Good Dosimetry Practices

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Conflict of Interest Disclosure

Under a licensing agreement between the GE Healthcare and the Johns Hopkins University, Eric Frey is entitled to a share of royalty received by the University on sales of iterative reconstruction software used to obtain some results in this presentation.

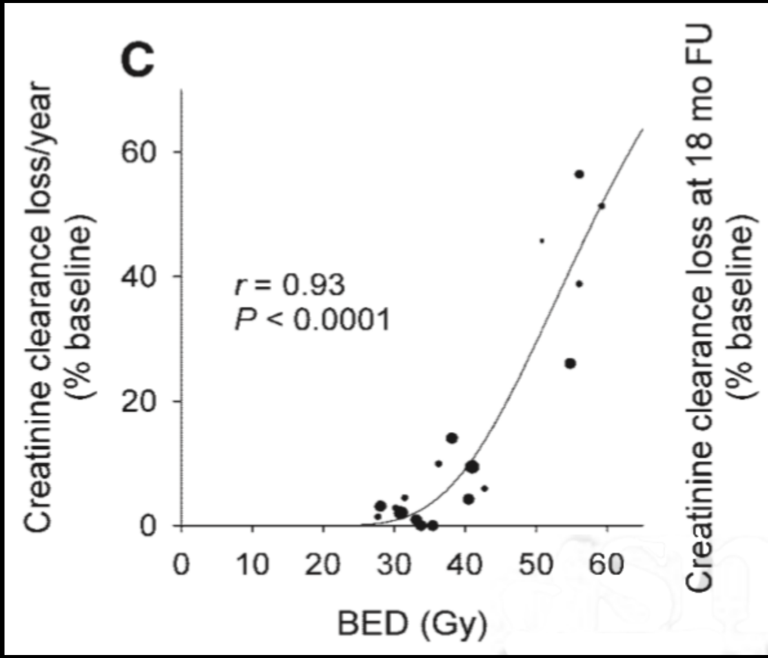
Eric Frey is a co-founder of Radiopharmaceutical Imaging and Dosimetry, LLC and currently devotes 25% effort to this company. This company was founded to provide quantitative imaging and dosimetry service to developers of radiopharmaceutical therapy agents.

These interests have been disclosed and are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

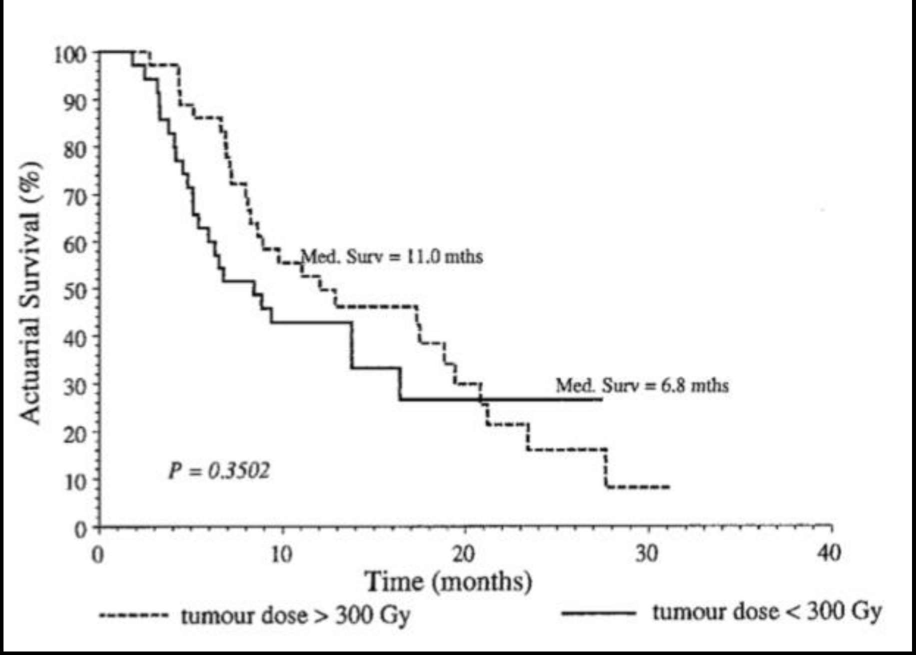
- **Good**: having the qualities required for a particular role.
- **Dosimetry**: The measurement, calculation and assessment of the absorbed energy per unit mass in the human body resulting from a source of ionizing radiation.
- **Practice**: The actual application or use of an idea, belief, or method as opposed to theories about such application or use.

Goal of Dosimetry in RPT

- Optimal dosing of RPT
  - Avoid normal organ toxicities
  - Cause a tumor response

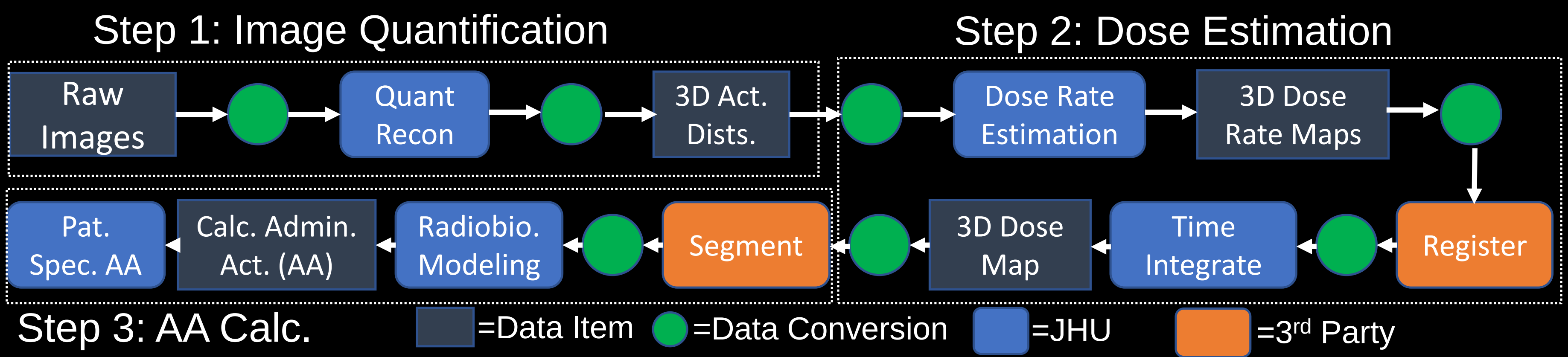


Barone, R., F. Borson-Chazot, et al. (2005). "Patient-specific dosimetry in predicting renal toxicity with (90)Y-DOTATOC: relevance of kidney volume and dose rate in finding a dose-effect relationship." J Nucl Med 46 Suppl 1: 99S-106S.

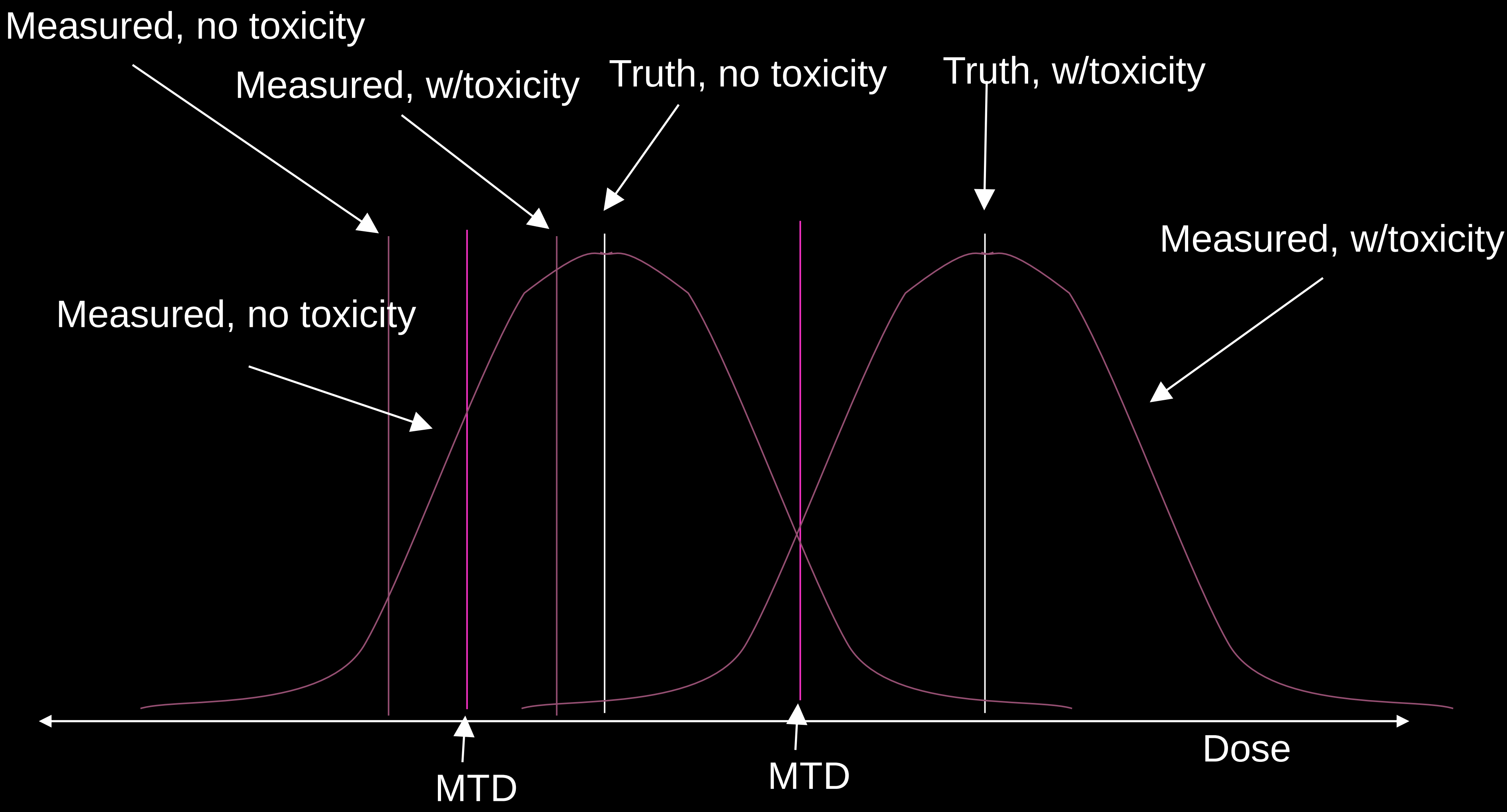


Ho, S., W. Y. Lau, T. W. Leung, M. Chan, P. J. Johnson and A. K. Li (1997). "Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer." Eur J Nucl Med 24(3): 293-298.

RPT Dosimetry Workflow



Effects of Accuracy and Precision on Reliability of Treatment Plan



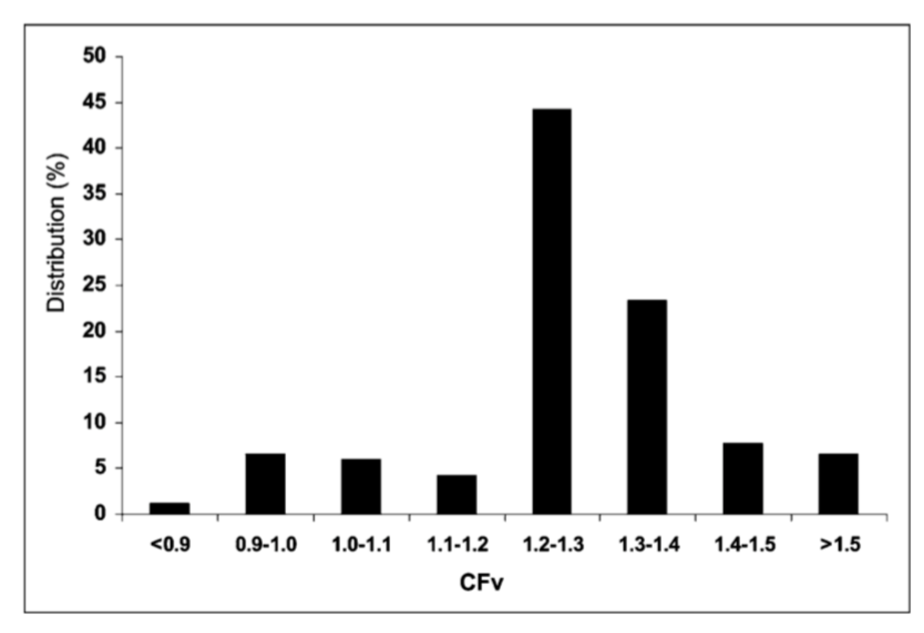
Dose uncertainty can result in conservative MTD and treatment errors

Outline

- Activity Measurement
- Imaging Protocol
- Activity Distribution Estimation
- Image Analysis
- Dose Estimation
- Predicting Response and Toxicity
- Reporting Results

Activity Measurement

- Study of Calibration Factor (CF) for I-123
  - 177 Dose Calibrators (Activity Meters)
  - 138 sites
  - 11 manufacturers



Jacobson, A. F., R. Centofanti, O. I. Babalola and B. Dean (2011). "Survey of the performance of commercial dose calibrators for measurement of (1)(2)(3)I activity." J Nucl Med Technol 39(4): 302-306.

