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Quantitative Imaging and Dosimetry in Targeted Radionuclide Therapy

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Patient Specific Dosimetry in Radionuclide Therapy

- Pre-treatment imaging-based dosimetry
  - For planning therapy to improve efficacy)
    - Often using a surrogate. e.g. Y-90 DOSISPHERE Trial (France)
- During treatment imaging-based dosimetry
  - After each cycle to adapt subsequent cycles
    - e.g. Lu-177 DOTATATE ILUMINET Trial (Sweden)
- Post-treatment imaging-based dosimetry
  - Documentation, Verification, Intervention
    - e.g. Y90 SIRT + SBRT Trial (Univ of Michigan)
  - Establish dose vs. effect for future treatment planning

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Targeted Radionuclide Therapy Planning

- Current approach:
  - Fixed activity ("one dose fits all") or weight-based adjustment
    - Convenient, but variability in pharmacokinetics & anatomy not considered
    - Potential for under-treatment or over-treatment

- Desired
  - Absorbed dose guided treatment planning
    1) Adjust activity to keep absorbed dose to critical organ < MTD
       - Few ongoing trials/clinical studies
    2) Adjust to deliver therapeutic absorbed dose to lesion at acceptable toxicity to normal organs
       - Currently, limited to research

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Radionuclide Therapy Dosimetry: Main Steps

- **Image Acquisition**
  - Planar, Hybrid Planar/SPECT, SPECT, PET
  - Typically, multi time point. Simplify by single time point methods
- **Image Reconstruction**
- **Quantification**
  - Camera Calibration/Sensitivity. Partial Volume Correction. PET vs. SPECT.
- **Volume-of-interest Segmentation**
  - Manual segmentation is tedious/variable. Can we automate?
- **Time - activity fitting** or dose-rate fitting
- **Absorbed dose** estimation

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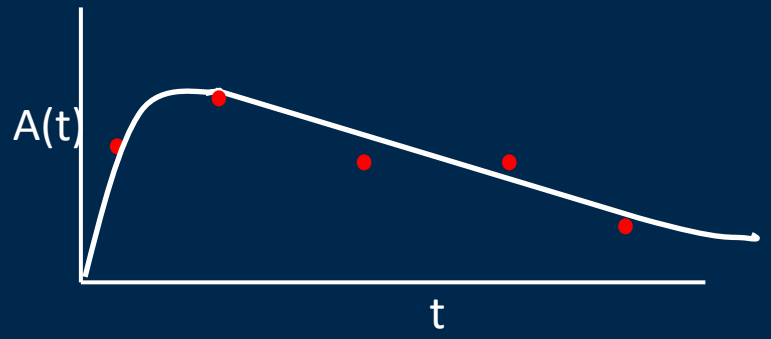
Absorbed Dose Estimation

- MIRD schema: widely used for calculating absorbed dose

$$D(r_T, T_D) = \sum_{r_S} \tilde{A}(r_S, T_D) S(r_T \longleftarrow r_S)$$

Source region time integrated activity (total number of decays) determined by serial quantitative imaging



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

- Voxel Dosimetry: Monte Carlo radiation transport or voxel dose kernel convolution

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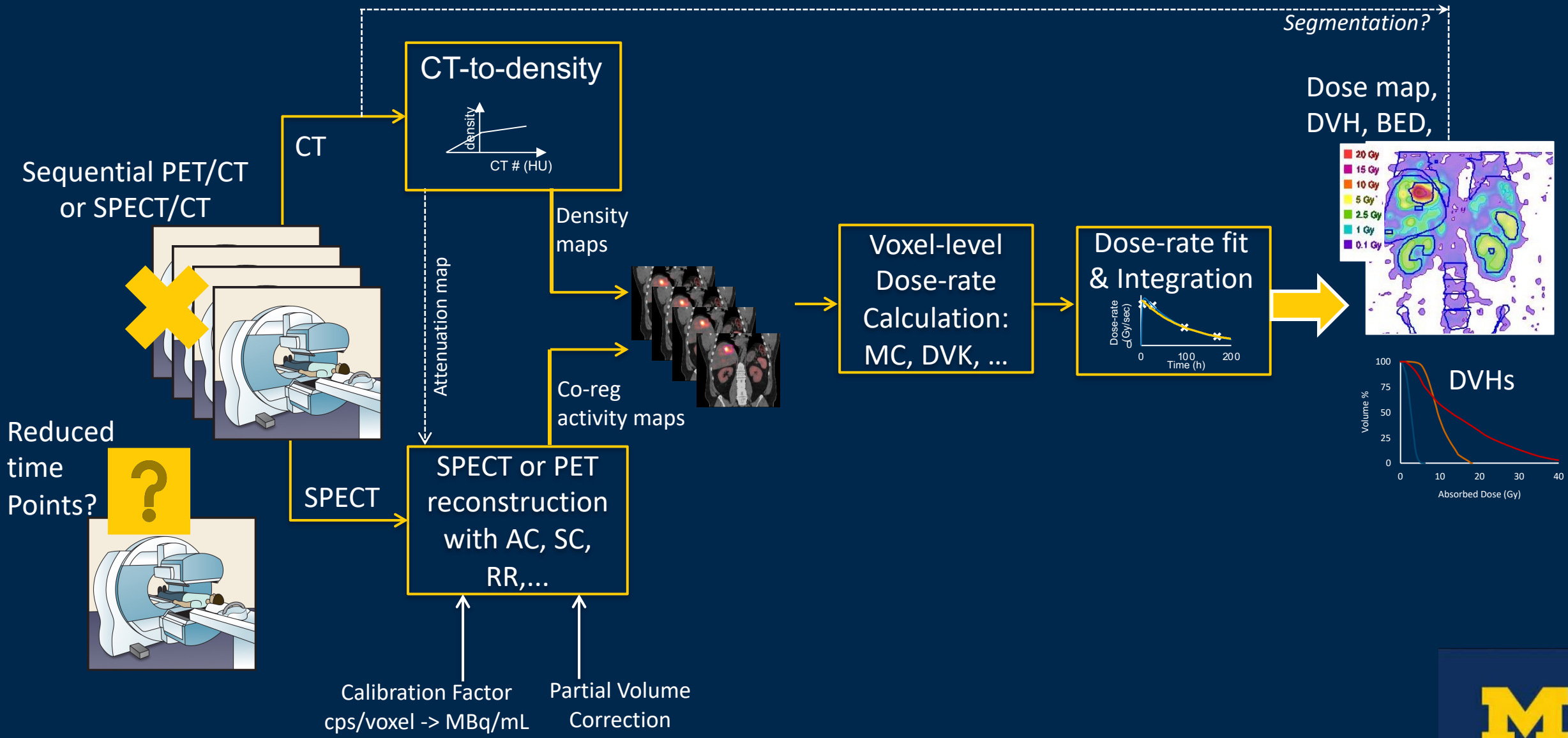
Patient Specific Dosimetry in Radionuclide Therapy



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Why SPECT for Radionuclide Therapy Dosimetry?

