U.S. FOOD & DRUG ADMINISTRATION

Alpha-emitting therapeutic radiopharmaceuticals: nonclinical studies prior to initiating a human study, dose selection, and impact of impurities

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Abbreviations

- BSA: body surface area
- BW: body weight
- D: radiation absorbed dose
- CV: cardiovascular
- CNS: central nervous system
- FIH: first-in-human
- %ID: percent of injected dose (percent of injected activity)
- LET: linear energy transfer
- mAb: monoclonal antibody
- PK: pharmacokinetics
- RBE: relative biological effectiveness
- $T_{1/2}$: half-life
  - Te: effective half-life

Overview of this presentation

- Nonclinical studies in support of FIH studies
  - Described in the FDA Guidance:

    Oncology Therapeutic Radiopharmaceuticals: Nonclinical Studies and Labeling Recommendations

    https://www.regulations.gov/docket?D=FDA-2018-D-1772
- FIH dose selection
  - Described in the FDA guidance (see above)
- Alpha-emitting radionuclides

Nonclinical studies in support of FIH studies

- Pharmacology
  - Proof of concept
  - Could be used to determine the maximum tolerated radiation dose in animals
- Safety pharmacology (CNS, CV, respiratory)
  - Stand-alone studies usually not needed
  - Assessment through:
    - Biodistribution study (information re: radiation)
    - General toxicology (information re: cold pharmaceutical)

Nonclinical studies in support of FIH studies (cont'd)

- Animal biodistribution, to aid in:
  - FIH dose selection (for human dosimetry)
  - Assessing toxicities from radiation, based on distribution of radiation and the knowledge of organ-specific radiation toxicities. Toxicity endpoints (e.g. non-sacrificial) may be added.
- A toxicology study, to assess:
  - *Ligand related effects
    - ❖ *A toxicology study to assess radiation-induced toxicities usually not needed*

* *Targeting or chelating agent*

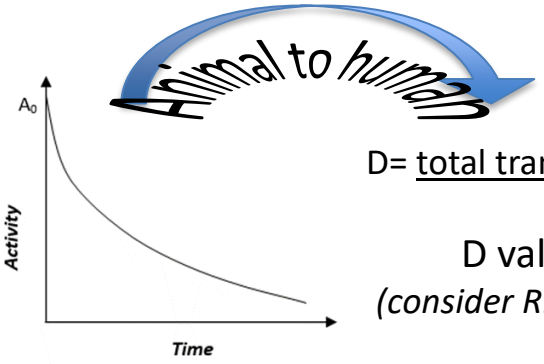
Nonclinical studies in support of FIH studies: Animal biodistribution

Needed to support human dosimetry. Usually:

- Single dose administration
- One species

Activity over time in organs of animals: *total # of decays*

- *Can be used to estimate time-integrated activity in human organs → estimate absorbed doses in human organs*



D= <u>total transitions</u> x energy per transition x fraction absorbed from source/ mass

D values in human organs used to set the FIH dose for human dosimetry

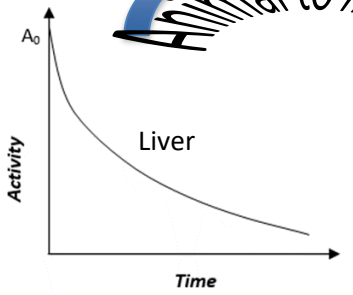
(consider RBEs for equivalent doses when comparing to organ threshold from external beams)

Use human dosimetry data to select the therapeutic dose of the radiopharmaceutical

Use of theranostic pairs *(assume no relevant clinical data)*

- The clinical candidate is not appropriate for imaging/ dosimetry in animals or humans? alpha-or beta-emitting
- The product used in animals cannot be used for imaging/ dosimetry in humans?

111-In-Ligand (gamma; Tp= 67 h)



90-Y-Ligand (beta; Tp= 64 h)

D= <u>total transitions</u> x energy per transition x fraction absorbed from source/ mass

The pair should have similar PK data in animals and humans, e.g: distribution and $T_{1/2}$

Consider the effective T1/2 (Te)

Animal biodistribution and dosimetry (cont'd)

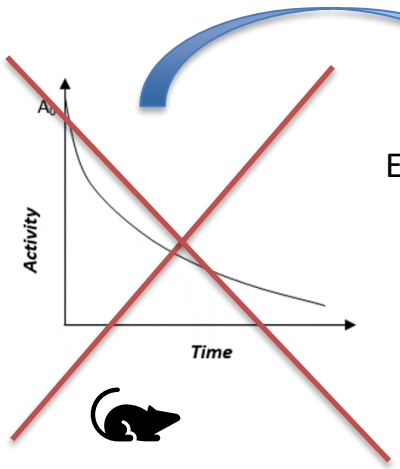
- Estimates at best
- May underpredict effects in humans
  - Biological targeting moiety may be immunogenic in animals
    - higher clearance → reduced # of transitions

From the guidance

"When there is experience with the radionuclide or the ligand components of the radiopharmaceutical being developed, the nonclinical program can be abbreviated as needed, and the FIH dose can be based on clinical data, as appropriate."

Abbreviated nonclinical program:

example



^{131}I- CD20 mAb

Estimation of absorbed doses in human organs

^{131}I- CD20 mAb'

Human dosimetry

Human therapeutic phase

FIH dose selection

(in the absence of relevant clinical data)

- **Mass dose (cold pharmaceutical):** Follow recommendations in ICH S9 guidance. May not be essential (e.g. mcg doses)
- **Radiation dose**
  - Selection of the activity to be administered (Bq or Ci) per BW or BSA for patient dosimetry should be based on
    - the animal biodistribution and dosimetry data,
    - the estimated absorbed radiation doses in human organs, and
    - tolerance of human organs to radiation
  - For organ tolerance in patients: can use literature on external radiation therapy as a starting point.
    - May use an RBE of 5 for alpha-emitting radiopharmaceuticals

Alpha-emitting radiopharmaceuticals

Pros	Cons
High potency: • DNA double strand break • A high linear energy transfer (LET) that increases the radiation dose in tumors • High relative biological effectiveness (RBE)	Due to the short range, the resulting dose distributions in tumors can be nonuniform
A short/ moderate pathlength (50–100 µm) range may potentially reduce injury to healthy tissues surrounding the tumor	Imaging and dosimetry could be challenging
May be suitable for micrometastases	After emission, daughter nuclides experience a recoil energy, resulting in decoupling from the chemical bond and redistribution
	Daughter radionuclides resulting in additional doses
	The high LET may result in injury to healthy tissues when/if the radionuclides detach and redistribute

Alpha emitting radiopharmaceuticals :

essential properties in drug development

- Ligand properties: Reduce effects related to recoil and re-distribution of the radionuclides
  - fast delivery to the tumor
  - internalization
  - extended tumor retention

  Daughter radioisotopes recoiling from an alpha-emitting parent (breaching the chemical bonds) would travel a relatively short distance
- Physical $T_{1/2}$: not too short (potent cytotoxic effect and ability to deliver desired doses post manufacturing). Not too long (patient safety; environmental exposure)
- Imaging capabilities

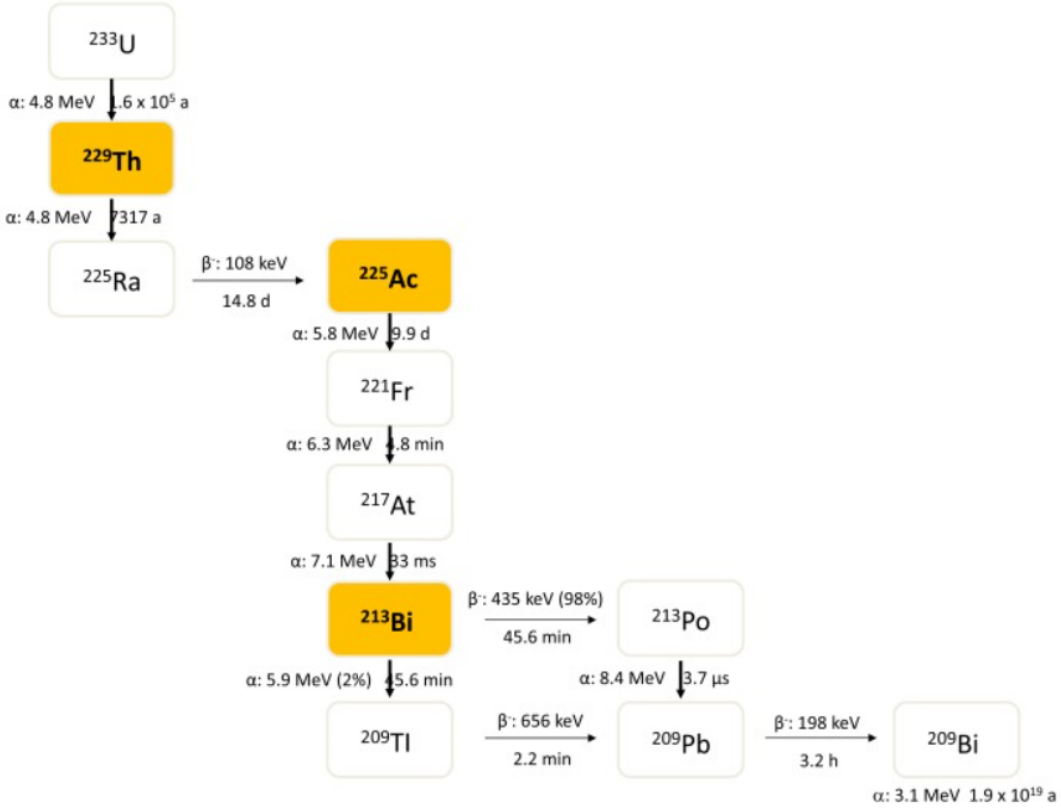
Alpha particle: Imaging, biodistribution/ dosimetry

- Dissecting organs and using scintillation counters
- Theranostic strategy
- Imageable signals in a decay chain (approach has been used for ^{223}Ra)
  - Conventional gamma cameras, single-photon emission computed tomography (SPECT), and
  - positron emission tomography (PET)
- Imaging technology for the ex vivo detection of α-particles in tissues

https://jnm.snmjournals.org/content/51/10/1616.long
https://jnm.snmjournals.org/content/55/supplement_1/50
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6554362/

Why ^{225}AC?

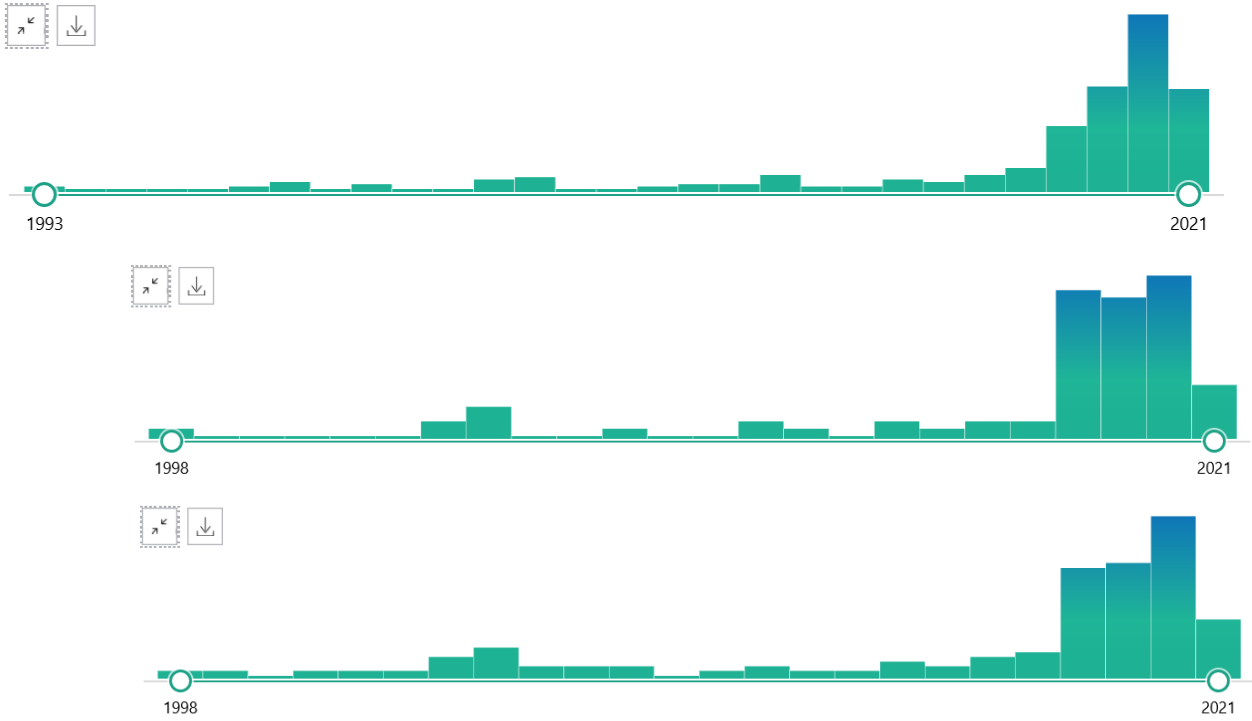
- Availability of clinical data with ^{225}Ac
- Availability of clinical data with ^{213}Bi ?



