Dosimetry Needs and Methods for SRT: Lu-177

Yuni Dewaraja

Department of Radiology
University of Michigan

University of California, Davis; University of Iowa

NCI Workshop on Dosimetry of Systemic Radiopharmaceutical Therapy (SRT) Rockville, MD, April 19-20, 2018

Disclosures

- Yuni Dewaraja is a consultant for MIM Software, Inc.

MICHIGAN MEDICINE

Lu-177 Imaging/Dosimetry

- Used in targeted radionuclide therapies
  - PRRT for NETs (Lu-177 DOTATATE)
  - Lu-177 PSMA for metastatic prostate cancer
  - RIT for NHL (177Lu-Lilotomab Satetraxetan)

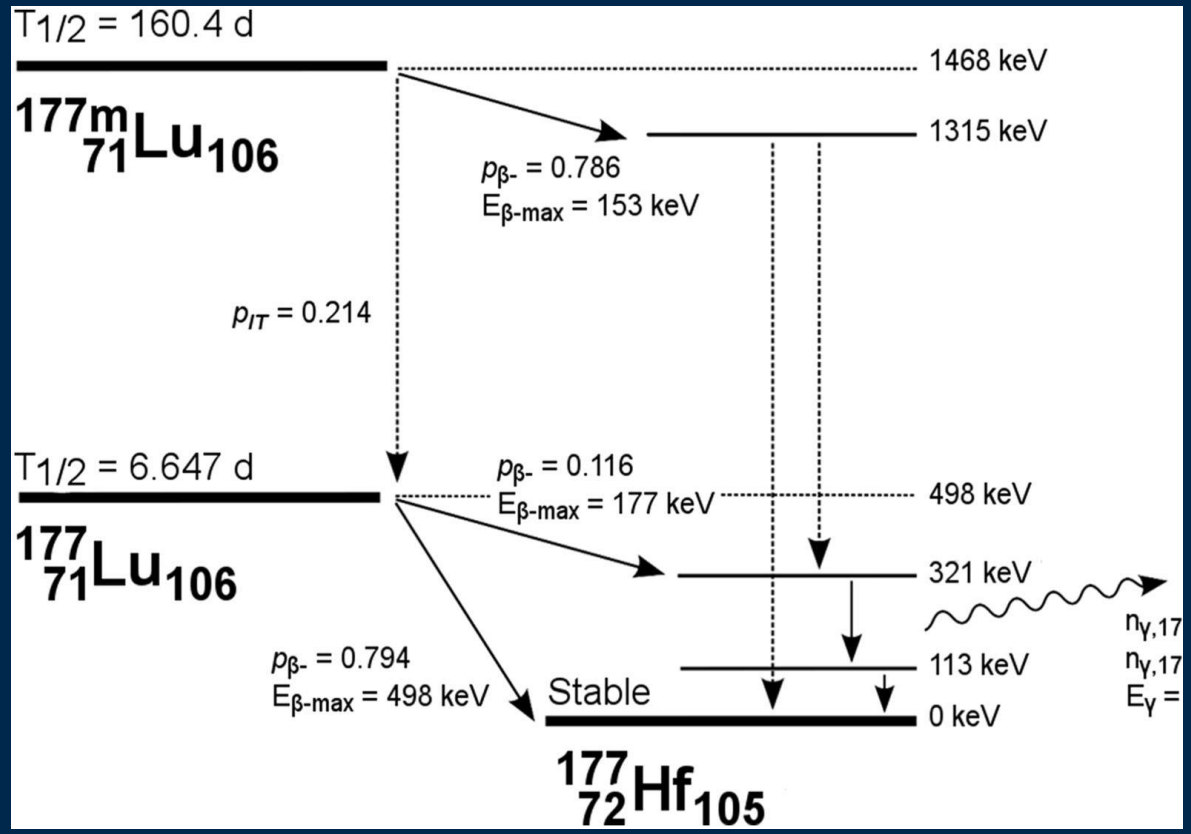
- β-emitter: E_{ave}=147 kev; E_{max}= 498 keV; mean tissue penetration=0.7 mm, max = 1.5 mm; $T_{1/2}$=6.7 d
  - More suitable for irradiating small tumor with less damage to normal tissue compared with Y-90
  - Gamm-ray emissions suitable for single-photon imaging

MICHIGAN MEDICINE

Decay Scheme

- Two low intensity γ rays
  - 208.4 (10.36%),112.9 keV(6.17%)
    - Typically not used for pre-therapy tracer imaging

- Produced by neutron activation by $^{176}Lu(n,\gamma)^{177}Lu$ reaction.
  - Long lived isomer ^{177m}Lu < 0.05% at a reference time of production



Katarina Sjögreen Gleisner et al. J Nucl Med 2015;56:976-984

MICHIGAN MEDICINE

Quantitative Lu-177 SPECT/CT for Dosimetry

MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative ^{177}Lu SPECT Applied for Dosimetry of Radiopharmaceutical Therapy

Michael Ljungberg[1], Anna Celler[2], Mark W. Konijnenberg[3], Keith F. Eckerman[4], Yuni K. Dewaraja[5], and Katarina Sjögreen-Gleisner[1]

In collaboration with the SNMMI MIRD Committee: Wesley E. Bolch, A. Bertrand Brill, Frederic Fahey, Darrell R. Fisher, Robert Hobbs, Roger W. Howell, Ruby F. Meredith, George Sgouros, and Pat Zanzonico, and the EANM Dosimetry Committee: Klaus Bacher, Carlo Chiesa, Glenn Flux, Michael Lassmann, Lidia Strigari, and Stephan Walrand.

[1]Department of Medical Radiation Physics, Lund University, Lund, Sweden; [2]Radiology Department, Medical Imaging Research Group, University of British Columbia, Vancouver, Canada; [3]Department of Nuclear Medicine, Erasmus University Medical Center, Rotterdam, Holland; [4]Easterly Scientific, Knoxville, Tennessee; and [5]Department of Radiology, University of Michigan Medical School, Ann Arbor, Michigan

The accuracy of absorbed dose calculations in personalized internal radionuclide therapy is directly related to the accuracy of the activity (or activity concentration) estimates obtained at each of the imaging time points. MIRD Pamphlet no. 23 presented a general overview of methods that are required for quantitative SPECT imaging. The present document is next in a series of isotope-specific guidelines and recommendations that follow the general information that was provided in MIRD 23. This paper focuses on ^{177}Lu (lutetium) and its application in radiopharmaceutical therapy.

Key Words: image processing; oncology; endocrine; radiobiology/dosimetry; radionuclide therapy; SPECT/CT; guideline; lutetium; quantitative SPECT

J Nucl Med 2016; 57:151–162

been used in radioimmunotherapy clinical trials to label different kinds of monoclonal antibodies (*7–15*).

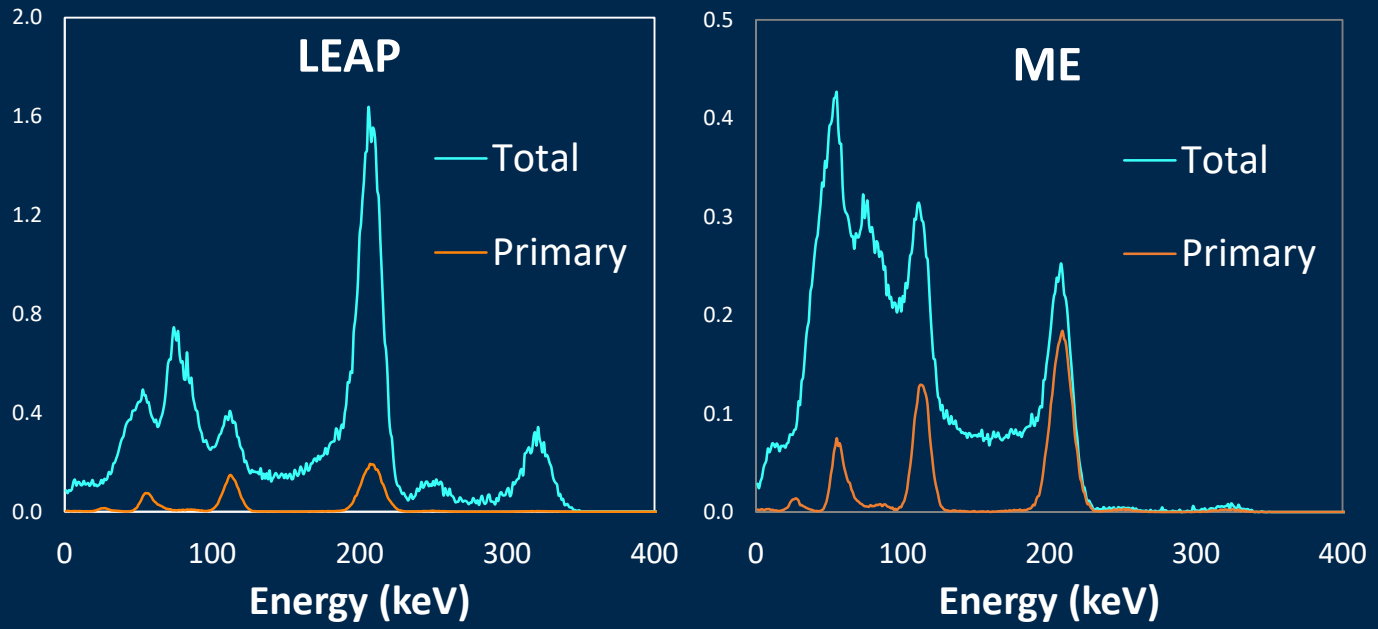
There is a growing body of evidence that radionuclide therapy should follow patient-specific planning protocols, similar to those that are being routinely used in external-beam radiation therapy. Recent literature reviews show correlations between absorbed dose and tumor response as well as normal-tissue toxicity (*16*). Such correlations indicate that treatments should be based on personalized dosimetry, aiming to deliver therapeutically effective absorbed doses to tumors, while keeping doses to organs at risk below the threshold levels for deterministic adverse effects. In clinical PRRT studies, the primary adverse effects have been mainly renal and hematologic toxicities (*2,6*).

