4	20.8	18	**Gy**	843	**mCi**
Liver	5.7	11.5	31	**Gy**	2626	**mCi**
Lungs	4.2	8.5	16.5	**Gy**	1898	**mCi**
Red Marrow	1.7	3.5	12	**Gy**	3347	**mCi**
Small Intestine	2.2	4.3	40	**Gy**	9009	**mCi**
			Max allowable activity (mCi)=		843	

Activity & Organs-at-Risk Dose Prescriptions

	Treatment 1	Treatment 2	
Prescribed Activity (mCi)	**422**	**422**	(Each 1/2 of Maximum allowable activity)
	Dose (Gy)	Dose (Gy)	
Kidneys	**9.0**	**9.0**	
Liver	**5.0**	**5.0**	
Lungs	**3.7**	**3.7**	
Red Marrow	**1.5**	**1.5**	
Small Intestine	**1.9**	**1.9**	

“Treatment Planning” (TP) Software

CT organ VOI contouring

Scanner workstation software; 3rd-party (e.g, MIM, OsirixMD); freeware (e.g., MIPAV, 3D Slicer)

^{131}I whole body planar organ ROI contouring and total counts tabulation

Scanner workstation software; 3rd-party (e.g, MIM, Hermes HD, ABX-CRO QDOSE (EU)); freeware (e.g, ImageJ, Fiji)

Geometric mean TAC analysis and TIAC calculation

Commercial software (e.g., Hermes HD, QDOSE (EU), MS Excel, GraphPad Prism)

Olinda 1.1 (legacy from Vanderbilt, if you already have it) or Olinda 2.0 (current, from Hermes Medical Solutions)

MIRD dose calculation

Olinda 1.1 or Olinda 2.0

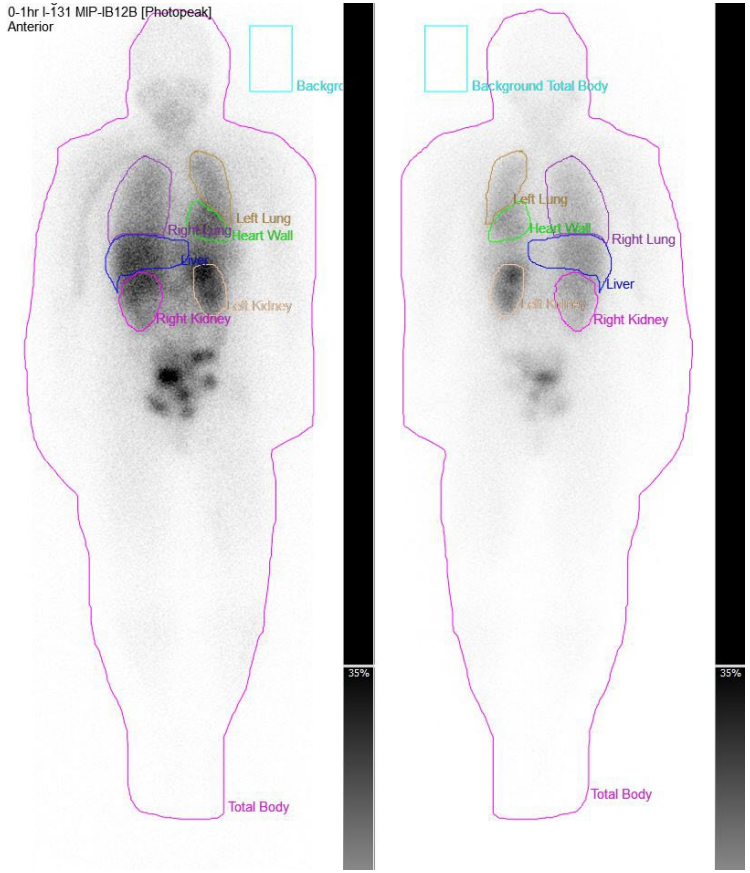
IDAC-Dose2.1 (https://www.idac-dose.org/, used by QDOSE)

