# Current Dosimetry Methods for Systemic Radiopharmaceutical Therapy

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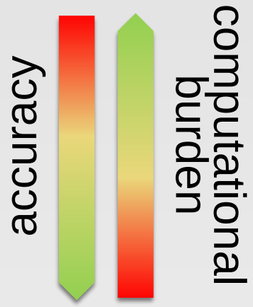
# Outline

- The role of dosimetry in Systemic Radiopharmaceutical Therapy (SRT)
- Clinical dosimetry methods and limitations
  - MIRD
  - Voxel S-values
  - Monte Carlo & Analytical methods
- Image-based dosimetry
- Case studies
  - I-131 immunotherapy
  - Y-90 radioembolization
- Towards new methods



# Targeted Radionuclide Therapy: Promises and Challenges

A promising treatment approach…

- Limited toxicity
- Targeting potential

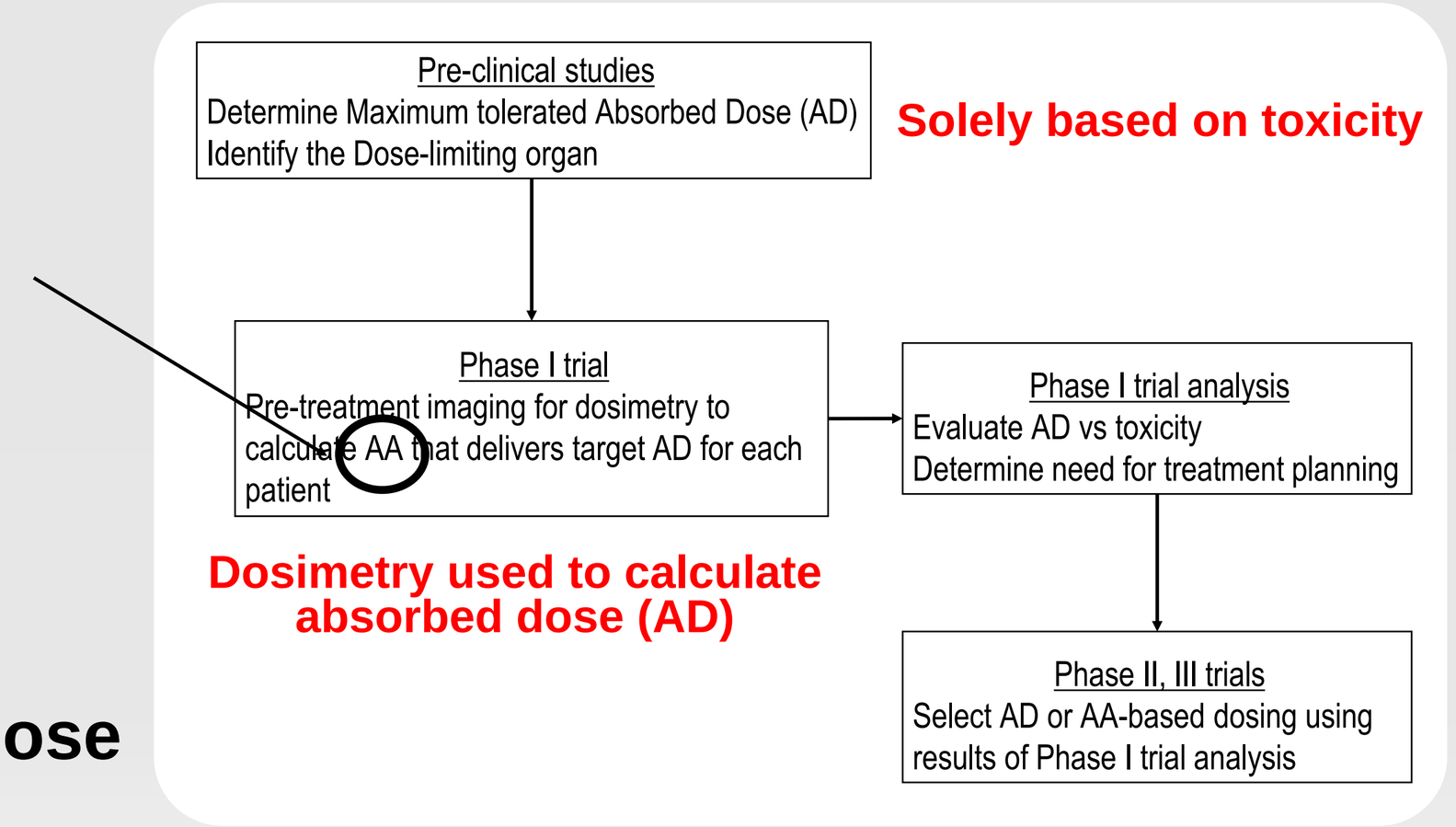
But…

- Radiation dose response poorly understood / characterized
- Dosing of administered activity largely based on toxicity studies

# The role of dosimetry in SRT

- Main variable= **administered activity**
- Based on patient's body surface area
- Dosing only based on target **absorbed dose** (**AD**)

**How is the absorbed dose calculated?**



# Calculate the Absorbed Dose in Target and Organs-at-risk

## Absorbed dose = cumulative dose

- Cumulative activity (activity x time), $\tilde{A}$
- Energy per radioactive decay $E$
- Absorbed fraction = fraction of energy absorbed within target, $\phi$

## Dosimetry systems

- Medical Internal Radiation Dose Committee from the Society of Nuclear Medicine (MIRD)
- Voxel S-values
- Monte Carlo & Analytical methods

# MIRD Schema

*"The virtue of the MIRD approach is that it systematically reduces complex dosimetric analyses to methods that are relatively simple to use."*

MIRD general equation

$$AD(target) = \sum_{sources} \tilde{A}_{source} \cdot S(target \leftarrow source)$$

