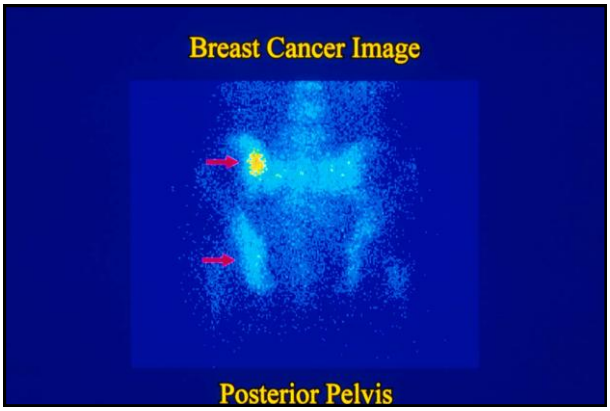
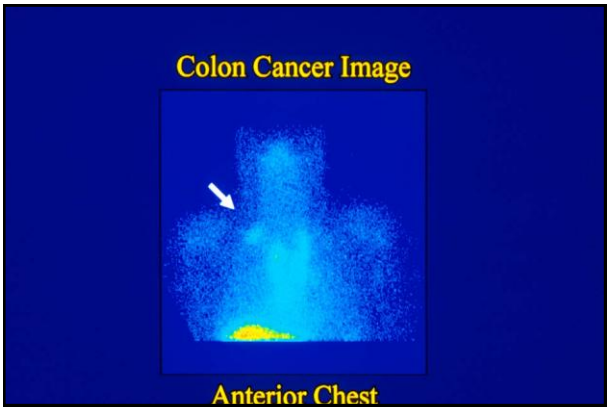
Dose Estimation for Internal Emitters

Lawrence E. Williams
City of Hope
Duarte CA
lwilliams@coh.org





FDA-approved internal emitter therapies

- SIR Spheres (plastic c ^{90}Y) for liver mets.
- Theraspheres (glass c ^{90}Y) for hepatoma.

These agents rely on catheter placement. Use ^{99m}Tc- MAA to define lung accumulation and toxicity. AAPM Task group 144 is reviewing these protocols.

- Bexxar Tositumomab (^{131}I) for B-Cell Lymphoma.
- Zevalin Ibritumomab (^{90}Y) for B-Cell Lymphoma.

These agents are injected IV and circulate.

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 from external beam work

Organ	**TD 5% complications/5 yrs**	**TD 50% /5 yrs**
Liver	30 Gy	40 Gy
Kidney	23 Gy (whole organ)	28 Gy(whole organ)
Bone marrow	? 1.5 Gy Acute Effects	? 2.0 Gy

Emami et al Int. J. Rad. Oncol. Biol. Phys. 21: 109-122, 1991

Tumor doses achieved via iv injection

Agent	Disease	Tumor	RM	Liver
Zevalin	NHL	1484 cGy (61 – 24000)	71 cGy (18 – 221)	532 cGy (234 – 1856)
Anti-CEA	Colon	1320 (46- 6400)	64 (19 – 198)	912 (534 –1719)

Note similarity of values for each tissue. Both antibodies c ^{90}Y

Outline of Dose Estimation

1. Canonical Dose Estimation Formula $D = S \cdot \tilde{A}$
2. Determination of Activity in the patient: A(t)
   a. There are at least six methods
   b. What are the uncertainties in A?
3. Integration of A to form $\tilde{A}$
   a. Various Models
   b. Other methods
4. Changes in S due to target mass variability
5. Uncertainties in dose due to A, $\tilde{A}$, and S variations

The Canonical Form of internal emitter dose estimation: $D = S \cdot \tilde{A}$

- Where **S** contains the spatial efficiency of energy deposition in the target mass given the source's emissions and location. $\tilde{A}$ is the total number of source decays (MBq-sec). It is the integral of the source activity curve.
- 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 target mass depends on time (t). Then, one uses $dD/dt = S(t) \cdot A(t)$. This effect has been seen in lymphoma therapy at Lund U., UC. Davis and U. of Michigan.

