The value of single time point imaging to make RPT dosimetry practical for the clinic

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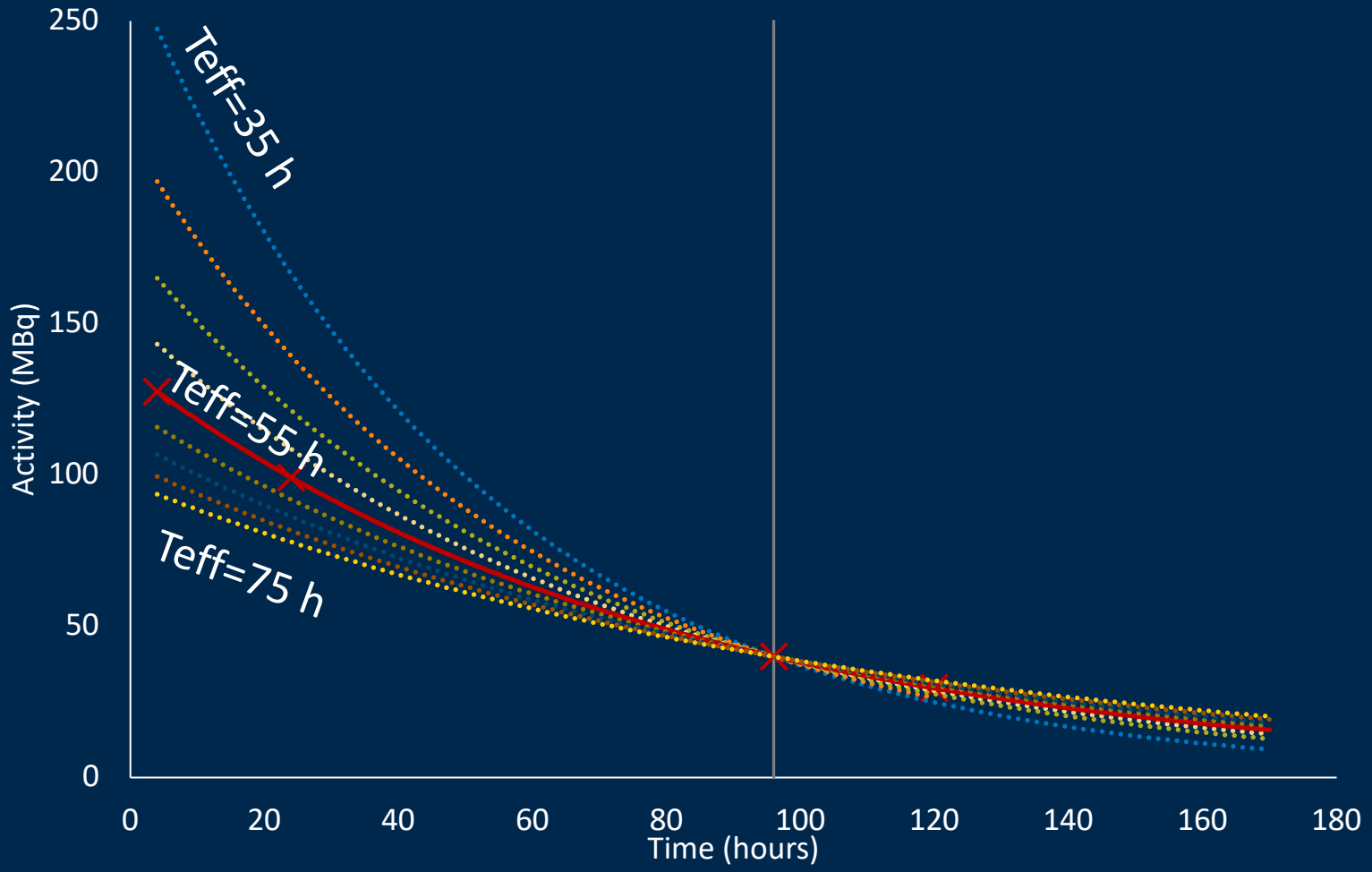
Single Time Point Methods to determine time integrated activity (TIA):

Why it Works? Even wide variations in effective half-life gives similar TIA

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



Teff (h)	Diff in TIA
35	-27%
40	-15%
45	-7%
50	-3%
55	0%
60	1%
65	2%
70	2%
75	1%

Madsen, Med Phys 2018; Hanscheid et al, JNM 2018

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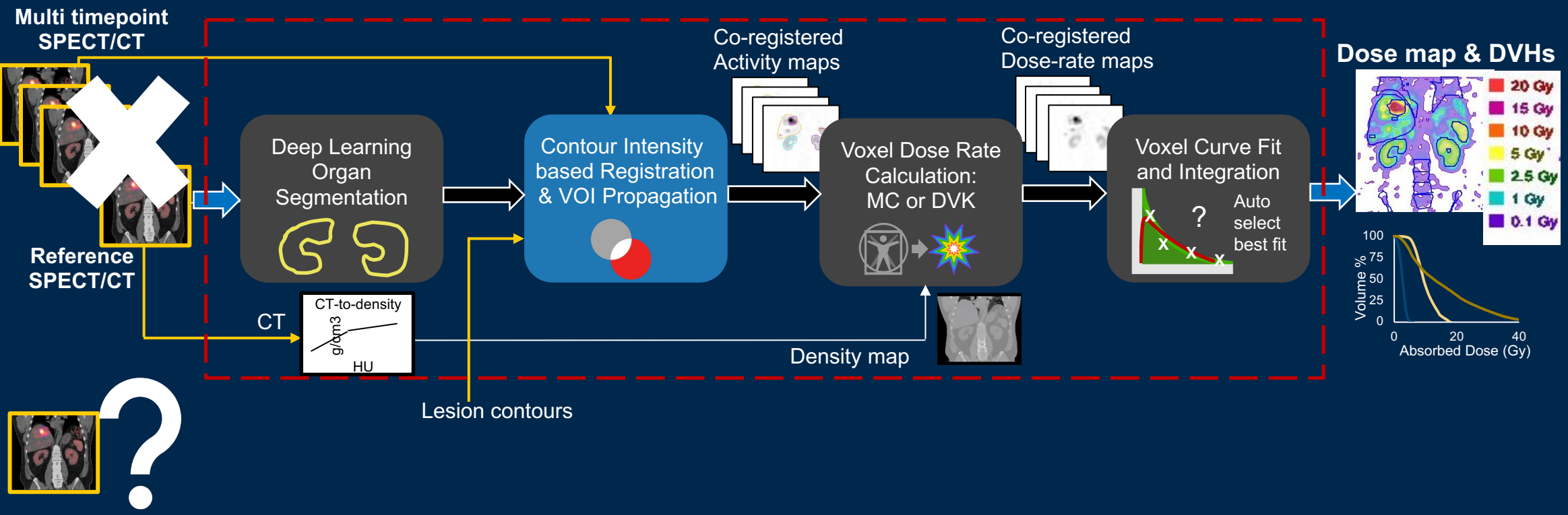
Evaluation of STP imaging in 177Lu-DOTATATE: using Michigan multi-timepoint data



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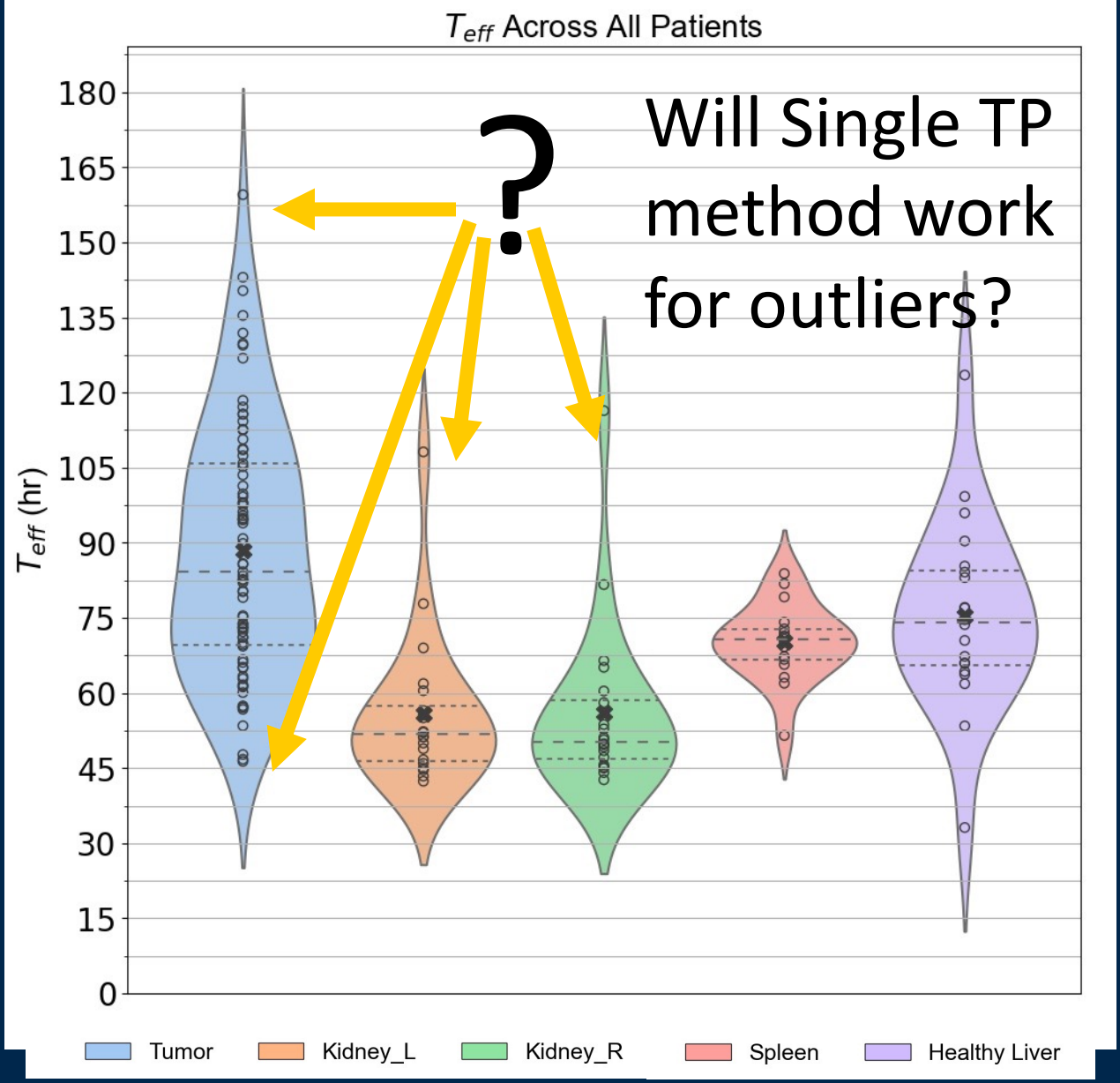
Variation in Teff across patients: Univ Mich Data



Teff (h)	Tumor	L Kidney	R Kidney	Spleen	Normal Liver
Median	85.4	52.3	50.7	71.4	74.9
Min	47.9	41.6	40.7	51.2	32.2
Max	159.5	107.0	112.3	84.4	124.7
STD	26.5	15.1	16.3	7.8	19.1

Kidney median (range): Sundlov et al 51.6 h(38-69); Hanscheid et al , 51 h (40-106)

Will the same single time point work for lesions and organs?

