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Activity quantification and dosimetry in PSMA Radioligand Therapy

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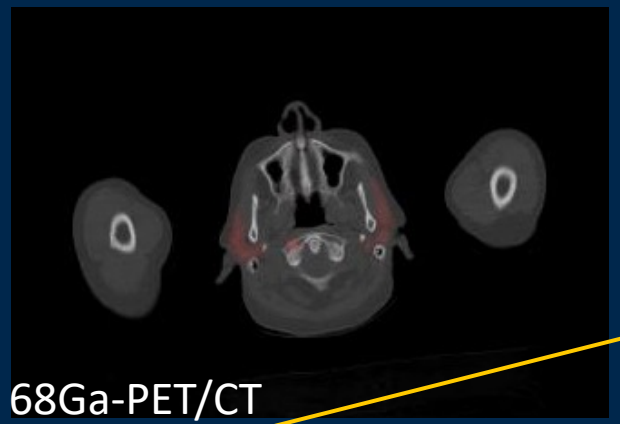
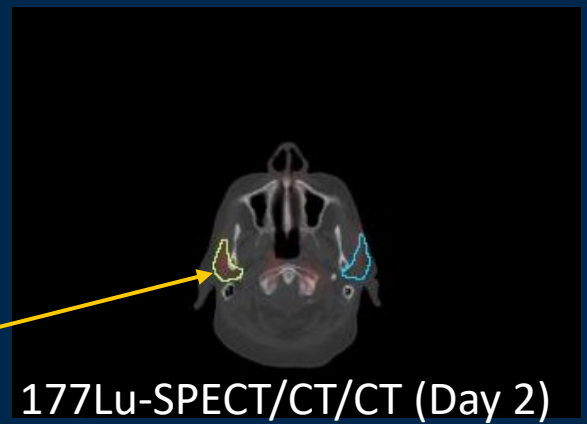
Example ^{177}Lu-PSMA RLT Dosimetry Calculation: Imaging & Segmentation

- Patient treated at U Mich
- Two-bed quantitative ^{177}Lu-SPECT/CT at day0,2, 4 and 6 after Cycle 1
  - Activity directly from image (Bq/mL units)
  - Recovery Coefficients (RC) applied for Partial Volume Correction (PVC)

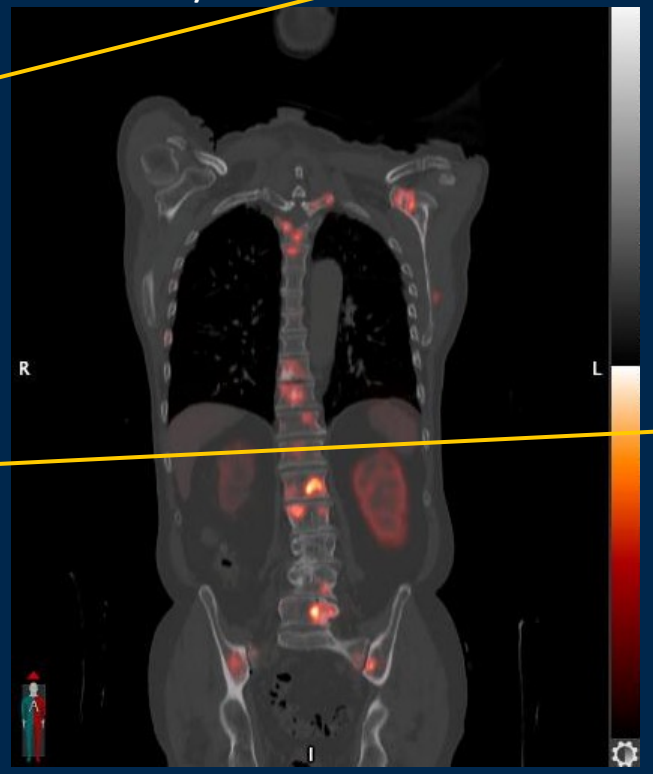
- Segmentation
  - Salivary glands, kidney, liver, spleen: deep learning tools + checked by radiologist
  - Lesions: manually on baseline CT by radiologist or PET-gradient based auto-tools
  - Bones, lung: CT thresholding

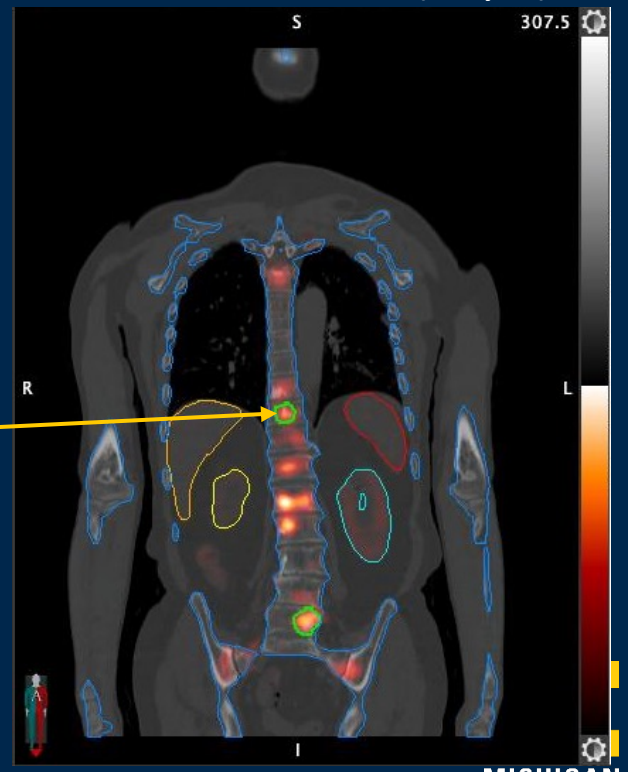


68Ga-PET/CT



177Lu-SPECT/CT/CT (Day 2)