Does bias in calibration factor matter for dosimetry?

$$\mathrm{TIAC} = \int \frac{\mathrm{A}(\mathrm{t})}{\mathrm{AA}} dt$$

$$\mathrm{AA} = \mathrm{CF}_{\text{Activity Meter}} \times \mathrm{AA}_{\text{Activity Meter}}$$

$$\mathrm{A}(t) = \mathrm{CF}_{\text{Imaging}} \times A_{\text{Imaging}}(t)$$

$$\mathrm{CF}_{\text{Imaging}} = \frac{A^{\text{Phantom}}}{A^{\text{Phantom}}_{\text{Imaging}}} = \frac{\mathrm{CF}_{\text{Activity Meter}} A^{\text{Phantom}}_{\text{Activity Meter}}}{A^{\text{Phantom}}_{\text{Imaging}}}$$

$$\mathrm{TIAC} = \int \frac{\left(\frac{\mathrm{CF}_{\text{Activity Meter}} A^{\text{Phantom}}_{\text{Activity Meter}}}{A^{\text{Phantom}}_{\text{Imaging}}} A_{\text{Imaging}}(t) \right)}{\left(\mathrm{CF}_{\text{Activity Meter}} \times \mathrm{AA}_{\text{Activity Meter}} \right)} dt = \frac{A^{\text{Phantom}}_{\text{Activity Meter}}}{A^{\text{Phantom}}_{\text{Imaging}}} \int \frac{A_{\text{Imaging}}(t)}{\mathrm{AA}_{\text{Activity Meter}}} dt$$

CF bias does not matter if:

- Calibration by scale factor is valid
- Only care about relative activities (TIAC)
- Activity measurements used to calibrate image system and activity meter are consistent
  - Same volume
  - Same container
  - Same position
  - No activity meter drift

Outline

- Activity Measurement
- **Imaging Protocol**
- Activity Distribution Estimation
- Image Analysis
- Dose Estimation
- Predicting Response and Toxicity
- Reporting Results

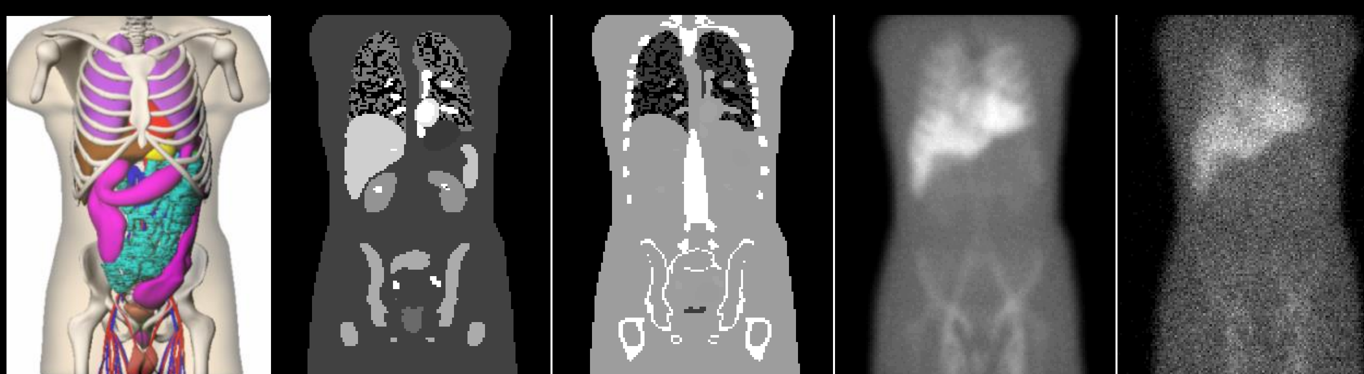
Imaging Protocol

- Modality (Planar vs Tomographic)
- Number and distribution of imaging time points
- Collimator
- Energy window
- Acquisition duration

See MIRD 23 (General), 24 (I-131), 26 (Lu-177), …

Planar vs. Tomography

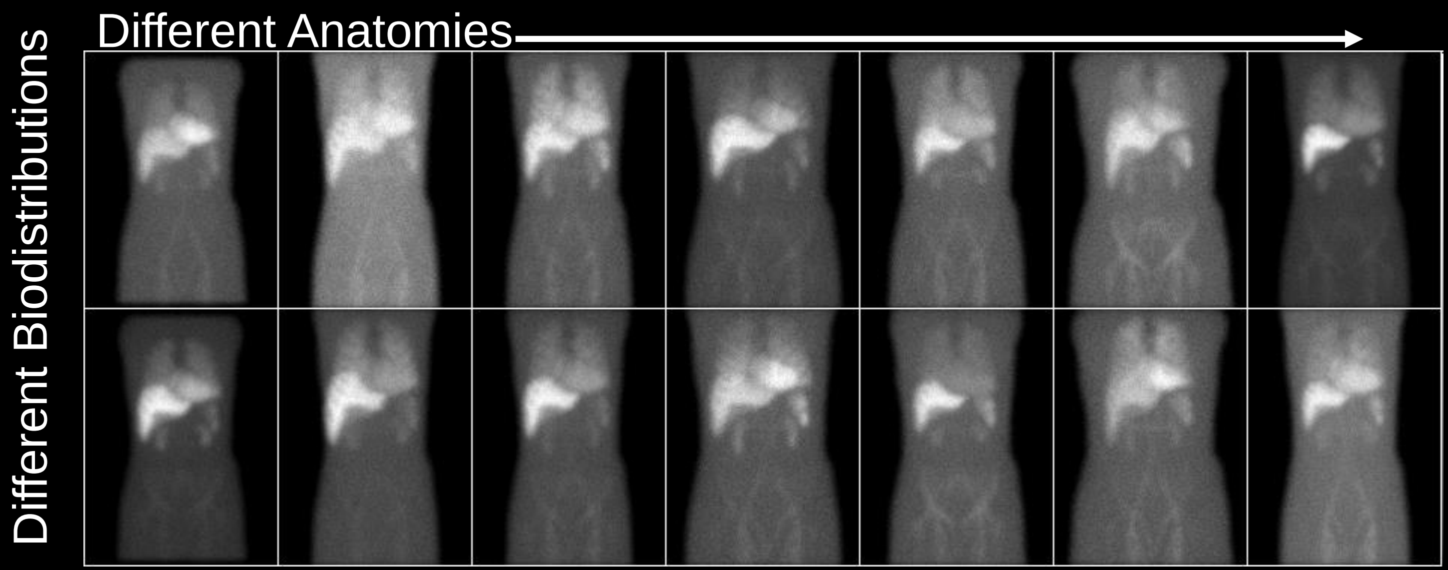
- 3D NCAT phantom:
  - Organ activity concentrations based on 8 clinical studies using In-111 Zevalin
  - Non-uniform activity distribution in heart and lungs.
- Simulation:
  - Parameters for a GE VH/Hawkeye camera (1” crystal, MEGP collimator)
  - Used a modified version of the SimSET/PHG code
  - Generated 50 realizations of Poisson noise
    - SPECT: ~30 seconds per view, 120 views over 360°
    - Planar: used two projection view from SPECT



Phantom | Activity Distribution | Attenuation Map | Low-noise Projection | Noisy Projection

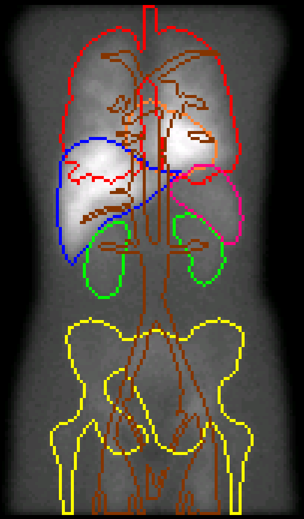
Patient Variations

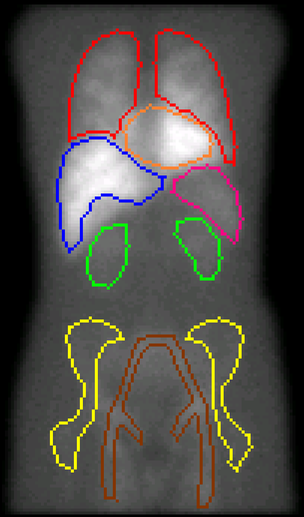
- Patients have different
  - Anatomies
  - Biokinetics



MC Study: C-Planar Overlap Correction

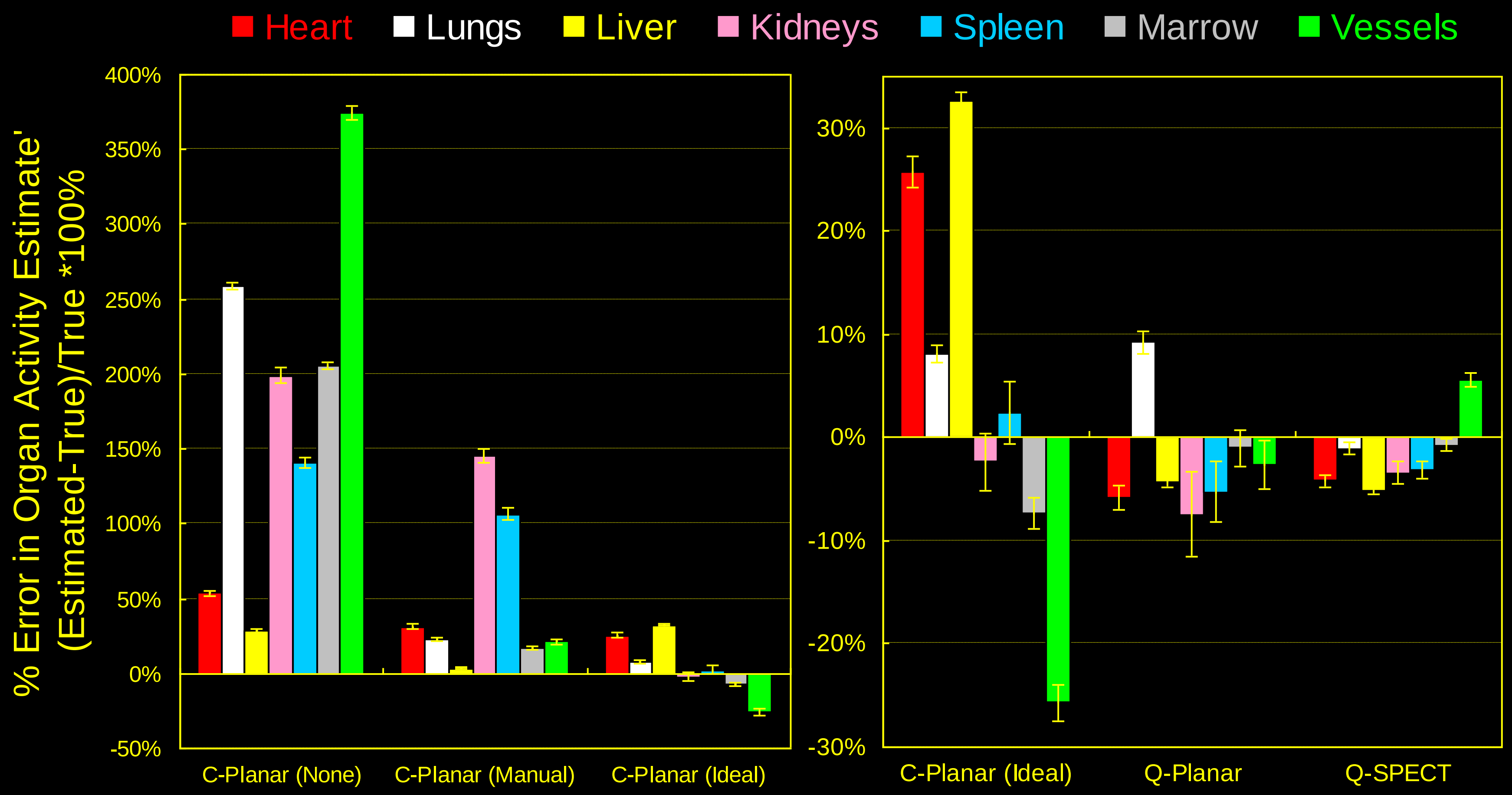
- Ideal
  - Quantification using isolated organ projection
  - No overlap
- None
  - ROIs defined from projection of organ VOIs
  - Maximum overlap
- Manual
  - Using smaller manually drawn ROIs to
    - avoid overlap
    - compensate for background activity
  - Somewhat subjective





MC Study: Accuracy and Precision

- Q-Planar performed better than C-Planar, approaching to Q-SPECT, but had slightly poorer precision than C-Planar
- Q-SPECT provided most accurate estimates

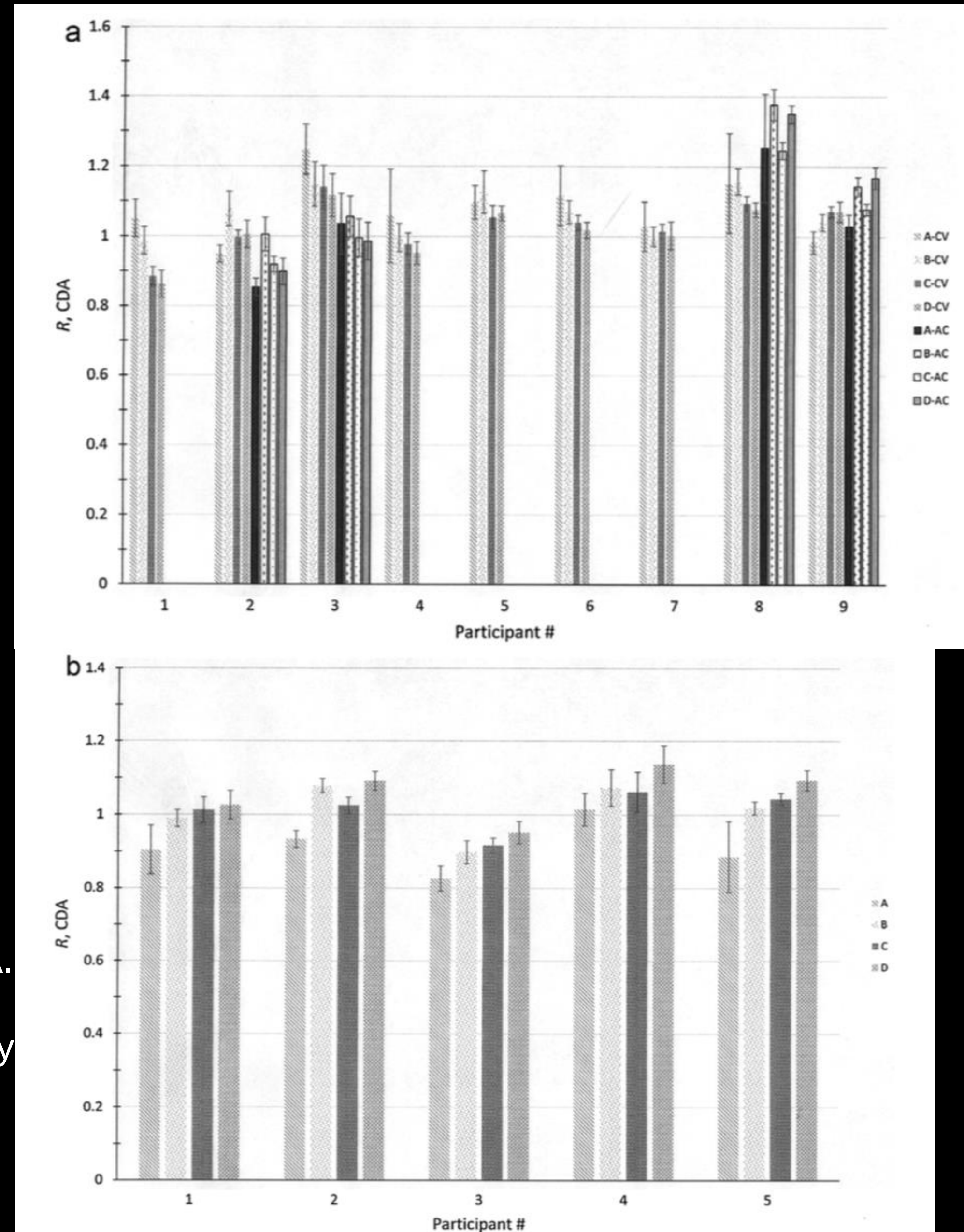


Planar vs. SPECT

Methods	Heart	Lungs	Liver	Kidneys	Spleen
GM-STBV	-13.2±5.7%	27.0±17.9%	8.4±5.7%	-14.7±7.7%	**-15.5±9.7%**
QPlanar	-1.8±1.4%	12.4±1.9%	-0.1±0.7%	-5.1±3.8%	**2.7±1.5%**
QSPECT	-1.9±1.2%	-5.0±5.6%	-0.7±0.7%	-4.3±2.5%	**1.0±1.6%**

GM-STBV: Geometric Mean, TEW Scatter, Transmission Scan, Background, Volume Compensation (requires knowledge of 3D organ VOI)
Qplanar: Planar using 3D organ shapes and same compensations as QSPECT
QSPECT: Iterative reconstruction with compensation

R=RatioMeasured/True



- 4 epoxy-filled Ba-133 rod sources
- 3.8 cm long
- 2.86, 1.43, 1.27 and 0.794 cm diam
- From US NIST via IAEA
- 9 centers (5 w/SPECT/CT)

Zimmerman, B. E., D. Grosev, I. Buvat, M. A. Coca Perez, E. C. Frey, A. Green, A. Krisanachinda, M. Lassmann, M. Ljungberg, L. Pozzo, K. A. Quadir, M. A. Teran Gretter, J. Van Staden and G. L. Poli (2016). "Multi-centre evaluation of accuracy and reproducibility of planar and SPECT image quantification: An IAEA phantom study." Z Med Phys.

