Advances in Internal Dosimetry

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Marinelli/Quimby method

Publications by Marinelli et al. and Quimby and Feitelberg, gave the dose from a beta emitter that decays completely in a tissue as

\[
D_\beta = 73.8 C E_\beta T
\]
Strigari et al.: Tumor control probability in systemic radiotherapy
Medical Physics, Vol. 33, No. 6, June 2006

Fig. 7. Calculated dose distribution after administration of $^{131}$I-MIBG superimposed on axial CT scan.

Fig. 8. Differential dose volume histogram for normal liver and metastasis of the case presented in this study.
Standardization
MIRD Pamphlet No. 16: Techniques for Quantitative Radiopharmaceutical Biodistribution Data Acquisition and Analysis for Use in Human Radiation Dose Estimates


Nuclear Physics Enterprises, Cherry Hill, New Jersey; University of Cincinnati, Division of Medical Physics, Cincinnati, Ohio; Radiation Dosimetry Systems of Oak Ridge, Inc., Knoxville, Tennessee; Oak Ridge Institute for Science and Education, Radiation Internal Dose Information Center, Oak Ridge, Tennessee; Veterans Affairs Medical Center 640/151, Palo Alto, California; Department of Nuclear Medicine, University of Michigan, Ann Arbor, Michigan; Gaithersburg, Maryland; Division of Radiation Research, Department of Radiology, University of Medicine and Dentistry of New Jersey, Newark, New Jersey; Department of Radiology, George Washington University Medical Center, Washington, DC; Pacific Northwest National Laboratory, Richland, Washington; Department of Radiation Research, University of California Davis Medical Center, Sacramento, California; Department of Radiology, Vanderbilt University School of Medicine, Nashville, Tennessee

This report describes recommended techniques for radiopharmaceutical biodistribution data acquisition and analysis in human subjects to estimate radiation absorbed dose using the Medical Internal Radiation Dose (MIRD) schema. The document has been prepared in a format to address two audiences: individuals with a primary interest in designing clinical trials who are not experts in

pling error analysis techniques and selected calculational examples. The utilization of the presented approach should aid in the standardization of protocol design for collecting kinetic data and in the calculation of absorbed dose estimates.

Standardized method and resources

- **RADAR** is the **RAdiation Dose Assessment Resource**, which is an task group of the US Society of Nuclear Medicine that maintains resources for internal and external dose calculations, on a US and European web site, and in a number of open literature publications.

- The **Organ Level INternal Dose Assessment code**, **OLINDA**, with an **EXponential Modeling (EXM)** function, is the update and replacement of the MIRDOS personal computer software.
RADAR is all about helping people get standardized, high quality dose information!
The RADAR Web Site
www.doseinfo-radar.com

- Standardized information
- Reliable information
- Information when people need it, which is generally “right now, please”.
- Consistency over time
- Minimizing confusion
- Teaching and training
standardized, but.......
MIRD

\[ D(r_T, T_D) = \int_0^{T_D} \dot{D}(r_T, t)dt \]

\[ = \sum_{r_S} \int_0^{T_D} A(r_S, t)S(r_T \leftarrow r_S, t)dt, \]

\[ S(r_T \leftarrow r_S, t) = \frac{1}{M(r_T, t)} \sum_i E_i Y_i \phi(r_T \leftarrow r_S, E_i, t) \]

ICRP

\[ H_{50,T} = \sum_S U_S SEE(T \leftarrow S) \]

\[ SEE = \frac{k \sum_i n_i E_i \phi_i Q_i}{m} \]
\[ D = N \times DF \]

N is the number of disintegrations that occur in a source region.

DF is the dose factor, which gives the dose absorbed in a target per disintegration in a source.

Chapter 1. Uses of Dosimetry Information in Nuclear Medicine

Chapter 2. Fundamental Concepts – Calculating Radiation Dose

Chapter 3. Models and Resources for Internal Dose Calculations

Chapter 4. Steps in Dose Calculations

Chapter 5. Case Studies

Chapter 6. Biological Effects of Radiation

Chapter 7. Regulatory Aspects of Dose Calculations
Xu and colleagues – Rensselaer Polytechnic Institute
VIP man realistic model
NURBS Phantoms

Developed by William Paul Segars, Johns Hopkins Medical Institutes.

4D NURBS-based cardiac-torso (NCAT) phantom: realistic and flexible model of the human anatomy and physiology for medical imaging research.

Organ models are based on NURBS, non-uniform rational B-splines, as used in computer graphics.

NURBS, which define continuous surfaces, allow the phantom to be defined at any spatial resolution.