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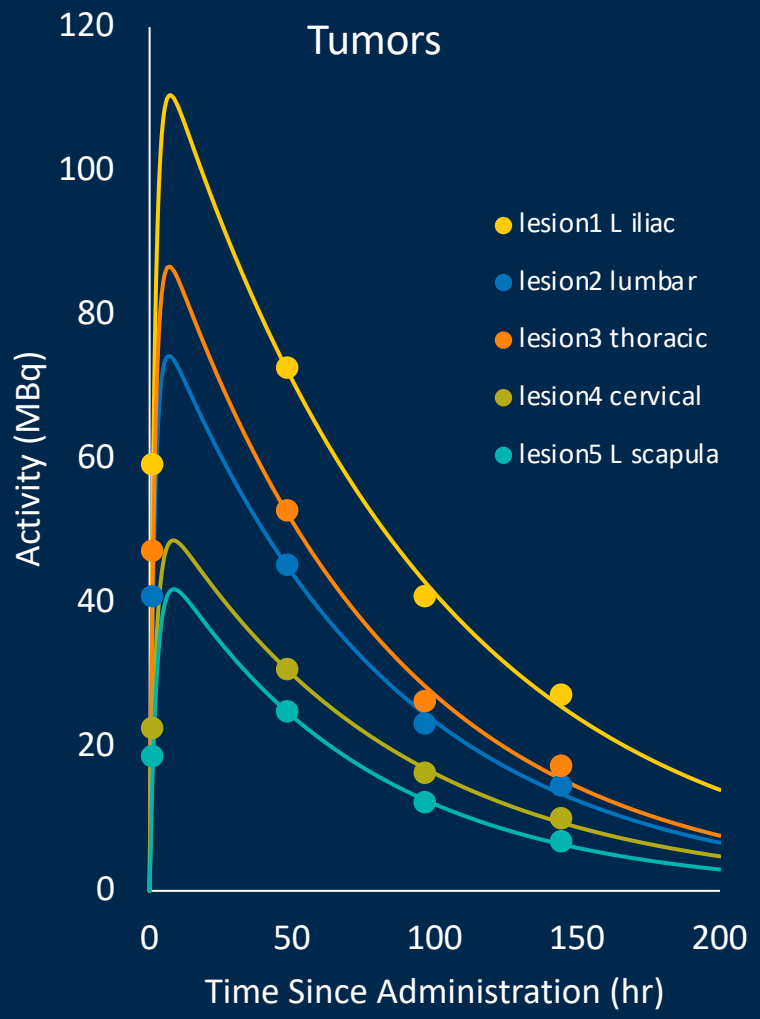
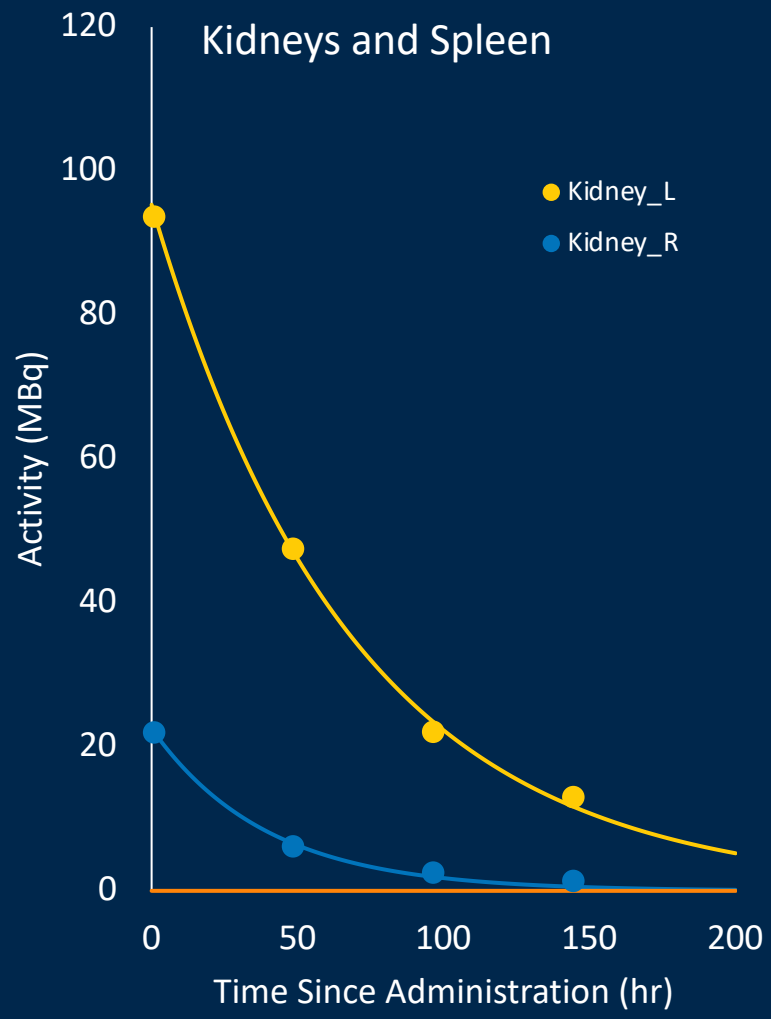
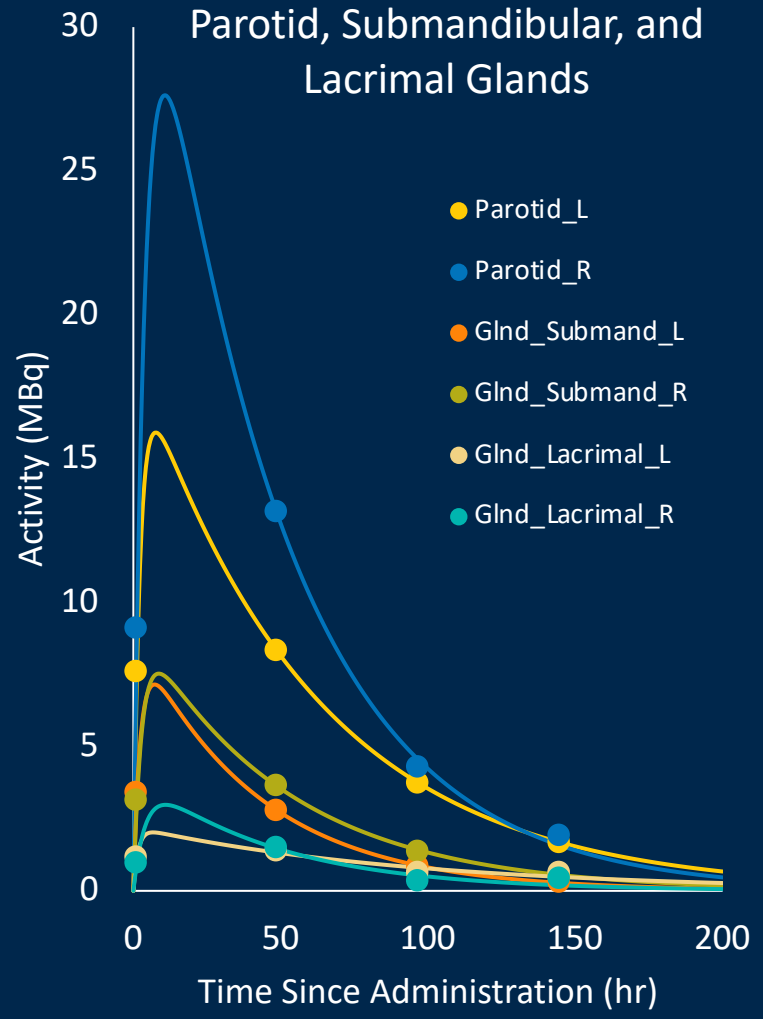
Example ^{177}Lu-PSMA RLT Dosimetry Calculation: Time-activity







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Patient Example Absorbed Dose Calculation: MIRD Formalism

- Absorbed dose to target region:

$$\bar{D}(r_T) = \sum_{r_S} \tilde{A}(r_S) S(r_T \leftarrow r_S)$$

- Kidney, liver, spleen: Reference phantom S-values
  - Mass scaling for self-dose S

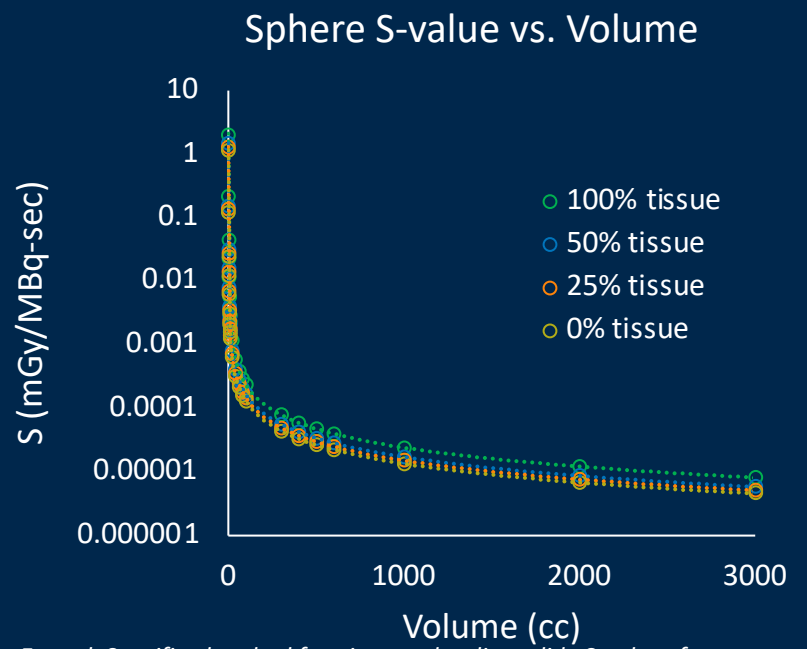
$$\bar{D}(kid) = \tilde{A}(kid) S(kid \leftarrow kid) * m_{kid\_pat}/m_{kid\_std} + \tilde{A}(spl) S(kid \leftarrow spl) + \tilde{A}(liv) S(kid \leftarrow liv) + \tilde{A}(rb) S(kid \leftarrow rb)$$

- Tumor, parotids, submandibular: Sphere model S-values

$$Self\ Dose\ only\text{: } \bar{D}(\text{tumor}, t) = \tilde{A}(\text{tum}) S(sph \leftarrow sph)$$

^{177}Lu S-values (mGy/MBq-s) from MIRDcalc v1.1 for ICRP133 Adult Male phantom.

		Targets				
Sources	Total	Kidneys	Liver	Prostate	Salivary glands	Spleen
	Kidneys	5.70E-05	1.40E-07	3.37E-09	9.59E-10	1.85E-07
	Liver	1.40E-07	1.05E-05	1.46E-09	2.81E-09	4.13E-08
	Lungs	2.82E-08	9.64E-08	3.68E-10	1.24E-08	1.24E-07
	Prostate	3.54E-09	1.39E-09	1.32E-03	1.13E-11	9.63E-10
	Salivary gl.	1.13E-09	3.17E-09	2.19E-11	2.64E-04	3.01E-09
	Spleen	1.85E-07	4.13E-08	9.63E-10	2.68E-09	1.05E-04
	Total body	3.66E-07	3.64E-07	3.64E-07	3.46E-07	3.62E-07



Olguin E, et al. Specific absorbed fractions and radionuclide S-values for tumors of varying size and composition. Phys Med Biol. 2020;65(23):235015.

