

# Radiopharmaceutical Therapy (RPT) Dosimetry

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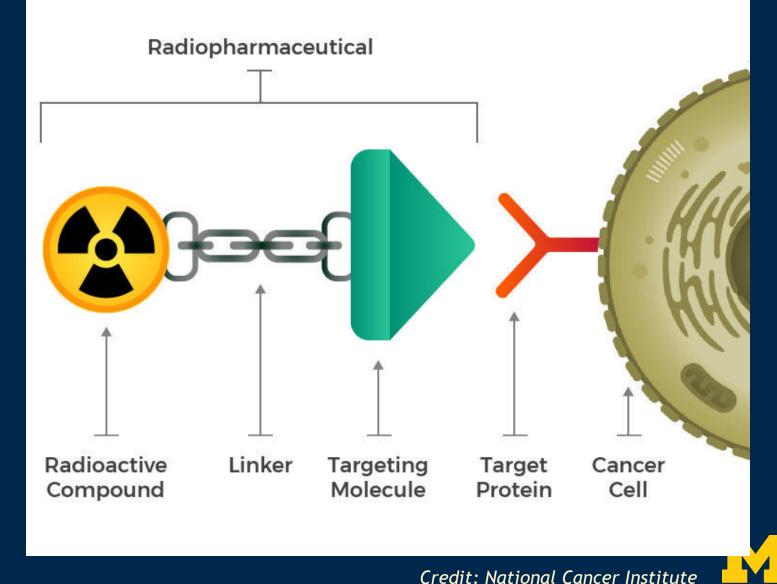
# Disclosures

- Yuni Dewaraja
  - Grant support from Varian
  - Software support from MIM Software, Inc
  - Software support from Siemens Molecular Imaging
  - Consultant for MIM Software, Inc.



# Radiopharmaceutical therapy (RPT)

- Also referred to as internal emitter therapy, radionuclide therapy, ...
- Radiopharmaceuticals: consist of a radioactive molecule, a targeting molecule, and a linker that joins the two
  - 177Lu-PSMA, DOTATATE
  - Radioiodine therapy: the radioisotope (1311, 1241 or 1231) can be directly mediated by the sodium-iodide symporter in the thyroid cells.
  - Radioembolization: intraarterial administration of Y-90 microspheres



# Radiopharmaceutical Therapy

- <u>Current</u>: Fixed activity ("one dose fits all") or weight-based
  - Convenient, but variability in pharmacokinetics & anatomy not considered
  - Potential for under-treatment or over-treatment
- <u>Desired:</u> Absorbed dose guided treatment planning
  - Adjust activity to keep absorbed dose to critical organ < MTD.
  - Adjust to deliver therapeutic absorbed dose to lesion at acceptable toxicity

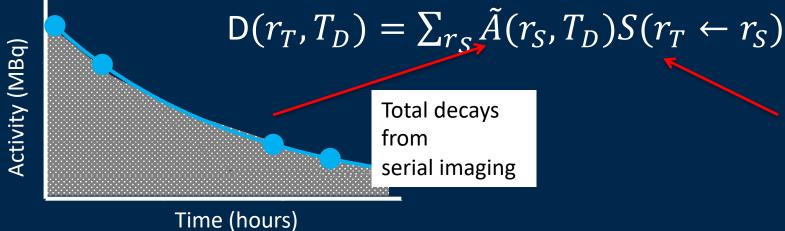
# • Why Change?

- With fixed activity promising tumor control, but poor complete response and survival rates
- Low/mild toxicity, but are we underdosing most patients?
- Potential for improved efficacy with dosimetry guided treatment