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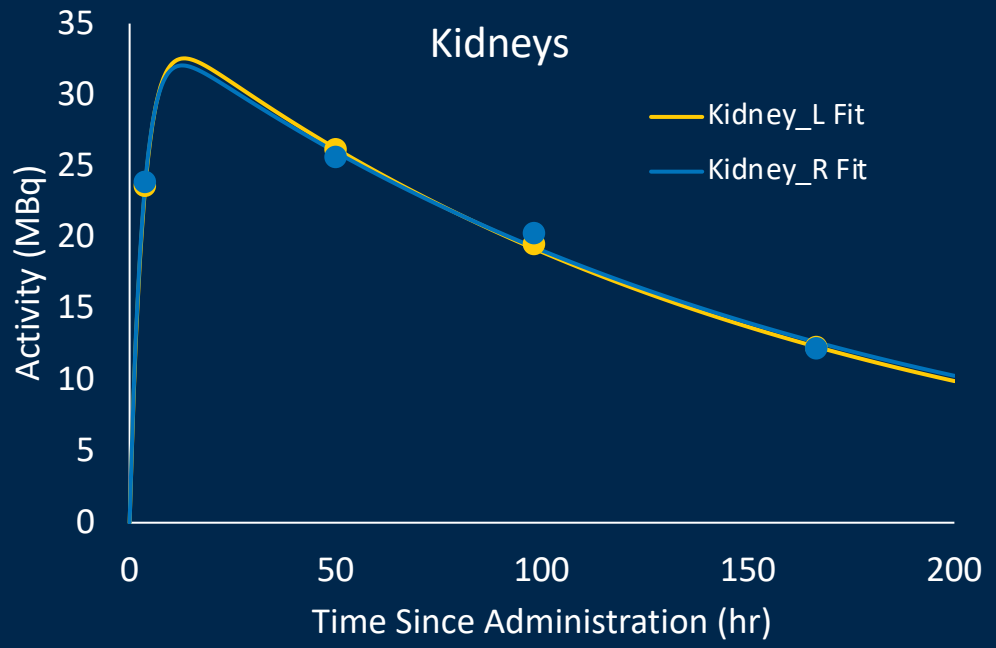
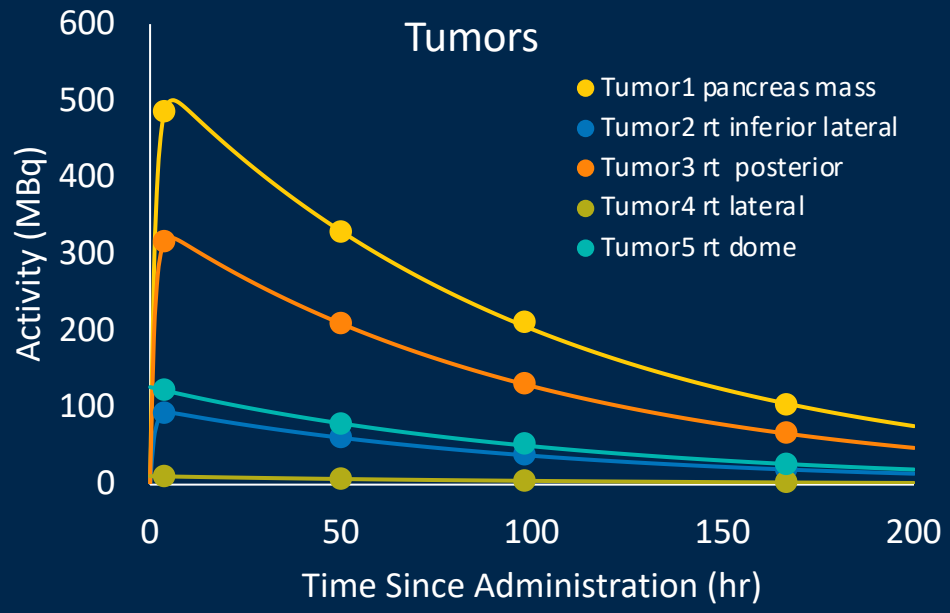
Single TP Results Patient example 1: Slow kidney clearance





	Teff (h)	Diff in AUC between Single & Multi TP	
		Single TP= 50h	Single TP= 98 h
L Kidney	107	31%	-1%
R Kidney	112	34%	-2%

	Teff (h)	Diff in AUC between Single & Multi TP	
		Single TP= 50h	Single TP= 98 h
Tumor 1	71	13%	-10%
Tumor 2	71	13%	-9%
Tumor 3	70	12%	-8%
Tumor 4	84	21%	-3%
Tumor 5	74	17%	-10%

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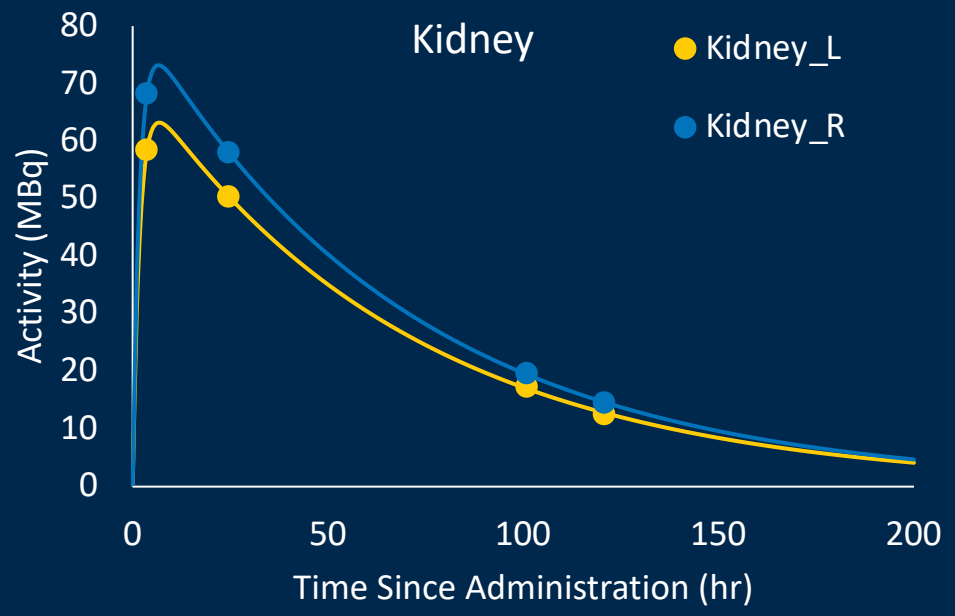
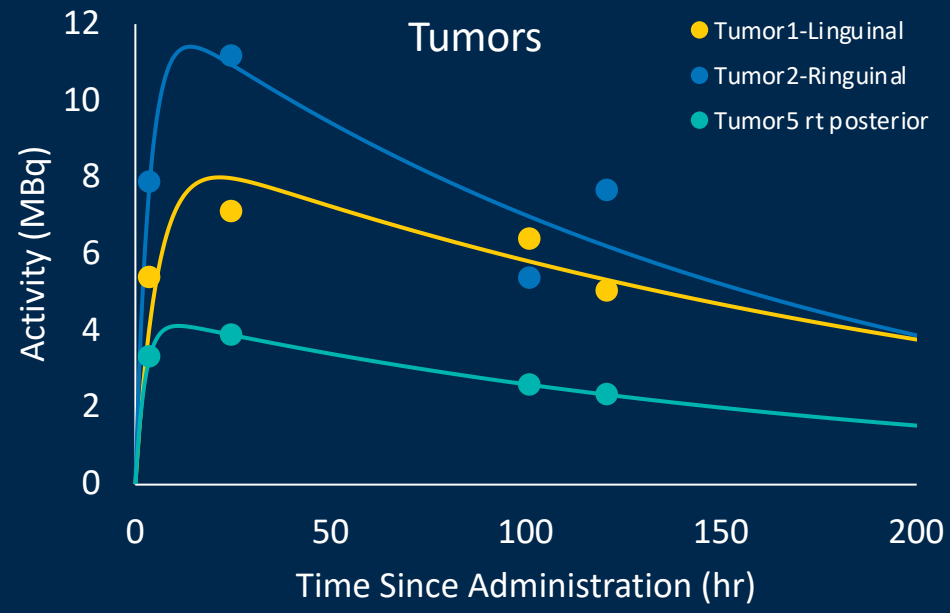
Single TP results, example 2: Tumor-slow clearance & noisy





	Teff (h)	Diff in AUC between Single & Multi TP	
		Single TP= 100h	Single TP= 120 h
L Kidney	49	-3%	-11%
R Kidney	48	-2%	10%

	Teff (h)	Diff in AUC between Single & Multi TP	
		Single TP= 100h	Single TP= 120h
Tumor 1	160	8%	13%
Tumor 2	117	26%	-27%
Tumor 3	118	-1%	2%
Tumor 4	160	18%	6%
Tumor 5	131	9%	1%