For radiation effects, is dose(D) the final answer?

- Because of biological results, a QF (quality factor) may be multiplied by dose (gray) values to yield a result in sieverts. Alpha rays are an example with QF = 20 compared to photons or beta rays.
- 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 .
- Biological Effective Dose (BED) = $\alpha D + \beta D^2$,where α and β are organ and tumor dependent, may be more important then dose (D) in therapy and toxicity.

Internal emitter dose estimation in three steps

1. Determination of activity (A) in tissues of interest at various times (t). Many methods, moderately difficult.
2. Integration of A(t) out to long times ($t \rightarrow \infty$?) to form $\tilde{A}$. Various techniques and relatively simple.
3. Converting $\tilde{A}$ to dose (D) via the matrix transformation $D = S \cdot \tilde{A}$. Straightforward except that S may need to be very different from OLINDA or MIRD standard phantom values. If uncorrected, S can be in error by factors of two to three-fold. Use CT or MRI data to make corrections.

Dose is estimated; what are the uncertainties in the estimates?

- Uncertainty in the A measurement
- Variability in integration of A to form $\tilde{A}$
- Errors in target organ mass and geometry determination (S)

- We will discuss these in the order given. Target organ mass uncertainty can be the largest source of dose estimation error if organ mass is unknown

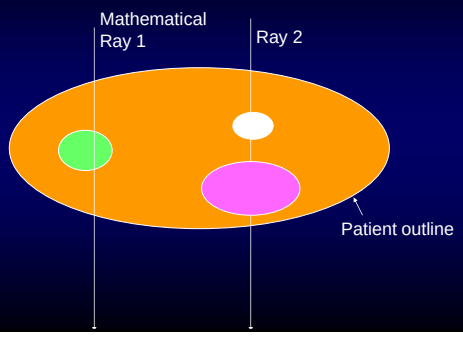
Step 1: Finding A or "The Problem" of Nuclear Medicine

- After 50 or more years, there is no standard technique to estimate activity (A) at-depth in a patient or animal. Multiple methods have been used. A typical clinical study will probably require a combination of techniques over the 1 to 10 day period allocated. Measurements are generally unique so that error estimates are not easily done and are often unknown.

Step 1: There are at least six methods for determining organ activity (A).

- Direct sampling of blood, surgical and excreta
- Probe counts of surface lesions or whole body
- Geometric Mean (GM) of two opposed views
- CAMI method using CT and whole body images
- Quantitative SPECT (QSPECT) from fused or hybrid (nuclear/CT) scanning
- PET or PET/CT imaging with quantitative SUV results

The Nuclear Medicine Imaging Situation



Methods to determine A are **not** mutually exclusive!

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

- Blood Sampling
- GM of whole body (WB) images
- Quantitative SPECT (QSPECT) Hybrid Scanner or Image Fusion). This is beginning to be a commercial option

Determining A method I: Direct sampling of blood (or tissues) using well counters

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

Bone marrow dose estimation

- Ã (rm→ rm) = f * Ã (blood) * 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 Immunoconj and Radiopharm. 3 213-233 1990 and Sgouros J. Nucl. Med. 34: 689-694 1993.

Determining Activity Method II: Single probe counting

- May be used on essentially external sites such as thyroid, lymph node, melanoma, or sarcoid tissue
- Attenuation and backscatter corrections probably not needed but can be tested. Fix geometry over time.
- Inverse square law needed for efficiency correction
- May be used for whole body clearance; position the patient in the same geometry for such measurements
- Counting standard is required

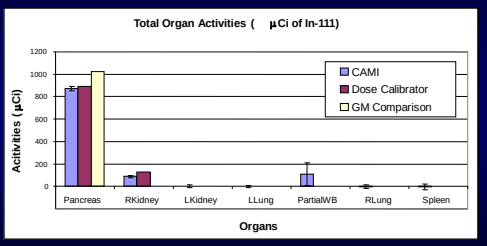
Determining Activity Method III: Geometric mean (GM) imaging

- 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)

