ADVANCED PHYSICS AND DOSIMETRY TOPICS

CE SESSION: PHYSICS REQUIREMENTS FOR IMPLEMENTING A RADIOPHARMACEUTICAL THERAPY (RPT) PROGRAM

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AAPM/COMP Annual Meeting, July 15th 2020

Disclosure: Consultant for Radiopharmaceutical Imaging and Dosimetry, LLC (RAPID)

RPT AT AAPM

- Resurgence of interest led to creation of Ad Hoc Committee for Radionuclide Therapy
- Awaiting decision on placement for permanent Committee
- Focus on Guidelines and Education
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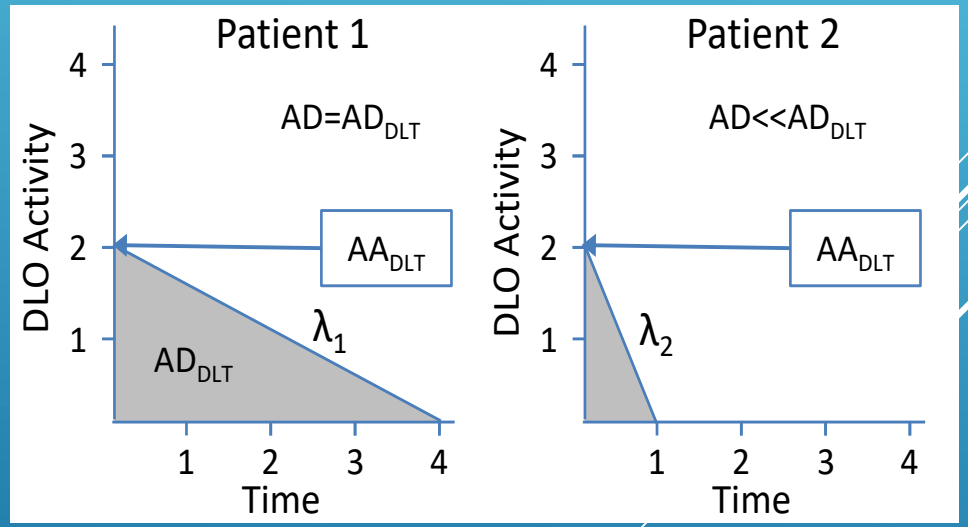
OUTLINE

1. Introduction
    a. Motivation for dosimetry-based approach
    b. Feasability
    c. Uses for dosimetry [1]
2. Dosimetry Methodologies
    a. Absorbed Fraction (MIRD) method
    b. Voxelized (Dose rate-based) method
3. Radiobiology
    a. BED
    b. External beam equivalence
4. Targeted Alpha Therapy [2]

SAM Questions:

NORMAL ORGAN AD-BASED TREATMENT PLANNING FOR RPT

- Standard is the chemotherapy paradigm of dose escalation
- AA limit is set by patients with maximum retention
- BUT great inter-patient variability – Xbeam is limited by NO toxicity
- RPT is radiation just as Xbeam



PRINCIPLES OF AD-BASED TREATMENT PLANNING FOR RPT

- Pre-therapeutic activity (possibly a surrogate) is administered (~ 5 mCi), SPECT or PET images measure pharmacokinetics
- Account for change in isotope HL (Ga-68//Lu-177)
- Calculate dose to organs per unit activity
- Scale to Organ MTD and obtain administered therapeutic activity
- AAPM, SNMMI, ASTRO, IAEA, NCI advocates

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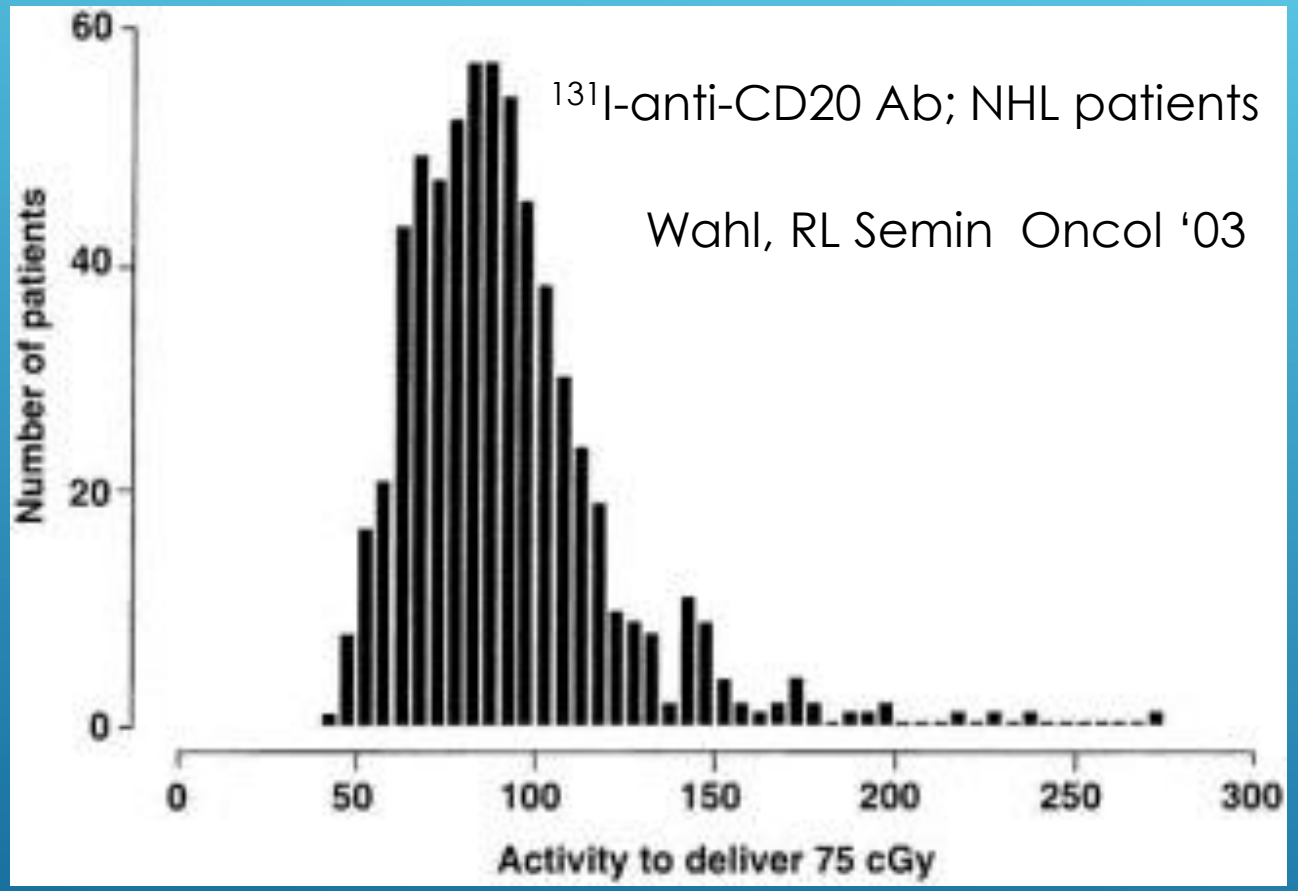
Admin Activity (AA) vs Abs Dose