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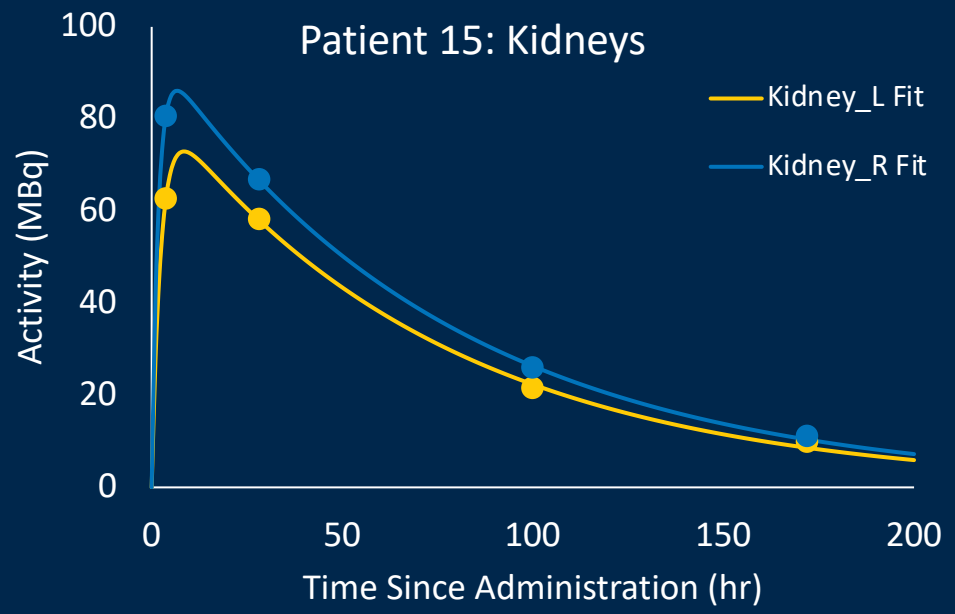
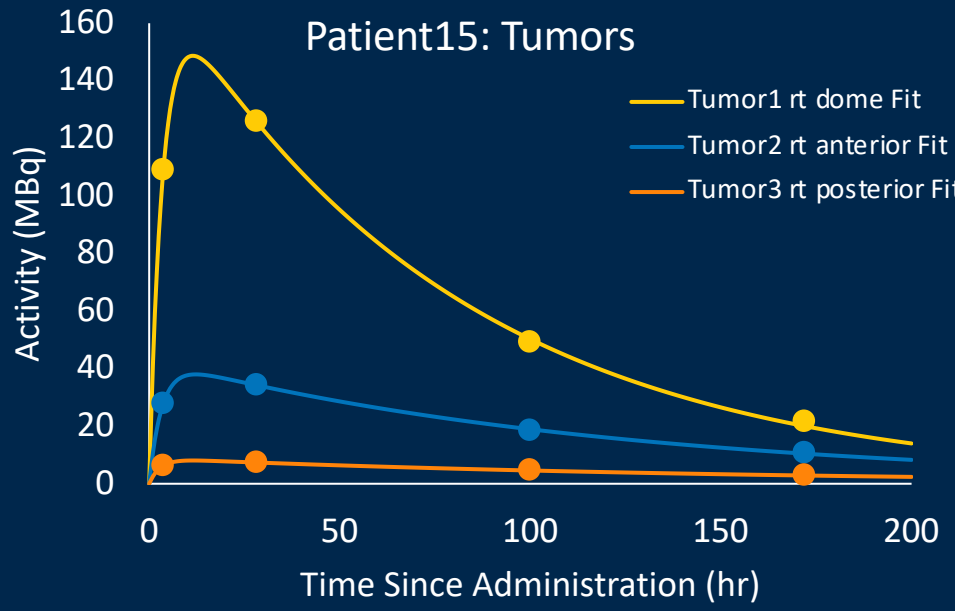
Single TP Results, patient example 3: wide range of tumor Teff





	Teff (h)	Diff in AUC between Single & Multi TP	
		Single TP= 100h	Single TP= 171 h
L Kidney	52	-1%	21%
R Kidney	54	-3%	25%

	Teff (h)	Diff in AUC between Single & Multi TP	
		Single TP= 100h	Single TP= 171h
Tumor 1	54	-5%	21%
Tumor 2	84	-5%	-5%
Tumor 3	106	-1%	-6%

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Prior Information Method: How much does pharmacokinetics change between cycles?

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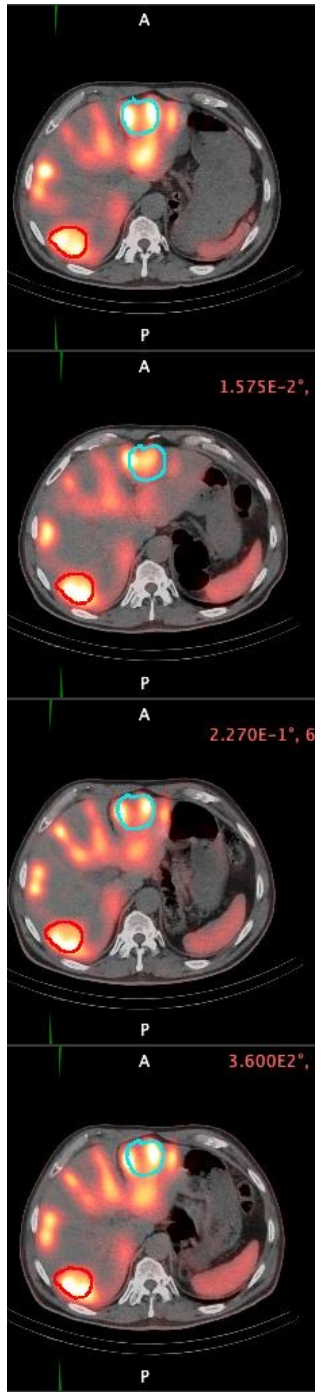
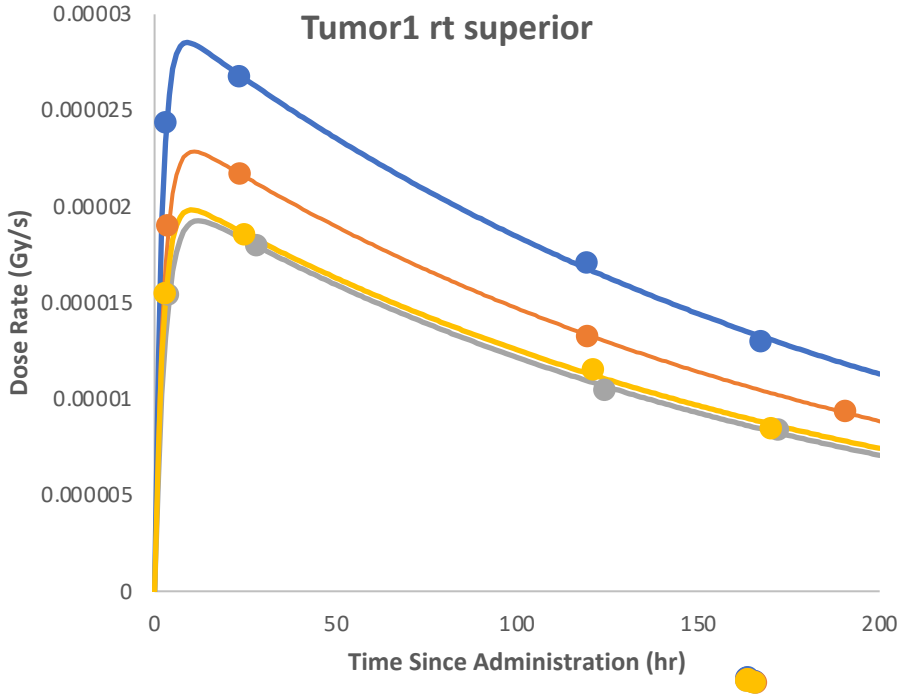
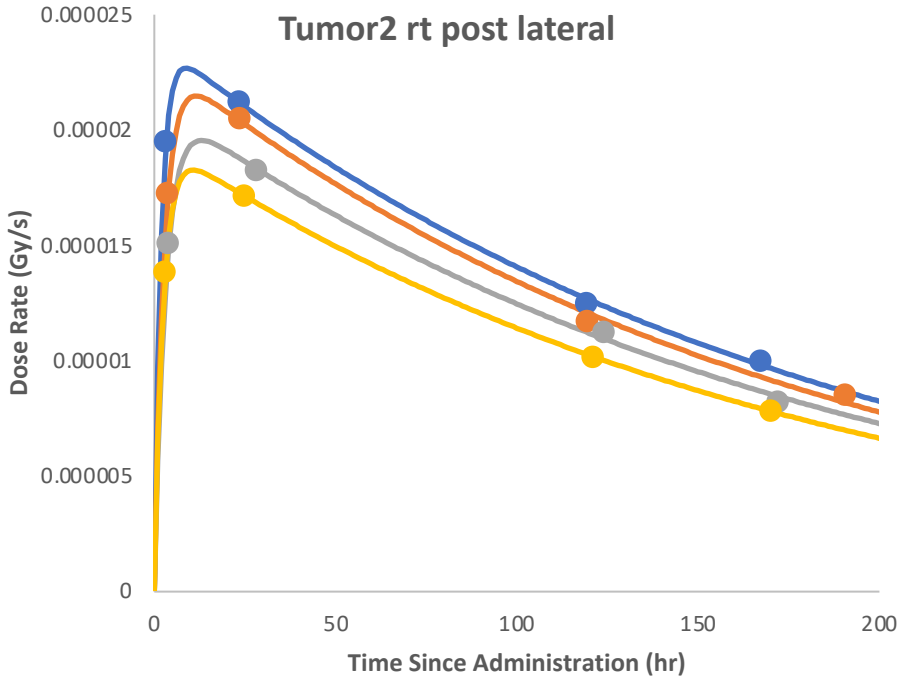
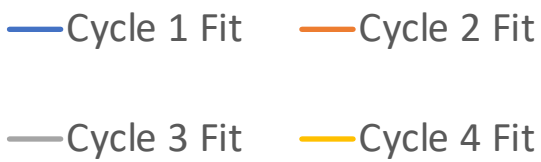
Example 4-Cycle Time-Activity Curves: Typical Tumors