Although several studies have reported estimates of absorbed doses

MICHIGAN MEDICINE

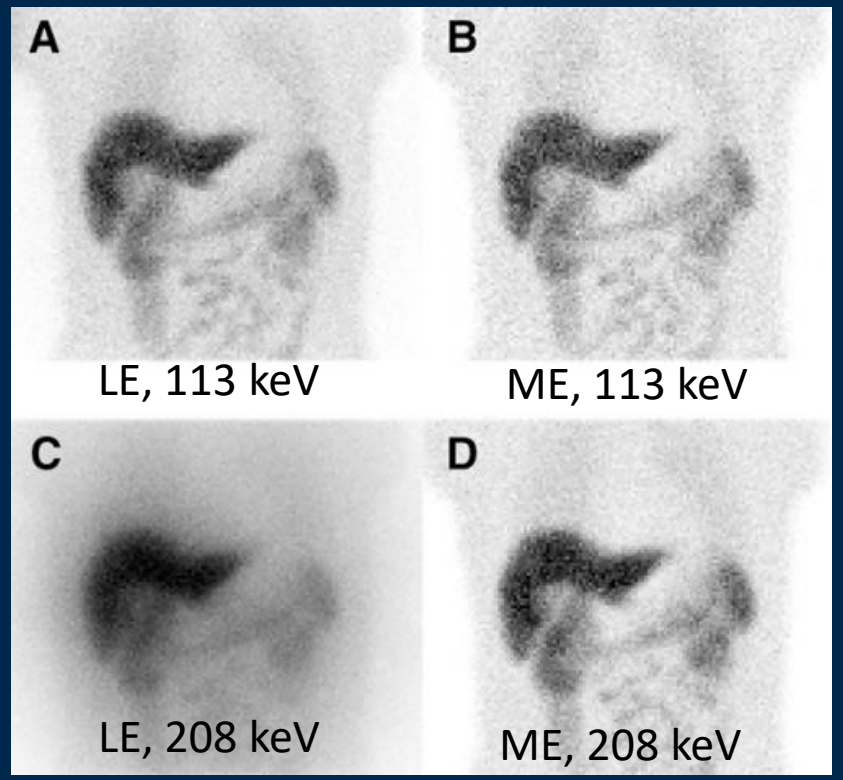
MIRD 26: Guidelines for SPECT

- Medium Energy Collimator, 208 keV photopeak window



Ratios of Scattered Photons to Total Number of Photons Detected Within Energy Window (15% or 20%)

		113-keV window		208-keV window	
Crystal	Collimator*	15%	20%	15%	20%
3/8″	HE	0.60	0.55	0.27	0.22
3/8″	ME	0.60	0.55	0.27	0.22
3/8″	LEGP	0.53	0.49	0.21	0.18
3/8″	LEHR	0.49	0.47	0.20	0.17

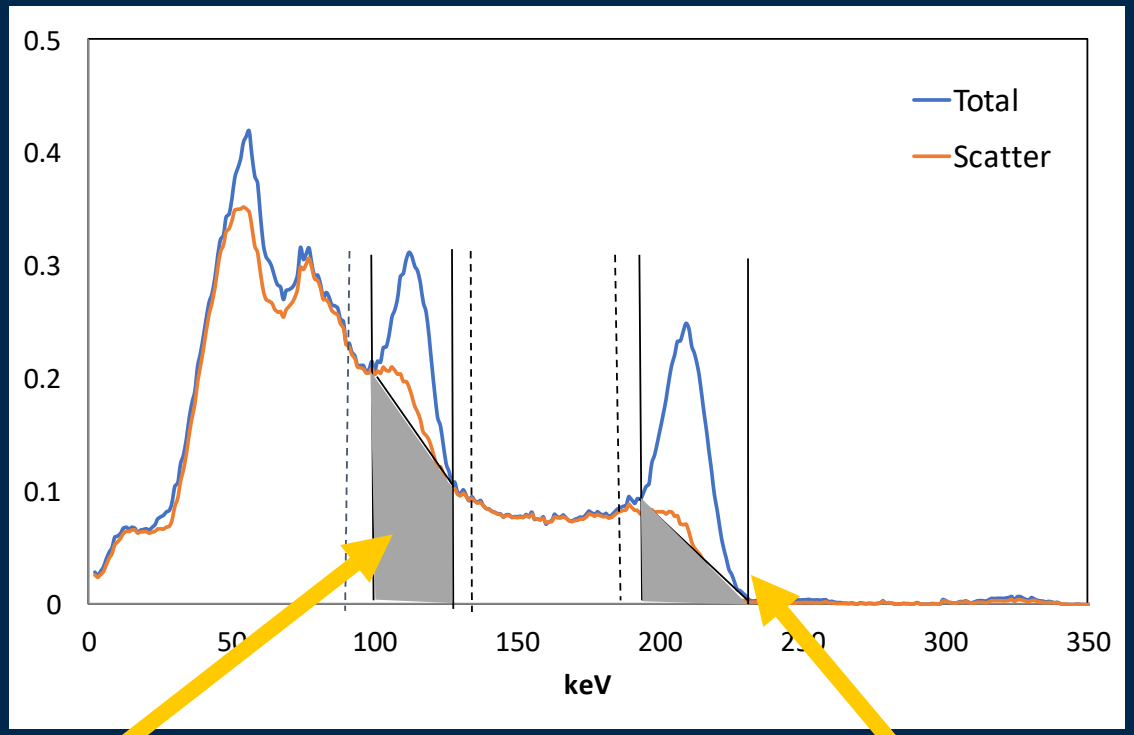


Ljungberg et al, MIRD 26, JNM 2016

MICHIGAN MEDICINE

Scatter correction

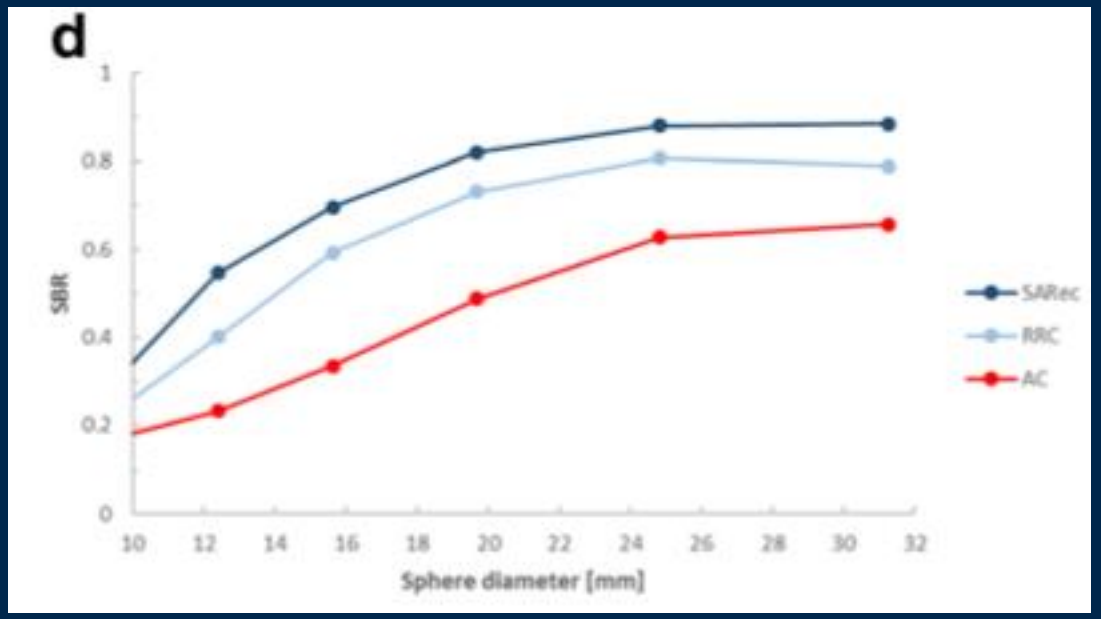
- Triple Energy Window



Use 3 windows when there is downscatter from higher peak
Trapezoidal estimate of scatter