Example of patient variability

Previously demonstrated that 75 cGy to WB increases RM toxicity

Increasing database shows consistent large disparities in NO dose up to an order of magnitude

OTHER REASONS TO DO DOSIMETRY

Retrospective dose-effect correlations – tumor dosimetry (Garin Y-90, Jentzen I-131, Strigari PRRT)

Database of activity – OAR dose

Dose Reporting

Equivalence for EBRT therapy – Radiobiology – Rational Combination Therapy

DOSIMETRY BASICS

2 methods

1. Activity-based with phantom derived S values ("MIRD method")

2. "Voxelized" Dose rate-based using Monte Carlo and patient-specific anatomy (gold standard)

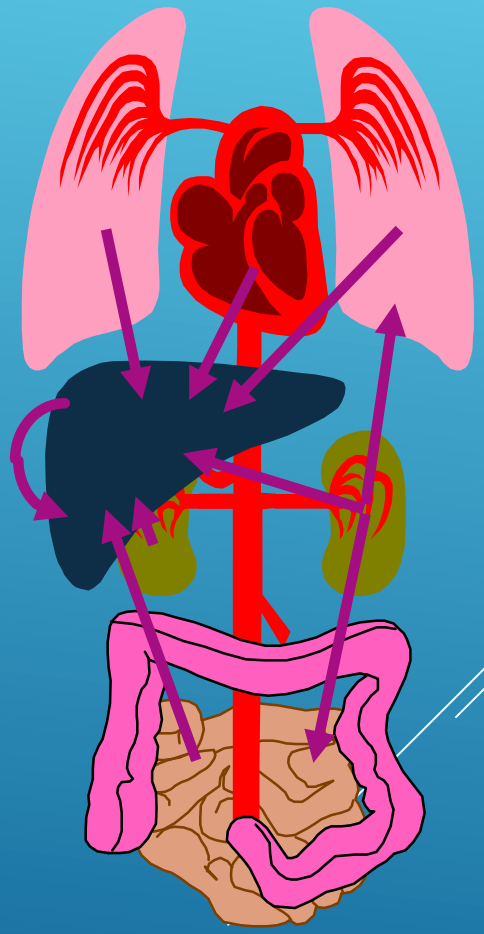
Both 'require' multiple time point 3D in vivo emission and transmission images (SPECT/CT or PET/CT), therefore depend on accurate activity quantification, registration, and segmentation, choice of time points for dose rate or activity integration

DOSIMETRY – ABSORBED FRACTION

Absorbed Dose: Energy (damage) absorbed per unit mass. Unit: Gy

$$\frac{\text{Number of disintegrations} \times \text{Energy released per dis.} \times \text{Fraction that is absorbed}}{M_t}$$

Assumes uniform activity in source region – gives average AD in target region



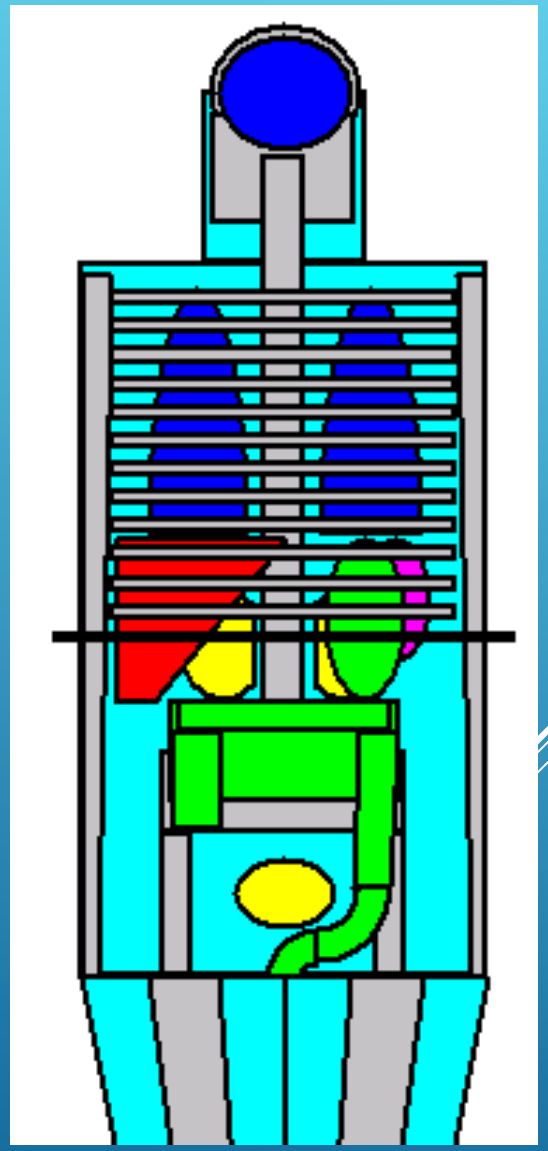
S values

Absorbed fraction methodology uses MIRD S values[a] determined from idealized geometrical model (no tumors) and Monte Carlo

