$^{223}Ra\text{-}Cl_2$

Biodistribution, dosimetry and radiation protection

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THE ROYAL MARSDEN

Skåne University Hospital

Radium

Marie and Pierre Curie discovered radium in 1898

- Glow-in-the-dark paint
  - Dial painters

- Radium soap, creme, water, chocolate, etc

Some Radium-Isotopes

- ^{226}Ra
  - Marie Curie
  - Unit: 1 Curie = the activity in 1 gram of ^{226}Ra
  - 1 mCi = 37 MBq
- ^{224}Ra – ankylosing spondylitus
- ^{223}Ra – treatment of skeletal metastases

$^{223}Ra\text{-}Cl_2$ – 'Xofigo'

Decay data

$$
\begin{tikzcd}
{}^{223}\mathrm{Ra} \arrow[r] & {}^{219}\mathrm{Rn} \arrow[r] & {}^{215}\mathrm{Po} \arrow[r] & {}^{211}\mathrm{Pb} \arrow[r] & {}^{211}\mathrm{Bi} \arrow[r] \arrow[dr] & {}^{207}\mathrm{Tl} \arrow[r] & {}^{207}\mathrm{Pb}\ (\text{stable}) \\
& & & & & {}^{211}\mathrm{Po} \arrow[ur] &
\end{tikzcd}
$$

Decay data

$$^{223}\mathrm{Ra} \rightarrow {}^{219}\mathrm{Rn} \rightarrow {}^{215}\mathrm{Po} \rightarrow {}^{211}\mathrm{Pb} \rightarrow {}^{211}\mathrm{Bi} \rightarrow {}^{207}\mathrm{Tl} \rightarrow {}^{207}\mathrm{Pb}\ \text{(stable)}$$

$$^{211}\mathrm{Bi} \rightarrow {}^{211}\mathrm{Po} \rightarrow {}^{207}\mathrm{Pb}$$

Decay data

$^{223}Ra \rightarrow {}^{219}Rn \rightarrow {}^{215}Po \rightarrow {}^{211}Pb \rightarrow {}^{211}Bi \rightarrow {}^{207}Tl \rightarrow {}^{207}Pb$ (stable)

$^{211}Bi \rightarrow {}^{211}Po \rightarrow {}^{207}Pb$

Radionuclide	Mode of decay	Halflife
$^{223}Ra \rightarrow {}^{219}Rn$	α	11.4 d
$^{219}Rn \rightarrow {}^{215}Po$	α	4 s
$^{215}Po \rightarrow {}^{211}Pb$	α	1.8 ms
$^{211}Pb \rightarrow {}^{211}Bi$	β^-	36 min
$^{211}Bi \rightarrow {}^{207}Tl$	α	2 min
$^{207}Tl \rightarrow {}^{207}Pb$	β^-	4.8 min
$^{207}Pb \rightarrow$ -	Stable	-

Emitted energy

$^{223}Ra \rightarrow {}^{219}Rn \rightarrow {}^{215}Po \rightarrow {}^{211}Pb \rightarrow {}^{211}Bi \rightarrow {}^{207}Tl \rightarrow {}^{207}Pb$ (stable)

$^{211}Bi \rightarrow {}^{211}Po \rightarrow {}^{207}Pb$

- 4 alpha emitters
- 2 beta emitters
- 12 gammas
- 6 X-rays

28 MeV per decay

95 % from alphas

Radioprotection

$$^{223}Ra \rightarrow {}^{219}Rn \rightarrow {}^{215}Po \rightarrow {}^{211}Pb \rightarrow {}^{211}Bi \rightarrow {}^{207}Tl \rightarrow {}^{207}Pb \text{ (stable)}$$

$$^{211}Bi \rightarrow {}^{211}Po \rightarrow {}^{207}Pb$$

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^{219}Rn: Inert gas

Short half-life (4 s) → unlikely to diffuse and become volatile

Radioprotection

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$^{211}Bi \rightarrow {}^{211}Po \rightarrow {}^{207}Pb$