Don't need upper window when no downscatter
Triangular estimate of scatter

- Monte Carlo based reconstruction
  - Improved recovery



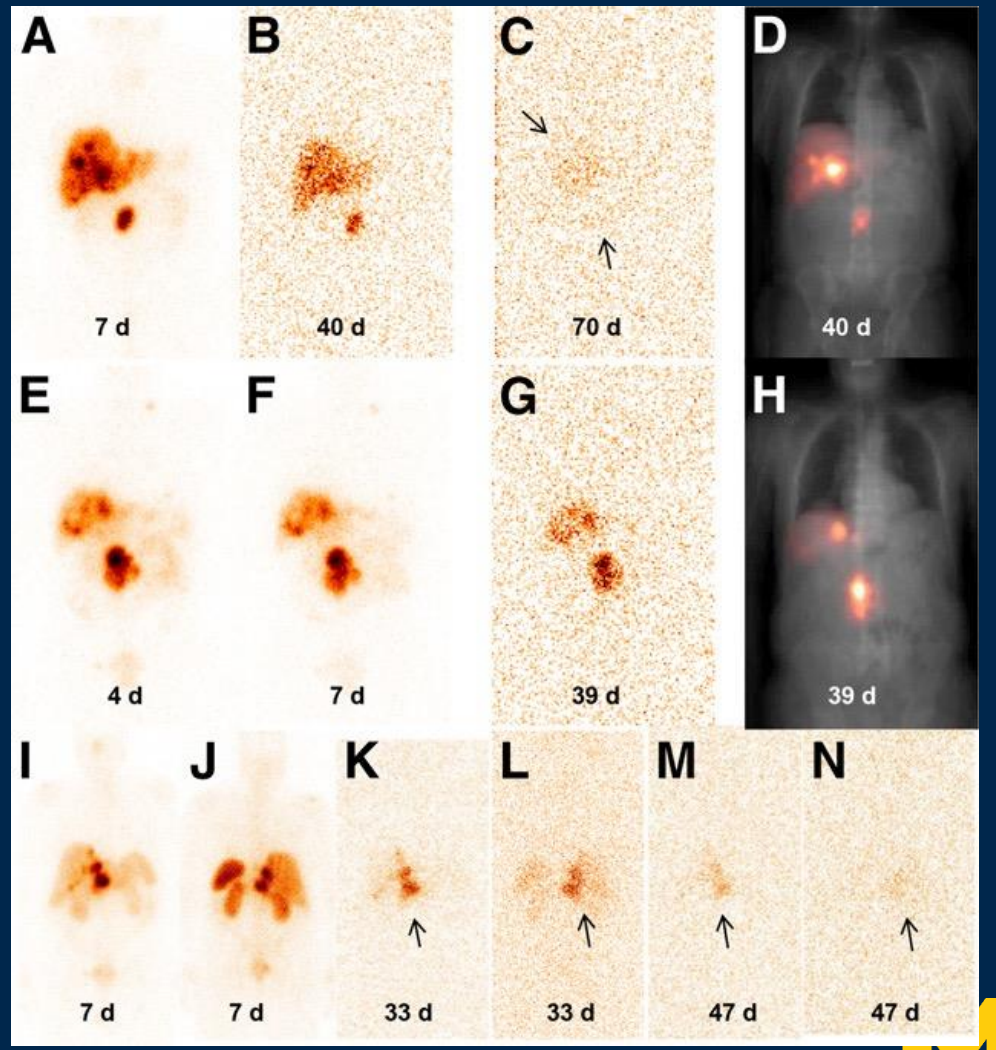
Rydén et al. EJNMMI Physics (2018) 5:1

MICHIGAN MEDICINE

Long-term retention of Lu-177/Lu-177m

- Validity of extrapolating the 0 – 7 day time-activity fitted function to infinity

- 7 patients imaged at 5 – 7 weeks
  - Well visualized tumor uptake
  - Kidney uptake in 1 case
  - AD to WB and tumor 5 - 6% higher if later point is included
  - Tumor retension of Lu-177
  - Contribution from impurity Lu-177m negligible



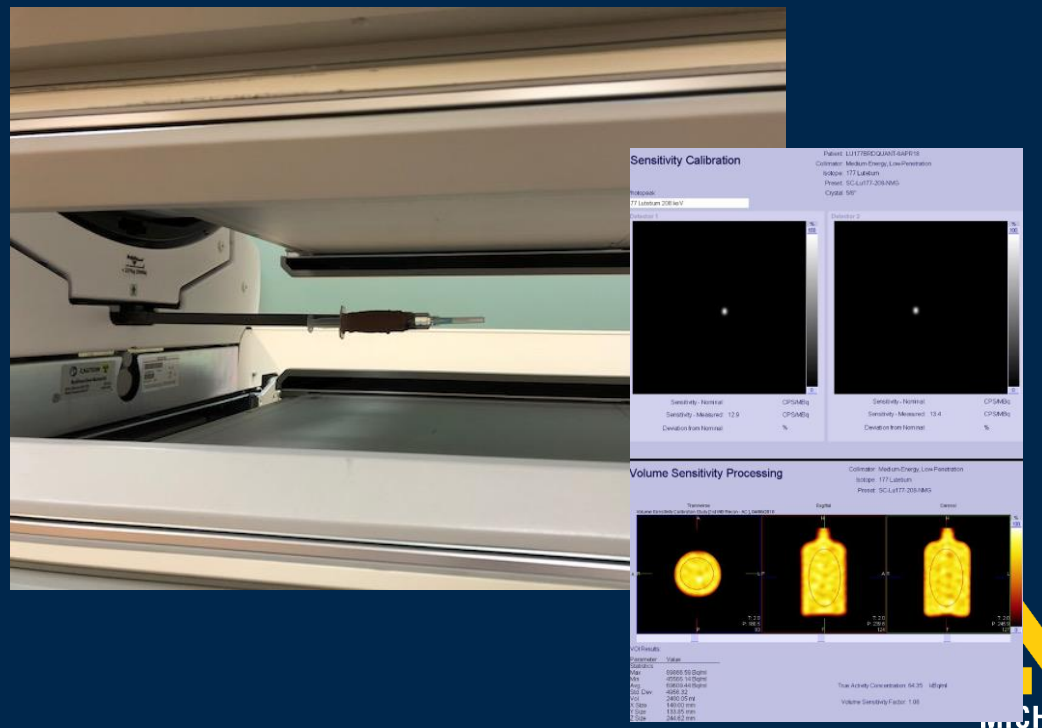
Katarina Sjögreen Gleisner et al. J Nucl Med 2015;56:976-984