$$\frac{\tilde{A}_S \times \Delta \times \phi_{t \leftarrow s}}{M_t}$$

S value

OLINDA/EXM[b] is a widely used software which uses S values, requires only TIA

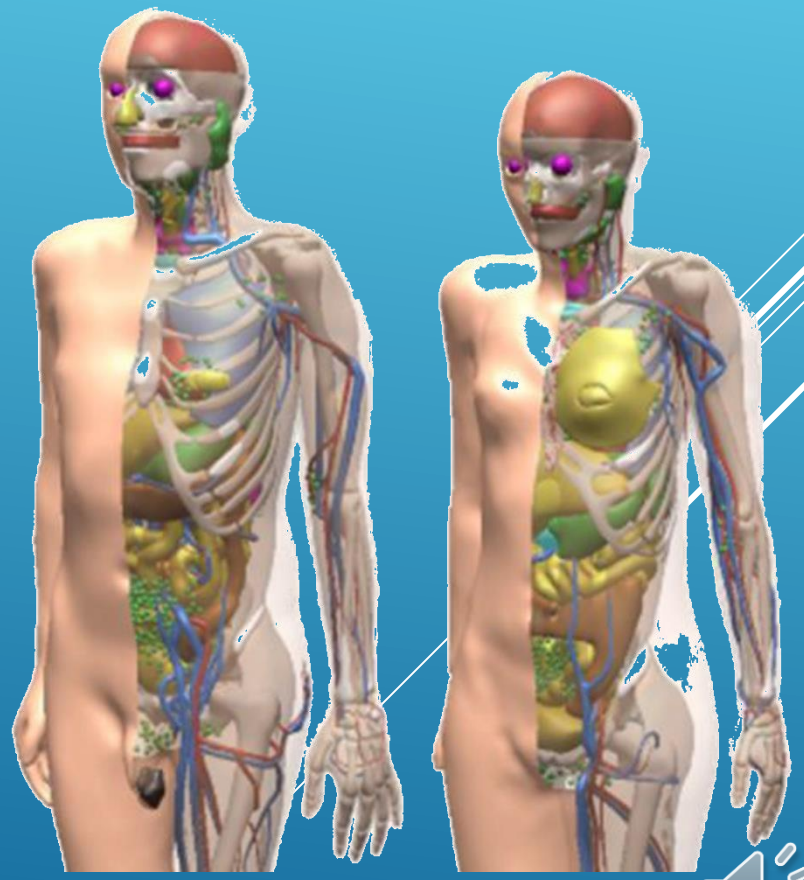


[a] MIRD Pamphlet #11
[b] Stabin *et al.* JNM '05

“Organ” S Value Method

- For a given radioisotope, how much decay energy is transmitted (on average) from organ A to organ B (“s-value”)
- Matrix of time-integrated activities multiplied against s-value matrix to obtain average dose for each organ

Method is more than organ only
Phantoms have become more realistic (splines, mesh, voxelized)



Time-integrated activity (“Residence Time”)*

Energy transfer matrix (“s-values”)

$$[R_A \quad R_B \quad R_C \quad \dots R_n] * \begin{bmatrix} S_{A\to A} & S_{A\to B} & S_{A\to C} \\ S_{B\to A} & S_{B\to B} & S_{B\to C} \\ S_{C\to A} & S_{C\to B} & S_{C\to C} \\ \dots & \dots & \dots \\ S_{n\to A} & S_{n\to B} & S_{n\to C} \end{bmatrix} = [\overline{D}_A \quad \overline{D}_B \quad \overline{D}_C]$$

Mean organ doses

*Time integrated activity coefficient

TIME-INTEGRATED ACTIVITY*

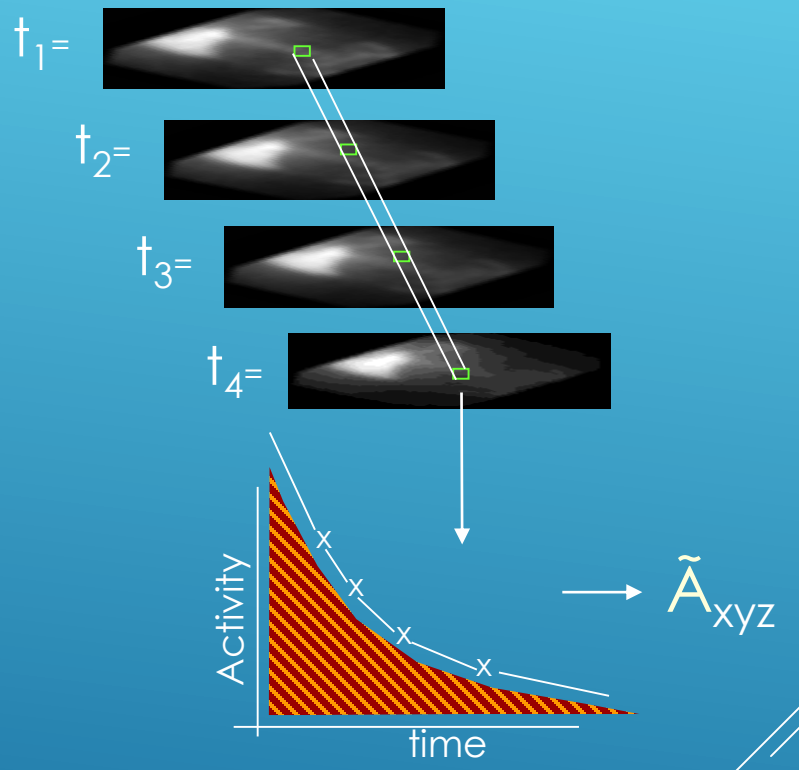
Pre-therapeutic activity images

(1). planar, use anterior – posterior methodology [a]

Involves background subtraction (artistic), technical problems of scatter and attenuation only poorly corrected - very high uncertainty, whole organ only.

2. SPECT or PET, 3 – dimensional images enable better reconstruction [b]

*(fka cumulated activity) [c]



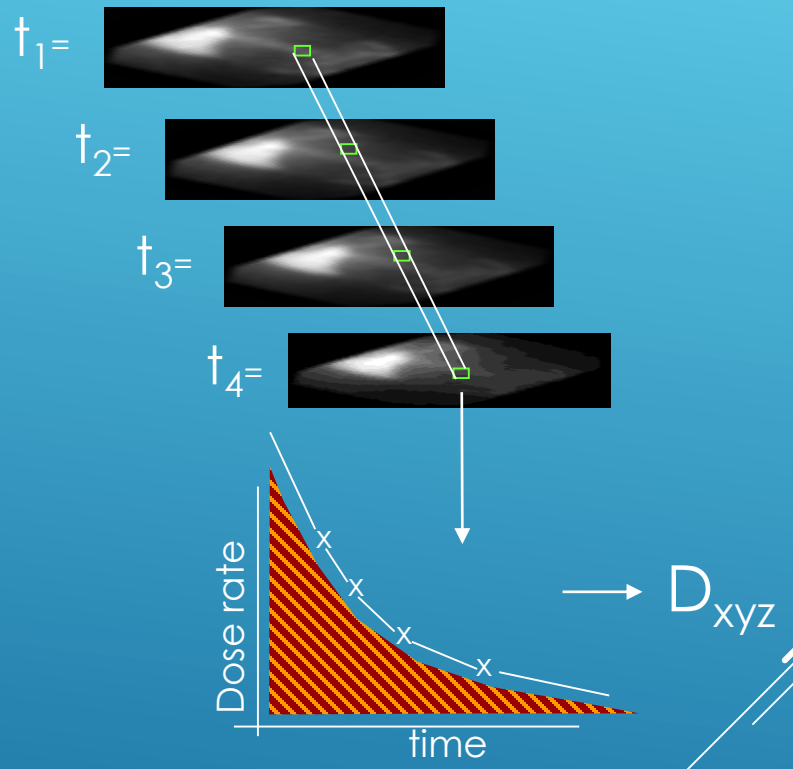
$$\tilde{A}(x,y,z) = \int_0^\infty A(x,y,z,t)dt$$

