Patient Specific Dosimetry in TRT: To What Extent Can It be Simplified to Move from Research to The Clinic

Yuni Dewaraja, PhD,

Department of Radiology,
University of Michigan

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Targeted radionuclide therapy (TRT): why dosimetry ?

- Current TRT: ‘one dose fits all’ or weight based adjustment
  - Convenient, but potential for under- or over-treatment
    - Variability in pharmacokinetics, anatomy, activity distribution not considered
  - Examples: ^{177}Lu PRRT (‘one size’), ^{90}Y RE (liver mass), ^{90}Y RIT (body weight)

- Treatment planning based on absorbed dose:
  - Simplified protocols for clinical practice
    - Activity adjusted to keep absorbed dose to critical organ < MTD
  - Highly patient specific protocols
    - Taylor to deliver therapeutic absorbed dose to lesion at acceptable toxicity. Standard in EBRT but limited to research setting in TRT

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Targeted radionuclide therapy: why do dosimetry?

- Pre-treatment dosimetry
  - For planning therapy to improve efficacy (theranostics)
    - Often using a surrogate

- Peri-therapeutic dosimetry (during treatment)
  - Dosimetry after each cycle to modify subsequent cycle, real time dosimetry to adjust activity during treatment

- Post-treatment dosimetry
  - Verification, early assessment of safety & response (additional therapies/interventions when needed), establish dose vs. effect

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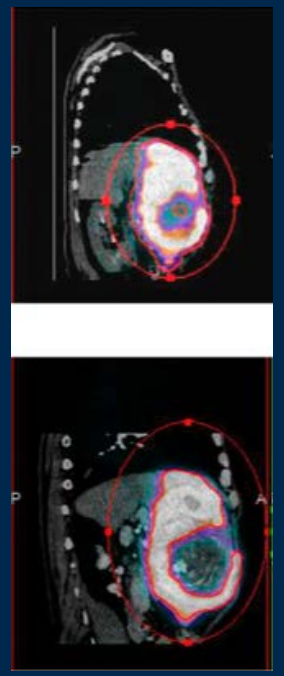
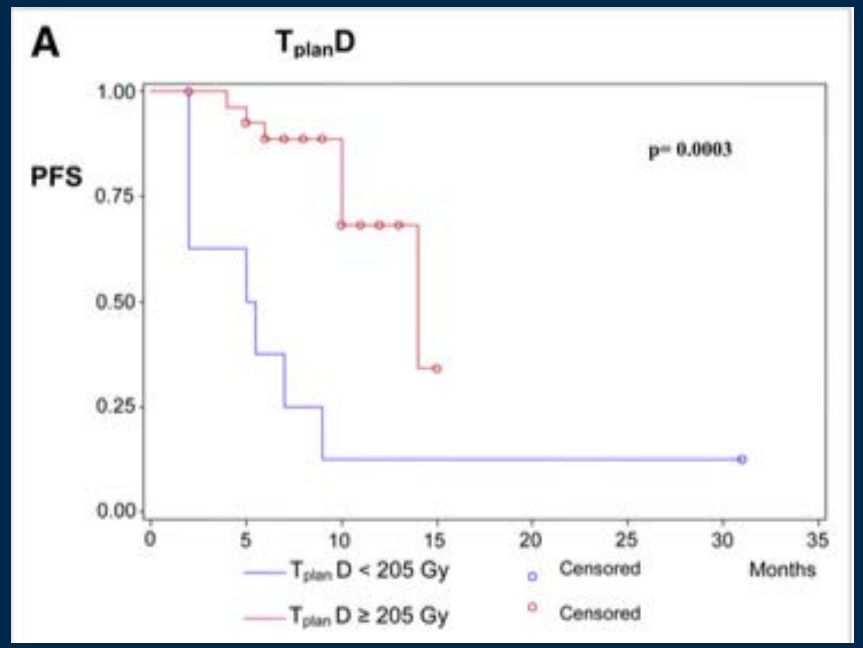
Benefit of pre-treatment dosimetry: example from 90Y RE

- Initial study (n=36):Tc-MAA SPECT/CT based tumor dosimetry, standard therapy (liver 120 Gy, lung < 30 Gy)
  - Established 205 Gy to tumor as threshold for response





- Intensification study (n=41): Activity based on MAA dosimetry. Tumor >205 Gy, normal liver<120 Gy,lung<30 Gy
  - 37% received higher activity
  - Improved Survival: TD < 205 Gy, 4 mo
  - TD > 205 Gy, 18 mo (*P* = 0.005)
  - No increase in toxicity

Garin et al, JNM 2015;339-346

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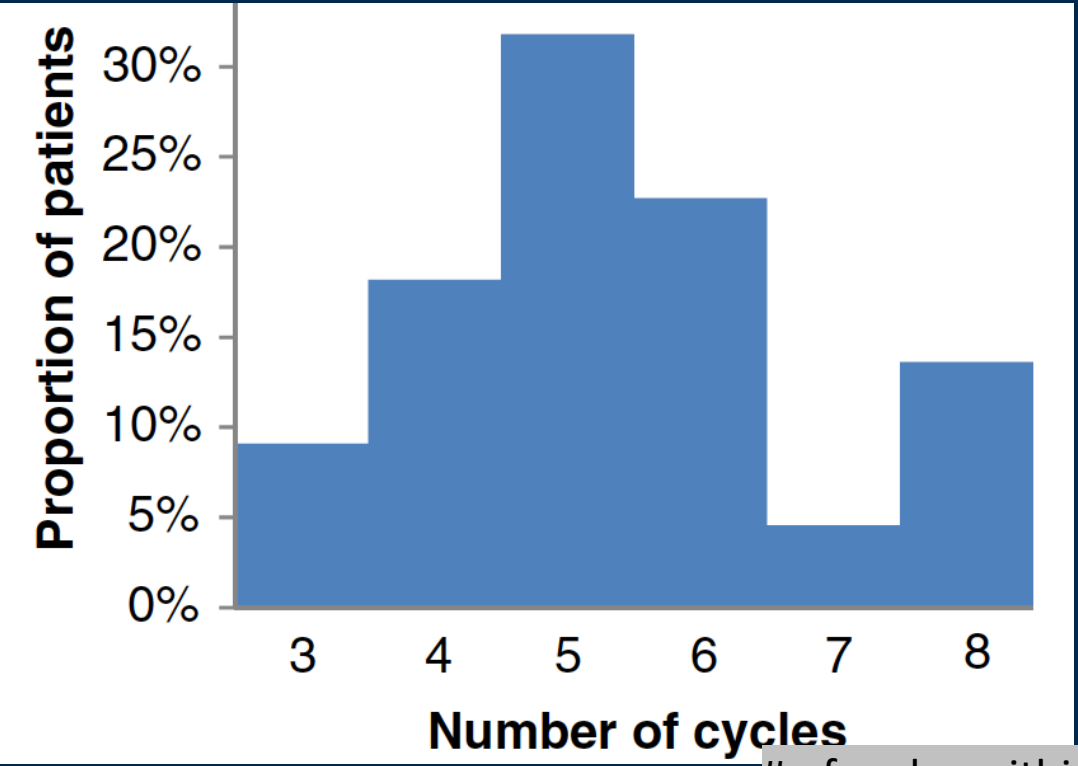
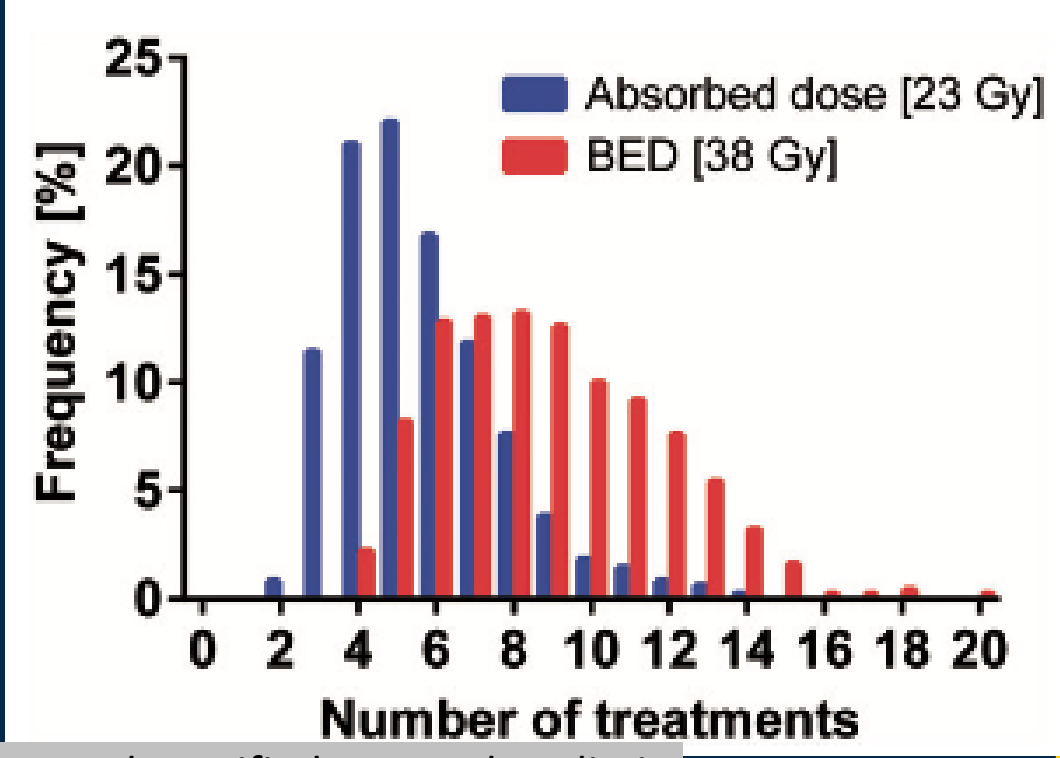
Benefit of dosimetry during treatment: examples from ^{177}Lu PRRT

- *Sundlov et al, EJNMMI 2017*
  - Treatment based on renal dosimetry with BED < 27Gy
- *Sandstrom et al, ACTA ONCOL. 2018*
  - With BED < 38 Gy to kidney and AD < of 2 Gy to marrow 95% could get > 4 cycles