MICHIGAN MEDICINE

Quantitative Lu-177

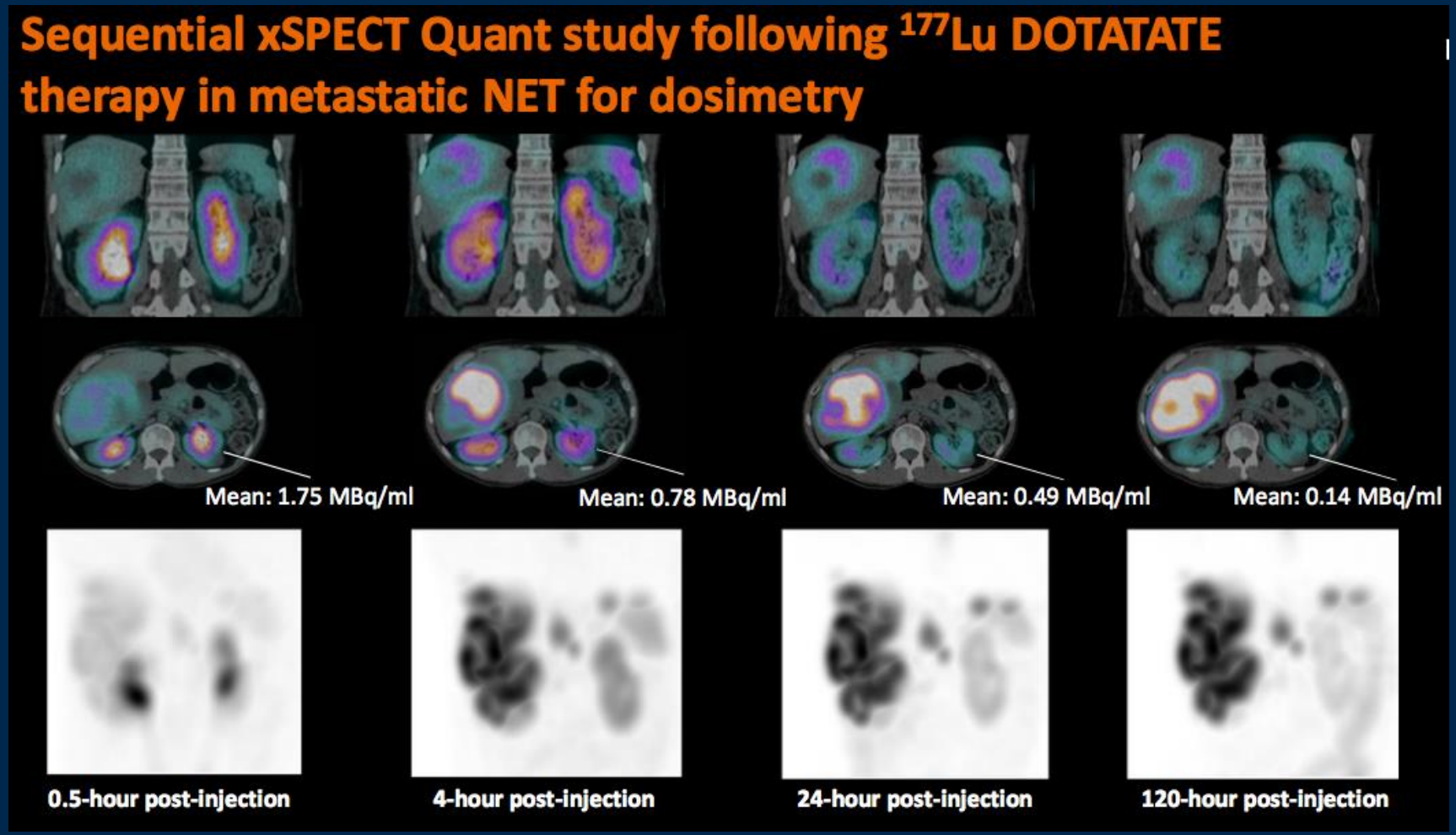
- xSPECT Calibration

- ‘Manual’ Calibration

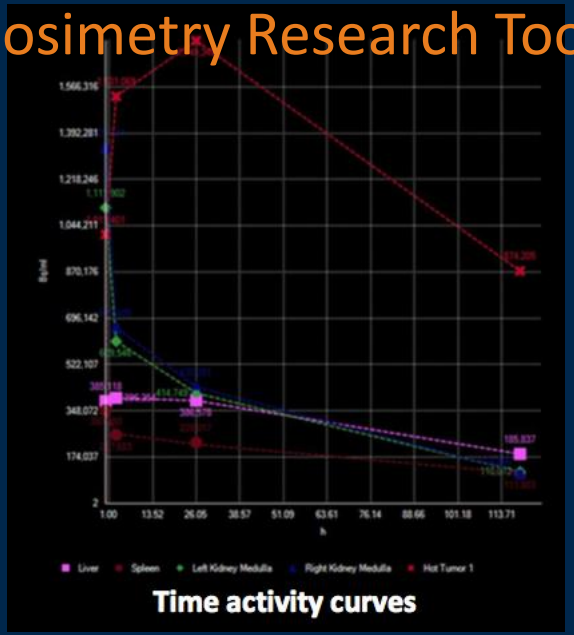


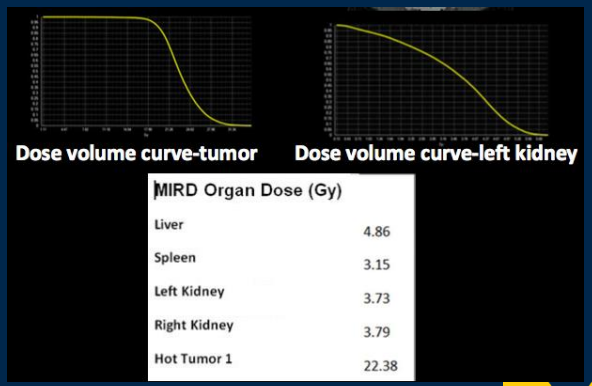
MICHIGAN MEDICINE

Commercially available tools: XSPECT Quant



Dosimetry Research Tool





Courtesy of Johannes Zeintl, Siemens Healthineers

MICHIGAN MEDICINE

Quantitative Lu-177 SPECT/CT Evaluation

- **Optimizing Image Quantification for ^{177}Lu SPECT/CT Based on a 3D Printed 2-Compartment Kidney Phantom**

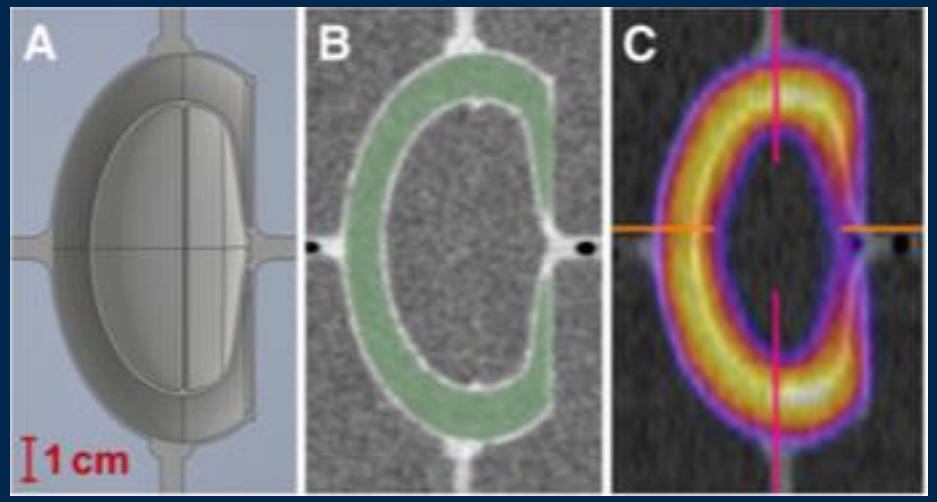
Johannes Tran-Gia and Michael Lassmann

Department of Nuclear Medicine, University of Würzburg, Würzburg, Germany

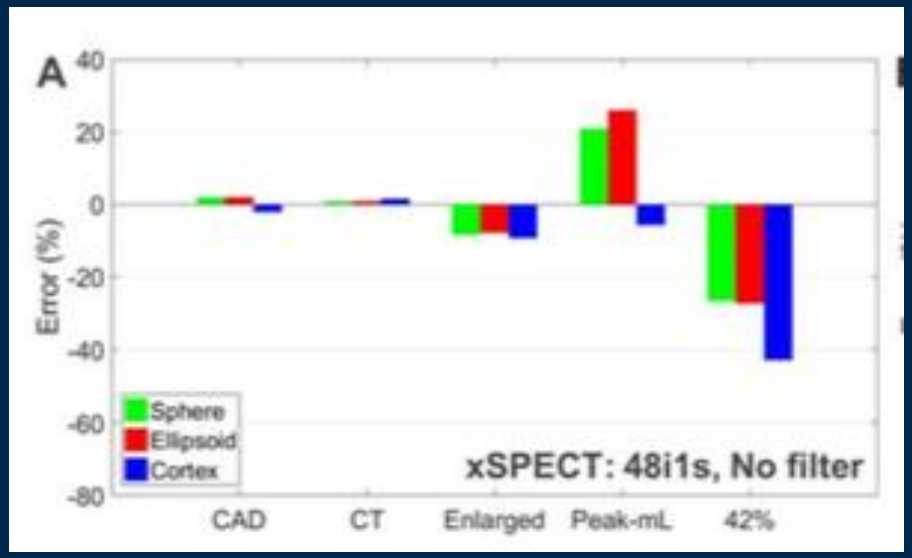
The aim of this work was to find an optimal setup for activity determination of ^{177}Lu-based SPECT/CT imaging reconstructed with 2 commercially available methods (xSPECT Quant and Flash3D). For this purpose, 3-dimensional (3D)–printed phantoms of different geometries were manufactured, different partial-volume correction (PVC) methods were applied, and the accuracy of the activity determina-