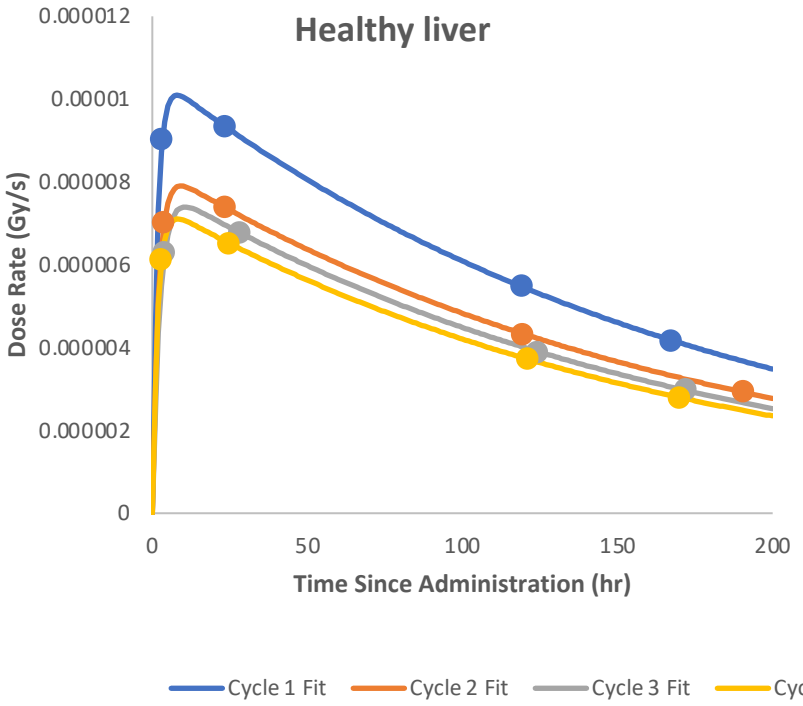


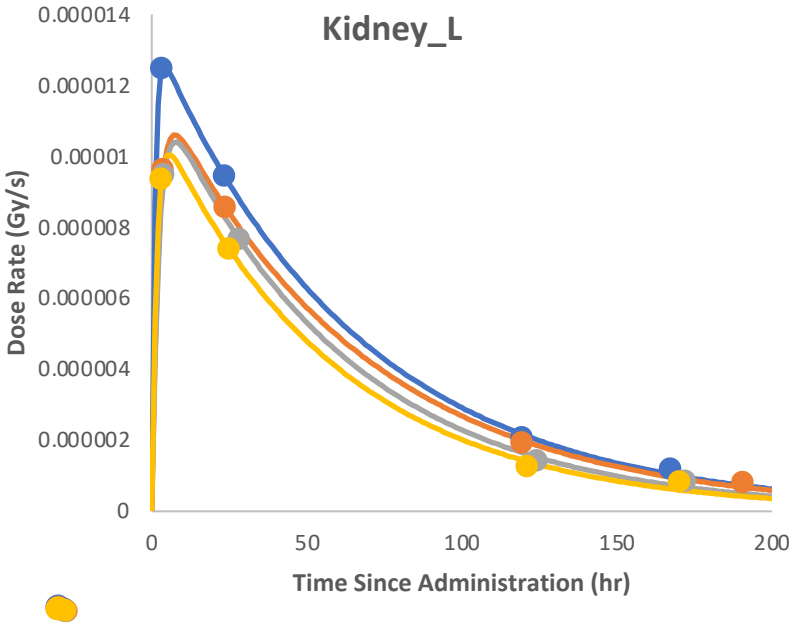


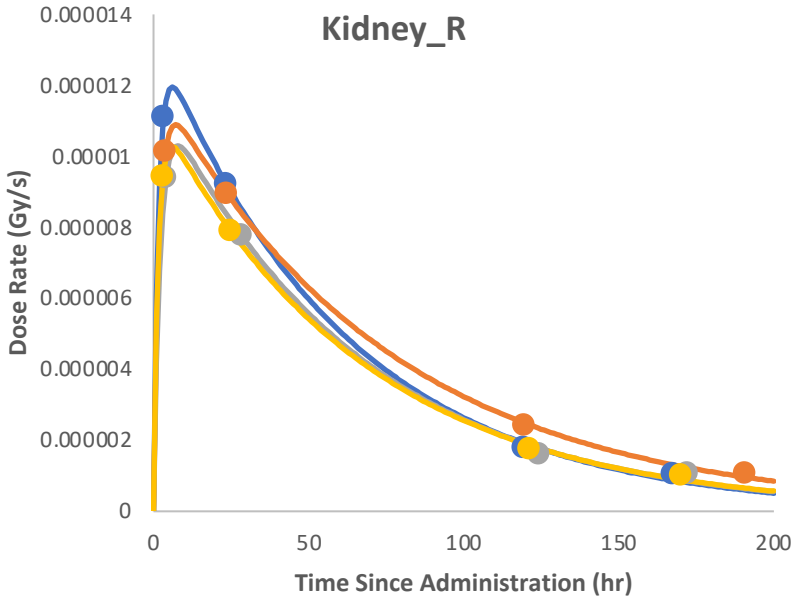


	Effective Half-life (hr)			
	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Tumor1	141	136	128	132
Tumor2	130	127	129	128
Tumor3	146	130	137	131
Tumor4	136	125	135	124
Tumor5	129	134	134	130

Example 4-Cycle Time-Activity Curves: Typical Kidney





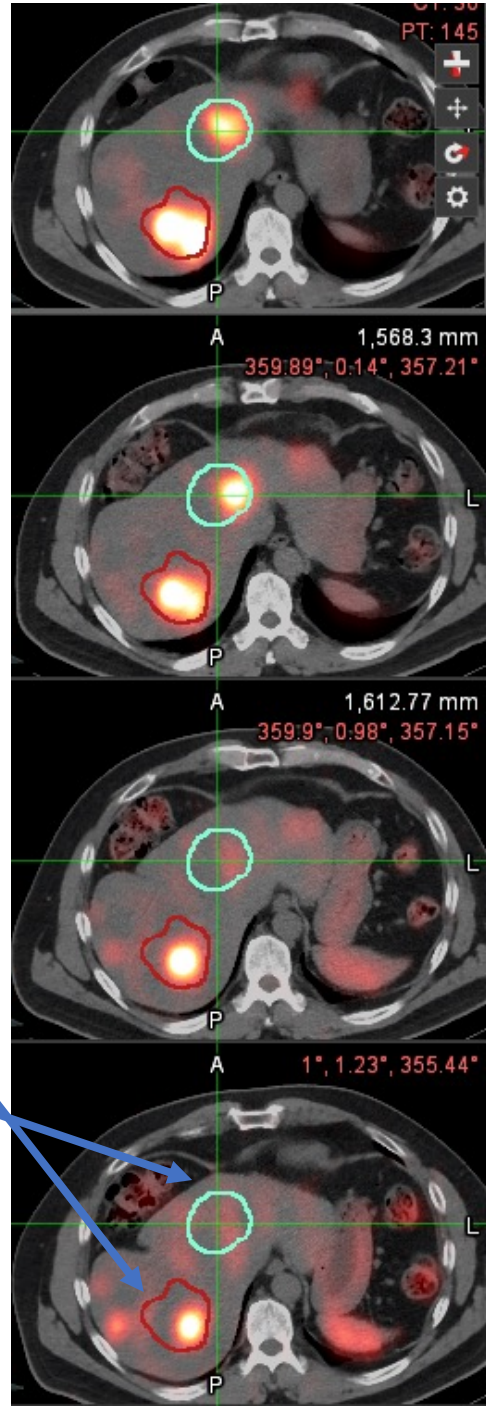


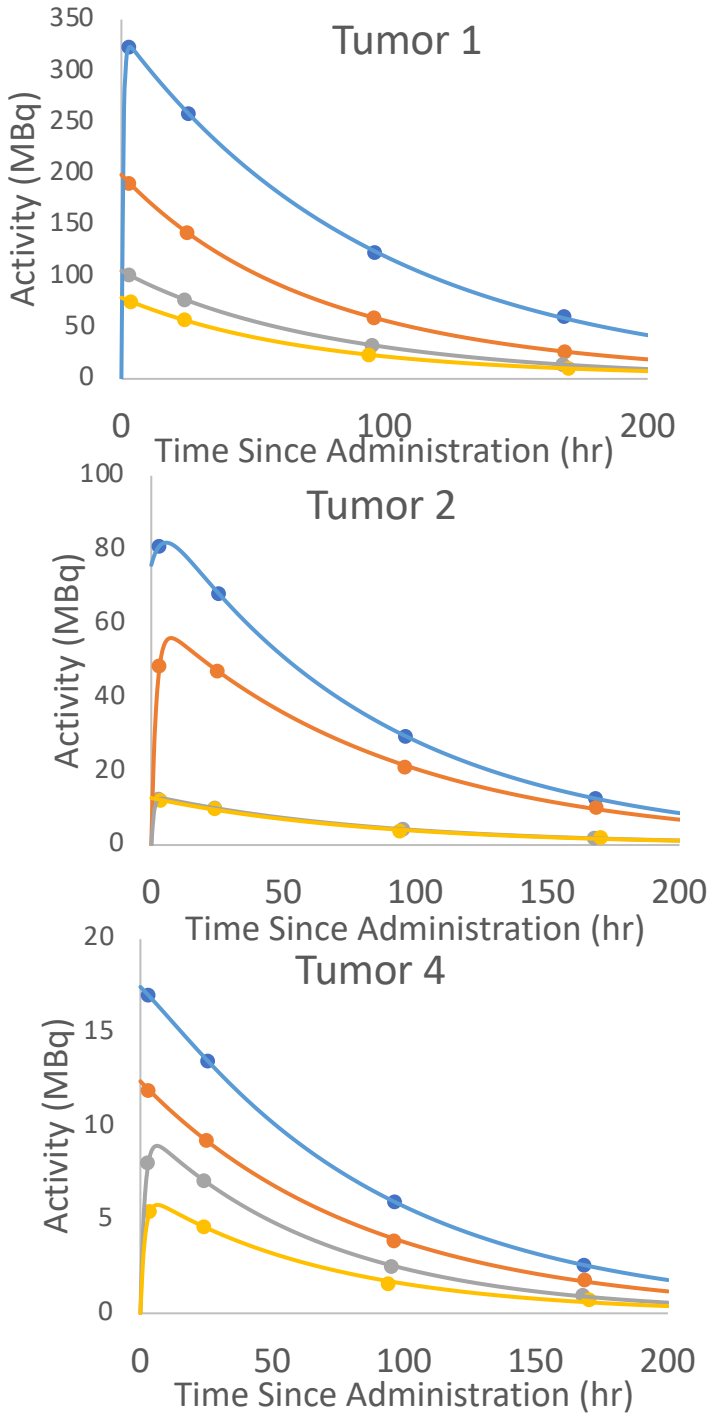
	Effective Half-life (hr)			
Structure	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Healthy liver	124	125	121	119
spleen	71	68	65	70
Kidney_L	45	46	41	40
Kidney_R	42	52	45	46

4 Cycle Results: Example case with lesion shrinkage during 4 cycles (rare)

Tumor 1: significant shrinkage during treatment

Tumor 2: Nearly disappeared during treatment





	Effective Half-life (hr)			
	Cycle 1	Cycle 2	Cycle 3	Cycle 4
Tumor1	67	71	59	160
Tumor2	59	63	58	58
Tumor3	57	61	53	54
Tumor4	59	59	48	49
Tumor5	72	62	53	54

^{177}Lu DOTATATE: performance of single TP method for tumor/organs at different imaging TPs

SINGLE TP (Hanscheid approach)

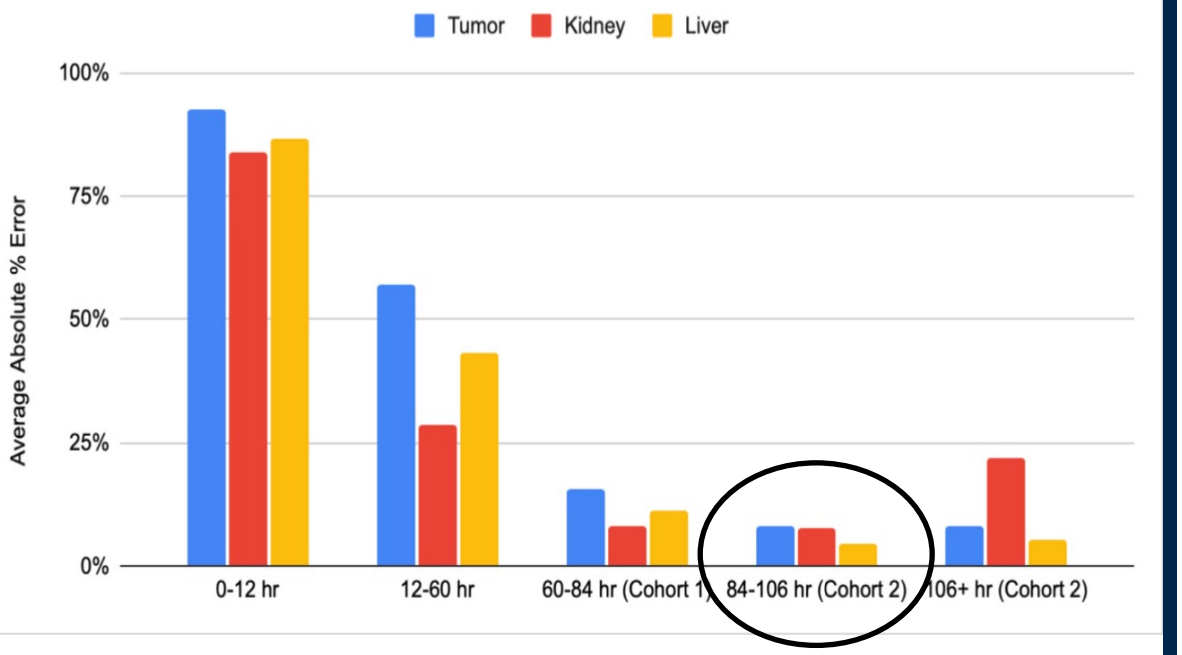


FIGURE 5. Average absolute percent error in single-timepoint dosimetry with Hänscheid approach. Results are shown for kidney, liver, and tumor ROIs in bins for the acquisition time post-injection. Early timepoints from Day 0 or Day 1 include results from both patient cohorts.