#### Absorbed Dose Estimation in RPT: Main Steps

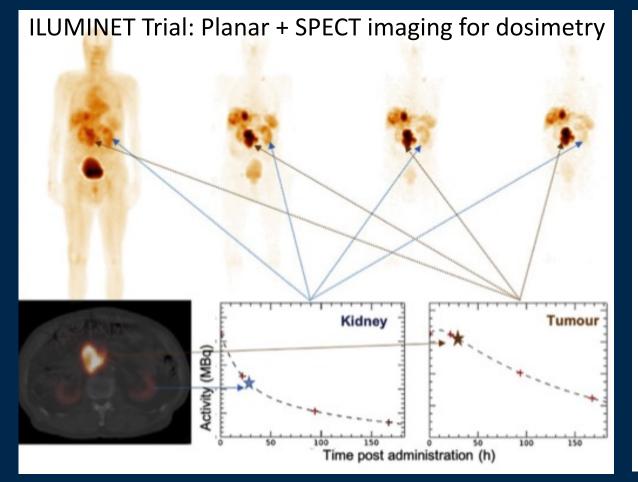
- Image Acquisition usually at multi time points for kinetics
  - Pre-therapy usually with surrogate or post-therapy directly
- Image Reconstruction, Quantification, Partial Volume Correction
- Image Registration
- Organ/lesion Segmentation
- Time activity fitting
- Absorbed dose estimation. MIRD schema widely used

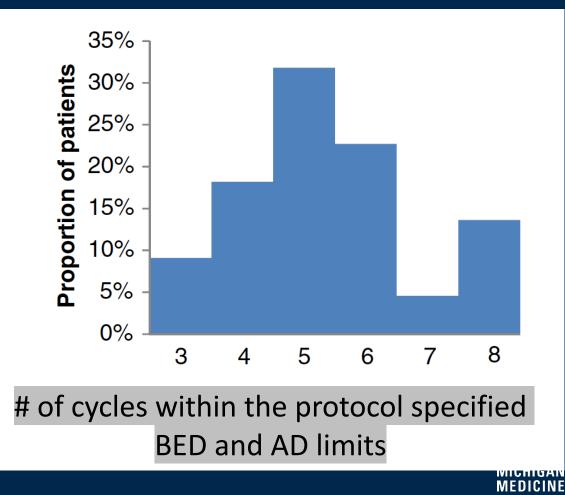


Absorbed dose to target per transformation in source. S-values can be at organ/ sub-organ/voxel/cellular levels

#### Example showing value of patient specific dosimetry: <sup>177</sup>Lu DOTATATE Trial

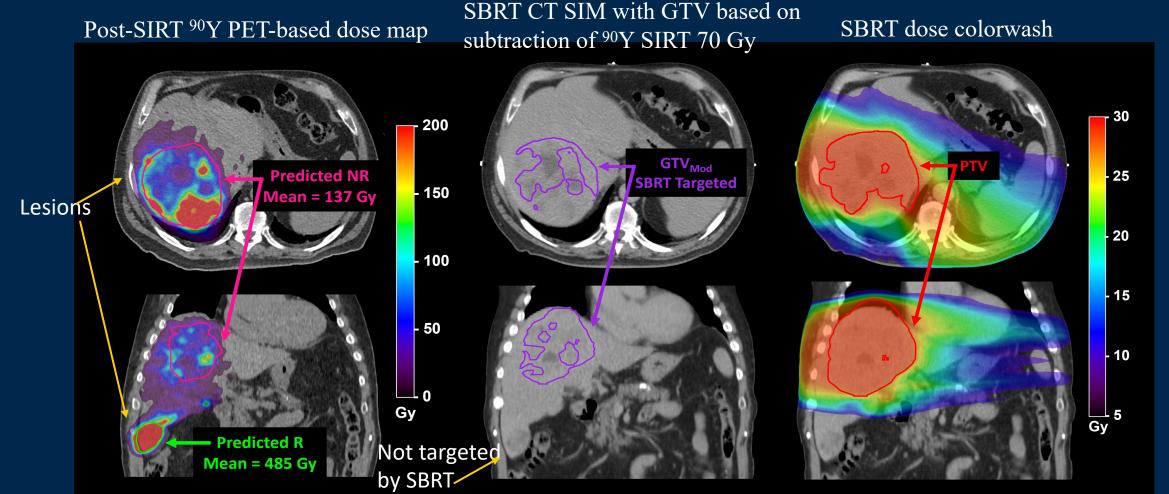
- Current standard: 4 cycles at 7.4 GBq/cycle
- Trial: As many cycles without exceeding kidney dose limit (MTD 27 Gy BED)
- Demonstrated: Cycles can be increased in most patients w/o reaching MTD