Key Words: radionuclide therapy; 2-compartment kidney phantom; 3D printing; partial volume correction; quantitative SPECT/CT; xSPECT Quant

J Nucl Med 2018; 59:616–624
DOI: 10.2967/jnumed.117.200170



With PVC, accuracy of activity in sphere, ellipsoid, cortex



MICHIGAN MEDICINE

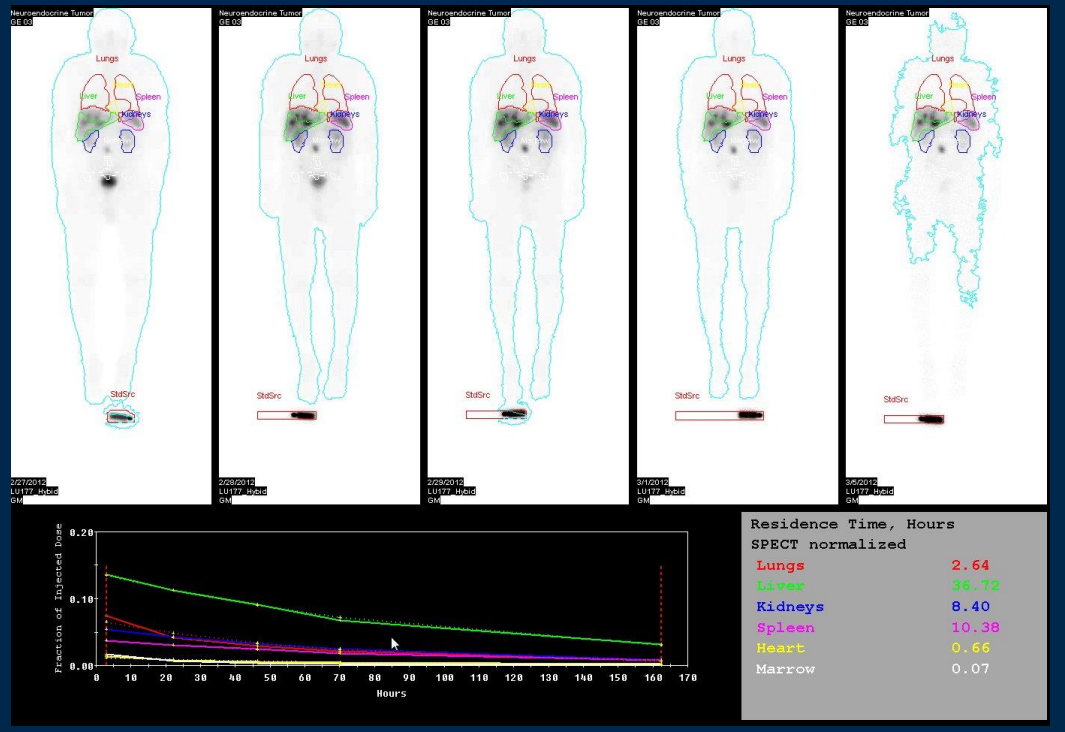
Commercially available software: GE Dosimetry Toolkit

RESEARCH ARTICLE PLOS ONE | https://doi.org/10.1371/journal.pone.0187570 November 6, 2017

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[1,3], 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-Guericke University Magdeburg, Magdeburg, Germany, 2 Department of Nuclear Medicine, Charité—



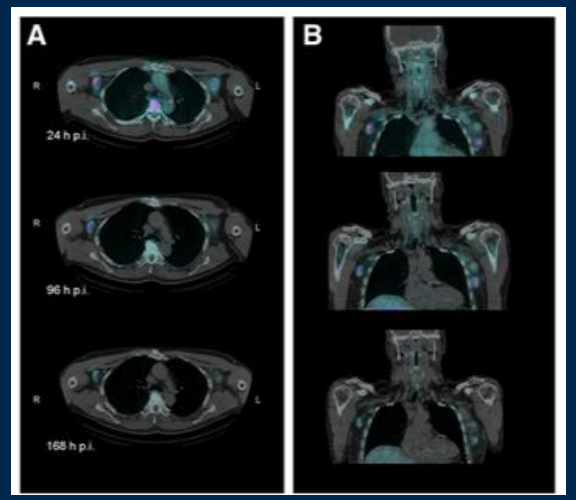
- Analysis using GE Dosimetry Toolkit coupled with OLINDA
  - Quantification, registration, segmentation, time-activity fit
  - Compared Multi SPECT/CT, WB only and hybrid WB -SPECT/CT

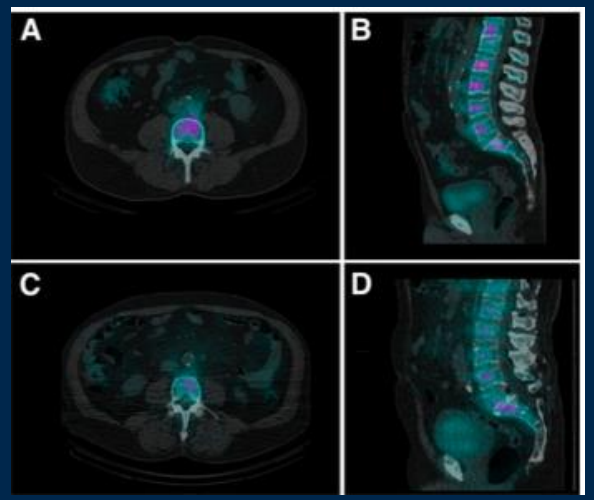
	Absorbed dose per admin. activity (Gy per GBq)		
	Multi SPECT/CT	Hybrid	Planar
Lesions	2.58 ± 1.47	3.09 ± 2.16	5.32 ± 6.26
Kidney	0.48 ± 0.18	0.59 ± 0.30	0.76 ± 0.43

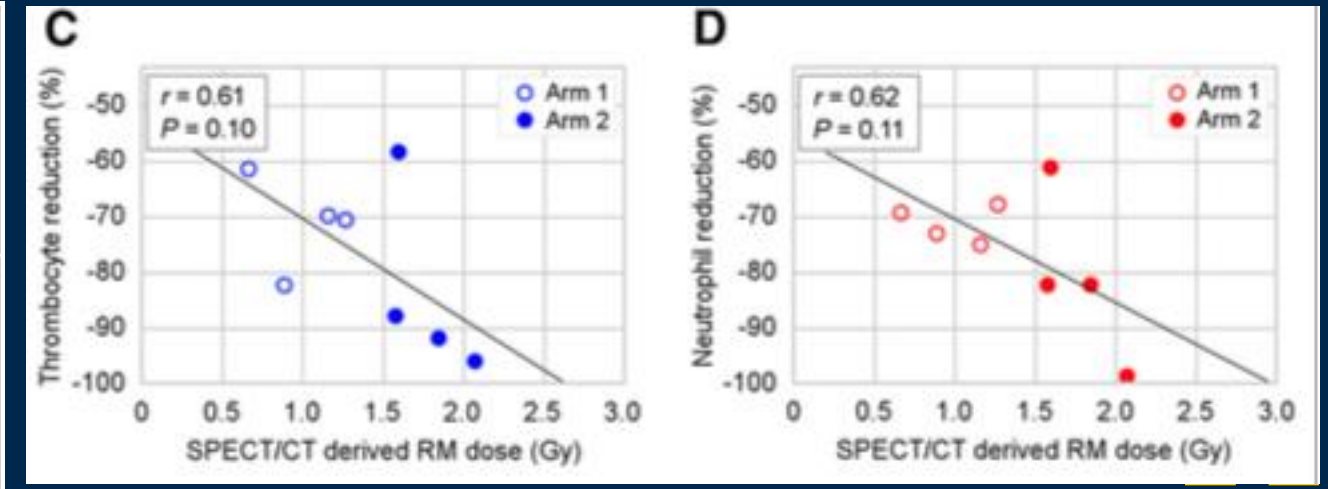
MICHIGAN MEDICINE

SPECT/CT based dosimetry in Lu-177 Lilotomab RIT of NHL

- 8 patients, SPECT/CT at 24, 96, 168 h
  - Tumor dosimetry using OLINDA sphere model
  - Imaging (lumbar vertebrae) based bone marrow dosimetry
- Median tumor absorbed dose 264 cGy (range 75 – 794 cGy)
- Red marrow dose 57 to 208 cGy
  - Statistically significant dose-toxicity (not with blood-based calc.)







