Radiopharmaceutical Dosimetry

by

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MIRD

Medical Internal Radiation Dose

- Recognized as a method to perform dose calculation for internal emitters
- Name of a standing committee of the Society of Nuclear Medicine
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 radiate energy from the source organs is called a target organ.
Self Dose

Any one organ can be simultaneously designated as both a source and target organ. In this case, the energy deposited in that organ is called the self dose.
Sources and Targets (Self-Irradiation)

\[ {^{131}}I \text{ - Iodide} \]
Source and Targets – Cross Irradiation
Sources and Targets (Combination)
Absorbed Fraction

The fraction of the energy emitted by source and deposited in the target is called the absorbed fraction ($\phi_i$).
Absorbed Fraction – Example 1

Carbon-14
100% of the electrons are absorbed

\[ \phi_{np} = 1.0 \]
Absorbed Fraction – Example 2

Iodine-123
16% of the photons are absorbed
\[ \phi_\gamma = 0.16 \]
Absorbed Fraction – Example 3

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

\[ \phi_Y = 0.16 \]

\[ \phi_{np} = 1.0 \]
Absorbed Fraction
(continued)

This depends on:

- Type and energy of the radiation
- Size, shape and composition of the source and target
- Distance between source and target as well as the type of material separating them
Cumulated Activity (Å)

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

$$\tilde{A}_h = \int_{0}^{\infty} A_h(t) \, dt$$
Cumulated Activity (cont)

Measurement of radioactivity distribution and turnover within human tissues is a major task.

Models of Cumulated Activity:

1. Uptake by organ is instantaneous with no biologic excretion

2. Uptake by organ is instantaneous with elimination by biologic excretion only

3. Uptake by organ is instantaneous with removal by both physical decay and biologic excretion

4. Uptake by organ is not instantaneous
Hence, the radiation energy emitted by the source activity cumulated \( (\tilde{A}_h) \) over the time interval of interest is given by:

\[
\tilde{A}_h \Delta
\]

where \( \Delta \) is the total mean energy emitted per nuclear disintegration.
Dose Equation (cont.)

If we now consider a radiopharmaceutical that emits several kinds of radiation (e.g. beta and gamma), each is characterized by its own mean energy per particle \( E_i \) and number of particles \( n_i \), then:

\[
\Delta_i = K \ n_i \ E_i
\]

where \( K \) is a constant

and is dependent on units
Dose Equation
(continued)

Therefore, the energy absorbed by a target \((r_k)\) from a source region \((r_h)\) irradiation is given by:

\[ \tilde{A}_h \Delta_i \phi_i \]
Absorbed Dose to Organ (Single Source)

The mean absorbed dose (\( \overline{D}_k \)) to target organ \( k \) with mass (\( M_k \)) from a single source organ \( h \) is given by:

\[
\overline{D}_k = \frac{\tilde{\Lambda}_h \Delta \phi_i}{M_k}
\]
Absorbed Dose to Organ (Single Source)

To sum the contributions for all radiations from source $h$ to target $k$:

$$
\bar{D}_k = \frac{\tilde{A}_h \sum \Delta_i \phi_i}{M_k}
$$
The previous equation may be separated into two parts 1) cumulated activity and 2) those factors dependent on radionuclide properties relative to a size and position of various organ in a model phantom. This latter quantity is labeled the S factor and is defined mathematically as:

$$S(r_k \leftarrow r_h) = \sum_i \Delta_i \phi_i / M_k$$
If we also define a specific absorbed fraction as:

\[ \Phi = \frac{\phi_i}{M_k}, \]

then the dose equation simplifies to be:
MIRD Dose Equation
(Simplified)

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

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

and

S is the mean absorbed dose per cumulated activity or S-factor
Dose Equation (cont)  
(Multiple Sources)  

Ordinarily there will be many source organs \((r_h)\) contributing dose to the target \(r_k\). Hence the total dose equation summed over all sources is given by:

\[
\bar{D}(r_k) = \sum_{h} \bar{D}(r_k \leftarrow r_h)
\]
Residence Time

The concept of residence time ($\tau_h$) has also found to be useful to describe an organ into which the activity $A_0$ is administered at time $t = 0$. The area under $A_h(t)$ equals the area of the rectangle.
Residence Time