[a] MIRD #16 Siegel *et al*. JNM '99
[b] He *et al.* Phys Med Biol '05
[c] MIRD #21 Bolch *et al*. JNM '08

MONTE CARLO - DOSE RATE INTEGRATION

3-D dose rate images

$$D(x,y,z) = \int_0^{\infty} \dot{D}(x,y,z,t)dt$$

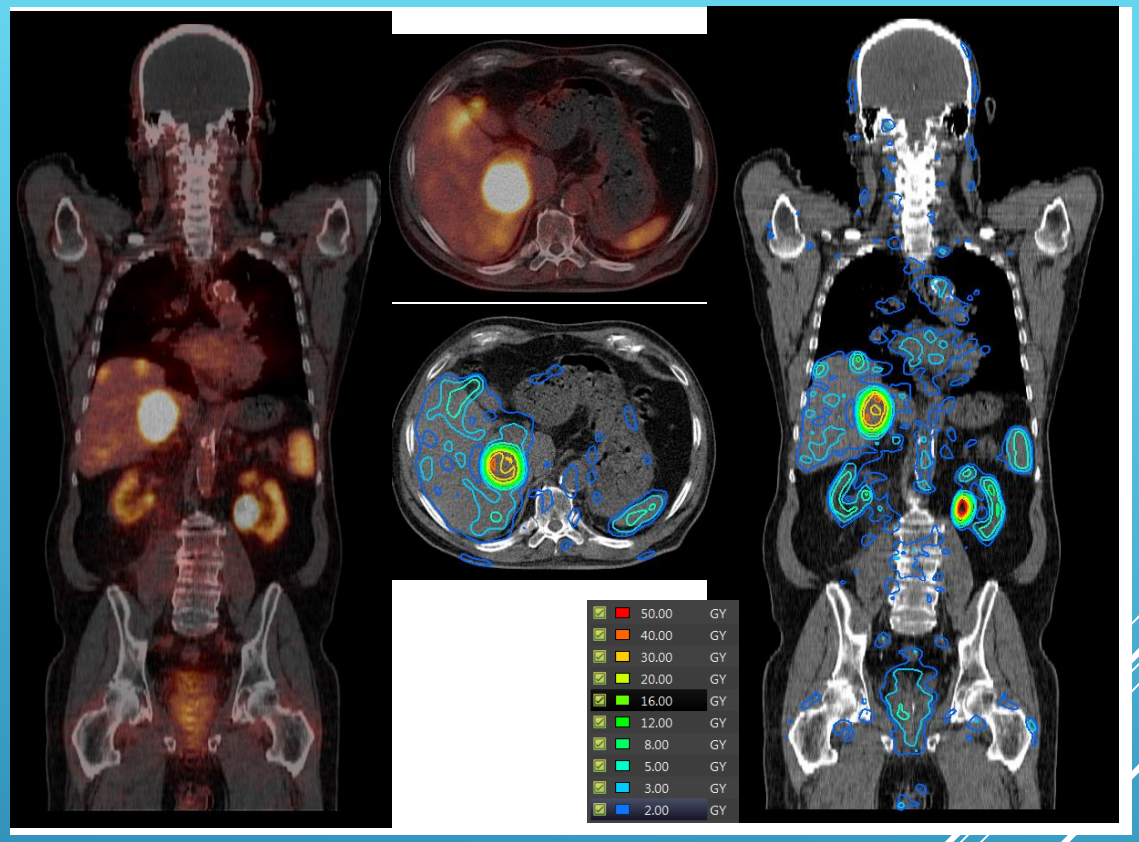


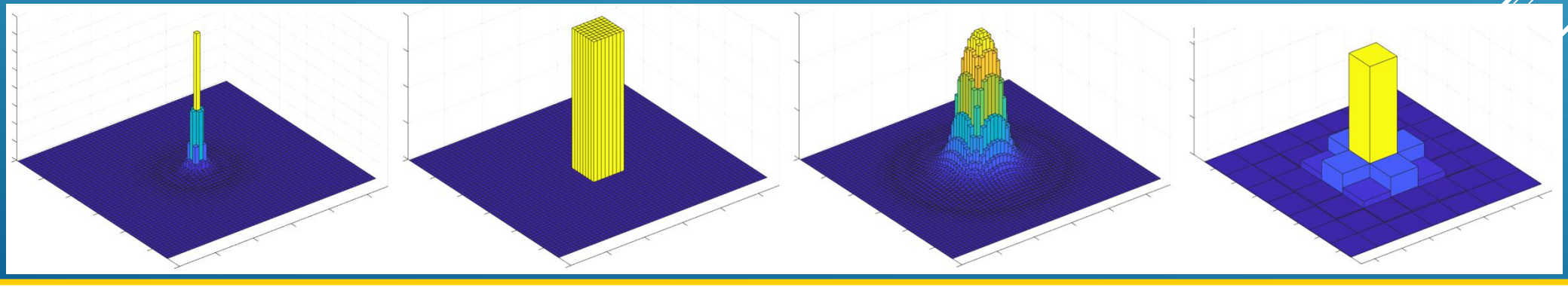
Advantages?