A nice innovation is the extension of NURBS to a fourth dimension, time, to model the cardiac and respiratory motions.
Anterior views of the NURBS models of the adult male (left) and adult female (right)
RADAR Dose Factors

We have calculated dose factors for our >800 radionuclides for the traditional models:

<table>
<thead>
<tr>
<th>Adult Male</th>
<th>Adult Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-year-old</td>
<td>3 month pregnant female</td>
</tr>
<tr>
<td>10-year-old</td>
<td>6 month pregnant female</td>
</tr>
<tr>
<td>5-year-old</td>
<td>9 month pregnant female</td>
</tr>
<tr>
<td>1-year-old</td>
<td>MIRD Head and Brain Model</td>
</tr>
<tr>
<td>Newborn</td>
<td>Prostate Gland Model</td>
</tr>
<tr>
<td>Unit Density Sphere Model</td>
<td>Peritoneal Cavity Model</td>
</tr>
</tbody>
</table>

- Get the data free, by electronic download, at our site.
- Data for the new models will arrive soon.
### ICRP 89 Organ Masses (g)

<table>
<thead>
<tr>
<th></th>
<th>NB female</th>
<th>NB male</th>
<th>1 yr female</th>
<th>1 yr male</th>
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<th>5 yr male</th>
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<td>950</td>
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<td>6</td>
<td>6</td>
<td>24</td>
<td>24</td>
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<td>34</td>
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<tr>
<td>Lungs</td>
<td>60</td>
<td>60</td>
<td>151</td>
<td>151</td>
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<td>300</td>
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<tr>
<td>Liver</td>
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<td>130</td>
<td>330</td>
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<tr>
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<td>1.3</td>
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<td>1.8</td>
<td>3.4</td>
<td>3.4</td>
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<tr>
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<td>13</td>
<td>13</td>
<td>30</td>
<td>30</td>
<td>30</td>
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<tr>
<td>Esophagus</td>
<td>2</td>
<td>2</td>
<td>5</td>
<td>5</td>
<td>10</td>
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### NURBS Organ Masses (g)

<table>
<thead>
<tr>
<th></th>
<th>NB female</th>
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<th>1 yr male</th>
<th>5 yr female</th>
<th>5 yr male</th>
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<td>33.6</td>
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<td>58.7</td>
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<td>149</td>
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<td>300</td>
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<tr>
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<td>557</td>
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<td>70.9</td>
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<td>4.8</td>
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<tr>
<td>Thyroid</td>
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<td>1.3</td>
<td>1.7</td>
<td>1.8</td>
<td>3.3</td>
<td>3.4</td>
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<td>29.6</td>
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<tr>
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## ICRP 89 Organ Masses (g)

<table>
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<tr>
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<th>15 yr male</th>
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<th>Adult male</th>
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<td>44</td>
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<tr>
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<td>500</td>
<td>750</td>
<td>900</td>
<td>950</td>
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<tr>
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<td>1300</td>
<td>1300</td>
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<td>7.9</td>
<td>7.9</td>
<td>12</td>
<td>12</td>
<td>17</td>
<td>20</td>
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<tr>
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<td>30</td>
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<td>25</td>
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<td>30</td>
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## NURBS Organ Masses (g)

<table>
<thead>
<tr>
<th></th>
<th>10 yr female</th>
<th>10 yr male</th>
<th>15 yr female</th>
<th>15 yr male</th>
<th>Adult female</th>
<th>Adult male</th>
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<tbody>
<tr>
<td>Brain</td>
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<td>505</td>
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<td>875</td>
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<td>1403</td>
<td>1766</td>
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<td>182</td>
<td>243</td>
<td>244</td>
<td>277</td>
<td>299</td>
</tr>
<tr>
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<td>6.9</td>
<td>9.1</td>
<td>10.1</td>
<td>12.9</td>
<td>13.6</td>
</tr>
<tr>
<td>Thyroid</td>
<td>7.8</td>
<td>7.8</td>
<td>12.2</td>
<td>11.8</td>
<td>17.0</td>
<td>19.7</td>
</tr>
<tr>
<td>Thymus</td>
<td>34.0</td>
<td>34.0</td>
<td>29.8</td>
<td>33.6</td>
<td>19.5</td>
<td>24.2</td>
</tr>
<tr>
<td>Esophagus</td>
<td>17.7</td>
<td>17.7</td>
<td>30.3</td>
<td>28.5</td>
<td>35.2</td>
<td>38.3</td>
</tr>
</tbody>
</table>
Selected photon SAF values, adult female

Liver >> Liver

Liver >> Spleen

Spleen >> Spleen

Spleen >> Lungs
Selected photon SAF values, 10-yr-old female

- Lungs >> Lungs
- Lungs >> Liver
- Spleen >> Liver
- Liver >> Lungs

![Graphs showing SAF values for different tissues and energies.](image)
Selected electron SAF values

Electron AFs - Source = Liver, Adult Male

Electron AFs - Source = Spleen, Adult Male

Electron AFs - Source = Lungs, Adult Male

Electron AFs - Source = Liver, Adult Female
Normal weight adult female models of different stature: modeled changes in organ mass
Selected photon SAFs, Normal Weight Adult Male Models of different stature

Liver to Lungs

Kidneys to Kidneys

Lungs to Heart

Kidneys to Liver
Phantoms of moderate and severe obesity:

The visceral adipose tissue (VAT) areas, comprising the abdominal organs at the T-4 vertebra, for each BMI group were found and used to expand the large and small intestines in the AP and lateral dimensions from the median individual using an ellipsoidal shape.