The residence time in source organ \( h \) is defined as:

\[
\tau_h = \frac{\tilde{A}_h}{A_0}
\]

where \( A_0 \) is the administered activity and \( \tilde{A}_h \) is the cumulated activity in organ \( h \).
Residence Time ($\tau$)

When uptake phase can be neglected and maximal source activity is $A_h$,

$$\tau_h = \frac{1.443(T_h)_{\text{eff}} A_h}{A_0}$$
Residence Time ($\tau$) (continued)

In case of bolus administration where all the activity ($A_0$) is located in organ at $T = 0$ (e.g. blood),

$$\tau_h = 1.443 (T_h)_{\text{eff}} \quad (A_h = A_0)$$

$\tau$ is simply the effective mean lifetime (1.443 T) of the activity in the organ multiplied by $A_0$. 
Practical Example

This example illustrates a method for estimating absorbed dose to an organ from the biologic behavior of a radiopharmaceutical.

Injected Tc - 99m sulfur colloid is deposited in the liver, which becomes the source organ. We will calculate the dose from the source organ to target organs, which include the self dose from the liver.
The dose from the source organ, liver, to itself as the target organ (self-dose) and to other organs of the body can be calculated from the basic equation:

$$\bar{D} = \bar{A} \, S = A_0 \tau \, S$$

- \(\bar{D}\) mean dose
- \(A_0\) administered activity
- \(\tau\) residence time
- \(S\) S - Factor
Example – cont.

Assume the injection of 1 mCi of Tc-99 m sulfur colloid and that 85 % remains in the liver.
Calculation of Residence Time

Residence time is defined as:

\[ \tau_h = \frac{\tilde{A}_h}{A_0} \]

where \( \tilde{A}_h \) is the cumulated activity in organ h, which is defined as the sum of the activity at each moment in time:

\[ \tilde{A}_h = \int_0^\infty A_h e^{-(\lambda + \lambda_b)t} \, dt \]
Residence Time (cont)

If $\lambda$ is defined as the physical decay constant and

$\lambda_b$ is defined the biologic clearance constant.

In this example, there is no biologic clearance from the liver, so

$\lambda_b = 0$
Calculation of Residence Time (continued)

Integration gives:

\[ \tilde{A}_h = A_h \int_{0}^{\infty} e^{-\lambda t} dt = \frac{A_h}{\lambda} \]

From the physical half-life \( T_{1/2p} \) of 6.02 hours (h) for \( {}^{99m}Tc \), we can calculate \( \lambda \) as:

\[ \lambda = \frac{\ln 2}{T_{1/2p}} = \frac{0.693}{6.02 \text{ h}} = 0.115 \text{ h}^{-1} \]
Calculation of Residence Time
(continued)

We were given \( A_h / A_0 = 0.85 \). Thus,

\[
\tau = \frac{\tilde{A}_h}{A_0} = \frac{A_h}{A_0} \frac{1}{\lambda} = \frac{0.85}{0.115 \ h^{-1}} = 7.39 \ h
\]
## S Values for Tc-99m

Source Organ (Liver)

<table>
<thead>
<tr>
<th>Target organ</th>
<th>rad/μCi h</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI (ULI wall)</td>
<td>2.5E-06</td>
</tr>
<tr>
<td>GI (LLI wall)</td>
<td>2.3E-07</td>
</tr>
<tr>
<td>Kidneys</td>
<td>3.9E-06</td>
</tr>
<tr>
<td>Liver</td>
<td>4.6E-05</td>
</tr>
<tr>
<td>Lungs</td>
<td>2.5E-06</td>
</tr>
</tbody>
</table>
The absorbed dose can now be calculated.