^{219}Rn: Inert gas

Short half-life (4 s) → unlikely to diffuse and become volatile

^{211}Pb: Longest half-life

36 minutes → too short to relocate from bone

(Henriksen et al, J Nucl Med 2003)

Radioprotection

$$^{223}Ra \rightarrow {}^{219}Rn \rightarrow {}^{215}Po \rightarrow {}^{211}Pb \rightarrow {}^{211}Bi \rightarrow {}^{207}Tl \rightarrow {}^{207}Pb \text{ (stable)}$$

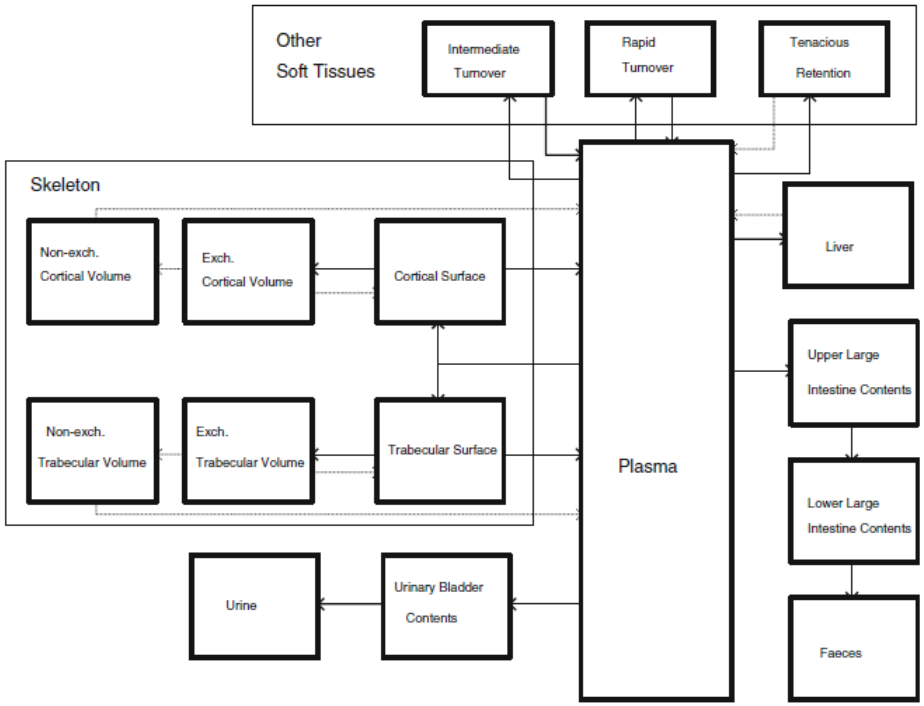
$$^{211}Bi \rightarrow {}^{211}Po \rightarrow {}^{207}Pb$$

“Normal” protection:

- Gloves
- Shielding (lead pot, etc)
- Time
- Distance
- Fume hood

Biodistribution and dosimetry

ICRP 67, Age-dependent doses to members of the public…, (1992)



Biodistribution and dosimetry

Biokinetic model of radium in humans and beagles; Polig et al, Health Phys (2004)

- Update of the ICRP model
- ^{226}Ra
- No dosimetry

Biodistribution and dosimetry

High-linear energy transfer irradiation targeted to skeletal metastases by the α-emitter 223Ra: Adjuvant or alternative to conventional modlaities? Bruland et al, Clin Cancer Res (2006)

- Highest effective doses to (w_R=5):
  - Bone endosteum 3700 mSv/MBq
  - Liver 180
  - LLI wall 110
  - ULI wall 48
  - Bladder wall 17

Biodistribution and dosimetry

Dosimetry of ^{223}Ra-chloride: dose to normal organs and tissues;

Lassmann et al, EJNMMI (2012)

- Based on the model in ICRP67

- Highest effective doses to (w_R=5):

– Bone endosteum	3800 mSv/MBq
– Red marrow	370
– Liver	180
– LLI wall	110
– Colon	73