# of cycles within the protocol specified BED and AD limits

# of cycles can be increased in most patients without reaching toxicity limits

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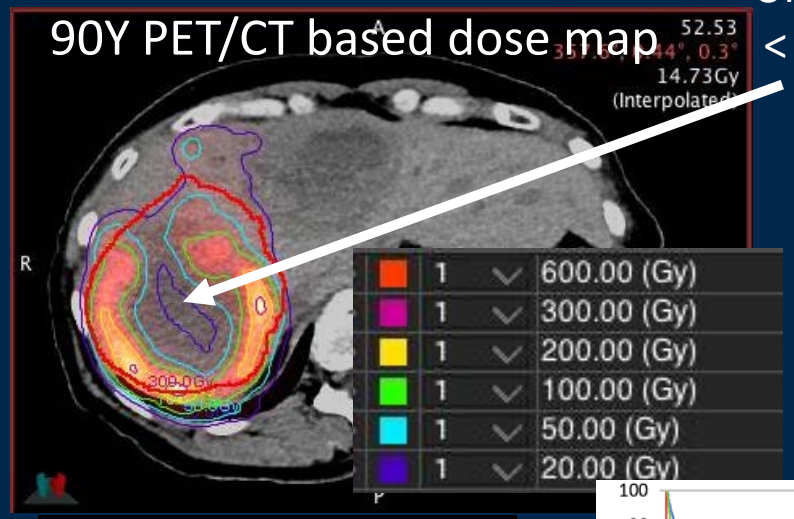
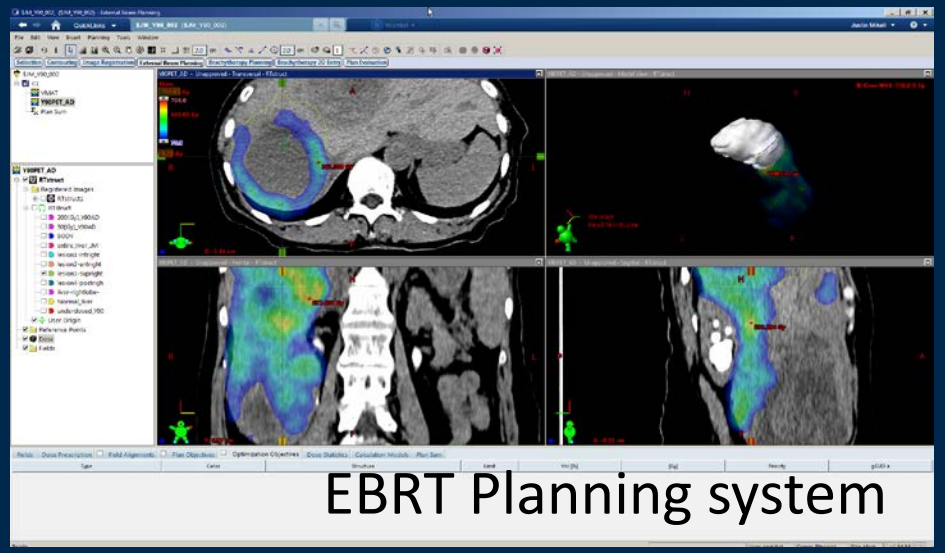
Benefit of post-treatment dosimetry: example from Y-90 RE

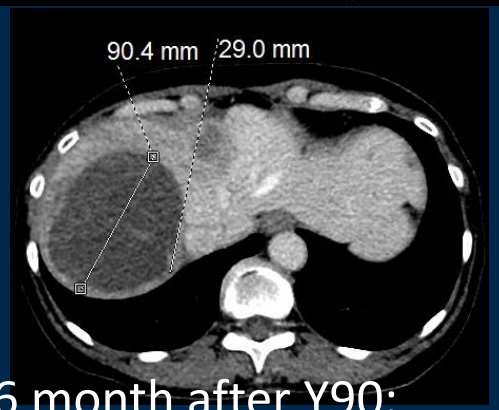
- Dose maps can be used to plan EBRT (boost under-dosed region)



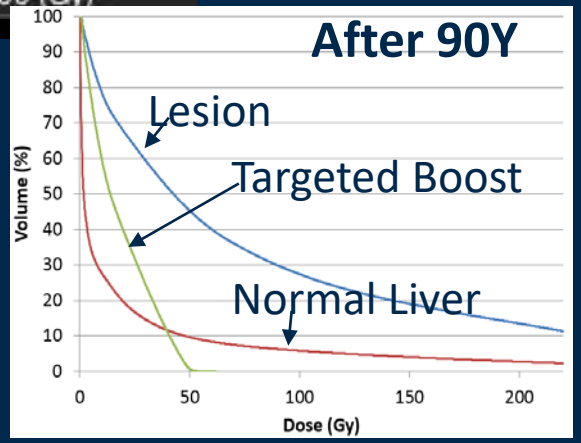
Under dosed
< 20 Gy

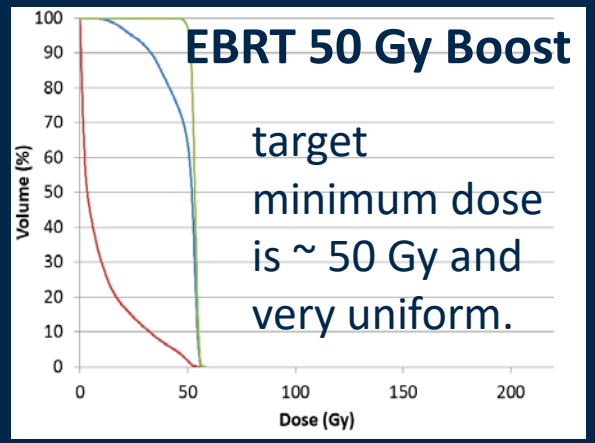


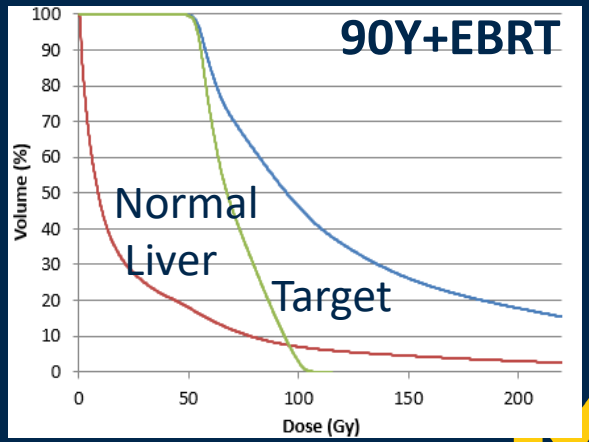
Increase in target and lesion minimum dose. They are now covered. Small increase in normal liver mean dose.



6 month after Y90:
poor response







Courtesy of Justin Mikell, Radiation Oncology, University of Michigan

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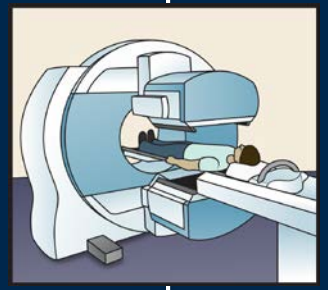
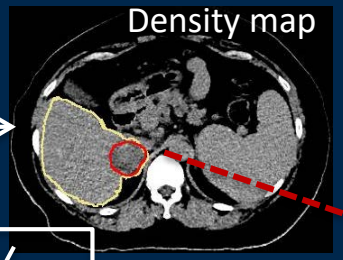
SPECT/CT or PET/CT based patient specific dosimetry

Can this process be simplified ?

PET/CT or SPECT/CT Acquisition



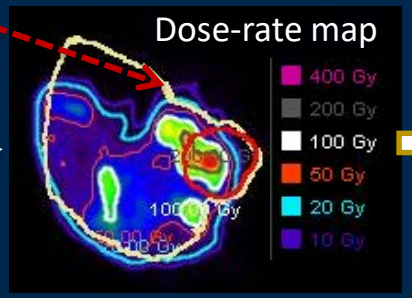
CT reconstruction

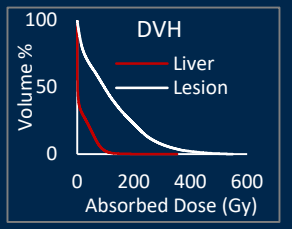


VOI

Attenuation map

Voxel-level Dose-rate Calculation

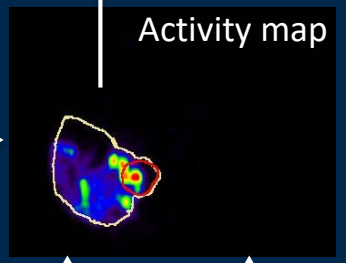




AD, DVH, BED

Repeat at multi-time points (except Y-90 RE)

SPECT or PET reconstruction with AC, SC, RR,...



Calibration Factor cps/voxel -> MBq/mL

Partial Volume Correction

CT information

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Patient specific dosimetry in TRT: simplification to move to clinic

- Do we need specialized reconstruction software & calibrations
- Do we need a radiologist for target segmentation?
- Do we need multiple-imaging time points
- Do we need Monte Carlo Dosimetry

Two therapies will be discussed as examples: Y-90 Radioembolization (RE) and Lu-177 Peptide Receptor Radionuclide Therapy (PRRT)

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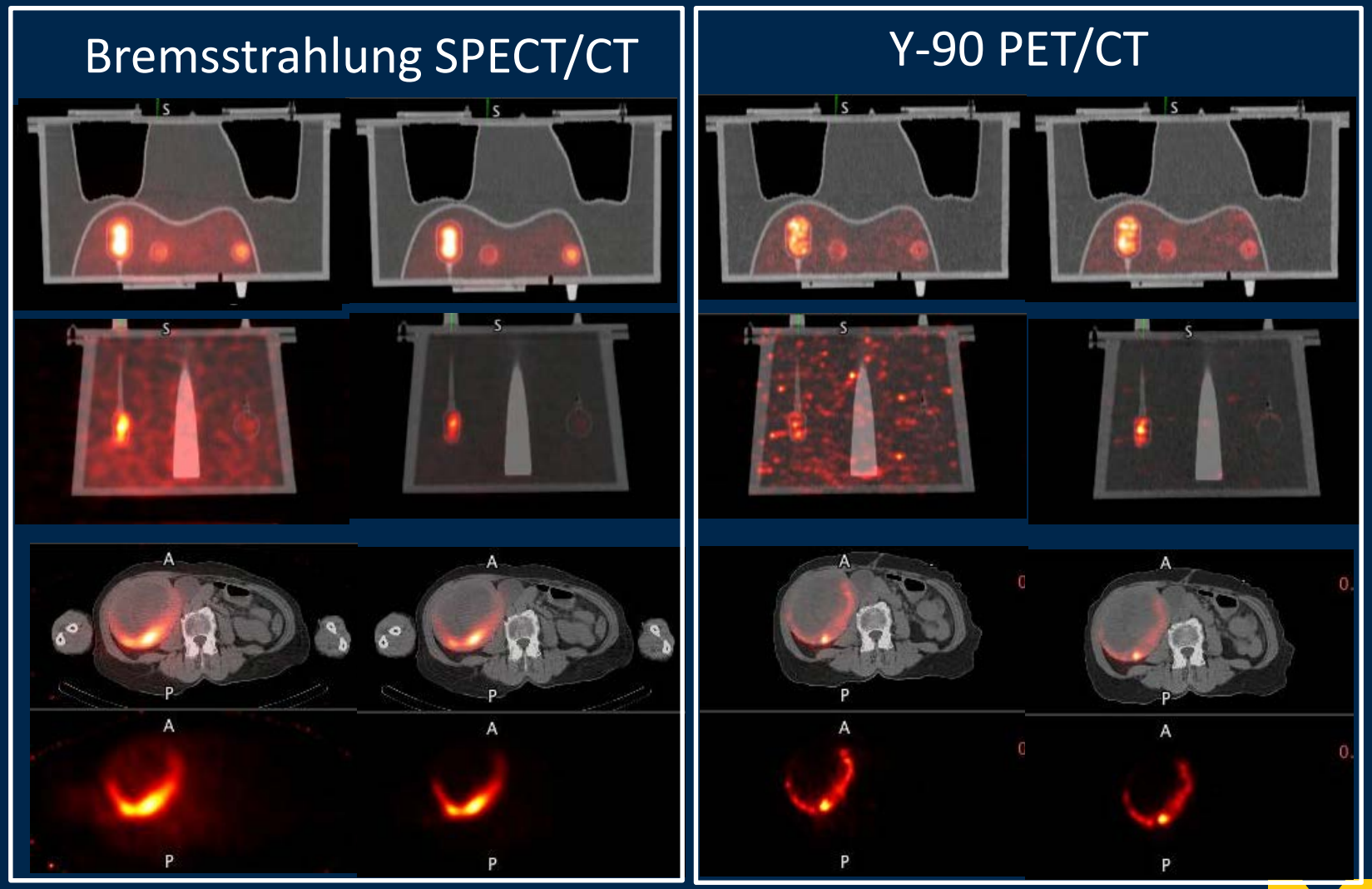
Y-90 RE example: Reconstruction & calibration