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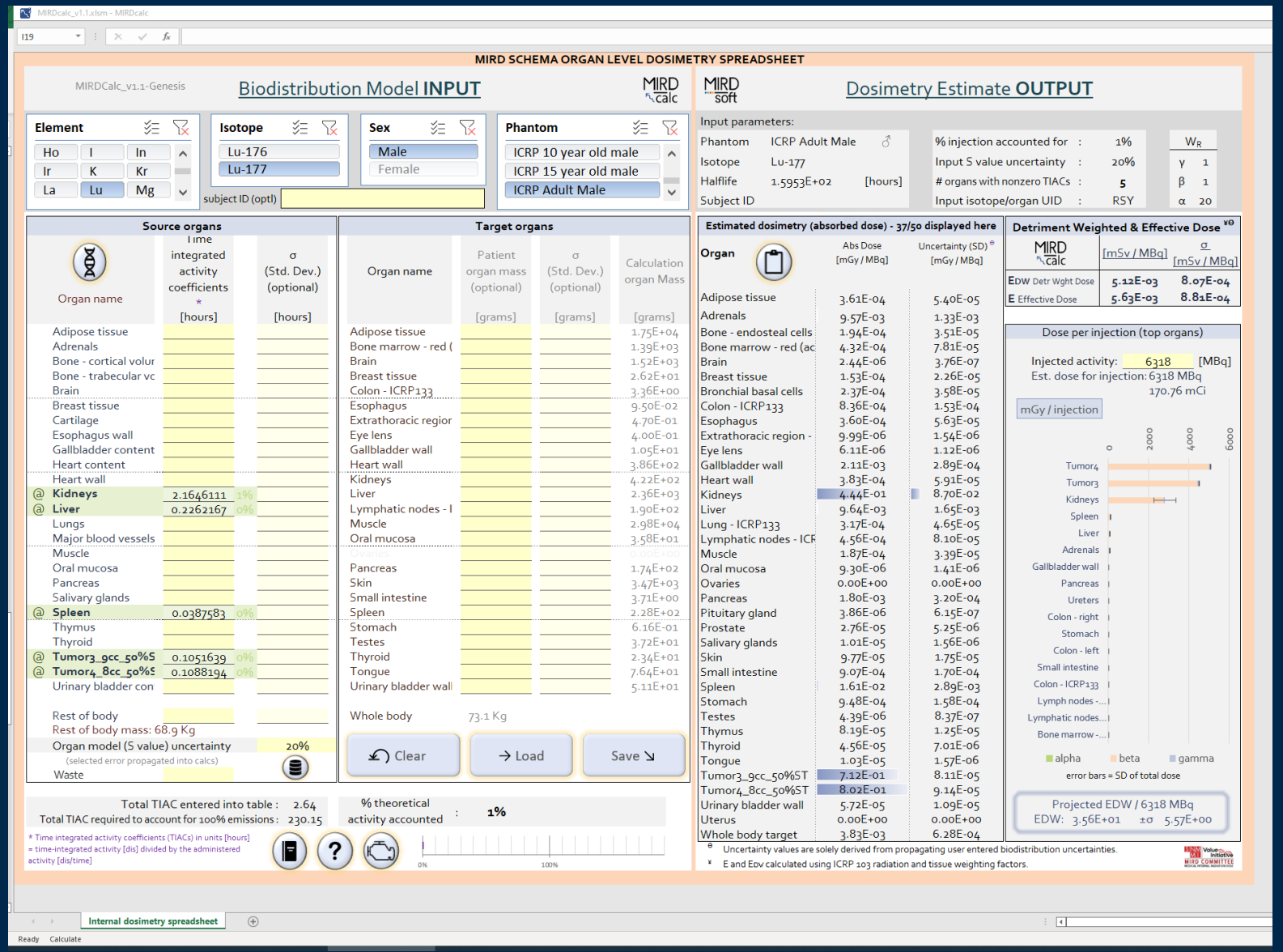
Example ^{177}Lu-PSMA RLT Dosimetry: using MIRDCalc v1.1



https://mirdsoft.org/mirdcalc

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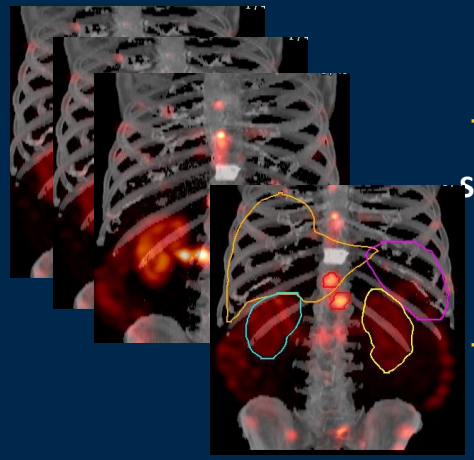
Example ^{177}Lu-PSMA RLT Calculation: Voxel dosimetry using automated contouring, registration and curve fitting coupled with Monte Carlo

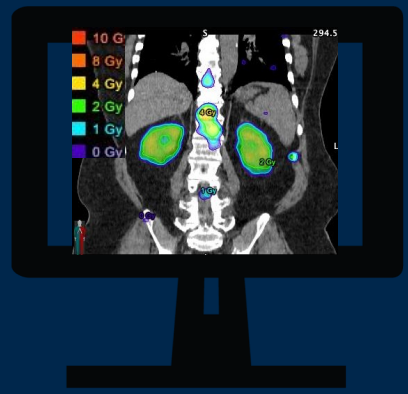
177Lu-SPECT/CT after Cycle 1

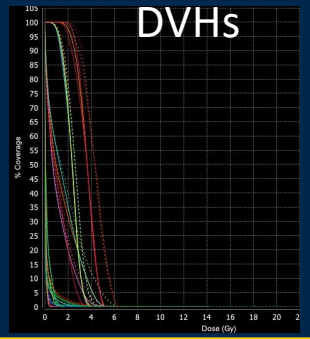


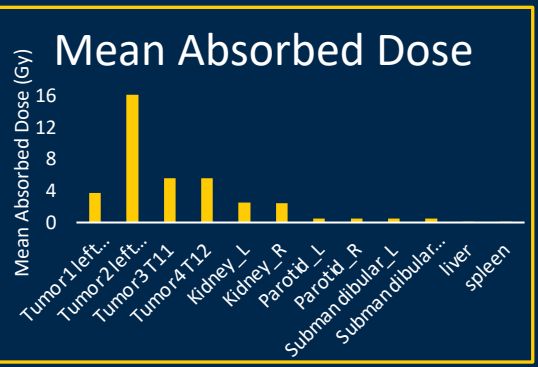
Automation

CNN Segmentation → Registration & VOI Propagation → Monte Carlo Dosimetry → Voxel-level Dose-rate Fit (Auto select best fit)

Patient Specific Absorbed Dose Map







Dewaraja et al, A pipeline for automated voxel dosimetry: application in patients with multi-SPECT/CT imaging following ^{177}Lu peptide receptor radionuclide therapy. J Nucl Med. 2022 doi: 10.2967/jnumed.121.263738. Epub ahead of print

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Example ^{177}Lu-PSMA RLT Patient Dosimetry Results

Cycle 1 Mean Absorbed dose following 7.3 GBq of ^{177}Lu-PSMA 617

	Volume (mL)	Effective Half-life (h)	Mean Absorbed Dose using MIRD Gy (%diff using MC)
Tumor 1 (L Iliac)	22	64	36 (0%)
Tumor 2 (L Lumbar)	14	55	31 (2%)
Tumor 3 (Thoracic)	15	55	39 (-18%)
Tumor 4 (Cervical)	8	57	36 (-5%)
Lesion5 (L scapula)	7	48	32 (5%)
Kidney	186	(47, 27)	3.4 (0%)
L Parotid	21	42	4.2 (5%)
R Parotid	24	31	5.5 (5%)
L Submandibular	7	29	4.4 (1%)
R Submandibular	7	35	5.7 (2%)
L lacrimal	0.6	66	29 (-4%)
R lacrimal	0.3	33	40 (-2%)

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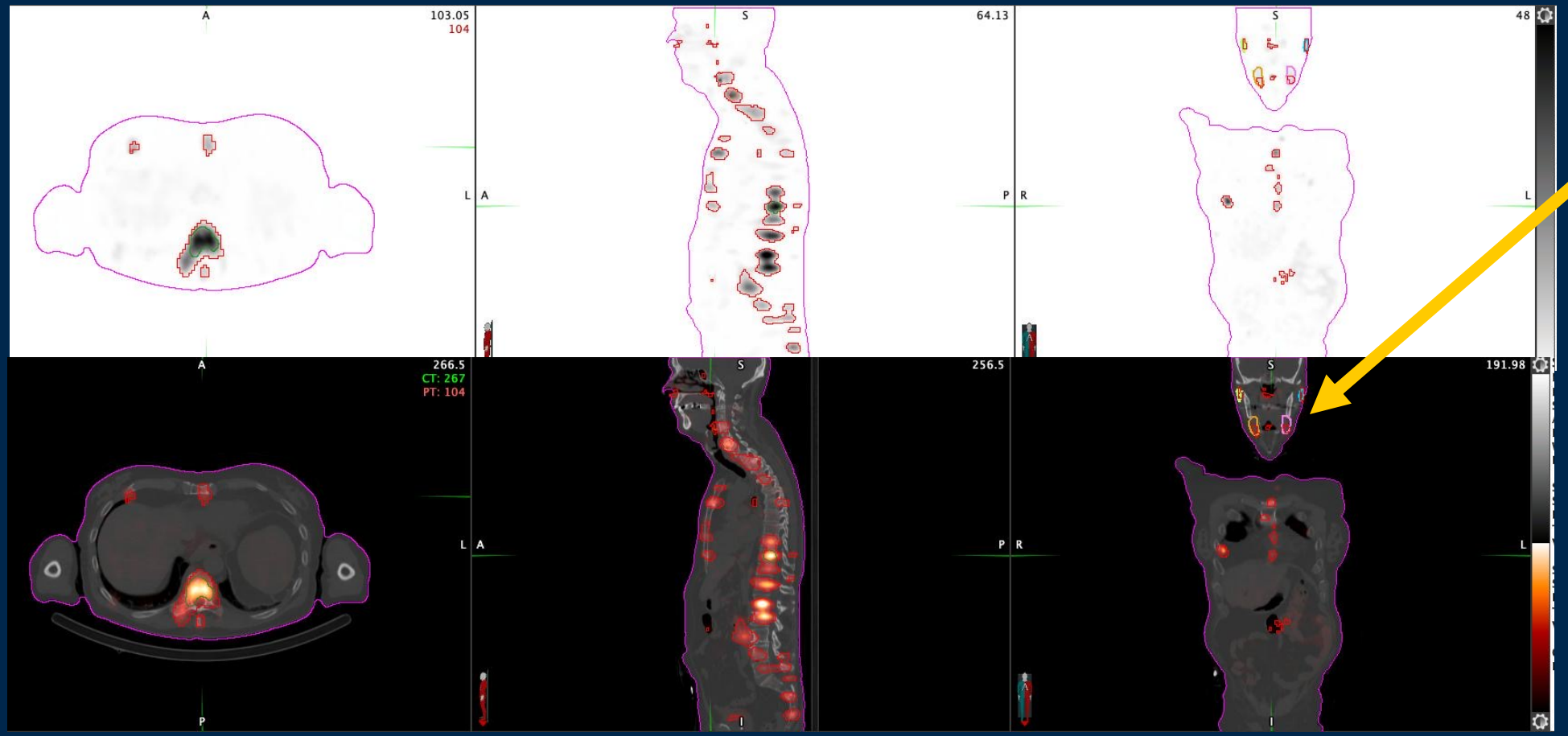
Another approach for lesion segmentation