Determining Activity Method IV: CAMI (CT assisted matrix inversion)

- Uses CT (or MRI) 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)

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



Determining Activity Method V: Quantitative SPECT

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

Commercial hybrid (SPECT/CT) systems

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

- An optimal partial volume correction is not available
- CT Images may be inferior to stand-alone CT
- Organ Motion between CT and SPECT

Several of the research groups involved in quantitative SPECT (QSPECT)

- Johns Hopkins University
- Lund University (Sweden)
- U of Michigan
- U of Massachusetts

QSPECT results for Hawkeye I

	Collimator	Type
Organ	MEGP	MEGPII
Liver	- 6 % error	- 4 % error
Kidney	- 11 %	- 14 %
Lungs (R,L)	-7, -6 %	-3, -3 %
Average	- 7.5 %	- 6 %

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

Determining Activity Method VI: PET/CT using SUV values

Advantages

- SUV should give an accurate result.
- No collimator required – hence 100-fold higher efficiency compared to gamma camera and SPECT/CT.

Disadvantages

- In practice multiple SUV values are cited. Which one is best for A(t)?
- What radiolabel?
- ^{18}F has a 110 m half life.
- ^{124}I has 100 h, but only 23% emission of 511 keV
- ^{64}Cu is 12 h and 19%
- ^{86}Y is 14.7 h and 33%

Currently optimal method to determine Activity by Ken Koral

- Obtain whole-body GM images at all important time points - including t = 0. Required by radiologist for tumor discovery/assessment
- Add one QSPECT imaging session near the maximum uptake time point for the study
- Calibrate the whole-body GM data using the QSPECT results at that single overlapping time point.

Reprise of the talk so far

- Absorbed dose estimation is our objective. Dosimetry is not possible due to physical, ethical and cost reasons
- Absorbed Dose = S*Ã is the most common approach to the problem
- Many ways to find A and hence Ã
- Optimal method for activity measurement is probably QSPECT or CAMI (error in A = +/- 7%)

Step 2: Pharmacokinetic (PK) analysis to determine Ã given A(t)

1. We assume organ Activity A(t) is known using one or more of the six methods given above

2. Simple Model uses separate multiple-exponential fits to tumor, blood and other tissues. These represent eigenfunctions of the differential equations

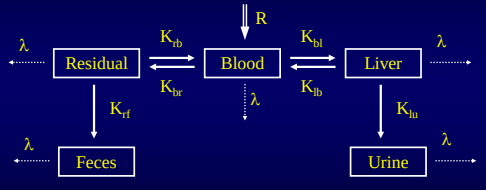
3. Multi-Compartmental model with connected organs. This process leads to the differential equations

4. Fit data as taken with radiodecay as model parameter

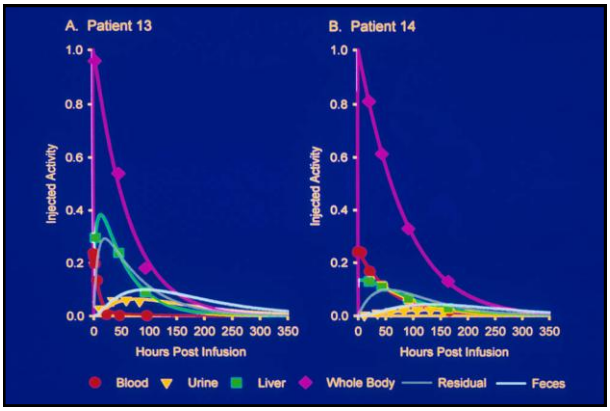
Reasons for Pharmacokinetic (PK) modeling

- Integration of A(t), via model parameters, to form Ã
- Determination of kinetic variables for animals and patients. Comparing such data. Patient sub-populations.
- Checking for incorrect data
- Converting from gamma emitter (image) label to the beta emitter (therapy) label. For example, going from ^{111}In-Antibody to ^{90}Y-Antibody

Five Compartment City of Hope Pharmacokinetic Human and Animal Data Model



Note that λ represents decay



Step 3: Methods to estimate S in the standard D = S*Ã dose equation

- 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 very local
- Complete Monte Carlo analysis. The eventual method of choice for a particular patient

Two types of internal emitter absorbed dose estimates in patients.