- ^{90}Y dosimetry is easy
  - Microspheres are trapped: only need one time point
  - No gamma-rays, so little cross dose

BUT

- Imaging is complex
  - Bremsstrahlung photons for SPECT
  - low abundance positrons for PET



Dewaraja et al, Med Phys 2017;6363-6376

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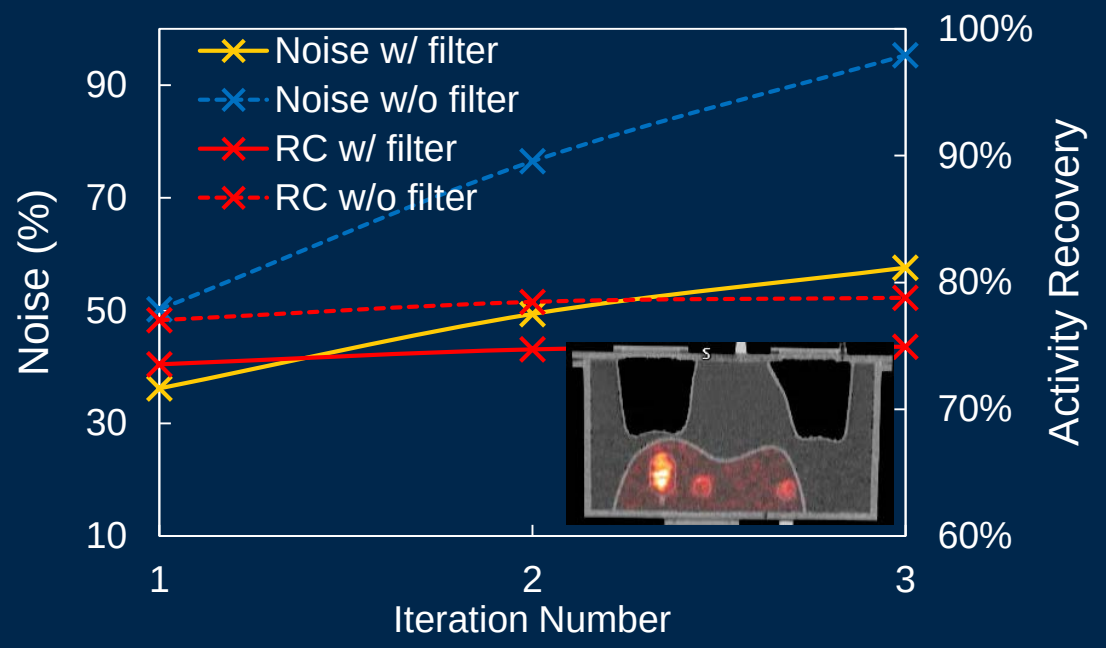
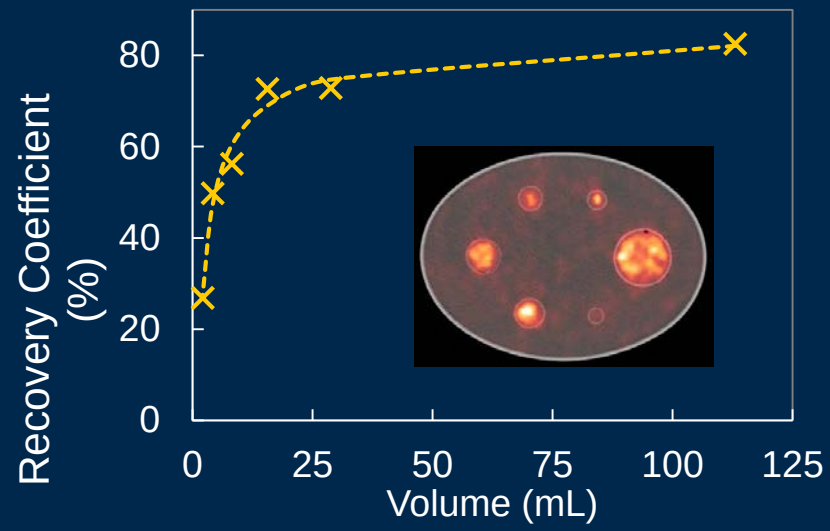
Y-90 PET reconstruction, quantification

- Commercial reconstruction tools sufficient, but need TOF+RR
  - Phantom studies to identify optimal reconstruction parameters
- Direct Bq/mL from ^{90}Y PET, but need partial volume correction (PVC)
  - Quantification accuracies within 5% for healthy liver within 10% for 'lesions' with PVC. Similar results by others*





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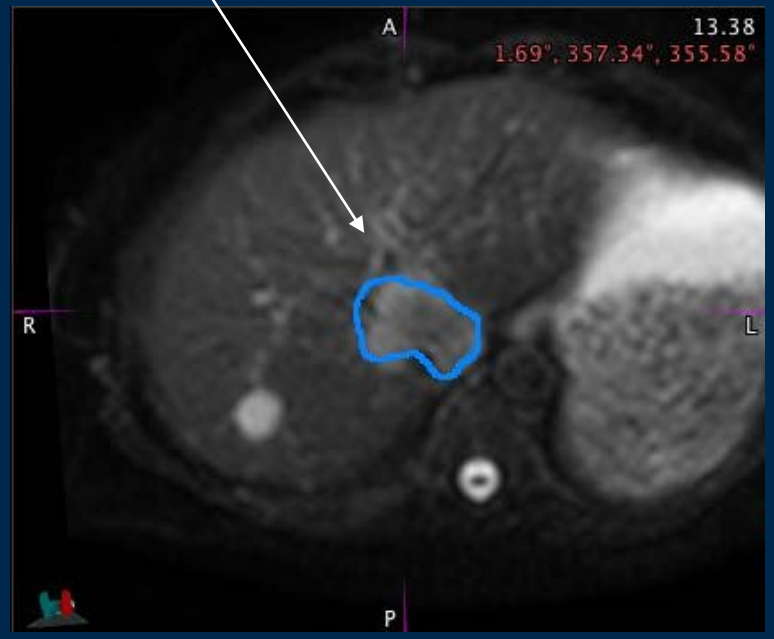
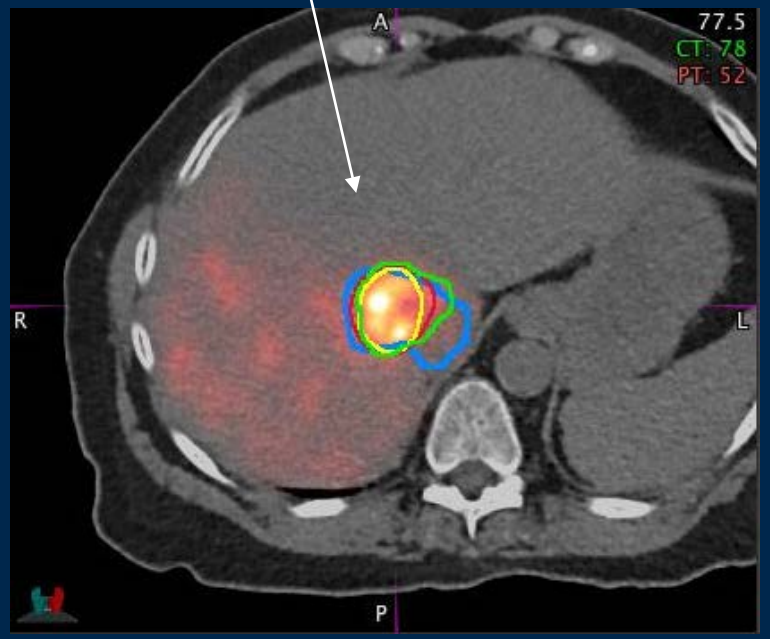
Y-90 RE: Do we need a radiologist for segmentation?

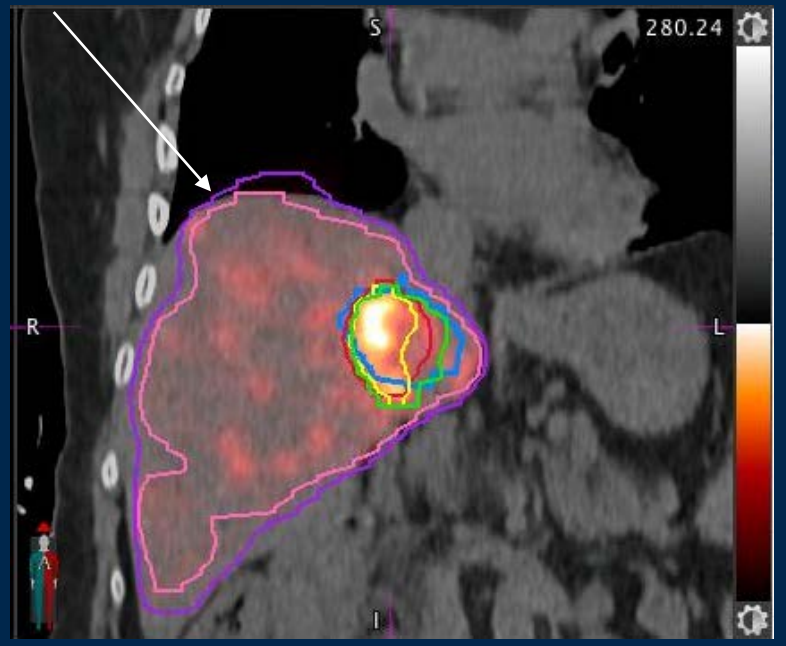
Lesion defined by Radiologist on MR: 30 cc