Planar vs Tomography

- Tomography: just do it

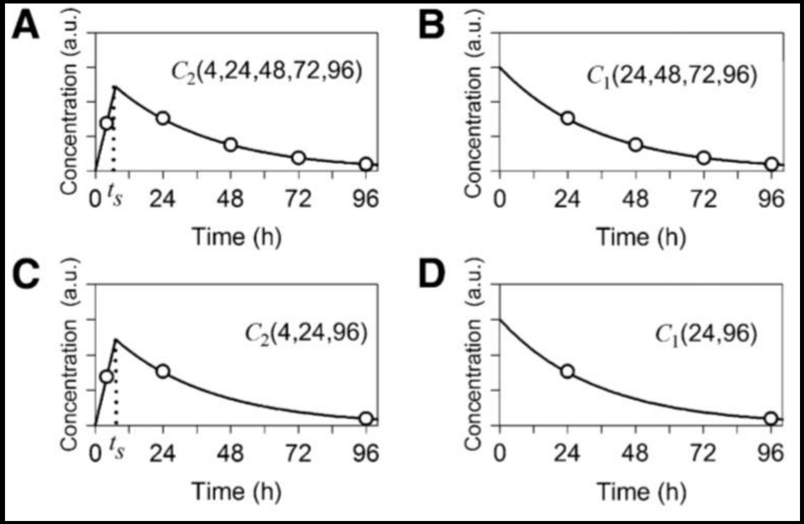
Imaging Protocol

- Modality (Planar vs Tomographic)
- **Number and distribution of imaging time points**
- Collimator
- Energy window
- Acquisition duration

Number and Distribution of Acquisitions

- Traditionally 3-5
- Some work on reducting this
- Dose dominated by late phase

Number and Distribution of Acquisitions



Approach	Low LDpA (n = 14)			Medium LDpA (n = 9)			High LDpA (n = 14)		
	ρ	95% CI	Δ	ρ	95% CI	Δ	ρ	95% CI	Δ
C_1(24,96)	0.82	0.65–0.99	29	0.89	0.76–1.02	8	0.99	0.98–1.00	5
C_1(48,96)	0.31	0.06–0.57	62	0.84	0.64–1.05	12	0.99	0.99–1.00	6
C_2(4,24,96)	0.92	0.84–1.00	16	0.91	0.79–1.03	8	0.99	0.97–1.00	6
C_2(4,48,96)	0.74	0.55–0.93	32	0.95	0.88–1.02	5	0.99	0.99–1.00	5
C_2(4,24,48,96)	0.99	0.98–1.00	5	0.97	0.93–1.01	4	0.99	0.97–1.00	5
Adapted C_2(24,96)	0.92	0.84–1.00	12	0.91	0.78–1.03	8	0.99	0.98–1.00	5

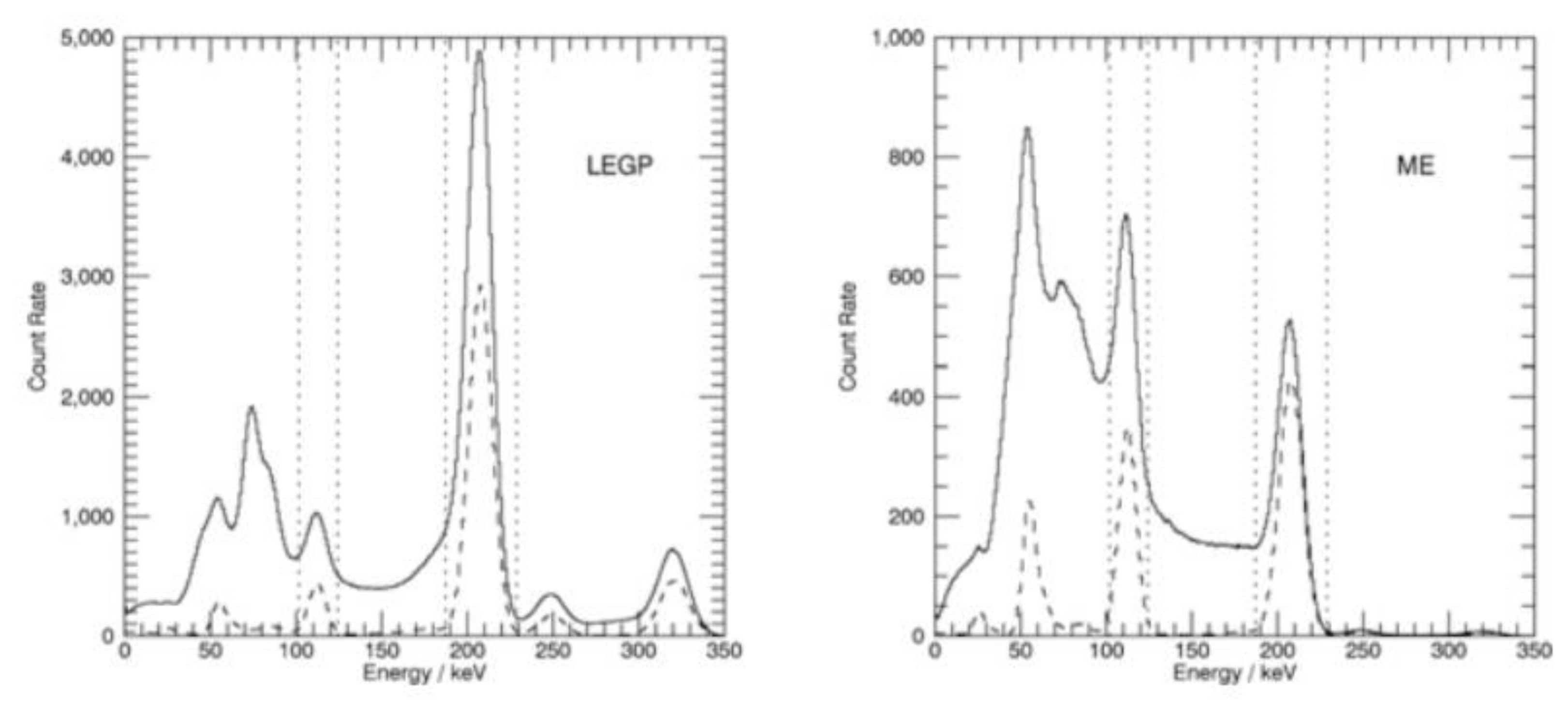
Jentzen, W., L. Freudenberg, E. G. Eising, W. Sonnenschein, J. Knust and A. Bockisch (2008). "Optimized 124I PET dosimetry protocol for radioiodine therapy of differentiated thyroid cancer." J Nucl Med 49(6): 1017-1023.

Imaging Protocol

- Modality (Planar vs Tomographic)
- Number and distribution of imaging time points
- **Collimator**
- **Energy window**
- Acquisition duration

Collimator/Energy Window

Lu-177



Ljungberg, M., A. Celler, M. W. Konijnenberg, et al. (2016). "MIRD Pamphlet No. 26: Joint EANM/MIRD Guidelines for Quantitative 177Lu SPECT Applied for Dosimetry of Radiopharmaceutical Therapy." <u>J Nucl Med</u> 57(1): 151-162.

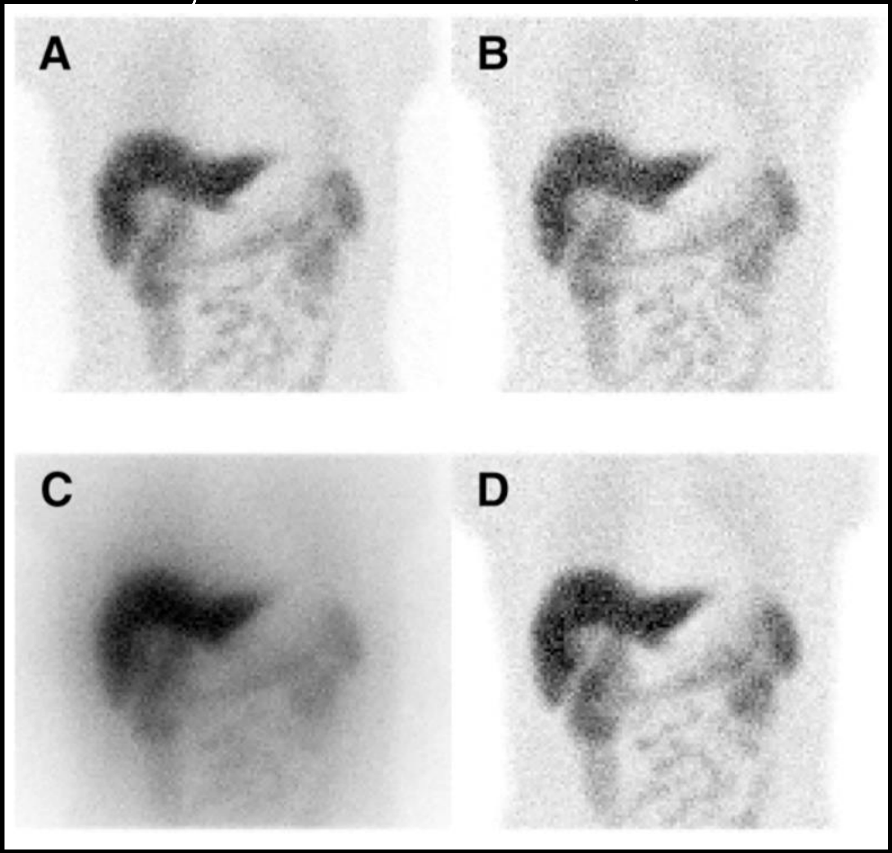
Collimator/Energy Window

Lu-177

MIRD 26

LEGP, 113 keV

MEGP, 113 keV



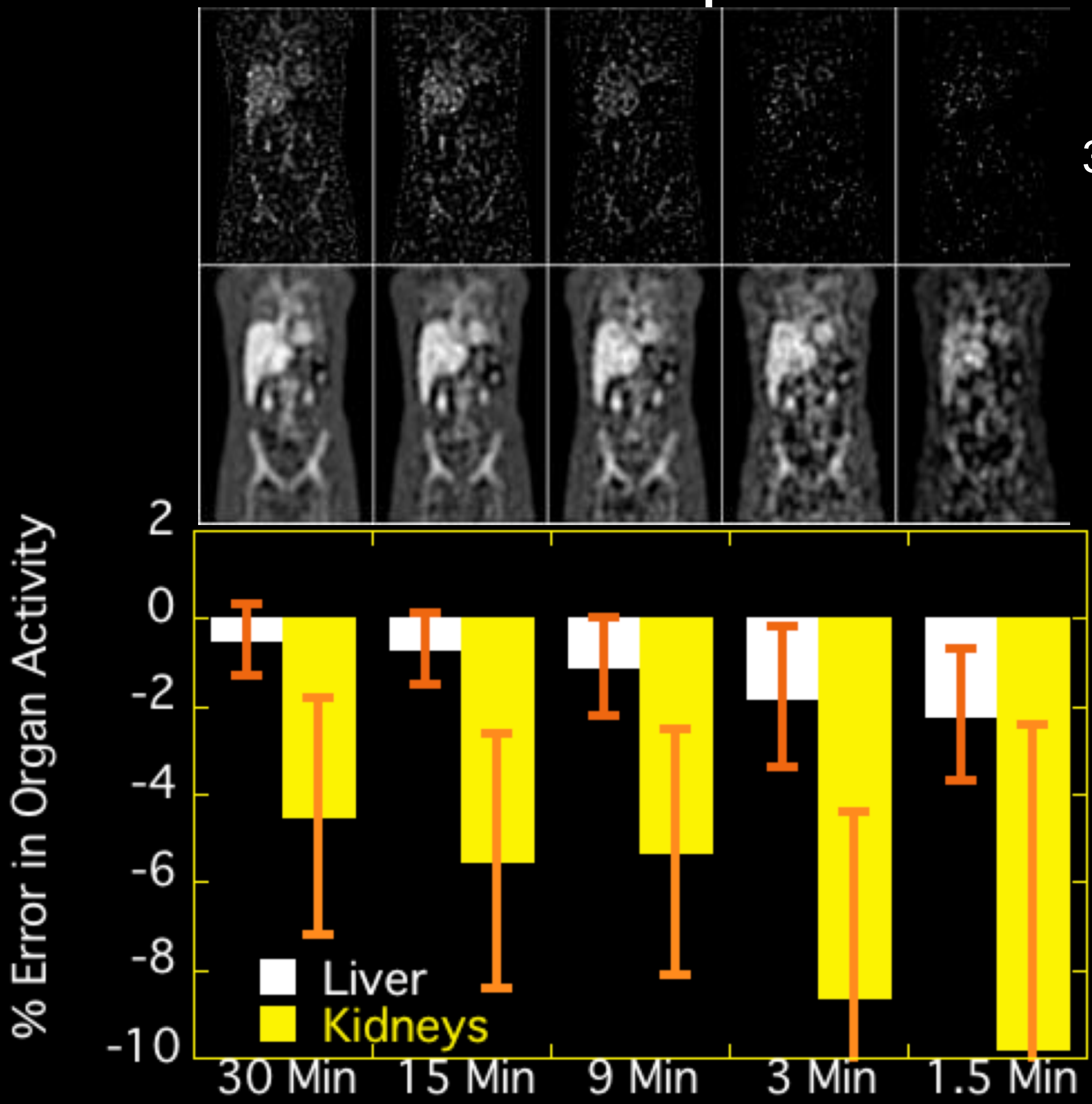
LEGP, 208 keV

MEGP, 208 keV

Imaging Protocol

- Modality (Planar vs Tomographic)
- Number and distribution of imaging time points
- Collimator
- Energy window
- **Acquisition duration**

Effect of Acquisition Duration



30 iterations OS-EM, 24 subsets

After Butterworth Filtering

- Simulated 24 hr ^{111}In Zevalin Images
- Uptake and counts based on patient data w/5 mCi injection
- 49 phantom/activity distribution combinations
- Reconstructed using OS-EM w/atten, CDR and scatter compensation
- Quantified using true organ boundaries