- No dependency on modelized anatomy.
- "**Voxelized**" results
- Tumor dosimetry

Kernel Convolution

1. Generate an energy deposition kernel for a specific isotope
2. Convolve it with an activity map
3. Result is a dose-rate map
4. Register dose-rate maps across multiple time-points and integrate D(t) for each voxel





PROGRESSION OF QUANTITIES

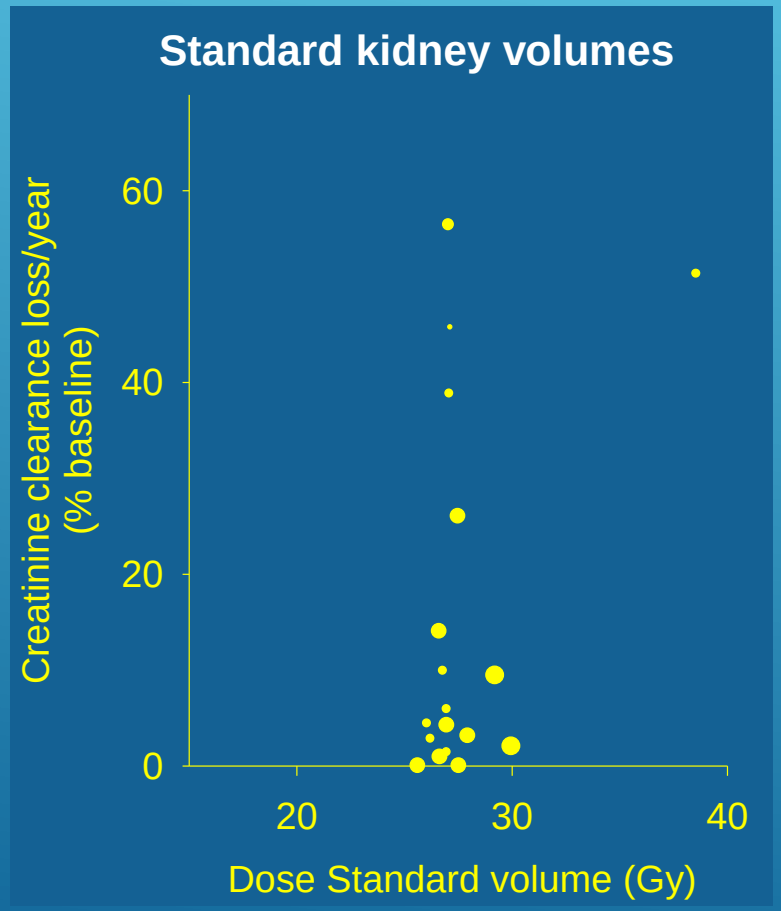
Dose – still very little biology, using patient pharmacokinetics. No genetics, no immune response assessment, physical quantity

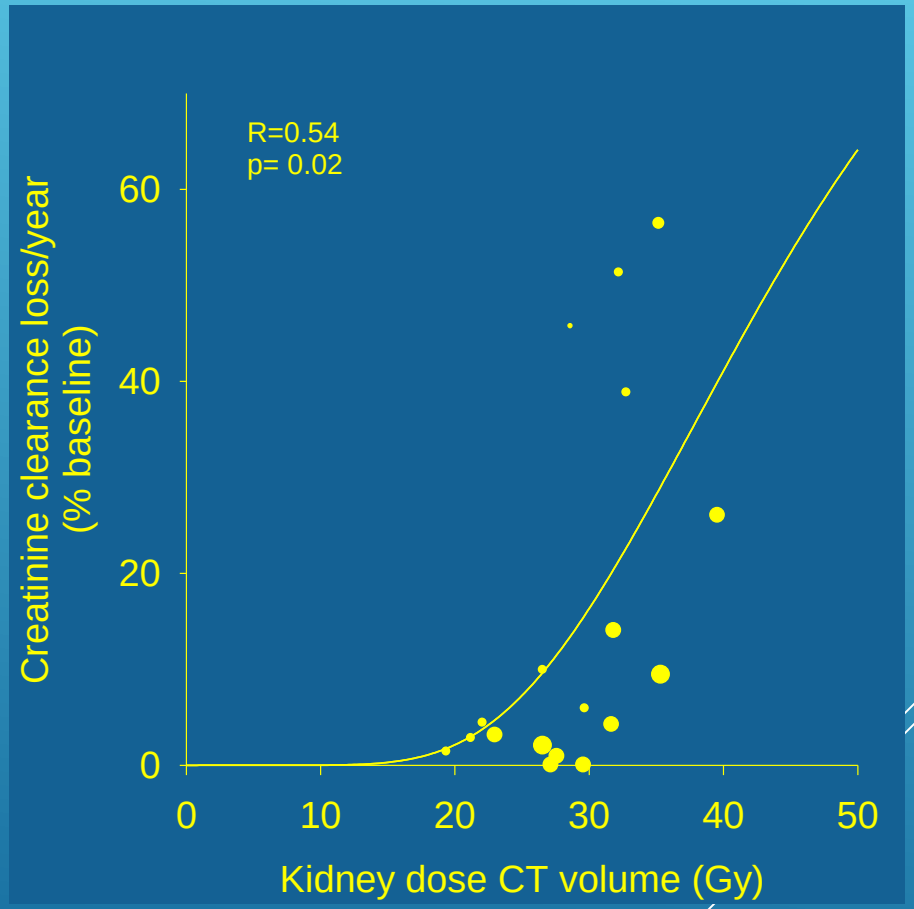
Standardized Dose – BED or EQD2 – Doses vary from one patient to another within the same modality; **for comparison to external beam, EQD2 is needed**

Variations between modalities… (Y-90 microspheres S. Walrand) or combination therapies

Patient PK and BED – dose standardization

Correlation between kidney dose (Gy) and creatinine clearance loss/year (% baseline) N=18