- Threshold whole body to capture all regions above a dose level (5 Gy used by Violet et al. JNM 2019)
- For previous example (WB tumor dose was 12 Gy)



Clean to exclude
Normal uptake

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PSMA RLT in mCRPC: Challenges for dosimetry

- Small lesions (often bone mets), and small organs (lacrimal glands)
  - Difficult to segment
    - For lesions include all voxels above a pre-determined threshold, but need to manually remove regions of physiological uptake (Violet et al, JNM 2019)
  - Partial volume effects can be substantial
    - Use Recovery coefficients or an expanded VOI to capture 'spill-out', but challenging …
  - Mis-registration of serial images especially problematic
  - Planar imaging also especially problematic. Hybrid planar/SPECT
- Multiple SPECT bed positions
  - Promise of single timepoint methods demonstrated for ^{177}Lu-PSMA
- Complexity of bone marrow dosimetry
  - Conventional methods likely unreliable. Direct Monte Carlo models may help
- Challenges of imaging α emitters (^{225}Ac-PSMA) due to low activity
  - Specialized reconstruction algorithms

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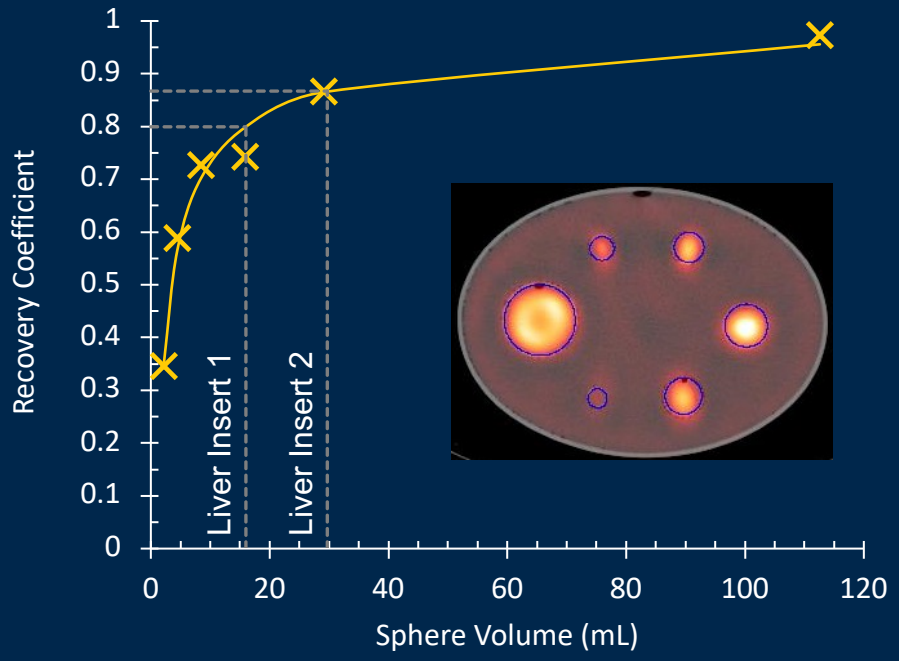
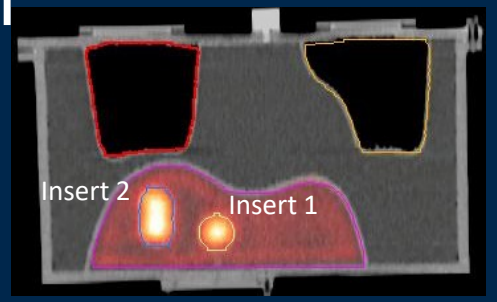
Recovery Coefficients (RC) & Validation of Quantification

- RCs for mean value Partial Volume Correction (PVC)
  - RC vs. volume curve using phantom meas.
  - Practical, but limitations
  - Voxel-level corrections still under development



Dewaraja et al, MIRD 23, J Nucl Med 2012

- Validation of quantification process using a different phantom



	Volume mL	True MBq/mL	SPECT MBq/mL	SPECT MBq/mL w/RC
Ellipsoid	30	0.376	0.323 (14%)	0.374 (1%)
Sphere	16	0.376	0.312 (17%)	0.392 (-4%)
Liver minus lesions	1126	0.099	0.105 (-6%)	0.103 (-4%)
Sphere-to-liver ratio		3.80	2.98 (22%)	3.81 (0%)

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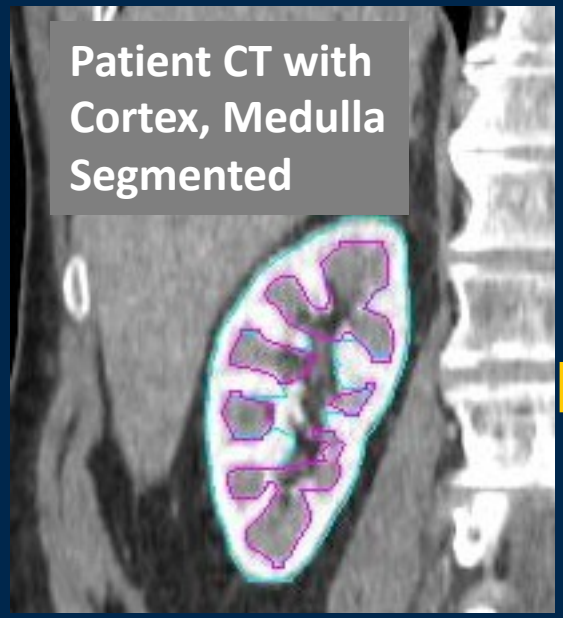
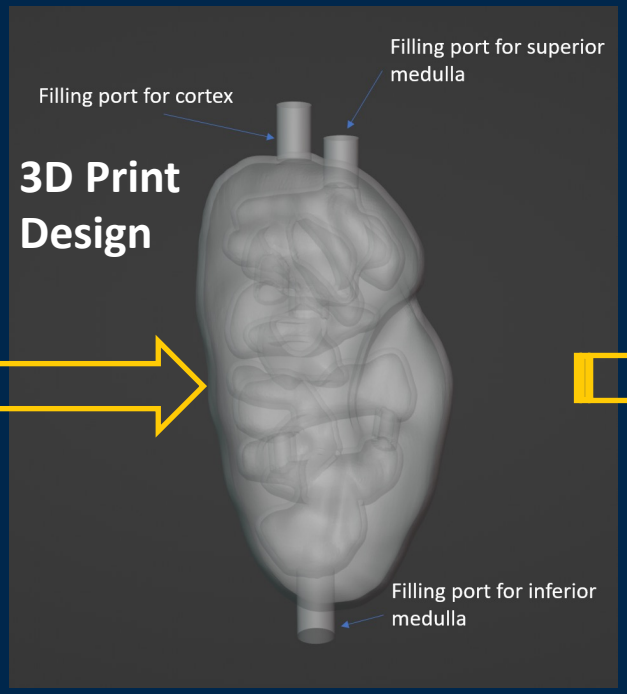
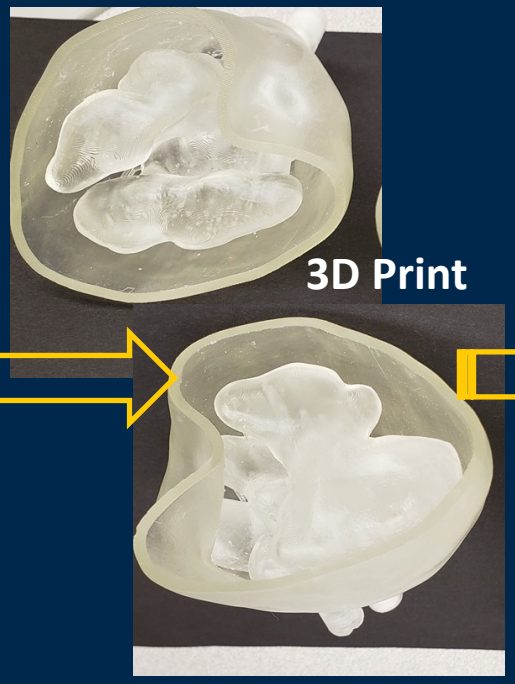
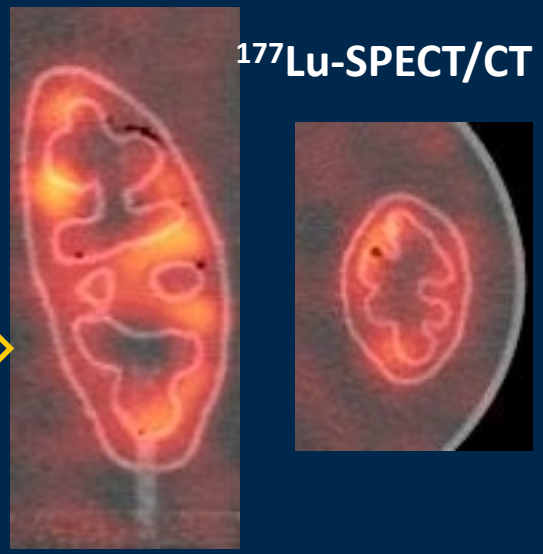
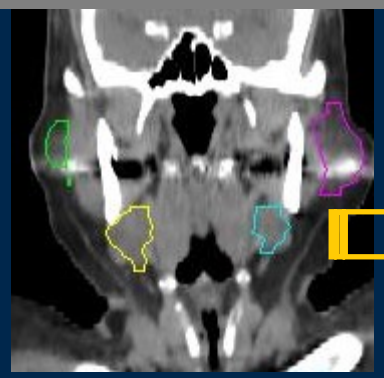
RCs depend not only on volume and reconstruction method: Study to look at impact of object shape, target-to-background activity ratio …