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6237921

PubMed advanced search (June 2021)

- Keywords
  - (actinium) AND (clinical)--- 211 hits
  - (actinium-225) AND (clinical)--- 75 hits
  - (actinium-225) AND (cancer)--- 121 hits



Why ^{225}AC (cont'd)

- Half-life not too short or too long
- Nonclinical and clinical data reported in published articles
- While ^{225}AC does not have its own imageable emission, several daughter radionuclides have gamma emissions (e.g. ^{213}Bi)

Case study

- Clinical candidate was ^{225}Ac-chelator-mAb (^{225}Ac-XX)
- Publications cited by the Sponsor for use of ^{111}In as a theranostic pair of ^{225}Ac. The tumor and normal organ biodistribution of ^{225}Ac-labeled antibodies was similar to the ^{111}In-labeled antibodies
- Limited human dosimetry data was also available with ^{111}In-XX (same indication)
- The organ specific radiation dosimetry estimates of ^{225}Ac-XX in animals consistent with the results of the clinical study with ^{111}In-XX.

The radiation starting dose of ^{225}Ac-XX was determined based on the results from the clinical study with ^{111}In-XX

Examples of articles on ^{111}In and ^{225}Ac:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7295045/
https://pubs.acs.org/doi/pdf/10.1021/acs.molpharmaceut.9b00542

^{225}Ac with ^{227}Ac impurity

- The amount of generator-produced ^{225}Ac (Oak Ridge National Laboratory, managed by the DOE Isotope Program) is limited. Alternative sources of ^{225}Ac may be needed to support the growing clinical demand.
- To increase the supply of ^{225}Ac, the DOE Isotope Program has developed an alternative method to produce a ^{225}Ac; accelerator-produced ^{225}Ac.
  - Results in co-production of ^{227}Ac, at activity levels of 0.1 to 0.2% relative to the activity of ^{225}Ac at production (proposed levels by sponsors could be higher at the time of use).
  - ^{225}Ac and ^{227}Ac cannot be chemically separated.
  - ^{227}Ac has a long half-life of 21.8 years (^{227}Ac → ^{227}Th; mostly beta-emitting).

  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6237921/pdf/CRP-11-200.pdf
- Safety concerns:
  - Patient level
  - Environmental/ waste
  - Safe handling/ disposal of unused materials

Safety concerns: patient-level

- ^{227}Ac remaining with the ligand/ stability?
  - To indicate that ^{227}Ac will not dissociate from the product before removal by biological processes. If data indicates that ^{227}Ac remains with the ligand , then ^{227}Ac may be eliminated from the body with the elimination of the ligand (consistent with the effective half-life, Te).

- When conducting biodistribution/dosimetry in animals, take into consideration absorbed doses from ^{225}AC, ^{227}Ac, and daughter decays
  - If any decay is not included in the calculation (e.g. short half-life), indicate this in the submission and the rationale

- *Switching to accelerator-produced ^{225}Ac after animal studies and cohorts of human studies completed? May consider the following approaches:*
  - See the first bullet
  - Modeling: may use the worst-case scenario of ^{227}Ac impurity separating and distributing
  - An abbreviated animal dosimetry and excretion/mass balance study

Questions for the FDA review team?

You can ask for a meeting

Questions?

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Challenges to Safety Assessments in Early Phase Clinical Trials for Radiopharmaceuticals

Mitchell S. Anscher, MD
Medical Officer
CDER/OND/DO1

Disclosures

- Nothing to disclose
- I will not be speaking about off-label use of drugs or devices

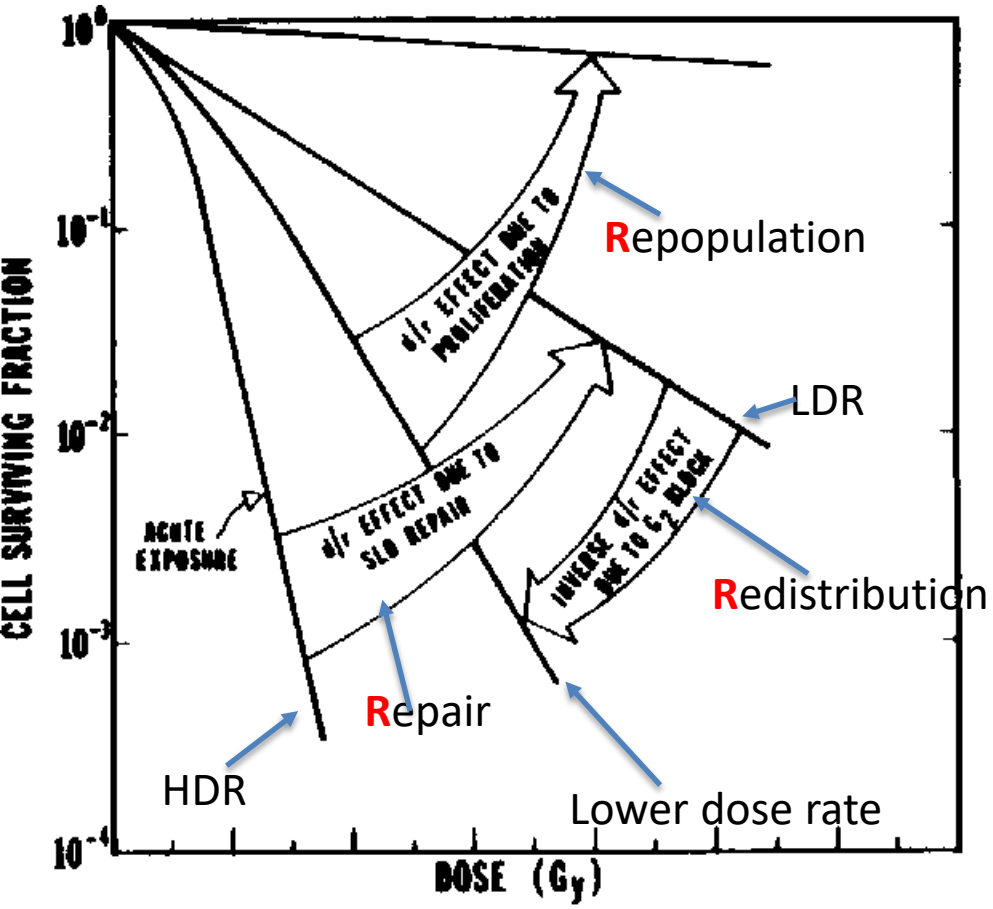
Radiopharmaceutical Therapy-the Good, the Bad and the Ugly

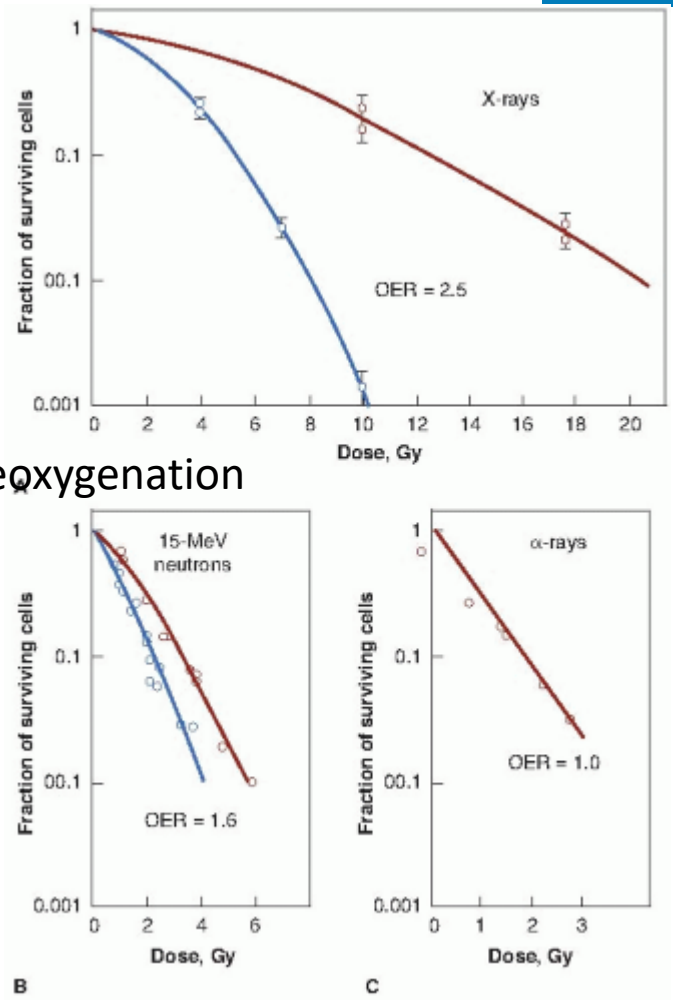
- Good
  - Targeted
  - High dose to tumor
  - Low energy (rapid fall off)
  - Combine imaging and therapy
- Bad
  - Target not necessarily tumor-specific (PSMA)
  - Depth of penetration may be too low (alphas) or too high (gammas)
  - Can't always image, correlation between imaging and therapy
- Ugly
  - Dosimetry combines challenges of pharmacology and radiotherapy
  - Explosion in new applications
  - Lack long-term follow-up data to establish true tolerance doses

Dosimetry of Radiopharmaceuticals vs External Beam Radiation

- Limited dose input data (few sample points)
- Non-uniform dose distribution
- Lower/variable dose rates
- Models/software designed for low exposure imaging studies
  - Assume uniform dose distribution in a tissue
  - Do not provide dose gradients at tissue boundaries
  - Do not provide direct tumor dose correlations
- Tolerance dose estimates based on conventionally fractionated external beam radiation
  - Evidence suggests tolerances doses are very different
  - **Acute** hematologic toxicity may be more of an issue for radiopharmaceuticals

