Role of Dosimetric Studies in Clinical Development of Radiotherapeutic Products

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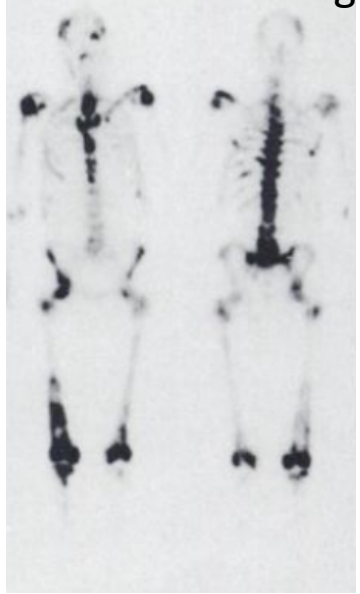
Disclosure

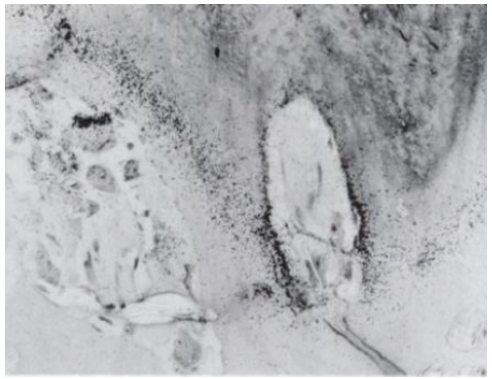
- William Goeckeler is an employee of Bayer US

^{153}Sm-lexidronam: Human Biodistribution and Dosimetry Estimates

Gamma Camera Imaging



Bone Biopsy Autoradiograph



Organ Residence Times Observed in Patients Studied for Radiation Dosimetry

Source Organ	Mean	Residence time (hr) standard deviation
Kidneys (n = 6)	0.029	±0.026
Liver (n = 7)	0.021	±0.010
Lungs (n = 6)	0.020	±0.010
Skeleton (n = 7)*	41.6	±12.6
Urinary bladder contents (n = 7)†	2.56	±1.10

*Activity in skeleton equally divided between cortical and cancellous bone for dosimetry calculations.
†Bladder voiding interval 4.8 hr.

	Gy/MBq	
Target Organ	Mean	Standard deviation
Kidneys	18	±14.1
Liver	5	±1.1
Lungs	8	±1.6
Ovaries	9	±0.9
Red marrow	1514	±261
Bone surfaces	6686	±1354
Testes	5	±0.8
Urinary bladder wall	964	±407

Administered Dose Range
1.9 – 11 GBq

Hematologic Toxicity

Dose (mCi/kg)	Dose range (mCi)	Neutrophils*		Platelets†	
		Grade II	Grades III/IV	Grade II	Grades III/IV
1.0	51–105	1/20	2/20	3/20	2/20
1.5	138–176	2/4	1/4	1/4	0/4
2.0	147–220	1/4	1/4	0/4	0/4
2.5	149–299	10/20	7/20	5/20	8/20
3.0	224–294	2/4	2/4	1/4	1/4

Learnings

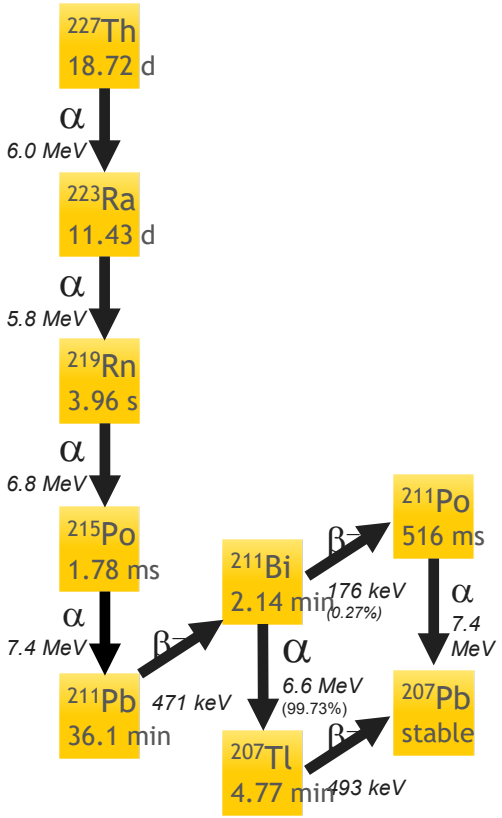
- A variety of methods can be employed to obtain time dependent biodistribution data
  - Gamma camera imaging
  - Biopsy
  - Blood and urine sampling
- Administration of GBq levels of radioactivity enables relatively high precision of measurement
- Interpatient variability in dose estimates can be 25% or more based on biodistribution differences
- Non-homogenous penetration of particles in target organs significantly complicates interpretation of dose estimates
  - Dose to red marrow from activity residing on bone surfaces