Energy deposition terms all lumped in S-value

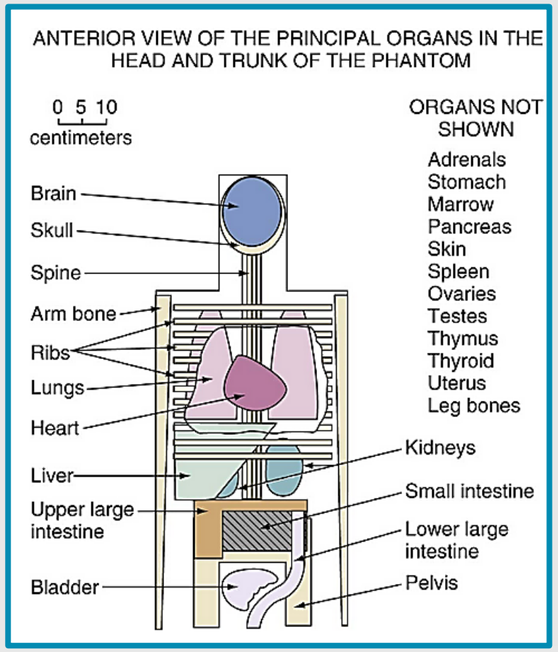
MIRD schema is entirely based on the S-values

# MIRD Schema: S-value

- S-values calculated at the organ level, assuming a **uniform** tissue and activity*

$$S \propto \frac{\sum_i n_i E_i \phi_i}{m}$$

$i$ = number of radiation in decay scheme
$n_i$ = number of radiation with $E_i$ per decay
$E_i$ = energy emitted per decay for i$^{th}$ radiation
$\phi_i$ = fraction of energy absorbed
$m$ = mass of target




- S-values are tabulated for each radionuclide, using phantom data for $\phi$

*W.S. Snyder *et al.*, MIRD Pamphlet no. 11. Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs,1975

