Dosimetry (Dose Estimation) of Internal Emitters.

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Outline
1. Dose Estimation Formula $D = S \cdot A$
2. Determination of $A(t)$
   a. six methods
   b. errors in $A$
3. Integration of $A$ to form $\bar{A}$
   a. Open Model
   b. Closed Model
4. Calculation of Dose
5. Errors in Dose due to $A$, $\bar{A}$, and $S$ errors.

Estimation of Dose and not Dosimetry

- Dosimetry is the measurement of absorbed dose in erg/g or Joules/kg. This isn’t easily or ethically done in living tissues. Thus, use of the term is not appropriate in the context of radiation therapy.

- We can only estimate the internal emitter dose. Our limitation is similar to that found in external beam work. “They don’t do dosimetry either”.

For Radiation Effects, is Dose the only Answer?

- Because of biological effectiveness, a QF (quality factor) may be multiplied by dose (Gray) values to yield a result in Sieverts. Alpha ray examples.

- If this is done, however, the reader must be shown both values – not just the equivalent dose (Sv).

- Effective dose is not appropriate for specific patient risk calculations and is intended as a comparison parameter to use for stochastic calculations.
The General Strategy of Internal Emitter Dose Estimation

\[ \text{Dose} = S \times \bar{N} \]

- Where \( S \) contains the spatial efficiency of energy deposition in the target mass given the source’s emissions and location. \( \bar{N} \) is the total number of source decays (time effects).
- The formula is generally applied to whole organ sources and targets. It should hold down to cellular-sized systems.
- Space/time dichotomy will not hold if mass \( (t) \). Effect seen in lymphoma therapy at U. C. Davis and U. of Michigan.

Possible Radionuclides of Interest for Internal Emitter Therapy

<table>
<thead>
<tr>
<th>Nuclide</th>
<th>Beta (MeV)</th>
<th>Range</th>
<th>T1/2</th>
<th>Gamma (keV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I-131</td>
<td>0.61 MeV</td>
<td>2.0 mm</td>
<td>8 days</td>
<td>500 (80%)</td>
</tr>
<tr>
<td>Y-90</td>
<td>2.27</td>
<td>11</td>
<td>2.7 d</td>
<td>None</td>
</tr>
<tr>
<td>Re-186</td>
<td>1.07</td>
<td>5</td>
<td>3.1 d</td>
<td>157 (9%)</td>
</tr>
<tr>
<td>Re-188</td>
<td>2.12</td>
<td>10</td>
<td>17 h</td>
<td>155 (15%)</td>
</tr>
<tr>
<td>Lu-177</td>
<td>0.30</td>
<td>2</td>
<td>6.7 d</td>
<td>113 (6%)</td>
</tr>
<tr>
<td>P-32</td>
<td>1.70</td>
<td>8</td>
<td>14 d</td>
<td>None</td>
</tr>
<tr>
<td>Sm-153</td>
<td>0.81</td>
<td>4</td>
<td>1.9 d</td>
<td>103 (29%)</td>
</tr>
</tbody>
</table>

Uptakes Anticipated in a Mouse Biodistribution.

If we assume 100% of the injected dose (ID) were uniformly distributed in a 20 g mouse, the normal organ or tumor “tracer density” should be:

\[ 100 \text{% ID}/20 \text{ g} = 5 \text{% ID}/ \text{g (mouse)} \]

This is a non-targeting result. Also, we have corrected for radiodecay of the label. If we do not correct, the numerator is % injected activity (% IA). A similar result occurs for the adult patient with a denominator of 70 kg. The corresponding result:

\[ 1.4 \text{% ID}/ \text{kg (human)} \]

Motivation for Internal Emitter Cancer Therapy

- Ga-67 Citrate; non-specific, 6% ID/g in mouse tumor.
- Liposomes; non-specific, 30% ID/g in mouse tumor.
- Antibodies; specific, 60% ID/g in mouse tumor.
- Predicted Human Tumor Uptake \( \equiv 20\% \) ID/kg.
- Absorbed Dose (\( \alpha \) or \( \beta \) emitter) is proportional to %ID/g in tumor (or tissue).
Other Data of Interest to the FDA: Imaging Proof of Targeting; Nude Mouse Model with LS174T Human Colon Tumor. VFC with SynCo-57.

