Overview of Dosimetry for Targeted Radionuclide Therapy

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Simplified Dosimetry for a diverse audience
Dosimetry Definition

Process of relating the administered amount of radioactivity to the absorbed radiation dose of an organ or the whole body
Radionuclide Dosimetry

Overview

• How are absorbed doses determined?
• How accurate are dose estimates?
• How do dose estimates correlate with toxicity?
• How is administered activity planned?
Some Purposes of RIT Dosimetry

- For agents with significant and variable excretion, estimate individual patient distribution/clearance to optimize IA

- Compile database of normal organ radiation absorbed doses

- Assure normal organ radiation doses are within safe range before therapy
Sources of data acquisition

- Radioactivity deposited in organ of interest or WB can be estimated by:
  - Extrapolation from animal data
  - External measurements using a scintillation camera ***commonly used
  - Estimation through use of a compartmental model
  - Measurement of excretory fluids & blood pharmacokinetics
  - Direct measure, e.g. TLD, biopsies
Resources for Dosimetry

MIRD

Medical Internal Radiation Dose

• Name of a standing committee of the Society of Nuclear Medicine

• Recognized as a method to perform dose calculation for internal emitters
Radiation emissions:

- Penetrating vs. non-penetrating
- Beta vs gamma radiation
- surrogate for $\beta^-$ $^{111}\text{In}$ for $^{90}\text{Y}$
Tracer Principle

• small amount of radiopharmaceutical can be used to predict spatial & temporal distribution of larger amount in the same patient

• assumes that the biologic system is not perturbed by the diagnostic study
Imaging-based time-activity curve

In-111 Day 4, posterior

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Common Imaging Procedures

• > 3 planar studies; WB +/- regions

• Correct for scatter & attenuation
  -scatter: dual window Jaszczak method
  -attenuation: transmission scan
Common Imaging Procedures-2

- Use Standard to convert counts to MBq
- Draw ROI for organs, marrow, background
- Obtain time-activity curves for ROI
- Use CT or MRI to assess volumes vs. phantom

*MIRD 16 Siegel JA, et al.. J Nucl Med, 40, 37s –61s, 1999
Calculation of Absorbed Dose to an Organ

\[
\text{Absorbed Dose} = \frac{\text{Energy Absorbed from Ionizing Radiation}}{\text{Mass of Organ}}
\]
Source and Target Organs

For the administration of a radiopharmaceutical to a human, the time-dependent localization of activity in an organ is designated a source organ.

The organ that is the recipient of this radiation energy from the source organs is called a target organ.
Any organ can be simultaneously both a source & target. The energy deposited in that organ by activity in it is self dose.
Sources and Targets (Self – Irradiation)

![Diagram showing sources and targets](image-url)

$^{131}$I - Iodide

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Absorbed Fraction

The fraction of the energy emitted by source and deposited in the target is called the absorbed fraction \( \phi_i \).
Specific absorbed photon fractions Thyroid source, I-131

- Thyroid → Thyroid $1.61 \times 10^{-3}$
- Thyroid → eyes $4.55 \times 10^{-7}$
- Thyroid → skin of head $4.06 \times 10^{-7}$
Absorbed Fraction – Example

Carbon-11
16% of the photons & 100% of the positrons are absorbed

\[ \phi_Y = 0.16 \]
\[ \phi_{np} = 1.0 \]
Absorbed Fraction
(S value)

depends on:

• Type and energy of the radiation

• Size, shape and composition of the source and target

• Distance between source and target, & type of material separating them
Cumulated Activity (Ã)

The Cumulated Activity is represented by the area under the time activity curve and has the dimensions of activity x time (uCi • hr)
Cumulated Activity (cont)

Activity

Area under the curve

Time
Cumulated Activity (cont)

The cumulated activity ($\tilde{A}_h$) in an organ h can be mathematically expressed as:

$$\tilde{A}_h = \int_{0}^{\infty} A_h(t) dt$$
MIRD Dose Equation (Simplified)

\[ D = \tilde{A} \times S \]

Where: \( \tilde{A} \) is the Cumulated Activity

and

S is the mean absorbed dose per cumulated activity or S-factor
“How to” Information sources