- SPECT: Most therapy radionuclides **emit gamma-rays**
  - Direct imaging . No need for surrogate

	$T_{1/2}$	Decay	E , Emax (MeV)	E_γ (keV)
^{32}P	14.3 d	β^-	1.70	None
^{64}Cu	12.7 h	β^-, EC+β^+	β^- 0.58; β^+ 0.65	None
^{67}Cu	2.58 d	β^-	0.58	91(7%), 93(16%), 185(49%)
^{89}Sr	50.5 d	β^-	1.49	None
^{90}Y	2.67 d	β^- ,β^+	2.28	None
^{131}I	8.02 d	β^-	0.61	80(2.6%), 284(6%), 364(82%), 637(7%)
^{153}Sm	1.95 d	β^-	0.81	103(30%)
^{166}Ho	26.8 h	β^-	1.85	81(7%), 1379(0.93%), 1582(0.19%)
^{177}Lu	6.71 d	β^-	0.50	113(6), 208(11%)
^{186}Re	3.72 d	EC,β^-	1.07	137(9%)
^{67}Ga	3.26 d	EC		91(3%), 93(39%),185(21%), 300(17%)
^{111}In	2.8 d	EC		171(90%), 245(94%)
^{117m}Sn	13.6 d	IT		159(86%)
^{223}Ra	11.4 d	β^- ,α	5.6	82(20%), 154(15%), 270(10%), 351, 405

- PET in Radionuclide therapy:
  - Typically, used as an imaging **surrogate**. Exploiting the superior spatial resolution and sensitivity

- Theranostic pairs
  - ^{68}Ga PET/^{177}Lu DOTATATE, PSMA
    - Typically for uptake visualization only due to short half-life of ^{68}Ga
  - ^{64}CuPET/^{67}Cu SarTATE PRRT
    - Potential for dosimetry?
  - ^{124}I-PET/^{131}I radioiodine therapy
    - Used for dosimetry

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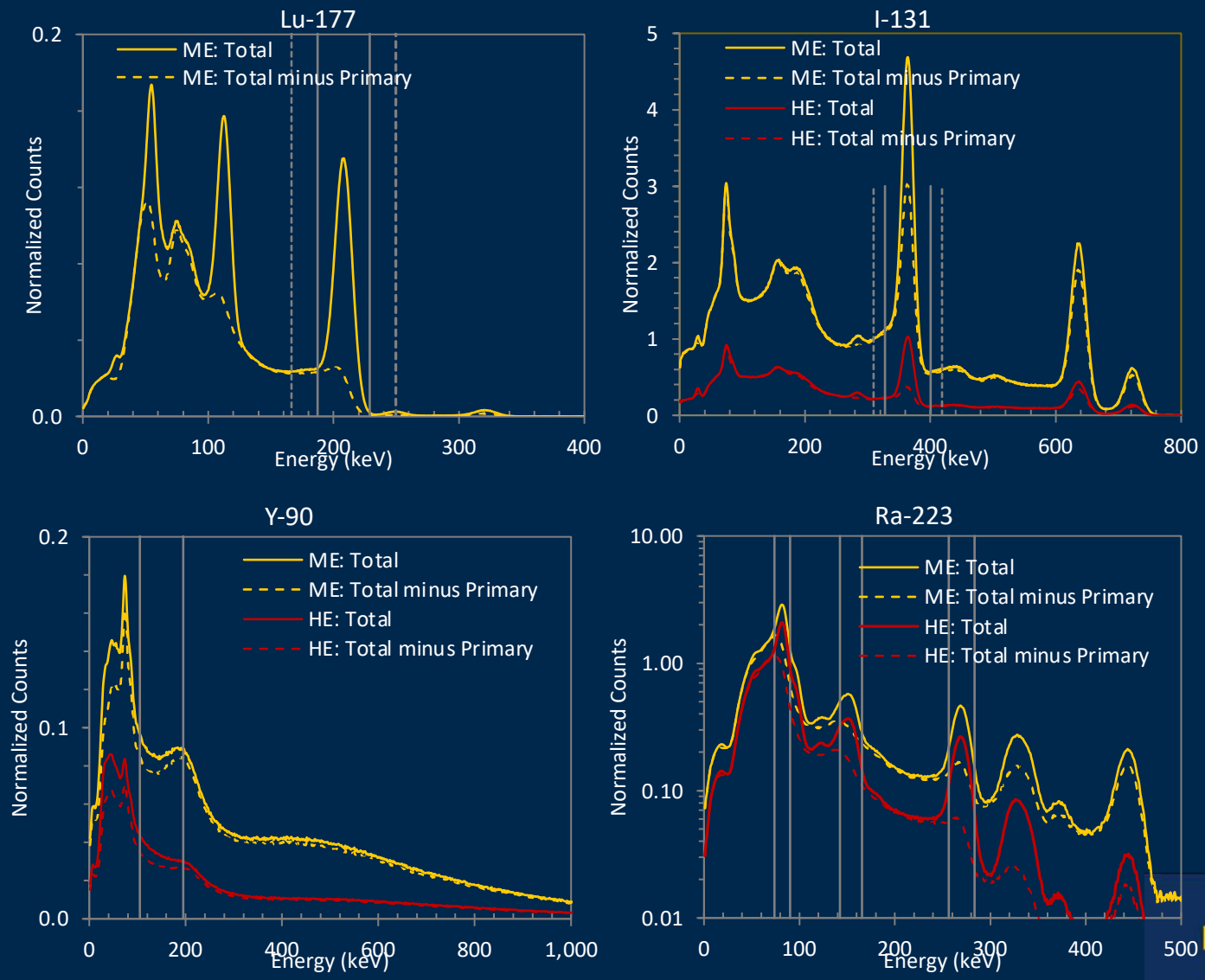
Quantitative SPECT Imaging of Therapy Radionuclides

- More challenging than diagnostic radionuclides
  - Higher energy and/or multiple emissions
    - Downscatter
    - Poor resolution of HE collimators
  - Low yields
  - Choice of collimator is important
  - Correction for scatter and collimator-detector response (CDR) especially important