OPTIMAL: ~ 60 - 106 h for kidney, longer for tumor (due to prolonged retention) but 96 h good compromise across all tissue

4 TPs in cycle 1+ SINGLE TP at others

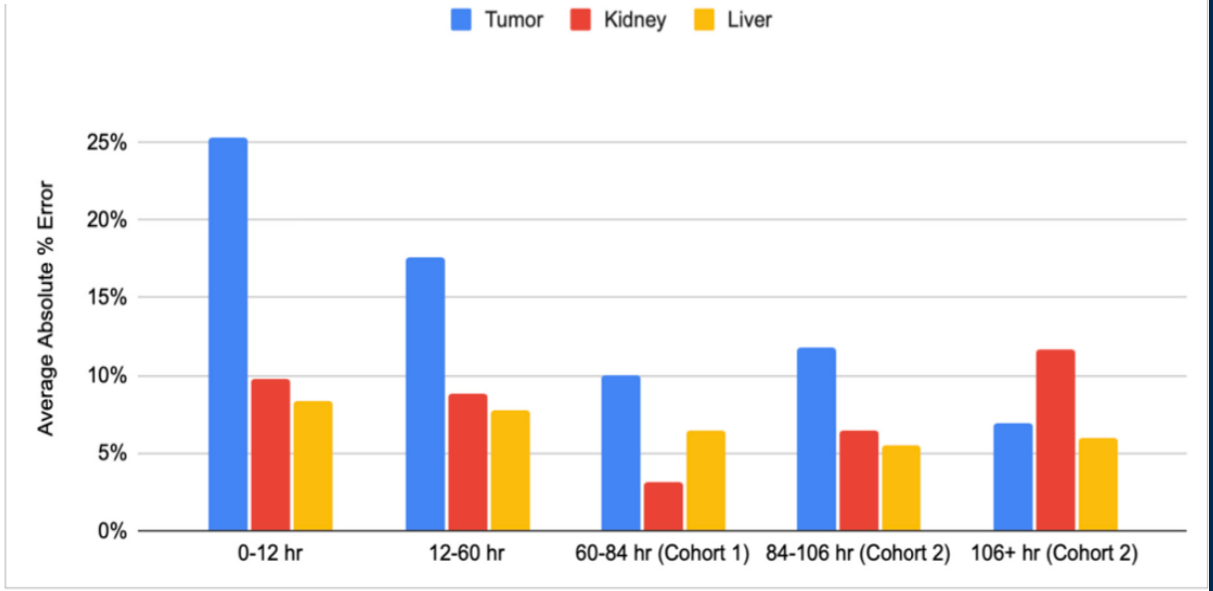
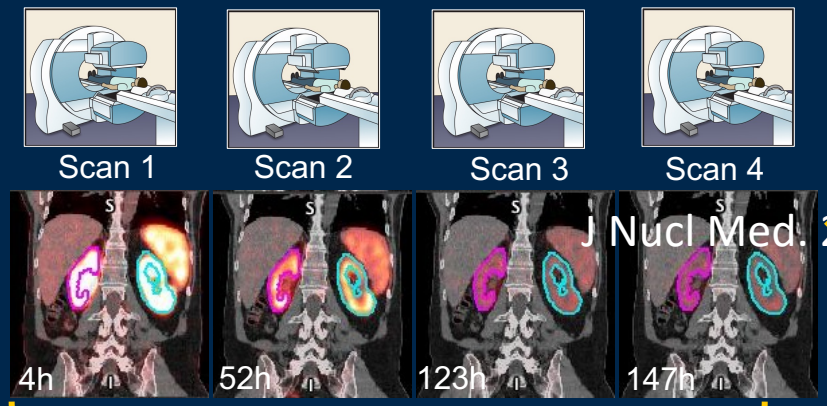
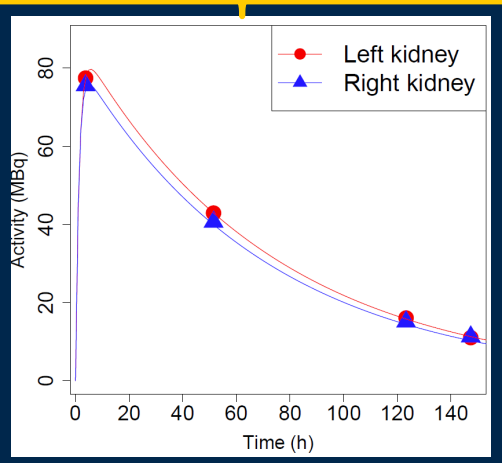


FIGURE 7. Average absolute percent error in single-timepoint dosimetry with the prior-information approach. Results are shown for kidney, liver, and tumor ROIs in bins for the acquisition time post-injection. Early timepoints from Day 0 or Day 1 include results from both patient cohorts.

Reasonable at any TP > 12h, optimal 60 -106 h

Other STP models: Time-activity information sharing using nonlinear mixed effects models (NLME) in ^{177}Lu DOTATATE PRRT





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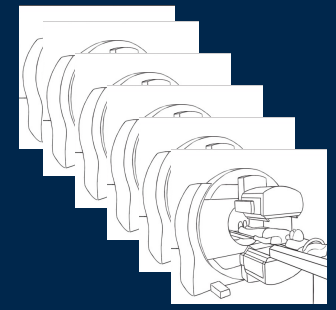
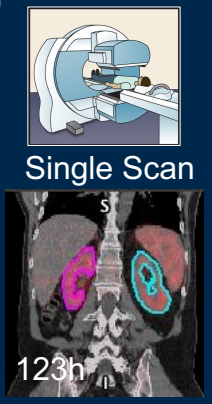
New patient

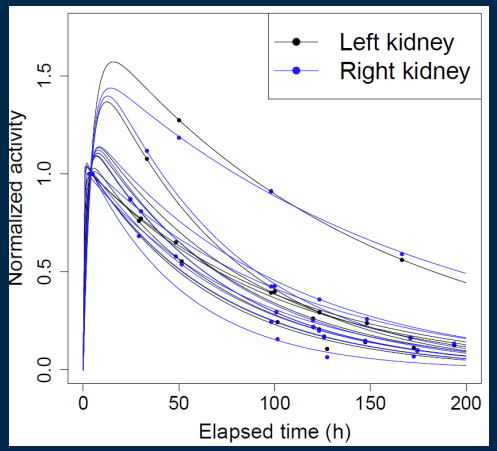
?

NLME model: Fitting bi-exponential parameters by simultaneously fitting this new patient's single measurement with all data points of all other patients in prior cohort





+ Historic multi-TP data



Devasia T, Dewaraja YK, Frey KA et al. J Nucl Med. 2021 Aug 1;62(8):1118-1125

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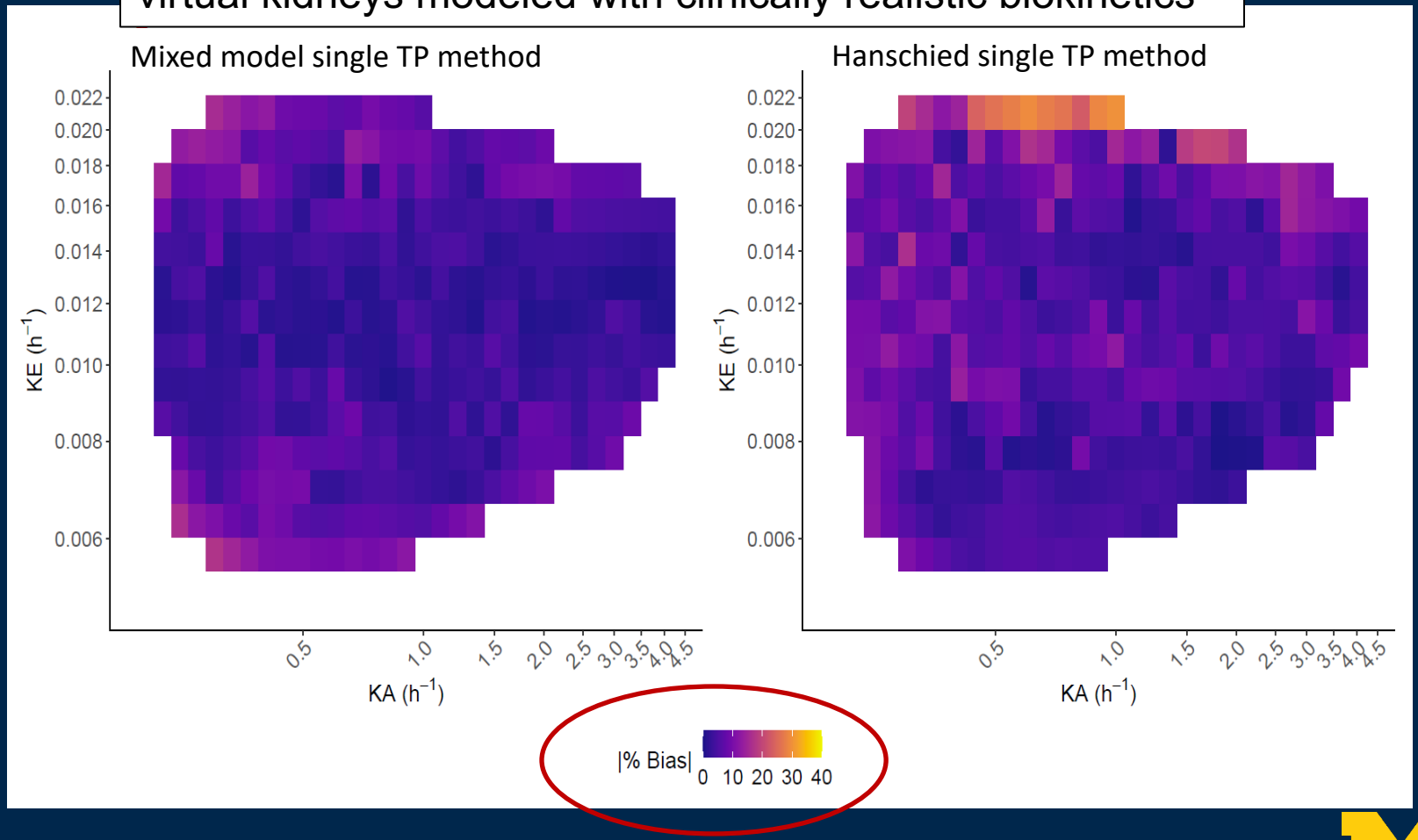
Time-activity information sharing using nonlinear mixed models: study demonstrated potential to reduce outliers