Radiologist defined lesion: 30 cc
SPECT 40% threshold : 16 cc
SPECT 20% threshold : 44 cc
PET Gradient based : 30 cc



SPECT 3% threshold :1100 cc
SPECT 6% threshold : 807 cc



- Current semi-automatic segmentation tools sufficient for organs, but typically need radiologist guidance for lesions

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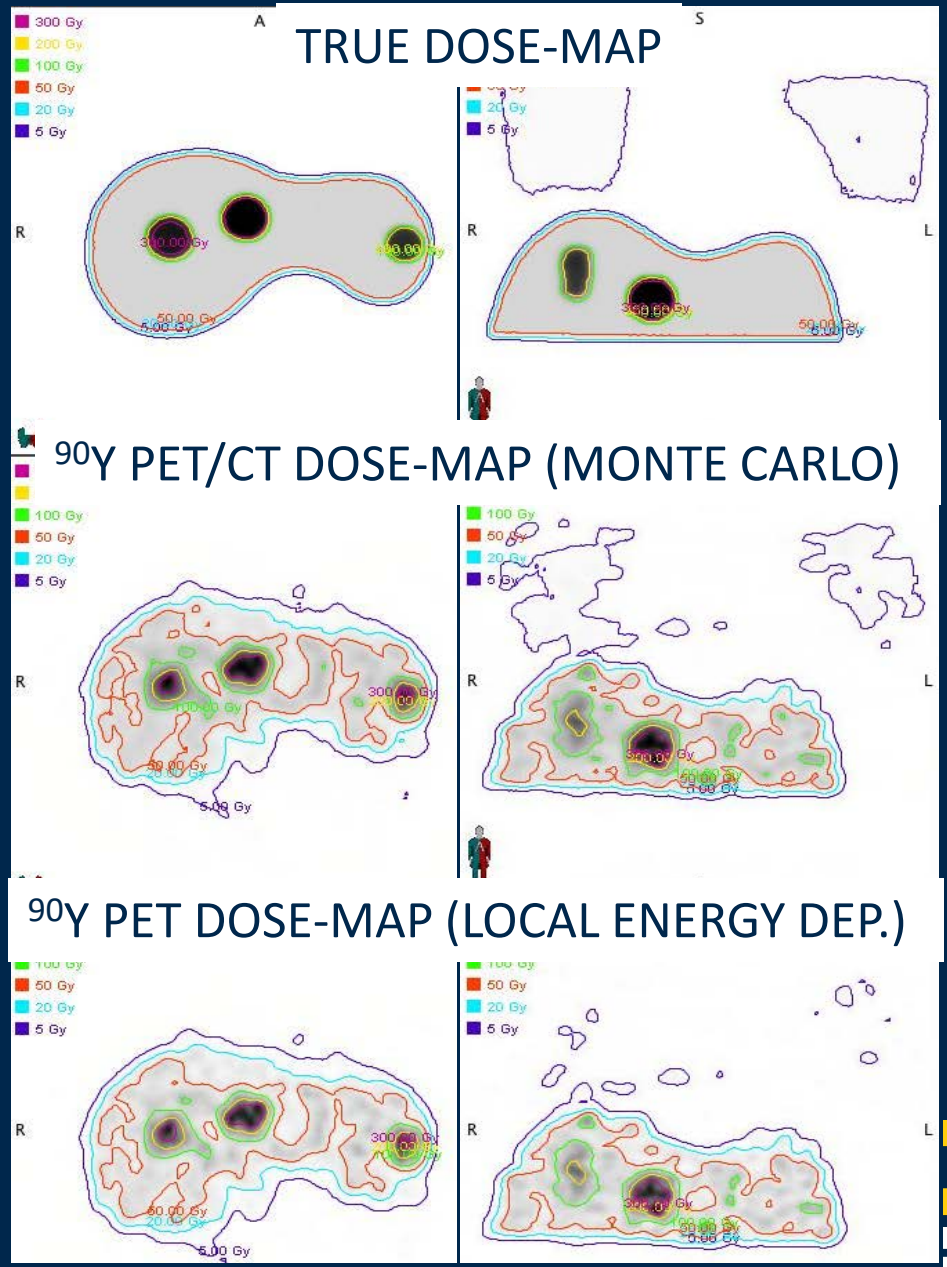
Y-90 RE dosimetry: Do we need Monte Carlo?

- Comparison of estimates from MC with estimates from voxel S value kernels and local energy deposition (LDM)

	DPM* Monte Carlo Absorbed Dose (Gy)	Difference compared with Local Energy Deposition
8 mL sphere	191	2.5%
16 mL sphere	246	1.6%
29 mL ovoid	249	0.8%
Healthy liver	59	-1.6%
L Lung	4.5	-144% (-10%)
R Lung	4.8	-144% (-6%)

with density correction

Wilderman and Dewaraja. IEEE Trans Nucl Sci 2007;54:146.



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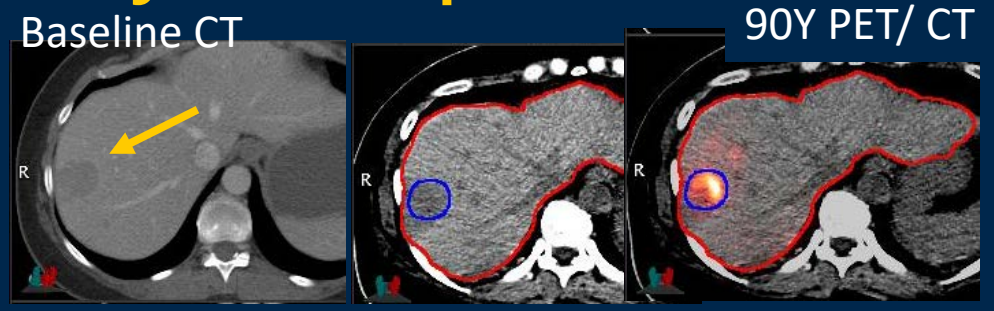
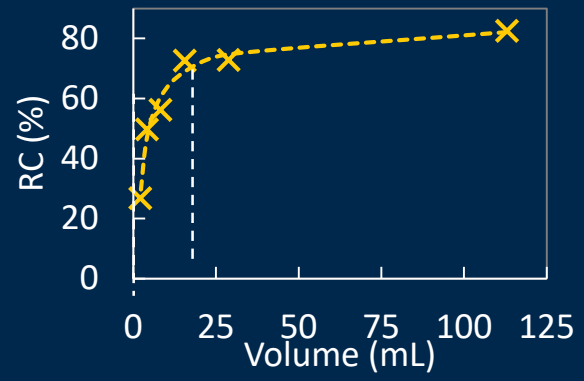
Y-90 RE patient dosimetry example

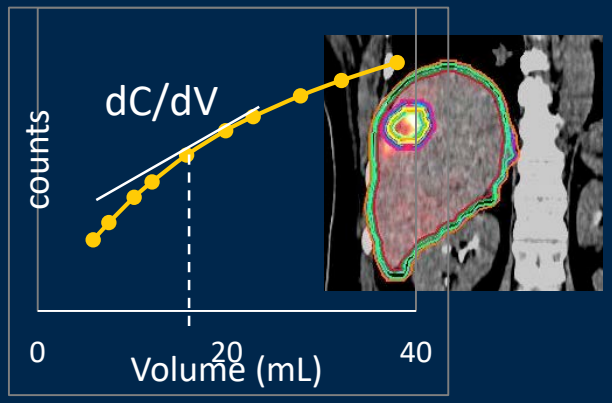
- Segmentation:
  - Lesion (radiologist), liver (semi-auto)
- Registration & transfer contours
  - Commercial software
- Activity map: direct PET Bq/mL
- Voxel-level dosimetry (LDM)

  D(Gy) = 49.3 * A (GBq)/M (kg)
- Mean value PVC using RCs
- Uncertainty*

$$\frac{u(D_{VOI})}{D_{VOI}} = \sqrt{\left(\frac{u(A_{VOI})}{A_{VOI}}\right)^2 + \left(\frac{u(M_{VOI})}{M_{VOI}}\right)^2 - 2\frac{u(A_{VOI}, M_{VOI})}{A_{VOI} M_{VOI}}}$$







	PET Activity (GBq)	RC	LDM AD (Gy)	Relative STD Uncert.	MC AD (Gy)
Lesion	0.15	0.69	686	10%	676
Normal liver	1.55	0.92	51	5%	55

* Gear et al, EJNMMI 2018

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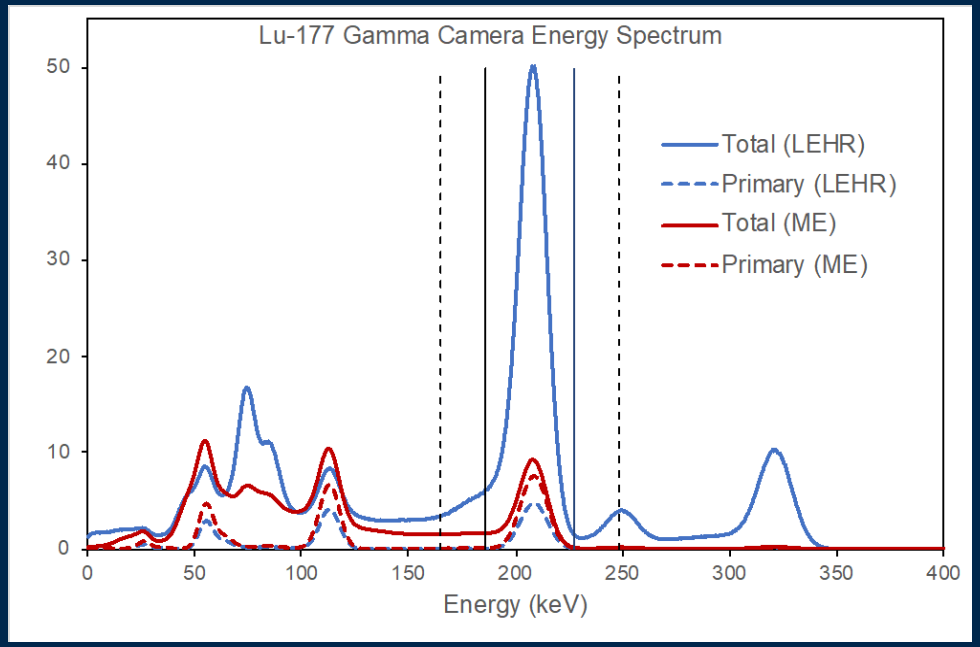
Lu-177 PRRT example: reconstruction and quantification

- Image acquisition: ME collimator, typically using 208 keV peak (10%). Also 113 keV peak (6%)
- SPECT reconstruction: standard OS-EM
- Quantification:
  - Point source or phantom based calibration
  - Some new systems have ‘in-built’ Lu-177 calibration
    - Image in units of Bq/mL
  - RC still needed



Ljungberg et al, MIRD 26. JNM 2016

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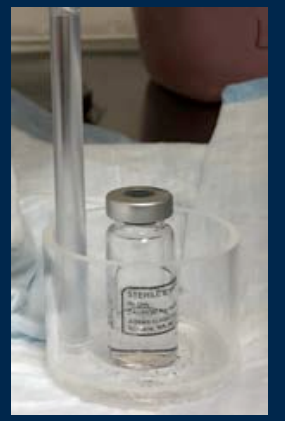
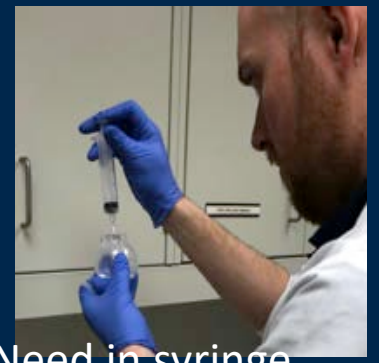
Calibration factor for absolute SPECT quantification

- NIST recommendation[1] (0.9 % uncertainty)
  - 3 mL ^{177}Lu in a 10 mL Schott vial: CRC-15R setting 449x10
- Transferring calibration to a new geometry (10 mL syringe)
- With the syringe in the dose calibrator adjust setting to get correct reading
  - for 3 mL in syringe: 480 x 10
- Calibration Factor
  - 12.9 cps/MBq (head 1), 13.4 cps/MBq (head 2)
  - within 1 % of manuf. specified value



'NIST geometry' for dose calibrator



Need in syringe for filling phantom and camera sensitivity

Syringe taped to Source holder

. Bergeron DE, Cessna JT. Nucl Med Commun. 2018 Jun;39(6):500-504.

