Activity Quantitation and Dose Estimation from Nuclear Medicine Imaging.

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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

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 " dosimetry " is not appropriate in the context of radiation therapy.
- Generally, 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".

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 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 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 rays are the best example.
- 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 usual strategy of internal emitter dose estimation

Dose = **S** * Ã

- Where **S** contains the spatial efficiency of energy deposition in the target mass given the source's emissions and location. Ã 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). Effect seen in lymphoma therapy at Lund U., U. C. Davis and U. of Michigan.

Possible radionuclides of interest for internal emitter therapy

Nuclide	Beta (MeV)	Range	T1/2	Gamma (keV)
I-131	0.61 MeV	2.0 mm	8 days	360 (80%)
Y-90	2.27	11	2.7 d	None
Re-186	1.07	5	3.7 d	137 (9%)
Re-188	2.12	10	17 h	155 (15%)
Lu-177	0.50	2	6.7 d	113 (6%)
P-32	1.70	8	14 d	None
Sm-153	0.81	4	1.9 d	103 (29%)

Examples of tumor targeting agents

Agent	MW	Application	Label
MIBG	130 Da	Neuroendocrine	^{131}I
Antibody	20-150 kDa	lymphoma	^{90}Y
Antibody	"	solid tumors	^{90}Y
SHALs	2 kDa	lymphoma	^{131}I
Nucleotides	10 kDa	solid tumors	^{99m}Tc
Spheres	30 µM	Hepatic	^{90}Y

Uptakes anticipated in mouse or human biodistribution

Assume 100% of the injected dose (ID) were **uniformly** distributed in a 20 g mouse, normal organ or tumor " tracer density" or uptake would be:

100 %ID/20 g = 5 % ID/g (mouse)

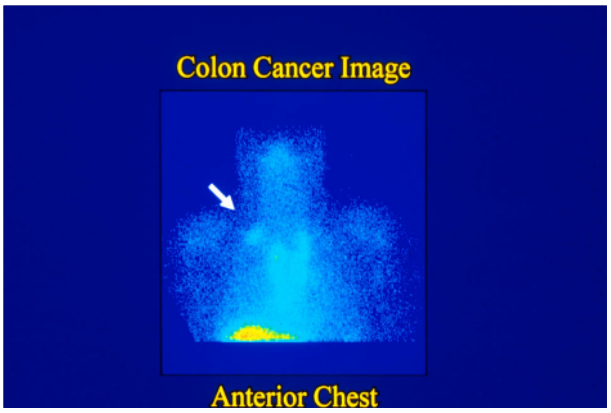
Note that we have corrected for label radiodecay. A similar result occurs for the adult patient with a denominator of 70 kg:

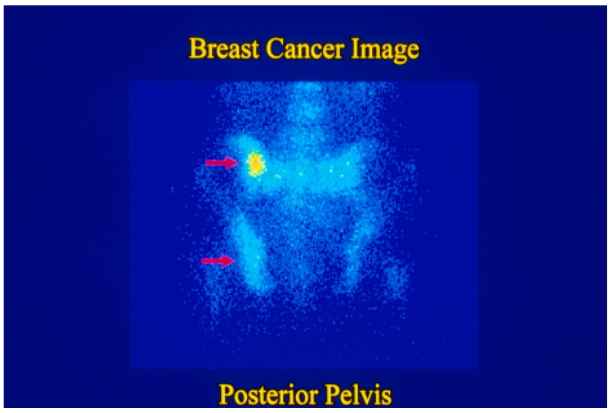
1.4 %ID/ kg (human)

If we can exceed these values for tumors, we have evidence of targeting. Radiation dose rate is proportional to uptake values.

Biodistribution motivation for internal emitter cancer therapy

- ^{67}Ga Citrate; non-specific, 6% ID/g in mouse tumors. This result is not too encouraging for Rx.
- Liposomes; non-specific, 30% ID/g in mouse tumor.
- Antibodies; specific, 60% ID/g in mouse tumor.
- Predicted Human Tumor Uptake ≅ 20% ID/kg.
- Absorbed dose rate(α or β emitter) is proportional to %ID/g in tumor (or tissue).





Proteins are the poster children for specific tumor-targeting agents

- Specific to the tumor-associated antigen
- Can be labeled with different radionuclides
- Engineered for molecular weight
- Engineered to be human-like
- Mono or multi-valent.