**Calculation of Visceral Abdominal Tissue (VAT)**

**Men:** \( \text{VAT} = -453.7 + (6.37 \times \text{waist}) \)

**Women:** \( \text{VAT} = -370.5 + (4.04 \times \text{waist}) + (2.62 \times \text{age}) \)
<table>
<thead>
<tr>
<th></th>
<th>Percent Difference per kg Difference in Total Body Mass from 10th to 90th Percentile Adult Male Phantom</th>
<th>Absolute Percent Difference from 10th to 90th Percentile Phantom</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Kidneys</td>
<td>Liver</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.59</td>
<td>0.85</td>
</tr>
<tr>
<td>Liver</td>
<td>1.01</td>
<td>0.89</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.46</td>
<td>0.74</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.47</td>
<td>1.08</td>
</tr>
<tr>
<td>Heart</td>
<td>0.40</td>
<td>0.45</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.62</td>
<td>0.72</td>
</tr>
</tbody>
</table>
FIGURE 3. Images of un-modified ROBY and MOBY models (13), showing length of each model.
Scaled Models - Mouse

- **Lil MOBY**
  - Body: 22.7 g

- **MOBY**
  - Body: 28.1 g

- **Big MOBY**
  - Body: 33.2 g
### TABLE 1. Organ Masses in 3 Mouse Models

<table>
<thead>
<tr>
<th>Organ</th>
<th>25-g mouse</th>
<th>30-g mouse</th>
<th>35-g mouse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>0.466</td>
<td>0.568</td>
<td>0.666</td>
</tr>
<tr>
<td>Heart</td>
<td>0.235</td>
<td>0.291</td>
<td>0.342</td>
</tr>
<tr>
<td>Stomach</td>
<td>0.055</td>
<td>0.069</td>
<td>0.082</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1.74</td>
<td>2.12</td>
<td>2.49</td>
</tr>
<tr>
<td>Large intestine</td>
<td>0.583</td>
<td>0.709</td>
<td>0.830</td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.302</td>
<td>0.374</td>
<td>0.432</td>
</tr>
<tr>
<td>Liver</td>
<td>1.74</td>
<td>2.15</td>
<td>2.57</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.087</td>
<td>0.107</td>
<td>0.131</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.305</td>
<td>0.378</td>
<td>0.450</td>
</tr>
<tr>
<td>Skeleton</td>
<td>2.18</td>
<td>2.61</td>
<td>3.01</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.111</td>
<td>0.136</td>
<td>0.157</td>
</tr>
<tr>
<td>Testes</td>
<td>0.160</td>
<td>0.197</td>
<td>0.228</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.014</td>
<td>0.016</td>
<td>0.020</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.060</td>
<td>0.075</td>
<td>0.088</td>
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<tr>
<td>Body</td>
<td>24.11</td>
<td>29.80</td>
<td>35.27</td>
</tr>
</tbody>
</table>

### TABLE 2. Organ Masses in 5 Rat Models

<table>
<thead>
<tr>
<th>Organ</th>
<th>200-g rat</th>
<th>300-g rat</th>
<th>400-g rat</th>
<th>500-g rat</th>
<th>600-g rat</th>
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</thead>
<tbody>
<tr>
<td>Brain</td>
<td>1.57</td>
<td>2.32</td>
<td>3.16</td>
<td>3.93</td>
<td>4.54</td>
</tr>
<tr>
<td>Heart</td>
<td>1.80</td>
<td>2.64</td>
<td>3.55</td>
<td>4.39</td>
<td>5.28</td>
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<tr>
<td>Stomach</td>
<td>0.941</td>
<td>1.40</td>
<td>1.89</td>
<td>2.37</td>
<td>2.86</td>
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<tr>
<td>Small intestine</td>
<td>10.6</td>
<td>15.5</td>
<td>20.8</td>
<td>25.6</td>
<td>30.8</td>
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<tr>
<td>Large intestine</td>
<td>7.86</td>
<td>11.5</td>
<td>15.5</td>
<td>19.2</td>
<td>23.1</td>
</tr>
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<td>6.09</td>
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<tr>
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<td>7.55</td>
<td>11.2</td>
<td>15.2</td>
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<tr>
<td>Lungs</td>
<td>0.594</td>
<td>0.884</td>
<td>1.21</td>
<td>1.50</td>
<td>1.82</td>
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<tr>
<td>Pancreas</td>
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<td>0.535</td>
<td>0.732</td>
<td>0.908</td>
<td>1.10</td>
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<tr>
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<td>29.2</td>
<td>35.2</td>
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<td>0.884</td>
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<tr>
<td>Body</td>
<td>226</td>
<td>335</td>
<td>443</td>
<td>547</td>
<td>643</td>
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</table>
Photon SAF Comparison across Mouse Model Sizes
Electron SAF Comparison across Rat Model Sizes