- Clinical data: The STP mixed models outperform the Madsen & Hanscheid methods for 94% (17/18), 72% (13/18) of kidneys
- Simulated data: Mixed model resulted in more than a two-fold reduction in the proportion of kidneys with |bias| > 10% (6% vs. 15%).
- The mixed models eliminated extreme outliers with 0/500 virtual and 0/18 clinical kidneys showing bias ≥ 25%
- Potential for subgroup models: separate models could be built based on baseline factors

Heat maps of |% bias| vs. biexponential parameters in 500 virtual kidneys modeled with clinically realistic biokinetics



Devasia T, Dewaraja YK, Frey KA et al. J Nucl Med. 2021 Aug 1;62(8):1118-1125

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Other STP models: Combining pharmacokinetic (PBPK) model and a nonlinear mixed effects approach

Single-time-point estimation of absorbed doses in PRRT using a non-linear mixed-effects model

Deni Hardiansyah [a], Ade Riana [a], Ambros J. Beer [b], Gerhard Glatting [b,c,*]

[a] Medical Physics and Biophysics, Physics Department, Faculty of Mathematics and Natural Sciences, Universitas Indonesia, Depok, Indonesia
[b] Department of Nuclear Medicine, Ulm University, Ulm, Germany
[c] Medical Radiation Physics, Department of Nuclear Medicine, Ulm University, Ulm, Germany

- 8 patients with either NETs or meningioma scheduled for 2 to 3 cycles of PRRT using 90Y-DOTATAT E
- Biokinetic data of 111In-DOTATATE using planar imaging at ~ 3, 5, 23, 47, 71 h post injection.
- Relative difference between TIAC from STP and 5 point fits: kidney: 5 [1, 21]% , tumor 2 [15, 21]% . Optimal STP is T4

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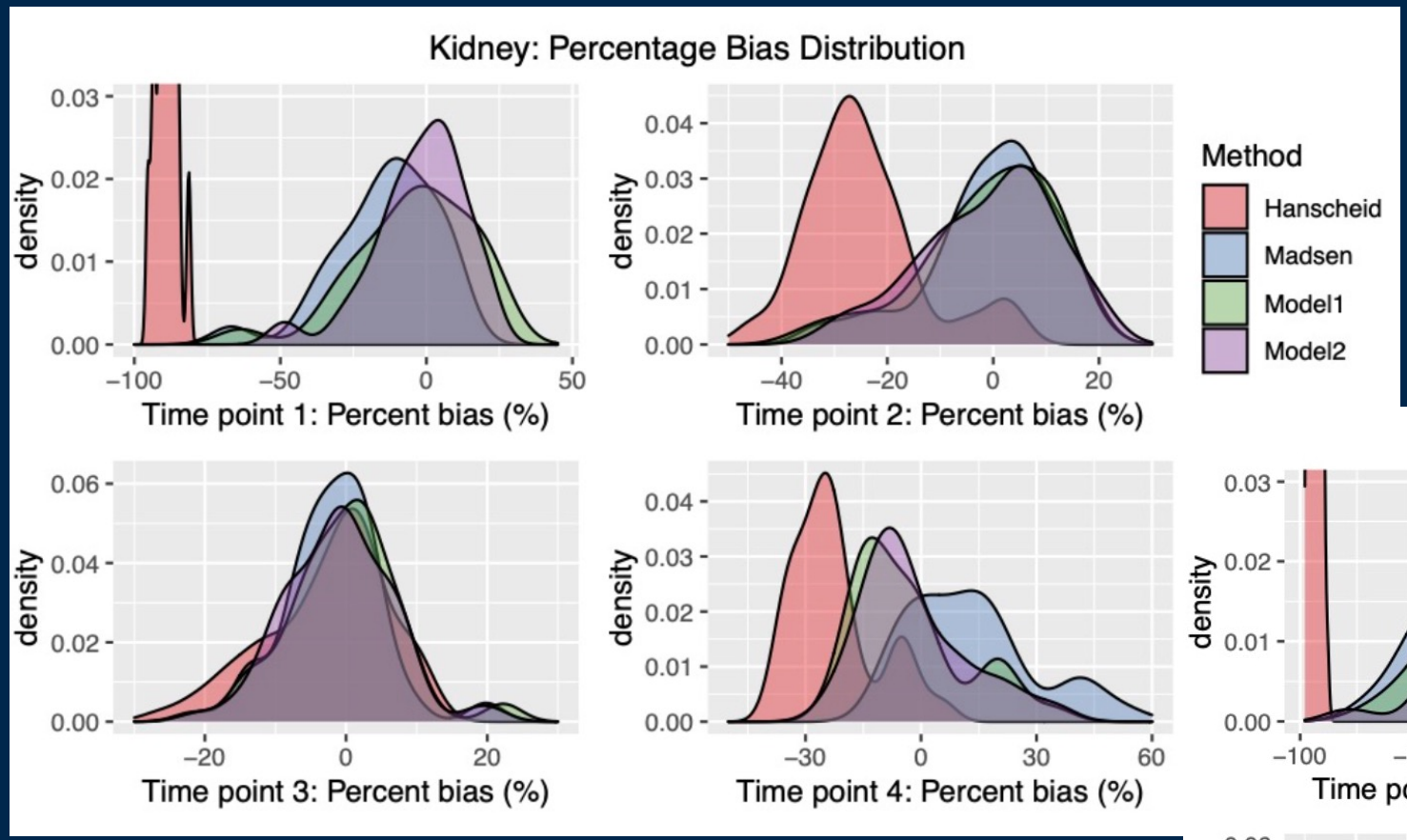
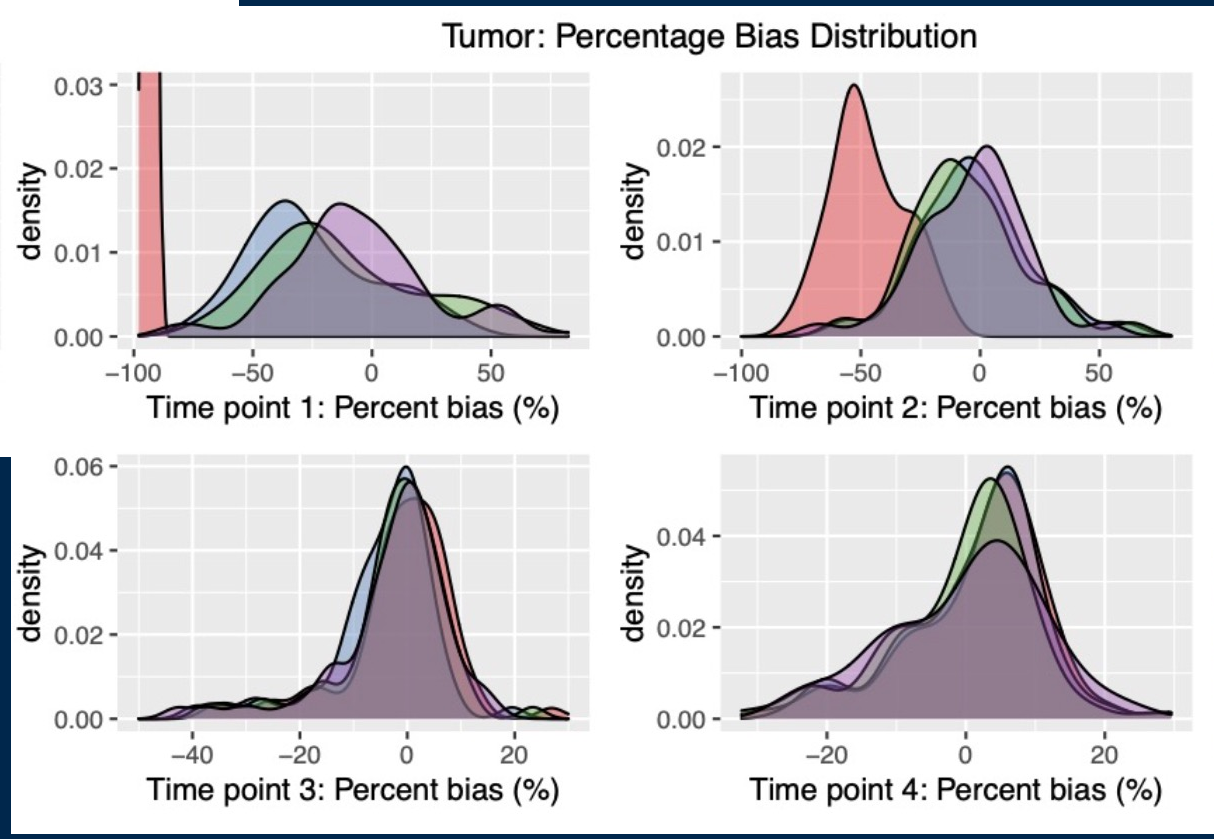
Other models: Can we further improve STP estimates? Data driven models



EANM 2022: EPS-209

Regression models for single time point dosimetry optimized across range of timepoints with application in 177 Lu-DOTATATE therapy

C. Wang[1], A. B. Peterson[2], K. Wong[1], M. J. Schipper[1], Y. K. Dewaraja[1]; [1]University of Michigan, Ann Arbor, MI



Single TP methods: What about other radionuclides, therapies …?