# MIRD Schema: Absorbed Dose Table for $^{131}I$

S, ABSORBED DOSE PER UNIT CUMULATED ACTIVITY, (RAD/UCI-H)
IODINE-131 HALF-LIFE 193. HOURS

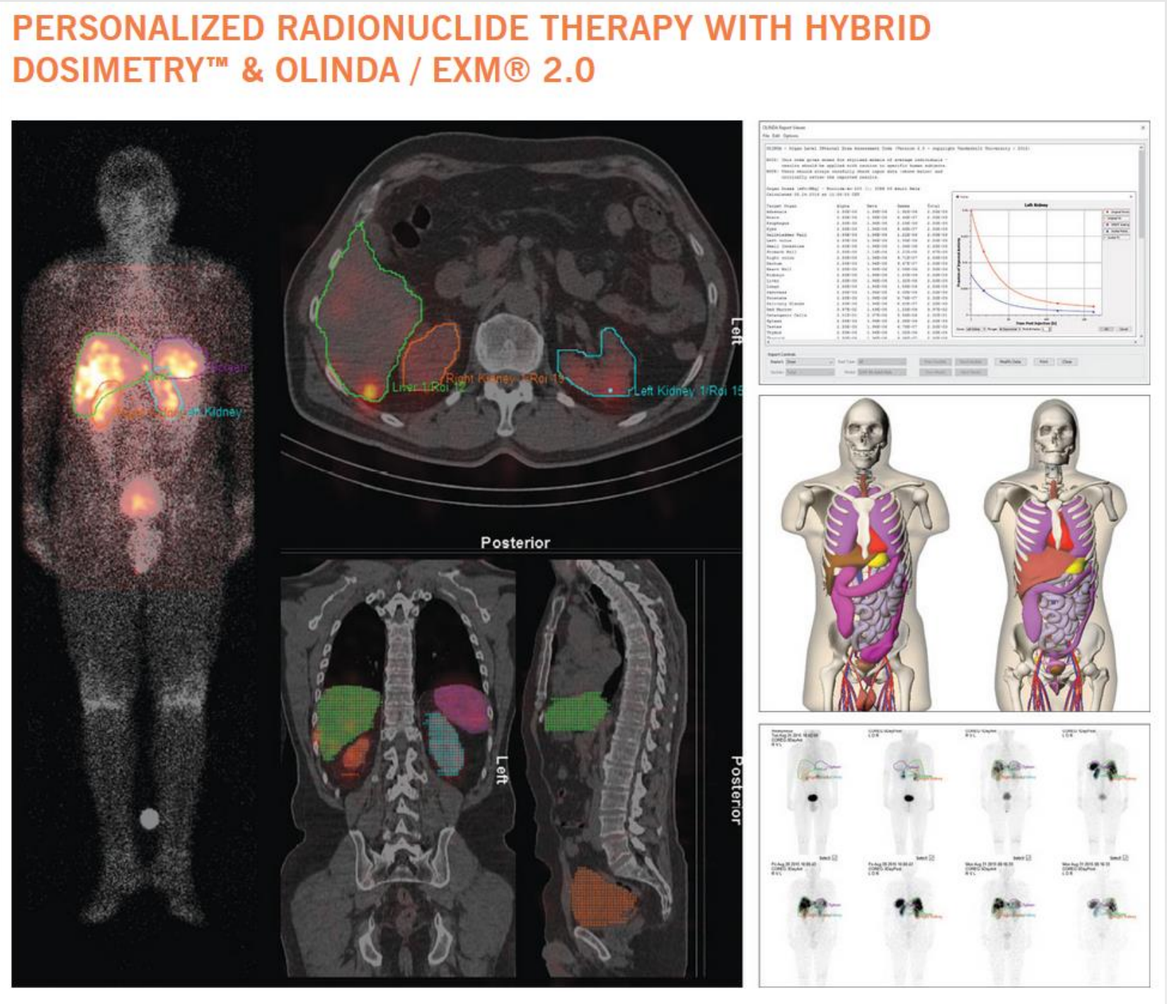
| TARGET ORGANS | SOURCE ORGANS: ADRENALS | BLADDER CONTENTS | INTESTINAL TRACT: STOMACH CONTENTS | INTESTINAL TRACT: SI CONTENTS | INTESTINAL TRACT: ULI CONTENTS | INTESTINAL TRACT: LLI CONTENTS | KIDNEYS | LIVER | LUNGS | OTHER TISSUE (MUSCLE) |
|---|---|---|---|---|---|---|---|---|---|---|
| ADRENALS | 3.1E-02 | 6.1E-07 | 6.3E-06 | 3.9E-06 | 2.7E-06 | 1.4E-06 | 3.2E-05 | 1.4E-05 | 6.9E-06 | 4.2E-06 |
| BLADDER WALL | 3.3E-07 | 1.2E-03 | 1.0E-06 | 8.5E-06 | 5.6E-06 | 1.7E-05 | 1.0E-06 | 7.4E-07 | 1.8E-07 | 5.0E-06 |
| BONE (TOTAL) | 4.1E-06 | 1.8E-06 | 1.8E-06 | 2.5E-06 | 2.2E-06 | 3.2E-06 | 3.0E-06 | 2.3E-06 | 3.0E-06 | 3.0E-06 |
| GI (STOM WALL) | 8.2E-06 | 8.8E-07 | 9.7E-04 | 9.9E-06 | 1.0E-05 | 5.0E-06 | 9.4E-06 | 5.4E-06 | 5.2E-06 | 3.9E-06 |
| GI (SI) | 2.6E-06 | 7.6E-06 | 7.3E-06 | 6.0E-04 | 4.6E-05 | 2.6E-05 | 7.8E-06 | 4.6E-06 | 6.9E-07 | 4.4E-06 |
| GI (ULI WALL) | 2.8E-06 | 6.6E-06 | 9.5E-06 | 6.5E-05 | 1.1E-03 | 1.2E-05 | 8.1E-06 | 7.0E-06 | 9.1E-07 | 4.6E-06 |
| GI (LLI WALL) | 8.4E-07 | 2.0E-05 | 3.6E-06 | 1.9E-05 | 8.4E-06 | 1.7E-03 | 2.4E-06 | 8.1E-07 | 2.6E-07 | 4.8E-06 |
| KIDNEYS | 3.2E-05 | 9.6E-07 | 9.5E-06 | 8.7E-06 | 7.7E-06 | 2.5E-06 | 1.5E-03 | 1.1E-05 | 2.7E-06 | 4.0E-06 |
| LIVER | 1.4E-05 | 7.2E-07 | 5.6E-06 | 5.1E-06 | 7.1E-06 | 9.0E-07 | 1.1E-05 | 3.0E-04 | 6.8E-06 | 3.1E-06 |
| LUNGS | 6.7E-06 | 1.1E-07 | 5.0E-06 | 8.5E-07 | 8.9E-07 | 2.8E-07 | 2.5E-06 | 6.8E-06 | 4.5E-04 | 3.7E-06 |
| MARROW (RED) | 7.5E-06 | 4.1E-06 | 3.2E-06 | 7.9E-06 | 6.9E-06 | 9.7E-06 | 7.6E-06 | 3.3E-06 | 3.8E-06 | 4.1E-06 |
| OTH TISS (MUSC) | 4.2E-06 | 5.0E-06 | 3.9E-06 | 4.4E-06 | 4.1E-06 | 4.8E-06 | 4.0E-06 | 3.1E-06 | 3.7E-06 | 1.9E-05 |
| OVARIES | 1.6E-06 | 1.9E-05 | 1.4E-06 | 2.7E-05 | 3.4E-05 | 5.0E-05 | 3.4E-06 | 9.6E-07 | 4.0E-07 | 5.6E-06 |
| PANCREAS | 2.4E-05 | 7.9E-07 | 5.0E-05 | 5.8E-06 | 5.8E-06 | 2.0E-06 | 1.8E-05 | 1.2E-05 | 7.5E-06 | 5.0E-06 |
| SKIN | 1.8E-06 | 1.7E-06 | 1.5E-06 | 1.4E-06 | 1.4E-06 | 1.6E-06 | 1.8E-06 | 1.6E-06 | 1.8E-06 | 2.4E-06 |
| SPLEEN | 1.8E-05 | 5.6E-07 | 2.7E-05 | 4.4E-06 | 3.7E-06 | 2.5E-06 | 2.4E-05 | 2.7E-06 | 6.2E-06 | 4.1E-06 |
| TESTES | 1.7E-07 | 1.4E-05 | 1.3E-07 | 1.0E-06 | 1.2E-06 | 5.7E-06 | 3.9E-07 | 3.0E-07 | 5.7E-08 | 3.4E-06 |
| THYROID | 5.2E-07 | 2.1E-08 | 3.9E-07 | 9.5E-08 | 1.0E-07 | 4.1E-08 | 2.4E-07 | 5.7E-07 | 3.0E-06 | 3.8E-06 |
| UTERUS (NONGRVD) | 3.4E-06 | 4.3E-05 | 2.4E-06 | 2.5E-05 | 1.3E-05 | 1.7E-05 | 2.6E-06 | 1.2E-06 | 2.7E-07 | 5.9E-06 |
| TOTAL BODY | 1.1E-05 | 5.9E-06 | 6.7E-06 | 1.0E-05 | 8.2E-06 | 8.8E-06 | 1.1E-05 | 1.1E-05 | 9.9E-06 | 9.8E-06 |

DECAY DATA REVISED-MARCH, 1972. REFERENCE-MIRD PAMPHLET NO. 10.
DATE OF ISSUE-05-13-75

$^{131}I$

# MIRD-based Software: OLINDA/EXM

- Organ-level dosimetry
- Uses MIRD S-value dose tables
- ICRP 89 “NURBs” phantoms included*
- Accepts kinetic data from users
- Generates **average** absorbed dose for target and organs-at-risk




*Stabin M. G., et al. OLINDA/EXM: The second-generation personal computer software for internal dose assessment in nuclear medicine, 2005

# Voxel S-values

- Voxel S-value = mean absorbed dose to target voxel per radioactive decay in source voxel. Both voxels are in infinite, homogenous medium

MIRD equation for Voxel S-value

$$AD(target\ voxel) = \sum_{source\ voxels} \tilde{A}_{source\ voxel} \cdot S(target\ voxel \leftarrow source\ voxel)$$