Liver Self-Absorbed Electron SAFs by Rat Size

Liver to Heart Electron SAFs by Rat Size
ICRP 30 Kinetic model for the GI tract

- $\lambda_{ST}$: Stomach
- $\lambda_{SI}$: Small Intestine
- $\lambda_{ULI}$: Upper Large Intestine
- $\lambda_{LLI}$: Lower Large Intestine
- $f_i$: Absorption to systemic circulation

Fecal Excretion
ICRP 100 – New Human Alimentary Tract (HAT) model
Urinary Bladder – Voiding Model

\[ N = A_0 \sum_i f_i \left[ \frac{1 - e^{-\lambda_i T}}{\lambda_i} - \frac{1 - e^{-(\lambda_i + \lambda_p) T}}{\lambda_i + \lambda_p} \right] \left[ \frac{1}{1 - e^{-(\lambda_i + \lambda_p) T}} \right] \]
### OLINDA - Organ level INternal Dose Assessment Code (Version 1.1, copyright Vanderbilt University, 2007)

**NOTE:** This code gives doses for stylized models of average individuals - results should be applied with caution to specific human subjects. **NOTE:** Users should always carefully check input data (shown below) and critically review the reported results.

**Organ Doses (mSv/MBq), Nuclide: In-111 (2.80E00 day), Adult Male**
**Calculated: 05.21.2009 at 07:52:17 CDT**

<table>
<thead>
<tr>
<th>Target Organ</th>
<th>Alpha</th>
<th>Beta</th>
<th>Photon</th>
<th>Total</th>
<th>EDE Cont.</th>
<th>ED Cont.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>0.00E00</td>
<td>2.06E-02</td>
<td>2.24E-01</td>
<td>2.45E-01</td>
<td>1.47E-02</td>
<td>6.12E-04</td>
</tr>
<tr>
<td>Brain</td>
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<td>2.06E-02</td>
<td>9.23E-02</td>
<td>1.13E-01</td>
<td>0.00E00</td>
<td>2.62E-04</td>
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<tr>
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<td>9.44E-02</td>
<td>1.15E-01</td>
<td>1.72E-02</td>
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<tr>
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<td>2.93E-01</td>
<td>1.75E-02</td>
<td>0.00E00</td>
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<tr>
<td>LLI Wall</td>
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<td>1.45E-01</td>
<td>1.65E-01</td>
<td>0.00E00</td>
<td>1.98E-02</td>
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<tr>
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<td>4.62E-04</td>
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<tr>
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<td>2.06E-02</td>
<td>1.81E-01</td>
<td>2.02E-01</td>
<td>0.00E00</td>
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<tr>
<td>ULI Wall</td>
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<td>1.69E-01</td>
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<td>4.75E-04</td>
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<tr>
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<td>1.84E-01</td>
<td>2.04E-01</td>
<td>0.00E00</td>
<td>0.00E00</td>
</tr>
</tbody>
</table>

**Note:** you must enter MBq or convert mCi to MBq BEFORE multiplying.

**mCi to MBq calculator**

[<<<Convert]
Patient-Specific Adjustments to Standard Models
Uncertainty
Uptake and retention of $^{99m}$Tc-RP527, a gastrin-releasing peptide (GRP) agonist for the visualization of GRP receptor–expressing malignancies in various subjects, as reported by Van de Wiele et al.
Cumulative excretion of Ho-166 DOTMP in twelve subjects (6 ♀, 6 ♂) with multiple myeloma. Breitz et al. J Nucl Med 2006

Figure 1. An example of absorbed dose distribution with 95% confidence interval.
Fig. 4. Estimated absorbed doses to critical organs ($D_{\text{organ}}$) for $^{90}$Y-DOTATOC therapy. The plots show the individual absorbed doses based on investigation with $^{86}$Y-DOTATOC PET ($^{86}$Y) and $^{111}$In-DTPA-octreotide scintigraphy ($^{111}$In)
Organ Mass Scaling

For electrons, the scaling is:

\[ DF_2 = DF_1 \frac{m_1}{m_2} \]

For photons, the scaling is:

\[ \phi_2 = \phi_1 \left( \frac{m_2}{m_1} \right)^{1/3} \quad \Phi_2 = \Phi_1 \left( \frac{m_1}{m_2} \right)^{2/3} \]
### Phantom organ masses (g) for the Adult Male

**= Modified by user

Hit <ret> to see changes immediately, or just DONE at end

<table>
<thead>
<tr>
<th>Next Phantom</th>
<th>Previous Phantom</th>
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</thead>
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<td>Brain</td>
</tr>
<tr>
<td>351.0</td>
<td>Breasts</td>
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<td>Gallbladder Wall</td>
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<td>167.0</td>
<td>LLI Wall</td>
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<td>677.0</td>
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<td>ULI Wall</td>
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<td>Heart Wall</td>
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<td>Kidneys</td>
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<tr>
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<td>Liver</td>
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<tr>
<td>1000.0</td>
<td>Lungs</td>
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<tr>
<td>28000.0</td>
<td>Muscle</td>
</tr>
<tr>
<td>8.71</td>
<td>Ovaries</td>
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**Alpha Weight Factor**: 5.0  
**Beta Weight Factor**: 1.0  
**Photon Weight Factor**: 1.0