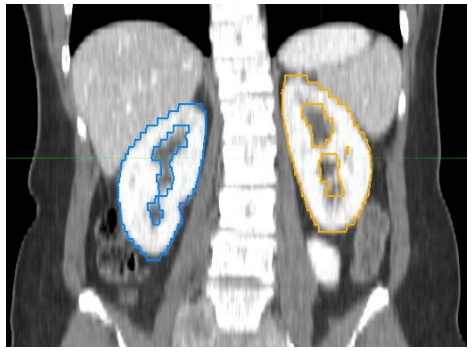
Obtain MIRD phantom dose factors (incl. lung, kidney and liver “self” β and photon) and calculate yourself

Commission your TP software, to ensure correctness, and find and fix (or workaround) any “bugs”.

Unusual Azedra Case 1

Dosimetry study (1st try)





Kidney vol (cc)	268.0	276.0	gram

Fitting parameters: $y = A_1e^{-k1x} + A_2e^{-k2x}$

	A1	k1	T1/2eff		TIAC
Left Ki...	0.0516	0.0320	21.7		1.6149
Right ...	0.0528	0.0247	28.1		2.1399

Therapy Radiation Doses & Limits on Dose/Administered Activity

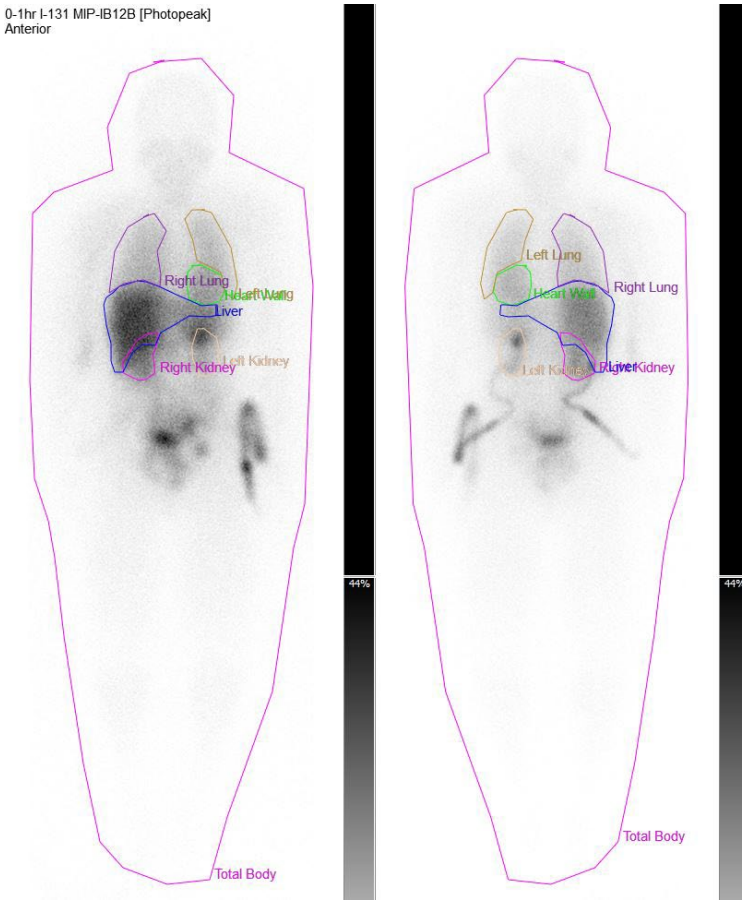
Proposed Activity (mCi)->	446.4	892.8				
	Gy	Gy	Limiting Dose		Limiting Activity	
Kidneys	28.9	57.8	18	Gy	278	mCi
Liver	6.2	12.5	31	Gy	2222	mCi
Lungs	8.3	16.7	16.5	Gy	883	mCi
Red Marrow	2.3	4.7	12	Gy	2284	mCi
Small Intestine	2.9	5.8	40	Gy	6178	mCi
			Max allowable activity (mCi)=		278	