Sundlov et al, Eur J Nuc Med Mol Imag 2017

- <sup>7</sup> Value of patient specific dosimetry: U of Mich combined <sup>90</sup>Y SIRT + SBRT <u>Current:</u> HCC lesions targeted by <sup>90</sup>Y selective internal radiation therapy or external radiotherapy
- <u>Trial: <sup>90</sup>Y PET absorbed dose map used to identify underdosed regions and boost with SBRT</u>



NIBIB R01EB022075

Courtesy of Dan Polan, PhD Radiation Oncology, University of Michigan



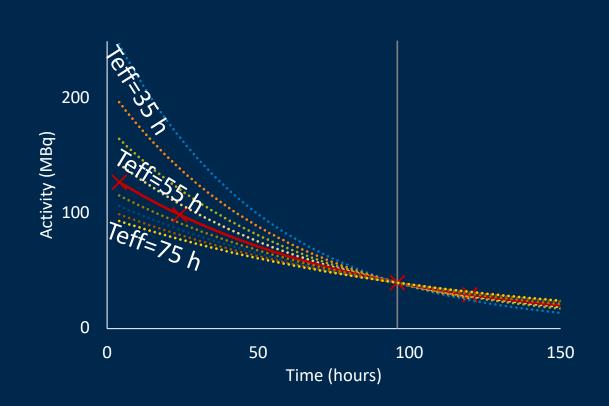
# RPT: Why dosimetry guided treatment is not standard practice

- Unlike in external radiotherapy, not standard practice in RPT
- Why?
  - Imaging burden
  - Lack of accurate <u>and</u> clinic friendly tools
  - Scarcity of well established dose effects relationships
    - Potentially related to insufficient data
- Recent developments
  - Potential for reduced time point imaging-based dosimetry and faster scans
  - AI-based tools for segmentation
  - Publicly available & commercial tools for patient specific dosimetry



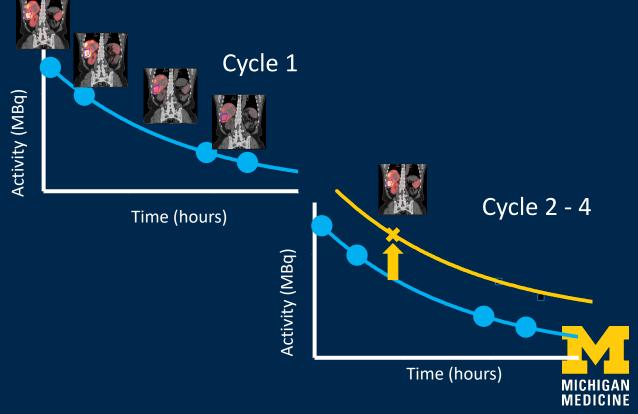
Single time point methods to reduce imaging burden of dosimetry

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



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

- Full Imaging in Cycle 1 + Single Timepoint at Others
  - Assumes kinetics are unchanged between cycles but allows for cycle specific changes in uptake



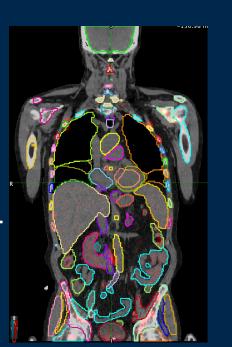
Madsen, Med Phys 2018; Hanscheid et al, JNM 2018

Developments that facilitate patient specific dosimetry: AI-Segmentation

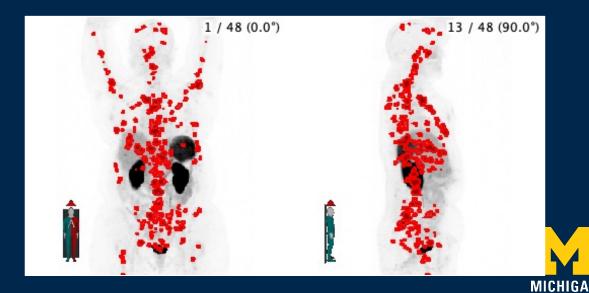
- Well-validated for normal organs
- Coupled with some dosimetry packages



- Free-ware
  - TotalSegmentator: 104 structures in CT
- https://arxiv.org/pdf/2208.05868.pdf