Outline

- Activity Measurement
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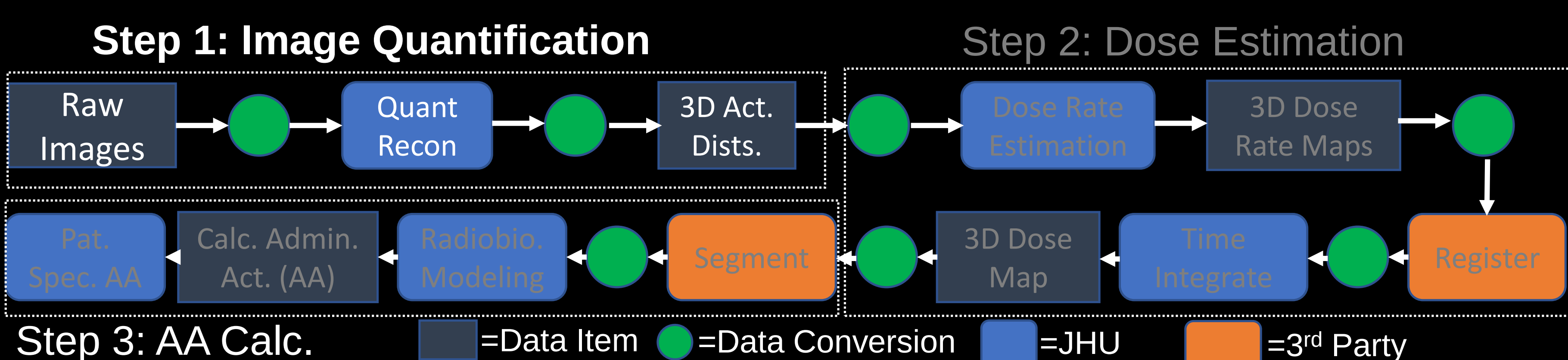
- **Activity Distribution Estimation**
- Image Analysis
- Dose Estimation
- Predicting Response and Toxicity
- Reporting Results



Physical Image Degrading Factors

- Attenuation
- Scatter (downscatter)
- Collimator-Detector Response (CDR)
  - Geometric response
  - Septal penetration and scatter responses
- Partial Volume Effects
- Statistical Noise

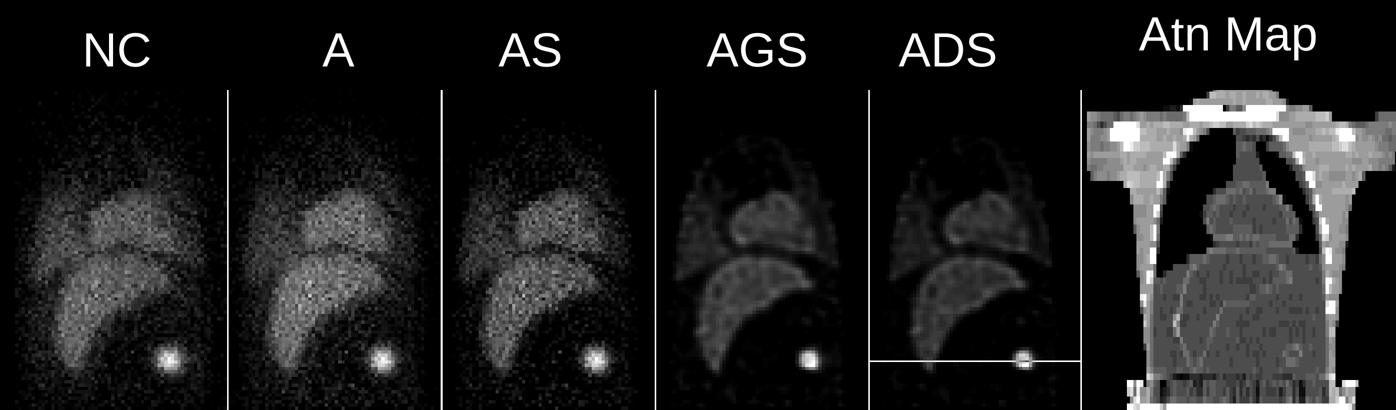
Effects of high-energy emissions

Quantitative Accuracy of SPECT: In-111 Imaging

RSD Torso Phantom

- ^{111}InCl solution placed in the heart, lungs, liver, and background with ratios of 19:5:20:1
- Two spherical lesions with diameters 25 mm and 35 mm were placed in the phantom (concentrations relative to background were 17:1 and 156:1).
- The total activity used was ~185 MBq (5 mCi)
- Imaged Using GE Discovery VH SPECT/CT system with 1” thick crystal
- MEGP collimator
- Manually defined VOIs using SPECT and CT images

Sample Reconstructed Images



NC=No Compensation
A=Attenuation Compensation
AD=Attenuation and CDR Comp

AS=Attenuation and Scatter Compensation
ADS=Attenuation, CDR and Scatter Comp

Accuracy of Activity Quantitation: RSD Phantom and In-111

% Error in total activity estimation: (true-estimate)/true x 100%

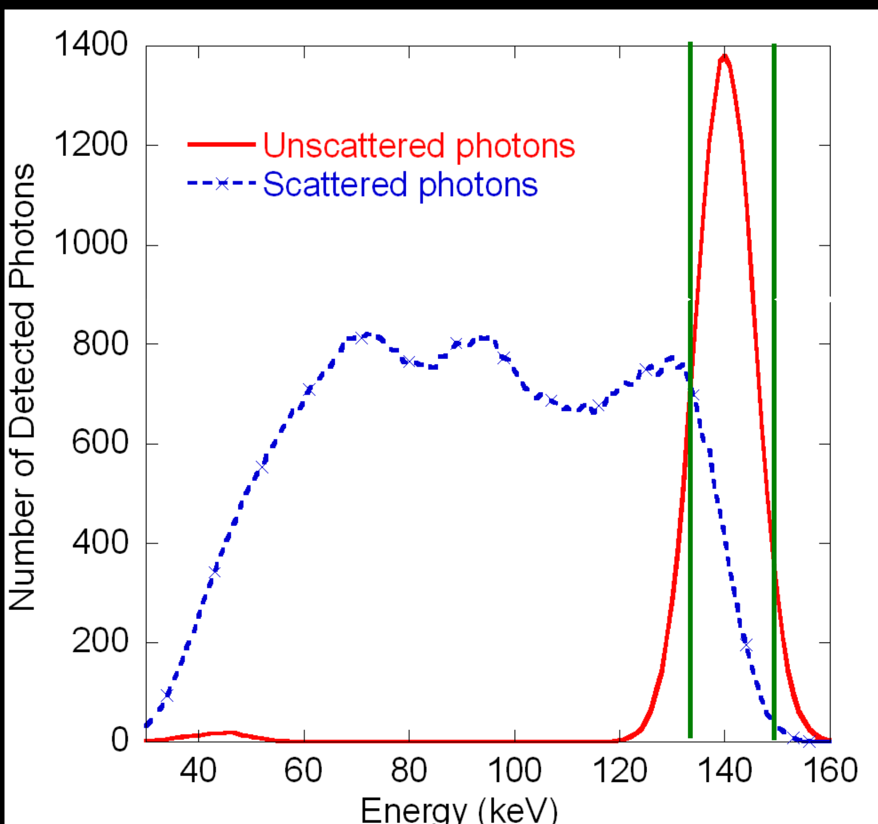
Organ	No Comp	Atten Comp	Atn+ Scat Comp	Atn + CDR + Scat Comp	Atn + CDR + Scat + PVC
Heart	-77.60%	24.63%	-11.76%	-3.72%	-2.11%
Lungs	-62.78%	31.39%	-0.96%	4.23%	6.45%
Liver	-74.38%	29.22%	-7.47%	2.71%	4.14%
3.4 cm diam sphere	-78.88%	-14.85%	-29.81%	-3.36%	-1.97%
2.2 cm diam sphere	-88.24%	-51.53%	-56.75%	-21.55%	-11.95%

More complete modeling yields better accuracy

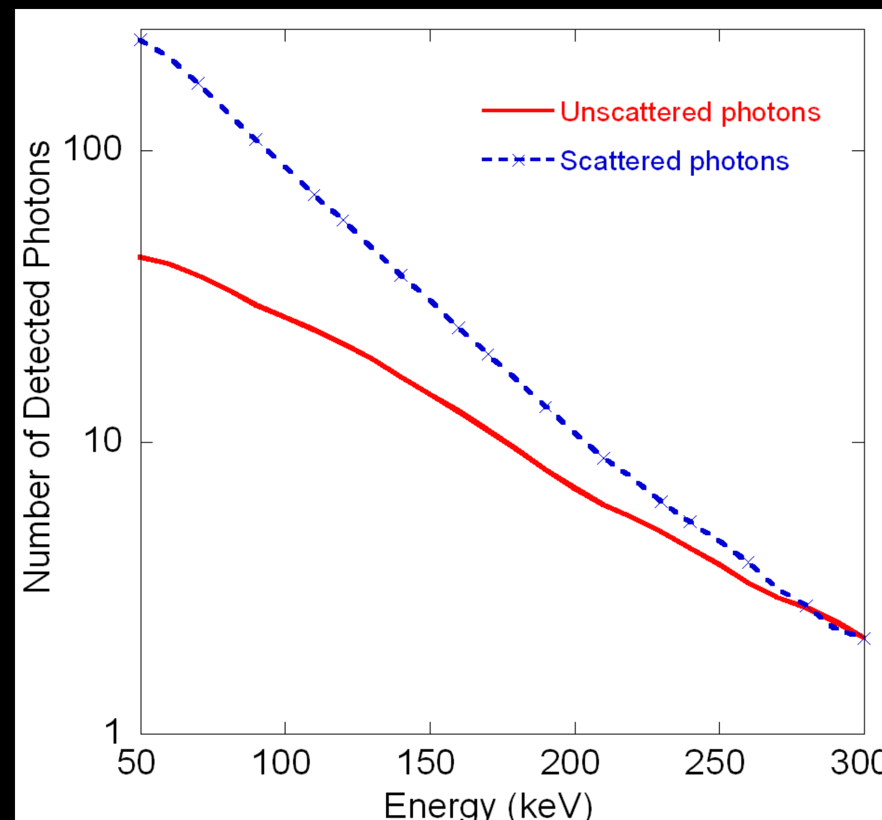
Y-90 QSPECT

- Ultimate challenge?
- Continuous energy spectrum

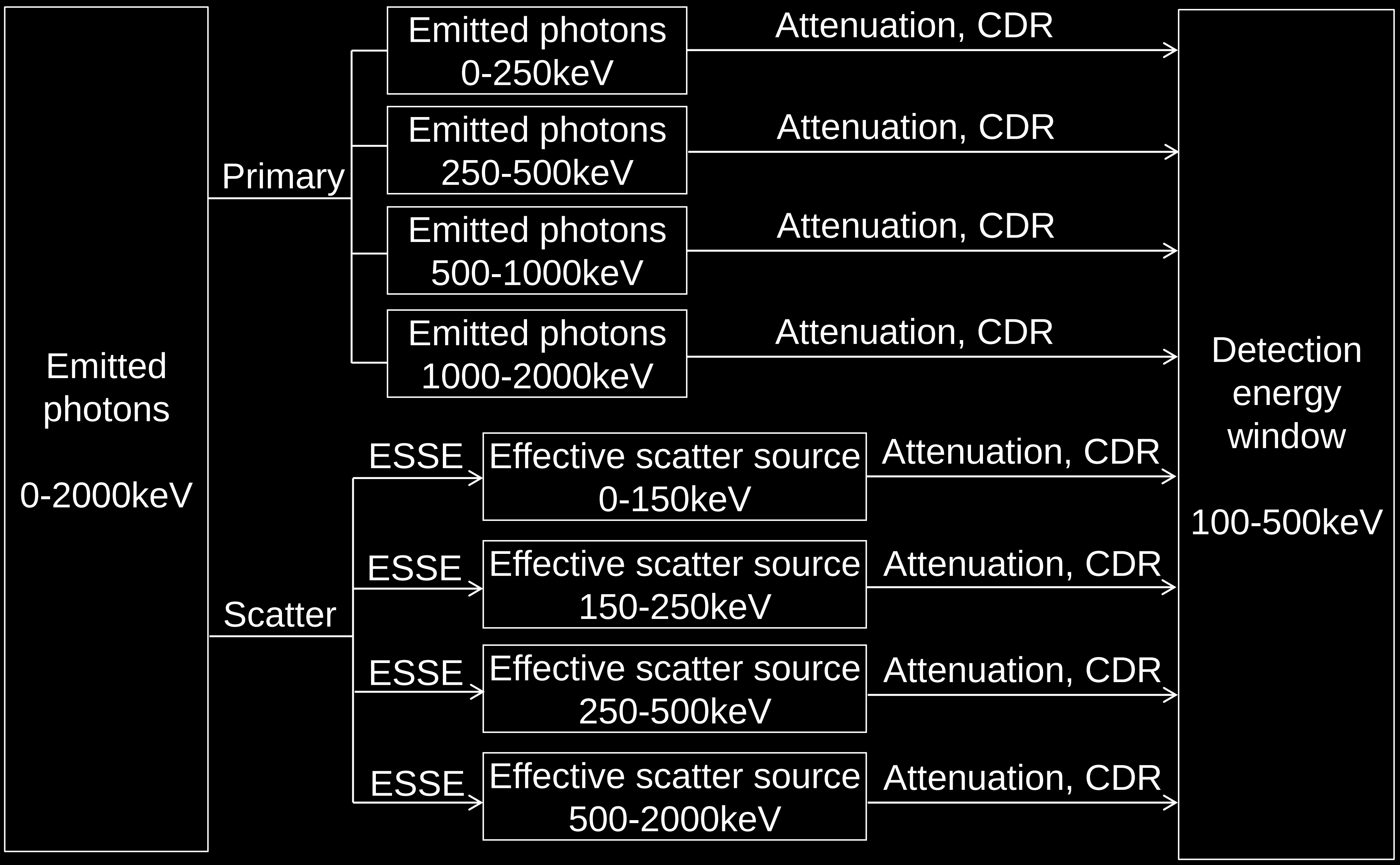
Tc-99m



^{90}Y



Multiple Energy Range (MER) method



Y-90 QSPECT

- Physical phantom experiment
  - Elliptical phantom with 3 spheres
  - Philips Precedence SPECT/CT: HEGP
  - Acquisition time per view: 45s/view
  - Crystal thickness: 9.525 mm
  - 128 projection views over 360º
  - Matrix size per view: 128*128
  - Pixel size: 4.664mm
  - VOIs defined from CT

Y-90 Physical Phantom Study

	5.5 cm diameter sphere	3.3 cm diameter sphere	1.5 cm diameter sphere
% Error	-7.0%	-9.7%	-10.2%