Dewaraja et al, MIRD 23. J Nucl Med 2012

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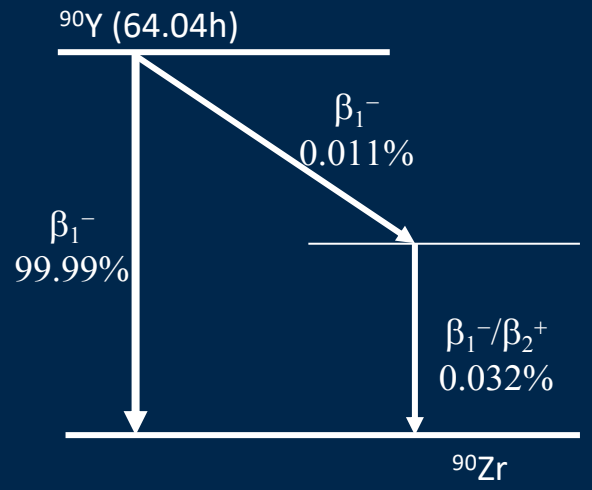
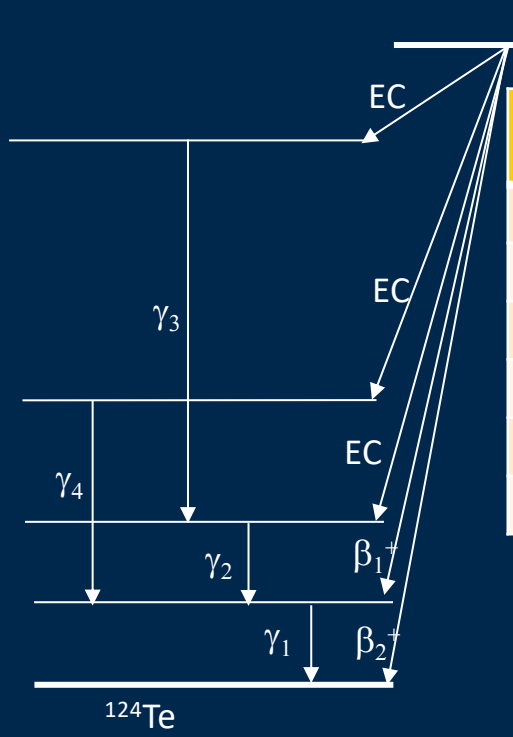
Quantitative PET Imaging of Therapy Radionuclides & Surrogates

- More challenging than diagnostic radionuclides such as ^{18}F
  - 'Non-pure' positron emitters
  - Low yields
  - Higher energy positrons
  - Correction for random coincidences and prompt gammas especially important

- Examples
  - ^{124}I: Low yield, prompt gammas
  - ^{90}Y: Ultra-low yield, bremsstrahlung photons
  - ^{86}Y: Low yield, prompt gammas
  - ^{68}Ga: Prompt gammas
  - ^{64}Cu: Low yield





Decay	Energy (keV)	probability* 100
β_1^+	1534.9	12%
β_2^+	2137.6	11%
γ_1	603	63%
γ_2	723	10%
γ_3	1510	3%
γ_4	1691	11%

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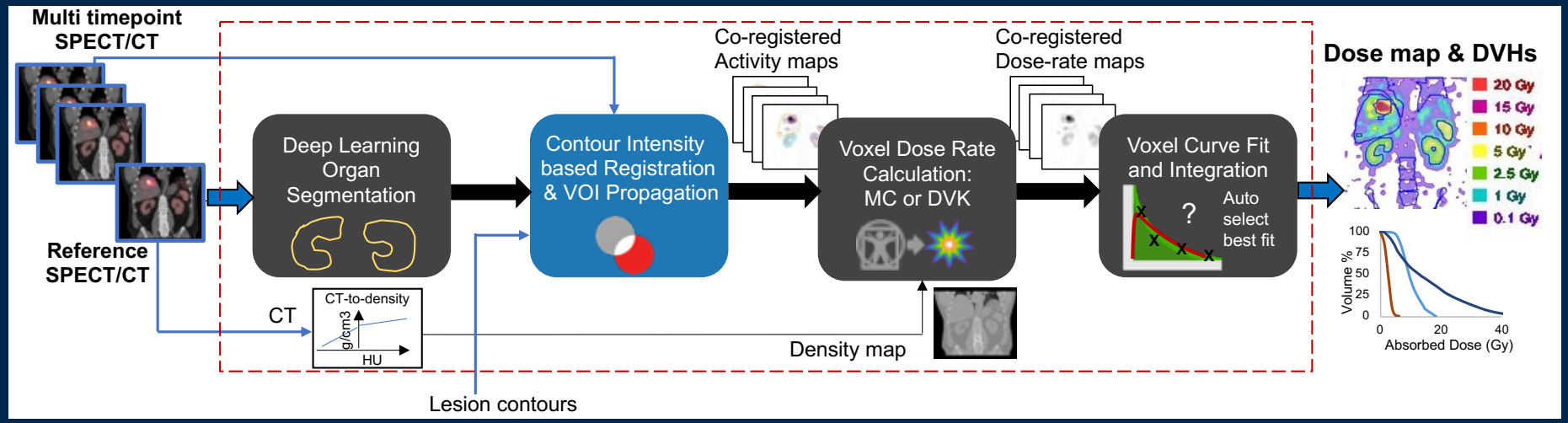
Conti, M., Eriksson, L. Physics of pure and non-pure positron emitters for PET: a review and a discussion. EJNMMI Phys 3, 8 (2016)

^{177}Lu DOTATATE PRRT: Retrospective Dosimetry Study at U Michigan

- 50 patients: Quantitative SPECT/CT at 4 time points after each cycle (7.4 GBq/cycle x 4)
- Segmentation: Lesions manually by radiologist, organs using deep learning tools
- Registration: contour intensity-based SPECT-SPECT
- Dosimetry: Monte Carlo (DPM code), voxel-level dose-rate fitting (auto select fit function)

GOALS

- Tools for practical & reliable dosimetry
- Establish simplifications
- Establish tumor dose - effect thresholds for future treatment planning



Dewaraja et al, A pipeline for automated voxel dosimetry: application in patients with multi-SPECT/CT imaging following 177Lu PRRT. J Nucl Med 2022 (In Press)