Multiply all masses by: 1.0

<table>
<thead>
<tr>
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<tr>
<td>Osteogenic Cells</td>
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<tr>
<td>Skin</td>
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<tr>
<td>Spleen</td>
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<td>Testes</td>
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<tr>
<td>Thymus</td>
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</tr>
<tr>
<td>Thyroid</td>
<td>20.7</td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>47.6</td>
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<tr>
<td>Uterus</td>
<td>79.0</td>
</tr>
<tr>
<td>Fetus</td>
<td>0.0</td>
</tr>
<tr>
<td>Placenta</td>
<td>0.0</td>
</tr>
<tr>
<td>Total Body</td>
<td>73700.0</td>
</tr>
</tbody>
</table>

[Reset organ values]

[DONE]
..the combined uncertainties in any given radiopharmaceutical dose estimate are typically, at a minimum, a factor of 2 and may be considerably greater, in general because of normal human variability, and particularly in disease states.

In therapy applications, if patient-individualized dosimetry is performed, ...the total uncertainty in an individual dose estimate can be reduced to a value of perhaps ~10%–20%.
FIGURE 3. (A) Summed coronal $^{124}$I PET image slices obtained on day of $^{124}$I administration (day 0) and on subsequent 2 days are depicted using same intensity level. Cross-hairs show plane of intersection for corresponding transverse slices through tumor 2, shown immediately below coronal images. (B) Image of absorbed dose distribution in tumor 2, magnified to highlight spatial distribution of absorbed dose within this tumor. Color-coded isodose contours are superimposed as follows: yellow = 75%, red = 50%, blue = 25%, and green = 10% of maximum absorbed dose to tumor (400 Gy). Three different foci of enhanced absorbed dose are observed and designated 1–3 as shown. Kolbert et al. J Nucl Med Vol. 45 No. 8 1366-1372.
Strigari et al.: Tumor control probability in systemic radiotherapy
Medical Physics, Vol. 33, No. 6, June 2006

Fig. 7. Calculated dose distribution after administration of $^{131}$I-MIBG superimposed on axial CT scan.

Fig. 8. Differential dose volume histogram for normal liver and metastasis of the case presented in this study.
Figure 1. Data for Patient A with CTV, PTV, spinal cord and kidneys outlined. a) CT image of corresponding slice; b) XBT isodose plot showing dose levels in Gy; c) XBT dose distribution; d) XBT BED distribution; e) TRT dose distribution; f) TRT BED distribution; g) Combined BED distribution; h) Equivalent external beam isodose plot for the combined therapy showing dose levels in Gy.
Patient-Specific Biological Response

• “Dose” – necessary, not sufficient – interest in biological response functions to modify dose
  • Biologically Effective Dose (BED)
  • Time-dose-fractionation (TDF) factors
Biologically Effective Dose (BED)

Protracted irradiation at a decaying dose rate

\[
\ln(SF) = -\alpha D - \frac{\lambda}{\lambda + \mu} \beta D^2
\]

\[
BED_{TRT} = D \left(1 + \frac{D \lambda}{(\mu + \lambda)(\alpha / \beta)}\right)
\]

BED for a fractionated high dose rate treatment

\[
BED_{XTB} = D \left(1 + \frac{D / n}{\alpha / \beta}\right)
\]

\(\alpha, \beta\) are radiosensitivity parameters
\(\lambda\) is the effective dose-rate decay constant
\(\mu\) is the repair constant
Time-dose-fractionation (TDF) factors

\[ TDF = 0.122 \sum_{i=0}^{\infty} r_i^{1.35} T_{eff} \]

\[ TDF = 1.554 \sum_{i} D_i^{1.35} T_{eff}^{-0.35} \]

- \( r_0 \) is the initial dose rate in cGy/h
- \( T_{eff} \) is the effective half-time in days
- \( D_i \) is the absorbed dose (Gy) delivered for treatment cycle \( i \)
A. Creatinine clearance loss/yr (% baseline) vs. \( \text{KAD}_{\text{StaVol}} \) (Gy)

B. Creatinine clearance loss/yr (% baseline) vs. \( \text{KAD}_{\text{CTVol}} \) (Gy)

C. Creatinine clearance loss/yr (% baseline) vs. BED (Gy)

D. Creatinine clearance at 18 mo FU (% baseline) vs. BED (Gy)

- A: \( r = 0.54 \)
  \( P = 0.02 \)

- C: \( r = 0.93 \)
  \( P < 0.0001 \)

- D: \( r = 0.89 \)
  \( P < 0.0001 \)
AAPM Report No. 49 - Dosimetry of Auger-Electron-Emitting Radionuclides:

“Cellular and organ studies have demonstrated that when Auger emitters are introduced into the cytoplasm of cells, the effects are typical of those caused by radiations of low-linear-energy transfer (LET).