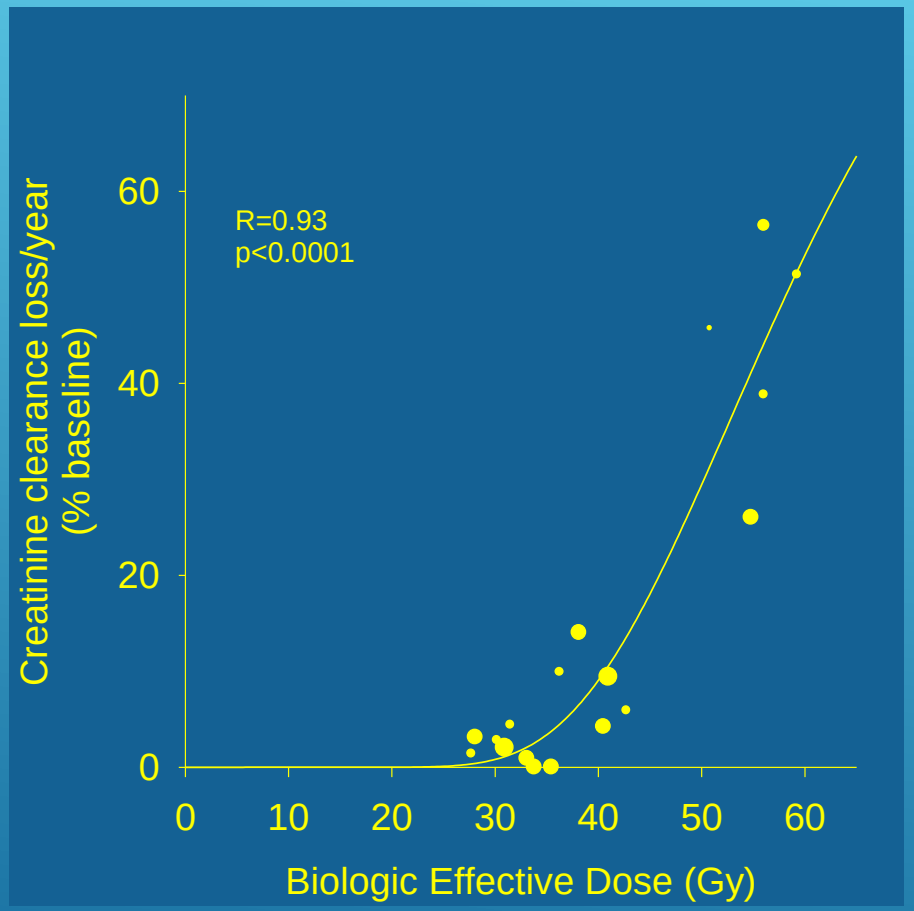




Barone, et al. JNM '05

UNIVERSITE CATHOLIQUE DE LOUVAIN

Correlation between BED and creatinine clearance loss/year



Barone R, Borson-Chazot F, Valkema R, et al. J Nucl Med. 2005 Jan;46 Suppl 1:99S-106S

MIRD 20

Results from Barone et al.

Compares to external beam response data translated to BED

Agreement

$$EQD2 = \frac{D_{RPT}\left(\alpha/\beta + D_{RPT} \cdot G_i(\infty)\right)}{\alpha/\beta + 2}$$

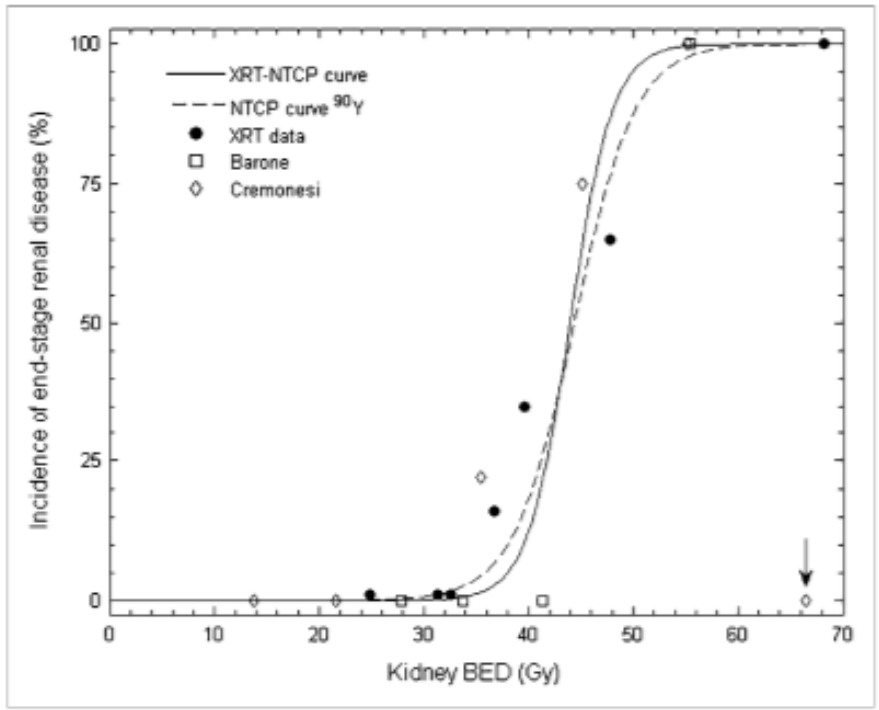


FIGURE 6. Dose–response curve for correlation between kidney BED and symptomatic radiation damage to kidneys for external-beam data, compared with ^{90}Y-DOTA-octreotide data.

DOSIMETRY IS MORE THAN AD

Dosimetry doesn't explain everything!

Other correlates exist!

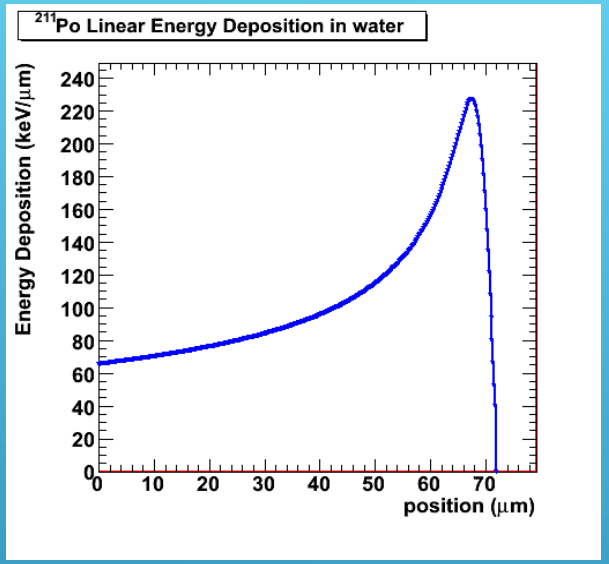
Dosimetry is more than calculation of absorbed dose, but whatever correlates exist, including the absorbed dose will only improve personalization of TP.

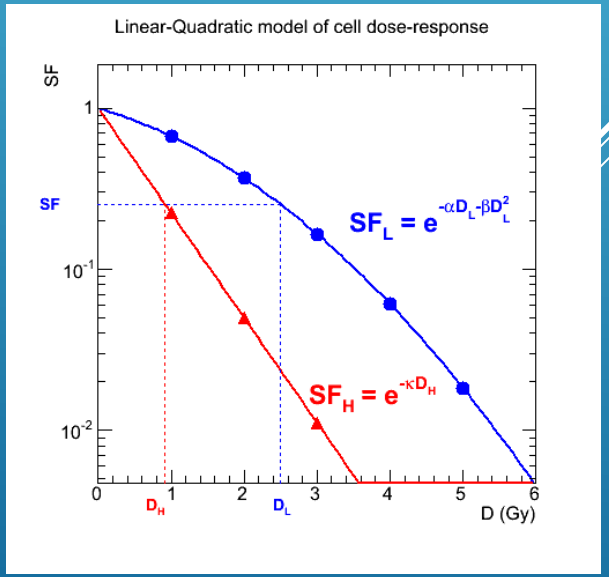
Dosimetry constantly becoming more sophisticated: PK models, small scale dosimetry, range of isotope, size and number of tumors, disseminated disease, orthogonal toxicities for combinations, different dose patterns or dose rates, RBE, dose non-uniformity