Dosimetry - comparison

Lassmann et al vs Bruland et al (w_R=5, Sv/MBq)

Organ	Dose coefficients This work Sv/Bq[a]	Dose coefficients Bruland et al. [1] 70 kg person Sv/Bq[a]
Bone endosteum	3.8E-06	3.7E-06
Breast	1.6E-08	1.6E-08
GI tract		
ULI wall	4.8E-08	4.8E-08
LLI wall	1.1E-07	1.1E-07
Kidneys	1.7E-08	1.6E-08
Liver	1.8E-07	1.8E-07
Red marrow	3.7E-07	–
Lungs	1.6E-08	1.6E-08
Bladder wall	1.7E-08	1.7E-08

Biodistribution and dosimetry

A phase 1, open-label study of biodistribution, pharmacokinetics and dosimetry of $^{223}Ra\text{-}Cl_2$

Challenge: To image ^{223}Ra

Challenge: Imaging of ^{223}Ra

Challenge 1: Emission data

^{223}Ra – Imaging of mother

$^{223}Ra \rightarrow {}^{219}Rn \rightarrow {}^{215}Po \rightarrow {}^{211}Pb \rightarrow {}^{211}Bi \rightarrow {}^{207}Tl \rightarrow {}^{207}Pb$ (stable)

Mother radioisotope	Energy [keV]	Probability [%]
^{223}Ra	122	1.2
^{223}Ra	144	3.3
^{223}Ra	154	5.7
^{223}Ra	269	13.9
^{223}Ra	324	4.0
^{223}Ra	338	2.8
^{223}Ra	84	2.5
^{223}Ra	81	15.2
^{223}Ra	95	11.5
^{223}Ra	12	22.9

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^{223}Ra – Imaging of daughters

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Mother radioisotope	Energy [keV]	Probability [%]
^{219}Rn	271	10.8
^{219}Rn	402	6.6
^{219}Rn	11	1.0
^{211}Pb	405	3.8
^{211}Pb	427	1.8
^{211}Pb	832	3.5
^{211}Bi	351	12.9
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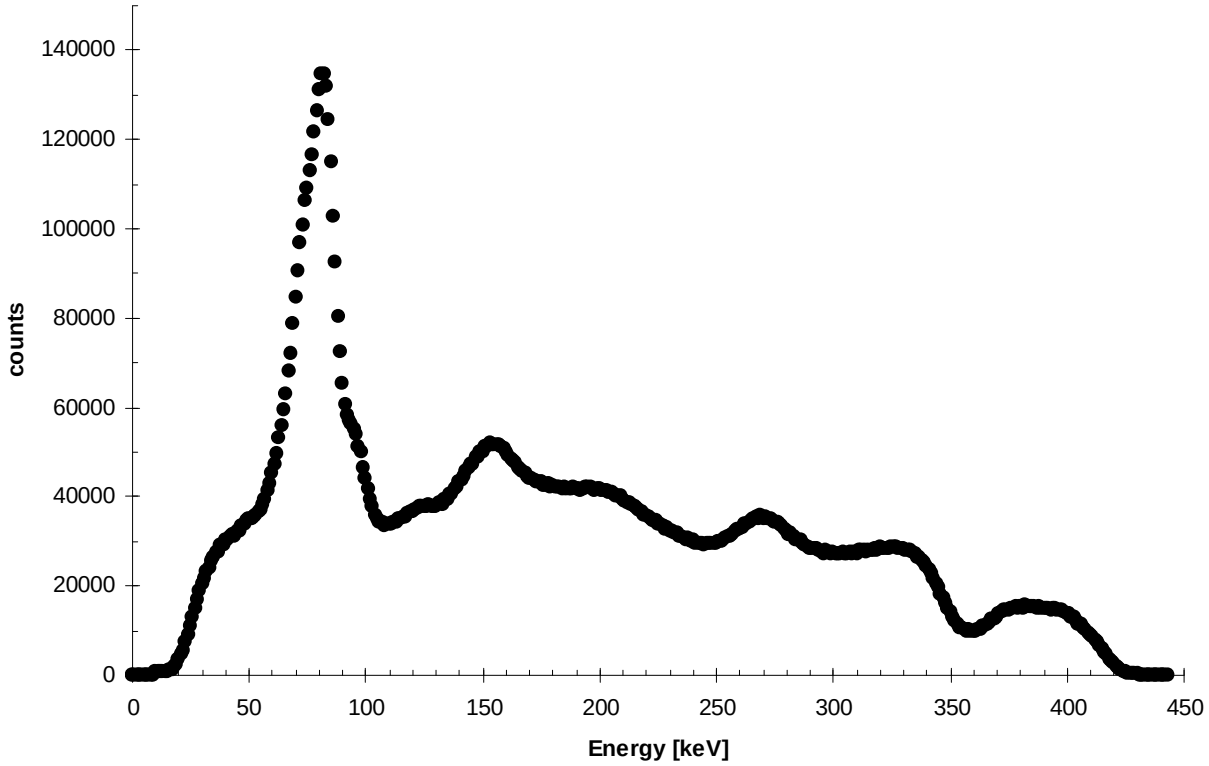
^{223}Ra – Energy spectrum