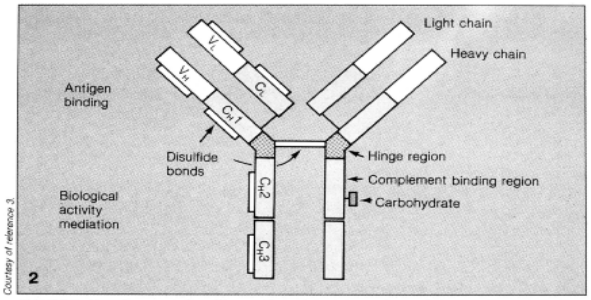
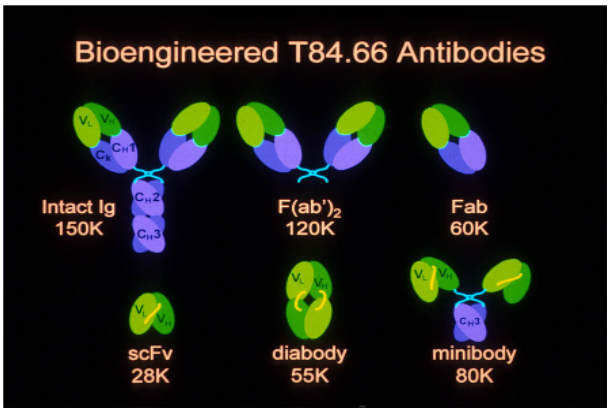


FIGURE 2. **Structure of IgG antibody. V_L and V_H denote the variable regions of the light and heavy chains. C_L and C_H denote the constant regions of the light and heavy chains.**



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.

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

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

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 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 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. 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.

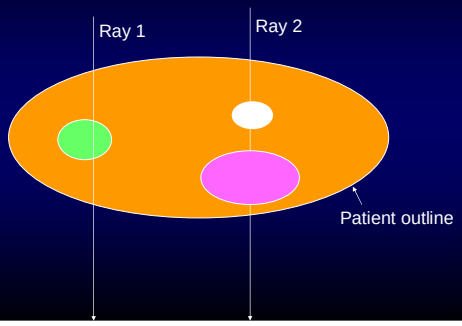
"The Problem" of Nuclear Medicine

- 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. Error estimates are not easily done and are often unknown.

Step 1: There are at least six methods for calculating patient activity (A).

- Blood, surgical and excreta direct sampling
- Probe counts of surface lesions or whole body
- Geometric Mean (GM) of two opposed views
- CAMI method
- 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, 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 (QSPECT) Hybrid Scanner or Image Fusion). This is not quite a commercial option

Direct sampling of blood (or tissues).

- Blood values needed for bone marrow dose estimates.
- Blood curve kinetics also gives 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.
- 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.

One 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.

Single probe counting

- May be used on essential external sites such as melanoma, sarcoid or thyroid tissues.
- 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.
- Counting standard is required.

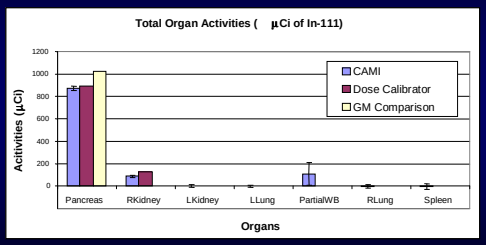
Geometric mean (GM) imaging

- 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).

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).

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



Quantitative SPECT

- Requires CT (MRI) anatomic data to correct for attenuation and other factors
- 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

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

PET/CT scanning to determine A

Advantages

- SUV should (!) give an accurate result.
- No collimator required – hence 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%

Probable optimal method to determine A by Ken Koral

- Obtain whole-body images at all important time points - including t = 0. Required by radiologist.
- Add one QSPECT imaging session near the maximum uptake time point (24 – 48 h for intact antibodies).
- Calibrate the whole-body GM data using the QSPECT results at the overlapping time point.