Proteins are the Poster Children for Tumor-Targeting Molecules.

- Specific to the Tumor-associated Antigen.
- Labeled with Different Radionuclides.
- Engineered for Molecular Weight.
- Engineered to be Human-like.
- Mono or Multi-Valent.
FDA-approved Internal Emitter Therapies

- SIR Spheres (plastic with Y-90) for Liver mets.
- Theraspheres (glass with Y-90) for Hepatoma.
  The above agents rely on catheter placement of agent.
  Use Tc-99m MAA to define lung toxicity.

- Bexxar Tositumomab (I-131) for Lymphoma.
- Zevalin Ibritumomab (Y-90) for Lymphoma.
  These agents are injected IV and circulate.

Internal Emitter Dose Estimation.

In order of decreasing difficulty the process has three steps.

1. Most difficult: Determination of activity (A) in tissues of interest at various times (t). Many methods.
2. Next most difficult: Integration of A(t) over very long times (∞) time to form A. Various techniques.
3. Least difficult (usually): Converting A to dose (D) via the matrix transformation D = S * A. However, S may need to be very different from OLINDA or MIRD standard phantom values. Use CT or MRI data.
Two Types of Internal Emitter Absorbed Dose Estimates in Patients.

- Type I: Legal/Scientific: FDA regulations for Phase I Trial in patients. Here, an OLINDA or MIRD phantom is used for the $S$ factor. $A$ (from animals) is adjusted to suit phantom. Uniform uptake assumed in source. Dose refers to whole organ targets.

- Type II: Patient-Specific: Evaluate toxicity and therapy in clinical trials. Thus, anatomic (CT or MRI) data are required. $S$ factor is made to be patient-specific. $A$ is used directly from the patient. Uptake may be non-uniform.

“The Problem” of Nuclear Medicine

- After 60 or more years, there is still no standard technique to estimate activity ($A$) in a patient. Multiple methods have been proposed and used, but a typical clinical study will probably require a combination of techniques over the 1 to 10 day period allocated to the patient study.

Step 1: Six Methods for Determination of Human Activity ($A$).

- Blood, Surgical and Excreta Sampling.
- Probe Images of Surface Lesions or Whole Body.
- Geometric Mean (GM) of Two Opposed Views.
- CAMI Method.
- Quantitative SPECT from Fused or Hybrid (nuclear/CT) Scanning.
- PET or PET/CT Imaging with quantitative SUV Results.

Methods to Determine $A$ are not MutuallyExclusive

In a typical clinical study, data takers will need to use 2 to 3 simultaneous methods for measurement of $A$. The most important are:

- Blood Sampling.
- GM of whole body (WB) images.
- Quantitative SPECT (Hybrid Scanner or fusion).
Direct Sampling of Blood (Tissues).

- Blood values needed for bone marrow dose estimates.
- Blood gives patient subgroup determinations. Patients do not fall on a Gaussian curve.
- Blood data taken at each imaging time point and several times for the first biological half-life.
- Tissue sample may provide normalization of image results; e.g., an OR specimen.
- All are counted with a standard from the pharmacist.

Bone Marrow Dose Estimation

\[ \tilde{\lambda}_{\text{rm}} = f \, \tilde{\lambda}_{\text{blood}} \times \frac{1500}{5000} \]

Where \( f \) is a coefficient on the order of 0.3 and the numerator and denominator are RM and whole blood masses respectively. This approximation neglects specific marrow uptake which must be handled separately if present. Cf. Siegel et al. Antibody Immunococonj and Radiopharm. 3: 213-233 1990 and Sgouro J. Nucl. Med. 34: 689-694 1993.

Single Probe Counting

- May be used on essential external sites such as melanoma, sarcoid or thyroid tissue.
- Attenuation correction can be simple.
- Inverse square law needed for efficiency correction.
- May be used for whole body clearance.
- Counting standard is required.

The Nuclear Medicine Imaging Situation

Ray 1
Ray 2
Patient outline
Geometric Mean Imaging

- Typically uses anterior-posterior projection.
- Tissue attenuation is corrected with CT, MRI or direct measurement (external source).
- Should have standard source in the field of view.
- Suffers from possible organ and tumor overlap.
- May also suffer from observer confusion: hot spot anterior image ≠ hot spot posterior image.
- Typical errors are +/- 30% (literature).