82 keV

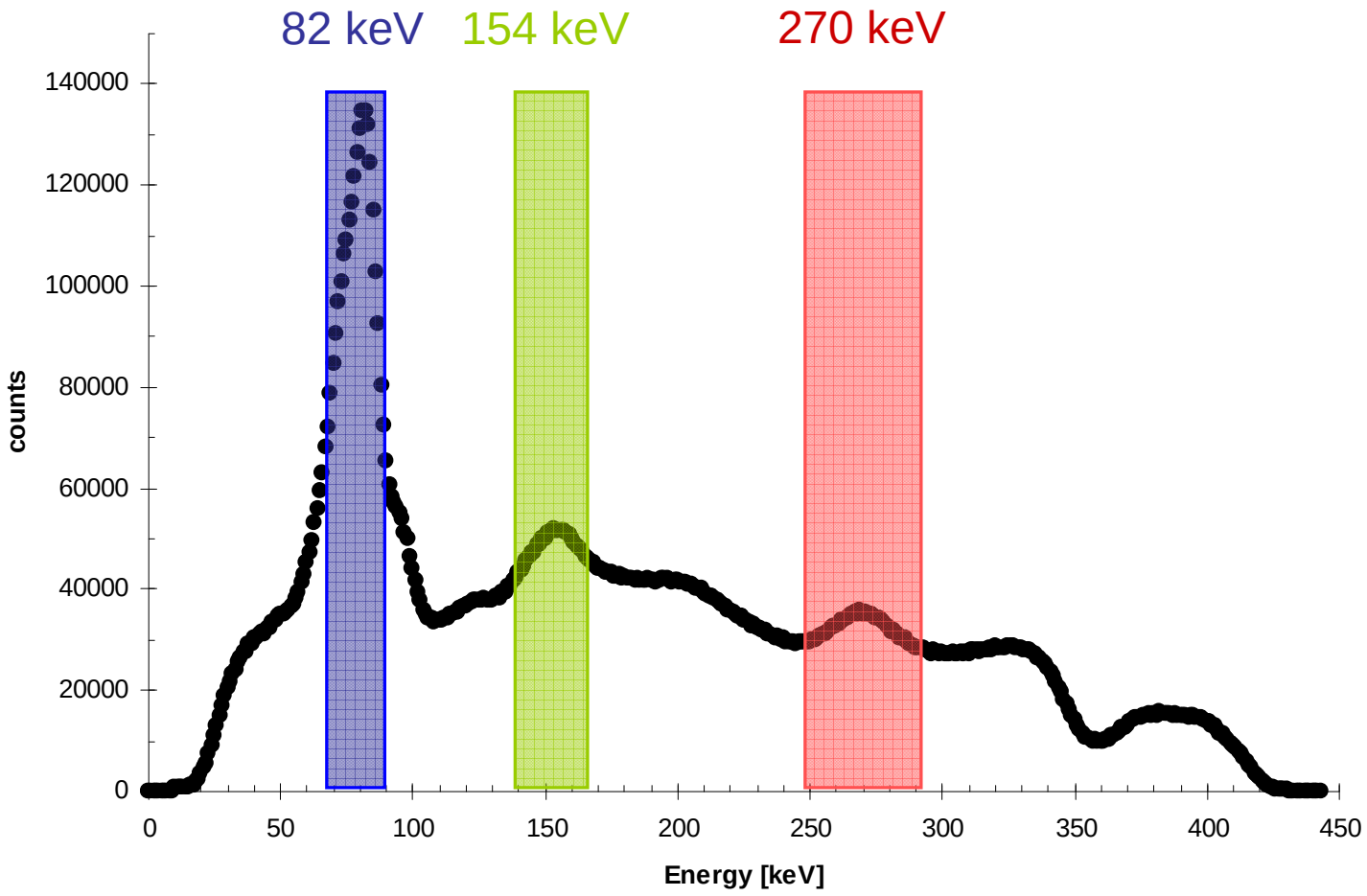
154 keV

270 keV

351 keV



^{223}Ra – Energy window settings



Challenge: Imaging of ^{223}Ra

Challenge 2: Administered activity

- Administered activity of Alpharadin for therapy (6 injections, 4 weeks apart)
  - 50 kBq/kg body weight
  - 3.5 MBq (70 kg)

Challenge: Imaging of ^{223}Ra

Challenge 2: Administered activity

- Administered activity of Alpharadin for therapy (6 injections, 4 weeks apart)
  - 50 kBq/kg body weight
  - 3.5 MBq (70 kg)
- Administered activity for biodistribution (2 injections, 6 weeks apart)
  - 100 kBq/kg body weight
  - 7 MBq (70 kg)

Challenge: Imaging of ^{223}Ra

Challenge 3: Quantitative imaging

- 3D imaging
  - SPECT: to few photons emitted
- 2D imaging
  - Whole body scans
  - Planar spot images