Reprise of the talk so far

- Motivation for targeted therapy of tumors due to a large number of novel agents – esp. proteins
- Targeting is proven if uptake > uniform value 10X increase seen in engineered agents
- Dose = S*Ã
- Many ways to find A and hence Ã
- Optimal method for activity quantitation is QSPECT and planar imaging (A error = +/- 7%)

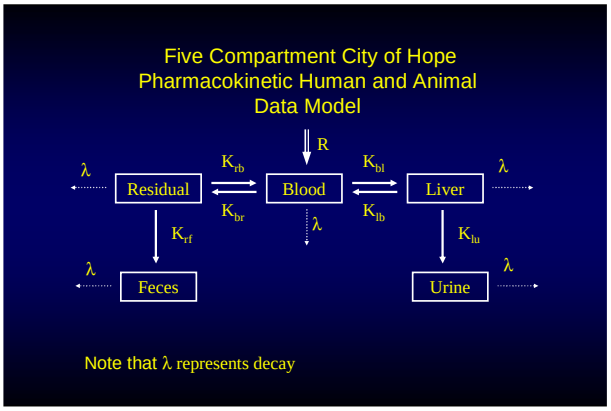
Step 2: Pharmacokinetic (PK) analysis to determine Ã given A(t).

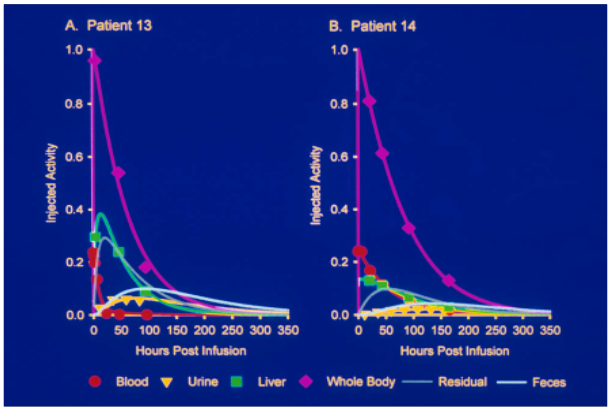
1. Simple Model uses separate multiple-exponential fits to tumor, blood and other tissues. These represent eigenfunctions of the differential equations.

2. Multi-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 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.





Step 3: Methods to determine S in the absorbed Dose (D = S*Ã) 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 local.
- Complete Monte Carlo analysis; no use of S (!).

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 estimate.
- Correct S (OLINDA or MIRD) to allow patient-specific estimation of absorbed dose. Type II estimate; rarely done.

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	$\tilde{A}$
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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Comparison of Two RIT Protocols.

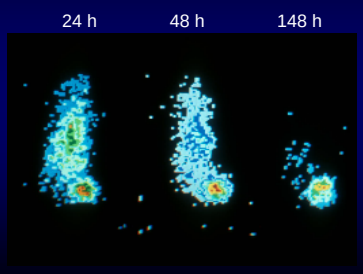
CD20 + NHL.
- Zevalin c Y-90

- Tumor: Not given
- Liver: 17 cGy/mCi
- Spleen: 27 cGy/mCi
- Red Marrow: 2.4 cGy/mCi

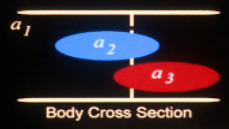
CEA + Solid Tumors.
- cT84.66 c Y-90. Protocols 91064 and 91169.

- Tumor: 25 cGy/mCi
- Liver: 27 cGy/mCi
- Red Marrow: 3.1 cGy/mCi

Other Data of Interest to the FDA: Imaging Proof of Targeting; Nude Mouse Model with LS174T Human Colon Tumor. VFC with 2μCi Co-57.



CT Assisted Matrix Inversion Method (CAMI)



Body Cross Section

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

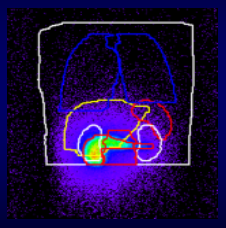
$$C_i \cong [\sum_{j=1}^{n} \overline{a_j}\, \overline{B_j}\, (\frac{e^{-\mu l_{1,j}} - e^{-\mu l_{2,j}}}{\mu})]\, CF$$

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

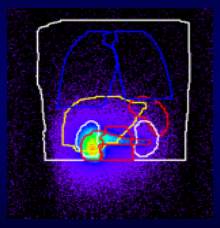
$$[a]^{n\times 1} = [H^{-1}]^{n\times N}\, [C]^{N\times 1}$$

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)