CAMI Method

- Uses CT data to correct attenuation along rays of interest thru the patient’s major organ systems.
- May be used from a single whole body scan.
- Problem of activity becomes a set of activity densities (kBq/cm) along rays of interest.
- Organs may overlap.
- Problem is over-determined; least-square fitting.
- Errors are +/- 10% (literature).

CT Assisted Matrix Inversion Method (CAMI)

Radioactivity estimation with CAMI and GM method
Two overlapping organs (pancreas and right kidney)
Radioactivity estimation with CAMI and GM method
Two overlapping organs (pancreas and right kidney)

Total Organ Activities (µCi of In-111)

- Pancreas
- Kidney
- Liver
- Lung
- Portal Vein
- Liver
- Spine

Quantitative SPECT

- Requires CT (MRI) anatomic data to correct for attenuation and other factors.
- Commercial systems are becoming available.
- Four steps are ideal in the algorithm:
  - Attenuation.
  - Scatter.
  - Collimator correction.
  - Small Volume recovery correction.

Commercial Hybrid (SPECT/CT) Systems

- GE Hawkeye I and II
- Siemens Symbia
- Philips Precedence

- The partial volume correction is not available on any system at this time.
- CT Images may be inferior to stand-alone CT.
- Organ Motion between CT and SPECT

Several of the Research Groups involved in Quantitative SPECT

- Johns Hopkins
- Lund University (Sweden)
- U of Michigan.
- U of Massachusetts
PET/CT Scanning to Determine $A$

- SUV should (!) give an accurate result.
- No collimator required – hence high efficiency compared to camera and SPECT/CT.
- Yet in practice multiple SUV values are cited. Which one is best for A(t)?
- F-18 has a 110 m half life.
- I-124 has 100 h, but only 23% emission of 511 keV.

SPECT/CT Results for Hawkeye I

<table>
<thead>
<tr>
<th>Organ</th>
<th>MEGP</th>
<th>MEGPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>- 6 % error</td>
<td>- 4 % error</td>
</tr>
<tr>
<td>Kidney</td>
<td>- 11 %</td>
<td>- 14 %</td>
</tr>
<tr>
<td>Lungs (R.L)</td>
<td>-7.6 %</td>
<td>-3.3 %</td>
</tr>
<tr>
<td>Average</td>
<td>-7.5 %</td>
<td>-6 %</td>
</tr>
</tbody>
</table>

In-111 in a RSD torso Phantom with 3 JH Corrections

Step 2: Pharmacokinetic (PK) Analysis To Determine $\hat{A}$ Given $A(t)$.

1. **Open** Model uses Multiple Exponential Fits to Tumor, Blood and other tissues. These represent eigenfunctions of the differential equations.

2. **Closed** Compartmental Model with connected organs. Blood-organ interactions are seen more clearly in this mammillary format.

Reasons for PK Modeling

- Integration of $A(t)$, via model parameters, to form $\hat{A}$.
- Determination of kinetic variables for animals and patients. Comparing such data.
- Checking for Incorrect Data.
- Converting from Gamma Emitter (Image) Label to the Beta Emitter (Therapy) Label. For example, going from In-111-Antibody to Y-90-Antibody.
Step 3: Methods to Determine Absorbed Dose ($D = S^*A$)

- **OLINDA, MIRDOSE3 or MIRDOSE2** Programs; $S$ depends upon a given phantom. Traditional Method; favored by regulatory agencies and most users of radioactivity.
- **Voxel-Based Calculation (MAVSK)**; $S$ is local.
- **Point-Source Kernels**; $S$ is local.
- **Complete Monte Carlo Analysis**; no use of $S$ (!).

Two Corrections to OLINDA Estimations of Absorbed Dose.