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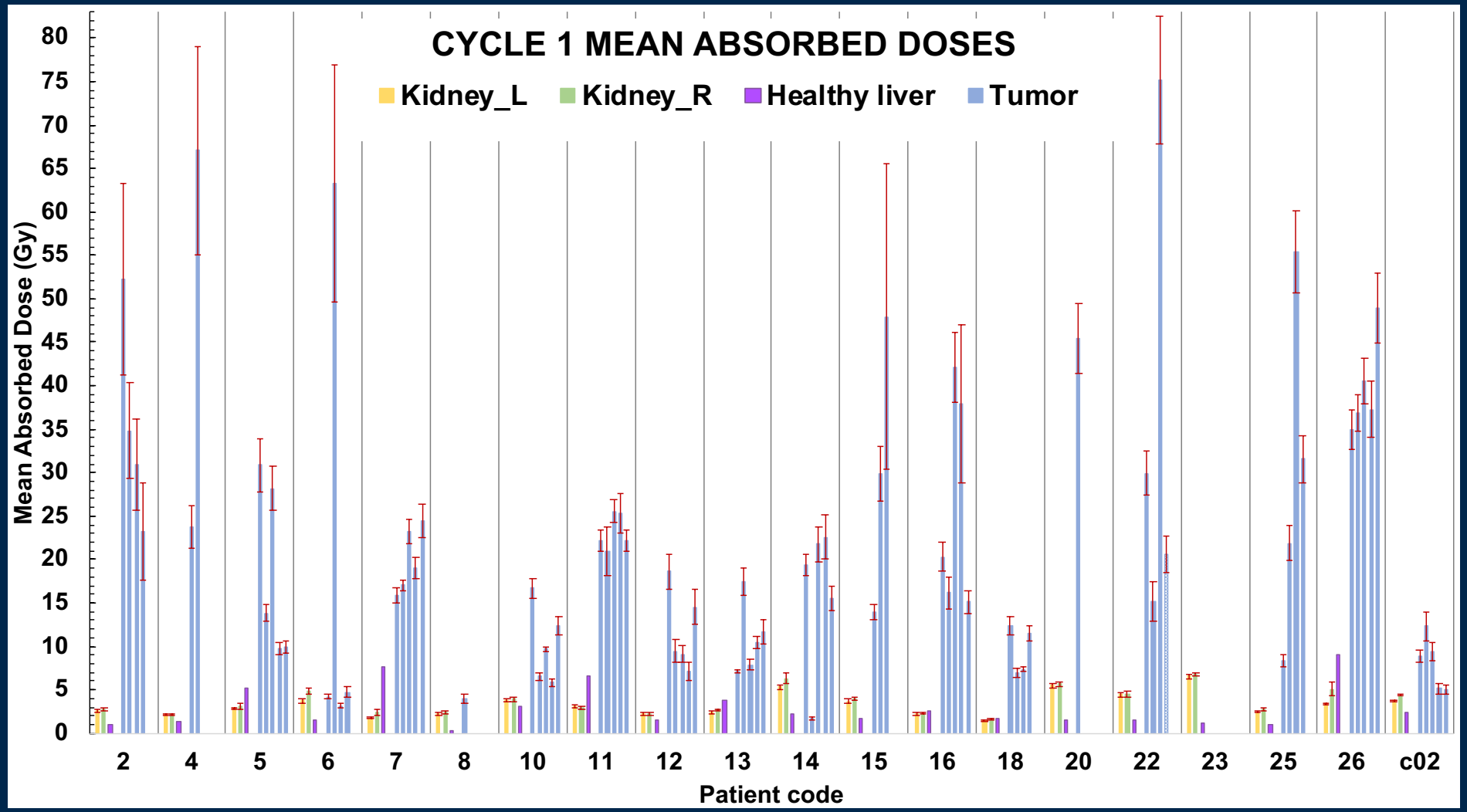
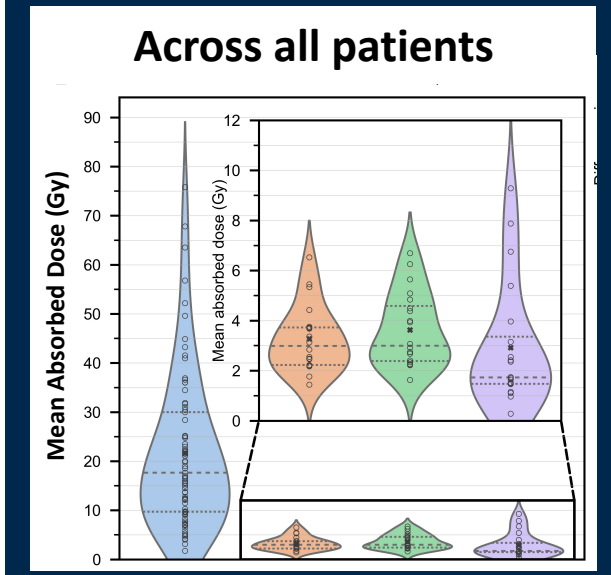
^{177}Lu DOTATATE Michigan Study: Variability in Dosimetry Results