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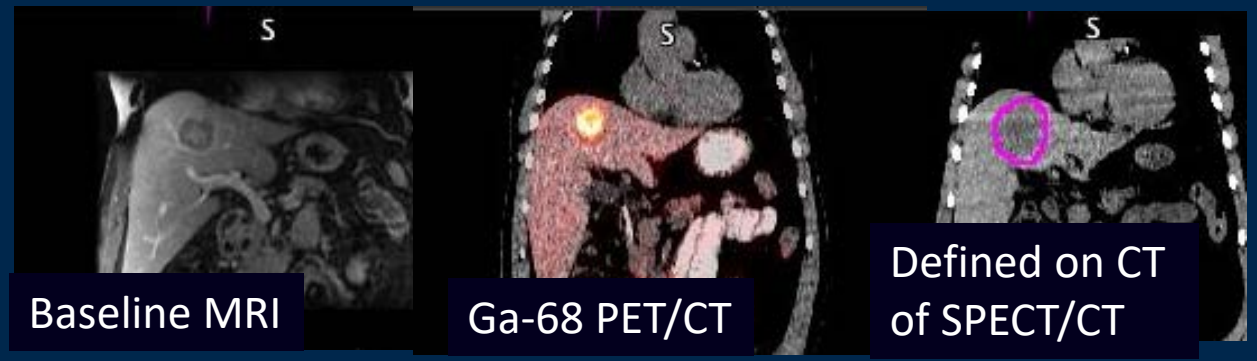
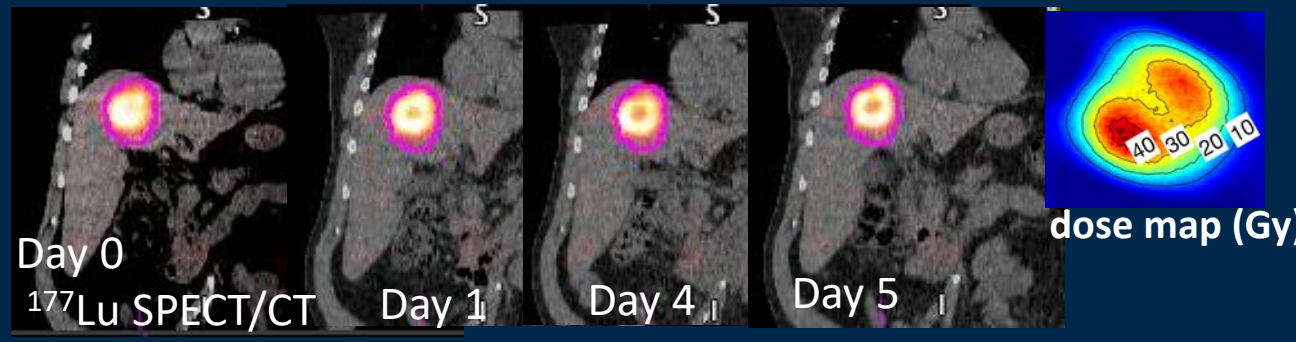
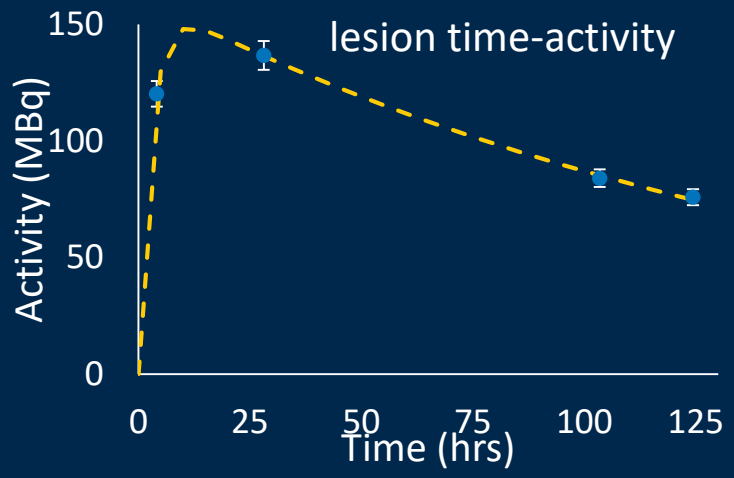
Lu-177 PRRT patient example: time-activity

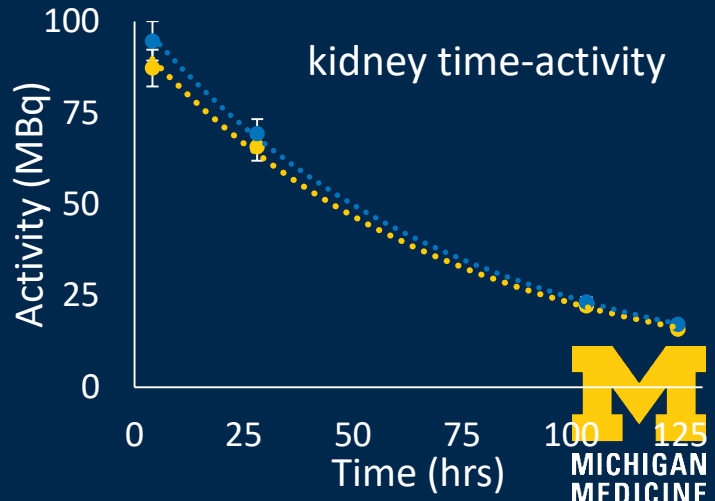
- SPECT/CT day 0,1,4,5
- Co-registered time-points
- Activity directly from SPECT or apply calibration
- Apply RCs for PVC
- Mono- or bi-exponential fit





	RC	Activity (Uncert.) MBq			
		Day 0	Day 4	Day 5	Day 7
Lesion	0.93	120 (5%)	137 (6%)	84 (4%)	76 (3%)
R kidney	0.96	87 (5%)	66 (4%)	22 (1%)	16 (1%)
L kidney	0.96	95 (5%)	69 (4%)	23 (1%)	17 (1%)





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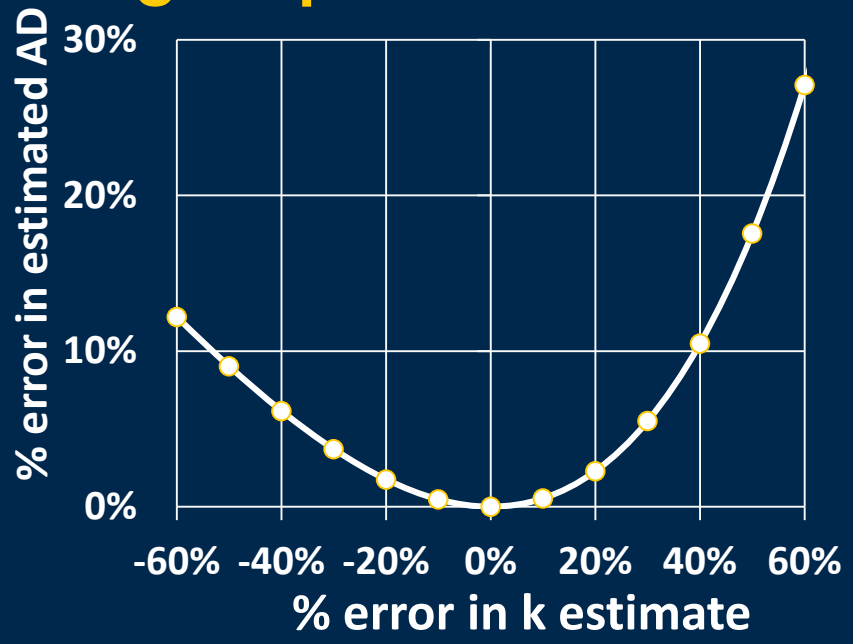
Do we need multi-time points? single-point dosimetry

- Recently reported by Madsen for Y-90 DOTATOC & Hanscheid et al, for Lu-177 PRRT
- The time integrated activity estimated from a single activity measurement and population mean kinetics parameters

$$\tilde{A}^* = A(T)e^{\hat{k}T}/\hat{k}$$

ideal sampling point T = τ (1/k)

For Lu-177 DOTATATE ~ 96 h



Deviation from true (multi-point) time-integrated activity

Tissue	Quantile	24 h	48 h	72 h	96 h	120 h	144 h
Kidneys	1 (maximum)	−18%	+17%	+ 25%	+17%	+7%	+7%
	0.9	−24%	+9%	+16%	+10%	+2%	−7%
	0.5 (median)	−33%	0%	+6%	+5%	−5%	−18%
	0.1	−40%	−8%	+4%	−3%	−16%	−31%
	0 (minimum)	−61%	−33%	−15%	−9%	−25%	−41%
NET	1 (maximum)	−36%	−1%	+15%	+16%	+11%	+10%
	0.9	−40%	−6%	+8%	+10%	+10%	+7%
	0.5 (median)	−49%	−17%	0%	+6%	+5%	+5%
	0.1	−60%	−32%	−13%	−2%	+2%	−6%
	0 (minimum)	−67%	−43%	−24%	−11%	−3%	−14%