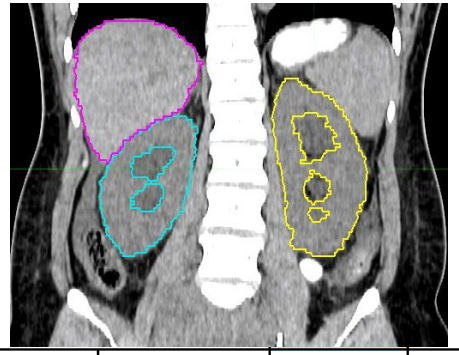
Activity & Organs-at-Risk Dose Prescriptions

	Treatment 1	Treatment 2	
Prescribed Activity (mCi)	139	139	(Each 1/2 of Maximum allowable activity)
	Dose (Gy)	Dose (Gy)	
Kidneys	9.0	9.0	
Liver	1.9	1.9	
Lungs	2.6	2.6	
Red Marrow	0.7	0.7	
Small Intestine	0.9	0.9	

Unusual Azedra Case 1

Dosimetry study (2nd try, post-double nephrostomy)





Kidney vol (cc)	390.7	402.4	gram

Fitting parameters: $y = A_1e^{-k1x} + A_2e^{-k2x}$

	A1	k1	T1/2eff		TIAC
Left Ki...	0.0271	0.0521	13.3		0.5191
Right ...	0.0433	0.0601	11.5		0.7202

Therapy Radiation Doses & Limits on Dose/Administered Activity

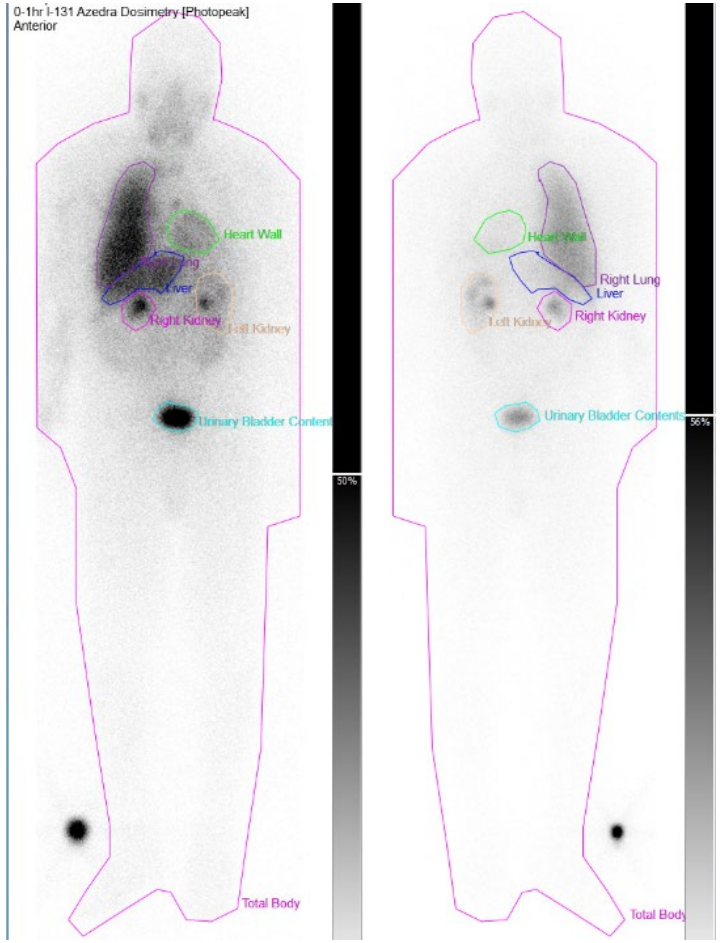
Proposed Activity (mCi)->	403.2	806.4				
	Gy	Gy	Limiting Dose		Limiting Activity	
Kidneys	7.1	14.3	18	Gy	1018	mCi
Liver	5.2	10.4	31	Gy	2401	mCi
Lungs	4.3	8.5	16.5	Gy	1559	mCi
Red Marrow	1.2	2.5	12	Gy	3941	mCi
Small Intestine	1.5	3.0	40	Gy	10865	mCi
			Max allowable activity (mCi)=			806