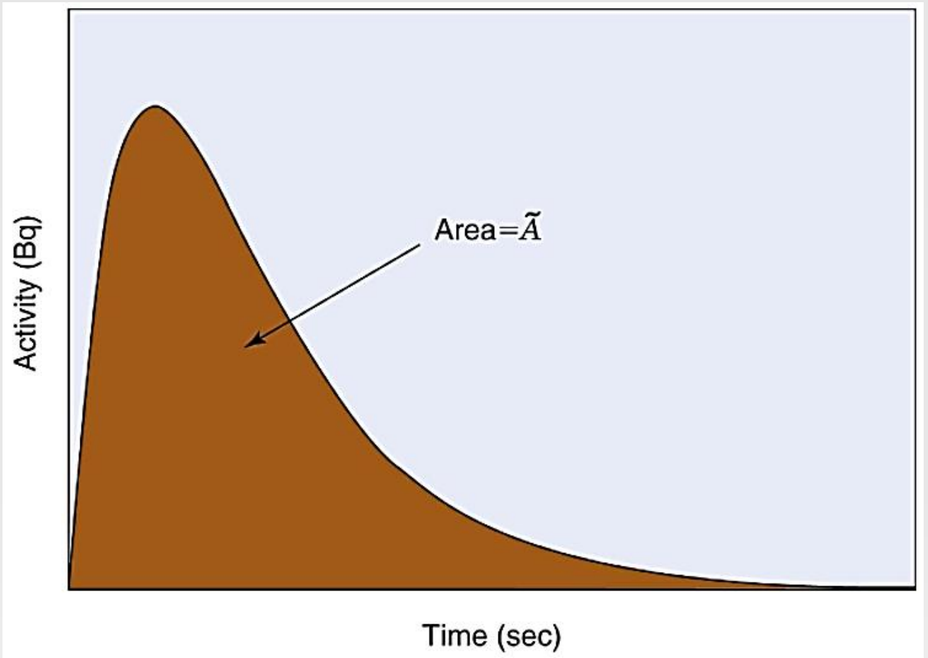
- Voxel S-values can be convolved with cumulative activity distribution*
- Must be computed for each clinical setting…

*Bolch W E, et al. MIRD pamphlet no. 17: The dosimetry of nonuniform activity distributions—radionuclide s values at the voxel level,1999

# Cumulative Activity

$$\tilde{A} = AA \cdot \tau$$

organ residence time




*Time activity curve*

# Analytical Methods: Dose Point Kernel

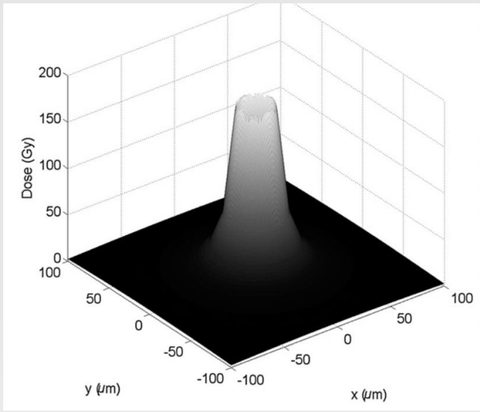
**Patient specific**

Cumulative activity (PET or SPECT) $\otimes$ DPK$(r)$ = Absorbed Dose $(r)$

Dose point kernel (DPK)*:

- Radial distribution of mean absorbed dose around isotropic point source in infinite homogenous medium
- Function of distance $r$ from point source

Efficient, accurate solution for uniform tissues




Gulec et al. 2006

*Botta F, et al. Calculation of electron and isotopes dose point kernels with FLUKA Monte Carlo code for dosimetry in nuclear medicine therapy, 2011

# Monte Carlo Approaches

Anatomical data (CT or MRI)

+

Cumulative activity (PET or SPECT)

→

Radiation transport model

- EGSnrc
- MCNP
- PENELOPE
- FLUKA
- GATE / GEANT4

=

**Patient specific**

Absorbed Dose distribution

Toward accurate patient-specific absorbed dose…

…But computationally intensive

Sarrut D, et al. A review of the use and potential of the GATE Monte Carlo simulation code for radiation therapy and dosimetry applications, 2014

# Image-based Dosimetry

Imaging is critical to:

- Determine the volume of the target and organs-at-risk (anatomical imaging)
- Measure the activity distribution in these regions (functional imaging)
- Account for non-uniform (temporal and spatial) activity distributions

Imaging requirements for dosimetry:

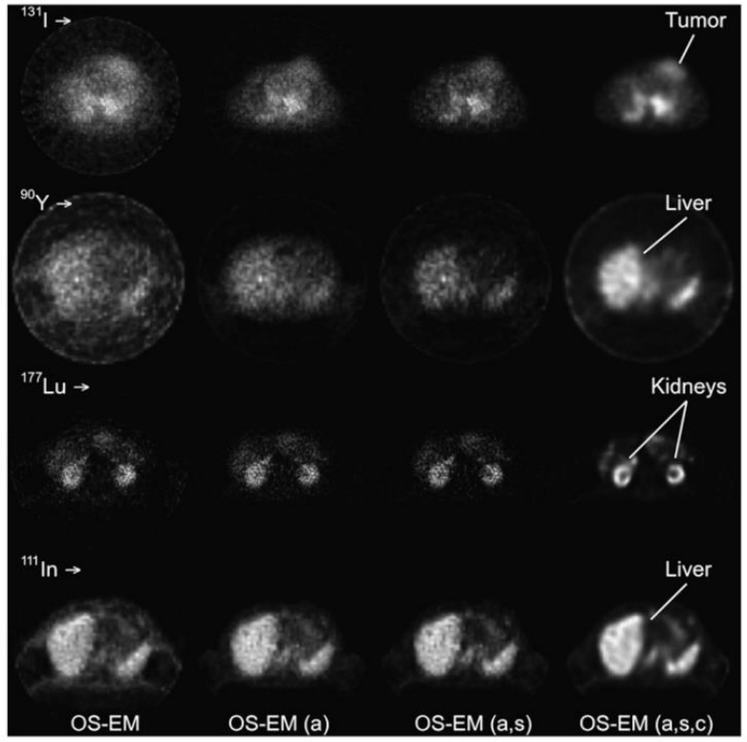
- **Quantification** is needed to convert counts into activity (Mbq) and then dose (Gy)
- Spatial resolution is important to account for heterogenous distributions **within** the target

# Quantitative Imaging for Dosimetry

- Data corrections applied before, during, or post reconstruction*,**
- Iterative reconstruction is preferred
- 3D imaging improves quantification

## Can we achieve absolute quantification?

- Requires good models of attenuation and scattering
- Requires scanner calibration