Error = (EstimatedActivity – TrueActivity) / TrueActivity × 100%

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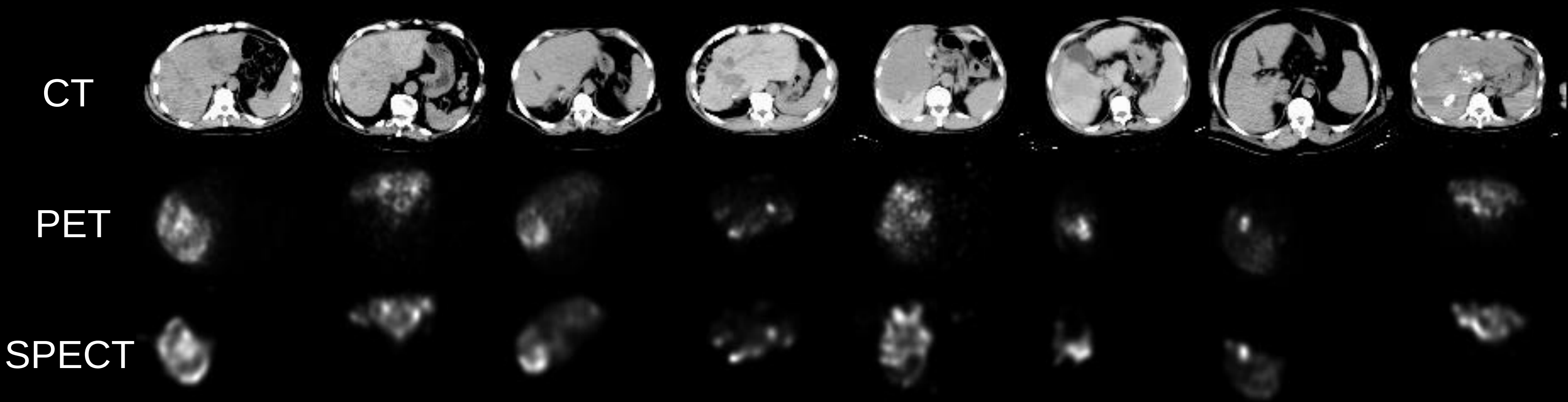
Comparison of Y-90 PET and Quantitative Bremstrahlung SPECT (QBSPECT)



Jianting Yue, Thibault Mauxion, Jeff Geschwind,
Rob Hobbs, Anders Josefsson, Joe Herman

Comparison of Activity in Liver

	PET (MBq)	SPECT (MBq)	PET/Injected ratio	SPECT/Injected ratio	(SPECT-PET)/PET *
Patient 1	3666	3601	99%	97%	-2%
Patient 2	1678	1698	92%	93%	1%
Patient 3	3694	3809	89%	92%	3%
Patient 4	2564	3026	83%	98%	18%
Patient 5	1884	2139	81%	92%	14%
Patient 6	730	769	86%	91%	5%
Patient 7	3364	3009	99%	89%	-11%
Patient 8	1006	1016	92%	92%	1%
Patient 9	4711	4726	89%	89%	0%
Patient 10	4504	4258	94%	89%	-5%
Patient 11	3614	2860	109%	87%	-21%
Patient 12	1361	1447	NA	NA	6%
Patient 13	1447	1446	NA	NA	0%
Patient 14	1969	1975	NA	NA	0%
Patient 15	3688	3518	NA	NA	-5%
				Average	0±9%

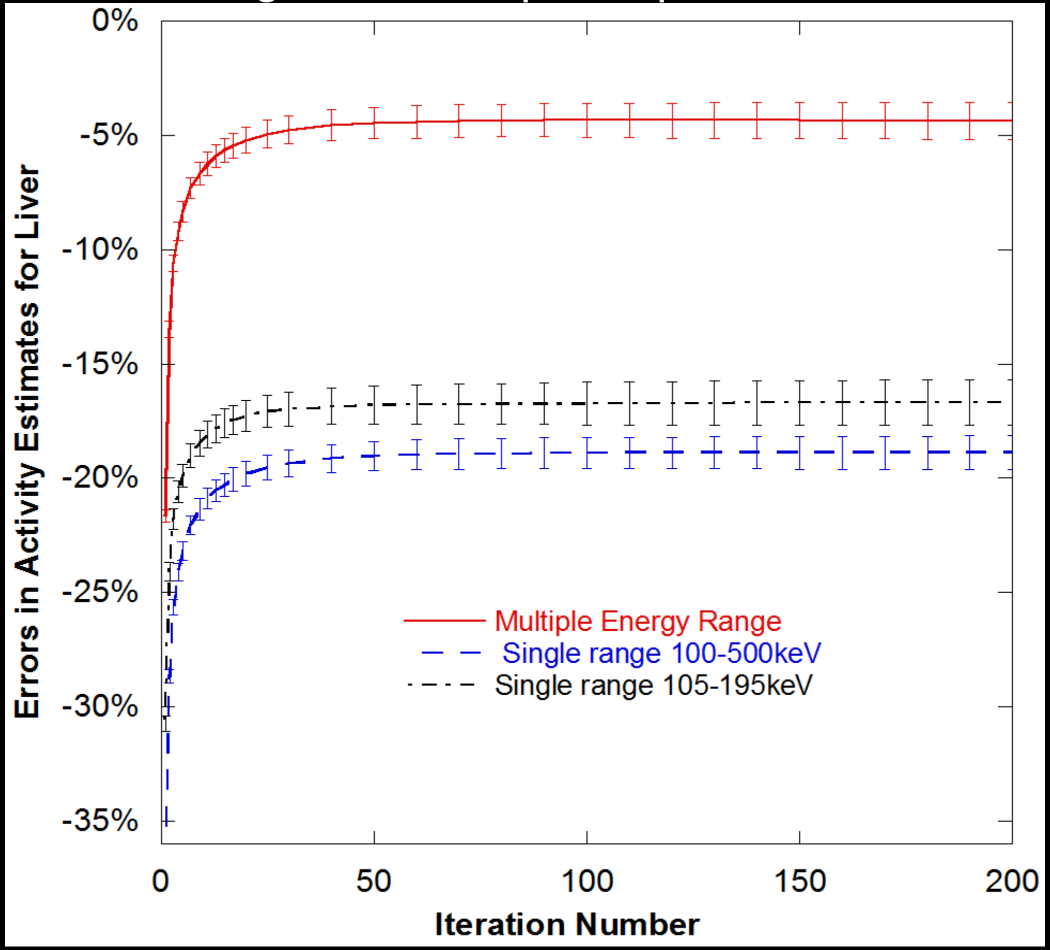
Accuracy for 3.2 cm Diam Sphere (ADS)

Radionuclide	Collimator	Accuracy (%)
In-111	GE MEGP	3.3
I-131	Philips HEGP	14.5
Y-90	Philips HEGP	10

Resolution is more of a limiting factor than the radionuclide

Results: Accuracy & Precision

Mean and standard deviation of errors in the liver activity estimates computed over 50 Poisson noise realizations as a function of the iteration number (16 subsets per iteration) for simulated Y-90 glass microsphere patient



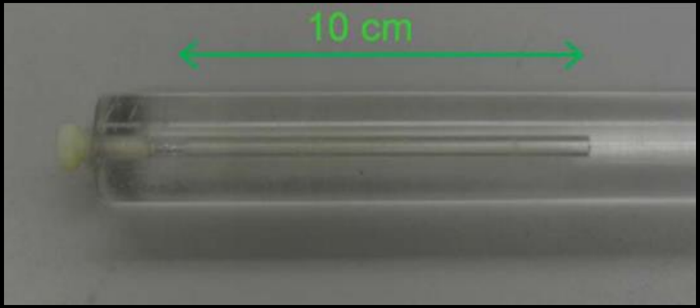
% Error = (True Activity – Estimated Activity)/(True Activity)*100%

Calibration

- Required because of imperfections in knowledge of imaging system
- Planar calibration (sensitivity)
  - Static image of standard source in air at known distance from camera
  - Sensitivity = std. counts/(std. activity * acq. time)
  - If using full CDR compensation, need geometric sensitivity
- Phantom-based calibration
  - Acquire SPECT study of object with known activity
  - Reconstruct and compute counts
  - Calibration factor=true phantom activity/image counts
  - Is the same as planar calibration for "ideal" reconstruction/compensation

Limitations of Planar Calibration Quantitative Y-90 SPECT

- Planar Calibration



Scanner	Calibration Factor
GE Discovery 670	1.14
Siemens Symbia	1.08

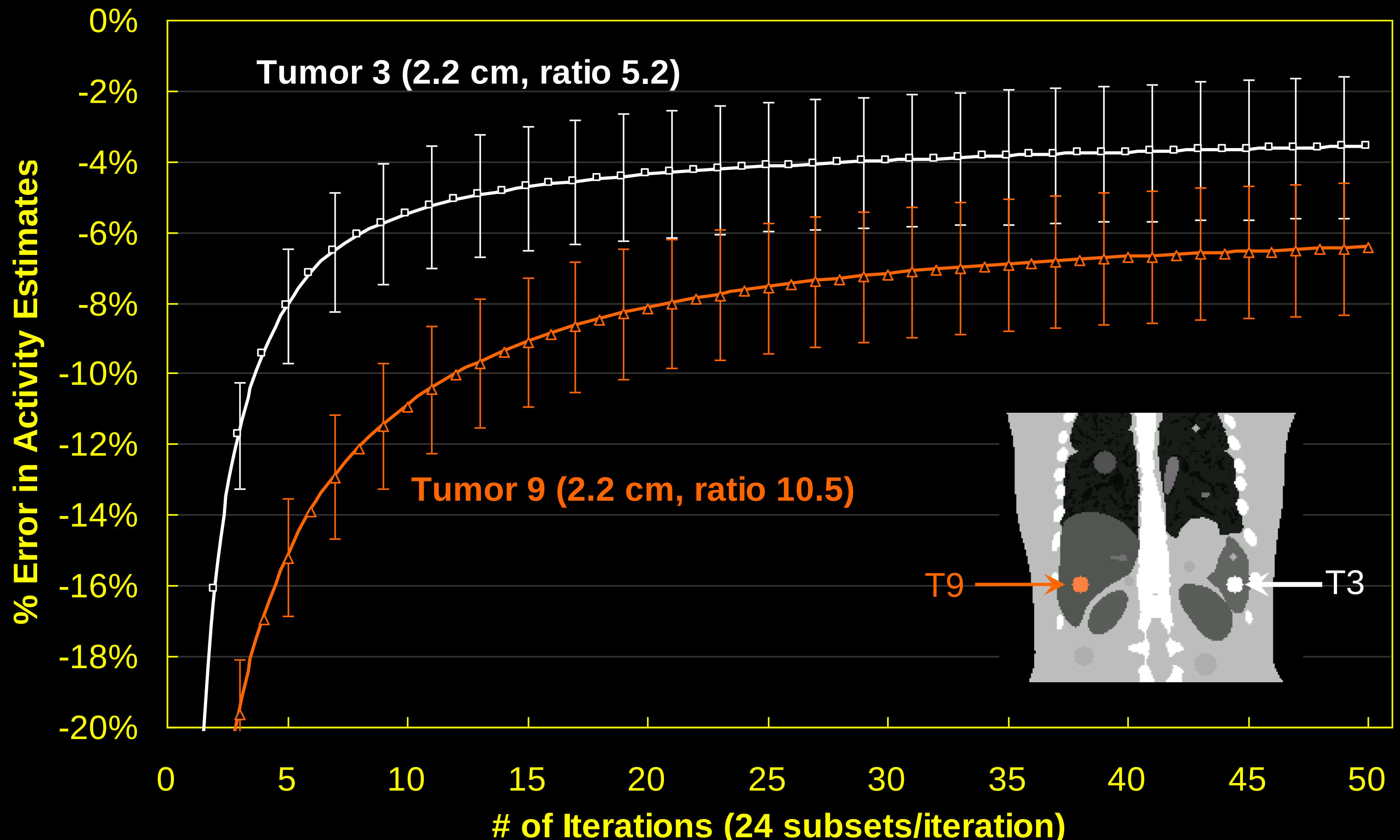
- SPECT Calibration

Phantom	Dimensions
Large Uniform Cylinder	20 cm diameter
Small Uniform Cylinder	4.6 cm diameter
Sphere in cold Elliptical Phantom	5.5 cm diameter sphere in 32x20 phantom

Scanner	Calibration Factor
GE Discovery 670	1.21-1.23
Siemens Symbia	1.15-1.18

Precision for Small Objects

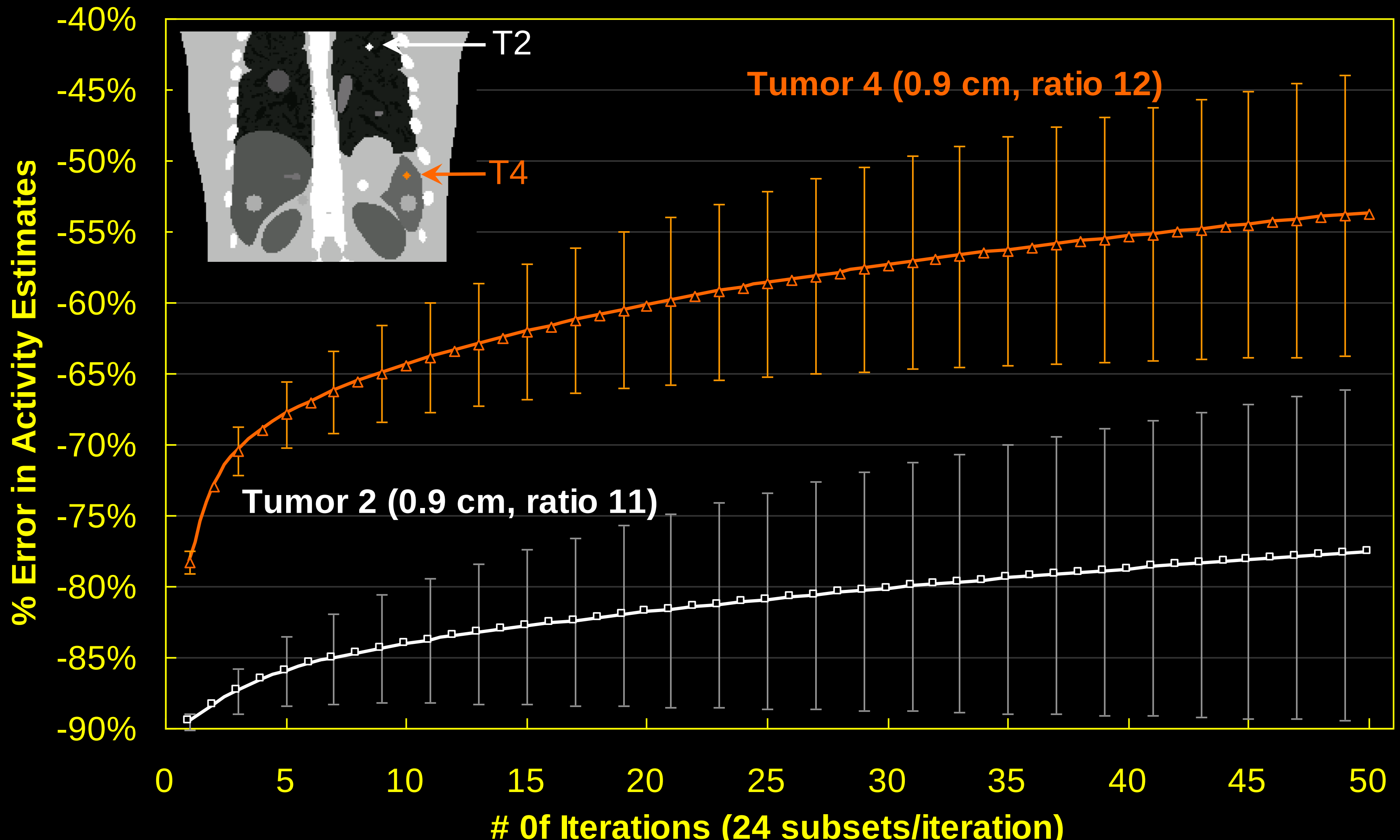
- 2.2 cm diameter tumors



OS-EM w/attenuation, CDR and scatter compensation (no PVC)