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Single time point dose estimation in other therapies

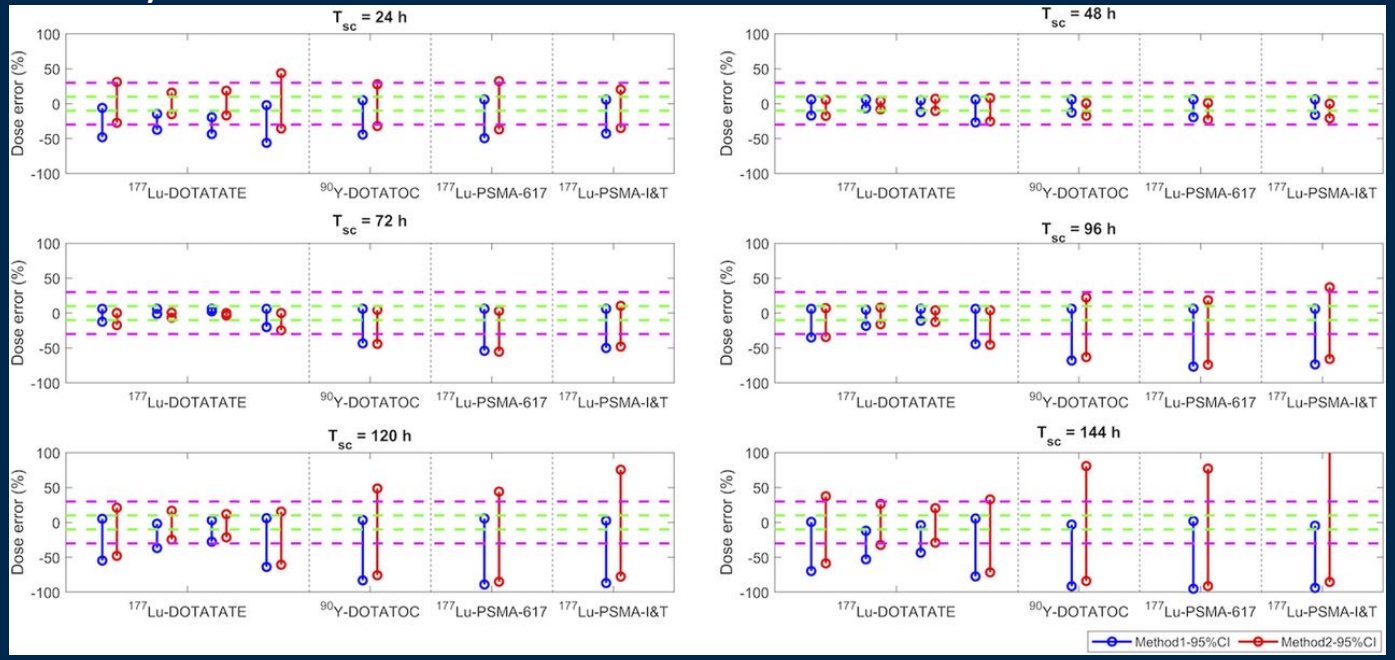
Feasibility of Single-Time-Point Dosimetry for Radiopharmaceutical Therapies

Xinchi Hou[1], Julia Brosch[2], Carlos Uribe[1,3], Alessandro Desy[4,5], Guido Böning[2], Jean-Mathieu Beauregard[4,5], Anna Celler[1], and Arman Rahmim[1,3,6]

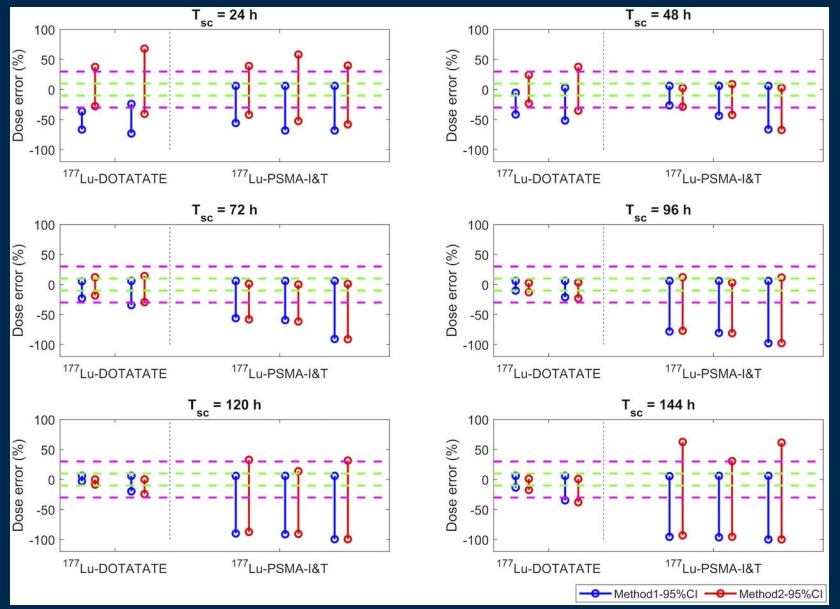
J Nucl Med 2021; 62:1006–1011

butions. The STP framework was promising for dosimetry of ^{177}Lu-DOTATATE and for kidney dosimetry of different radiopharmaceuticals (errors < 30%). Meanwhile, for some radiopharmaceuticals, STP accuracy was compromised (e.g., in bone marrow and tumors for ^{177}-labeled prostate-specific membrane antigen [PSMA]). The optimal SPECT scanning time for ^{177}Lu-DOTATATE was approximately 72 h p.i., whereas 48 h p.i. was better for ^{177}Lu-PSMA. **Conclusion:** Simplified

Kidney Results



Bone Marrow Results



DEs (%) of kidney doses estimated using method 1 (blue) and method 2 (red) when patient Teff is within simulated 95% CI range listed in Table 2. Green and magenta dashed lines indicate 610% and 630% of DEs, respectively. Four sets of results shown in 177Lu-DOTATATE column correspond to Teff data from studies 1–4.

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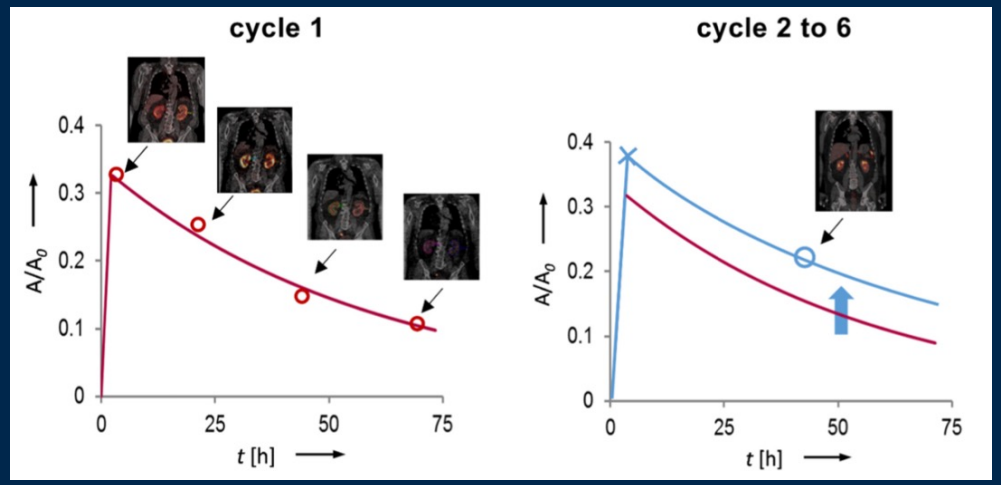
177Lu-PSMA: Full Imaging in Cycle 1 + Single Timepoint at Others:

Streamlined Schemes for Dosimetry of ^{177}Lu-Labeled PSMA Targeting Radioligands in Therapy of Prostate Cancer

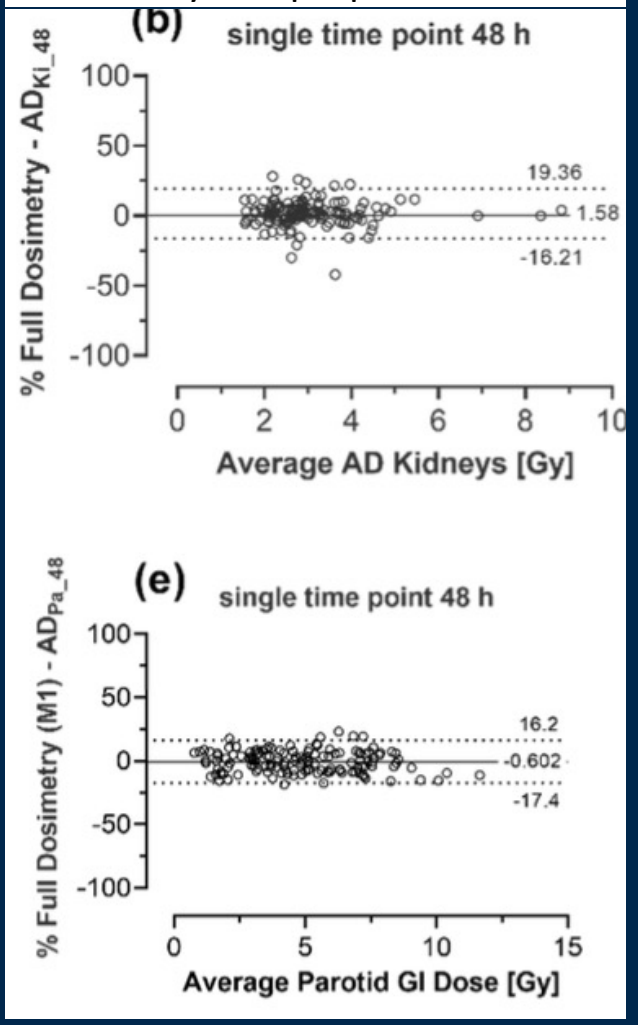
Cancers 2021, *13*, 3884

Jens Kurth [1,*], Martin Heuschkel [1], Alexander Tonn [1], Anna Schildt [1,2], Oliver W. Hakenberg [3], Bernd J. Kra and Sarah M. Schwarzenböck [1]

- Compared dosimetry with 4 timepoints (2,24,48,72h) after each cycle with 4 timepoints in cycle 1 + single timepoint at subsequent cycles



% Difference between full dosimetry and proposed method



- Difference: ~ ±6% for kidney and ±10% for parotids
- Small increase in kidney T_{eff} (38 to 41 h) & AD (0.5 to 0.6 Gy/GBq) over 5 cycles
  - Tumor sink effect?
  - Repeat full dosimetry once?

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Optimal single timepoint varies with tissue & radiopharmaceutical

- PRRT of NETs
  - for Lu-177 DOTATATE PRRT. *Hanscheid et al, J Nuc Med, 2018*. Considering both tumor and kidney 96h
    - Several others confirming this
  - Y-90 DOTATOC PRRT. *Madsen et al. Med Phys 2018*. Optimal time for kidney 48 h
- ^{177}Lu-PSMA Radioligand Therapy of mCRPC
  - ^{177}Lu-PSMA-617 : *Jackson PA et al. J Nucl Med. 2020;61:1030-1036*. Optimal time for kidney, parotid 48 h; tumor 120 h. Presented scale factors to convert single timepoint measurement at any timepoint to TIA and the expected uncertainty
  - ^{177}Lu-PSMA I&T: *Rinscheid, et al. EJNMMI Phys 2020. 7, 41*. Considering kidney and tumor optimal time was 52 h, tumor; 72 h
  - ^{177}Lu-PSMA-617 and I&T: Hou X et al.*J Nucl Med*. 2021;62:1006-1011. Kidney 48h; tumor 48h (for I&T); unreliable for bone marrow

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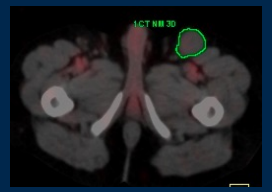
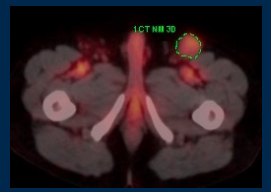
^{131}I RIT for NHL: Revisiting Michigan data to see if STP would have worked?