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

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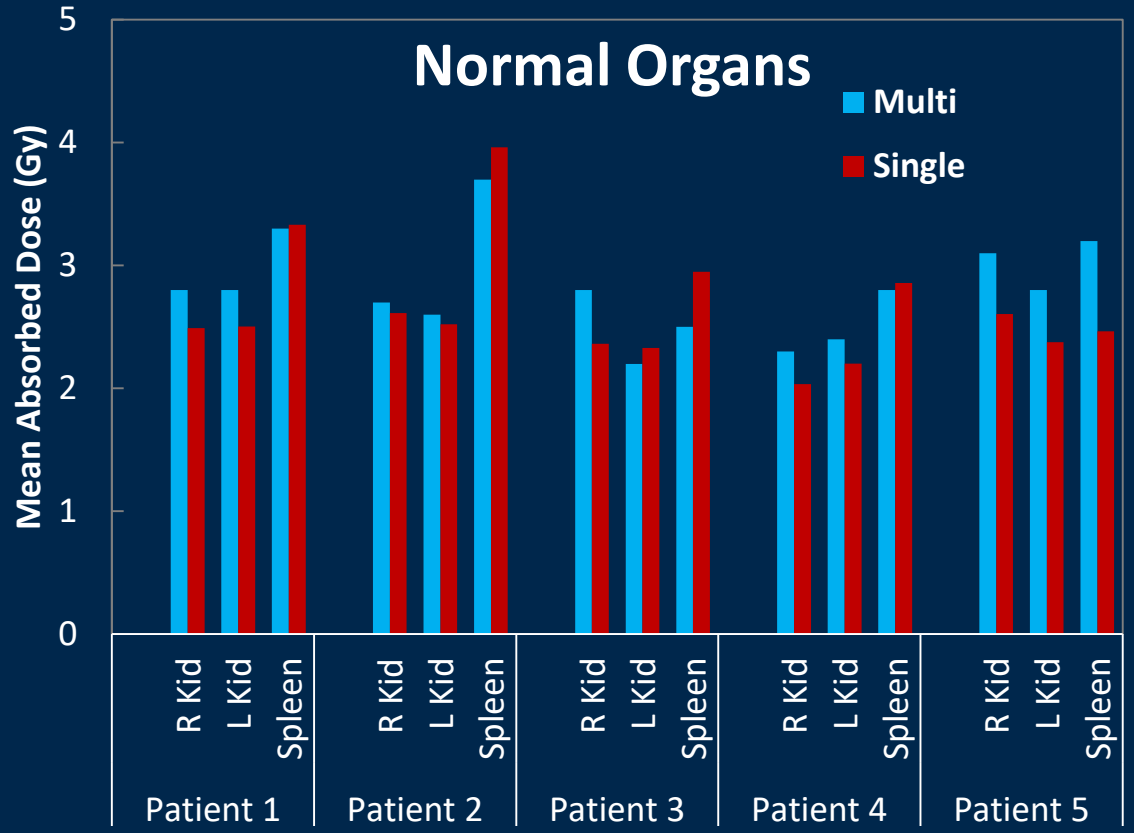
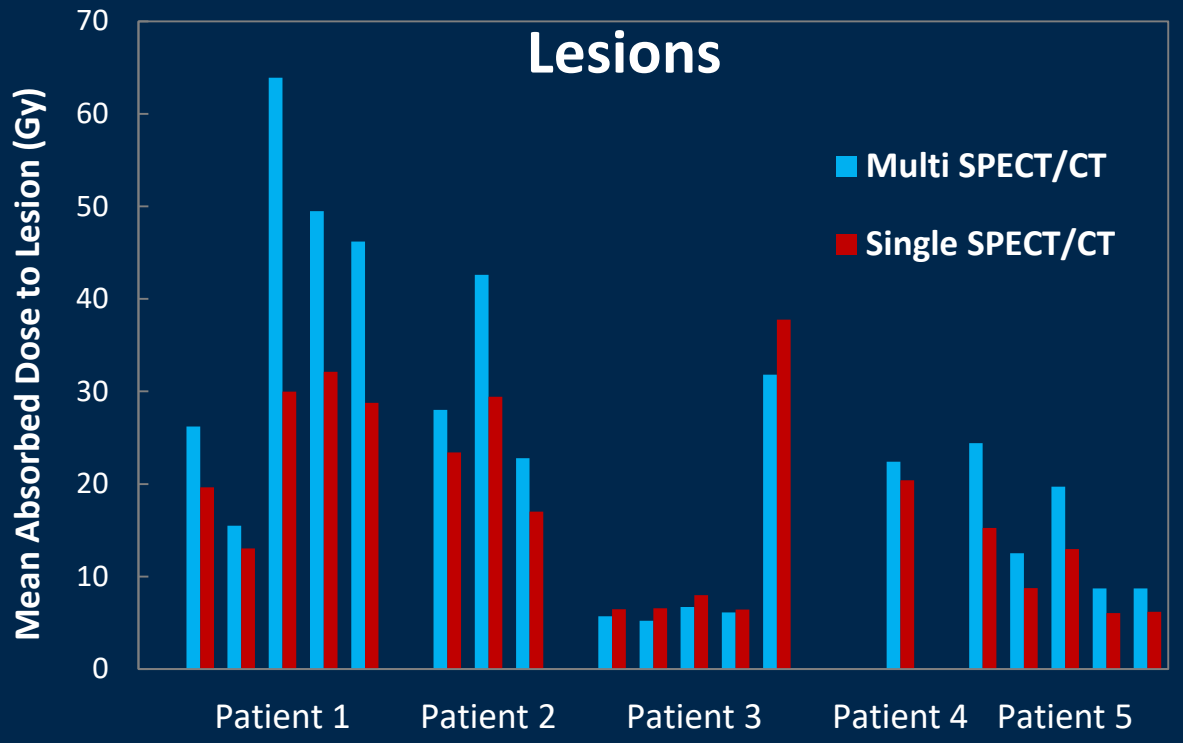
Lu-177 DOTATATE: Do we need multiple time points?

- University of Michigan pilot study: absorbed doses from SPECT/CT at 4 time points vs. at a single time point





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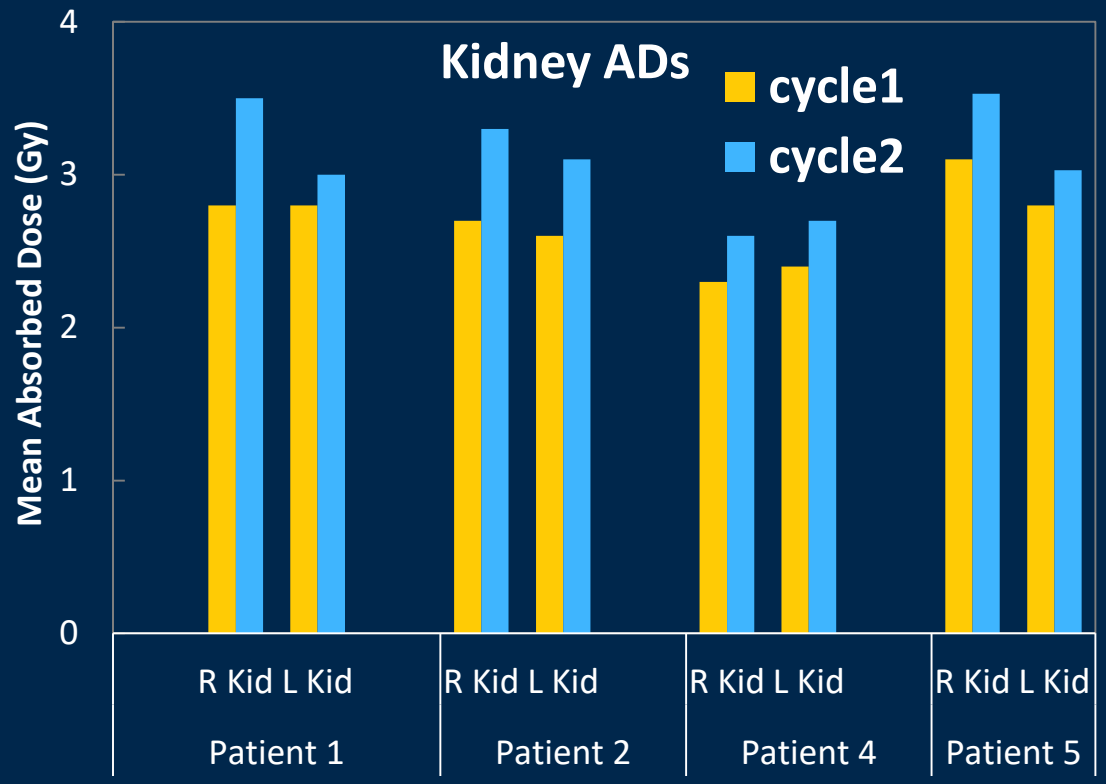
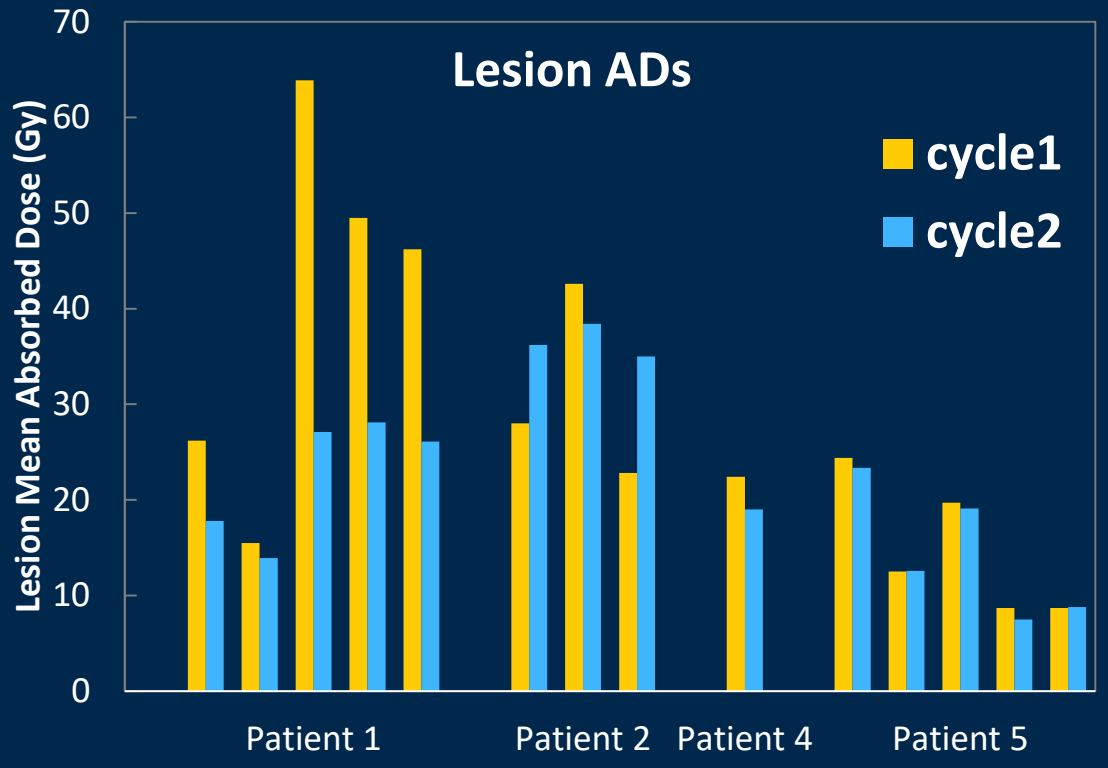
Do we need to image after each cycle?