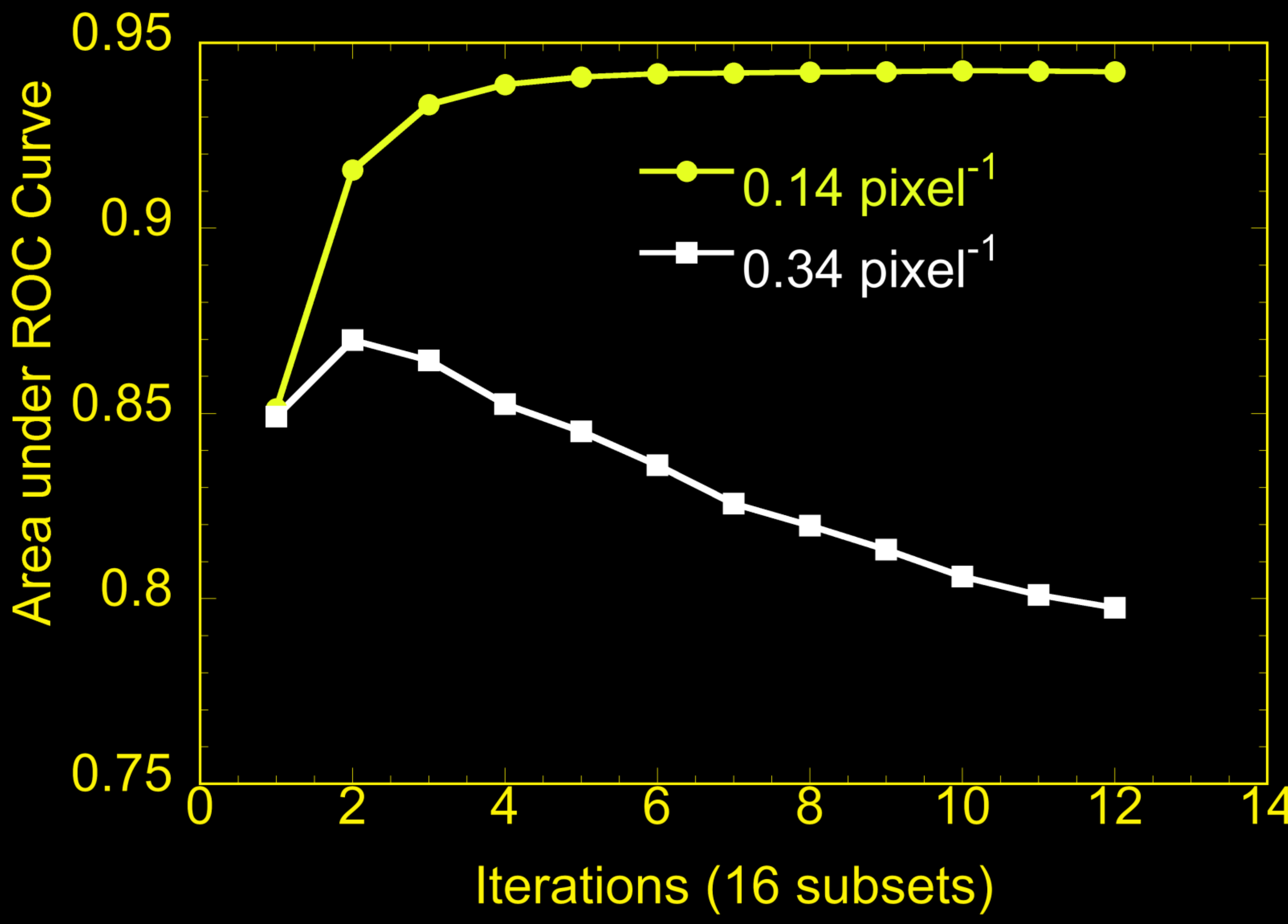
Quantification of Very Small Objects

- 0.9 cm diameter tumors



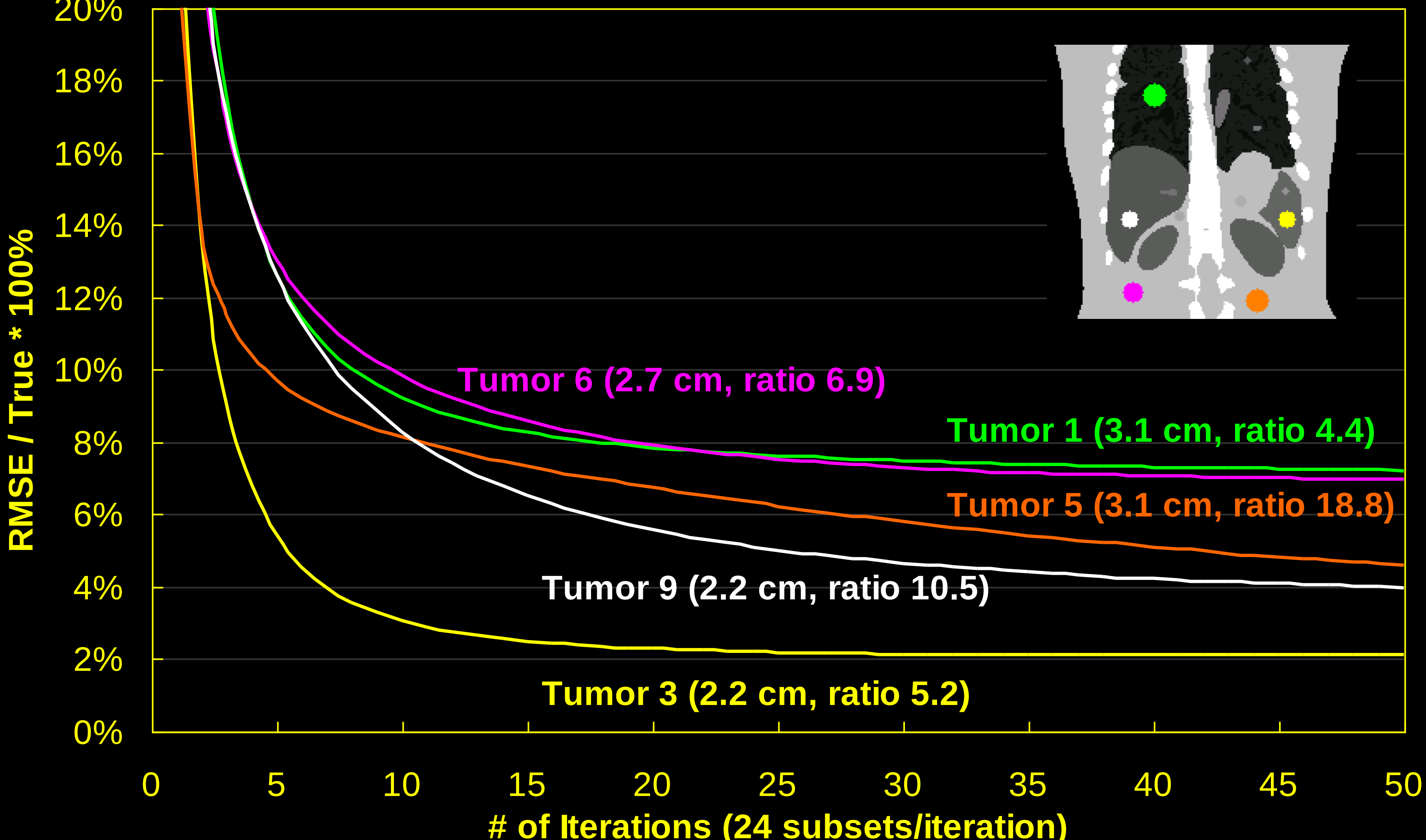
OS-EM w/attenuation, CDR and scatter compensation (no PVC)

Optimal Number of Iterations Detection



Optimal Number of Iterations

- Tumors w/diameter > 2.0 cm



OS-EM w/attenuation, CDR and scatter compensation (no PVC)

Reconstruction/Compensation

Factor	Large Object	Small Object	Commercially Available
Attenuation	Yes	Yes	Yes
Scatter	Yes	Yes	Energy-based: yes Model-based: limited
Geometric Response Compensation	No	Yes	Yes
Full CDR Compensation (High Energy)	Desirable for HE, ME radionuclides	Desirable for HE, ME radionuclides	No
Partial volume compensation	No	Yes	No
Noise Regularization	No	Yes?	Filtering

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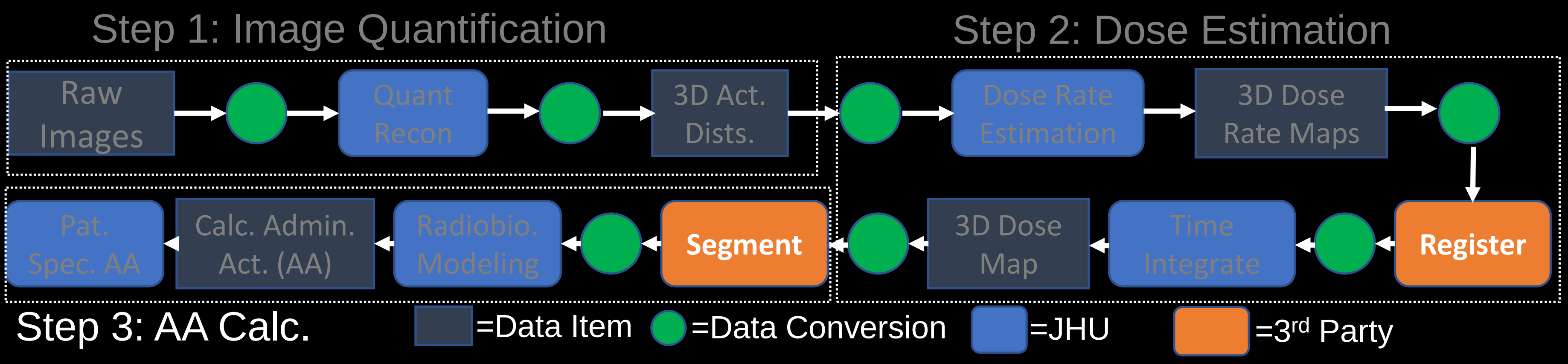
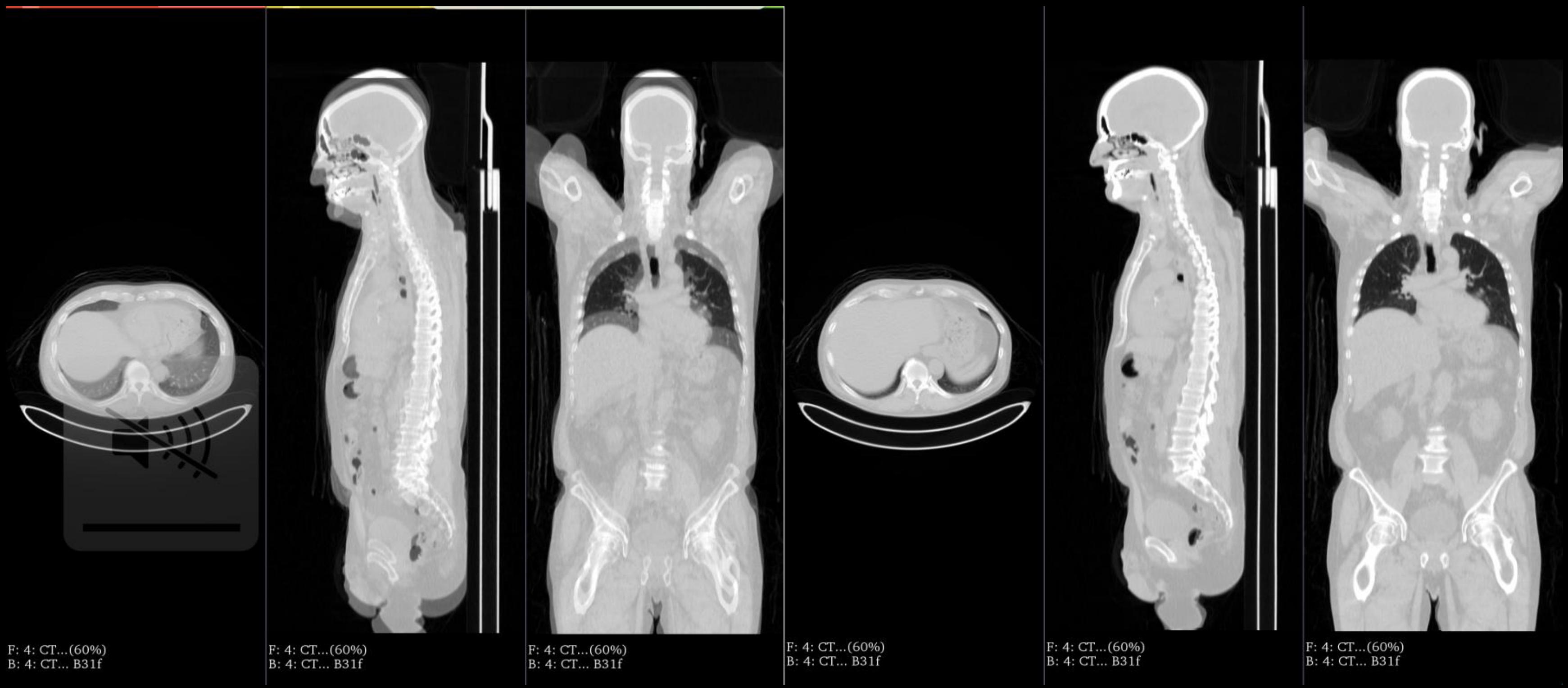


Image Analysis

- Registration
  - Co-registration of CT and ECT images
  - Images from multiple time points
    - Required for 3D (voxel) dosimetry
    - Eases segmentation for organ dosimetry
- Segmentation
  - Required for organ dosimetry
  - Provides region for calculating dose metrics for organ dosimetry

Non-Rigid Image Registration Available Commercially and Open Source



Non-Rigid Image Registration

Consistent patient positioning is essential

SPECT/CT Registration

- Misregistration of SPECT/CT affects
  - Accuracy of attenuation compensation
  - Accuracy of region definition