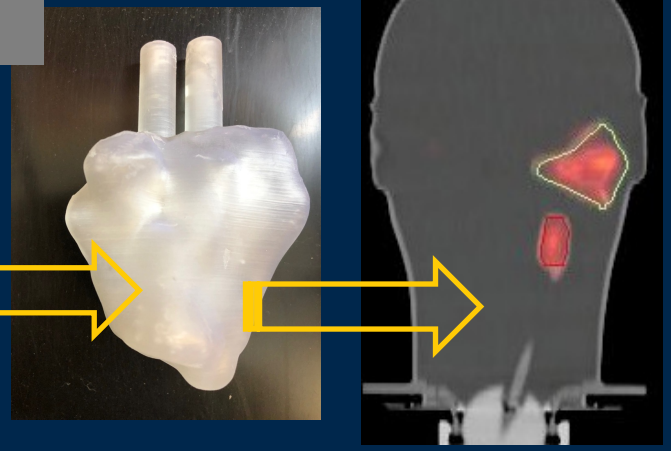


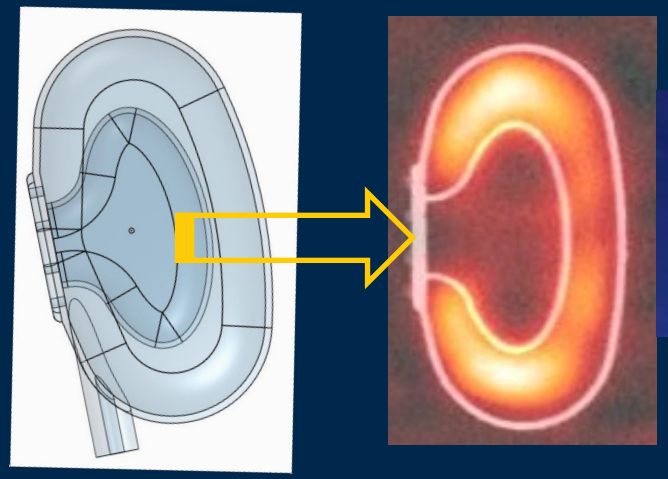


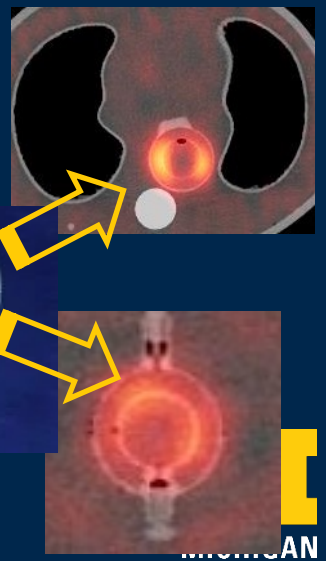




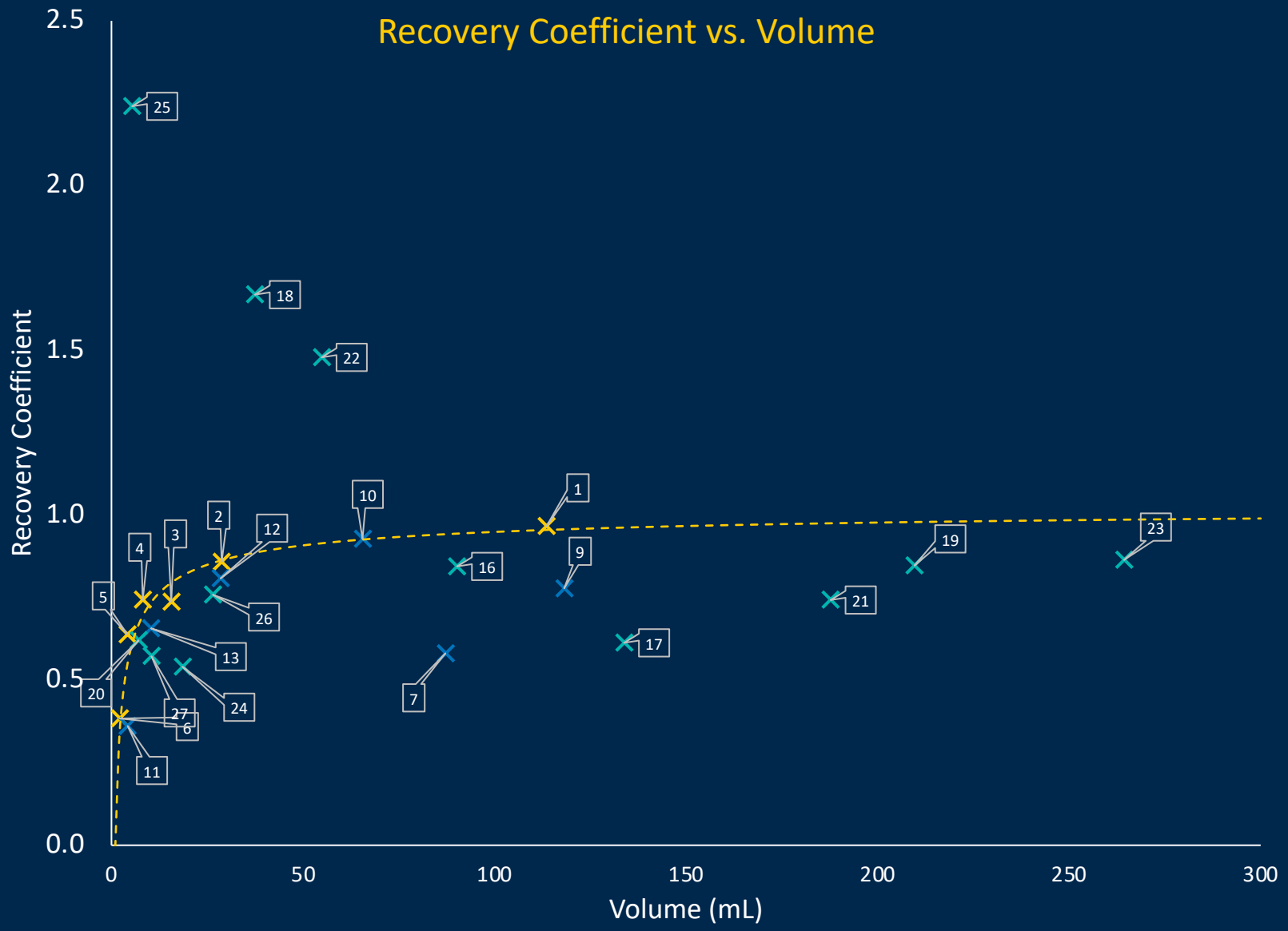








Impact of object shape and target-to-background on recovery



		Volume (mL)	RC
1	Sphere	114	1.0
2	Sphere	29	0.9
3	Sphere	16	0.7
4	Sphere	8	0.7
5	Sphere	4	0.6
6	Sphere	2	0.4
7	Large Shell- Outer	87	0.6
8	Large Shell - Inner	27	
9	Large Shell - Total	118	0.8
10	Large Sphere - Liver	66	0.9
11	Small Sphere - Liver	4	0.4
12	Large Ellipsoid - Liver	28	0.8
13	Small Ellipsoid - Bkg	10	0.7
14	Liver	1155	1.0
15	Healthy Liver	1057	1.0
16	Sphere	90	0.8
17	3D Kidney - Cortex	134	0.6
18	3D Kidney - Medulla	37	1.7
19	3D Kidney - Total	210	0.8
20	Ovoid	7	0.6
21	Geom Kidney - Cortex	188	0.7
22	Geom Kidney - Medulla	55	1.5
23	Geom Kidney - Total	264	0.9
24	Small Shell - Outer	19	0.5
25	Small Shell - Inner	5	2.2
26	Small Shell - Total	26	0.8
27	Submandibular	10	0.6