**Dewaraja et al. 2012

*Siegel J A, et al. MIRD pamphlet no. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates, 1999

**Dewaraja Y K, et al. MIRD pamphlet no. 23: Quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy, 2012

# Quantitative Imaging for Time-integrated Activity

- Serial quantitative imaging is needed
- Registration between image datasets may be challenging
- Optimal timing depend upon activity clearance
- Radionuclides with potential rapid clearance may rely on 4D imaging

**Image-based dosimetry is critical to patient-specific dosimetry**

Dewaraja Y K, et al. MIRD pamphlet no. 23: Quantitative SPECT for patient-specific 3-dimensional dosimetry in internal radionuclide therapy, 2012

# Dosimetry can improve patient outcome:

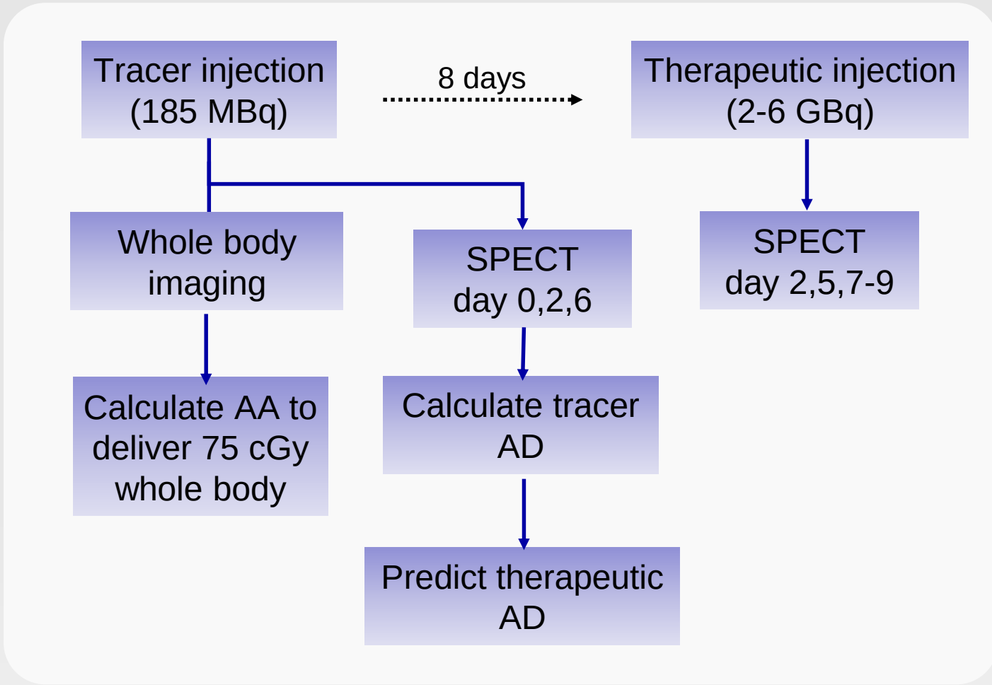
# The case of $^{131}$I-Tositumomab Radioimmunotherapy

# I-131 Radioimmunotherapy

**Tumor-Absorbed Dose Predicts Progression-Free Survival Following $^{131}$I-Tositumomab Radioimmunotherapy**

Yuni K. Dewaraja[1], Matthew J. Schipper[2], Jincheng Shen[3], Lauren B. Smith[4], Jure Murgic[5], Hatice Savas[1], Ehab Youssef[1], Denise Regan[1], Scott J. Wilderman[6], Peter L. Roberson[2], Mark S. Kaminski[7], and Anca M. Avram[1]

- Distribution of radiolabeled antibodies is non-uniform in tumor ⇒ non-uniform dose distribution
- 3D image-based dosimetry therefore critical to assess non-uniformities
- Patient-specific dosimetry with imaging tracer **prior** to therapy is performed



# I-131 Radioimmunotherapy image-based dosimetry

Tracer-predicted mean tumor dose correlated nicely with therapy-delivered mean tumor dose (248 and 275 cGy)

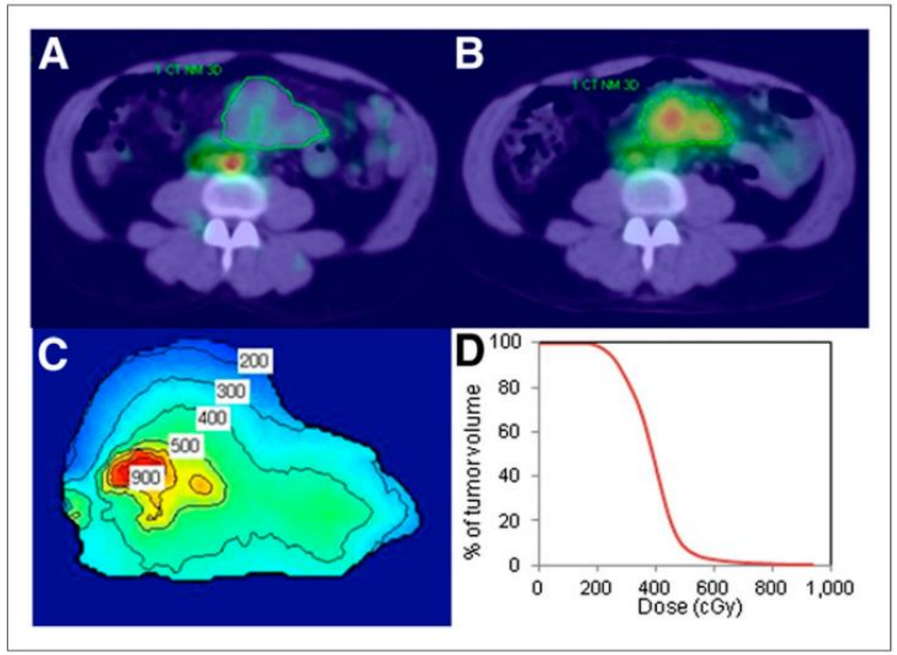



**FIGURE 1.** Imaging and dosimetry. Day 0 posttracer (A) and day 2 posttherapy (B) SPECT/CT images of patient with CT-defined tumor outlines. Tumor-absorbed dose distribution with isodose contours in cGy (C) and tumor dose-volume histogram (D).