In contrast, when Auger emitters are incorporated into the DNA of cells, the resulting survival curves are similar to those for high-LET alpha particles.

Finally, recent in vivo studies with radioprotectors show that the intense local damage imparted by Auger cascades can be mitigated despite the fact that they impart high-LET-type effects.”
“The absorbed dose from Auger emitters must be calculated at a level suited to the biological system employed. Hence, a number of target volumes are of interest: individual strands or bases of the DNA molecule, supercoiled DNA, cell or cell nucleus, bulk tissue.

Choosing the target volume, however, is complex. The radiation properties of the radionuclide certainly play a role in this regard. Just as important is the distribution of the radioactivity within the cells, which in turn depends on the chemical nature of the radiocompound. Hence, the appropriate target volume must be determined on a case-by-case basis.”
Bystander Effects – in vitro studies

Hall:

“The plethora of data now available concerning the bystander effect fall into two quite separate categories, and it is not certain that the two groups of experiments are addressing the same phenomenon.”

1. Medium transfer experiments
2. Microbeam irradiation experiments
Bystander Effects – in vitro studies

Medium transfer:

Irradiated cells secreted a molecule into the culture medium that was capable of killing cells when that medium was transferred onto unirradiated cells.

The effect produced by epithelial cell cultures is dependent on the cell number at the time of irradiation, can be observed as soon as 30 min post irradiation, and is still effective if taken from the irradiated cells up to 60 h after irradiation.

This bystander effect can be induced by radiation doses as low as 0.25 mGy and is not significantly increased up to doses of 10 Gy.

In addition to increased levels of cell death and reduced cloning efficiency, medium transfer experiments have shown an increase in neoplastic transformation as well as genomic instability in cells that have not themselves been irradiated.
Bystander Effects – in vitro studies

Microbeam studies

Irradiated human fibroblasts - cells of one population were lightly stained with cyto-orange, a cytoplasmic vital dye, while cells of another population were lightly stained blue with a nuclear vital dye.

The two cell populations were mixed and allowed to attach to the culture dish, and the computer controlling the accelerator was programmed to irradiate only blue-stained cells with 10 alpha particles directed at the centroid of the nucleus.

The cells were fixed and stained 48 h later, at which time micronuclei and chromosome bridges were visible in a proportion of the nonhit (i.e., orange-stained) cells!
Bystander effects – in vivo studies

Irradiation of the lung base in rats, marked increase in the frequency of micronuclei in the shielded lung apex.

However, radiation of the lung apex did not result in an increase in the chromosome damage in the shielded lung base.

This suggests that a factor was transferred from the exposed portion of the lung to the shielded part and that this transfer has direction from the base to the apex of the lung.
Bystander Effects

In another experiment, exposure of the left lung resulted in a marked increase in micronuclei in the unexposed right lung.

Experiments suggest that bystander effects are limited to the organ irradiated, and have been demonstrated primarily in experiments with alpha particles.

These results challenge the traditional notion of the relationship of dose and effects.
Surviving fraction vs Dose/Gy graph with markers and error bars. The graph shows a decline in surviving fraction with increasing dose. There are two distinct points labeled \( \alpha_s \) and \( \alpha_r \).
Sawant et al. Radiation Research, 156, 177–180 (2001)
In Vivo Bystander Effects: $^{123}$I UdR and $^{125}$I UdR

Human LS174T adenocarcinoma (s.c.)

Live Dead* $^{123}$I UdR-labeled $^{125}$I UdR-labeled

$1E6$ $-\quad 1E6$ $-\quad -$

$1E6\quad 1E6\quad -\quad -$

$1E6\quad -\quad -\quad 1E6$

$123I \rightarrow sBE$
(Stimulatory Bystander Effect)

Control

$125I \rightarrow iBE$
(Inhibitory Bystander Effect)

* Freeze-defrost 3 times

Kassis – HMS - Boston
Relevance of Dosimetry to Clinical Practice
What is the Role of Dosimetry in Targeted Therapy?

- **Goal**: optimize patient therapy, maximize therapeutic efficacy.
- **Radiotherapy**:

  "The most important role of the clinical radiotherapy medical physicist is to ensure the accurate delivery of the prescribed dose distribution to the patient...there is a clinical need for accurate dose delivery to the tumor. The often stated goal is for 5% accuracy."

---

**Anniversary Paper: Fifty years of AAPM involvement in radiation dosimetry**

G. Ibbott et al.
Radiological Physics Center, University of M. D. Anderson Cancer Center, Houston, Texas 77030-4009

Med. Phys. 35 (4), April 2008
EURATOM Council Directive 97/43: medical exposures for radiotherapeutic purposes, including nuclear medicine, “exposures of target volumes shall be individually planned”.

COUNCIL DIRECTIVE 97/43/EURATOM
of 30 June 1997

on health protection of individuals against the dangers of ionizing radiation in relation to medical exposure, and repealing Directive 84/466/Euratom

THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Atomic Energy Community, and in particular Article
What is the Role of Dosimetry in Targeted Therapy?