^{223}Ra - Imaging

- Sensitivity

  10 x 10 x 0.2 cm, perspex

- Partial ‘volume’ effect

  Circles, radii: 5, 7, 10, 15, 25 mm

- Spatial resolution

  Two line sources, 5 cm apart

- Effective attenuation coefficients

  Perspex over source

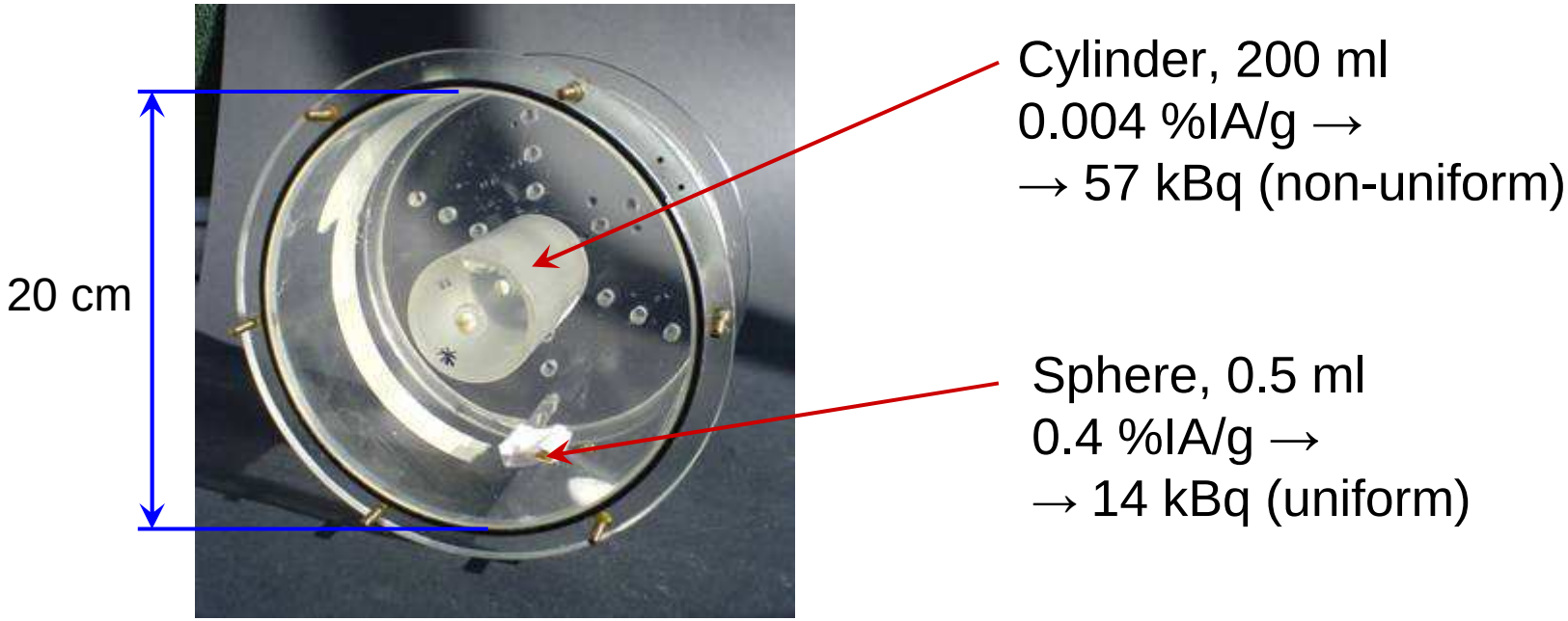
^{223}Ra – Clinical situation

Extrapolation of activity uptake