- D. Fisher- Sem Rad Onc 10:123, 2000

- AAPM primer www.aapm.org ➔ report, #40

- SNM & MIRD websites
Computer aids to calculation: MIRDOSE software

- MaBDOSE  T. Johnson, adds tumor
- MIRDOSE versions  M. Stabin ‘96
  PC based software for ORNL models (adult male =70kg)
- couples tabulated absorbed fractions & radionuclide decay data with source organ residence time ➔ mean radiation dose/unit IA
MIRDOSE Update – M. Stabin

• Newest version of MIRDOSE – OLINDA – Organ Level Internal Dose Assessment (Java, beta testing).

• Most MIRDOSE 3 models carried over.
• New models included: MIRD head/brain, Yale voxel phantom, prostate gland, peritoneal cavity, others.
• Will be ONLY research/teaching tool – separate, smaller codes for clinical application will be developed and submitted for FDA approval.

• Linked to new RADAR (RADiation Dose Assessment Resource) on-line system for internal/external dose assessment.
RADAR Web Site
www.doseinfo-radar.com

• Decay data for >800 radionuclides
• Absorbed fractions for 11 phantoms
• Kinetic data for many radiopharmaceuticals
• Dose factors (like MIRD S values) for all 800 nuclides and 11 phantoms
• Fetal dose factors, skin dose factors, external dose factors
• Risk information, consent form language
• On-line training courses – internal, external dose
• MORE! -------- M. Stabin –
Other web sites/links

- SNM
- MIRD
- ICRP
How Accurate are Radionuclide Dose Estimates

1. Uniform organ dose MIRD formalism \( \rightarrow \) \( \sim \) 2 fold variance
e.g. 200cGy calculated:actual = 100-400

2. Assumptions:
   homogeneous distribution;
   std man phantom masses & distance of organs
How Accurate Are Tracer Studies?
Comparison of tracer-predicted vs. therapeutic radiation doses measured

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
<th>Predicted/Received</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{131}$I-LYM-1</td>
<td>NHL</td>
<td>0.91 – 1.38</td>
<td>Tracer at day -7</td>
</tr>
<tr>
<td>$^{131}$I-antibodies</td>
<td>NHL, Leukemia</td>
<td>0.67 – 1.15</td>
<td>T1/2 for lung</td>
</tr>
<tr>
<td>$^{111}$In-cT84.66</td>
<td>CEA-positive cancer</td>
<td>Concordance 0.60-0.99</td>
<td>Most normal organs studied</td>
</tr>
</tbody>
</table>

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Special Considerations for Marrow dosimetry
Marrow toxicity =

dose-limiting in most non-SCR studies of radionuclide therapy
[except peptide]
Marrow Dosimetry

• Blood method AAPM ➔ Act. in ECF of marrow + Remainder Body [non-involved marrow]

• Sacral or Lumbar imaging [overlap with disease, organs]
Marrow Dosimetry

- Weak → Moderate correlation of calculated marrow dose (and/or other parameters) with hematologic toxicity in most RIT studies
Ex: 1 Y-90-Ibritumomab-tiuxetan (N = 349): Hematologic Toxicity

• 0.4 mCi/kg, 0.3 mCi/kg → platelets;

• Hematopoietic support (n = 211)
  – Growth factors 18% of patients
  – Red blood cell transfusion 20%
  – Platelet transfusion 22%
    – Grade 3-4 toxicity correlates with
  – Bone marrow involvement
  – Number of prior therapies/purine analogues
Lack of Y-90-Ibritumomab hematologic toxicity correlation with:

- Marrow radiation dose estimates
- Whole Body radiation dose
- Blood AUC
- Blood effective half-time
Example 2: Dosimetry Rationale for I-131-Tositumomab

- WB dose as predictor of hemat. toxicity
- Heterogeneity in individual pharmacokinetics is considerable among patients
- Standardized dosing based on mCi/kg would result in “over” and “under” dosing by > 10% in > 50% pt.
- Patient-individualized dosing treatment improve mean tumor dose by > 50%; ↓ chance of “under” or ”over” dosing for marrow toxicity