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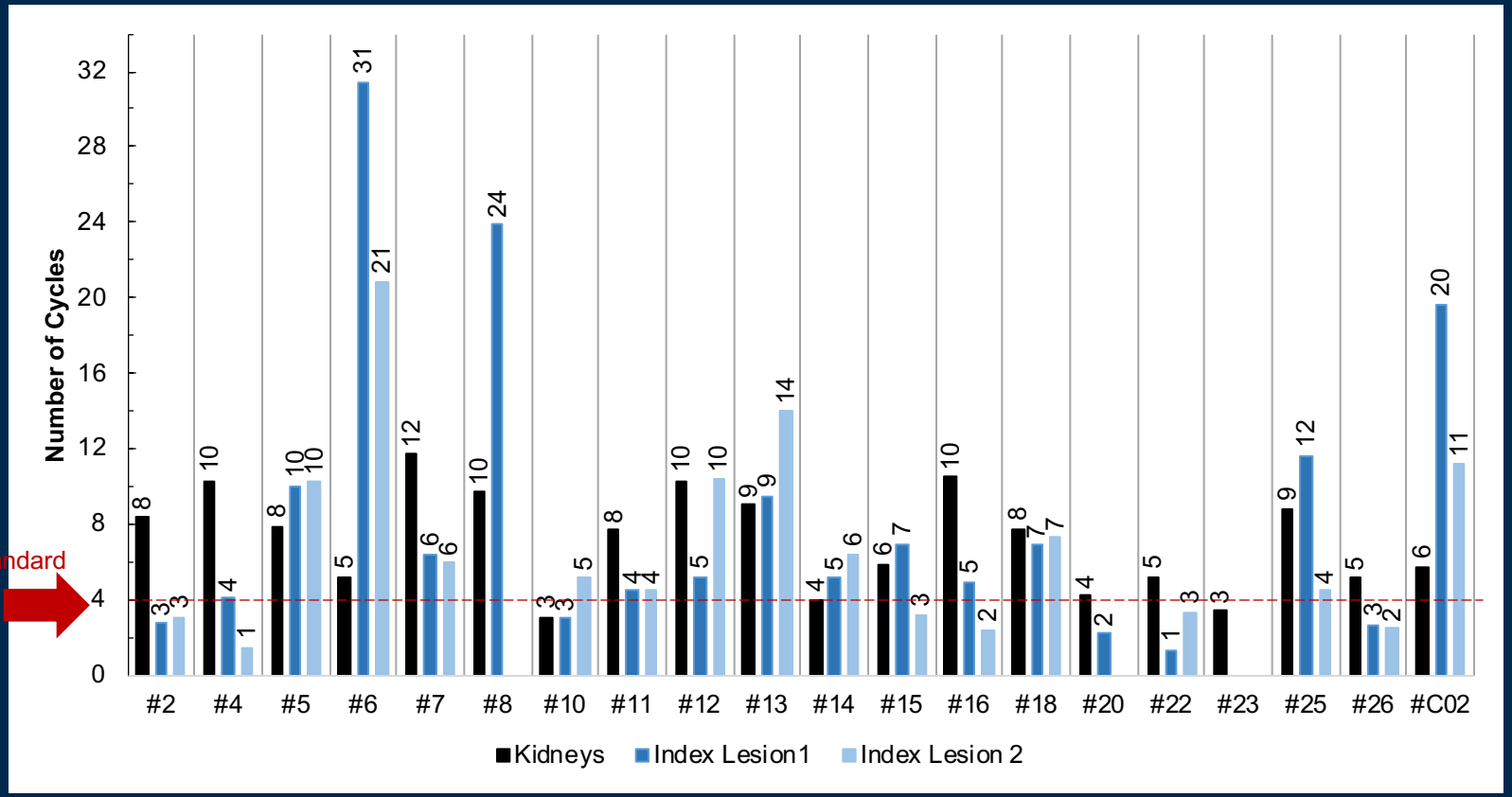
Dewaraja et al, A pipeline for automated voxel dosimetry: application in patients with multi-SPECT/CT imaging following 177Lu PRRT. J Nucl Med 2022 (In Press)

^{177}Lu DOTATATE PRRT: Retrospective Dosimetry Study at U Michigan

Retrospective analysis: Variation in number of (7.4 GBq) cycles needed to deliver 23 Gy to kidney and 100 Gy to tumor

- 23 Gy threshold from EBRT. 100 Gy estimate from prior dose vs. response studies
- Number of cycles highly variable. Demonstrates the value of patient specific dosimetry



Dewaraja et al, A pipeline for automated voxel dosimetry: application in patients with multi-SPECT/CT imaging following 177Lu PRRT. J Nucl Med 2022 (In Press)

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Why dosimetry guided treatment is not standard practice

- Unlike external beam radiotherapy, dosimetry guided treatment is not standard practice in radionuclide therapy.
- Why?
  - Imaging burden
  - Lack of tools for clinic friendly dosimetry until recently
    - Accuracy/practicality trade-off
  - Scarcity of established dose – effects relationships
    - Potentially related to insufficient data
- Recent developments
  - Methods to reduce imaging burden/cost. Single timepoint, planar/SPECT
  - Deep learning tools for auto-segmentation
  - SPECT images directly in activity units (Bq/mL) as with PET systems
  - Commercial voxel dosimetry software, Open Source (MIRDsoft.org)

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How to reduce the imaging burden? Single TP estimates

- Serial imaging to determine time integrated activity for dosimetry. Burdensome to clinic/patient.

- Time-integrated activity based on imaging at a single point
  - Madsen et al for Y-90 DOTATOC PRRT (*Med Phys 2018*)
  - Hanschieid et al for Lu-177 DOTATATE PRRT (*J Nuc Med, 2018*)
    - If there is some knowledge of the population biokinetics, a single measurement time can be chosen to get within 10% of true time-integrated activity.
    - 96 h measurement was suitable for both tumor and normal organs

- Prior cycle information approach: Multi timepoints for one cycle + single timepoint at subsequent cycles
  - Assumes similar biokinetics between cycles
  - Single measurement used to scale the prior cycle time-activity curve

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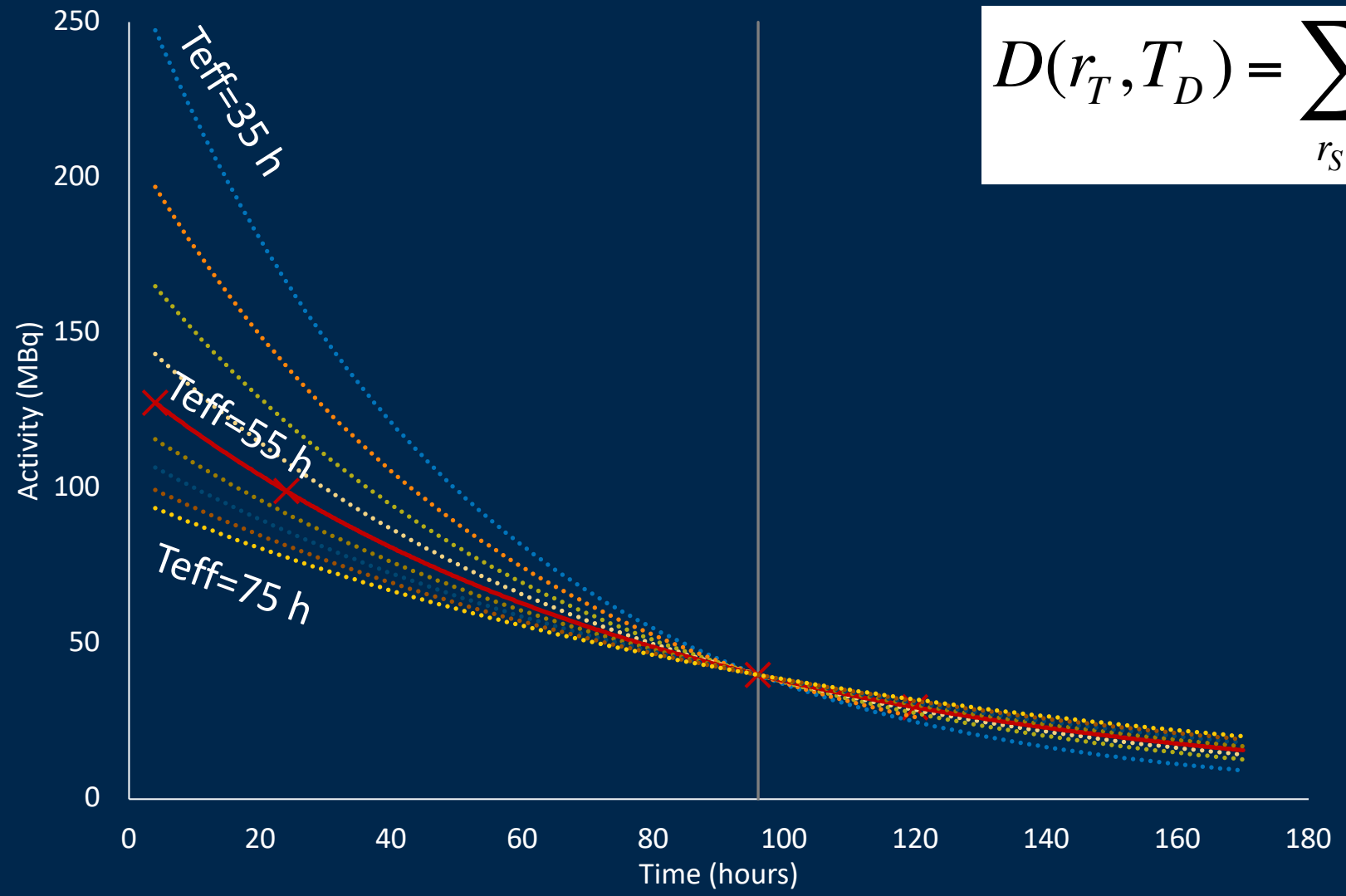
Single Time Point method: why it works?