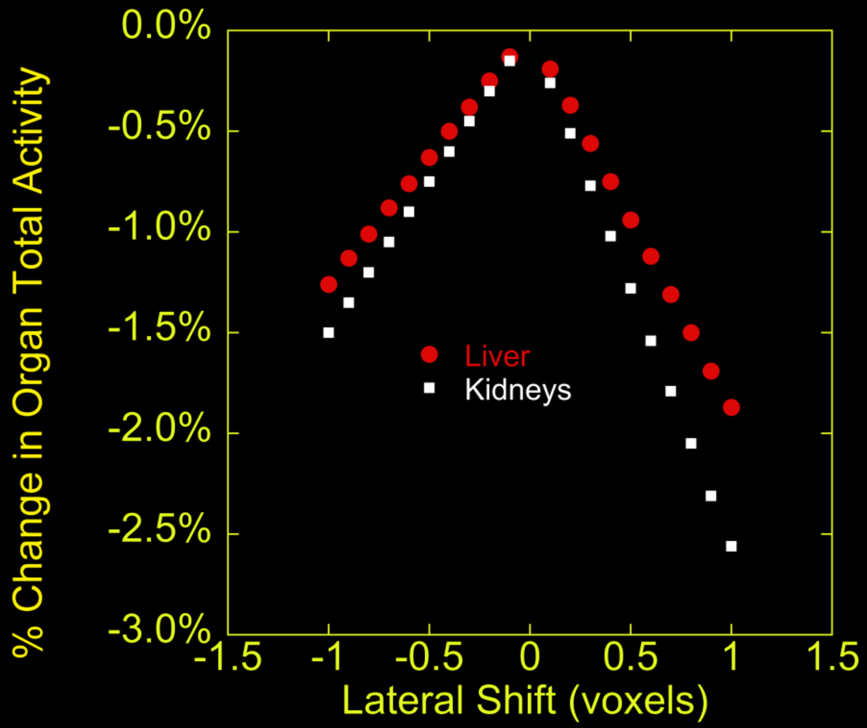
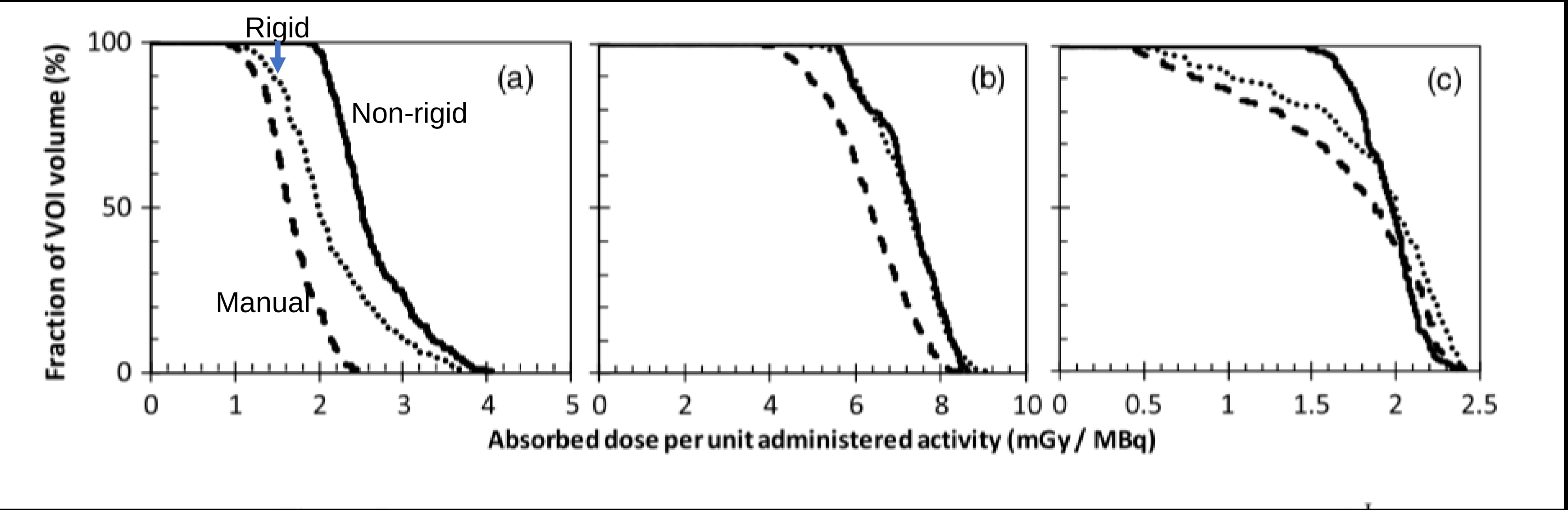


Image Registration and Voxel Dosimetry



Sjogreen-Gleisner, K., D. Rueckert and M. Ljungberg (2009). "Registration of serial SPECT/CT images for three-dimensional dosimetry in radionuclide therapy." Phys Med Biol 54(20): 6181-6200.

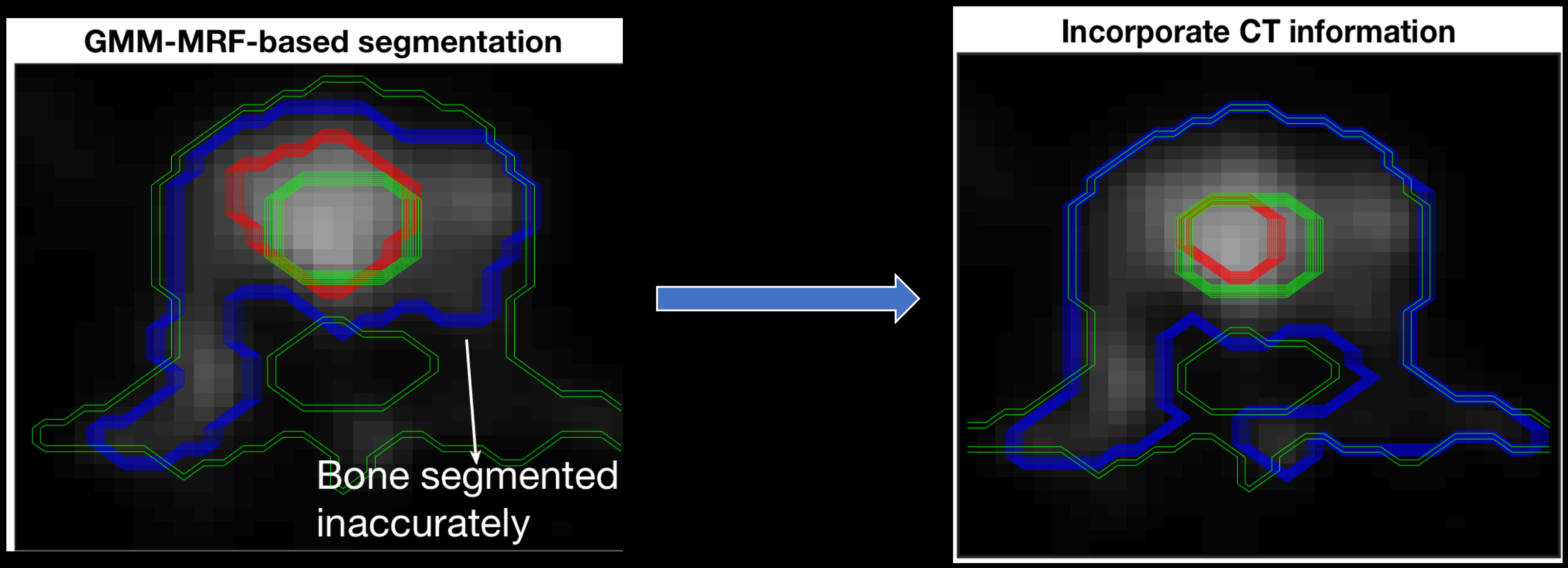
Image Segmentation

- Manual segmentation is commonly used
- Tedious and time consuming
- Automated segmentation of SPECT and PET images is challenging
- Atlas-based methods are promising
- Machine-learning methods have potential

Semi-Automatic Segmentation of Bone SPECT

Key idea 3: CT image provides information about the anatomical boundary of the bone region

Implementation: Segment CT image using the MRF-GMM technique and use boundary of bone region as prior information

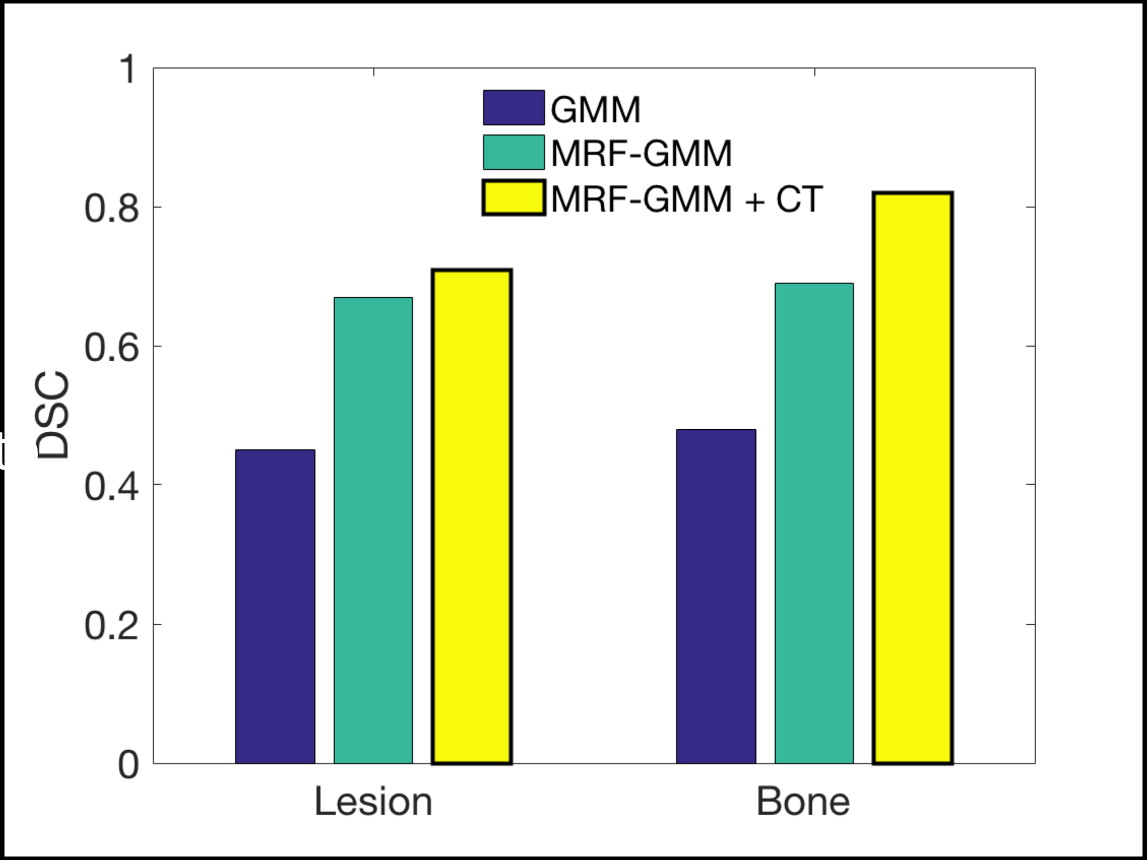


Results: Dice similarity coefficient (DSC)

$$DSC = 2 * \frac{n(T \cap S)}{n(T) + n(S)}$$

True seg. Semi-aut seg.

DSC quantifies region overlap: Higher value better



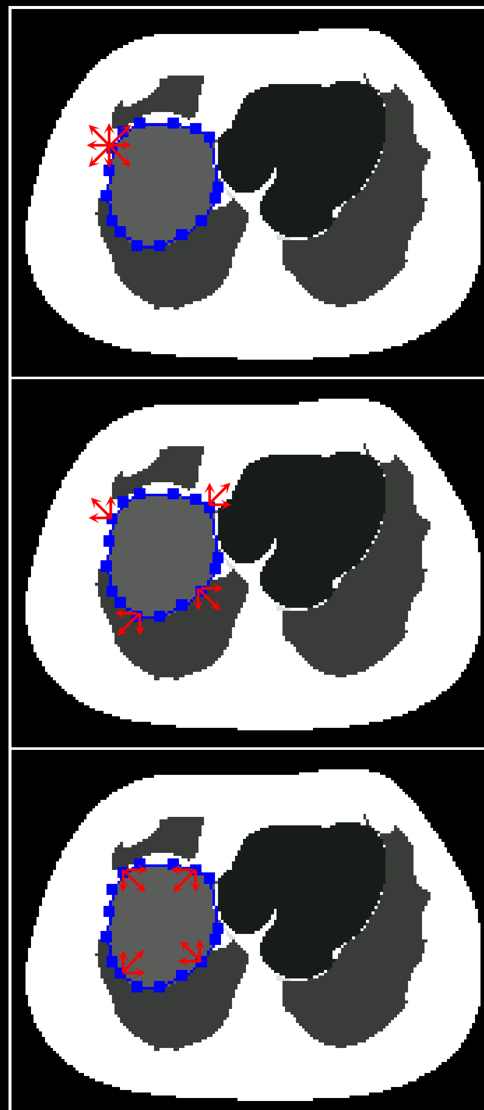
Proposed technique yields the highest DSC values: Most accurate
DSC values > 0.7 indicating accurate segmentation

Mis-definition of VOI

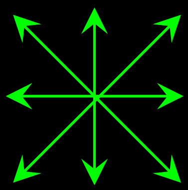
Random

Erosion

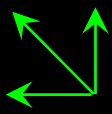
Dilation



1/16	2/16	1/16
2/16	4/16	2/16
1/16	2/16	1/16



1/4	1/4	
1/4	1/4	



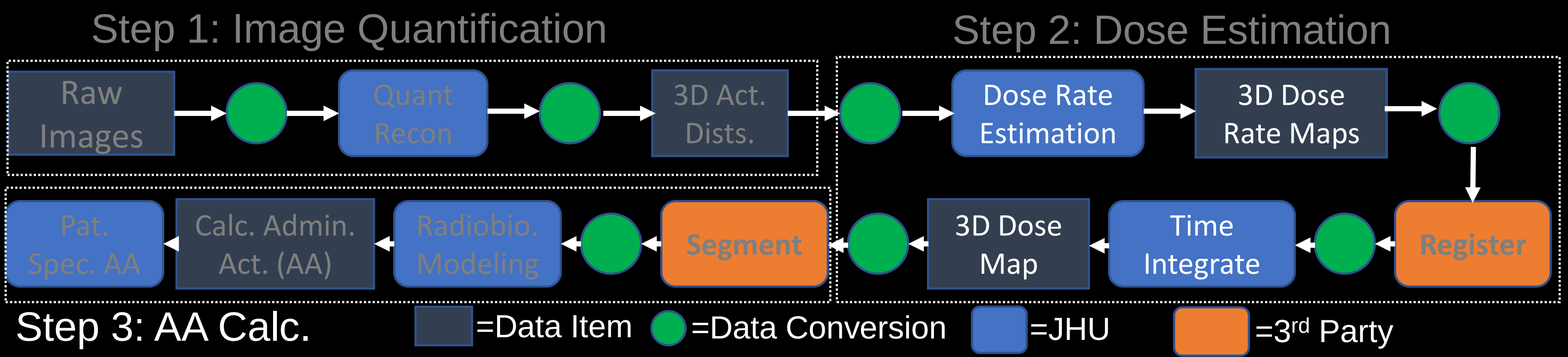
Effects of VOI Mis-definition

- Mis-definition has larger effects for smaller organ than for bigger organ
- Bias (inaccuracy) due to drawing VOIs too large or too small are larger than

Method \ Organs	Liver	Left Kidney
Random (Size correct on Avg)	-0.33±0.05 %	-1.24±0.38 %
Dilation (Large VOIs)	2.06±0.05 %	5.27±0.15 %
Erosion (Small VOIs)	-2.85±0.06 %	-7.52±0.19 %

Outline

- Activity Measurement
- Imaging Protocol
- Activity Distribution Estimation
- Image Analysis
- **Dose Estimation**
- Predicting Response and Toxicity
- Reporting Results