Deriving Dose Estimates for Alpha Emitters

- Alpha decay chains
  - Characteristics
  - Dosimetry aspects of daughter radionuclides
- Impact of administered dose levels on methods employed and precision of measurements
- Radiobiologic aspects of alpha dosimetry
  - Path length
  - RBE

Alpha Decay Chain Characteristics

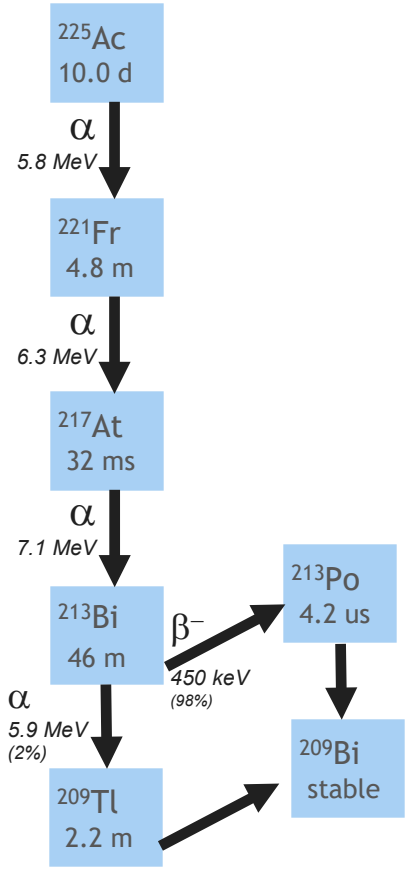
Th-227/Ra-223



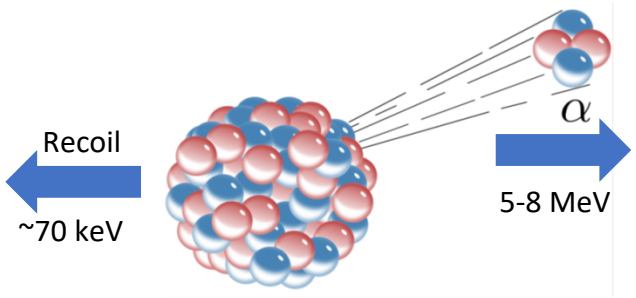
The most commonly used alpha emitters:

- Decay in chains
  - Requires consideration of multiple emissions
  - Secular vs transient equilibrium of daughters
    - Potential for redistribution
- Are administered at doses ~1000 fold less than betas
  - Reduces number of available photon emissions
  - Impacts the procedures used and precision of measurements of uptake and clearance
- Have half-lives of 10 - 20 days
  - Impacts the time course for measurements of clearance