4 R's of Radiobiology



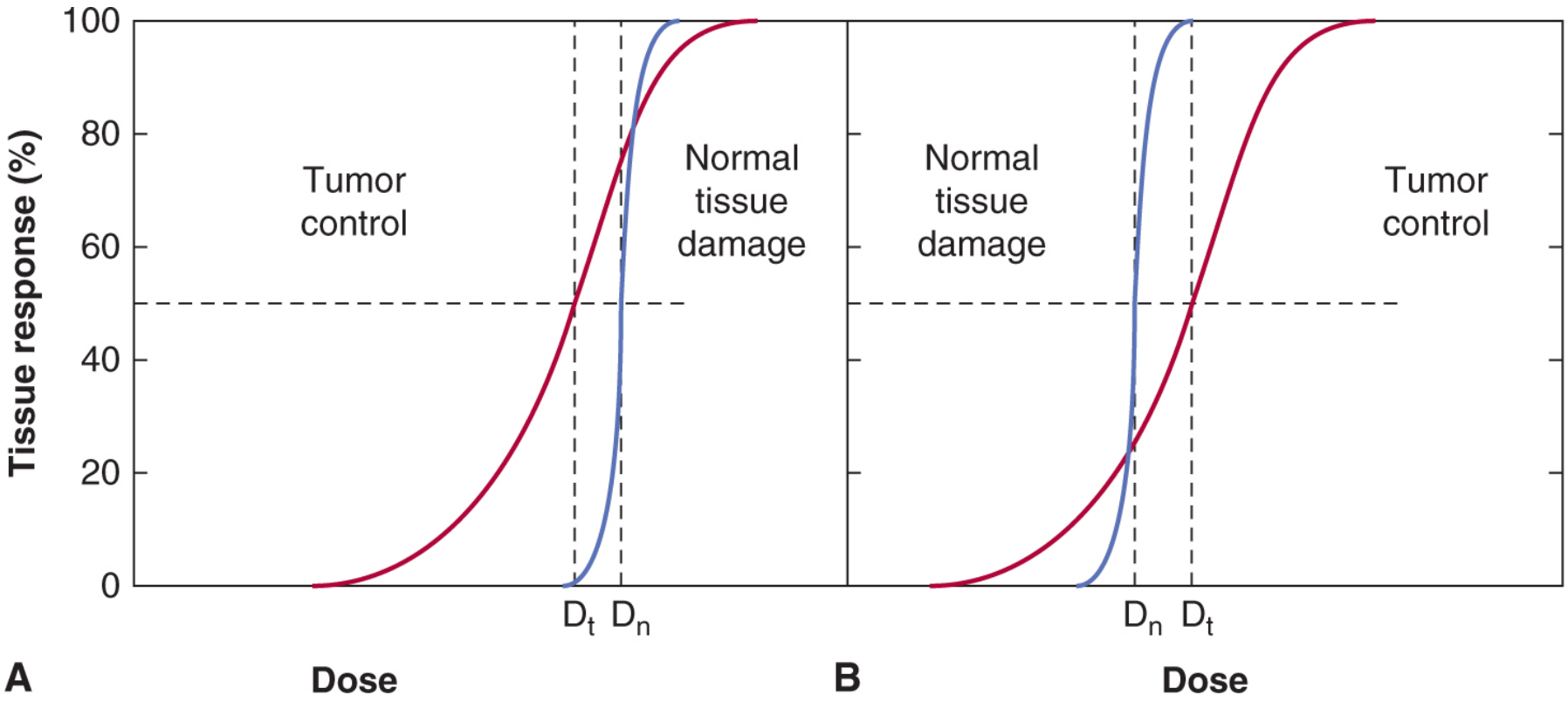


Hall, EJ & Brenner, DJ. IJROBP 21: 1403, 1991; Hall EJ. Radiobiology for The Radiologist, 1994, p136

Potential Advantages of α-Particles

- Densely ionizing vs photons, protons, β-particles
  - High linear energy transfer (LET)
  - Nearly ideal LET, as the average separation between ionizing events is roughly equal to the diameter of a DNA double helix (~2nm)
- The 4 R's don't apply
  - No repair of sublethal damage
  - No cell cycle redistribution
  - No enhanced effect of oxygen
  - No repopulation
  - No dose rate effect
  - Short path length
- Therefore, much higher relative biological effect (RBE) vs photons, protons, β-particles

How is Radiation Prescribed?: Therapeutic Ratio



Hill, RP and Bristow, RG. chapter 16: Tumor and Normal Tissue Response to Radiotherapy. In: The Basic Science of Oncology, ed: Tannock, Hill, Bristow and Harrington, 5th edition

What Types of Radiation Injury Determine the Therapeutic Ratio

- Usually, it's the late effects
  - Traditionally defined as those persisting or occurring >90 days after treatment
  - RT injury is basically dysregulated wound healing
  - Process begins immediately with the first exposure
  - May take years to develop
  - Wide individual variation, which is not always well-predicted
  - Limited therapeutic options if late effects develop
  - Prevention is key
  - Requires accurate knowledge of RT dose distributions at the individual patient level for every administration

What Influences Therapeutic Ratio?

- Patient factors
  - Underlying illnesses (diabetes, chronic lung disease, heart disease, chronic liver disease, collagen-vascular diseases, inflammatory bowel disease)
  - Lifestyle issues (smoking)
  - Genetics (known and unknown)
  - Epigenetics
- Treatment factors (radiation)
  - Total dose, dose/fraction, dose rate, modality (EBRT, brachy), volume of normal tissue
- Other treatments
  - Systemic agents, surgery, OTC stuff patients don't tell you about
- Tumor factors
  - Histology
  - Genetics
  - Epigenetics

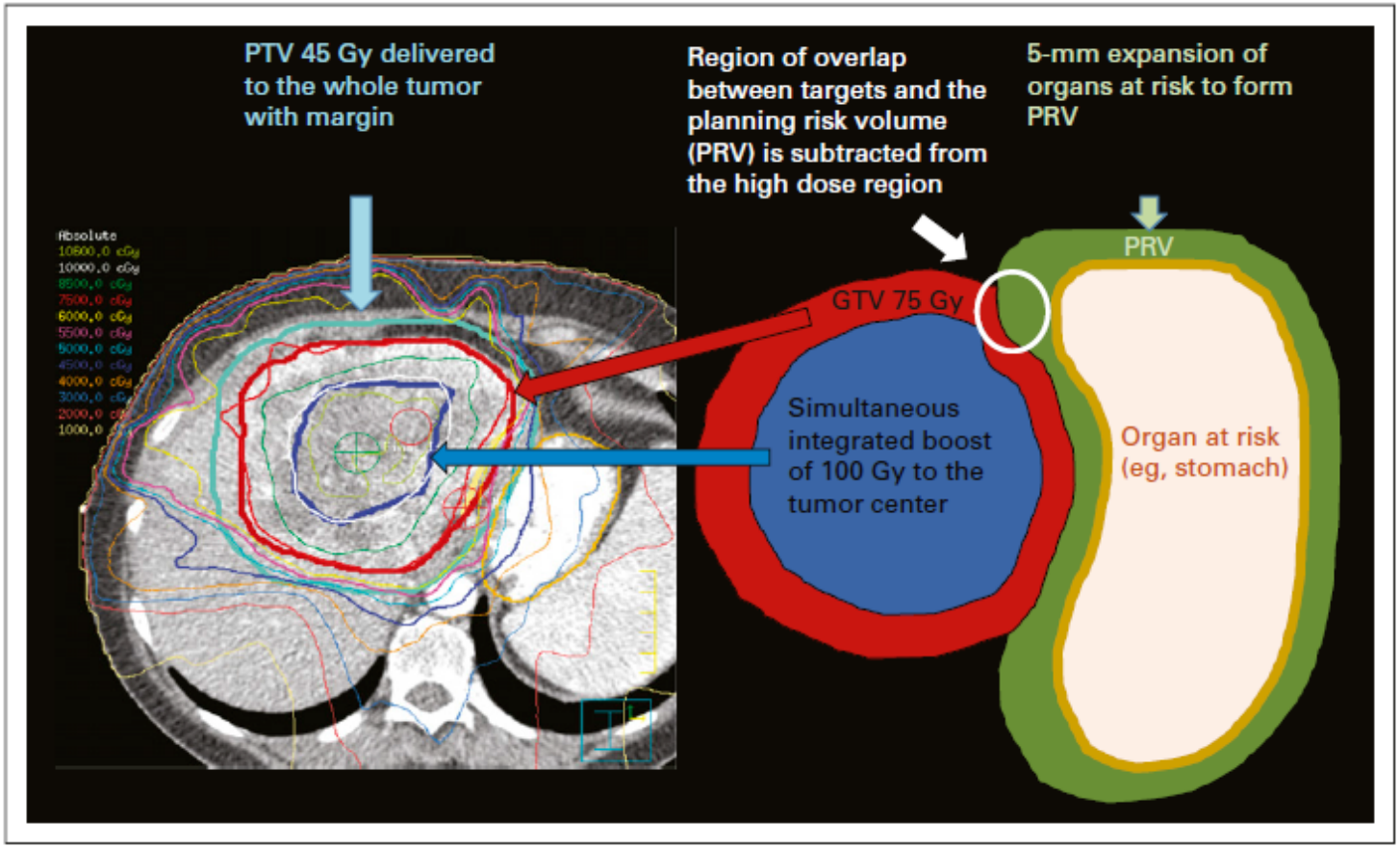
What Influences Can We Control?

- Patient factors
  - Underlying illnesses (diabetes, chronic lung disease, heart disease, chronic liver disease, collagen-vascular diseases, inflammatory bowel disease)
  - Lifestyle issues (smoking)
  - Genetics (known and unknown)
  - Epigenetics
- Treatment factors (radiation)
  - Total dose, dose/fraction, dose rate, modality (EBRT, brachy), volume of normal tissue
- Other treatments
  - Systemic agents, surgery, OTC stuff patients don't tell you about
- Tumor factors
  - Histology
  - Genetics
  - Epigenetics

Problems With Current Normal Tissue Dose-Volume Guidelines

- Mostly derived from retrospective analyses
- Complications probably under-reported and rarely graded
- May not hold up with very poor organ function (e.g., mean lung dose)
  - No spacial distribution considerations
- Heterogeneous patient populations
  - Co-morbidities, concurrent medications
  - Genetic contributions unknown
- Non-standardized normal tissue contouring guidelines
- Tend to be modality specific
  - Different for SBRT vs types of brachytherapy (LDR vs HDR) vs EBRT
- No clinically accepted biomarkers to help guide dosing decisions

Dose Distribution: EBRT



Tao et al. J Clin Oncol 34: 291, 2015

Dose Distribution: SIRT for Liver Tumors

Tumor with large necrotic center

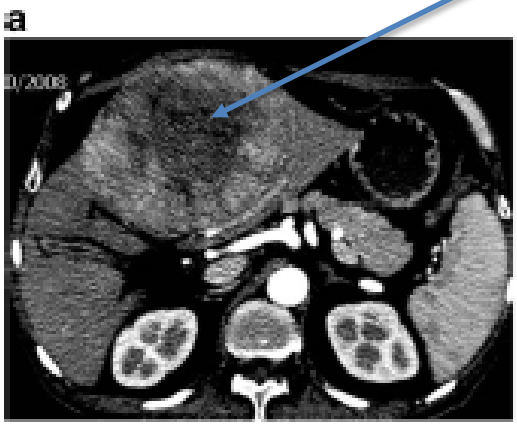
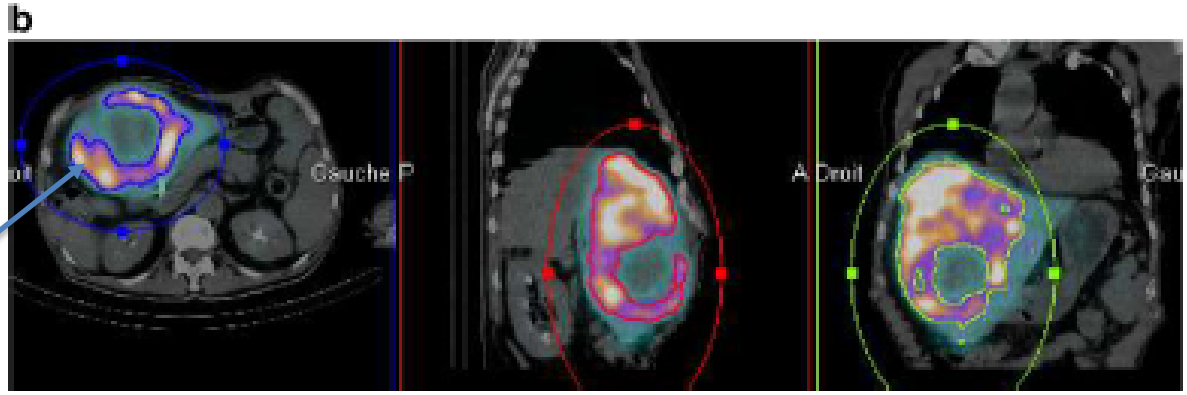


Fig. 1 Tumoral VOI delineation using MAA SPECT/CT. a) CT slide: huge tumor of 12.1×17.4×9.7 cm with a large part of central necrosis. b) MAA/SPECT CT tumor volume segmentation. Based on MAA SPECT/CT, tumor volume is only 900 cc due to a large part of necrosis. Using CT segmentation, tumor volume is 1310 cc. Doing the hypothesis of absence of radioactivity uptake in necrosis, tumor dose based on MAA segmentation (excluding necrosis volume) is 1.45 fold higher than tumor dose based on CT segmentation (including necrosis volume)