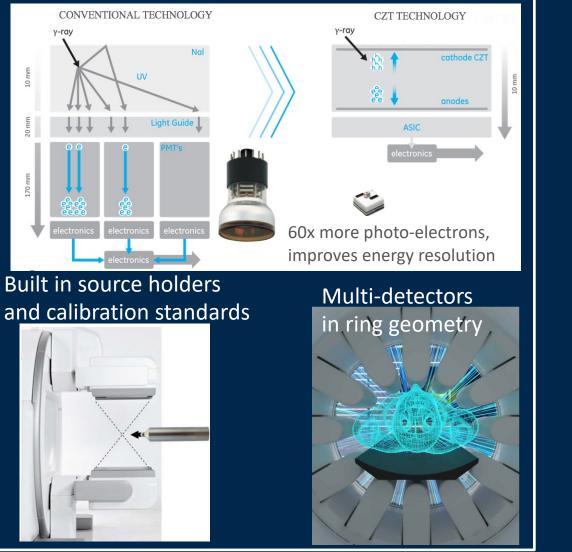
- Individual lesion segmentation is more challenging
- Semi-automated tools available for whole-body tumor segmentation with and without AI for 'cleaning' physiological uptake

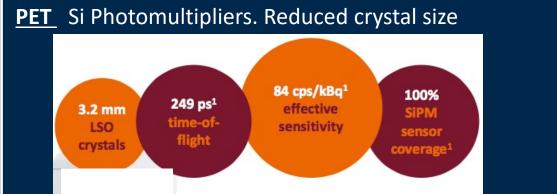


Kim et al, Evaluation of thresholding methods for the quantification of [<sup>68</sup>Ga]Ga-PSMA-11 PET molecular tumor volume ... Eur J Nucl Med Mol Imaging. 2023

#### Developments that facilitate dosimetry: Advances in SPECT & PET

**SPECT:** Cadmium Zinc Telluride semiconductor for direct conversion of gamma energy to charge carriers





Photon Counting Technology. Array of single photon avalanche diodes convert light from the scintillator directly to a digital signal

Digital DPC tile Scintillation photon			Tirst photon detected Microcell	
Total body PET. Gain in sensitivity:				
Improve SNR, reduce dose, or scan faster				
	TB-PET	Axial length	Gain in body sensitivity (1–2-m-long object) vs 20 cm axial length	
	and the second	70 cm	9–10 ×	
		100 cm	15–20 ×	
		140 cm	20–30 ×	
		200 cm	30-40 ×	

MEDICINE

GE CZT technology; StarGuide datasheet; xSPECT Quant and Biograph Vision, Siemens; Philips Vereos PET/CT, White Paper; State of the art in total body PET. EJNMMI Phys. 2020;7(1):35.

# Developments that facilitate dosimetry: faster SPECT scans

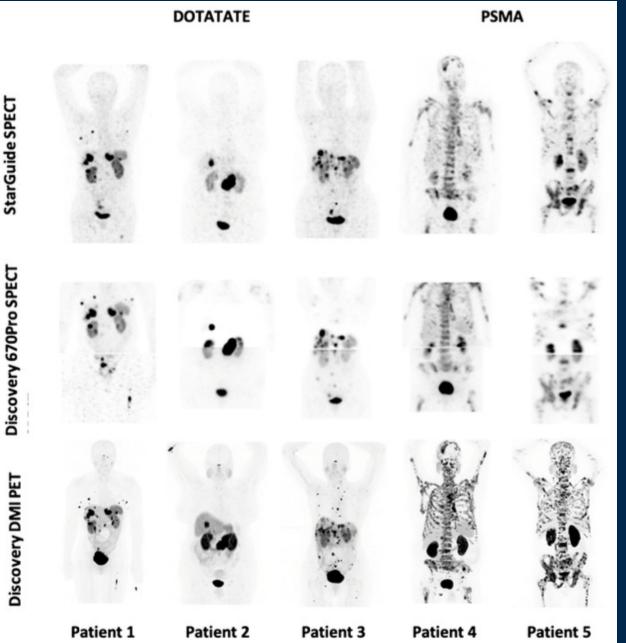
European Journal of Nuclear Medicine and Molecular Imaging https://doi.org/10.1007/s00259-023-06176-6