Radiobiology -> bioeffect modeling (BED, EUD)

4. α-particle RPT

- Alphas are 8000 more massive than electrons – plow through matter, more damaging
- High LET, more damage per unit of dose, different radiobiological effects (RBE)
- Short range, 50 - 100 μm, localized toxicity, scale smaller than most organs and tumors, only a few cell widths
- Ideal for micro-metastases – 2-3 hits for cell kill as opposed to thousands of EM tracks





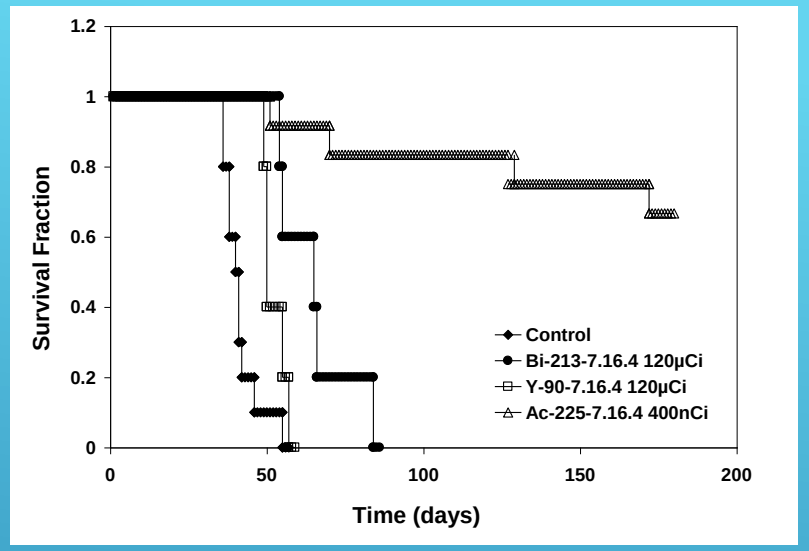
TAT DOSIMETRY

Traditional organ-level or voxelized dosimetry fails to adequately predict or interpret toxicity for targeted α-particle therapy.

Limited range of α-particles and localization of activity/dose below in vivo imaging resolution and organ FSU scale.

Example of ^{225}Ac-Ab targeting metastatic breast cancer in murine model

Calculated 2-3 Gy to kidneys (typical toxicity thresholds ~40 Gy BED or ~ 23 Gy EQD2)

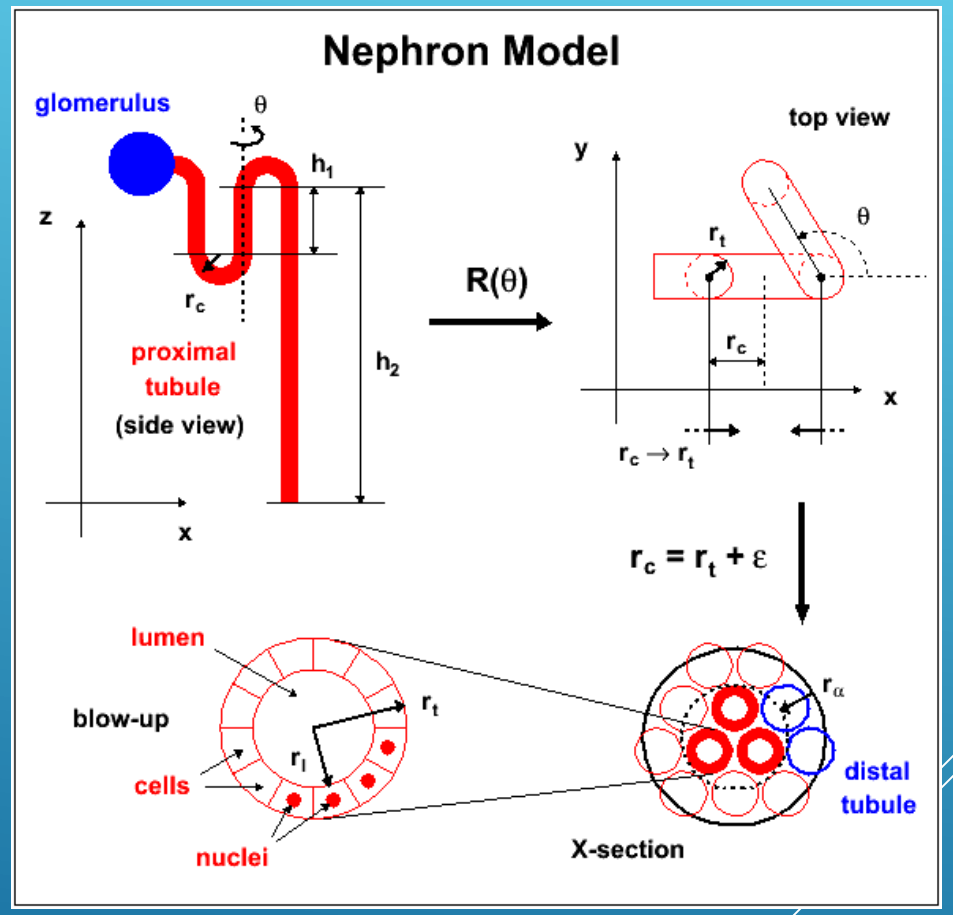


[a] Song *et al.* Clin Cancer Res '08
[b] Song *et al.* Cancer Res '09

NEPHRON MODEL

Use simple geometrical shapes (spheres, toroids cylinders) for S-values

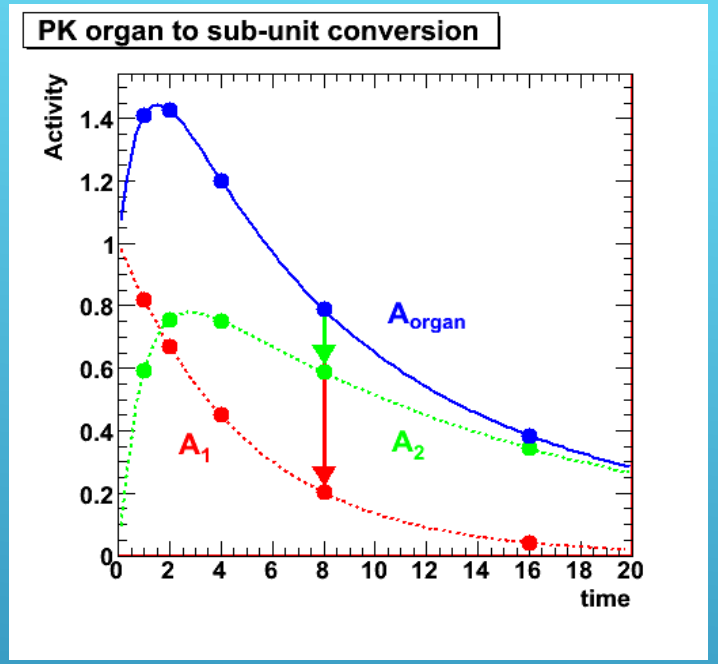
1. Fold tubules to simulate proximity
2. Discriminate between tubule cells (simple cuboidal epithelials) and lumina
3. Consider range of α's and ratios of proximal/distal neighbors