For the liver:

\[
\bar{D} = A_0 \tau S(\text{liver} \leftarrow \text{liver})
\]

\[
A_0 = 1,000 \mu\text{Ci} \text{ or (1 mCi)}
\]

\[
\tau = 7.39 \text{ h}
\]

\[
S_{\text{liver}} = 4.6 \times 10^{-5} \text{ rad/\muCi h}
\]
Solution - Liver Dose

\[ \overline{D}_{liver} = A_0 \tau S_{liver} \]

\[ = (1 \times 10^3 \ \mu Ci)(7.39 \ h)(4.6 \times 10^{-5} \ \text{rad/\mu Ci h}) \]

\[ = 0.340 \ \text{rad} \]
Similarly, for the kidney dose

\[ \overline{D} = A_0 \tau S \ ( \text{Kidney} \leftrightarrow \text{Liver}) \]

\[ A_0 = 1,000 \ \mu\text{Ci} \text{ or } (1 \text{ mCi}) \]
\[ \tau = 7.39 \ \text{h} \]
\[ S (\text{Kidney} \leftrightarrow \text{Liver}) = 3.9 \times 10^{-6} \ \text{rad/\muCi h} \]
Solution - Kidney Dose

\[
\overline{D}_{\text{kidney}} = A_0 \tau S_{\text{kidney}}
\]

\[
= (1 \times 10^3 \mu Ci)(7.39 \text{ h})(3.9 \times 10^{-6} \text{ rad/\mu Ci h})
\]

\[
= 0.029 \text{ rad}
\]
Summary - Dose Equation

Dose equation consists of two parameters:

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

1. Biological Parameters (\( \tilde{A} \))
   - The time that activity spends in source organ
   - Depend on physiologic behavior of radiopharmaceutical radioactive decay

2. Physical Parameters (\( S \) value)
   Depend on:
   - nature of the radiations
   - their absorption characteristics
   - the anatomic model
Knowledge of activity distribution in body can be estimated by:

- Extrapolation from animal data
- External measurements using a scintillation camera in planar or SPECT modes
- Estimation through use of a compartmental model
- Measurement of excretory fluids
II. Physical Parameters

1. Nuclear parameters for particular radionuclide: type of particle, number and energy of particles per transition, and energy emitted per transition (MIRD: Radionuclide Data and Decay Schemes, The Society of Nuclear Medicine, 1989).

2. Source/target organ configuration: absorbed fraction (MIRD Pamphlets No. 3 [1968], 5 revised [1978], 8 [1971] and Cristy and Eckerman, ORNL Pub. [1987]).

3. S values (MIRD Pamphlet No. 11 [1975]).
Reference List


Methods for Computing Absorbed Dose from Non-Uniform Activity or Gradient Activity Distributions

1. Dose Point Kernels for Electrons and Photons

2. Applications of Direct Monte Carlo Radiation Transport Codes

3. The Voxel S Value Approach

\[
\bar{D}(\text{voxel}_k) = \sum_{h=0}^{N} \tilde{A}_{\text{voxel}_k} \bullet S(\text{voxel}_k \leftarrow \text{voxel}_h)
\]
Point Kernel Approach (1)

• Dose point kernel:
  Radial distribution of absorbed dose around isotropic point source in an infinite homogeneous medium
Point Kernel Approach (2)
Calculation methods

- Transport equations
- OR
- Monte Carlo transport codes

- Lookup Tables
- OR
- Empirical Solutions
Point Kernel Approach (3)
Nonuniform Activity Distribution

- Convolution of activity data with dose point kernel

\[
\text{Dose} = \text{Activity} \ast \text{Dose Point Kernel}
\]
Point Kernel Approach (5)

- **Advantage**
  - Fast computer time required for dose calculation

- **Disadvantages**
  - Does not handle heterogeneities
  - Biased to spherical geometry
  - Geometry factors + dose convolution: complicated
Monte Carlo Approach (1)

- Simulation of a random process:
  - Transport of Electrons and Photons
- Two widely used Monte Carlo code in Medical Physics
  - EGS4: Electron Gamma Shower Version 4
    - Simulation of the electron-photon shower
  - MCNP Version 4B
    - Coupled transport of photons and neutrons + electrons
- Differences:
  - Physics of electron transport
  - Input / output
Monte Carlo Approach (3)