- Correct $A$ (patient) to Allow Substitution into Standard Program. Type I Estimate.
- Correct $S$ (OLINDA or MIRD) to Allow Patient-Specific Estimation of Absorbed Dose. Type II Estimate.
Correction to Patient Activity for use in a standard OLINDA Dose Calculation.

\[ \hat{A}(\text{MIRD}) = \hat{A}(\text{pt}) \times \frac{m(\text{MIRD})}{M(\text{MIRD})} \]
\[ \frac{m(\text{pt})}{M(\text{pt})} \]

where \( m \) is organ mass and \( M \) total body mass. \( \text{Pt} \) refers to the patient. Here, we assume use of standard phantom \( S \) values for use in a legal/scientific context such as an FDA application. Same correction as used by Jeff Siegel in red marrow analysis.

Correction for Organ \( S \) values in OLINDA to Compute a Patient-Specific Absorbed Dose.

\[ S_{S p}(\text{pt}) = S_{S p}(\text{MIRD}) \times \frac{m(\text{MIRD})}{m(\text{pt})} \]

Here, \( m \) refers to organ mass and \( n_p \) implies non-penetrating radiation such as beta or alpha rays. We assume \( \text{pt} \) and chosen phantom have the same total mass \( M \).

Table of Dose Correction Results

<table>
<thead>
<tr>
<th>Absorbed Dose Type</th>
<th>( S )</th>
<th>( A )</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>correct</td>
<td>Change by ( \frac{m(\text{MIRD})}{m(\text{pt})} )</td>
</tr>
<tr>
<td>II</td>
<td>Change by ( \frac{m(\text{MIRD})}{m(\text{pt})} )</td>
<td>correct</td>
</tr>
</tbody>
</table>

Example of the Use of Type I Dose Estimation.
Review of MIRD Reports 1 through 12

Of the first 12 MIRD Reports, it seems that two used an explicit correction for the mass of source organs and the whole body. These were Report 1 (75-Se-Methionine) and Report 2 (67-Ga Citrate). In both cases, autopsy data were available for analyses.

In the case of the other 10 Reports, it is unclear if any correction was made for organ mass/whole body (\( m/M \)) mass ratios. Thus, these results are probably not of Type I.
Errors in Absorbed Dose Estimates.

- The A value is uncertain to +/- 30% in GM. CAMI yields errors on the order of +/- 10%. SPECT/CT results are still being developed, but should be +/- 5% to +/- 10%. Stay tuned for improvements.
- \( \bar{A} \) is +/- 10% due to integration uncertainties.
- S tables can be incorrect by factors of two- or three-fold due to patient target organ masses. This is probably the largest possible error in the \( D = S* \bar{A} \) formula.

Comparison of Two RIT Protocols.

CD20 + NHL
- Zevalin c Y-90
- Tumor: Not given
- Liver: 17 cGy/mCi
- Spleen: 27 cGy/mCi
- Red Marrow: 2.4 cGy/mCi

CEA + Solid Tumors
- cT84.66 c Y-90. Protocols 91064 and 91169.
- Tumor: 25 cGy/mCi
- Liver: 27 cGy/mCi
- Red Marrow: 3.1 cGy/mCi

Normal Organ Toxicity Values

<table>
<thead>
<tr>
<th>Organ</th>
<th>TD 5% complications/5 yrs</th>
<th>TD 50% /5 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>30 Gy</td>
<td>40 Gy</td>
</tr>
<tr>
<td>Kidney</td>
<td>23 (whole organ)</td>
<td>28 (whole organ)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>? 1.5 Gy Acute Effects</td>
<td>? 2.0 Gy Acute Effects</td>
</tr>
</tbody>
</table>

Future Directions in Absorbed Dose Estimation.

1. Both types of estimates will need to be made. The phantoms will change into more human-appearing forms in OLINDA. The first kind of correction (\( \bar{A} \)) will continue to be used.

2. Both Types of Estimation will increasingly be made with Monte Carlo calculations by the user. Voxel or point source kernels instead of S matrices. This will eliminate the necessity of the 2nd kind of correction (S matrix).

3. Dose-volume histograms rather than only mean doses will become the standard output of the patient calculation.

4. A third type of estimate, for animals only, will become of interest in evaluating the pre-clinical effectiveness of RIT.
Some References for Internal Emitter Dose Estimation

• The Primer. AAPM Report No. 71, 2001. RIT.
• Stabin et al. JNM 46: 1023-1027, 2005. OLINDA.