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Bone Marrow (BM) Dosimetry in ^{177}Lu-PSMA RLT

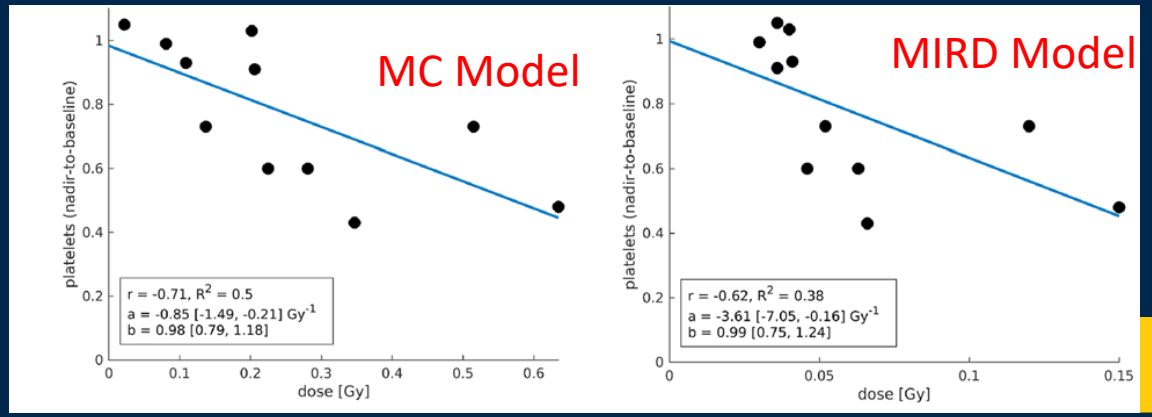
- BM should be considered an OAR
  - Important when heavily pre-treated and have intensive disease involvement in the BM
- Dosimetry complex due to high bone lesion load
  - Activity near BM sites
  - Altered BM distribution
- Method based on S-values and blood meas. likely unreliable
- 3D imaging of BM regions coupled with Monte Carlo (MC)

3D Monte Carlo bone marrow dosimetry for Lu-177-PSMA therapy with guidance of non-invasive 3D localization of active bone marrow via Tc-99m-anti-granulocyte antibody SPECT/CT

Gosewisch *et al. EJNMMI Research* (2019) 9:76

Astrid Gosewisch[1], Harun Ilhan[1], Sebastian Tattenberg[1], Andrea Mairani[2], Katia Parodi[3], Julia Brosch[1], Lena Kaiser[1], Franz Josef Gildehaus[1], Andrei Todica[1], Sibylle Ziegler[1], Peter Bartenstein[1] and Guido Böning[1*]

- MC model including the displacement of BM from the lesion location
  - Higher correlation between BM absorbed dose and decrease in platelet count with this MC model.



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^{225}Ac-PSMA-617 Dosimetry

Targeted α-Therapy of Metastatic Castration-Resistant Prostate Cancer with ^{225}Ac-PSMA-617: Dosimetry Estimate and Empiric Dose Finding

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 58 • No. 10 • October 2017

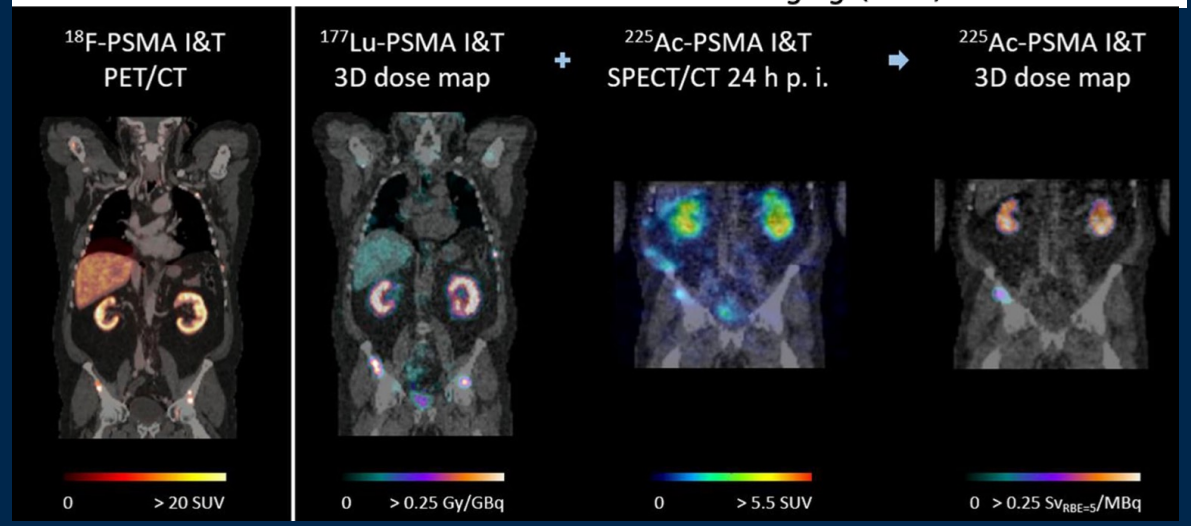
Clemens Kratochwil[1], Frank Bruchertseifer[2], Hendrik Rathke[1], Marcus Bronzel[3], Christos Apostolidis[2], Wilko Weicher
Uwe Haberkorn[1,5], Frederik L. Giesel[1], and Alfred Morgenstern[2]

- Direct imaging of ^{225}Ac challenging due to multiple low yield gamma-rays & low admin activity (4 -10 MBq)
- Dosimetry:
  - Time-activity approximated by serial ^{177}Lu-PSMA-617 scans extrapolated to physical half-life of ^{225}Ac assuming instantaneous decay of daughters
  - Rel. Biological Effect. (RBE) set to 5
  - Microdosimetry not performed
  - Salivary glands, kidney, BM: 2.3, 0.7, and 0.05 Sv_{RBE5}/MBq,

Image-based dosimetry for ^{225}Ac-PSMA-I&T therapy using quantitative SPECT

A. Gosewisch[1] · M. Schleske[1] · F. J. Gildehaus[1] · I. Berg[1] · L. Kaiser[1] · J. Brosch[1] · P. Bartenstein[1] · A. Todica[1]
H. Ilhan[1] · G. Böning[1]

Eur J Nucl Med Mol Imaging (2021) 48:1260–1261



- One patient, 8.1 MBq ^{225}Ac-PSMA-I&T
- Dosimetry: At 24 h direct imaging of ^{225}Ac using the 440 keV (26%) gamma-ray. 16 projections/head, 210 sec/proj
  - T_{eff} from prior ^{177}Lu-PSMA-I&T
  - Kidneys: 0.17 to 0.18 Sv_{RBE5}/MBq

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Studies Reporting Dosimetry and Dose – Response

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PSMA-RLT: Reported dosimetry