Activity & Organs-at-Risk Dose Prescriptions

	Treatment 1	Treatment 2	
Prescribed Activity (mCi)	403	403	(Each 1/2 of Maximum allowable activity)
	Dose (Gy)	Dose (Gy)	
Kidneys	7.1	7.1	
Liver	5.2	5.2	
Lungs	4.3	4.3	
Red Marrow	1.2	1.2	
Small Intestine	1.5	1.5	

Unusual Azedra Case 2

One (right) lung



Right Lung	1678.6 cc	530.6	gram

Fitting parameters: $y = A_1e^{-k1x} + A_2e^{-k2x}$

	A1	k1	T1/2eff	TIAC
Right Lung	0.1583	0.0481	14.4	3.2940

Therapy Radiation Doses & Limits on Dose/Administered Activity

Proposed Activity (mCi)->	500.0	1000.0				
	Gy	Gy	Limiting Dose		Limiting Activity	
Kidneys	7.9	15.8	18	Gy	1142	mCi
Liver	2.5	5.0	31	Gy	6253	mCi
Lungs	14.7	29.5	16.5	Gy	560	mCi
Red Marrow	1.3	2.5	12	Gy	4714	mCi
Small Intestine	1.6	3.1	40	Gy	12794	mCi
			Max allowable activity (mCi)=		560	

Activity & Organs-at-Risk Dose Prescriptions

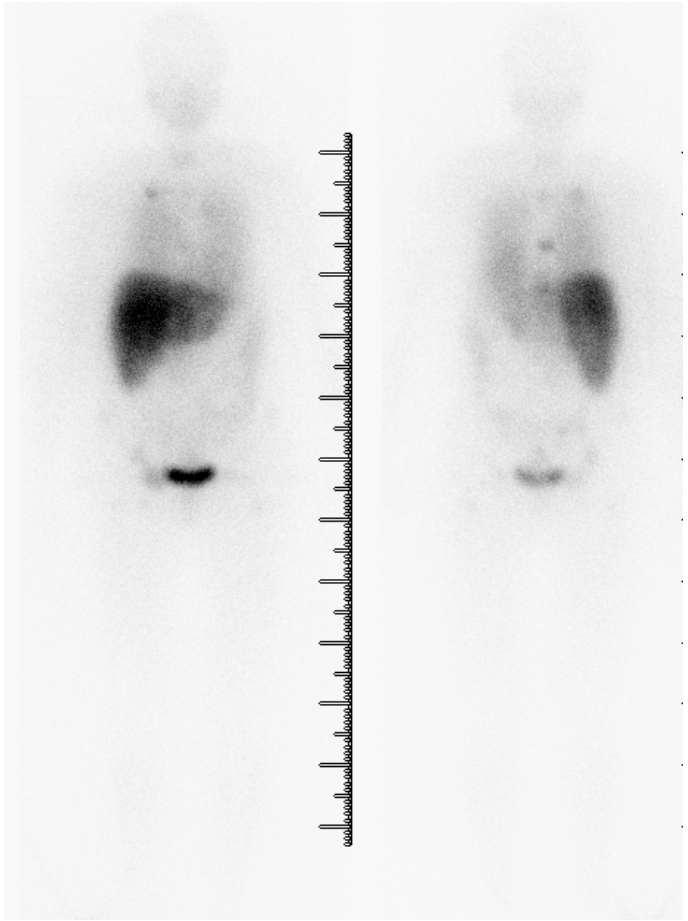
	Treatment 1	Treatment 2	
Prescribed Activity (mCi)	280	280	(Each 1/2 of Maximum allowable activity)
	Dose (Gy)	Dose (Gy)	
Kidneys	4.4	4.4	
Liver	1.4	1.4	
Lungs	8.3	8.3	
Red Marrow	0.7	0.7	
Small Intestine	0.9	0.9	

If MIRD reference phantom lung mass (1000 g) was assumed,

Tx activity would be 1000 mCi → ~2x the dose (31 Gy) to the lung!