- Advantages
  - Handle heterogeneities => very accurate
  - No longer biased to spherical geometry
- Disadvantages
  - Large amount of CPU time required
  - Still a complicated approach
MIRD Voxel S value Approach

(1)

MIRD Methodology

\[ \bar{D}_T = \frac{\text{Energy Deposited in } T}{\text{Mass of } T} \]

\[ \bar{D}_T = \frac{(\text{Total Energy emitted in } S)(\text{Fraction of Energy Absorbed in } T)}{\text{Mass of } T} \]
Define: \( S \) value

\[
S(T \leftarrow S) = \frac{\bar{D}_T}{\bar{A}_S} = \Delta \frac{\phi(T \leftarrow S)}{m_T}
\]

Finally:

\[
\bar{D}_T = \bar{A}_S \cdot S(T \leftarrow S)
\]

\( \bar{A}_S \) derive from planar, SPECT, or PET imaging

\( S \) value tabulated for Source/Target/Radionuclide
MIRD Voxel S value Approach

(4)

Nonuniform Activity Distribution

\[ D_{\text{target}} = \sum_{\text{all sources}} \tilde{A}_{\text{source}} S(\text{target} \leftarrow \text{source}) \]
MIRD Voxel S value Approach
(5)
Nonuniform Activity Distribution

• Advantages
  – Use the simple MIRD dose calculation methodology
  – Fast to perform (can use DFFT)
  – Accurate (S values match the geometry of activity data)

• Disadvantages
  – Does not handle heterogeneities
Application of Non-Uniform Dose Calculation Methods to Special Problems

1. Quantitative Autoradiography
2. Local deposition of dose from alpha and beta radiations
3. Intravascular Brachytherapy – balloon catheters
4. Sub-organ dosimetry – Kidney, Lung, Liver, GI, Brain and Bone Marrow
MIRDOSE Update – M. Stabin

- New version of MIRDOSE to be released this summer (2001).
- New name – OLINDA – Organ Level Internal Dose Assessment (written in Java).
- Linked to new RADAR (RAdiation Dose Assessment Resource) on-line system for internal/external dose assessment.
- 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.
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 – July 2001
Overview of the RADAR System - M. Stabin

Internal Sources:
- Kinetic Models - Radiopharmaceuticals
- Kinetic Models - Occupational Radionuclides

External Sources:
- External Source Configuration

Radionuclide Decay Data
Specific Absorbed Fractions - Phantoms

Dose Conversion Factors

Radiation Dose Estimates and Distributions

Linking of Radiation Doses to Biological Effects
Announcement
Seventh International Radiopharmaceutical Dosimetry Symposium

http://www.doseinfo-radar.com/symphome.html

- April 17-19, 2002 in Nashville, TN
- Topics include:
  - Therapy with internal emitters
  - Dose effects, models
  - Cellular, small scale dosimetry
  - Kinetic, animal models
  - Regulatory issues
- Call for abstracts on web site – now until Sept 30, 2001.
Fundamental Objectives for Radionuclide Therapy

1. To achieve appropriate treatment of disease through delivery of radiation dose to a tolerable cytotoxic level:

2. To avoid or minimize toxic effects: Both as acute reactions and late effects.

**Defined endpoints** – “Cure” or NED, increase in survival, control (full or partial), improvement in QOL (e.g. palliation).

Knox S, Seminars in Radiation Oncology, 10 : pp 71 - 167 (April 2000)
Response Evaluation

• % response, % CR, PR, MR, Mixed, Stable
• Duration, time to need for more therapy, QOL improvement
• Non-measurable disease—Time to progression
QOL Forms: Functional Index

- 1. Has nausea affected your daily functioning?
- 2. How much is pain interfering with your daily activities?
- 3. Do you feel well enough to make a meal or do minor household repairs?
# Early Use of Radionuclides in Therapy