- Type I: Legal/Scientific: FDA regulations for Phase I Trial in patients. Here, an appropriate OLINDA or MIRD phantom is used for the S factor. Ã (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, Ã is used **directly** from the patient. Uptake may be non-uniform.

Two corrections to OLINDA estimations of absorbed dose.

- Correct Ã (animal or patient) to allow substitution into a standard phantom calculation. Type I estimate. This is the most common dose estimate.
- Correct S (OLINDA or MIRD) to allow patient-specific estimation of absorbed dose. Type II estimate; rarely done.

Lowest-order correction to patient activity for use in a standard OLINDA dose calculation.

$$\tilde{A}(PHAN) = \tilde{A}(pt) * \frac{m(PHAN)/M(PHAN)}{m(pt)/M(pt)}$$

where m is organ mass and M total body mass. PHAN refers to the phantom, 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 the original red marrow analysis.

Correction for organ S values in OLINDA to compute a patient-specific absorbed dose for non-penetrating (np) radiation

$$S_{np}(pt) = S_{np}(PHAN) \cdot m(PHAN)/ m(pt)$$

here, m refers to organ mass and np implies non-penetrating radiation such as beta or alpha rays. We assume no cross-organ doses due to short range of the particles.

Errors in S due to mass variation

- In a set of colorectal patients, we found variations up to 3-fold in patient spleen and liver sizes as compared to MIRD phantoms. In 14 kidney evaluations, errors were within a 1.5 factor.
- Some of this variation is physiological and some is due to disease state.
- CT or other anatomic imaging is required for accurate S values for major organ systems.

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.

Mass Variation in the S Matrix

- For therapy with particulate radionuclides such as ^{90}Y or ^{32}P, the S matrix is diagonal with terms depending on the inverse of the target organ mass.
- Logically, this follows from the definition of dose being energy deposited per gram of target tissue.
- Being in the denominator, makes S very sensitive to the mass of the target.

Evidence for BED in Clinical Data

- Renal toxicity in DOTATOC studies
- Reproduces the sigmoid curve of effect vs radiation when BED is the amount of radiation.
- Reflects external beam therapy practice. Here, BED is generally used to correct for changing the timing of treatments.

Summary of errors in absorbed dose estimates.

- The A value is uncertain to +/- 30% in GM. CAMI yields errors on the order of +/- 10%. QSPECT results are in development, but are in the range +/- 5% to +/- 7%. PET results should be comparable, but need appropriate labels
- Ã has an additional error of +/- 10% due to integration uncertainties. This is a topic that is not studied sufficiently.
- 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 $D = S \cdot \tilde{A}$ canonical form.

Future directions in absorbed dose estimation.

1. Both types (phantom and patient) of dose estimates will need to be made. The phantoms will change into more human-appearing forms in OLINDA The first kind of correction (to Ã **)** will continue to be used to convert animal or other data into phantom format.

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) . Dose-volume histograms will be developed.

3. BED will be computed in addition to the dose for the whole organ or the voxels of interest. Biological effective dose compared to clinical results.

4. For variable mass targets, the dose rate equation should be used with mass given as m(t). Total dose is then the integral of dose rate over time.

Some useful references for internal emitter dose estimation

- TRT: The Primer. AAPM Report No. 71, 2001.
- OLINDA: Stabin et al. JNM 46: 1023-1027, 2005.
- Bone Marrow Dose Estimates: Siegel et al. Antibod. Immunoconj. Radiopharm. 3: 213-233, 1990.
- GM: Thomas et al. Med. Phys. 3: 253-255, 1976.
- CAMI: Liu et al Med. Phys. 23: 1919-1928, 1996.
- QSPECT: Blankespoor et al IEEE Trans Nuc Sci 43: 2263-2274, 1996

Thank you for your attention!

- Lwilliams@coh.org