Variations in effective half-life gives similar Area Under the Curve



$$D(r_T, T_D) = \sum_{r_S} \tilde{A}(r_S, T_D) S(r_T \longleftarrow r_S)$$

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

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^{177}Lu DOTATATE: performance of single timepoint method for tumor/organs and at different imaging points

Univ of Michigan 4 TP data and 3 TP data from another cohort

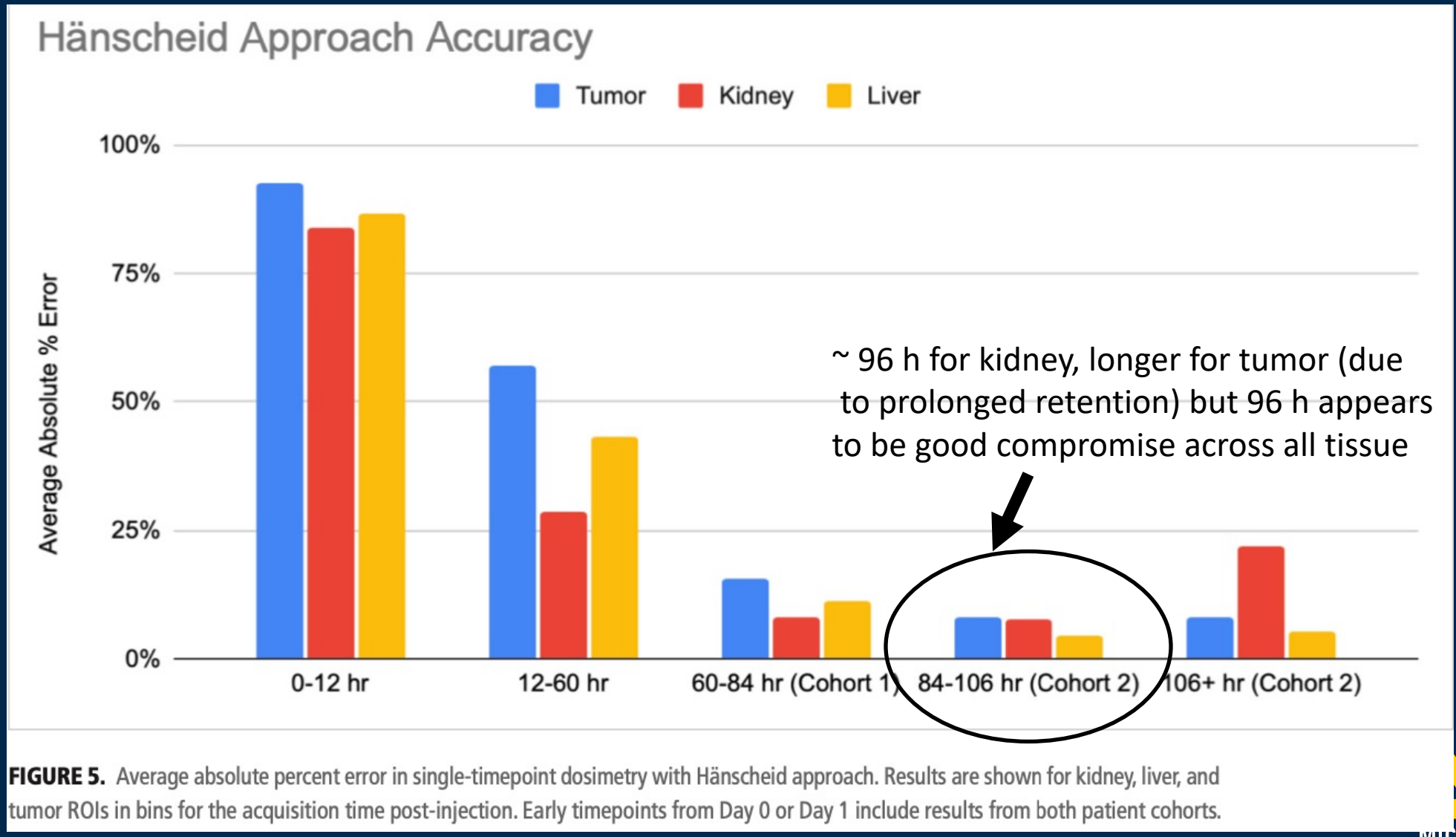


FIGURE 5. Average absolute percent error in single-timepoint dosimetry with Hänscheid approach. Results are shown for kidney, liver, and tumor ROIs in bins for the acquisition time post-injection. Early timepoints from Day 0 or Day 1 include results from both patient cohorts.