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Disease Type</th>
<th>Original/Early Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-32</td>
<td>Polycythemia Vera</td>
<td>1936</td>
</tr>
<tr>
<td>P-32</td>
<td>Lymphoproliferative</td>
<td>1938</td>
</tr>
<tr>
<td>P-32</td>
<td>Bone Pain</td>
<td>1937</td>
</tr>
<tr>
<td>Sr-89</td>
<td>Metastatic Cancer to Bone</td>
<td>1941</td>
</tr>
<tr>
<td>I-131</td>
<td>Hyperthyroidism</td>
<td>1942</td>
</tr>
<tr>
<td>I-131</td>
<td>Differentiated Thyroid Cancer (Remnant Ablation; Tumor/Metastases)</td>
<td>1944</td>
</tr>
</tbody>
</table>
I-131 Treatment of Thyroid Cancer or Ablation of Thyroid Remnants

1. High, fixed administered activity: 75-150 mCi.

2. Low, fixed administered activity: ~30 mCi

3. $A_0$ calculated to provide a predetermined radiation dose. Requires knowledge of remnant mass, effective half-time and 24-hr uptake.

4. Quantitative diagnostic work-up: $^{131}$I tracer to establish patient specific parameters.
Results in treating Thyroid Remnants

- Desired radiation dose:
  - H.R. Maxon: 30,000 cGy (~81% control rate)
  - Others: 25,000 to 100,000 cGy

- Complications:
  - Short term: Bone marrow depression; Acute or chronic sialdentin; thyroid storm (rare).
  - Long Term: leukemia; azoospermia; pulmonary fibrosis.
Phase I Study Design

Objective: Determine Maximum Tolerated Dose (MTD)

Design:

1. First dose level usually shows little or no toxicity

2. Fixed dose escalation in increments of usually 20-25%.

3. Dose based on patient specific parameters e.g. mCi/kg; AUC for pharmacokinetics curve or based on radiation dose to normal organs.
Phase I Escalation Examples

1. Y2B8 0.2-0.4 mCi/kg → 0.4 mCi/kg = MTD

2. I-131-anti-B1 WB 25-85 cGy; calculated from clearance rate, Phase II = 75 cGy

3. Seattle myeloablative therapy 15-31 Gy to normal organs, 27 Gy = 2nd critical organ MTD
Phase II Study Design

- Objective - define response rate
- MTD, next lower dose, or modestly reduced to 80%
- 1st 14 patients - if no response - small chance > 20% response rate. Number of responses in 1st 14 pt. allows determination of how many to study for response rate 20%
Modern Radionuclide Therapy

A. Systemic Radionuclide Therapy:

(1) Benign Disease

$^{131}$I sodium iodine: Graves’ disease; single functioning nodule; toxic multinodular goiter

$^{32}$P sodium phosphate: PV; thrombocytopenia.

$^{90}$Y colloid: Severe arthritis

$^{165}$Dy ferric hydroxide: Severe arthritis

(McDougall, Sem Rad Onc 10, 2000)
Modern Radionuclide Therapy

A. Systemic Radionuclide Therapy:

(2) Malignant Disease

$^{131}$I sodium iodine: ablation Thyroid CA, remnant
$^{131}$I MIBG: Metastatic neuroblastoma
$^{111}$In octreotide: neuroblastoma
$^{32}$P chronic phosphate: Intracavity therapy
$^{89}$Sr strontium chloride: Painful skeletal mets
$^{153}$Sm EDTPA: Painful skeletal mets
Modern Radionuclide Therapy

B. Systemic Radionuclide Therapy:
Radioimmunotherapy - (1) Solid Tumors

$^{131}$I-anti-EGFR: Recurrent gliomas - CNS site
$^{125}$I-425: Glioblastoma multiforme - CNS
$^{186}$Re-NR-LU-10: Ovary; breast, colon, lung
$^{90}$Y-anti-ferritin: Hepatoma
$^{125}$I-17-1A: Gastrointestinal
$^{90}$Y-ChT84.66 anti-CEA: Colon

(Knox/Meredith, Sem Rad Onc 10, 2000)
Modern Radionuclide Therapy

B. Systemic Radionuclide Therapy:
Radioimmunotherapy - (2) B Cell Lymphoma

Nonmyeloablative:
\[ {^{131}}I: \text{ Lym-1; LL2; Anti-B1; MB1} \]
\[ {^{90}}Y: \text{ B1; 2B8; C2B8} \]