- 3 TP SPECT/CT Lesion imaging

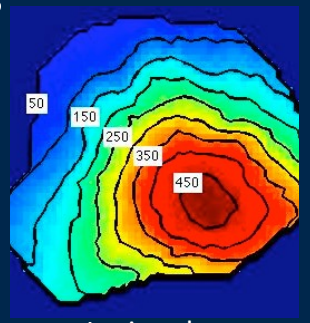


SPECT/CT: Day 0 post-tracer



Day 2 post-therapy

Day 8 post-therapy

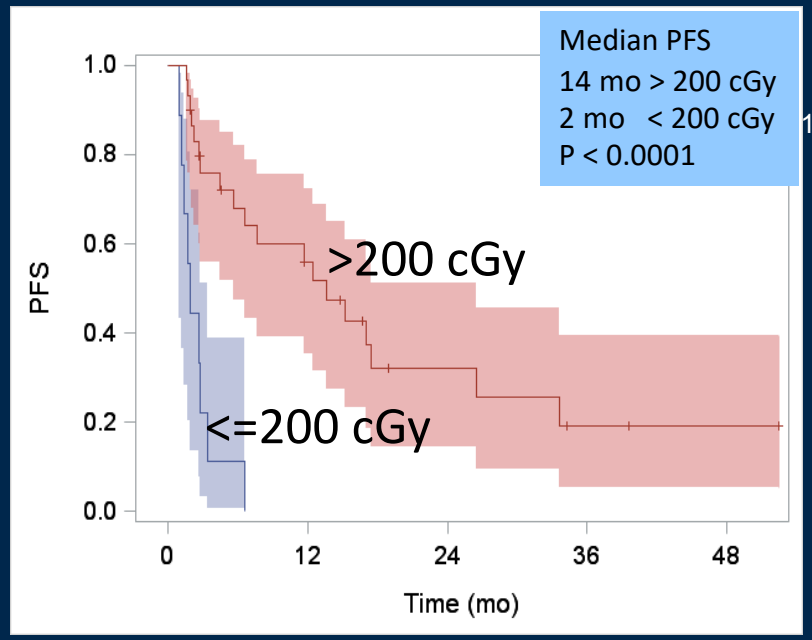


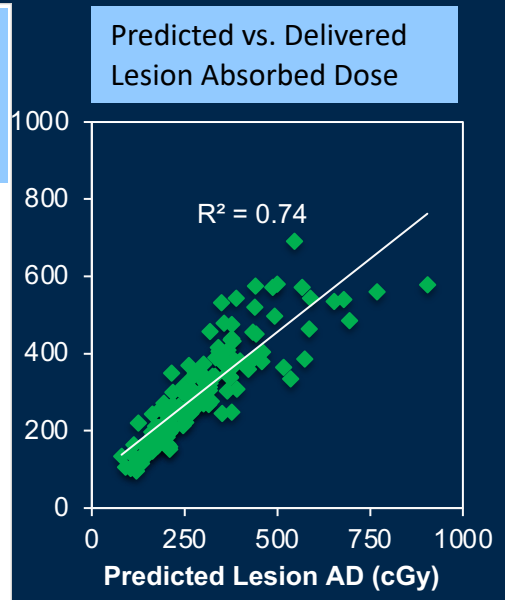
Lesion dose map

- Lumbar imaging

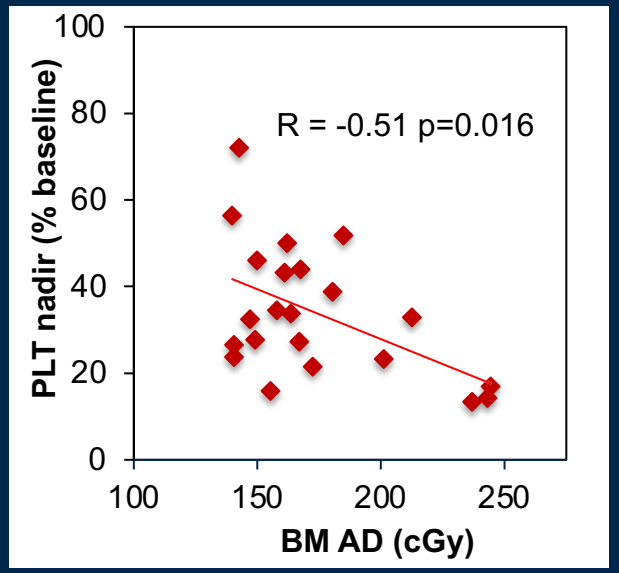
SPECT/CT based marrow dosimetry

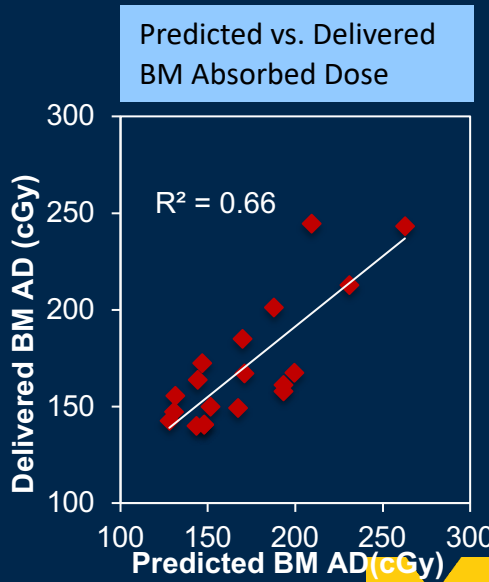
- Lesion dose – outcome





- Marrow dose - toxicity





Dewaraja et al, JNM 2014, 1047-53

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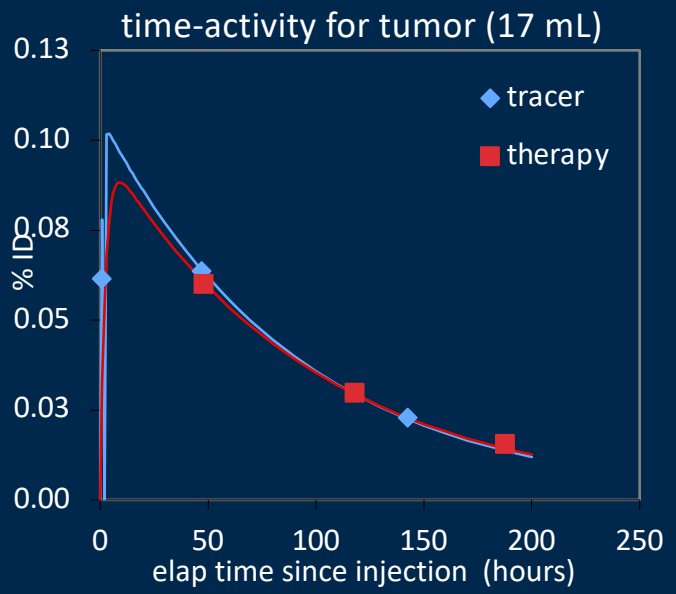
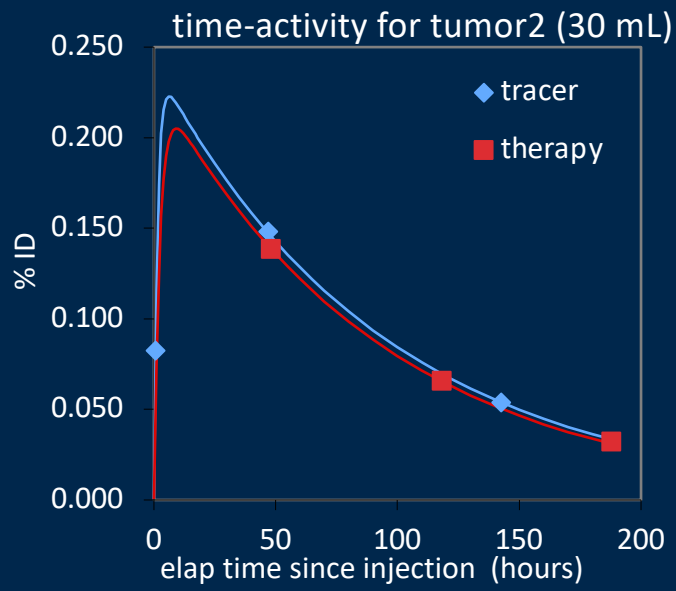
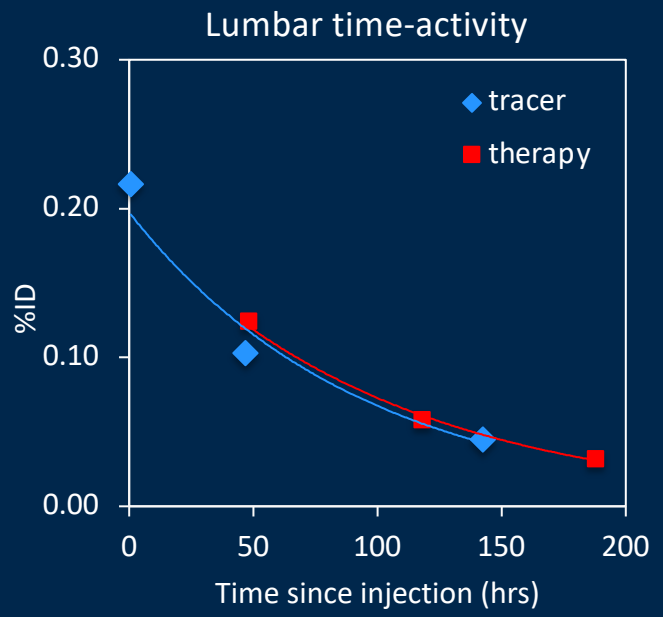
Revisiting I-131 RIT: Would single time point methods work?







Post-TRACER IMAGING

	Teff (h)	Diff in AUC between Single & Multi TP	
		Single TP= 47h	Single TP= 143h
Tumor 1	64	12%	4%
Tumor 2	66	11%	2%
Lumbar	65	24%	0.2%

Post-THERAPY IMAGING

	Teff (h)	Diff in AUC between Single & Multi TP	
		Single TP= 47h	Single TP= 118h
Tumor 1	65	11%	-8%
Tumor 2	64	9%	-6%
Lumbar	71	13%	0.1%

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Revisiting I-131 RIT: Summary of single TP performance

- 133 tumor in 39 patients
  - Difference between AUC from STP (Hanschied) and 3 point bi-exponential

	Time Point 1	Time Point 2	Time Point 3
Post-Tracer	~ 2 h	~ 2 d	~ 6 d
Median	98%	9%	4%
Range	91-100%	-16-73%	-77-62%
< +-20%		74%	
Post-Therapy	~ 2 d	~ 5 d	~ 8 d
Median	0%	-1%	36%
Range	-22-58%	-39-86%	-42-100%
< 20%	88%		

- one marrow and whole-body data not yet fully analyzed
- Large data set : well suited to identify and understand outliers

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