# Absorbed Dose Correlates with Progression-free Survival

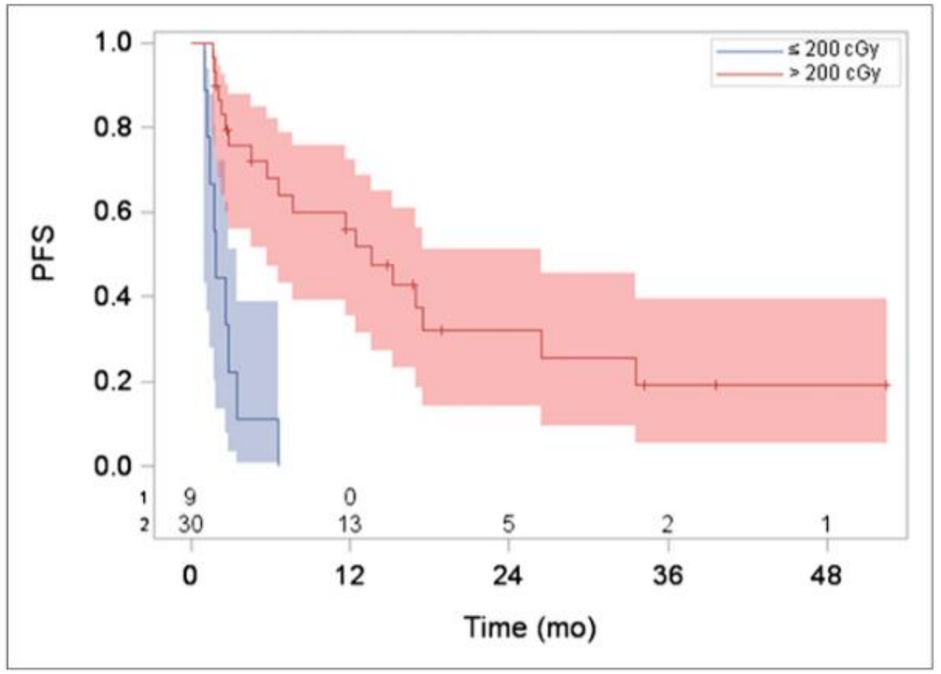


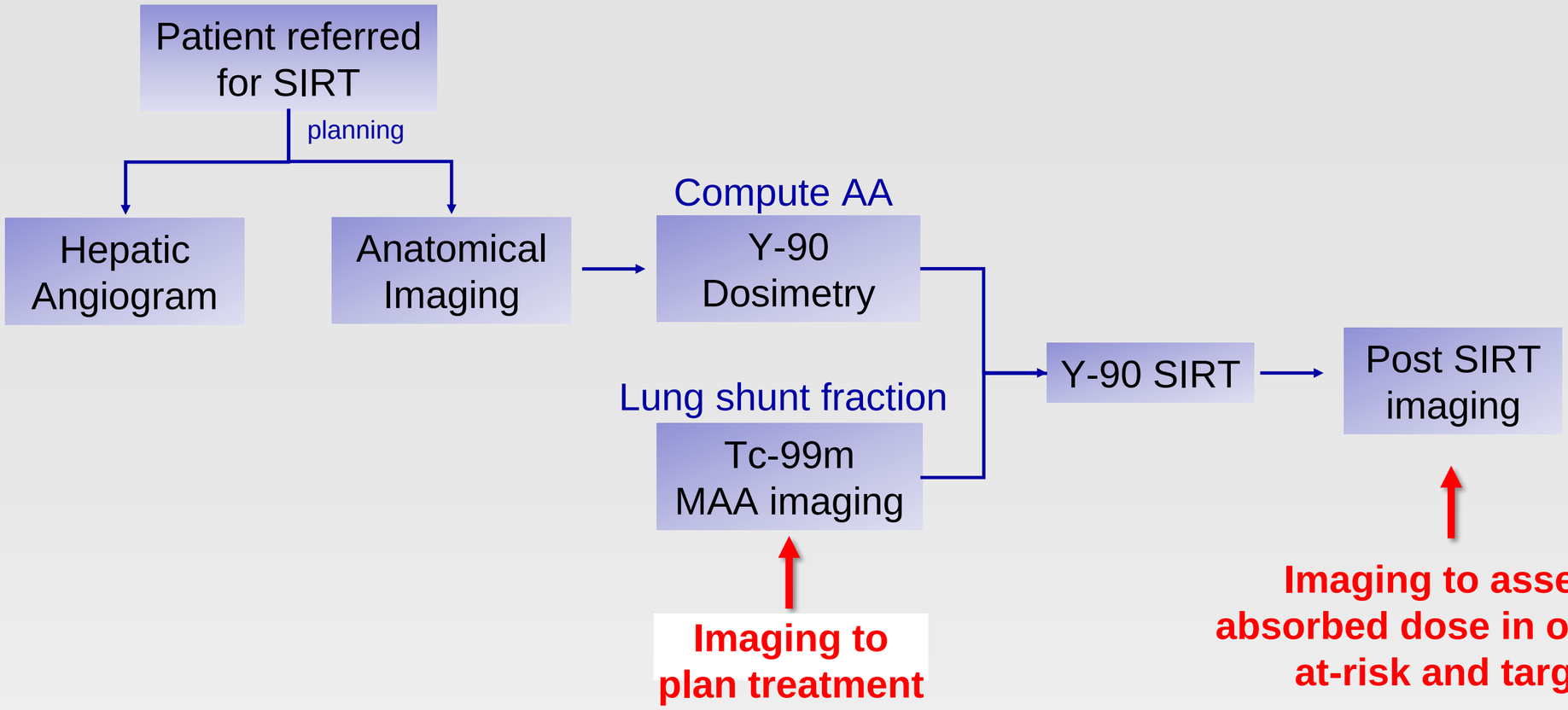

**FIGURE 4.** PFS (with number of subjects at risk and 95% confidence limits indicated) stratified by mean tumor-absorbed dose > 200 cGy and ≤ 200 cGy. Median PFS was 13.6 vs. 1.9 mo for the 2 dose groups (log-rank $P < 0.0001$).