Dose determination varies 45% between CT vs SPECT/CT based calculations

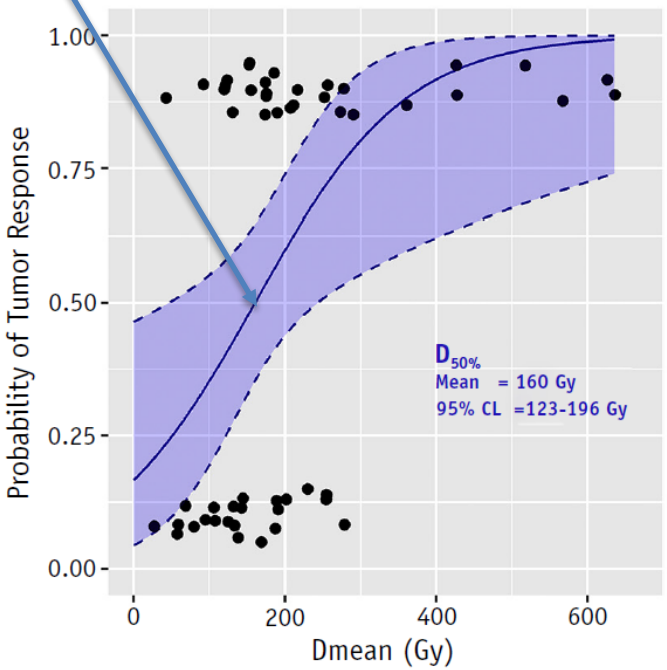


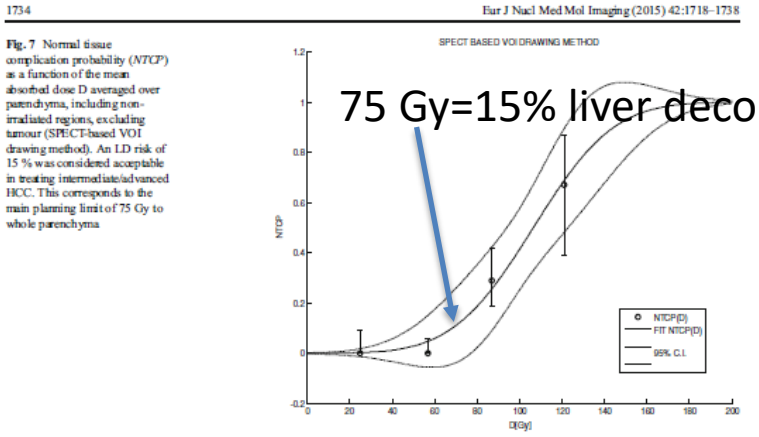
Non-uniform uptake

Garin et al. Eur J Nuc Med Mol Imaging 43: 559, 2016

Tumor vs Normal Tissue Dose Goals: SIRT for Liver Tumors

160 Gy=50% response





Kappadath et al IJROBP 102:451, 2018; Chiesa et al. Eur J Nuc Med Mol Imaging 42: 1718, 2015

Choosing the Appropriate Patient Population

- With the exception of Ra223 for selected patients with metastatic prostate cancer, no other alpha emitters are approved for use in patients.
- Current studies using alpha emitters are early phase dose escalation/dose expansion
  - Goal to determine a safe dose to study for effectiveness
- Patients enrolled are those with advanced cancers with few options other than clinical trials
  - Generally used as a monotherapy
  - Patients have limited life expectancy
    - How can you establish safety if late effects are the major concern?

Issues to Consider

- Unlike Ra223, most systemic agents are bound to a carrier, either a small molecule or an antibody designed to preferentially bind to a tumor.
  - Where else in the body is the target protein found?
    - Target proteins occurring in normal tissues will lead to radiation delivery to these tissues producing unwanted side effects
    - Is the binding greater in tumor vs normal tissues?
  - How is the carrier protein handled by the body?
    - Is it excreted through the kidneys or metabolized in the liver?
    - Is it preferentially retained in the tumor vs normal tissues?
    - Will impact on potential AEs

What is Known About Radionuclide Toxicity?

- Acute bone marrow toxicity is common
  - May limit the maximum single dose and the dosing interval
  - Dosing intervals tend to be longer with radiopharmaceuticals than drugs, due to the delayed onset of marrow toxicity and the longer interval for recovery vs many drugs
- Other acute effects depend more on the distribution of binding of the carrier in normal tissues
  - Example: PSMA and dry mouth
- Early phase trials are designed to capture this information
  - Often managed with dose reductions and/or dose interruptions

What Don't We Know About Radiopharmaceutical Toxicities?

- In many cases, we lack long term prospective information on late toxicities
  - Patient populations studied have relatively short life expectancies
  - Requires a commitment to systematic long-term follow-up
  - Will become increasingly important as these agents if these agents are used earlier in the course of a disease
  - Must balance the need for new, effective treatments while at the same time maintaining a commitment to long-term data collection

Future Challenges

- What is the optimal DLT observation period?
  - 30 days? 5 half-lives? Isotope dependent? Linker dependent?
- Is one cycle enough to determine DLTs if multiple cycles are intended?
  - Radiation effects are cumulative
  - May require continuous reassessment trial design
- Treating microscopic vs overt disease
  - Cannot image microscopic disease
  - Dosing may be based purely on normal tissue tolerance
    - Need better guidelines

Conclusions

- An increasing number of radiopharmaceuticals are being studied in patients with advanced cancers
- Owing to their unique method of delivering radiation, these agents hold great promise for the future
- The safe and effective prescribing of these agents will require not only a knowledge of their short-term side effects, but also a better understanding of the long-term risks associated with their use
- Long-term, preferably life-long, follow-up of patients enrolled in prospective trials will be the only way to accurately determine the risk of late complications and truly establish organ-specific tolerance doses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Dosimetry for Radiopharmaceutical Therapy

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CDER | US FDA

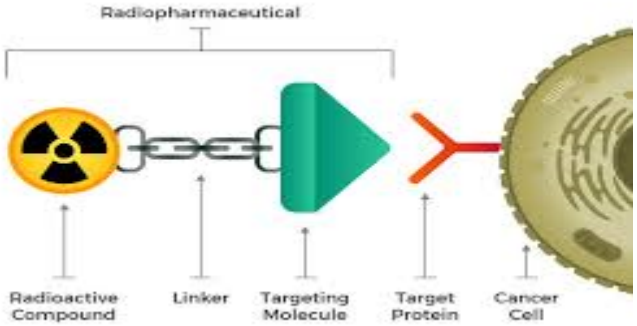
FDA-NRC Workshop: Enhancing Development of Targeted Alpha Emitting Radiopharmaceuticals, September 22, 2021

Content

- Radiopharmaceutical Therapy (RPT)
- MIRD Formalism for Internal Radiation Dosimetry
- Dosimetry for RPT
  - Challenges with Alpha Emitters
  - Ac-225

Radiopharmaceutical Therapy (RPT)

- **Disseminated Cancer**
- **Radiation Delivery**
  - Kill targeted cells by localized radiation therapy

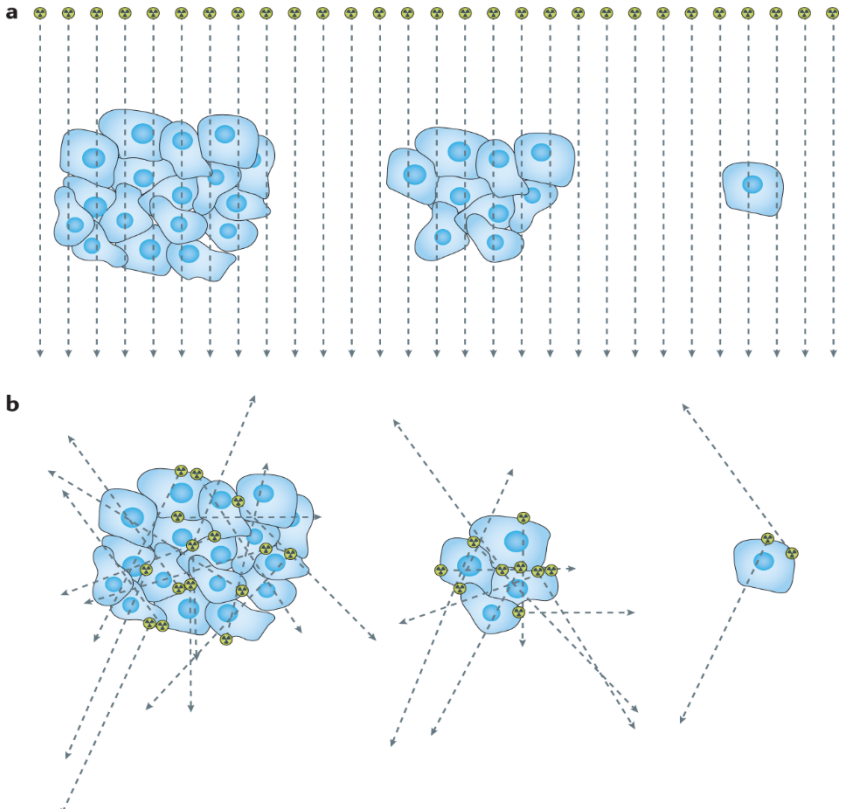


NCI Cancer.gov

Combination of a Radionuclide with a Biologically Active Pharmacophore

- Determines imaging and/or therapeutic properties
- Can also confer desired localization properties (for ex. radio-iodine)
- Overall chemical structure determines biological properties
- Acts as a carrier
- Determines localization and bio-distribution

Radiopharmaceutical Therapy (RPT)



EBRT (a) vs RPT (b)

External Beam Radiation Therapy (EBRT)

What is important for RPT

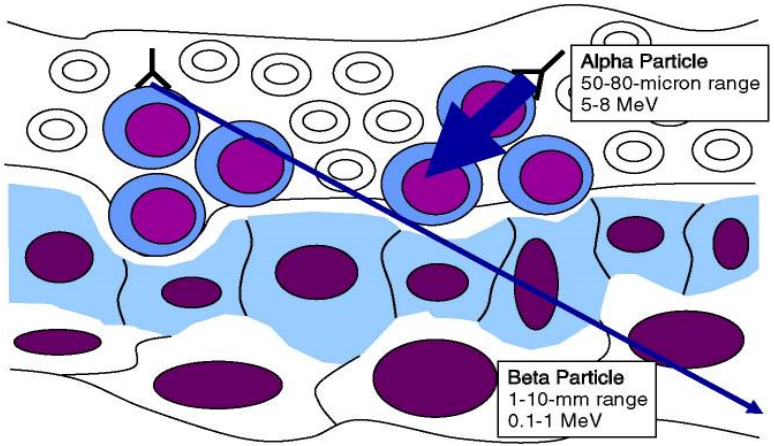
- Where does the drug concentrate, and for how long?
  - **Biodistribution** and/or **imaging studies** (theranostic approach or image therapeutic agent)
- What type of radiation is emitted?
  - **Depends on the radionuclide** (β, α-emitter)

Radionuclide Emissions

β-Particles
- Elementary particle
- Sparsely ionizing
- **Path length ~0.8-10 mm**
- 0.2 keV/μm (**LOW LET**)
- 10^3 to 10^4 tracks to kill cell
- DNA damage is repaired
- Recoil energy: ~10 eV

α-Particles
- He nucleus
- Densely ionizing
- **Path length: 50-100 μm**
- ~60-240 keV/μm (**HIGH LET**)
- 2-3 tracks kill cell
- Irreparable DNA damage
- Recoil energy: ~100 keV

Photons (γ-rays)
- Used for imaging



Milenic et al. Nature Rev. Drug. Disc. 2004, 3, 488

Therapeutic Radionuclides	
Beta Emitters	**Alpha Emitters**
Examples: **I-131, Y-90, Sm-153, Lu-177, Sr-89**	Examples: **Ra-223, Ac-225, Th-227**

FDA-Approved RPTs (Low LET Emitters)

Low LET Emitters	Manufacturer	Indication
I-131 (sodium iodide)	Jubilant Draximage	Treatment of hyperthyroidism, treatment of carcinoma of the thyroid
Y-90 (ibritumomab tiuxetan, Zevalin®)	Spectrum Pharmaceuticals	Treatment of relapsed or refractory, low-grade or follicular B-cell NHL; Treatment of previously untreated follicular NHL
Sm-153 (lexidronam, Quadramet®)	Lantheus Medical Imaging	Relief of bone pain of confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan
Lu-177 DOTATATE (LUTATHERA®)	Novartis/AAA	Therapy for neuroendocrine tumors and other somatostatin receptor expressing tumors
I-131 MIBG (iobenguane®)		Adult and pediatric patients (12 years and older) w/ iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma who require systemic anticancer therapy
Strontium-89 chloride	GE Healthcare	Relief of bone pain in patients with painful skeletal metastases confirmed prior to therapy
Y-90 loaded glass microspheres	BTG	Treatment of hepatic malignancies
Y-90 loaded resin microspheres	CDH Genetech/Sirtex	Treatment of hepatic malignancies

www.fda.gov

FDA-Approved RPTs (High LET Emitters)