- Brans et al. 2007: Targeted therapy: “…distinct similarities to, but also profound differences from the more commonly used external radiotherapy…[more evidence is needed that] that applied clinical dosimetry results in better patient outcome than is achieved with fixed activity dosing methods.”

- Flux et al. 2007: “It is essential that dosimetry studies are sufficiently resourced and are performed with adequate scientific rigour that the results can be judged with confidence.”
What is the Role of Dosimetry in Targeted Therapy?

- Individual patient dosimetry has the following goals:
  - To establish individual minimum effective and maximum tolerated absorbed doses
  - To establish a dose–response relation to predict tumour response and normal organ toxicity on the basis of pretherapy dosimetry
  - To objectively compare the dose–response results of different radionuclide therapies, either between different patients or between different radiopharmaceuticals, as well as to perform comparisons with the results routinely obtained with external radiotherapy
  - To increase the knowledge of clinical radionuclide radiobiology, in part with the aim of developing new approaches and regimens

What is the Role of Dosimetry in Targeted Therapy?

“The Case for Patient-Specific Dosimetry in Radionuclide Therapy

“Treating all nuclear medicine patients with a single, uniform method of activity administration amounts to consciously choosing that these patients be treated with a lower standard of care than patients who receive radiation externally for cancer treatments.”
What is the Role of Dosimetry in Targeted Therapy?

DeNardo and DeNardo 2010:

- “Although the accuracy of radionuclide dosimetry can be improved, it is precise ...and correlates with tissue response, when carefully performed.

- Treatment planning for an individual patient (“patient-specific radiation dosimetry”) for RIT must be the ultimate goal.
Radioiodine Therapy

- Fixed activity protocols are widely used, with reasonable success.
- Benua and Leeper (1986), thyroid cancer: whole body activity at 48 hrs <120 mCi, unless there is metastatic lung involvement (80 mCi).
- EANM Dosimetry Committee: target dose 80 Gy, marrow dose <2 Gy.
Radioiodine Therapy

- Jonsson and Mattsson, Graves disease, (n=200) (2004) compared theoretical levels of activity that could be given to patients using patient-specific dose calculations and actual practice to a fixed-activity approach.

- “…most of the patients were treated with an unnecessarily high activity, a mean factor of 2.5 times too high and in individual patients up to eight times too high, leading to an unnecessary radiation exposure both for the patient, the family and the public.”
Kobe et al. (2007), Graves disease:
- 571 subjects, target dose 250 Gy.
- Relief from hyperthyroidism was achieved in 96% of patients who received more than 200 Gy, even for those with thyroid volumes > 40 mL.
Radioiodine Therapy

- Since patients are almost always treated successfully in the first treatment and do not have to return multiple times for follow-up treatment, this results in:
  - More favorable outcomes and better quality of life for the patients.
  - Significant monetary savings for the institution.
I-131-mIBG therapy for neuroblastoma and phaeochromocytoma

- Fixed activity fractions (e.g. McCluskey 2005)
  - Simple and easy to implement quickly.
  - No understanding or correlations of dose/effect possible.

- Activity/kg body weight approach (e.g. Sisson et al. 1994)
  - Correlations of marrow toxicity with activity/kg of body weight.
  - Again, no dose/effect correlations possible.
Dose-based approaches (e.g. Matthay et al. 2001)

- Total body, marrow, and tumor doses.
- Hematologic toxicity was correlated with activity/kg, marrow dose, total body dose.
- Calculated tumor dose predicted response.
Correlation of TSARD with subsequent tumor volume decrease. Decrease in tumor volume is shown as positive percentage. Spearman rank correlation, $P = 0.02$. 

\[\text{Tumor Volume Decrease} (%) \propto \text{TSARD (cGy)}\]

<table>
<thead>
<tr>
<th>Variable (X)</th>
<th>Variable (Y)</th>
<th>$r_s$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red marrow irradiation</td>
<td>Blood irradiation</td>
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<td>0.04</td>
</tr>
<tr>
<td>Neutrophil nadir</td>
<td>Neutrophil nadir</td>
<td>-0.47</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Platelet nadir</td>
<td>Platelet nadir</td>
<td>-0.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Volume decrease (%)</td>
<td>Volume decrease (%)</td>
<td>0.48</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>
Radioembolisation of liver tumors

- Use of $^{90}$Y-microspheres has shown significant response rates
- Radiation complications – such as pneumonia, GI ulceration, and liver injury
- Kennedy et al. 2009 – 680 cases, many centers – “a predictive model is not yet possible, given the large variance of the data”.
- Techniques vary – fixed empirical values, patient’s body surface area, average radiation dose to the whole liver, or dosimetric partition model considering liver involvement.
Radioembolisation of liver tumors

- Cases of radiation pneumonia were found at lung doses > 10 Gy (range: 10 to 36 Gy), and one fatal event at 56 Gy.
- Whole liver dose 100-130 Gy typical. “…no dose-limiting organ toxicity has been observed in patients who have received nominal absorbed doses up to 150 Gy”
- Salem et al.: higher doses are tolerated with lower treated volumes.
Radioembolisation of liver tumors