- Comparison of dosimetry performed after 2 consecutive cycles





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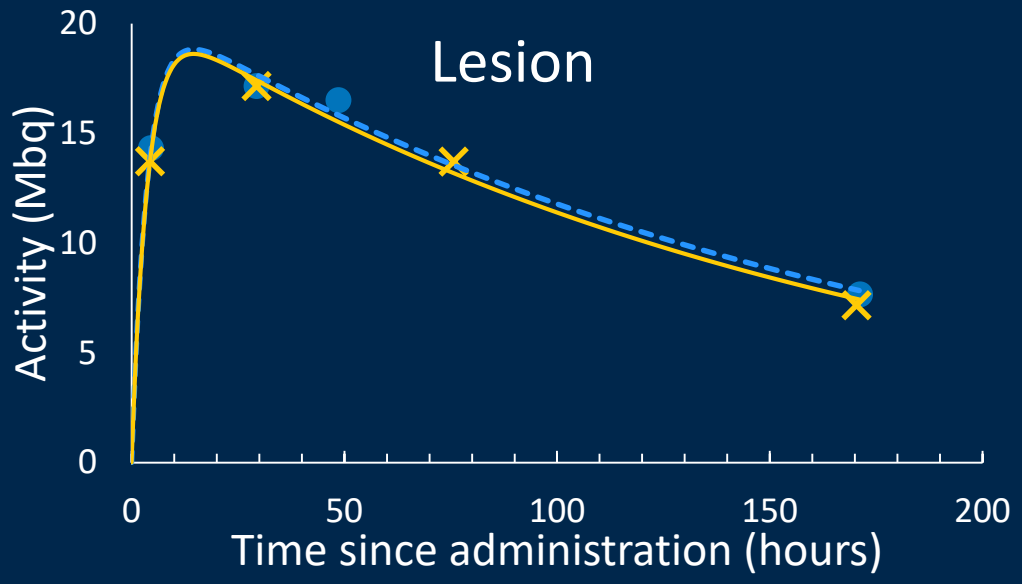
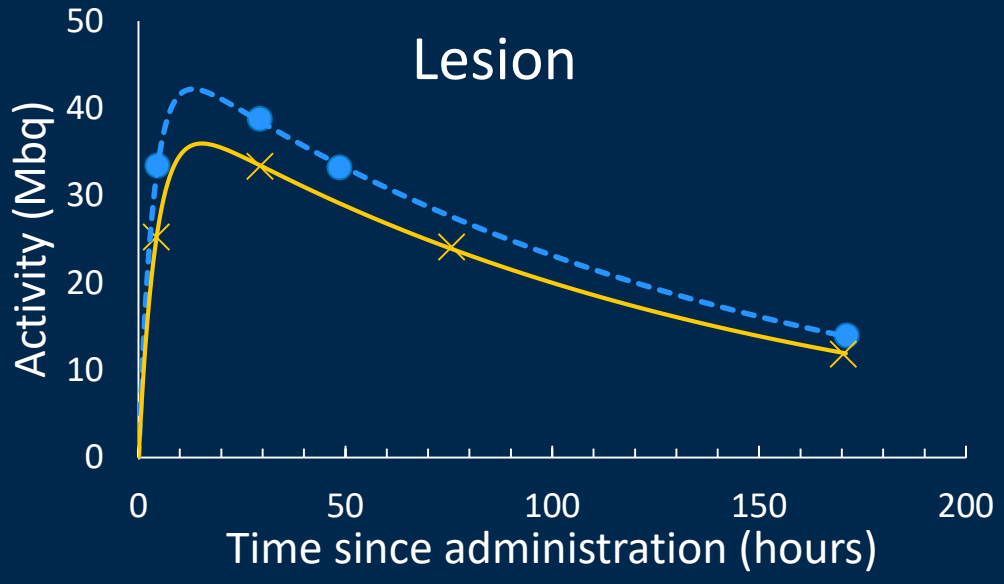
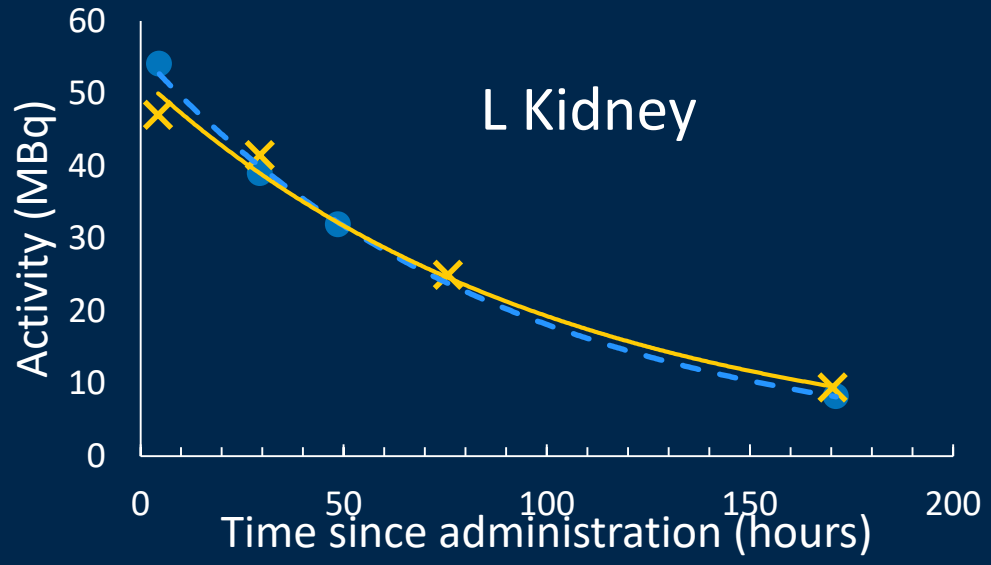
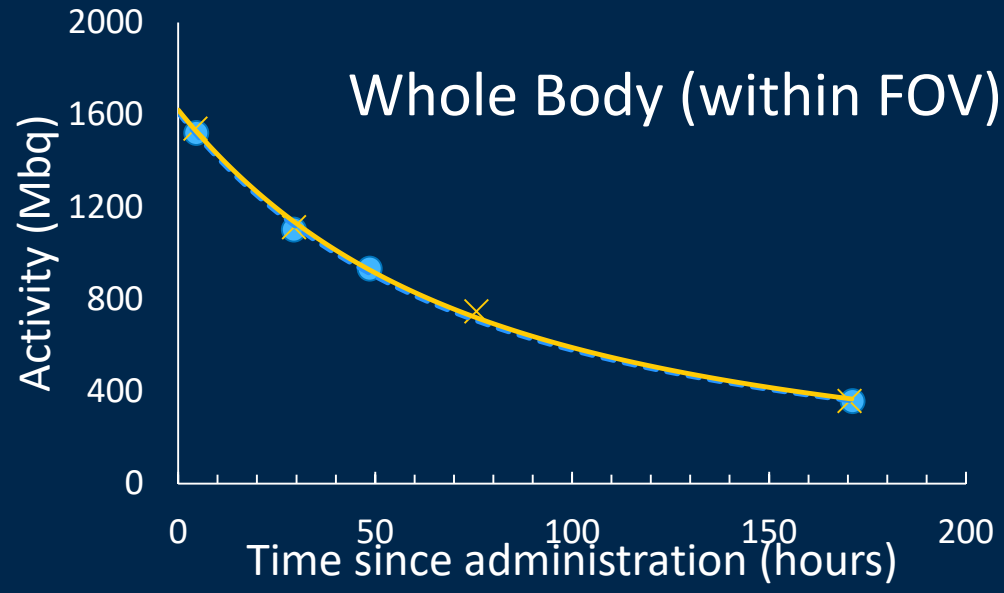
Patient #5: Cycle 1 vs 2









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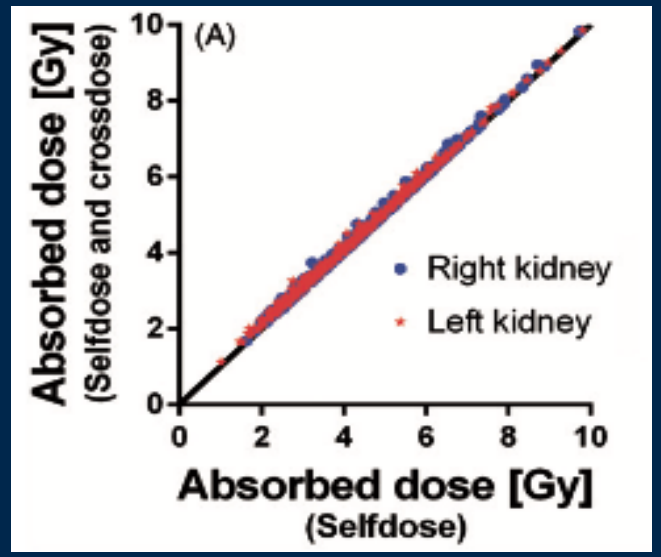
Lu-177 PRRT dosimetry simplification: ignore cross dose?

- How important is cross dose ?
  - Betas have short path length, gammas have low intensity
- 500 patients with NETs treated with Lu-177 DOTATATE
  - Kidney self dose from SPECT/CT. Cross dose from WB imaging



Sandström M, et al. Acta Oncol. 2018 Apr;57(4):516-521.

- Kidney self-dose 4.2 Gy (1.0 – 9.8) cross-dose 0.1 Gy (0.0 – 0.5)
  - < 10% cross dose in 97% of patients
  - > 10% only in patients with high tumor burden
- Important for tumor?
  - Simulation study showed minimal differences between MC and local energy absorption

Ljungberg M et al, Acta Oncologica, 2011; 50: 981–989

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Lu-177 PRRT simplification of dosimetry: AD vs. BED ?