**ORIGINAL ARTICLE** 

SPECT at the speed of PET: a feasibility study of CZT-based whole-body SPECT/CT in the post <sup>177</sup>Lu-DOTATATE and <sup>177</sup>Lu-PSMA617 setting

Hong Song<sup>1</sup> · Valentina Ferri<sup>1</sup> · Heying Duan<sup>1</sup> · Carina Mari Aparici<sup>1</sup> · Guido Davidzon<sup>1</sup> · Benjamin L. Franc<sup>1</sup> · Farshad Moradi<sup>1</sup> · Judy Nguyen<sup>1</sup> · Jagruti Shah<sup>1</sup> · Andrei Iagaru<sup>1</sup>

- New system: Vertex to mid-thighs post-therapy SPECT/CT scans with 4 bed positions, 3 min/bed and a total scan time of 12 min.
- Old system: 2 bed positions covering chest, abdomen, pelvis with total scan time of 32 min.
- Scans acquired with faster scanning time using new system had comparable detection/targeting rate



# Publicly Available Dosimetry Software

• MIRDsoft https://mirdsoft.org/

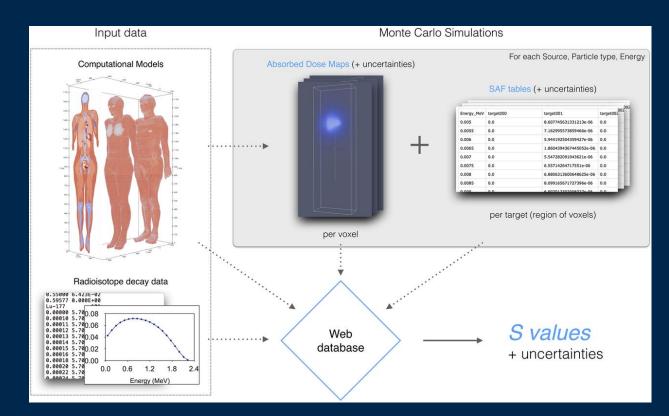


# MIRDsoft.org

MIRDcalc_v1.1.xlsm - MIRDcalc	Radiation Dosimetry C			
119 * : × √ fr				
MIRD SCHEMA ORGAN LEVEL DOSIMETRY SPREADSHEET				
MIRDCalc_v1.1-Genesis Biodistribut	De MIRD Dosimetry Estimate OUTPUT			
Element     Image: Second	Sex 🐲 🔀 Phantom 🐲 Male Female ICRP 10 year old male ICRP 15 year old male ICRP 15 year old male ICRP Adult Male	Input parameters:         %         Wg           A Inhatom         ICRP Adult Male         δ         % injection accounted for :         1%         Wg           A Isotope         Lou-377         Input 5 value uncertainty :         20%         γ         1           Hellifie         1.5955E+02         [hours]         # organs with nonzero TIACS :         \$         β         1		
subject ID (optl)		Subject ID Input isotope/organ UID : RSY α 20		
Source organs	Target organs	Estimated dosimetry (absorbed dose) - 37/50 displayed here Detriment Weighted & Effective Dose VO		
integrated σ activity (Std. Dev.) coefficients (optional)	Patient o Calc Organ name organ mass (Std. Dev.) orga (optional) (optional)	ass EDW Detr Wight Dose 5.12E-03 8.07E-04		
Organ name 🔺		Adipose tissue 3.61E-04 5.40E-05 E Effective Dose 5.63E-03 8.81E-04		
Adipose tissue Adrenals	[grams]         [grams]         [gr           Adipose tissue         1.7           Bone marrow - red (         1.3	04 Bone - endosteal cells 1.94E-04 3.51E-05 Dose per injection (top organs)		
Bone - cortical volur Bone - trabecular vc	Brain 1.55 Breast tissue 2.6	03 Brain 2.44E-06 3.76E-07 Injected activity: 6318 [MBq]		
Brain Breast tissue	Colon - ICRP133 3.3 Esophagus 9.5	00 Bronchial basal cells 2.37E-04 3.58E-05 170.76 mCi		
Cartilage	Extrathoracic region 4.7 Eye lens 4.0	D1         Esophagus         3.60E-04         5.63E-05           D1         Extrathoracic region -         9.99E-06         1.54E-06         8         8         8		