^{177}Lu DOTATATE: performance of single TP + multi TP for prior cycle

Univ of Michigan 4 TP data (cycle 1,2 only) and 3 TP data from another cohort

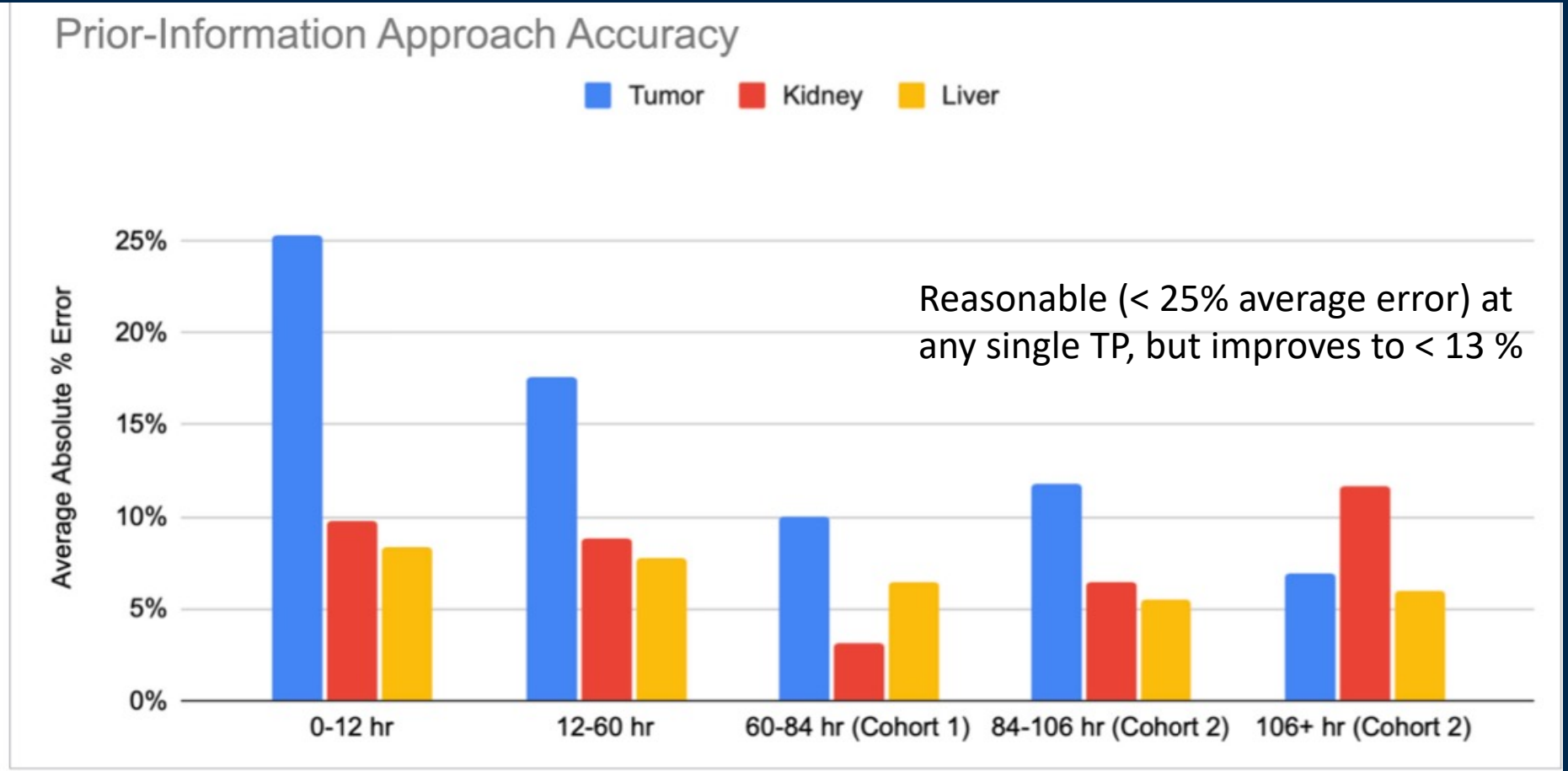


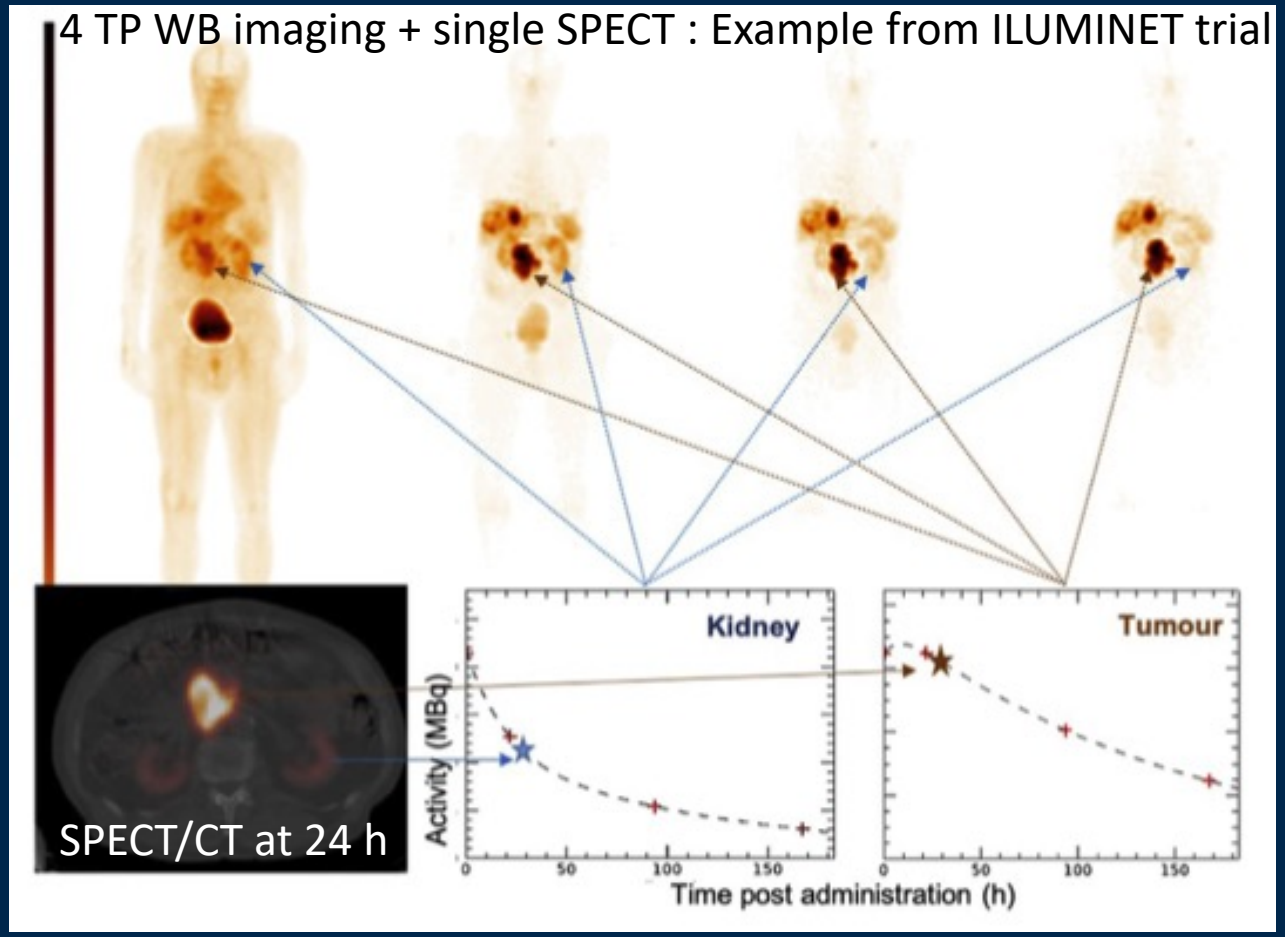
FIGURE 7. Average absolute percent error in single-timepoint dosimetry with the prior-information approach. Results are shown for kidney, liver, and tumor ROIs in bins for the acquisition time post-injection. Early timepoints from Day 0 or Day 1 include results from both patient cohorts.