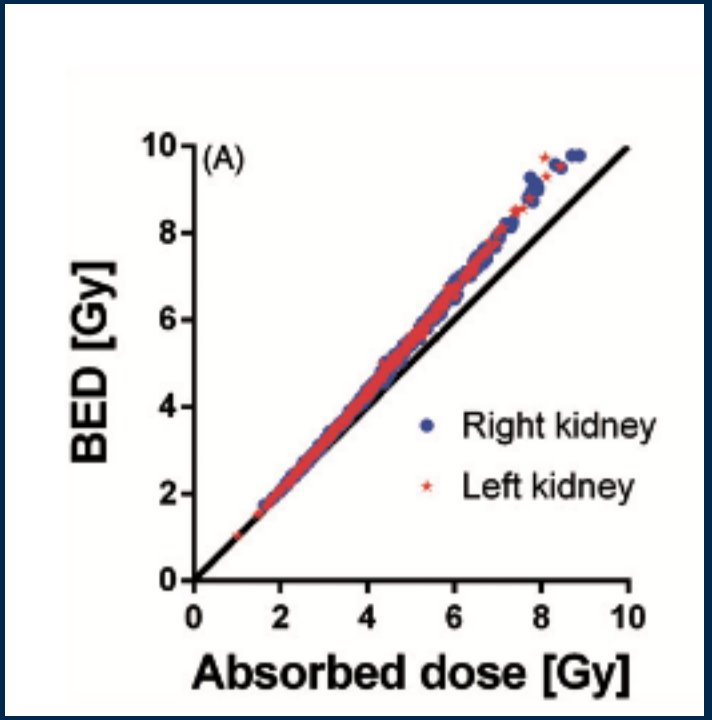
- BED was calculated as

$$BED = \sum_i D_i + \frac{\beta}{\alpha} \frac{t_{1/2}^{rep}}{t_{1/2}^{rep} + t_{1/2}^{eff}} \sum_i D_i^2$$

  - D_i is absorbed dose for cycle i
  - α/β = 2.6 Gy and t_{rep} = 2.8 h

- Results should be considered as approximations
  - α/β values used not specific to kidney and NETs

- 500 patients: BED only slightly higher than AD. Difference increases with absorbed dose



- But ...

Sandström M, et al. Acta Oncol. 2018 Apr;57(4):516-521.

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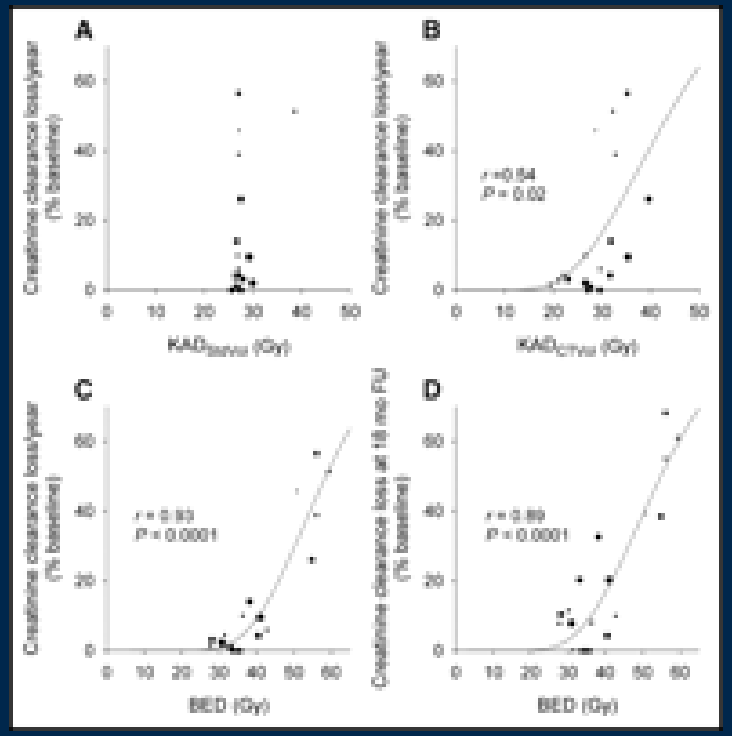
PRRT: AD vs.BED

Patient-Specific Dosimetry in Predicting Renal Toxicity with ^{90}Y-DOTATOC: Relevance of Kidney Volume and Dose Rate in Finding a Dose–Effect Relationship

J Nucl Med 2005; 46:99S–106S

Raffaella Barone, MD[1]; Françoise Borson-Chazot, MD, PhD[1]; Roelf Valkema, MD, PhD[2]; Stéphan Walrand, PhD[1];



- 'The use of a refined absorbed dose methodology led to the finding of a clear kidney dose–response relationship in patients treated with 90 Y-DOTATOC. Our data provide evidence that patient-specific anatomy and dose-rate effects cannot be neglected. The BED model appears to be a reliable predictor of toxicity and could thus be helpful in implementation of individual treatment planning'

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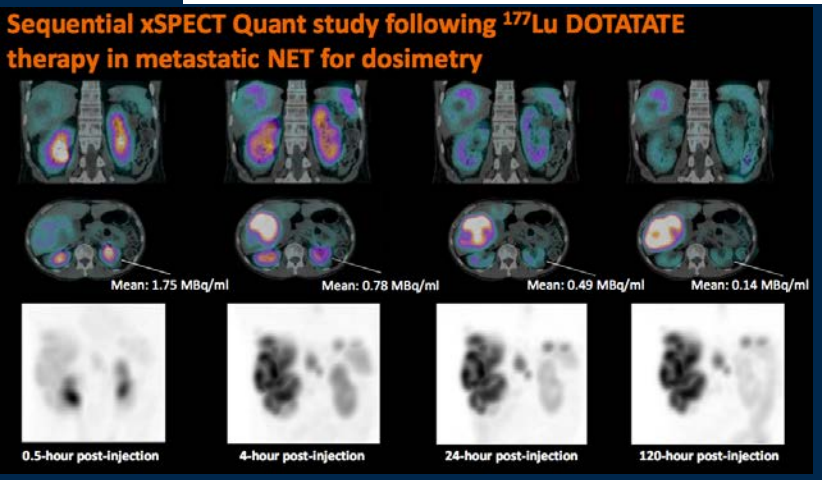
Several software options now available that facilitate patient specific dosimetry

Characterization of Noise and Resolution for Quantitative ^{177}Lu SPECT/CT with xSPECT Quant

Johannes Tran-Gia and Michael Lassmann

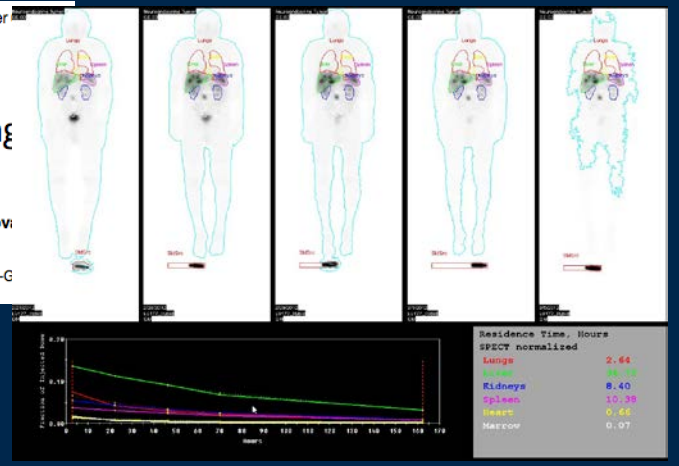


RESEARCH ARTICLE PLOS ONE | https://doi.org/10.1371/journal.pone.0187570 November

Software-assisted dosimetry in peptide receptor radionuclide therapy with ^{177}Lutetium-DOTATATE for various imaging scenarios

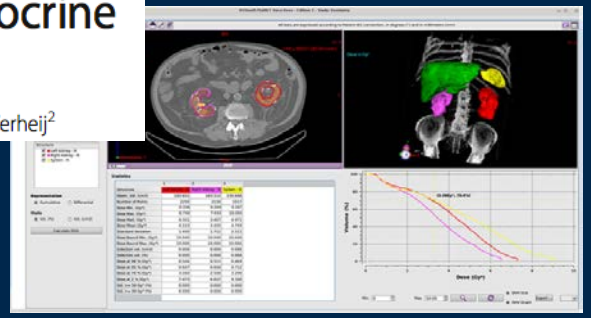
Dennis Kupitz[1]*, Christoph Wetz[1], Heiko Wissel[1], Florian Wedel[2], Ivayla Apostolova Thekla Wallbaum[1], Jens Ricke[1,4], Holger Amthauer[1,2], Oliver S. Grosser[1]

1 Department of Radiology and Nuclear Medicine, University Hospital Magdeburg A.ö.R., Otto-von-G University Magdeburg, Magdeburg, Germany, 2 Department of Nuclear Medicine, Charité—



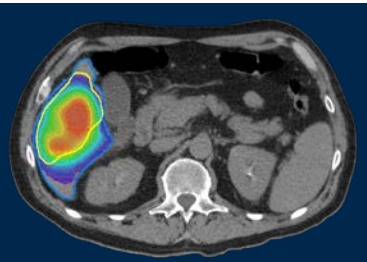
Dosimetry methods and clinical applications in peptide receptor radionuclide therapy for neuroendocrine tumours: a literature review

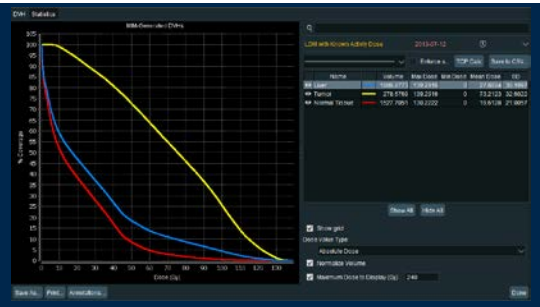
Daphne Merel Valerie Huizing[1], Berlinda Jantina de Wit-van der Veen[1], Marcel Verheij[2]



Validation of post-treatment PET-based dosimetry software for hepatic radioembolization of Yttrium-90 microspheres

Nichole M. Maughan and Jose Garcia-Ramirez
Department of Radiation Oncology, Washington University School of Medicine, St. Louis, MO 63110, USA

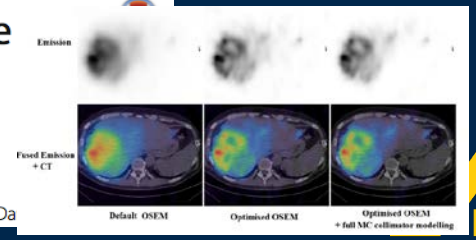




ORIGINAL RESEARCH Porter *et al. EJNMMI Research* (2018) 8:7

Phantom and clinical evaluation of the effect of full Monte Carlo collimator modelling in post-SIRT yttrium-90 Bremsstrahlung SPECT imaging

Charlotte A. Porter[1*], Kevin M. Bradley[2], Eero T. Hippeläinen[3], Matthew D. Walker[1] and Da



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Summary: Translating Patient Specific Dosimetry to the Clinic

- Do we need specialized reconstruction software & calibrations ?
  - Commercial software sufficient in several cases. Choose parameters.
- Do we need a radiologist for target segmentation ?
  - Commercial tools sufficient for organs, but typically not for lesions
- Do we need multiple-imaging time points ?
  - Single point methods possible, but must validate for each application
- Do we need Monte Carlo ?
  - LDM sufficient for soft tissue and pure β emitters or low intensity Photon emitters.
  - Consider voxel size, noise

	β (Mev) Max	β (Mev) Avg.	Max β range (mm)	γ (keV)
I-131	0.6	0.18	2	364 (82%) 637 (7%)
Y-90	2.3	0.94	11	
Lu-177	0.5	0.13	1.5	208 (10%) 113 (6%)

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Thank You

To patients who volunteered for the presented clinical studies.

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yuni@umich.edu

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