Determination of Dose to Individual Patients in Radionuclide Imaging Procedures including Planar, SPECT and PET

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Estimation of dose and not dosimetry

- Dosimetry is the **measurement** of absorbed dose in erg/g or Joules/kg. This isn't easily, ethically or economically done in living tissues. Thus, use of the term " dosimetry " is usually not appropriate in the context of nuclear medicine imaging or therapy
- Generally, we can only **estimate** the internal emitter dose to a patient. Our limitation is similar to that found in external beam work. "They don't do dosimetry either"

Outline

1. Dose Estimation Formula D = S*Ã
2. Determination of Activity in the patient: A(t)
   a. At least six methods
   b. Uncertainties in A
3. Integration of A to form Ã
   a. Various Models
   b. Other methods
4. Changes in S due to target mass variability
5. Uncertainties in dose due to A, Ã, and S variations

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

- Uncertainty in the A measurement
- Variability in integration of A to form Ã
- Errors in target organ mass and geometry determination (S)

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

For radiation effects, is dose (Gy) the only answer?

- A QF (quality factor) may be multiplied by dose (Gray) values to yield a result in Sieverts. Alpha rays
- If this is done, however, the estimator must show 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
- Time-dependent effects of dose are becoming a topic of some interest and may also be needed (α, β values)

The usual strategy of internal emitter dose estimation

Dose = **S** * $\tilde{A}$

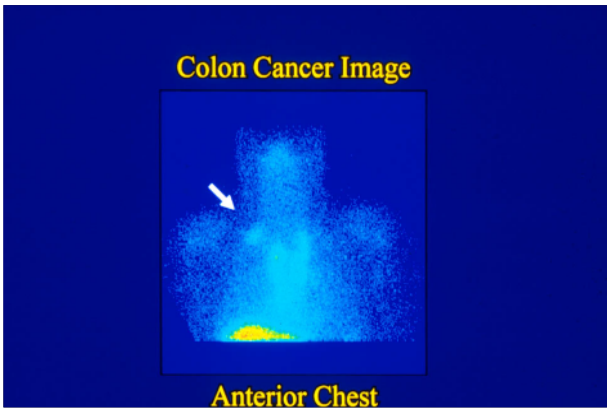
- Where **S** contains the spatial efficiency of energy deposition in the target mass given the source's emissions and location. $\tilde{A}$ is the total number of source decays (time effects).
- The formula is generally applied to whole organ sources and targets. It should hold down to cellular-sized systems.
- Space/ time dichotomy will not hold if target mass depends on time (t). In this case,

$$d D/dt = S*A$$

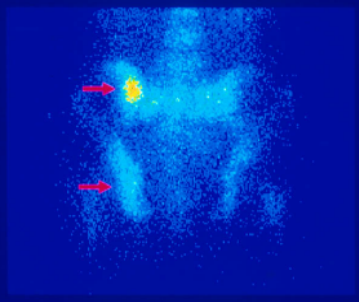
Where S is also time-dependent. This is more fundamental

Motivation for Patient-Specific Absorbed Dose Estimates

- Internal emitter therapy for malignant tissue
- Can treat primary and, in particular, metastatic disease
- Patient may have no other course of therapy when the tumor has gone to multiple metastatic sites
- Nanotechnology is used to provide multiple types of agents to target; liposomes, proteins, RNA, DNA and hybrids



Breast Cancer Image



Posterior Pelvis

Internal emitter dose estimation in three (not necessarily easy) 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 Ã. Various techniques
3. Least difficult (usually): Converting Ã to dose (D) via the matrix transformation D = **S** * Ã. However, **S** may need to be very different from OLINDA or MIRD standard phantom values. Use CT or MRI data to make corrections for specific patients.

Two clinical applications of internal emitter absorbed dose estimates

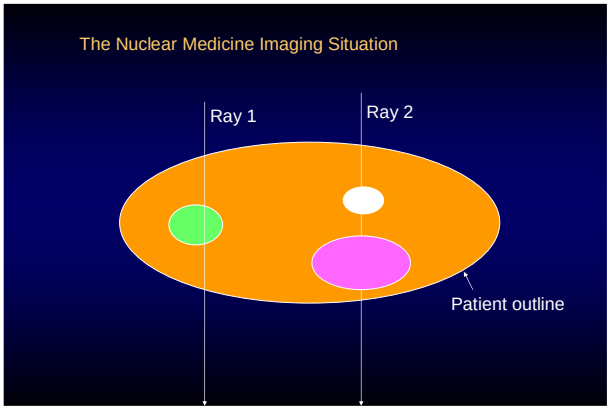
- Type I: Legal/Scientific: FDA regulations for Phase I Trial in patients. Here, an OLINDA or MIRD phantom is used for the S factor. Ã (from animals) is **adjusted** to suit phantom. Uniform uptake assumed in source. Dose refers to whole organ targets.
- Type II: Patient-Specific:Evaluate toxicity and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

"The Problem" of Nuclear Medicine

- After 50 or more years, there is no standard technique to estimate activity (A) in a patient. Multiple methods have been proposed and 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 of A are not easily done and are therefore often unknown.