Myeloablative:
\[ {^{131}}I: \text{ B1; MB1; LL2; 1F5; BC8} \]
\[ {^{90}}Y: \text{ B1} \]
\[ {^{213}}Bi: \text{ HuM-195} \]
Normal organ tolerance to radiation (cGy)

<table>
<thead>
<tr>
<th>Organ</th>
<th>External beam TD5/5, TD 50/5</th>
<th>Radionuclide – no toxicity</th>
<th>Radionuclide –+ toxicity</th>
<th>TBI single</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow</td>
<td>250 450</td>
<td>toxicity at 20</td>
<td>MTD ~ 200</td>
<td>? threshold</td>
</tr>
<tr>
<td>Lungs</td>
<td>1500 2500</td>
<td>2500</td>
<td>2725 Grade 3</td>
<td>Press, no chemo 700</td>
</tr>
<tr>
<td>Brain</td>
<td>5400 7000</td>
<td>16000 cyst wall</td>
<td></td>
<td>? IQ</td>
</tr>
<tr>
<td>Meninges</td>
<td></td>
<td>5800 $^{131}$Ab</td>
<td>20000</td>
<td>Aseptic meningitis</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>4500 5500</td>
<td>~1700</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>4500 15000</td>
<td>&lt; 15000</td>
<td></td>
<td>Synthroid used</td>
</tr>
</tbody>
</table>
## Normal Organ Toxicity

<table>
<thead>
<tr>
<th>Organ</th>
<th>External beam</th>
<th>Radionuclide – no toxicity</th>
<th>Radionuclide – + toxicity</th>
<th>TBI single</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>2000, 2500</td>
<td>? 2500</td>
<td>Delayed &gt;2170</td>
<td>↑ creatinine</td>
</tr>
<tr>
<td>Bladder</td>
<td>6000, 8000</td>
<td>~15000</td>
<td>~15000+chemo</td>
<td>hemorrhage</td>
</tr>
<tr>
<td>GI tract</td>
<td>4500, 5500</td>
<td>2700, mild &lt; ~6000</td>
<td>N/V/D&gt;6000, 6850-14000-Gr4</td>
<td>↑ nausea &lt; 2700 some prior RT</td>
</tr>
<tr>
<td>Bowel serosa</td>
<td>? NA</td>
<td>6000</td>
<td>8000</td>
<td>Adhesions obstruction</td>
</tr>
<tr>
<td>Liver</td>
<td>2500, 4000</td>
<td>2400, $^{90}$Y-CC49 2700, $^{131}$I-B1</td>
<td>~150 $^{186}$Re NR-LU-10</td>
<td>Mild N; LFT 1500</td>
</tr>
</tbody>
</table>
Comparison of Response duration for all patients vs.
Those achieving CR after 131I-ANTI-B1 Rit
RESULTS OF STRONTIUM-89 OPEN-LABEL TRIAL IN 83 PATIENTS

RESULTS OF STRONTIUM-89 DOUBLE-BLIND TRIAL IN 26 PATIENTS


Number of Patients

- Placebo
- ST-89

Degree of Response
- Improvement or Some Substantial Improvement
- No Improvement or Deterioration

N=26
P=0.01
STRONTIUM-89 AS ADJUNCT TO RADIOTHERAPY: IMPROVED QUALITY OF LIFE AT 3 MONTHS (N=126)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Sr-89</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (P&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Activity (P&lt;0.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Well-Being</td>
<td></td>
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</tr>
</tbody>
</table>

Establishing the Role for Dosimetry in Radionuclide Therapy Today

Fundamental Questions for Consideration:

How might patient specific factors be used most appropriately in the optimization of radionuclide therapy?
Establishing the Role for Dosimetry in Radionuclide Therapy Today

Fundamental Questions for Consideration:

For a specific disease, patient classification, and radionuclide therapy, should there be a standard treatment protocol?
Starting Point for Radionuclide Therapy Determining the Administered Activity

1. Fixed administered activity ($A_o$):
   Single administration

2. Fixed $A_o$ with multiple readministration dependent upon patient response according to defined indicators.

3. $A_o$ determined by basic patient specific parameters (e.g., body surface area, weight, target tissue mass)

4. $A_o$ determined by more extensive patient specific parameters including biokinetics and the desired radiation dose to be delivered.
The Role of Patient Specific Dosimetry in the Development of New Agents

- **Phase I Studies:** Essential to establish human pharmacokinetics and dosimetry for safety in preparation for clinical trials.