High LET Emitters	Manufacturer	Indication
Ra-223 (Xofigo®)	Bayer Healthcare Pharmaceuticals Inc.	Treatment of patients with castration-resistant PCa, symptomatic bone metastases and no known visceral metastatic disease

Under Development RPT Agents

- ClinicalTrials.gov started after 2010, active, recruiting, and completed trials

	# of trials
Lu-177	70
I-131	80
Cu-67	2
P-32	1
Sm-153	1
Ra-223	81
Ac-225	7
Th-227	4
Pb-212	2
At-211	2

Review Article | Published: 29 July 2020

Radiopharmaceutical therapy in cancer: clinical advances and challenges

George Sgouros ✉, Lisa Bodei, Michael R. McDevitt & Jessie R. Nedrow

Nature Reviews Drug Discovery **19**, 589–608(2020) | Cite this article

Table 2 Selected RPT agents that are on the market or under development

www.fda.gov

Radiation Dosimetry

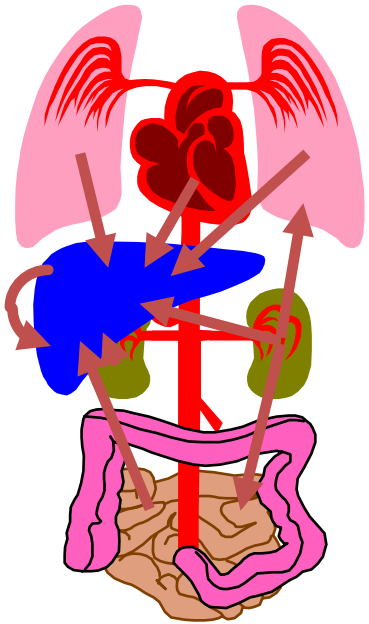
- Why do we need to perform radiation dosimetry?
  - A measure to predict potential toxicity/efficacy and risk associated with exposure to radiation
- Absorbed Dose
  - Amount of energy absorbed/mass in target organ/tissue
  - Most closely related to the biological effect
- Optimal dosing for RPT
  - Achieve good tumor response w/o causing normal organ toxicity

The Medical Internal Radiation Dose (MIRD) Formalism for Internal Radiation Dosimetry

Calculate the energy deposition density (energy absorbed/mass), Absorbed Dose, unit: Gy =

$$\frac{\text{Number of dis.} \times \text{Energy released per dis.} \times \text{Fraction that is absorbed}}{\text{mass of target tissue}}$$

Cumulated or Time-Integrated Activity, $\tilde{A}_S$



MIRD Pamphlet #21

Time-Activity or Pharmacokinetic (PK) Data

- Animal studies – usually performed for the submission of an Investigational New Drug (IND)
  - Larger animals (ex. monkeys, dogs) are done by imaging - smaller # of animals may be sufficient, 3M & 3F
  - Smaller animals (ex. mice, rats) are done by animal sacrifice, sufficient# of animals/time-point, radioactivity is counted (ex. gamma counter) and used to characterize biod.
  - ➢ Extrapolate to human organ PK data in order to get dose estimate to human organs
- Human studies – usually performed in Phase I, II or III of the approval of a New Drug Application (NDA) – involves imaging and/or blood, urine collection

MIRD Absorbed-Fraction Method
Image-Based Dosimetry

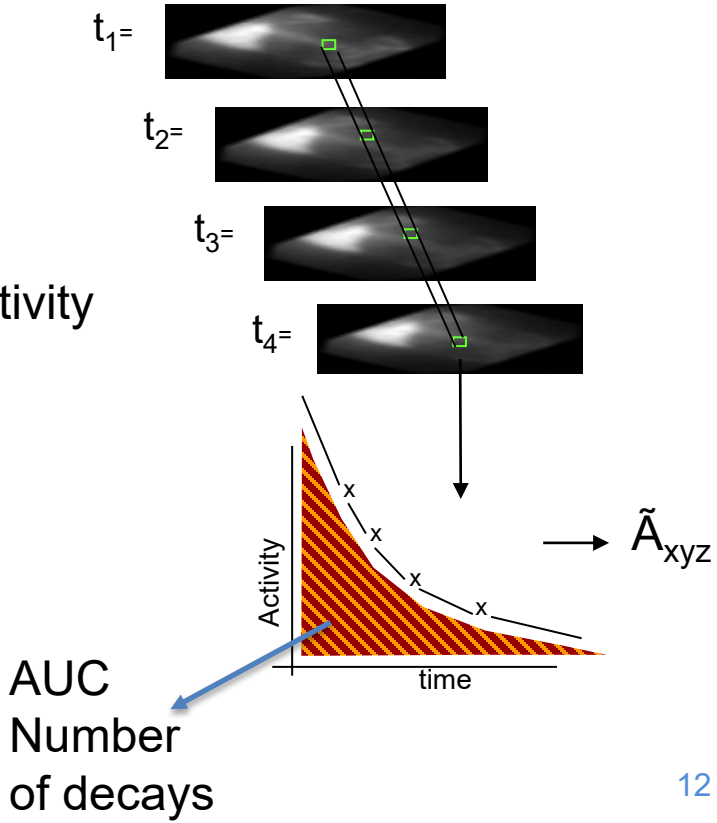
1. Serial quantitative imaging
2. Co-registration across time
3. ROI (organ, tumor) segmentation
4. Model fitting and integration of the time-activity curve

$$\tilde{A} = \int_0^\infty A(t)dt$$

$$\tau = \frac{\tilde{A}}{A_0}$$

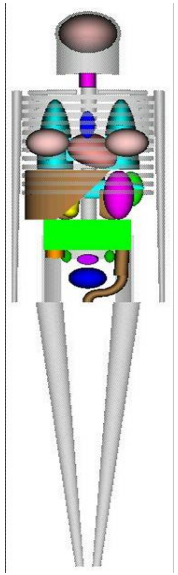
Time-Integrated Activity Coefficient (TIAC) or Residence Time

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



MIRD S-Value

Absorbed fraction



MIRD/ ORNL 1980's

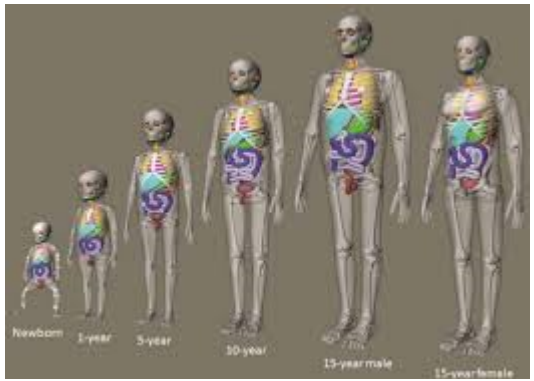
Energy absorbed per unit mass:

$$\frac{\tilde{A}_S \times \Delta \times \phi(t \leftarrow s)}{M_t}$$

Energy released per dis.

S-value, absorbed dose per unit time-integrated activity

$$D_t = \tilde{A}_{s1} \cdot S(t \leftarrow s1) + \tilde{A}_{s2} \cdot S(t \leftarrow s2) + \ldots.$$



Digital anthropomorphic phantoms of varying size and anatomy, Uni. of Florida

MIRD Absorbed-Fraction Dosimetry Method

1. Serial quantitative imaging
2. Co-registration across time
3. ROI (organ, tumor) segmentation
4. Model fitting and integration of the time-activity curve

$$\tilde{A} = \int_0^\infty A(t)dt$$

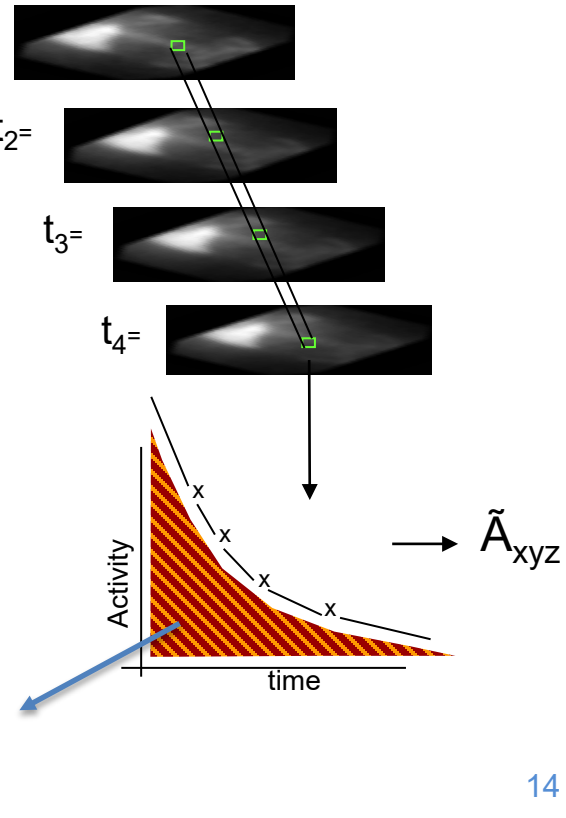
$$\tau = \frac{\tilde{A}}{A_0}$$

Time-Integrated Activity Coefficient (TIAC)

5. Time-integrated activity to dose conversion

$$D(r_T) = \sum_{r_S} \tilde{A}(r_S) \cdot S(r_T \leftarrow r_S)$$

OLINDA/EXM, Stabin M.G. et al. *JNM*, 2005; 46: 1023-7



AUC = Number of decays

Dosimetry Method

MIRD Absorbed Fraction Dosimetry

- Dosimetry for **risk evaluation** of diagnostic RPs
- **Stochastic effects**
- **Reference anatomy**: representative of a population, not patient-specific)
- **Tumor dosimetry**: assume spheres
- **Activity-based** calculation

A_{source}	$S_{(t \leftarrow s)}$	$D_{(t \leftarrow s)}$
Group of patients/healthy volunteers or extrapolated from animals	Model ± adjusted	Model ± realistic

In the Context of Therapy

Modify phantom organ masses based on organ volume identified on patient's CT

$$S(pt) = S(model) x \frac{Organ\ Mass(model)}{Organ\ Mass\ (pt)}$$

Dosimetry Method

Voxelwise Method

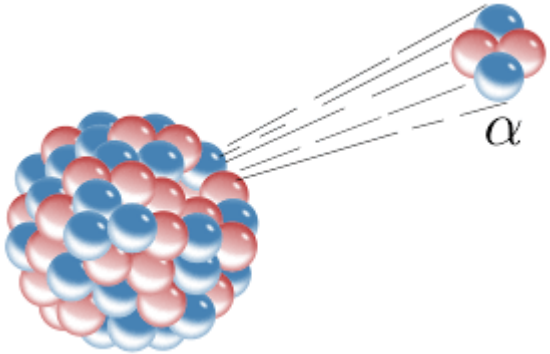
- **Organ toxicity/efficacy, tumor response**
- **Deterministic effects**
- **Patient-specific** dosimetry appropriate for RPT
- **Dose-rate based** calculation using Monte-Carlo
- Model **voxel-level** energy deposition for actual patient anatomy including tumors
- Can incorporate radiobiology (ex. calculate BED, EUD)

Table Dosimetry Platforms That Have Received 510(k) Clearance From the U.S. Food and Drug Administration, as of February 2020

Dosimetry Platform	510(k) Clearance Date	Dosimetry Method
OLINDA/EXM v1.0[27]	June, 2004	Absorbed Fraction
Hermes OLINDA/EXM v2.0	July, 2017	Absorbed Fraction
MIM SurePlan MRT	January, 2019	Voxelwise – Convolution
DOSIsoft PLANET Dose	March, 2019	Voxelwise – Convolution
Hermes Voxel Dosimetry	October, 2019	Voxelwise – Monte Carlo

Graves, S. A., & Hobbs, R. F. (2021, January). (Vol. 31, No. 1, pp. 37-44). WB Saunders