- Young et al.: The results showed that patients with lesser extent of the disease, received a higher cumulative dose than others before worsening of liver function (390 vs. 196 Gy).
- Interestingly, these results also confirm that patients with higher irradiation to the normal liver (because of both, lower liver involvement and higher whole liver dose), but distributed in more cycles, demonstrated higher tolerability.
Radiopeptide therapy for neuroendocrine tumours

- Large interpatient differences in radiopeptide uptake in normal organs and tumour tissues – thus patient-specific dosimetry is necessary for patient selection and therapy planning.
- \([^{90}Y\text{-DOTA}^0,\text{Tyr}^3]\)-octreotide – pretherapy imaging with \(^{111}\text{In}\) or \(^{86}\text{Y}\) for dose calculations.
  - \(^{111}\text{In}\) – somatostatin receptor binding affinity may be altered.
  - \(^{86}\text{Y}\) – good image resolution, but all phases of biological clearance may not be seen due to short half-life.
Radiopeptide therapy for neuroendocrine tumours

- $[^{177}\text{Lu-DOTA}^0,\text{Tyr}^3]$-octreotate
  - Can be used for both imaging and dose delivery
  - Octreotate has a six- to nine-fold higher affinity for somatostatin receptor 2
  - Kidney dose $\sim 3$ Gy (Forrer et al. 2005), compare to 20-30 Gy for $^{90}\text{Y-DOTATOC}$ therapy (Barone et al. 2005). Marrow $\sim 60$ mGy.
Radiopeptide therapy for neuro-endocrine tumours

Renal toxicity issues

- Barone et al. (2005) – importance of patient-specific dose calculations to avoid kidney toxicity with $^{90}$Y-DOTATOC
- Bodei et al., $^{90}$Y-DOTATOC (mainly) and $^{177}$Lu-DOTATATE in peptide receptor radionuclide therapy (PRRT): to maintain kidney BED values below 28 Gy, a patient-individualized evaluation of dosimetry should always be performed.
Figure 6. Tumor dose-response characterized by Pauwels et al.\textsuperscript{48} with $^{90}$Y-DOTATOC. Reprinted with permission of the Society of Nuclear Medicine.

Figure 7. Plot from Barone et al.\textsuperscript{51} showing prediction of kidney toxicity from patient-individualized dose calculations in the use of $^{90}$Y (DOTATOC). (Larger and smaller dots on the plot were used to indicate the number of treatment cycles received by different patients.) Reprinted with permission of the Society of Nuclear Medicine.
Radioimmunotherapy – non-Hodgkin’s Lymphoma

• Goldsmith 2010 – review of several trials
  • both approved agents (Bexxar, Zevalin) have high ORRs.
  • CRs much better for Bexxar
  • Complications for both – antibody response, marrow suppression.
  • Longer beta range of $^{90}\text{Y}$ may be better for bulkier tumors.
  • Dosimetry required for Bexxar, needed in cases of variable $T_{\text{eff}}$ for Zevalin.
Radiolabeled antibodies

  - Correlation of marrow toxicity with calculated total body dose.

- Chen et al. (2002) – $^{90}$Y-anti-TAG-72 murine antibody against non–small cell lung cancer:
  - Excellent correlations of marrow toxicity with calculated marrow dose, when patient-specific marrow mass estimated.
Figure 4 (A–C). Correlation of platelet (PLT) nadir and toxicity grade versus patient absorbed dose, with correction for patient-specific characterization of marrow mass (Shen et al.45). Reprinted with permission of the Society of Nuclear Medicine.
Radioimmunotherapy – nonHodgkin’s Lymphoma

- Wahl et al. (1998) – Patients receiving a whole-body absorbed dose between 0.65 and 0.85 Gy showed longer CR than patients receiving between 0.25 and 0.55 Gy.
- Liu et al. (1998) – using a myeloablative approach:
  - Markedly improved progression-free survival over 8 years post therapy.
  - Not dosimetric, but demonstrates possibilities if more aggressive therapy is done, using dosimetry.
Figure 3. Kaplan-Meier plots from Liu et al., showing progression free survival after $^{131}$I RIT involving myeloablative dose levels, compared with best results with other forms of therapy. © The American Society of Hematology. Reprinted with permission of the Society of Nuclear Medicine.
Conclusions

• Internal dosimetry has come a looooonng way from beta self dose to the thyroid.
• As in occupational internal dose, models are always evolving – more complex and realistic, but more difficult to use.
• Nuclear medicine internal dosimetry has become well standardized and automated.
• More routine use in therapeutic applications is needed.
Conclusions

• Evidence shows that better and more predictable outcomes can be achieved with patient-individualized dose assessment.
• Fixed activity or fixed activity/g or m² with no dosimetry cannot yield any meaningful information about dose/response or dose/toxicity.
• Proceeding with therapy with no knowledge of radiation dosimetry not in the best interests of patients.
• Much research is needed to characterize dose/response functions for internal emitters.