Blakkisrud et al, JNM 2017 ;48-54 and 55-61

MICHIGAN MEDICINE

Why patient specific dosimetry? Trial at Lund University

Eur J Nucl Med Mol Imaging (2017) 44:1480–1489
DOI 10.1007/s00259-017-3678-4

ORIGINAL ARTICLE

Individualised ^{177}Lu-DOTATATE treatment of neuroendocrine tumours based on kidney dosimetry

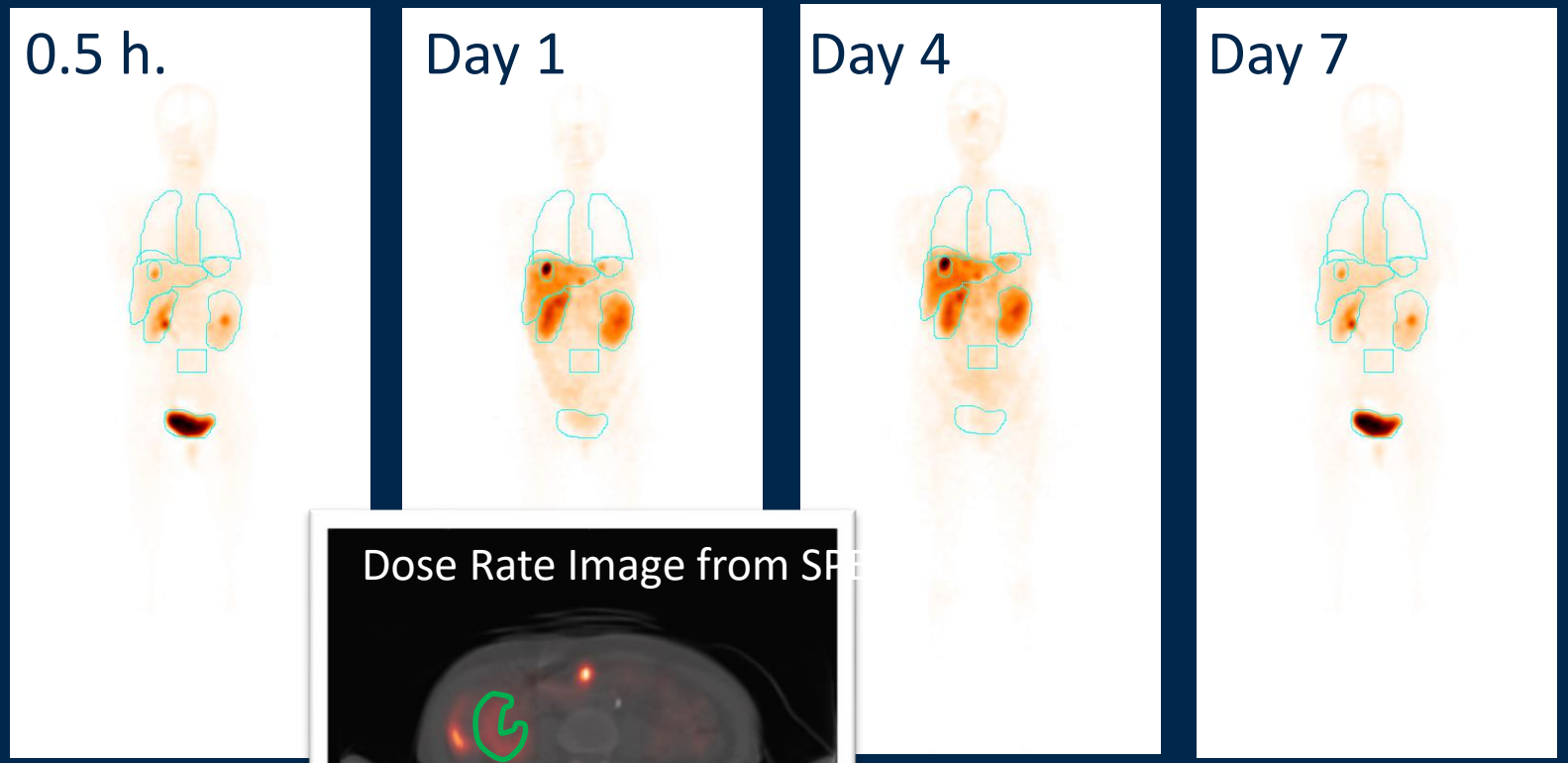
Anna Sundlöv[1,2] · Katarina Sjögreen-Gleisner[3] · Johanna Svensson[4] · Michael Ljungberg[3] · Tomas Olsson[2] · Peter Bernhardt[5,6] · Jan Tennvall[1,2]

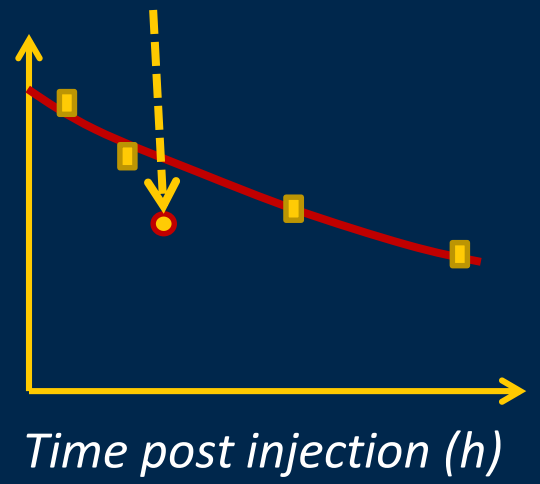
- Treatment based on renal dosimetry
- 51 patients with NET
- Purpose was to give as many standard (7.4 GBq) cycles keeping kidney BED < 27 Gy
- Detailed dosimetry using hybrid planar/SPECT approach

MICHIGAN MEDICINE

Lu-177 DOTATATE trial at Lund Univ.: Hybrid Planar/SPECT

Co-registered whole-body images





Courtesy of Michael Ljungberg, Lund University Sweden

MICHIGAN MEDICINE

Why Patient Specific Dosimetry? Lund Univ. Trial

- Treatment based on renal dosimetry
  - Considerable variation in number of cycles.
    - Median 5 cycles, range 3 – 7
    - No Grade 3-4 toxicity
    - Absorbed dose/cycle varied between patients and between cycles for the same patient
- Highlights the value of individualized dosimetry