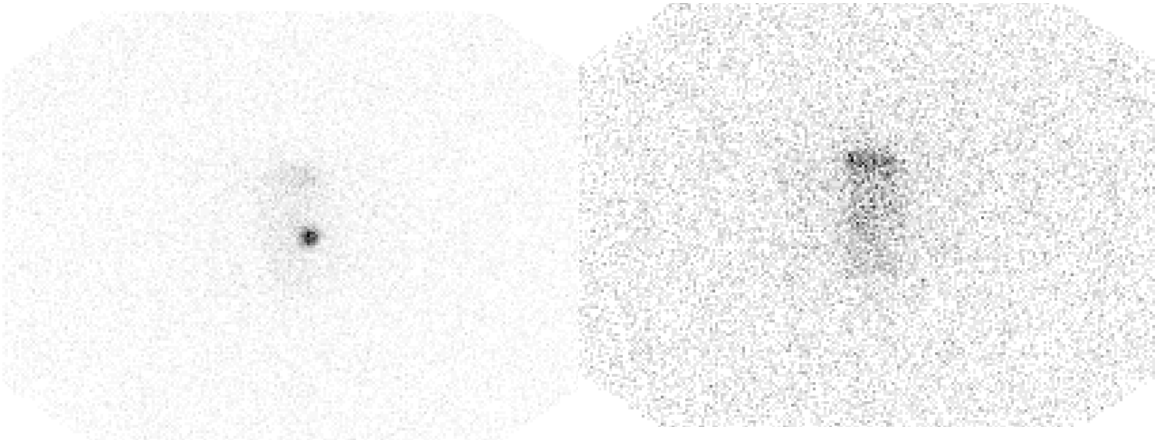
Species	Whole body weight	%IA/g	%IA/g * WB(weight)
Mouse	19 – 21 g	35 – 40 %IA/g	Appr. 800
Rat	120 – 150 g	6 %IA/g	Appr. 800
Human	70 kg	***0.01 %IA/g***	Assume 800

Mouse: Henriksen et al, J Nucl Med, 44, 252-259, 2003.
Rat: Henriksen et al, Cancer Research 62, 3120-3125, 2002.