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Range of mCi Required to Deliver Targeted WB Radiation Dose
75/65cGy* (N=634)

Total body radiation dose 75cGy (65 for Platelets < 150,000)
Impact of Fixed Dosing (mCi/kg) on Total Body Radiation Dose

Total Body Dose With Fixed 1.1 mCi/kg Dosing (N = 634)

LEGEND:
- **Green** - Below Target Range by ≥ 10%
- **Blue** - Within 10% of Target Range
- **Red** - Above Target Range by ≥ 10%

Zelenetz AD et al, Blood 2001:98 p134a
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Improving MIRD & other advances

• Model of **Prostate** Gland for Use in Internal Dosimetry. Stabin JNM 1994

• Revised Model of Adult **Head & Brain**. Bouchet et al JNM 1996

• MIRD #17: Non-uniform activity distributions-Radionuclide $S$ values at the **Voxel** level. Bolch et al JNM 1999

• MIRD #19: Absorbed Fractions for 6 Age-dependent **Multi-region** Models of the **Kidney**. Bouchet et al JNM 2003
Example-Improved dose calculation using models of different height

• Previously only 1 adult male & female
• Autopsy data show correlation between body size & organ mass

Clairand et al, Phys Med Biol 45:2771, 2000
3 new adult male phantoms

160, 170, 180 cm  Clairand et al Phys Med Bio
Correlation of increasing organ mass with height

![Graph showing the correlation between organ mass and body height. The graph includes data points for the right lung, left lung, and liver, each represented by different symbols. The x-axis represents body height in centimeters, ranging from 140 to 175 cm, and the y-axis represents organ mass in grams, ranging from 0 to 2,000 grams.]
Example-Improved dose calculation using models of different height

- Better correlation with height than mass

- ↑ Ht. 10cm ➔ 20-29% ➖ S value I-131
  - stomach, bladder

Clairand et al, Phys Med Biol 45:2771, 2000
Shen: individual organ masses vary from Std. Man phantom

• L-spine marrow specific mass
  increased correlation of marrow dose with heme toxicity,
  \( r = 0.29 \) for std. blood vs. 0.85

• Prediction not improved by adjustment for body weight, surface area, lean body mass. JNM 43. ‘02

• Liver/other organs changed dose 0.5-1.7x
Effort to Improve Accuracy

- Functional/anatomic fusion, e.g. PET/CT
- 3-D anatomically accurate dosimetry that includes non-uniformity - DVH
- Closer to actual size phantoms, individual organ masses
- Regional voxel-based S values
- More accurate calculations - OLINDA
Compromise is expected in correlation of dose calculations with toxicity due to:

* limitations of dosimetry model, e.g. non-uniform voxel activity

* non-dosimetry modifications
Calculated Dose Is $\neq$ Biologic Dose

**Physical/biologic** interaction factors
- heterogeneous distribution
- dose rate effects
- effective range of radiation
- RBE, other characteristics
Biologic Factors Affecting Tolerance

*age, prior therapies, time since prior Rx,
*disease status-e.g. anemia,
marrow replacement;
*genetic factors and/or physiologic conditions - hypoxia that affects radio-sensitivity & repair
Adjustment for Biologic Factors improves dose/toxicity correlation

- Juweid: Prior chemo, time since chemo
- Wessels: age, gender, XRT, chemo. SNM 2000 $r=0.57$ improved to $r=0.80$
- Siegel: several marrow dose methods $\rightarrow$ moderate correlation. FLT-3 (hematopoiesis stimulating cytokine) levels $\rightarrow$ improved correlation
Biologic Effectiveness of Radionuclide Therapy

Agents/factors not contributing to radiation dose estimates. Chemotherapy, other biologic response modifiers

- Radiosensitizers, Cytokines, Growth factor inhibitor
- BuDR, IL-1, IL-2, anti-EGFr

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CONCLUSIONS
Possibilities for Improvement of Dosimetry Accuracy & Dose/Response Correlation

• Improved patient-specific models
• Individualized organ masses - Shen
• Adjust for tracer vs. Therapy differences
• Adjustments for biologic/conversion factors
• Find parameters with best correlation ➔ further study