					Cycle 1 mean AD(Gy/GBq ± STD)			
	Ligand	GBq/cycle	N		Kidney	Parotid glands	Tumor	other
Scarpa, 2017	^{177}Lu-PSMA-617	6.1 (5.4-6.5) 2-3 cycles	10	WB planar (0.5,4,24,72,96h)+OLINDA	0.60±0.36	0.56±0.25	Bone: 3.4 ± 1.9 Node: 2.6 ± 0.4	BM:0.04± 0.03 Lacrimal:1.00±0.69 Spleen: 0.12±0.09
Violet, 2019	^{177}Lu-PSMA-617	7.8 (5.7-8.7)	30	SPECT(4,24,96, multi-exp)+DVK or OLINDA	0.39 ±0.15	0.58 ±0.43	Max for Bone: 5.3 (0.4-10.7) Node:3.9(0.5-16.2) 'WB tumor':12.6±4.2	Lacrimal:0.36±0.18 (voxel) 3.8±2.1 (sphere model) BM (image-based): 0.11 (0.10)
Peters, 2021	^{177}Lu-PSMA-617	9.0 (8.0-9.2) 2 Cycles	10 mHSPC	SPECT(1,24,48,72,168h, multi-exp)+ OLINDA	0.57 ± 0.16	0.46 ± 0.19	Bone: 1.5 (0.4-3.7) Node: 1.8 (0.5-10.3) (lesions < 1 mL)	Liver: 0.10±0.02 BM(blood based):0.0176±0.003
Kurth, 2021	^{177}Lu-PSMA-617	6.01±0.37 2 - 6 cycles	46	SPECT(2,24,48,72h, bi-exp)+OLINDA	0.49 ± 0.22	0.79 ±0.37		
Baum, 2016*	^{177}Lu-PSMA I&T		30	WB planar (5 TPs between 0.5 – 118h, multi-exp)+OLINDA	0.80 ±0.4	1.3 ±2.3 * *Average from all cycles*	Bone: 3.0 ± 10 Node: 4.0 ± 20	WB: 0.02 ±0.01 BM(blood based):0.01-0.04
Okamoto, 2017	^{177}Lu-PSMA I&T	7.3(6.5 -7.8) 4 cycles	18	WB planar (0.5-2, 24, 144-192h)+OLINDA	0.71 ± 0.25	0.56 ± 0.17	Bone: 3.8 ± 3.1 Node: 2.6 ± 0.89	Lacrimal:3.8 ± 1.5 Liver: 0.12 ± 0.07
Feuerecker, 2022	^{177}Lu-PSMA I&T	Pretherapy w/ ~ 1 GBq	6	WB planar (1,4, 24, 48,168h)+OLINDA	0.69		Bone: 1.7 ± 1.1 Node: 4.5 ± 2.7	BM(image-based):0.30 ±0.27
Feuerecker, 2022	^{177}Lu-rhPSMA-7.3	Pretherapy w/ ~ 1 GBq	6	WB planar (1,4, 24, 48,168h)+OLINDA	1.62		Bone: 4.1 ± 2.6 Node: 11.1 ± 8.8	BM(image-based):0.67± 0.62
Rathke, 2019	^{90}Y-PSMA-617	3.2 (2.8-3.7)	11	Extrapolated from ^{177}Lu-PSMA-617 imaging + OLINDA	3.5 ± 1.4	5.6 ± 1.3	22.8 (4.8-72)	BM (blood-based): 0.11± 0.04
Kratochwil, 2017	^{225}Ac-PSMA-617	3 – 19 MBq Up to 4 cycles	14	Extrapolated from ^{177}Lu-PSMA-617 imaging	2.33 Sv_{RBE5}/MBq	0.74 Sv_{RBE5}/MBq		BM0.05 Sv_{RBE5}/MBq

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Summary of Reported Dosimetry for ^{177}Lu-PSMA-617

- Data fairly consistent except for lacrimal glands
- Tumor: 1 – 15 Gy/GBq, typically 10 - 40 Gy from each cycle
  - Cumulative dose typically exceeds prescription in EBRT
- Renal : 0.4 to 1 Gy/GBq, typically 0.5 Gy/GBq
  - Threshold from EBRT 23 Gy. Can deliver ~ 50 GBq
- Salivary glands: 0.6 – 1.4 Gy/GBq
  - Threshold from EBRT for long term xerostemia: 25 Gy.
- Lacrimal glands: 0.4 – 2.8 Gy/GBq.
  - Variable due to partial volume effects. Lower values reported for voxel dosimetry
- Bone Marrow: 0.01 – 0.1 Gy/GBq
  - Variable due to complexity of calculation. Generally used threshold for RLT is 2 Gy
- Toxicity thresholds expected to be higher for RLT compared to EBRT due to low dose-rate, delayed fractionation, non-uniform dose deposition

Jackson P, Hofman M, McIntosh L, Buteau JP, Ravi Kumar A. Radiation Dosimetry in ^{177}Lu-PSMA-617 Therapy. Semin Nucl Med. 2022;52(2):243-254

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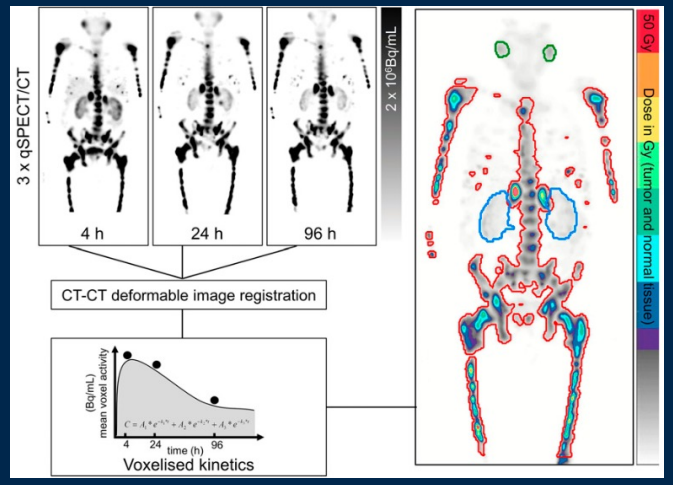
^{177}Lu PSMA RLT: Dose - response

Dosimetry of ^{177}Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes J Nucl Med 2019; 60:517–523

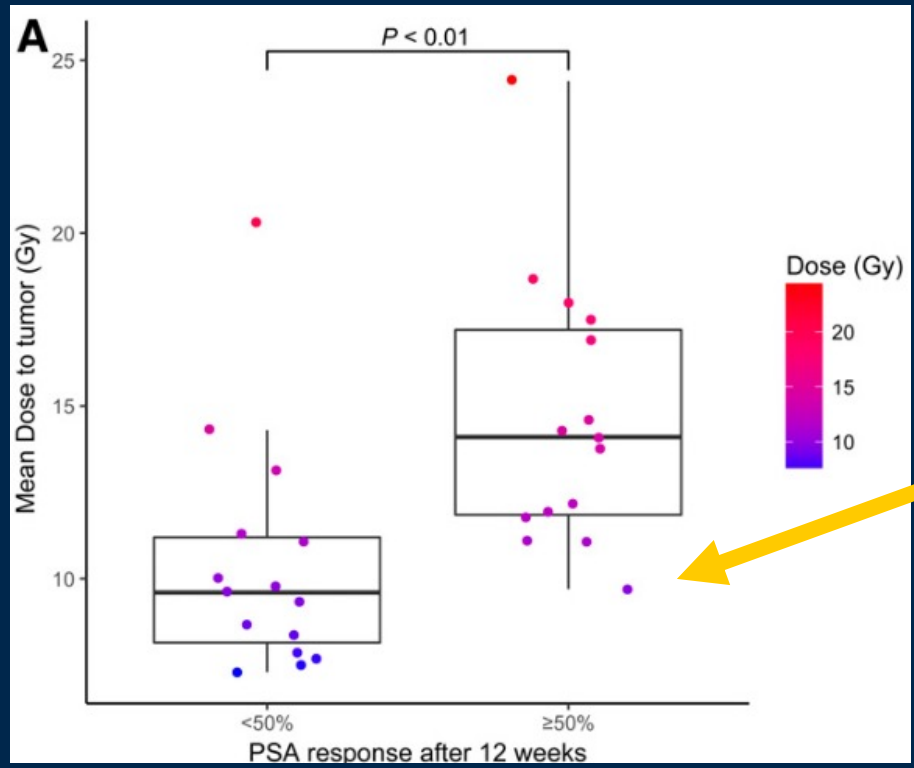
John Violet[1], Price Jackson[1,2], Justin Ferdinandus[2], Shahneen Sandhu[3], Tim Akhurst[2], Amir Iravani[2], Grace Kong[2], Aravind Ravi Kumar[2], Sue Ping Thang[2], Peter Eu[2], Mark Scalzo[2], Declan Murphy[4,5], Scott Williams[1,5], Rodney J. Hicks[2,5], and Michael S. Hofman[2,5]

- 30 patients



- Lesion Dosimetry (after Cycle 1):
  - 2 bed position serial ^{177}Lu SPECT/CT
  - Voxel-level multi-exp fits
  - Dose map using GATE-derived DVK
  - Whole Body (WB) tumor volume by applying a 5 Gy threshold to dose map and removing physiological uptake

- Significant correlation between WB tumor absorbed dose & PSA response



Only 1 responder with < 10 Gy in cycle1

- Median of 14.1 Gy in patients achieving a PSA decline >= 50%, vs. 9.6 Gy for those achieving a PSA decline < 50% (P < 0.01)

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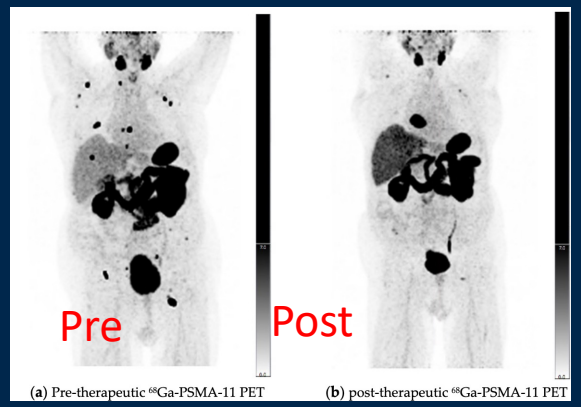
^{177}Lu PSMA RLT: Dose-response

Correlation of an Index-Lesion-Based SPECT Dosimetry Method with Mean Tumor Dose and Clinical Outcome after ^{177}Lu-PSMA-617 Radioligand Therapy *Diagnostics* **2021**, *11*, 428