Gallbladder content	Gallbladder wall 1.0 Heart wall 3.8	Gallbladder wall 2.11E-03 2.89E-04 Tumor4		
Heart wall           (a) Kidneys         2.1646111           (a) Liver         0.2262167	Kidneys         4.2           Liver         2.3           Lymphatic nodes - I         1.9	03 Kidneys 4.44E-01 8.70E-02 Kidneys		
Lungs Major blood vessels	Muscle 2.90 Oral mucosa 3.51	04 Lung ICRP133 3.17E-04 4.65E-05 Spleen		
Muscle Oral mucosa	Ovanes 0.0 Pancreas 1.74	Muscle 1.87E-04 3.39E-05 Adrenals		
Pancreas	Skin         3-4           Small intestine         3-7	00 Pancreas 1.80E-03 3.20E-04 Ureters		
(a) Spleen         0.0387583         0%           Thymus	Spleen         2.2i           Stomach         6.1           Testes         3.7:	21 Prostate 2.76E-05 5.25E-06 Changed		
(a) Tumor3_gcc_50%5 0.1051639_0% (a) Tumor4_8cc_50%5 0.1088194_0%	Testes         3.7.           Thyroid         2.3.           Tongue         7.6.	01 Skin 9.77E-05 1.75E-05 Coon-left		
Urinary bladder con	Urinary bladder wall 5.1:			
Rest of body Rest of body mass: 68.9 Kg	Whole body 73.1 Kg	Testes         4.39E-06         8.37E-07         Lymphatic nodes           Thymus         8.19E-05         1.25E-05         Bone marrow		
Organ model (S value) uncertainty 20% (selected error propagated into calcs) Waste		Thyroid         4,56E-05         7.01E-06           Tongue         1.03E-05         1.57E-06         alpha         beta         gamma           Tumora_gcc_50%57         7/12E-01         8.11E-05         error bars = 5D of total dose		
Total TIAC entered into table : 2.64	% theoretical	Tumor4_Bcc_50%ST         8.02E-01         9.14E-05           Urinary bladder wall         5.72E-05         1.09E-05         Projected EDW / 6318 MBq		
Total TIAC required to account for 100% emissions: 230.15 activity accounted  * Time integrated activity coefficients (TIACs) in units (hours)		Uterus         0.00E+00         0.00E+00         EDW: 3.56E+01         ± σ         5.57E+00           Whole body target         3.83E-03         6.28E-04         EDW: 3.56E+01         ± σ         5.57E+00		
- time-indigated study (skil divided by the administered  - time-indigated study (skil divided by the administered - time-indigated study (skil divided by the administered - time-indigated study (skil divided by the administered - time-indigated study (skil divided by the administered - time-indigated study (skil divided by the administered - time-indigated stu				
t i Internal dosimetry spreadsheet 💮				
Ready Calculate				

Radiation Dosimetry Community Platform

• OpenDose<u>https://www.opendose.org/</u>



SAFs produced by MC simulations are stored in database along with input data. Web application allows calculation, and downloading of SAFs and S values