Ac-225



Determining the Fate of the Daughters



Chemical bonds are typically 5-10 eV

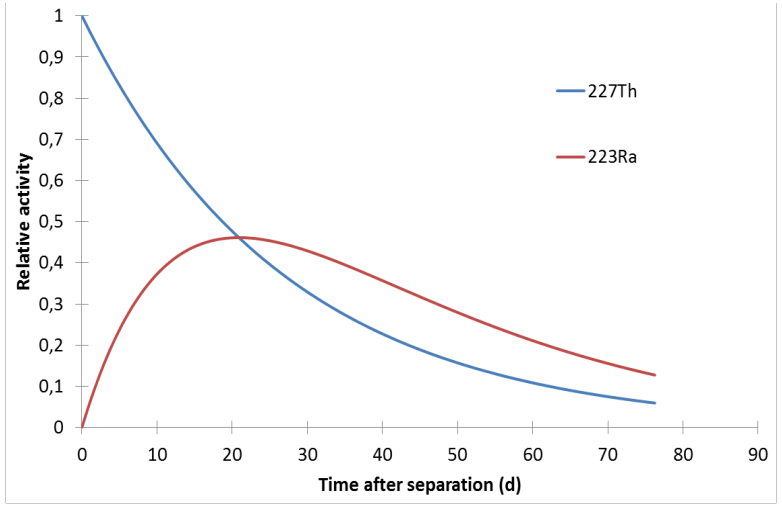
α recoil disrupts chemical bonds holding the decaying atom

Absorbed dose estimates of alpha emitters depend upon the pharmacokinetic fate of unstable daughters generated after decay of the conjugated parent.

Important factors include:

- **Half life and emission type of the daughter(s)**
- **Time dependent biodistribution of the daughter(s)**
- **Radiosensitivity of relevant target organs**

Th-227/Ra-223: Secular Equilibrium



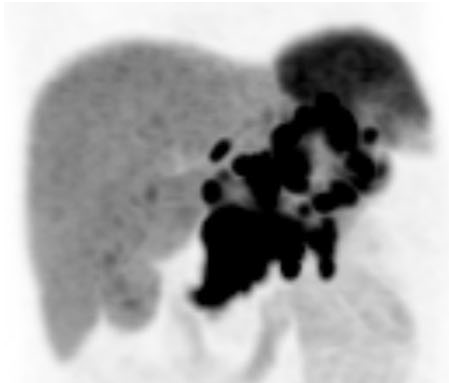
Medical Physics
The International Journal of Medical Physics Research and Practice

Theoretical estimation of absorbed dose to organs in radioimmunotherapy using radionuclides with multiple unstable daughters

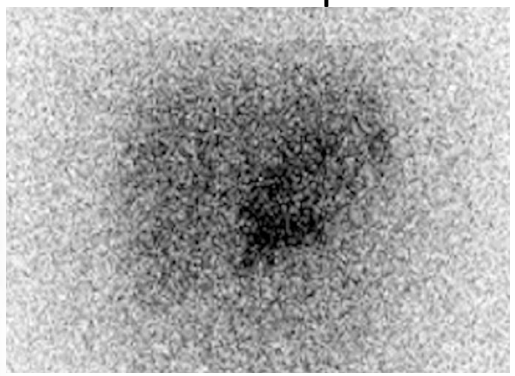
K. A. Hamacher and G. Sgouros
Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, New York 10021

Imaging of Alpha Emitters

Ga-68-DOTATATE

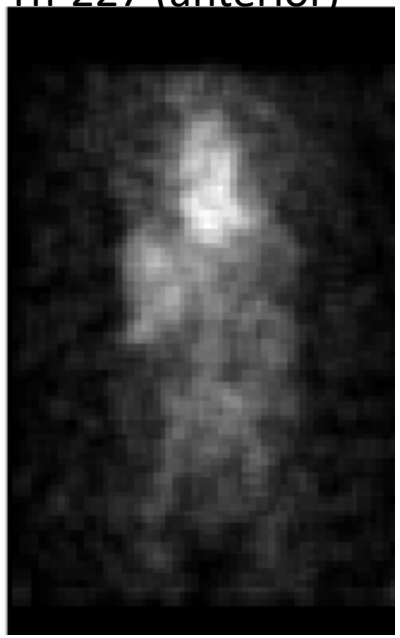


Ac-225-DOTATATE
7 MBq

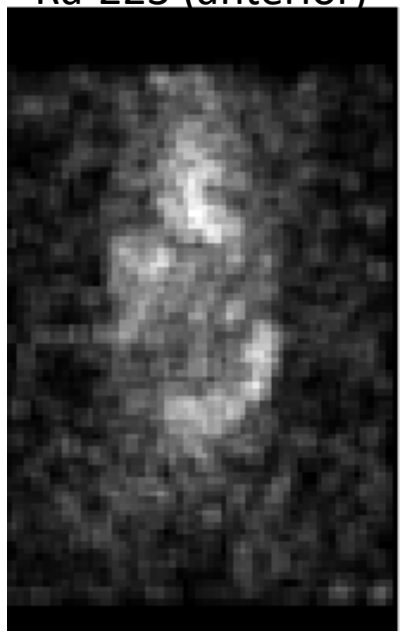


Th-227 Mab
2.8 MBq

Th-227 (anterior)