Dewaraja Y K, et al. Tumor-absorbed dose predicts progression-free survival following 131i-tositumomab radioimmunotherapy, 2014

# Dosimetry of Y-90 radioembolization

## (Selective Internal Radiation Therapy, or SIRT)

# Radioembolization Clinical Workflow



# Dosimetry models available

| | |
|---|---|
| MIRD | $$AA = \frac{Target\ Dose \cdot liver\ mass}{50}$$ $$AD\ (liver) = 50\frac{AA\ \cdot\ (1 - lung\ shunt\ fraction)}{liver\ mass}$$ |
| BSA | $$AA = (BSA - 0.2) +\ tumor\ involvement$$ $$BSA\ is\ a\ proxy\ for\ liver\ volume$$ fraction of tumor involvement determined from CT |

# Discrepancy Between MIRD and BSA

- Patient:
- 160 cm
- 74 kg
- Tumor involvement 60%
- Lung shunt fraction 4.4%

| | MIRD | BSA |
|---|---|---|
| Activity | 3.9 Gbq | 1.7 GBq |
| Tumor | 120 Gy | 40 Gy |
| Liver | 120 Gy | 10.3 Gy |
| Lungs | 8.5 Gy | 3.7 GY |

Large variation in recommended administered activity and subsequent dose to target and organs-at-risk (e.g. liver)

# Dose Matters…

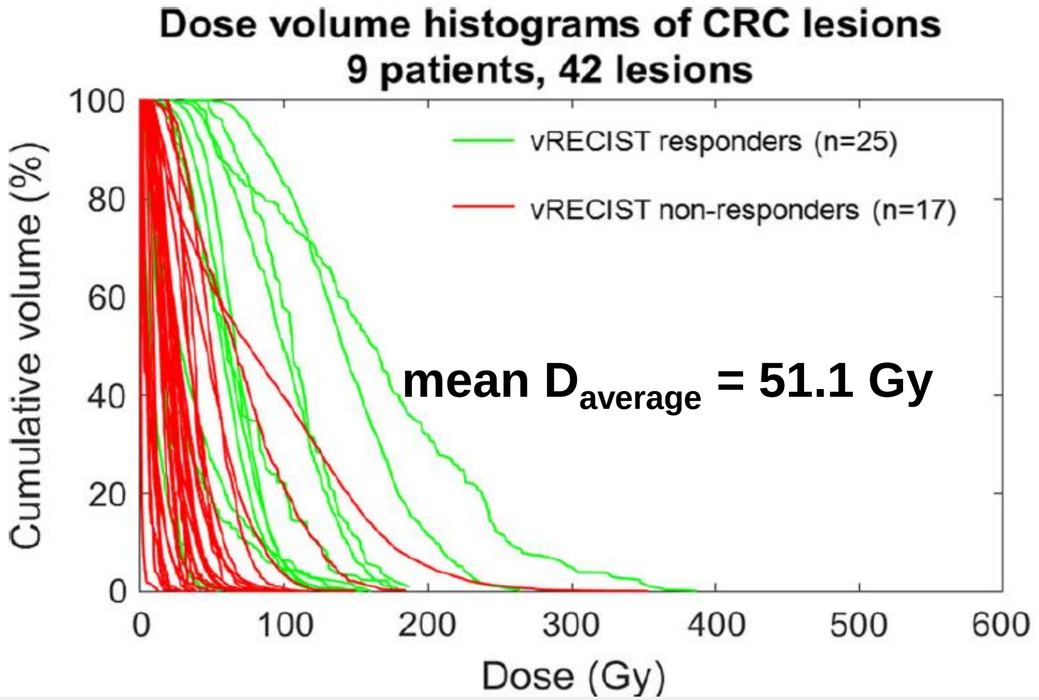
Cardiovasc Intervent Radiol (2016) 39:855–864
DOI 10.1007/s00270-015-1285-y

CIRSE CrossMark

CLINICAL INVESTIGATION INTERVENTIONAL ONCOLOGY

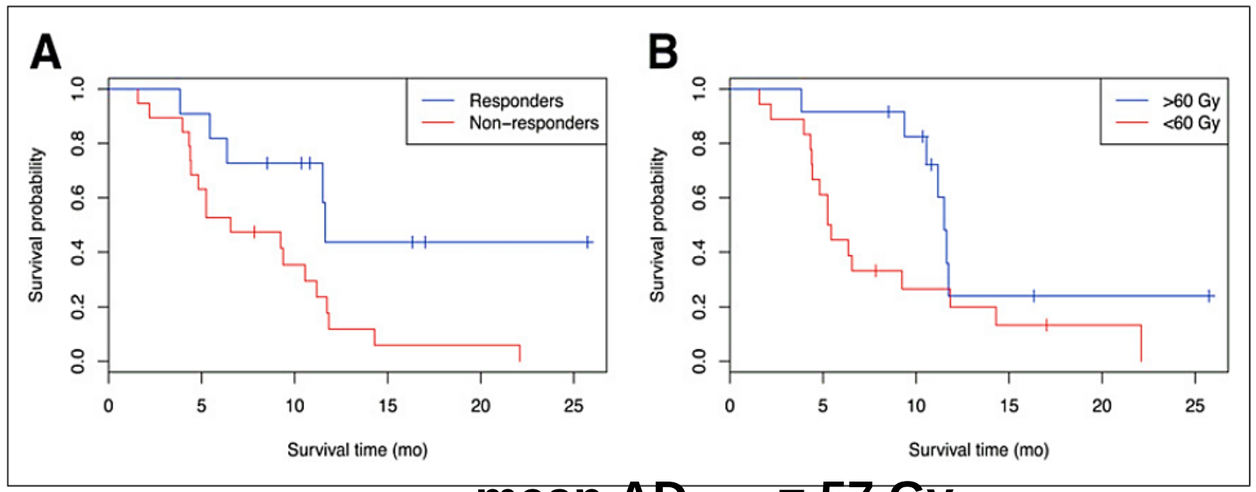
## PET/MRI of Hepatic 90Y Microsphere Deposition Determines Individual Tumor Response

Kathryn J. Fowler[1] · Nichole M. Maughan[2] · Richard Laforest[3] · Nael E. Saad[1] · Akash Sharma[3] · Jeffrey Olsen[4] · Christina K. Speirs[4] · Parag J. Parikh[4]