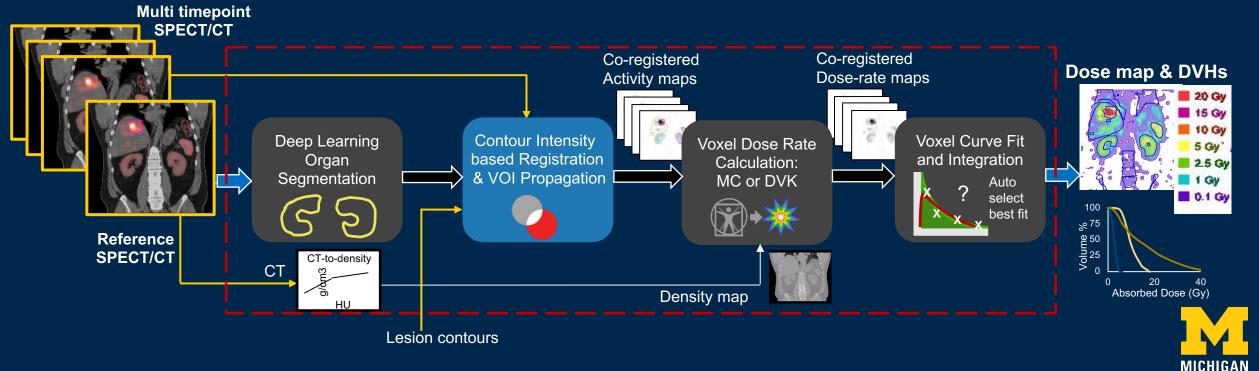


#### Kesner et al. J Nuc Med, 59 (supplement 1) 473;

# Automated Monte Carlo voxel dosimetry in minutes

#### A Pipeline for Automated Voxel Dosimetry: Application in Patients with Multi-SPECT/CT Imaging After <sup>177</sup>Lu-Peptide Receptor Radionuclide Therapy J Nucl Med 2022; 63:1665–1672

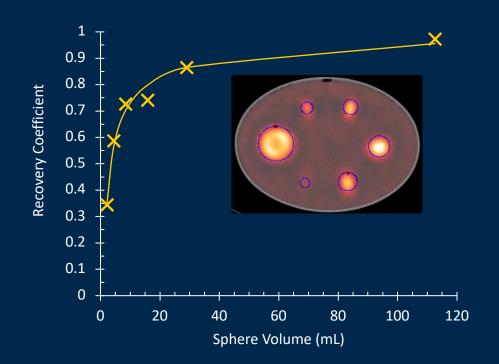
Yuni K. Dewaraja<sup>1</sup>, David M. Mirando<sup>2</sup>, Avery B. Peterson<sup>1,3</sup>, Jeremy Niedbala<sup>1</sup>, John D. Millet<sup>1</sup>, Justin K. Mikell<sup>4</sup>, Kirk A. Frey<sup>1</sup>, Ka Kit Wong<sup>1</sup>, Scott J. Wilderman<sup>1</sup>, and Aaron S. Nelson<sup>2</sup>



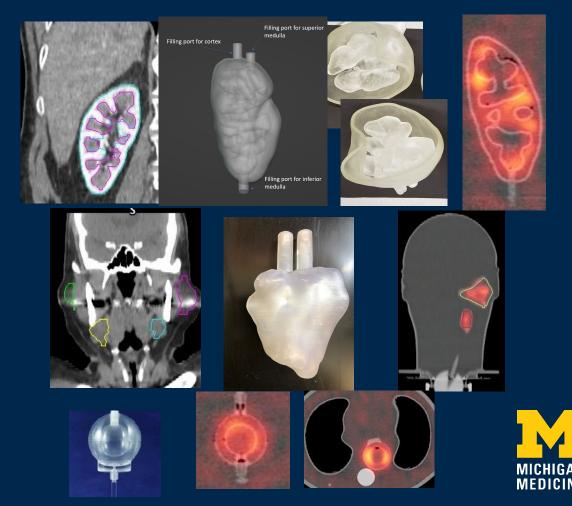
MEDICINE

### Poor SPECT resolution remains a challenge

- Recovery Coefficients for Partial Volume Correction
  - RC vs. volume curve using phantom meas.
  - Practical, but limitations, specially for small/complex structures
  - Mean value correction not voxel level



- Structures in body are not spheres ...
  - Limitations evident from phantom studies



#### Absorbed Dose Estimation in RPT: What is possible & remaining challenges

#### • Image Acquisition

- Reduced timepoints: Established for some therapies. Needed for others
- Shorter scans: new detector systems & AI-based denoising
- Image Reconstruction, Quantification & Partial Volume Correction
  - Problematic for small/complex structures due to resolution and motion effects. Voxel-level PVC unresolved problem
  - Additional challenges when imaging alpha-emitters
- Organ/lesion Segmentation
  - Automated methods available for organs, under development for lesions
- Absorbed dose estimation
  - Multiple options including free-ware. Fast, accurate voxel-level calculation possible



# Thank You yuni@umich.edu

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