- **Phase II Studies:** To be advise in limited patient clinical trials to address the efficacy aspects.

- **Phase III Studies:** Must show utility
Categories of Patient Specific Dosimetry

Level 1:

Measurement of the relevant biokinetic parameters prior to therapy for use in conjunction with standard anatomic and mathematical models to calculate radiation dose for extrapolation from the tracer study to the therapeutic administration.
Categories of Patient Specific Dosimetry

Level 2:

Extension of the database acquired through Level 1 by determination of additional anatomic and/or tissue distribution specific to the patient. To be used for minor adjustments to the standard anatomic models prior to calculation of radiation dose.
Level 3 (and beyond):

Definitive representation of the patient through 3-D techniques employing fusion of physiologic images with high resolution anatomic images. Ultimately, 3-D voxel representation of the patient with point kernel or MC techniques used to derive S values for use in the radiation dose calculations.
How accurate are tracer studies?

1. Meredith- AIR ’93  
   $^{131}$LYM-1 ratio  
   predicted/received - 0.91-1.38 Dose ratio

2. Eary- Med Phys ‘94  
   Percent error - 0.7- 28.6 in lung dose

3. Clark City of Hope- Med Phys ‘99  
   Concordance levels - 0.6 - 0.99

4. Macey IFN breast Ca,  
   Percent change residence time in blood & WB diagnostic to Rx dose = 7-25%
Multi-institutional Comparison of Bone Marrow Dosimetry

Results – 06-11-01

<table>
<thead>
<tr>
<th>Reporting Center Value</th>
<th>No. of Patients</th>
<th>Ratio (Institution/Task Group Value)</th>
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<tbody>
<tr>
<td>Institution A</td>
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<td>0.78</td>
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<tr>
<td>Institution B</td>
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<td>1.06</td>
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<td>Institution C</td>
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<td>Institution D</td>
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<td>Institution E</td>
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<td>Institution G</td>
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<tr>
<td>Institution F</td>
<td>2</td>
<td>0.86</td>
</tr>
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</table>

Average Ratio = $0.88 \pm 0.06$ (S.E.)
Arguments For and Against Patient Specific Dosimetry Protocols in the General Clinical Setting

Advantages:

- Provide a quantitative description of individual patient pharmacokinetics.
- Allow individual estimation of radiation dose to target and normal tissues.
- Provides the prospect for optimized delivery of the desired therapeutic radiation dose while minimizing toxicity.
- Allow predictions re hospitalization required.
Arguments For and Against Patient Specific Dosimetry Protocols in the General Clinical Setting

Disadvantages:

- Complexity of quantitative procedures.
- Time and cost.
- Inconvenience to the patient.
- Inherent components of error.
- Difficulty in transporting between institutions as a universal technique.
Potential Utility of Patient Specific Dosimetry in the Evaluation of Radionuclide Therapy

- **Treatment Planning**: To predict dose, minimize toxicity, increase safety for patients who may have widely differing pharmacokinetics and clinical status.

- **Follow-up Evaluation**: To obtain a better understanding of patient outcome and enable an informed decision on future therapeutic action.

- **Dose-Response Relationships**: To elucidate the relationship between absorbed dose and response.
Which Route to Go?

The Challenge Ahead ....


1. As long as simpler empirical methods provide safe and effective treatment, they should be considered valid.

2. For those who would like to claim that patient specific dosimetry methods are superior, it is necessary to demonstrate that the frequency of excess toxicities and/or target tissue under-treatment are significantly lower when treating at the MTD with each approach.