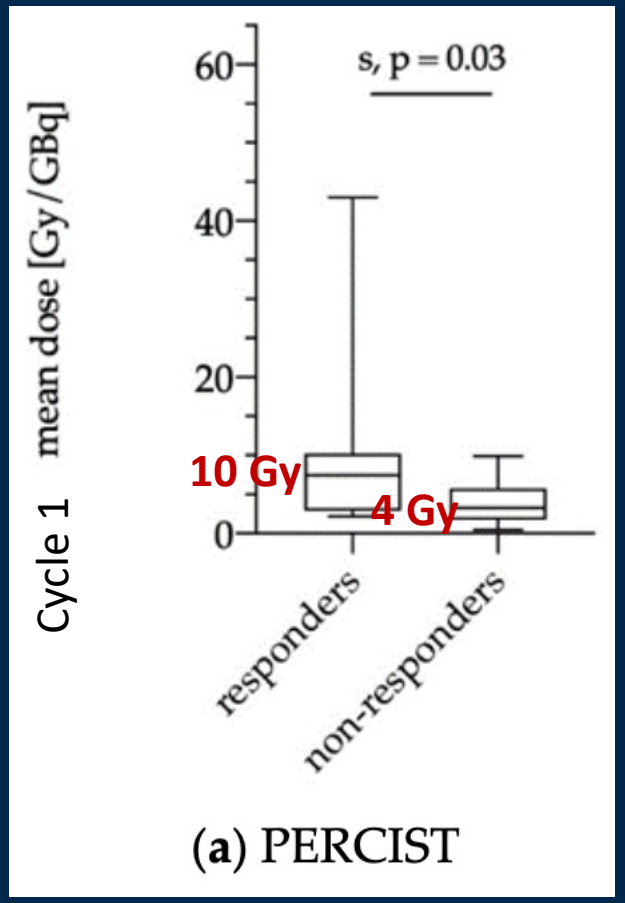
Friederike Völter [1], Lena Mittlmeier [1], Astrid Gosewisch [1], Julia Brosch-Lenz [1], Franz Josef Gildehaus [1], Mathias Johannes Zacherl [1], Leonie Beyer [1], Christian G. Stief [2], Adrien Holzgreve [1], Johannes Rübenthaler [3], Clemens C. Cyran [3], Guido Böning [1], Peter Bartenstein [1], Andrei Todica [1] and Harun Ilhan [1,*]

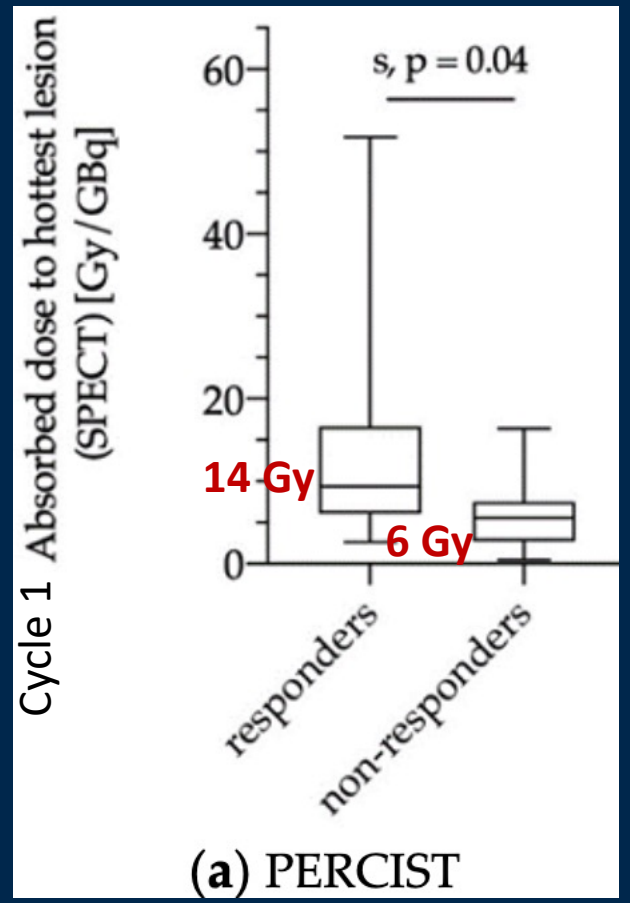
- 30 patients, 2 x 6 GBq/cycle
- Tumor Dosimetry: multi- SPECT/CT, threshold-based segmentation, mono-exp, sphere S-values
- Response from PERCIST, RECIST, PSA, PSMA-positive tumor volume

^{68} Ga-PSMA-11 Images for PERCIST



- Tumor absorbed doses correlated with ^{68} Ga-PSMA-11 PET PERCIST response but not with other response criteria





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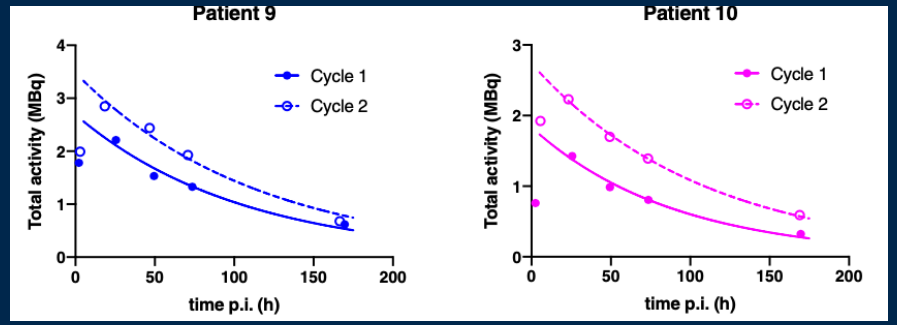
^{177}Lu PSMA RLT : Dose - response

Intra-therapeutic dosimetry of [^{177}Lu]Lu-PSMA-617 in low-volume hormone-sensitive metastatic prostate cancer patients and correlation with treatment outcome

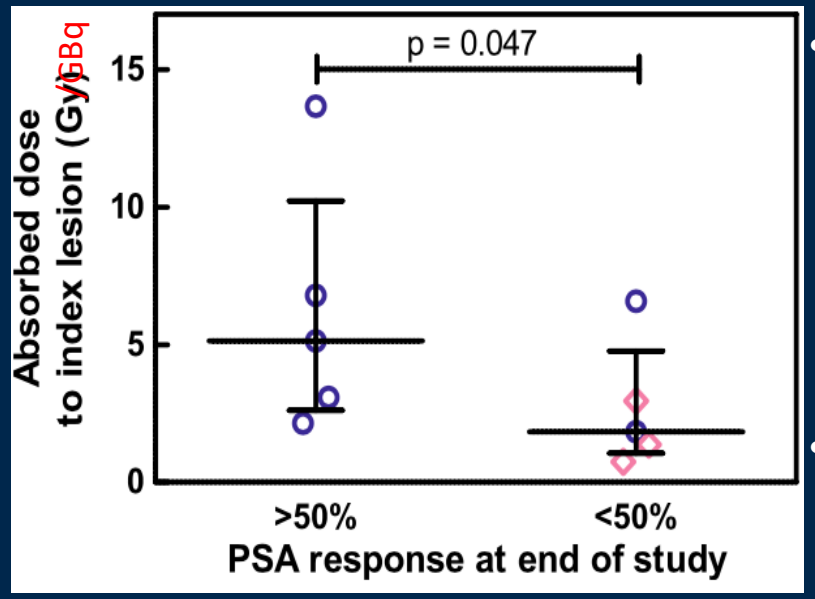
European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-021-05471-4

Steffie M. B. Peters[1] · Bastiaan M. Privé[1] · Maarten de Bakker[1] · Frank de Lange[1] · Walter Jentzen[2] · Annemarie Eek[1] · Constantijn H. J. Muselaers[3] · Niven Mehra[4] · J. Alfred Witjes[3] · Martin Gotthardt[1] · James Nagarajah[1] · Mark W. Konijnenberg[1,5]

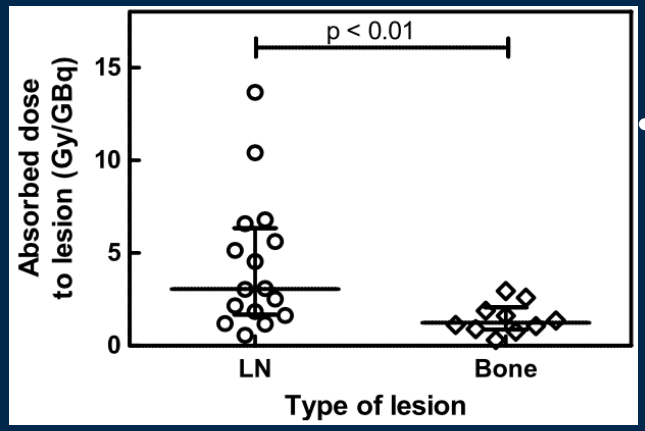
- 10 mHSPC cases, 2 Cycles (3+6 GBq)
- Lesions < 1 cm diameter. Oversized VOI (defined on ^{68}Ga PET/CT) to account for partial volume effects
- Lesion Dosimetry: serial ^{177}Lu SPECT/CT, mono-exp fit, sphere model S-values



- Response (PSA drop of <50% vs. > 50%) correlated with AD to index lesion



- Single index lesion dosimetry. Potential to simplify protocol for low volume disease?
- May not hold for high volume disease due to heterogeneity?
- Lesion AD higher in lymph node compared with bone lesions



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