Step 1: There are at least six methods for calculating patient 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



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 not yet a commercial option

Determining Activity 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 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.

A novel method to determine RM mass

- U of Florida predicts total spongiosa volume given whole body CT results vs only those in sacrum. Twenty cadavers used in the study; 10 of each sex.
- Accuracy was <10 % for 50 to 70 % of subjects
- Accuracy < 20 % for 70 to 90 % of subjects

- Pichardo et al in: JNM 48: 1880-1888, 2007.

Determining Activity Method II: Single probe counting

- May be used on essentially external sites such as thyroid, melanoma, or sarcoid tissue
- Attenuation and backscatter corrections probably not needed but can be tested
- 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

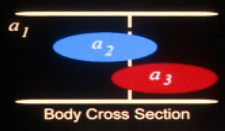
Determining Activity Method III: Geometric mean (GM) imaging

- 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)

CT Assisted Matrix Inversion Method (CAMI)



$$C_i = [\int_0^T a_i(x)\, B_i(x) e^{-\mu x}\, dx]\, CF$$

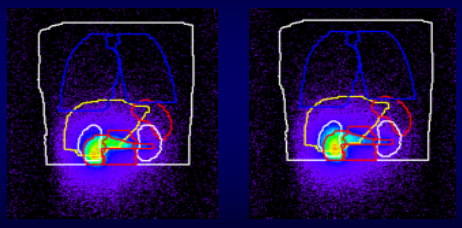
$$C_i \cong [\sum_{j=1}^{n} \overline{a_j}\, \overline{B_j} (\frac{e^{-\mu l_{1,j}} - e^{-\mu l_{2,j}}}{\mu})]\, CF$$

$$[C]^{N\times 1} = [H]^{N\times n}\, [a]^{n\times 1}$$

$$[a]^{n\times 1} = [H^{-1}]^{n\times N}\, [C]^{N\times 1}$$

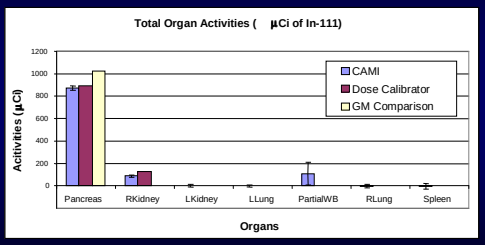
Where C_i is the counts recieved in pixel i. $B_i(x)$ is buildup factor. CF is camera calibration factor. n is the number of organs. $l_{1,j}$ and $l_{2,j}$ are the distances from the upper and lower boundary of the organ j to the body surface, respectively. N is the number of calculation points chosen.

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



Anterior Posterior(reversed)

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
- Commercial systems are becoming available
- Four sequential 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

- 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

Advantages

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

Disadvantages

- In practice multiple SUV values are cited. Which one is best for A(t)?
- ^{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 in tumor assay
- 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 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. Yet we may need the differential formula
- Many ways to find A and hence Ã
- Optimal method for activity quantitation is probably QSPECT and GM planar imaging (A error = +/- 7%)

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

1. We assume Activity (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

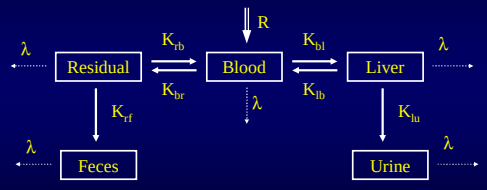
3. Multi-Compartmental model with connected organs. This process leads to the differential equations

4. Fit data as taken with radiodecay as model parameter

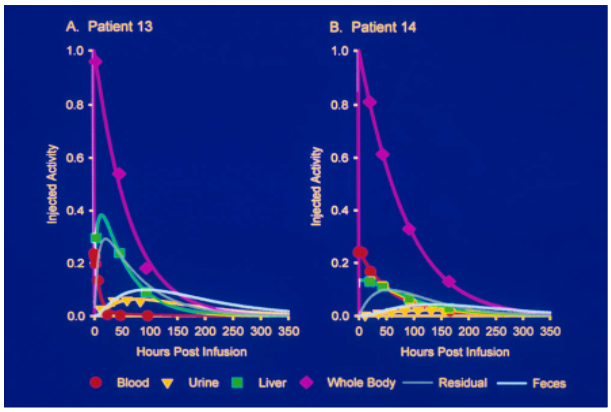
Reasons for Pharmacokinetic (PK) modeling

- 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 corrections to OLINDA estimations of absorbed dose.

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

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.

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

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.

Table of dose correction results

Absorbed Dose Type	S	Ã
I	correct	Change by m/M ratios
II	Change by m(PHAN)/m(pt)	correct

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 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

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%.
- 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* Ã formula

Future directions in absorbed dose estimation.

1. Both types of dose estimates will need to be made. The phantoms will change into more human-appearing forms in OLINDA The first kind of correction (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) .

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

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 references for internal emitter dose estimation

- RIT: 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!

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