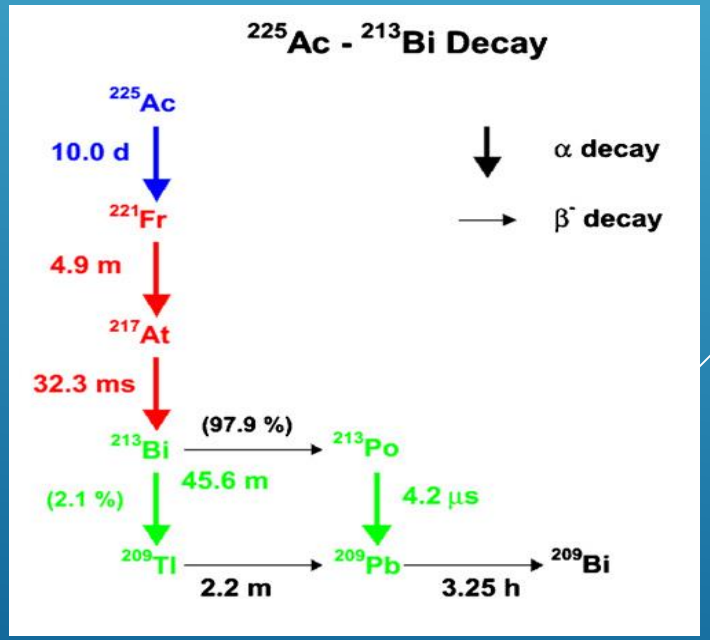


Hobbs *et al.* Phys Med Biol '12

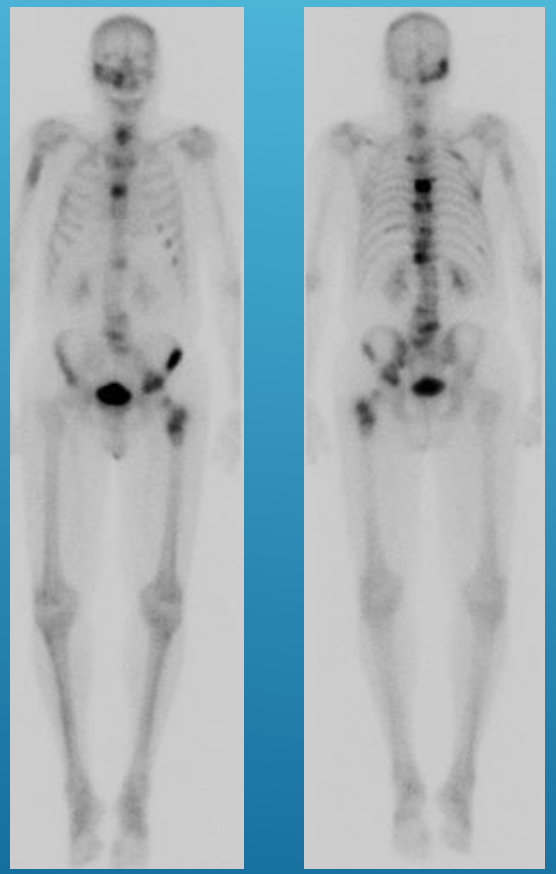
MACRO TO MICRO CONVERSION

- Measure (isotope) activity conc $a_{ij}(t)$ in compartments and whole organ
- Multiply by fraction of occupancy f_i to apportion fraction of activity g_i to compartments
- Free ^{213}Bi

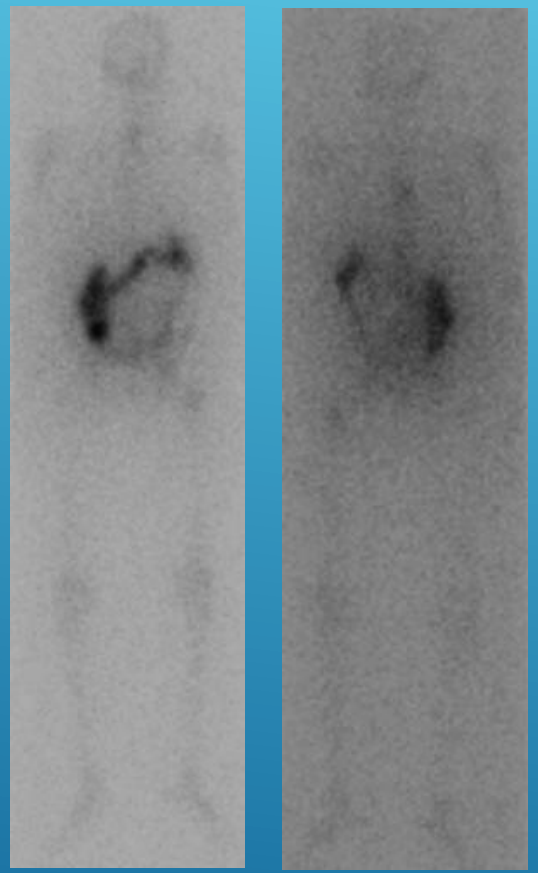




α-particle imaging



Tc-99m MDP –D20 ant & post



Ra-223 ant & post (24 h)

Standard patient dose

Challenge is low count rate because of low therapeutic activity (100-200 μCi)

Carrasquillo et al, Eur J Nucl Med Mol Imaging, 2013; 40(9):1384-93

CONCLUSIONS

- Be prepared. RPT is coming in a big way. Physician interest is extremely high, generally only for fixed activity administration
- Big push for dosimetry-based treatment planning – need guidelines and education
- Implement activity-based program and learn to do retrospective dosimetry
- Alpha-particle dosimetry is complex and not mature

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