Other methods for reducing imaging burden: planar/SPECT hybrid imaging

- Planar WB imaging: Time-activity
- Quantitative SPECT: at a single time point, t_i. Then

  $A(t) = A(t_i)_{SPECT} * C(t)_{planar}/C(t_i)_{planar}$

- Practical when multi-time point SPECT is infeasible
  - Less time/cost
  - Exploits SPECT quantification
  - Enables WB imaging
  - Reasonable agreement with multi-TP SPECT reported
- Patients need to return for imaging



Sundlöv, K. Sjögreen-Gleisner, Peptide Receptor Radionuclide Therapy – Prospects for Personalized Treatment, Clinical Oncology, 33 (2), 2021.

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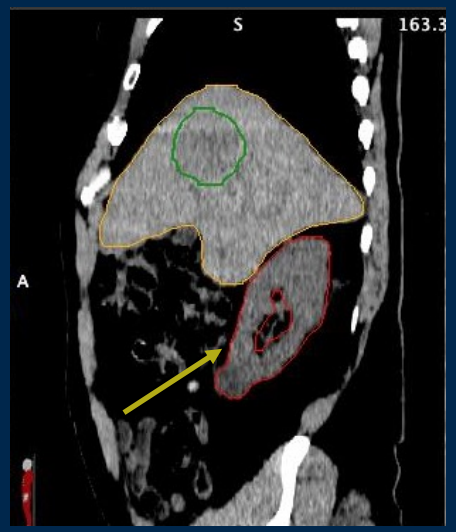
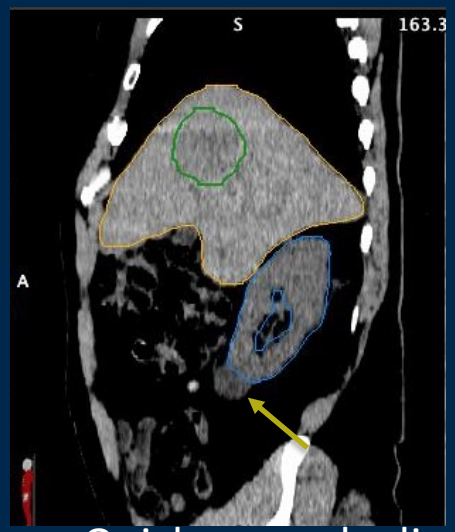
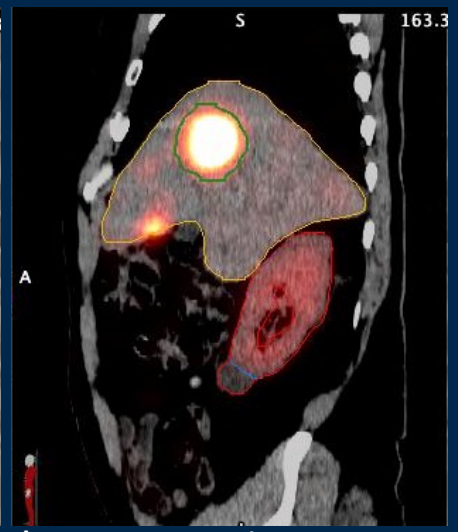
Deep Learning Organ Segmentation: Michigan 177Lu DOTATATE Study



CNN kidney segmentation



Quick manual adjust to exclude cyst



SPECT/CT displaying both contours

	Manual vs. Fully Automated CNN-segmentation*					Manual vs. CNN with fine tuning*				
	Volume Absolute Difference	Mean Dose Absolute Difference	DICE	HD (mm)	MDA (mm)	Volume Absolute Difference	Mean Dose Absolute Difference	DICE	HD (mm)	MDA (mm)
L Kidney										
Mean	5%	2%	0.92	10.7	0.92	4%	1%	0.93	8.3	0.80
Median	4%	1%	0.93	8.5	0.78	3%	1%	0.93	8.2	0.76
Min	0%	0%	0.85	6.0	0.68	0%	0%	0.86	6.0	0.68
Max	18%	5%	0.94	36.0	2.04	17%	5%	0.94	12.2	1.19
R Kidney										
Mean	8%	3%	0.91	11.4	0.99	5%	2%	0.93	9.9	0.81
Median	6%	2%	0.93	9.2	0.84	6%	1%	0.93	8.8	0.81
Min	0%	0%	0.77	4.5	0.68	0%	0%	0.91	4.5	0.68
Max	27%	21%	0.94	24.4	2.05	11%	4%	0.94	24.4	0.99

- CNN segmentation on CT:
  - < 1 min
  - High DICE scores and small difference in absorbed dose compared with manuel
  - Further improvement with CNN + quick manual tunning
    - Fine tunning not needed in most cases, but sometimes cysts (kidney), bowel loops (liver) included
  - Potential to further improve
    - Expanded training sets
    - Using both SPECT and CT

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Summary: Patient Specific Dosimetry in Radionuclide Therapy

- Evidence showing the value of performing pre-, during- and post-therapy imaging-based dosimetry

- Protocols can be simplified to make dosimetry more practical
  - Planar+SPECT/CT when WB imaging desired and multi-SPECT not practical
  - Single timepoint imaging
    - Prior to application, must be validated for each therapy and tissue type with optimal sampling time point carefully chosen based on comparison with multi-time point imaging
  - Deep learning methods for auto-segmentation
  - Commercial and Open-Source dosimetry tools/software

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