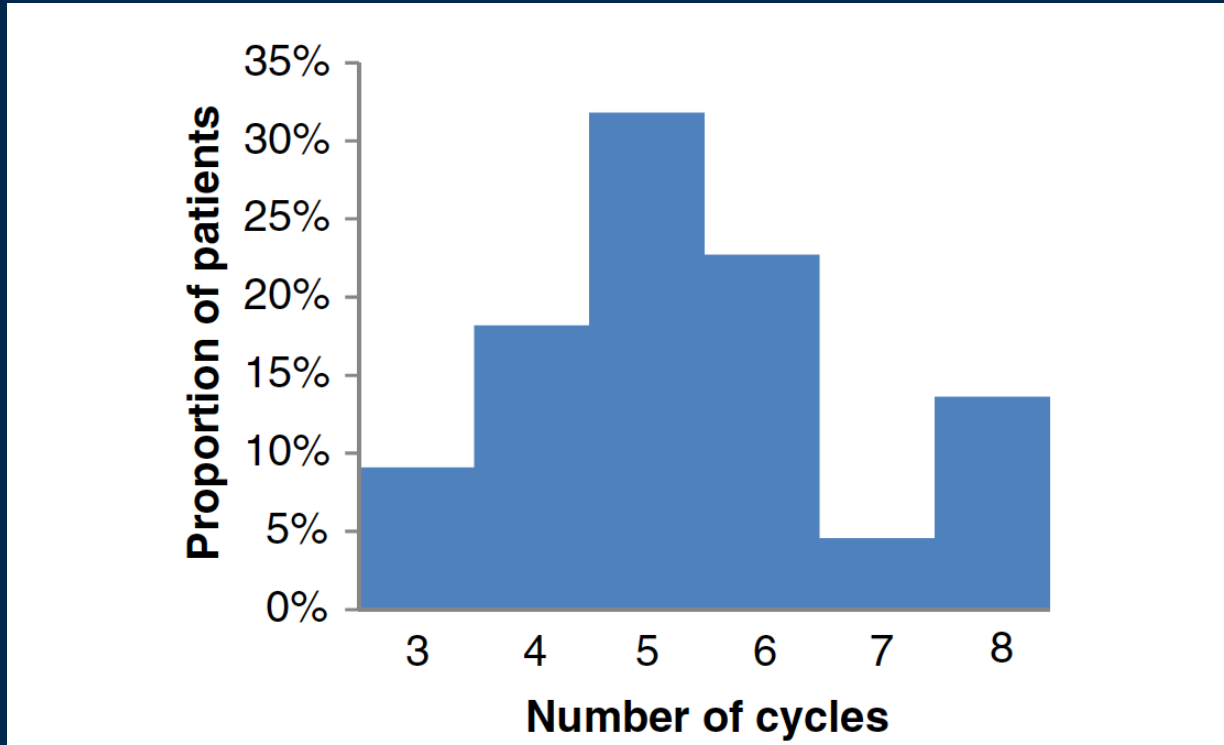


Fig. 3 Frequency distribution of number of cycles delivered within the protocol-specified BED-limits

MICHIGAN MEDICINE

Why patient specific dosimetry?

ACTA ONCOLOGICA, 2018
VOL. 57, NO. 4, 516–521
ACTA ONCOLOGICA, 2018
VOL. 57, NO. 4, 516–521
https://doi.org/10.1080/0284186X.2017.1378431

ORIGINAL ARTICLE

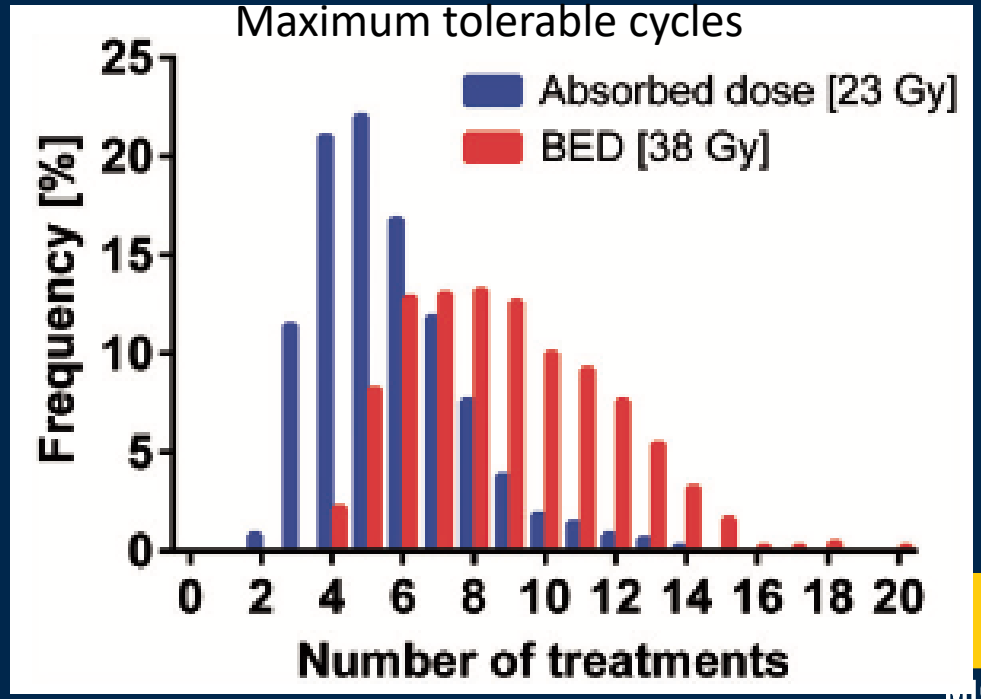
Kidney dosimetry during ^{177}Lu-DOTATATE therapy in patients with neuroendocrine tumors: aspects on calculation and tolerance

Mattias Sandström[a,b], Ulrike Garske-Román[a], Silvia Johansson[c], Dan Granberg[d], Anders Sundin[a] and Nanette Freedman[e,f]

- 500 patients: SPECT/CT and WB imaging at 1,4,7 d after cycle 1. Assumed same AD from all cycles

- Considerable variation in AD, BED
  AD 4.4 (1.7–9.8), 4.2 Gy (1.1–9.8)
  BED 4.7(1.7-11.6), 4.4Gy (1.0-11.8)
  for R & L kidney

- With BED limit of 38 Gy to kidney and AD limit of 2 Gy to marrow 95% could get > 4 cycles with only 0.5% reaching limit at 3 cycles.



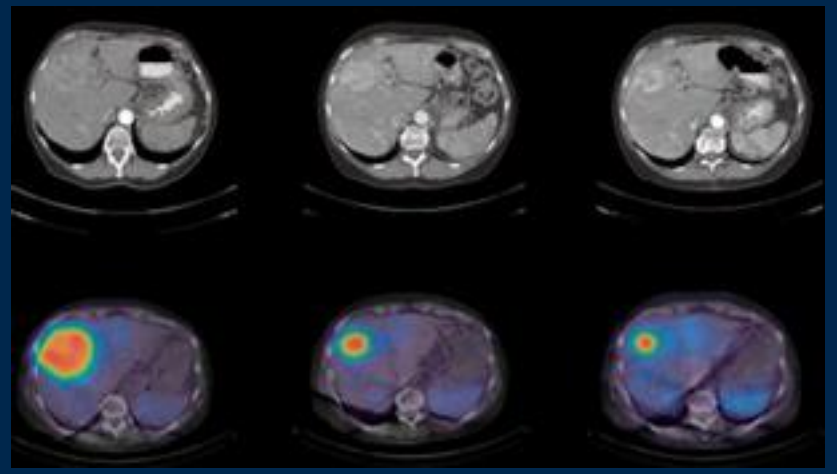
MICHIGAN MEDICINE

Why Patient Specific Dosimetry? Tumor dose-response

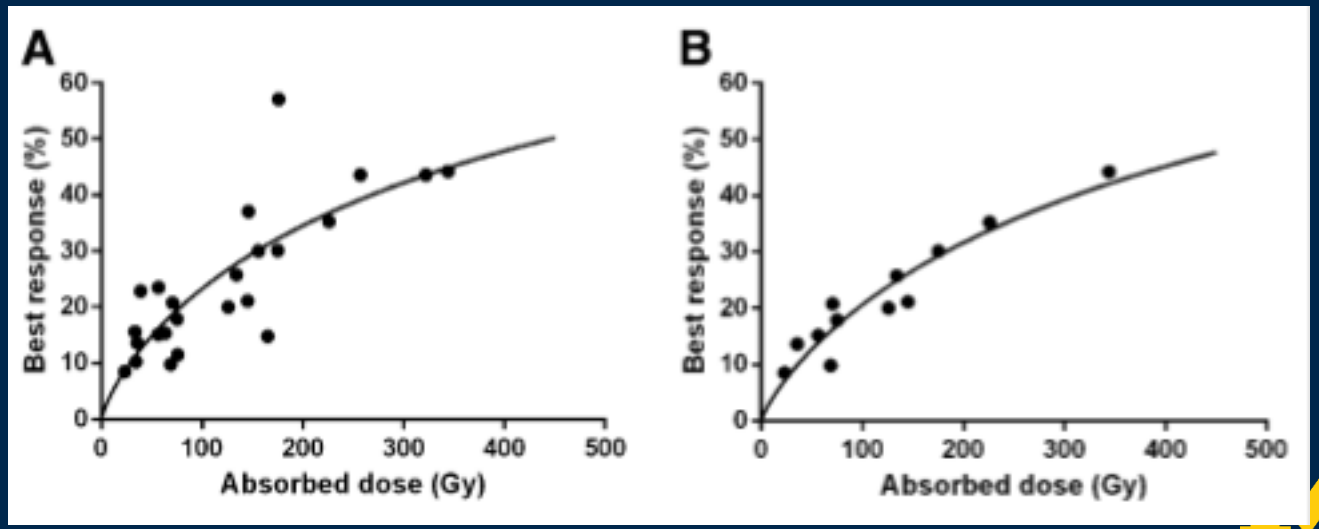
Dose Response of Pancreatic Neuroendocrine Tumors Treated with Peptide Receptor Radionuclide Therapy Using ^{177}Lu-DOTATATE