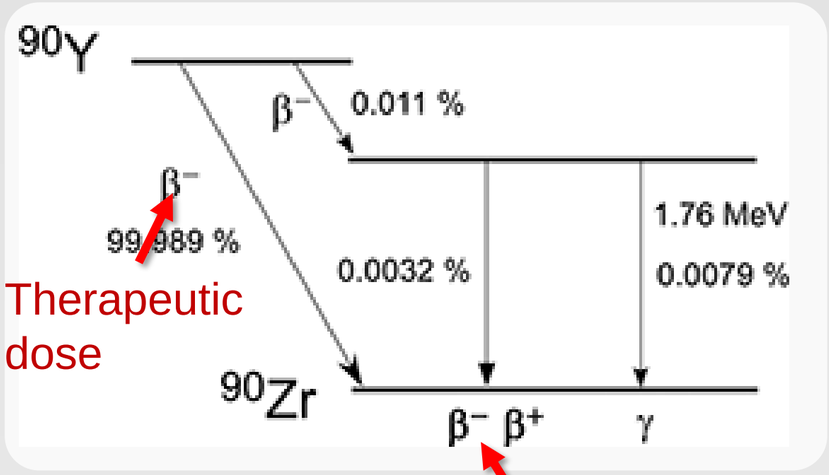

## Insights into the Dose–Response Relationship of Radioembolization with Resin $^{90}$Y-Microspheres: A Prospective Cohort Study in Patients with Colorectal Cancer Liver Metastases

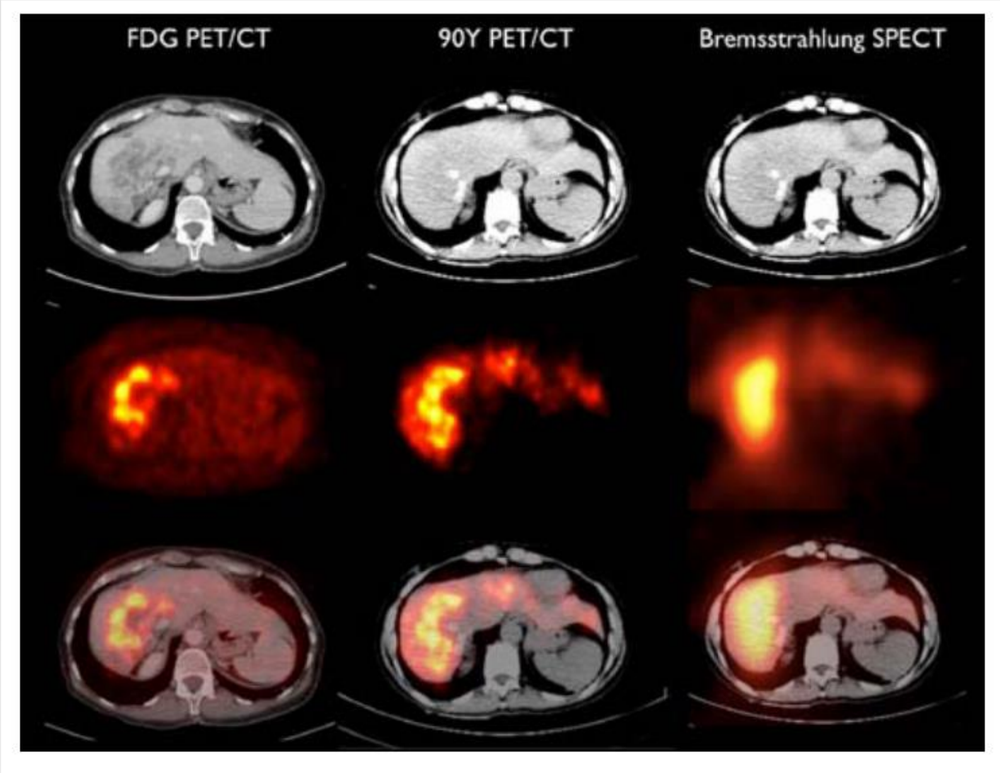
Andor F. van den Hoven[1], Charlotte E.N.M. Rosenbaum[1], Sjoerd G. Elias[1,2], Hugo W.A.M. de Jong[1], Miriam Koopman[3], Helena M. Verkooijen[1], Abass Alavi[4], Maurice A.A.J. van den Bosch[1], and Marnix G.E.H. Lam[1]




mean $AD_{mets}$ = 57 Gy

# Dose Response Established with Y-90 PET/CT




Lhommel R, et al., Yttrium-90 TOF PET scan demonstrates high-resolution biodistribution after liver SIRT.2009

# More on Quantitative Imaging…

Medical Physics
The International Journal of Medical Physics Research and Practice

Fifty-eighth annual meeting of the american association of physicists in medicine

## SU-F-J-08: Quantitative SPECT Imaging of Ra-223 in a Phantom

J Yue, R Hobbs, G Sgouros, E Frey

First published: 7 June 2016 | https://doi.org/10.1118/1.4955916



## 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.

# Conclusion

- Doses mainly calculated for approval of new radiopharmaceuticals
- Activity administered to patients based on fixed value per body weight

**Not optimal for therapeutics! In contrast, dose is adjusted for each patient in external beam therapy**

What do we need?

Measure uptake and clearance of activity in the various tissues…

… Using dynamic and quantitative imaging, possibly with a diagnostic level of the therapeutic radionuclide or surrogate (e.g. $^{111}$In-Zevalin for $^{90}$Y-Zevalin)

# Potential Sources of Error


**Potential error sources**

1. Physical modeling
2. Scatter, attenuation, spatial resolution compensation
3. Dose calibration

**Integration**

1. Registration
2. Segmentation

**Dose calculation**

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Theranostics. 2017; 7(18): 4551–4565. PMCID: PMC5695148
Published online 2017 Oct 13. doi: 10.7150/thno.19782 PMID: 29158844

Quantitative Imaging for Targeted Radionuclide Therapy Dosimetry - Technical Review

Tiantian Li,[1] Edwin C. I. Ao,[1] Bieke Lambert,[2,3] Boudewijn Brans,[4] Stefaan Vandenberghe,[5,✉] and Greta S. P. Mok[1,6,✉]