α-Particle Emitting Radionuclides



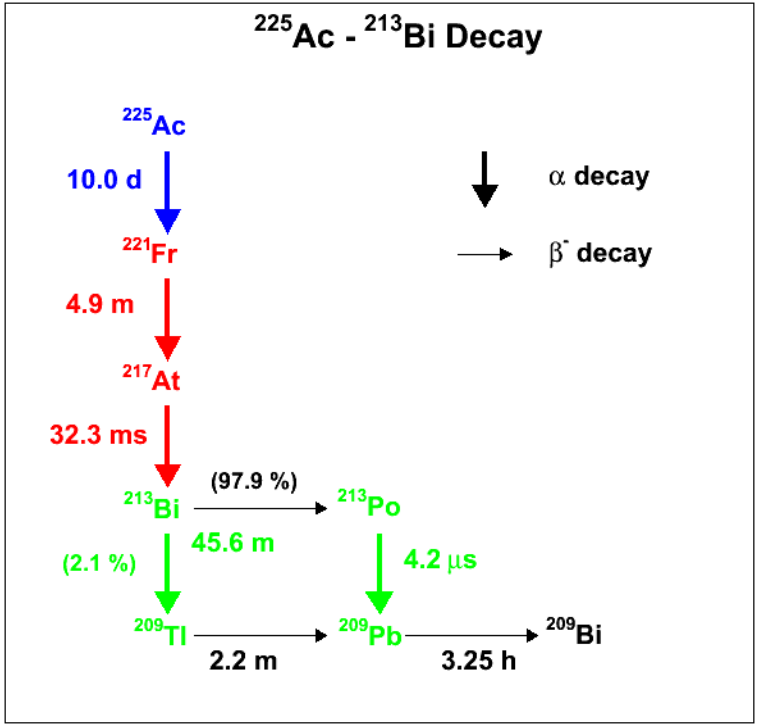
Criteria for α-Emitters:

- **Half-life** and **decay pathway,**
- Large fraction of **alpha emissions per decay,**
- High energy **photon emissions**,
- Availability in **high purity**, **cost of production**, **biological** and **chemical stability.**

- Potential for therapeutic use:
  - **^{225}Ac, ^{212}Bi, ^{213}Bi, ^{211}At, ^{212}Pb, ^{223}Ra, ^{227}Th**
- In 1997 - **^{213}Bi:** The first alpha emitter to be used in clinical trials for therapy
  - **^{213}Bi: short half-life** (45.6 min), decays with a 440 keV gamma ray - ideal for imaging
- In 2013 - **^{223}Ra:** The first FDA- approved radionuclide for the treatment of patients with castration-resistant PCa, with symptomatic bone metastases
  - **^{223}Ra: long half-life** (11.4 days), decays with four alpha emissions

Actinium-225 (Ac-225)

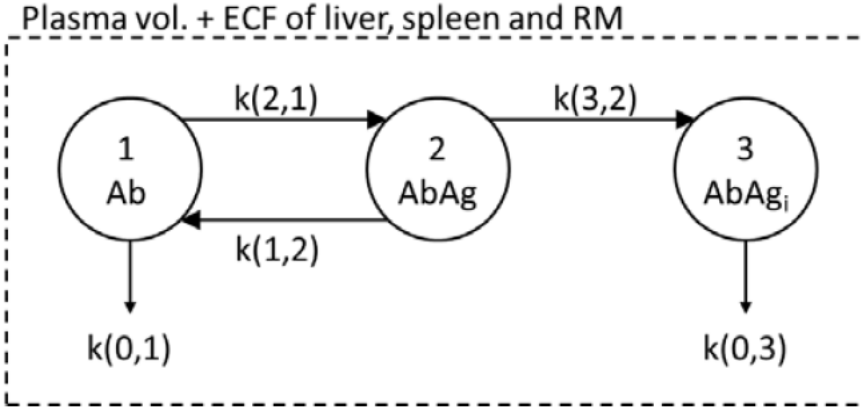
- **4 high energy alpha particles/decay**
- **Easily chelated to DOTA** and other chelating agents
- **Half-life**: 10 days, $E_{\alpha\text{-max}}$ = 6-8 MeV (23 MeV of energy overall)
- Available from ORNL
- Currently being used in a variety of preclinical and clinical trials



Dosimetry for α-Emitters

PK Fate of Daughter Nuclides

- AD estimates depend on the PK fate of unstable daughters
- Consider the half-life, biod. of daughters and radiosensitivity of organs
- Recoil energy: ~100 keV (α) vs. ~10 eV (β) - **Bond broken with agent**
- If imaging is not possible use **biokinetic modeling** to obtain time-activity curves



PK model for radiolabeled antibody – to derive kinetics of antibody-bound radionuclides
Sgouros, et al. JNM, 1993. 34(3): p. 422-30

Imaging of α-Emitting Radioisotopes

Seo, Y. (2019). *NMMI*, *53*(3), 182-188.

Ghaly, M., et al. (2019). *JNM*, *60*(supplement 1), 41-41.

Ghaly, M., et al. (2017), In *EJNMMI* (Vol. 44, pp. S180-S180).

Ghaly, M., et al.(2017). JNM, 58(supplement 1), 748-748.

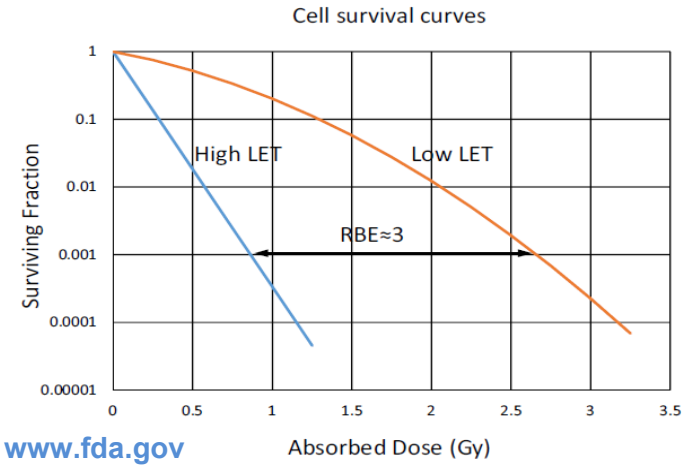
Dosimetry for α-Emitters

LET ~ 300-1200x higher than β-emitter

Relative Biological Effectiveness (**RBE**), **RBE~3-7** but **depends on AD, biological endpoint, tissue type**

$$RBE(x) = \frac{D_r(x)}{D_t(x)}$$

-> x-rays, γ-rays, β-particles
-> test radiation



www.fda.gov

RBE Value - MIRD Pamphlet #22

- Based on a review of experimental literature, an **RBE** value between **3-5** was recommended for cell killing by a panel convened by the DOE in 1996 (Feinendegen et al. Radiat. Res. 1997; 148: 195-201)
- **RBE = 5** was recommended for projecting the possible deterministic biologic effects associated with an estimated α-particle absorbed dose.
- **RBE = 5** accounts for the difference in biological effects of alpha-particle vs external beam irradiation.

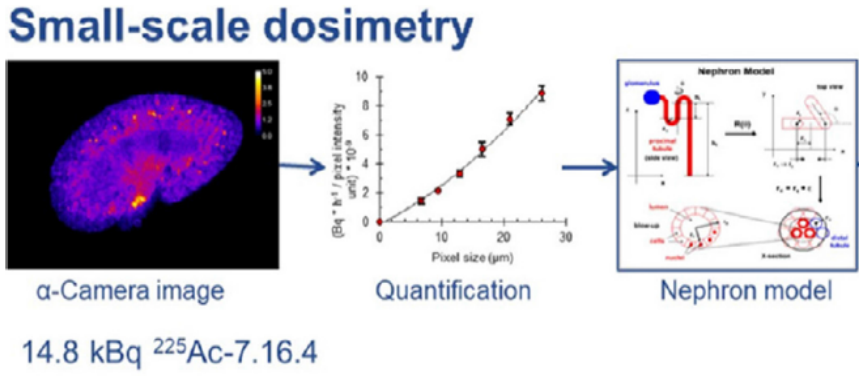
Dosimetry for α-Emitters

Range ~100 µm vs few mm

Dosimetry method should account for both **organ-level** and **micro-scale** distributions (range is 50-100 µm)

- **Organ-Level:** Patient-imaging
- **Micro-scale:** Combine whole-organ measurements with preclinical measurements – µ-scale biod./PK data in **sub-regions of critical organs**

Hobbs et al. PMB (2012)



Implement in the context of the MIRD methodology

MIRD Pamphlet #22

$$D_{RBE}(r_T, r_D) = RBE_{\alpha} \cdot D_{\alpha}(r_T, rD) + RBE_e \cdot De(r_T, rD) + RBE_{ph} \cdot Dph(r_T, rD)$$

Summary

- RPT is a systemic and targeted treatment modality for disseminated cancer.
- Dosimetry for RPT has its roots in the formalism established by the MIRD Committee to assess radiation risk for diagnostic radiopharmaceuticals.
- A more appropriate dosimetry scheme for RPT involves a more patient-specific approach, voxelized calculations and tumor dosimetry.
- Dosimetry for alpha emitters includes other special considerations: RBE value, micro-scale dosimetry.
- Pre-clinical and clinical dosimetry studies in general are essential for the development of new radiopharmaceuticals for RPT.

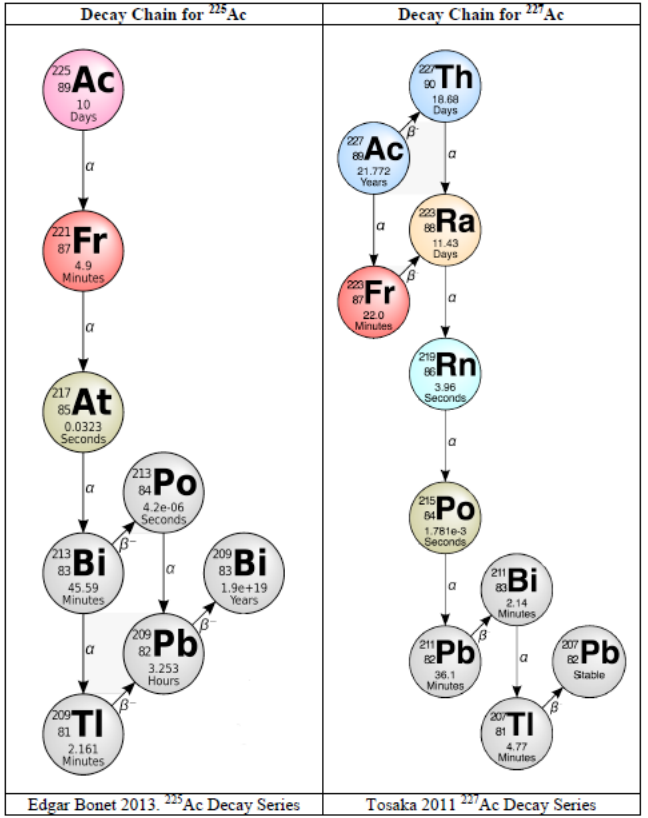
Thank You!

Additional Slides

Accelerator Produced Ac-225

Accelerator-produced Ac-225 (BNL, LANL, ORNL) -> ~0.12% Ac-227 (**half-life 218 years**) impurity in the final product

- Both Ac-225 and Ac-227 are α-emitters – daughters may become unconjugated during decay
- **Ac-225:** Daughter products decay in the same location as parent - However, re-distribution of **free Bi-213** to the kidneys can more than double the dose to kidneys (Schwartz 2011)
- **Ac-227: Fr-223** (1.4%, 22 min) and **Th-227** (98.6%, 18.7 days) -> **Ra-223** (11.4 days) - **Free Th-227** and **Ra-223** may accumulate in bone.
- Different scenarios can be considered: free and bound for Ac-225 and Ac-227 and daughters
- Biod. data for Ac-225 may be collected using surrogate imaging (In-111) – assume Ac-225 and Ac-227 remain bound
- ICRP bio-kinetic models for free radionuclides scenario
- Highest impact in added risk due to Ac-227 presence is when Th-227 becomes unconjugated.



Dosimetry of alpha emitter: and caution for extravasation.