Dose Estimation

- Methods
  - Local absorption
  - Standard phantom
  - 3D
    - Dose kernel
    - Photon transport
- Output
  - Organ level
  - Voxel level

Good Dose Estimation Practice

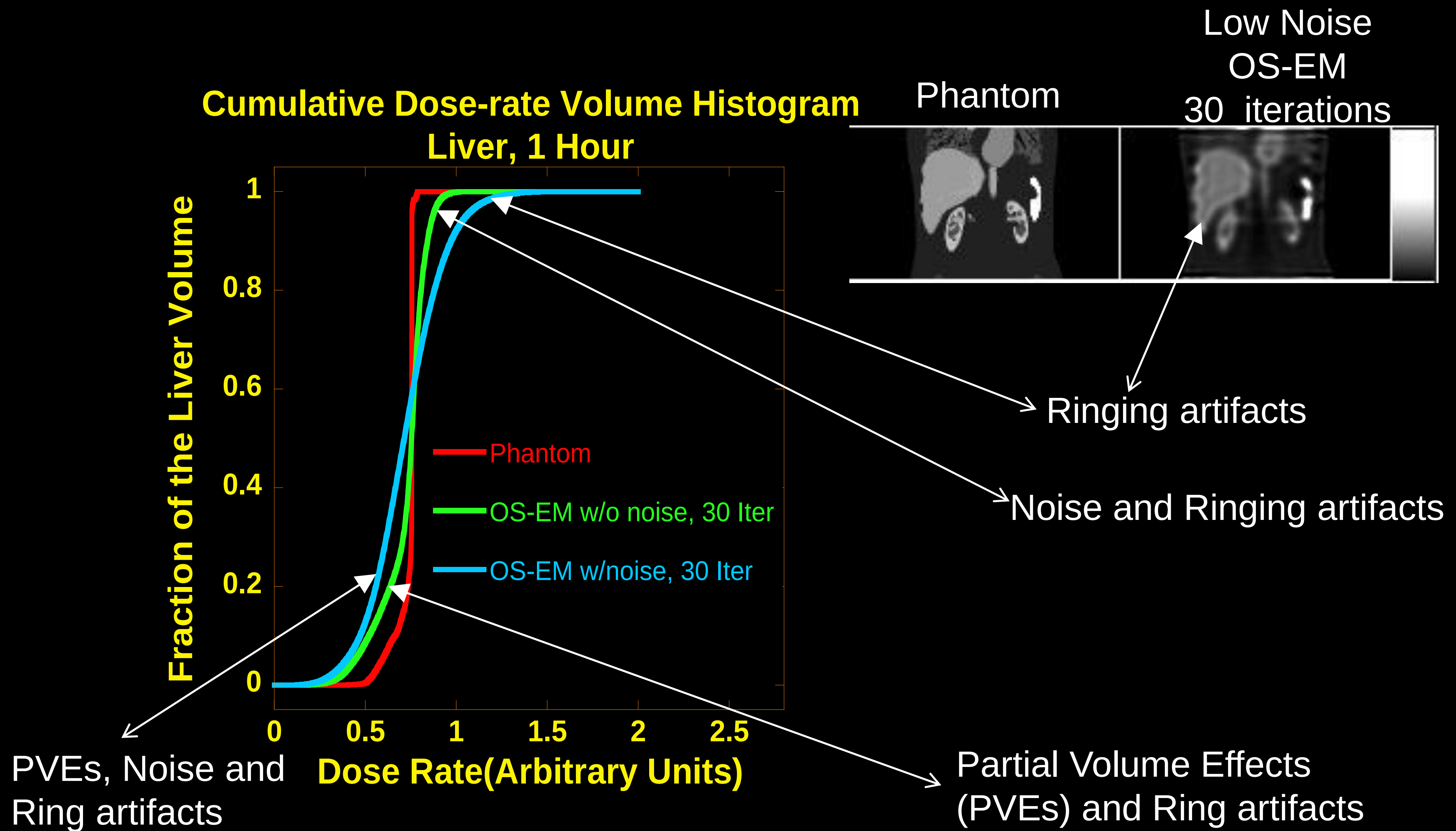
- Method depends on dose metric, particle type
  - Average organ dose
    - Alpha: local absorption o.k.
    - Electrons: standard phantom o.k.
  - Average tumor dose
    - Alphas: local absorption o.k.
    - Electrons: local absorption likely not good enough
  - Dose-volume histogram, minimum dose, maximum dose
    - Requires 3D

Predicting Toxicity and Response

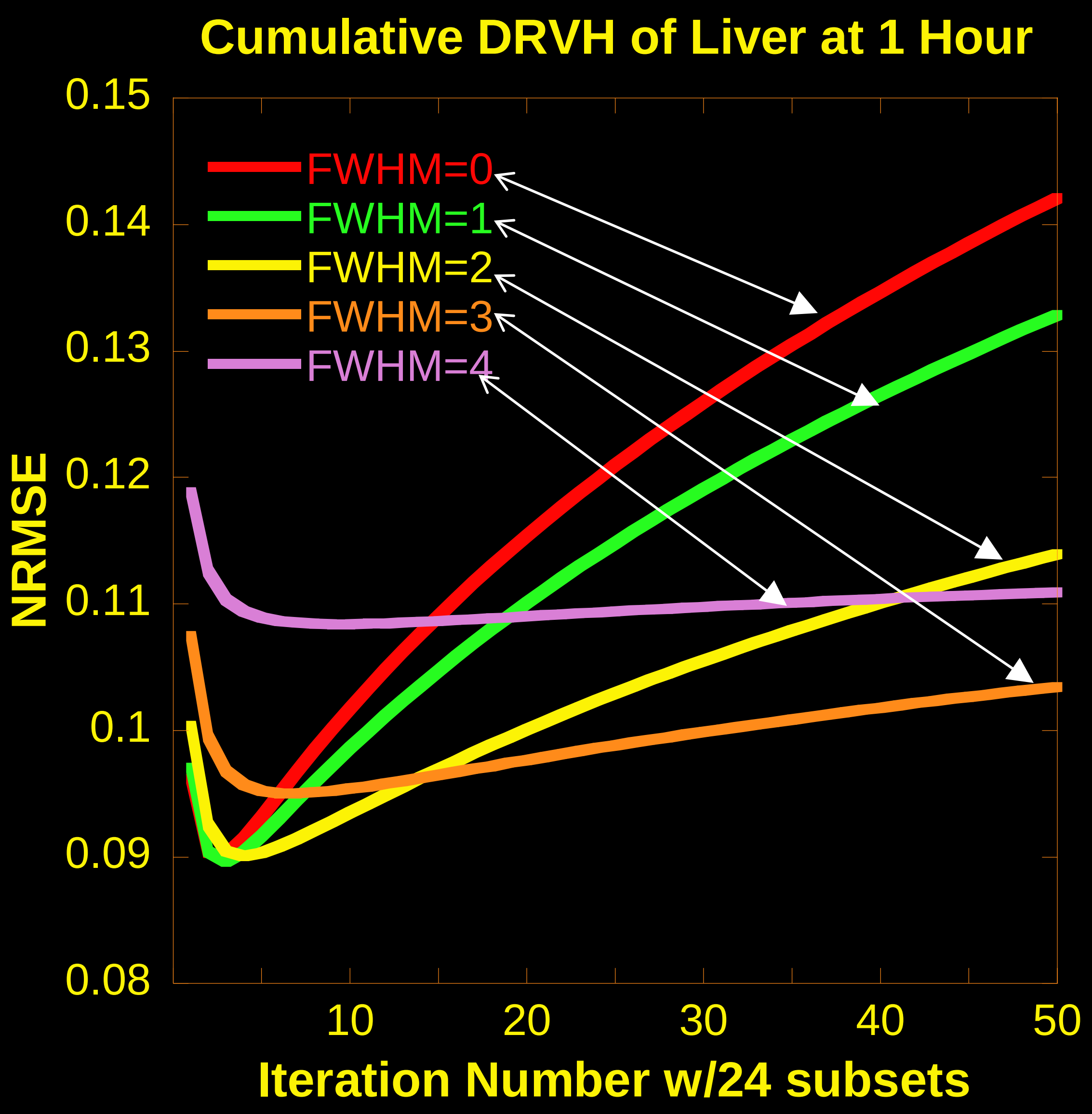
- Physical Metrics
  - Scalar: mean dose, maximum dose, …
  - Dose volume histogram
- Radiobiological Metrics
  - Biological Effective Dose
    - Considers dose rate
    - Important when comparing to external beam doses
    - May be important as patient kinetics varies
  - Consider dose non-uniformities
    - Effective uniform dose, Tumor control probability
    - Normal tissue complication probability
  - Importance of micro-dosimetry and modeling

Dose-Volume Histogram(DVH)

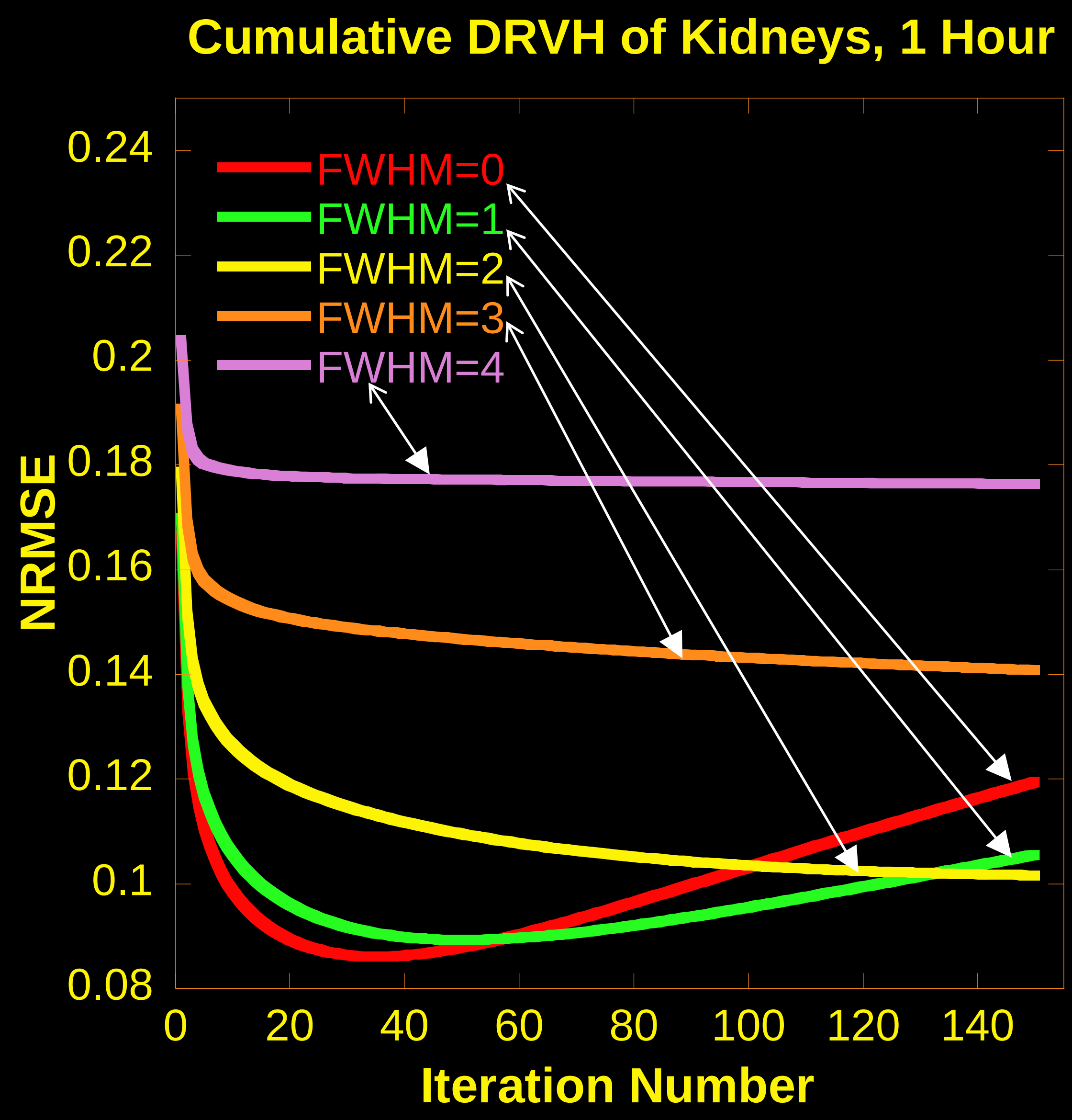
- Widely used, e.g., to compute Normal Tissue Complication Probability (NTCP) and Tumor Control Probability(TCP)



Results: Liver, Hour 1



Results: Kidneys, Hour 1



Reporting Results

EANM Dosimetry Committee guidance document: good practice of clinical dosimetry reporting

M. Lassmann · C. Chiesa · G. Flux · M. Bardiès

Procedure	Yes	No
Probe Measurements		
Is the probe used as a simple counter?		
In conjunction with gamma spectroscopy?		
Is the probe shielded and/or collimated?		
Are the geometric properties of the shielding/collimation given?		
Is the geometry of the patient measurement given?		
Are the background counts without any sources present given?		
Are the sensitivity and the window settings documented?		
Is the sensitivity range of the device provided?		
Are the dead time characteristics of the system known?		
Well Counter Measurements		
Are the geometry of the sample, the background, sensitivity and the window settings of the device documented?		
Dose Calibrators		
Are the QC procedures implemented and documented?		
Are measurements performed with traceable calibrated sources?		
Are the appropriate corrections for geometry dependencies done?		
Gamma-Cameras		
Gamma camera make (name of the manufacturer) and model (+ year)		
Crystal thickness		
Energy window(s) (number + range of each)		
Pixel size / Matrix size		
Number of heads used for the acquisition		
Software version		
Collimator		
Stopping conditions		
ROI location and size		
Corrections for overlapping organs		
Background correction		

Procedure	Yes	No
Method of scatter correction		
Method of attenuation correction		
Dead time correction		
SPECT		
Number of projections		
Orbit type		
Rotation parameters		
Reconstruction parameters		
Software used		
Partial volume effect correction		
PET		
Correction for “dirty” nuclides		
Phantom and Calibration Measurements		
Method of calibration		
Phantom type		
Activities used		
Biokinetics		
Number of data points for each patient		
Fitting procedures incl. error of fit parameters		
Treatment of the AUC before the first and after the last data point		
Residence Time		
Given for each patient individually?		
Dosimetry Calculation		
Computer and software		
Source of S-Values		
Mass determination – described how?		
Tumour dosimetry performed and described how?		
Is geometric or cross-talk corrections to tumour dosimetry applied?		
Propagation of error calculation performed		
Miscellaneous		
Is the choice of nuclides justified?		
Is there an external audit?		
Are the units used appropriate for the purpose?		
Are the confounding factors included?		

Summary

- Careful planning and documentation of entire imaging protocol and dosimetry workflow
- Standards-traceable calibration of activity meter
- Tomographic imaging
  - Validation and ‘optimization’ using phantoms or simulations
  - Careful calibration
- Reproducible patient positioning
- Selection of relevant dose metrics
- Selection of required image analysis and dosimetry estimation methods

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