Ezgi Ilan[1,2], Mattias Sandström[1,2], Cecilia Wassberg[1,3], Anders Sundin[1,3], Ulrike Garske–Román[1,3], Barbro Eriksson[4], Dan Granberg[4], and Mark Lubberink[1,2]

J Nucl Med 2015; 56:177–182



- 24 lesions (> 2.2 cm)
- Sequential SPECT/CT at 24, 96, 168 h after some cycles
- PVC, no SC, OLINDA AD calculation (self-dose)



MICHIGAN MEDICINE

Simplification of procedure: single time point dosimetry

- **Dose Mapping After Endoradiotherapy with ^{177}Lu-DOTATATE/DOTATOC by a Single Measurement After 4 Days**

  Heribert Hänscheid[1], Constantin Lapa[1], Andreas K. Buck[1], Michael Lassmann[1], and Rudolf A. Werner[1,2]

- Presented the theory to show that dose can be estimated within reasonable accuracy from a single measurement post-administration

Time integral ~ $u(r_s,t_1) * 2 * t_1/\ln(2)$

Single meas. at t_1

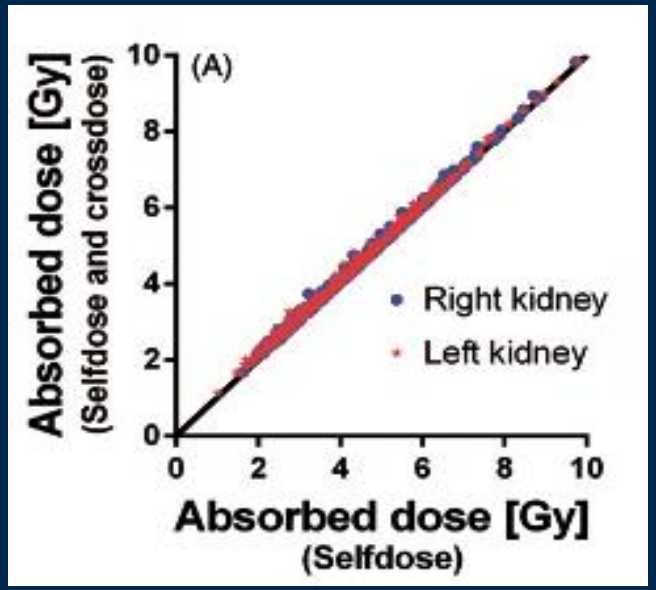
- Planar imaging of 29 patients at 4, 24, 38 and 96 h with mono and bi-exponential fits
- Deviations of the approx. from the 'true' time integral for t_1 =24, 48, 72, 96, 120, 144 h

		$\tilde{u}_1(r_S,t_1)/\tilde{u}(r_S) - 1$					
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%
Liver	1 (maximum)	−33%	−1%	+10%	+12%	+10%	+6%
	0.9	−37%	−6%	+7%	+9%	+8%	+5%
	0.5 (median)	−43%	−11%	+4%	+6%	+3%	−1%
	0.1	−52%	−21%	−4%	+3%	−1%	−11%
	0 (minimum)	−64%	−38%	−20%	−7%	−4%	−12%
Spleen	1 (maximum)	−31%	+3%	+20%	+20%	+17%	+13%
	0.9	−38%	−2%	+12%	+15%	+12%	+8%
	0.5 (median)	−44%	−12%	+5%	+8%	+6%	+1%
	0.1	−53%	−22%	−4%	+5%	+3%	−7%
	0 (minimum)	−58%	−27%	−9%	+2%	−4%	−16%
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%

Simplification of procedure: ignore cross dose?

- How important is cross dose for Lu-177?
  - Betas have short path length, gammas have low intensity
- 500 patients with NETs treated with Lu-177 DOTATATE
  - Kidney self dose from SPECT/CT at 1, 4, 7 d.
  - Cross dose from WB imaging and OLINDA dose factors

- Kidney self-dose 4.2 Gy(1.0–9.8),cross-dose 0.1Gy(0.0–0.5)



cross-dose
< 10% in
97% of patients

- Important for tumor?
  - Simulation study showed minimal differences between MC and local energy absorption

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

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

MICHIGAN MEDICINE

Simplification of procedure: AD vs. BED ?

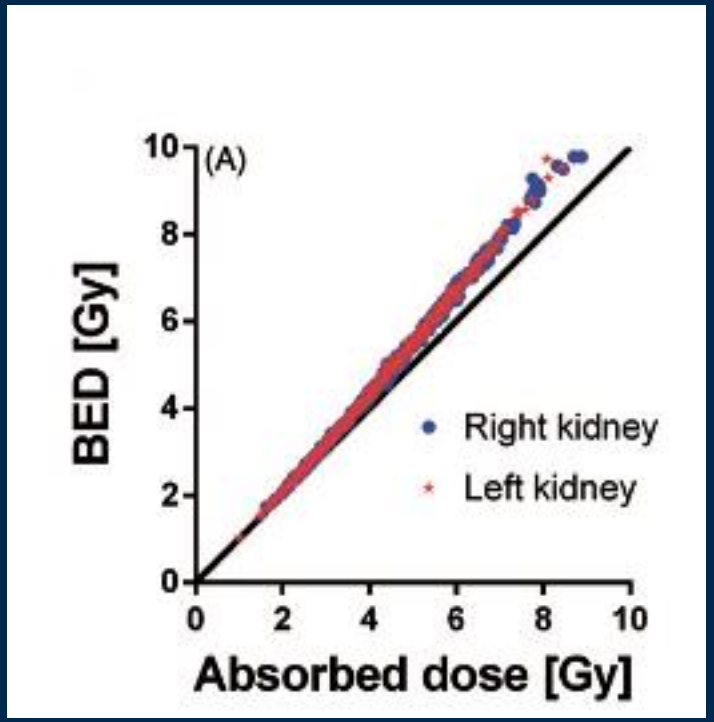
- BED was calculated as

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

  - 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 not specific to kidney and PRRT

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

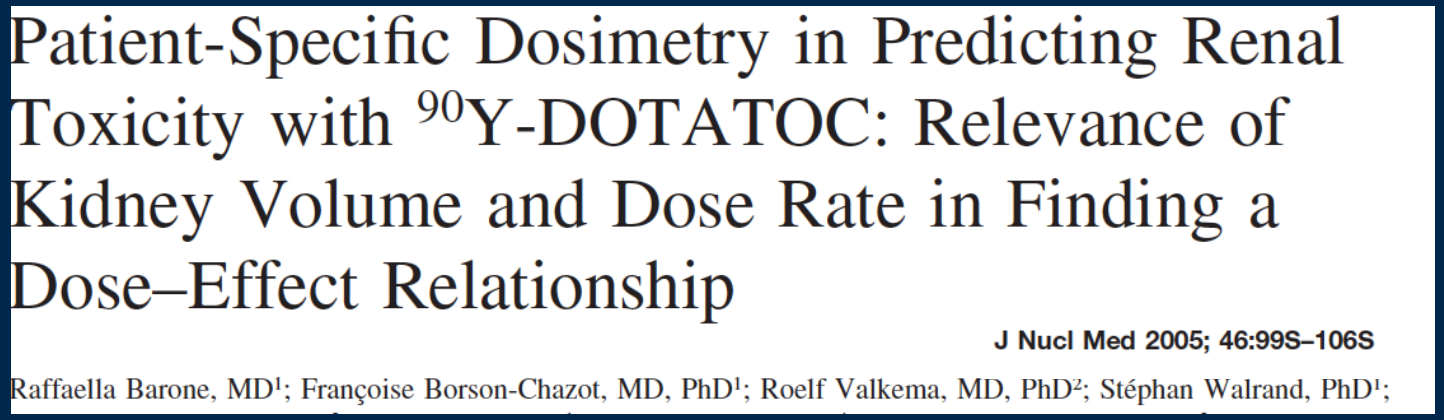


- But …

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

MICHIGAN MEDICINE

Simplifications?



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'

MICHIGAN MEDICINE

Thank You

yuni@umich.edu

MICHIGAN MEDICINE