Kish Chakrabarti, Ph.D., FAAPM
DIRM/OND/CDER

Overview

- Radium-223 dichloride Castration-resistant prostate cancer in patients with bone metastases: FDA Approved alpha emitter

Outline:

Discuss Dose calculations procedure provided by the sponsor :

- Pharmacokinetics: Glenn Flux
- Dosimetry: Sgouros

Extravasations from alpha emitters

2

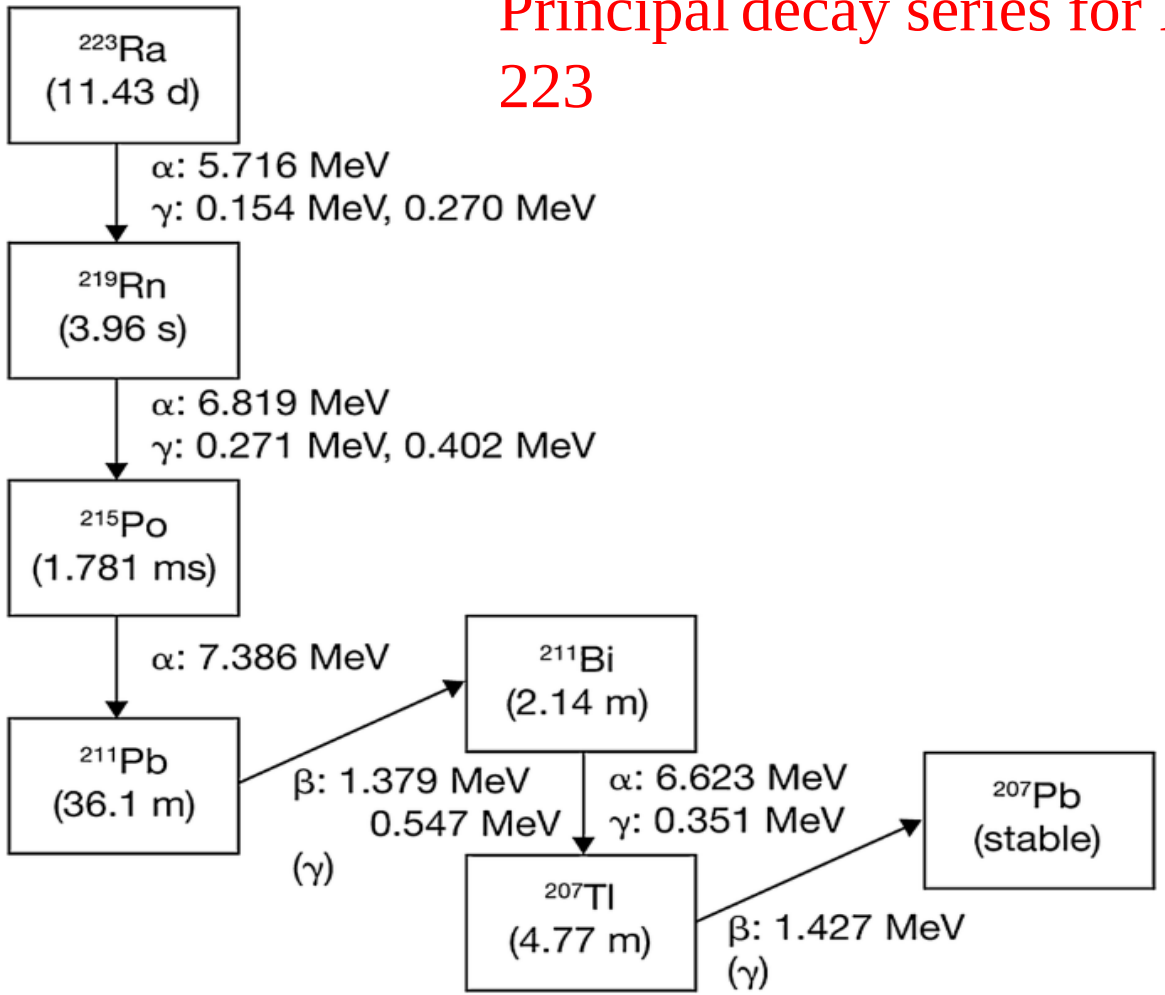
Table 1.

Decay chain for radium-223 (^{223}Ra). The relative proportions of the branched decay from bismuth-211 (^{211}Bi) are 0.997 and 0.003 for ^{211}Bi → thallium-207 (^{207}Tl) and ^{211}Bi → polonium-211 (^{211}Po), respectively

Radionuclide	Mode of decay	Abundance	Half-life
^{223}Ra → ^{219}Rn	α	100%	11.43 days
^{219}Rn → ^{215}Po	α	100%	3.96 s
^{215}Po → ^{211}Pb	α	100%	1.78 ms
^{211}Pb → ^{211}Bi	β^-	100%	36.1 min
^{211}Bi → ^{211}Po	β^-	0.276%	2.14 min
^{211}Bi → ^{207}Tl	α	99.72%	2.14 min
^{211}Po → ^{207}Pb	α	100%	0.516 s
^{207}Tl → ^{207}Pb	β^-	100%	4.77 min
^{207}Pb → –	Stable	–	–

^{207}Pb, lead-207; ^{211}Pb, lead-211; ^{219}Rn, radon-219.

Principal decay series for Ra-223



- Makoto Hosono et al. *Annals of Nuclear Medicine* **volume 33**, pages 211–221 (2019)

Radioactive Properties of Radium-223

- Radium-223 (223Ra) is a natural bone-seeking alpha emitter with high linear energy transfers (LET **80 keV/micrometer)** leads to a high frequency of double-strand DNA breaks in adjacent cells, resulting in an anti-tumor effect on bone metastases.

- **The alpha particle range from radium-223 dichloride is less than 100 micrometers (less than 10 cell diameters)** which limits damage to the surrounding normal tissue.
- **There are 5 alpha, 3 electron, 18 photons (12 gamma and 6 x-ray) emissions in the process.**

Radioactive Properties of Radium-223

- Ra-Dichloride clears quickly from the blood, with only 1.1% of administered activity remaining in the blood after 24 hours and a large amount (61% at 4 hours) taken up in the skeleton.

- **Radium-223 decays in six steps via a chain of alpha and beta emissions into stable lead, ^{207}Pb . The total amount of emitted energy per 223Ra-decay is 28.2 MeV.**

- **$^{223}Ra \rightarrow {}^{219}Rn \rightarrow {}^{215}Po \rightarrow PB \rightarrow {}^{211}Bi \rightarrow {}^{207}TI \rightarrow {}^{207}PB$ (stable)**

  $\searrow \quad \nearrow$

  ^{211}Po

6

Detection and Imaging Challenges of Ra-223

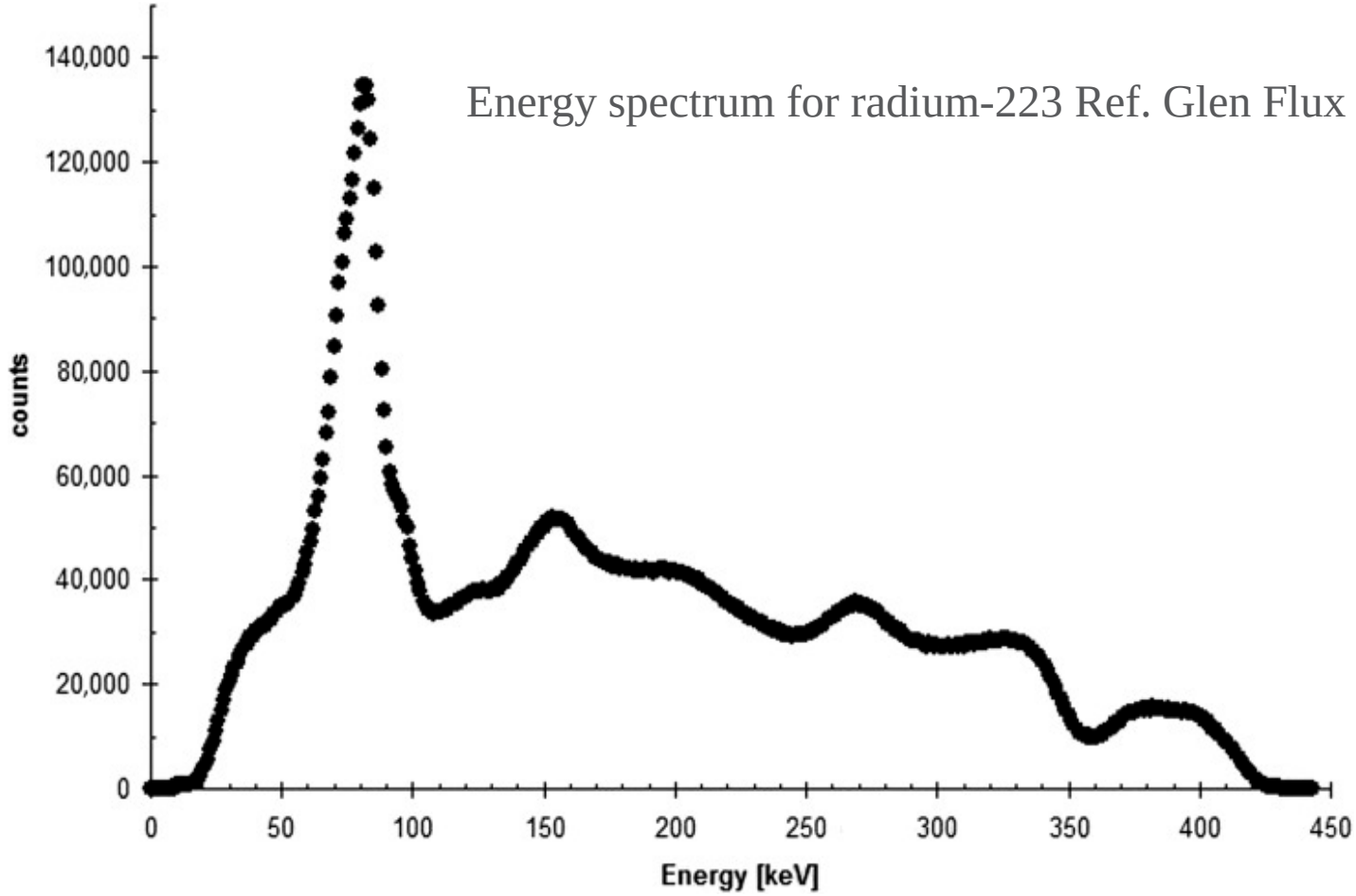
- ^{223}Ra undergoes a complicated decay scheme, with a series of six daughter products, before decaying to stable lead. The total emitted energy is 28.2 MeV, of which 95% is from alpha emissions, 3.2% from beta particles and <2% from gamma emissions.

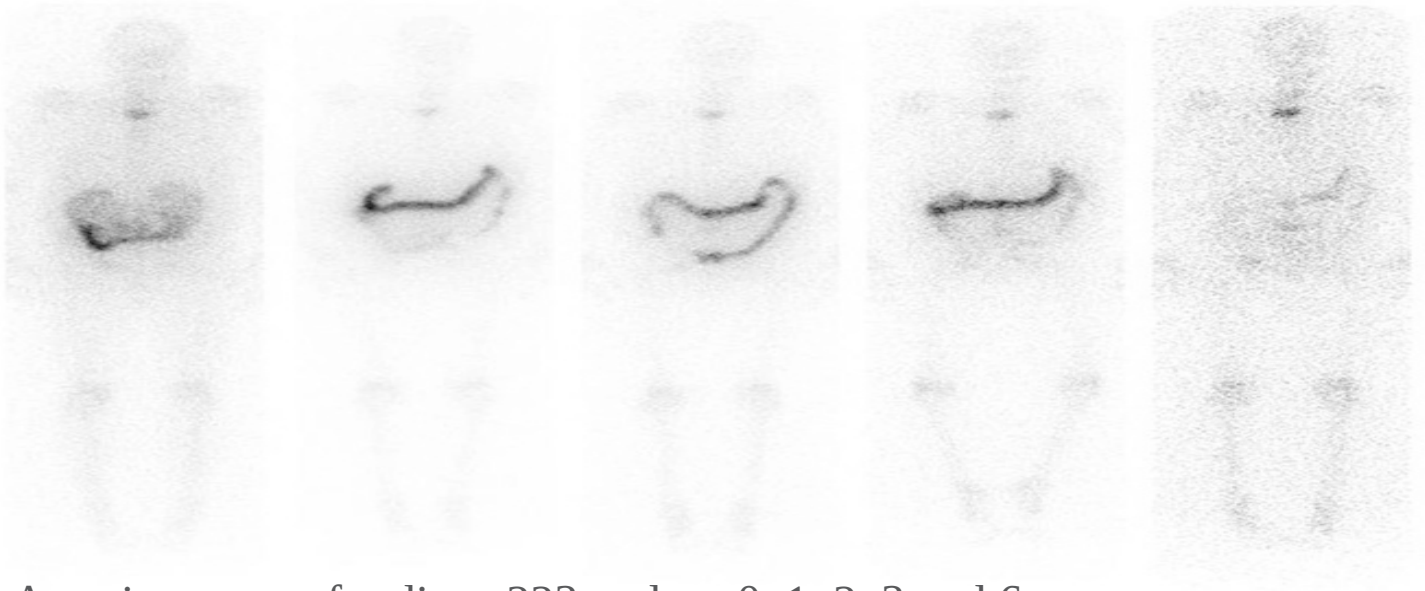
- This results in a low signal which can present challenges for quantitative imaging, but nevertheless, introduces the potential for individualized biodistribution studies.