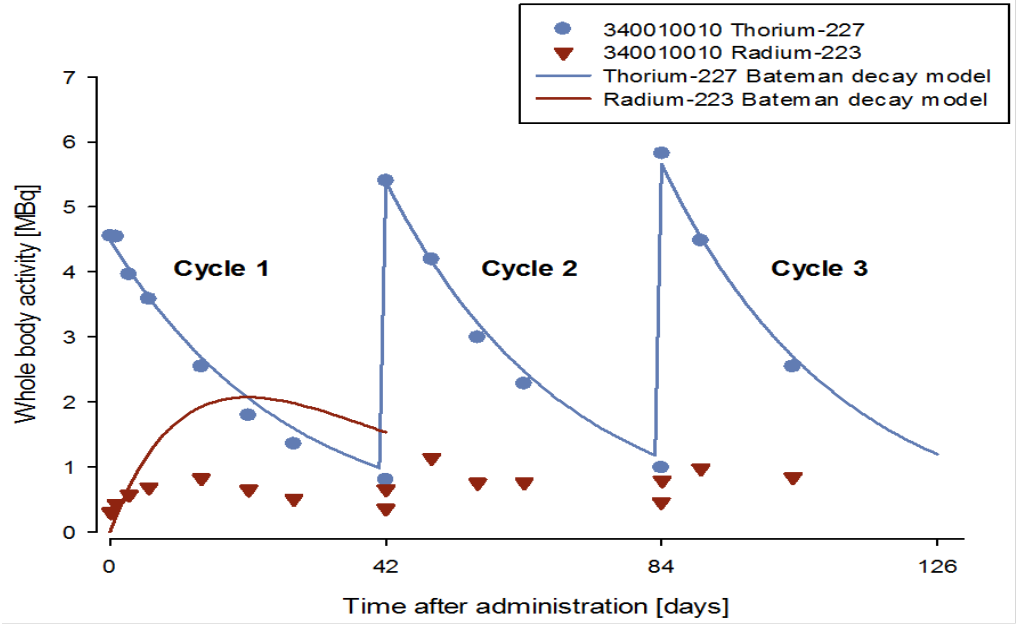
Ra-223 (anterior)



Quantification of uptake is difficult

- Gamma images are low resolution with poor signal to background
- Difficult to quantify
- Limited precision

HPGe Probe: Whole Body Radioactivity
4.6 MBq/cycle



Larrson E et al. Presented at the Annual Congress of the European Association of Nuclear

Radiobiologic Aspects of Alpha Particle Dosimetry

Path Length

- Alpha particles deposit high amounts of energy (5-8 MeV) over very short distances (50-100 µm)
  - Inter- and Intra Organ/Tissue dose heterogeneity (microdosimetry)
    - Bone Marrow
    - Kidney
    - GI Contents/Wall

Relative Biologic Effectiveness (RBE)

- High LET radiation is more lethal per unit of absorbed energy
  - RBE is the ratio of the biologic effects of one type of ionizing radiation to another for an equal amount of absorbed energy
  - RBE for photons and electrons is 1
  - RBE for alphas for deterministic events (e.g.,, safety, efficacy): ~ 3-7
  - Tissue specific RBE are less well characterized

Summary

- Quantification of uptake in organs and tissues to provide source data for derivation of dose estimates is an important component of the development of therapeutic radiopharmaceuticals
  - A variety of methods can be used to supplement quantitative imaging
- Microdosimetric effects can play a significant role for short range particles, both alpha and beta
- Alpha emitters:
  - Frequently decay in chains of multiple emissions
  - Are administered at ~1000 fold lower amounts of radioactivity than betas
  - Gamma images are low resolution with poor signal to background
- RBE values for alphas are not currently well characterized
  - This compounds the variability in measurement of uptakeand clearance