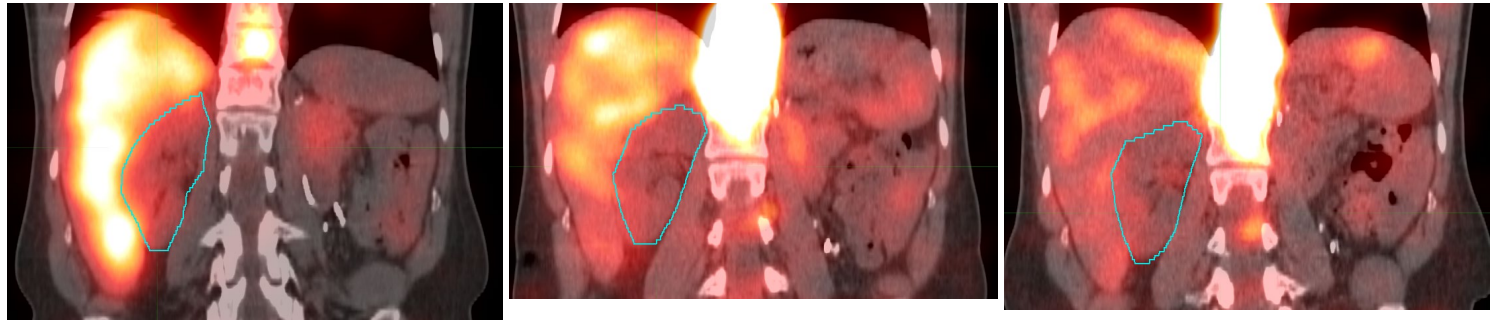
Unusual Azedra Case 3

One (right) kidney (completely overlapped by liver)



Quantitative SPECT TAC

Day 0 Day 1 Day 2



Q: FIA(t) = GM Planar FIA(t)? A: Probably not.

If not, then the derived TIAC, Gy/mCi and, potentially, therapeutic activity prescription could be significantly different.

(In this case, however, lung was the activity-limiting organ)

Summary

Azedra treatment planning is reasonably straightforward to implement

- CT lung, liver and kidney volumes plus three planar Azedra “dosimetric” whole body scans
- organ FIA = planar GM ROI total counts scaled to initial total body (normalized for scan speed)
- mono-exponential fit of organ FIA(t), and organ TIAC is simply $FIA(0)/\lambda_{eff}$
- simple cumulative mCi calculation ($8\ mCi/kg \times M_{TB} \times 2 \leq 1000$ or organ Gy limit ÷ Gy/mCi)
- can utilize a combination of scanner, commercial, free and/or in-house software

However, for MIRD dose (mGy/MBq) calculation step, one must:

Either already have OLINDA/EXM 1.1 (legacy) or purchase OLINDA/EXM 2.0

OR obtain IDAC-Dose2.1

OR obtain dose factors and develop in-house calculations

Summary

Azedra treatment planning (dosimetry of organs at risk) limitations

- overlap (liver/R kidney, kidneys/GI tract, heart wall/L lung, tumor/organ, organ/tissue background)
- accuracy/uncertainty of planar image-based FIA(t), TIAC and dose (including mass correction)?

  doses calculated dependent upon choice of "engine" (OLINDA vs. IDAC-Dose2.1 vs. in-house)
- guidelines and dose limits assume whole body planar image-based dosimetry

  quantitative effect of SPECT-based dosimetry (e.g., for R kidney only with liver overlap on planar)?
- May be a tedious manual process, with numerous steps that include manual entry of data

  plenty of room for mistakes, including those of the transcription kind

Regardless of methodology and tools used, commissioning and SOP development recommended

References

1. Jimenez C, Erwin W, Chasen B. Targeted radionuclide therapy for patients with metastatic pheochromocytoma and paraganglioma: from low-specific-activity to high-specific-activity iodine-131 metaiodobenzylguanidine. Cancers 2019; 11(7):1018; doi:10.3390/cancers11071018
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