- Imaging characteristics for ^{223}Ra, identifying three energy peaks as suitable for imaging of the 10 photon energies emitted with a probability >1%.

- Optimal energy windows were set at 82, 154 and 270 keV, each with a 20% width. Camera sensitivity was found to be 69, 31 and 34 counts per second (cps) MBq^{-1} from the three windows, respectively.

Energy spectrum for radium-223 Ref. Glen Flux





Anterior scans of radium-223 at days 0, 1, 2, 3 and 6 following administration of 55 kBq/kg. The study confirmed that activity was quickly cleared Ref. Glen Flux

Experimental:

- Mean absorbed radiation doses in major organs were calculated based on clinical and biodistribution data in **five patients with castration-resistant prostate cancer**

- Although whole-body dosimetry can be assessed from either whole-body scans or from external retention measurements, dosimetry for red marrow can be obtained from imaging and from blood sampling and should take into account the activity in the extracellular fluid, the blood, the bone marrow cells, the bone and major organs of uptake.

Patient data acquisition several detailed processes and equipment:

- 2 mm arc with NaI detector used in six different energy ranges 37 keV-890 keV. Whole-body measurements were performed
- Gamma spectroscopy of samples of urine and feces using a whole body counter
- Sample counter for all blood and samples counting using automatic gamma counter
- Gamma camera imaging in the energy range 74 keV to 284 keV

These provided Imaging, blood samples, excretion products and activity quantification

The study confirmed that activity was quickly cleared from the blood.

Theoretical Model and Calculations:

- The absorbed doses in normal organs were calculated using the OLINDA-EXM software (Organ Level Internal Dose Assessment/Exponential Modeling), **however the OLINDA-EXM program has been designed for use with established radionuclides, all of which are beta- and gamma-emitters i.e. long range particles. It is not yet adapted to the very short radiation range of alpha-emitters, and additional assumptions have been made to provide the best possible dosimetry calculations.**
- The dosimetry calculations are performed using **the biodistribution data by Glenn Flux** an internal report from the sponsor.
- Calculations of absorbed **radiation doses were performed Sgouros** using OLINDA reported through an internal report from the sponsor.

- Absorbed dose calculations were performed using the MIRD Committee S-value based method as described in pamphlet 21.

- The cumulative activity CA (MBq x h) in the source organs was derived from the whole body patient scans for all organs with quantifiable amounts of activity in the images.
- Residence time (MBq x h/MBq) is the is the input data for OLINDA-EXM program (OLINDA).
- an alpha particle-emitter, assumptions were made for intestine, red marrow and bone/osteogenic cells to provide the best possible absorbed radiation dose calculations, considering its observed biodistribution and specific characteristics. Additional particular modeling was applied for the lungs.

The absorbed dose to the lungs is estimated as the dose contribution **from ^{223}Ra and daughter decays in the blood-containing fraction of the lung mass and also the dose contribution from ^{219}Rn and daughter decays in the respiratory tract.**

Absorbed dose calculations(contd.)

The absorbed dose to all organs except for GI (incl. small and large intestines), RM, bone/osteogenic cells, and HW was obtained using OLINDA. Since the daughters have been confirmed, in preclinical and clinical studies, to decay at the site of parent decay, the residence time for ^{223}Ra was applied to all of the daughters and a separate OLINDA calculation was performed for each daughter. The resulting absorbed doses were weighted to reflect the yield of each daughter in the ^{223}Ra decay scheme, and summed to provide the total absorbed dose.

Details regarding the GI, RM, bone/osteogenic cells, and HW calculations are provided by Sgouros.

Table 1: Absorbed Radiation Doses per Administered Activity and Accumulated Dose

Organ	Mean (mGy/MBq)	Mean (rad/mCi)	Coefficient of variation (%)	Absorbed dose* (Gy)	Accumulated absorbed dose** (Gy)
Osteogenic cells	1152	4263	41	4.61	28
Red marrow	139	514	41	.556	3.34
LLI wall*	46	172	83	.184	1.10
Colon*	38	142	56	.152	.912
ULI wall*	32	120	50	.128	.768
Small intestine wall	7.3	27	45	.029	.174
Urinary bladder wall	4.0	15	63	.0160	.096
Kidneys	3.2	12	36	.013	.0780
Liver	3.0	11	36	.0123	.0738
Heart wall	1.7	6.4	42	.0068	.0400
Lungs	1.2	4.5	48	.0048	.0290
Ovaries	0.49	1.8	40	.00196	.018
Uterus	0.26	0.94	28	.001	.006
Gallbladder wall	0.23	0.85	14	.00092	.00552
Stomach wall	0.14	0.51	22	.00056	.0034
Adrenals	0.12	0.44	56	.00048	.0030
Muscle	0.12	0.44	41	.00048	.0030
Pancreas	0.11	0.41	43	.00044	.00264
Brain	0.10	.37	80	.00040	.00240
Spleen	0.09	.33	54	.00036	.0022
Testes	0.08	.31	59	.00032	.0021
Skin	0.07	.27	79	.00028	.00168
Thyroid	0.07	.26	96	.00028	.00168
Thymus	0.06	.21	109	.00024	.00144
Breasts	0.05	.18	120	.00020	.00120
Whole body	23	86	16	.092	.552

Adapted from the table in labelling where RBE value of 1 is used

Calculated absorbed radiation doses :

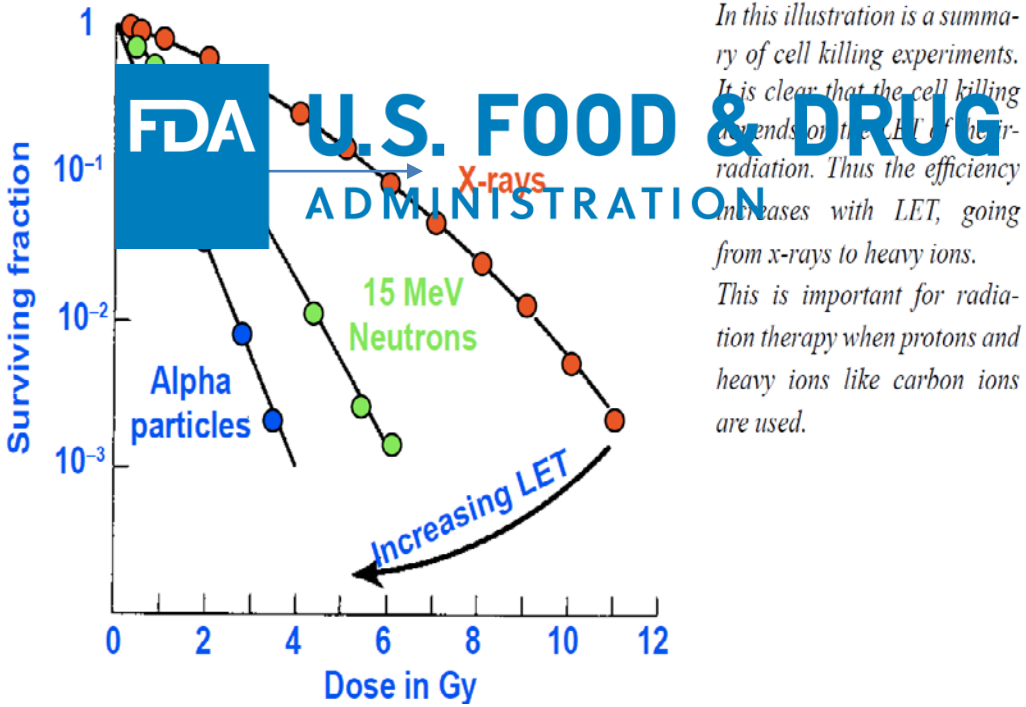
- The major radiation dose is to the **osteogenic cells** on bone surfaces as associated with bone metastases. The highest absorbed doses were calculated in the bone (osteogenic cells) (4.75 Gy for single and; 28.5 Gy after 6 administrations) and **the red marrow, which received an absorbed dose of 0.573 Gy**, for a single administration assuming repair takes place within the administration interval.
- As shown on table 1, the lung absorbed dose for a 73-kg adult male receiving 55 kBq/kg 223Ra is 4.9 mGy (with accumulated absorbed dose of 2.4 after 6 administration) , with range (2.8 Gy to 7.2 Gy) (2) still far below the 17.50 Gy level at which lung toxicity is seen following whole lung irradiation at 2000 mGy/fraction.

Estimates of the threshold doses for morbidity* or mortality in adults exposed to acute, fractionated or protracted, and chronic irradiation. The values are generated from ICRP 118 (9)

Table 2

Organ	1%: morbidity Associated with disease	Time to death or organ failure	Threshold absorbed dose (Gy) for !% rate mortality or organ failure
Bone Fracture		>1 year	25 in 2 Gy fraction
Red Marrow	Depression of hematopoiesis in 3-7 days; possible H-ARS mortality in 30-60 days[b]		10-14
Lungs	Pnumonitis mortality	1-7 months	17.5

Relative Biological Effectiveness (RBE), RBE~3-7 but depends on AD, biological endpoint, tissue type as discussed by Donika Plyku, PhD



In this illustration is a summary of cell killing experiments. It is clear that the cell killing depends on the LET of the irradiation. Thus the efficiency increases with LET, going from x-rays to heavy ions. This is important for radiation therapy when protons and heavy ions like carbon ions are used.

Absorbed dose vs Effective dose

The absorbed dose values presented in this report are expressed in Gy and not as effective doses in Sv. Although effective dose can be calculated, it does not apply to the therapeutic use of alpha-particle-emitting radiopharmaceuticals. A detailed explanation for this is provided in MIRD Pamphlet 21 and in the MIRD Committee's monograph on alpha-particle dosimetry

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Extravasation: Usual acute signs and symptoms

- pain,
- erythema,
- swelling,
- Compartmental syndrome
- local blistering (indicative of at least a partial-thickness skin injury),
- mottling/darkening of skin,
- ulceration (usually not evident until 1-2 weeks after injury),
- NOTE Extravasation can be asymptomatic

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Other clinical consequences

- Loss of diagnostic or therapeutic efficacy
- Delayed reactions
  - Ulceration, fibrosis

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Extravasation:

- The primary effect to the surrounding tissue can be attributed to nonpenetrating emissions, e.g. soft X-rays (10Kev).
- Extravasation of diagnostic radiopharmaceuticals is common. 99mTc, 123I, 18F, and 68Ga, purely β emitters do not require specific intervention
- Extravasation of therapeutic radiopharmaceuticals can give severe soft tissue lesions.
- Although not evidence based, surgical intervention should be considered. Dosimetry and follow up is advised.
- Pharmaceutical intervention has no place yet in the immediate care of radiopharmaceutical extravasation

Extravasation from Alpha emitter

- Cutaneous squamous cell carcinoma should be recognized as a rare but potential adverse event following cutaneous extravasation of radium-223 and is likely a side effect that is severely underreported. Katie E. Benjegerdes el alroc (Bayl Univ Med Cent) 2017;30(1):78–79

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Summary:

- We have discussed Radium-223 the sole alpha radionuclide approved by the FDA.
- Alpha emitters rapidly and increasingly finding use in nuclear medicine
- Want of proper imaging technology makes it very difficult to estimate absorbed organ doses
- Determination of proper RBE is also an important issue
- Extravasation incidents are still a few and far between. FDA continues to monitor through its post marketing reporting system