^{223}Ra – Clinical situation



^{223}Ra – Clinical situation



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Challenge: Imaging of ^{223}Ra

Recommendations when the administered activity is 100 kBq/kg body weight

- 2D imaging
  - Whole body scans: 6 cm/min scan speed
  - Planar spot images: 30 min acquisition time
- Energy window:
  - 82 keV ; 20% width
- Medium energy collimator

Imaging ^{223}Ra

Conclusions

- Quantitative imaging of ^{223}Ra during therapy is possible
- The sensitivity is the limiting parameter

  high absorbed dose per decay → injected activity is low
- Imaging of the daughters seems to be difficult

Hindorf et al, Nucl Med Commun. 2012 Jul;33(7):726-32

Dose calibrator

- Published dial settings for ^{223}Ra for commercial dose calibrators
- Dependence on source geometry
  - different dial settings for vials and syringes

Bergeron et al, Development of secondary standards for 223Ra; Applied Radiation and Isotopes (2010)

^{223}Ra-chloride – Clinical study

- Patients diagnosed with skeletal metastases from hormone refractory prostate cancer
- Two intravenous injections of ^{223}Ra-chloride (100 kBq/kg body weight), 6 weeks apart
- Collect pharmacokinetic data after each injection
- Dosimetry

Biodistribution

- No specific uptake visible on scintillation camera images in normal organs such as:
  - Kidneys
  - Liver
  - Spleen

- The activity concentration in blood or urine was used to get an upper limit of the absorbed dose.

Dosimetry

- Absorbed dose to the total body: 30 mGy/MBq

- Absorbed doses to:

– Bone endosteum	2577 mGy/MBq
– Bone marrow	420
– LLI wall	78
– ULI wall	48
– SI wall	7
– Kidneys	7

^{223}Ra-chloride

Conclusions

- The bio-distribution and pharmacokinetics for the first and second injection are similar.
- The main route of excretion is via faeces
- The activity leaves blood quickly and is taken up in bone.
- No major organs are visible in images.

Dosimetry - comparison

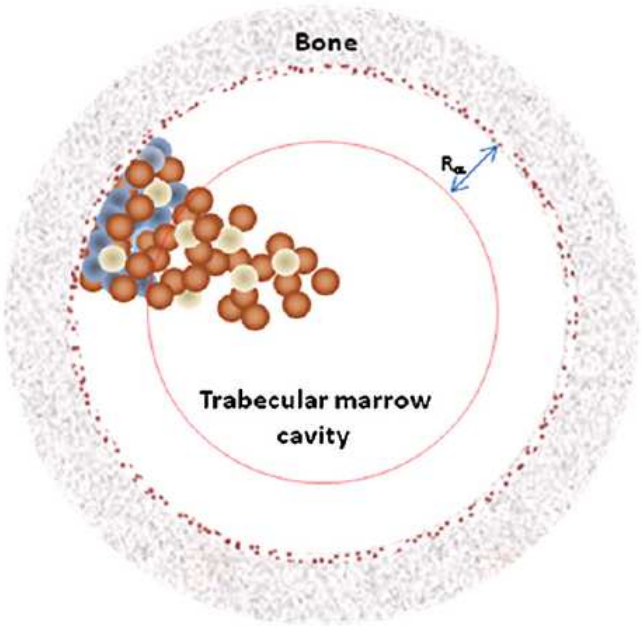
Absorbed dose per injected activity [mGy/MBq]

	Lassmann et al	This study
Bone	-	-
Bone endosteum	790	2577
SI wall	5	7
LLI wall	88	78
ULI wall	35	48
Lung	4	
Spleen	4	
Liver	42	3
Kidney	4	7
Bone marrow	95	420
UB wall	5	1

Bone marrow

Bone marrow toxicity model for ^{223}Ra alpha-emitter radiopharmaceutical therapy

Hobbs et al, Phys Med Biol (2012)



Bone marrow

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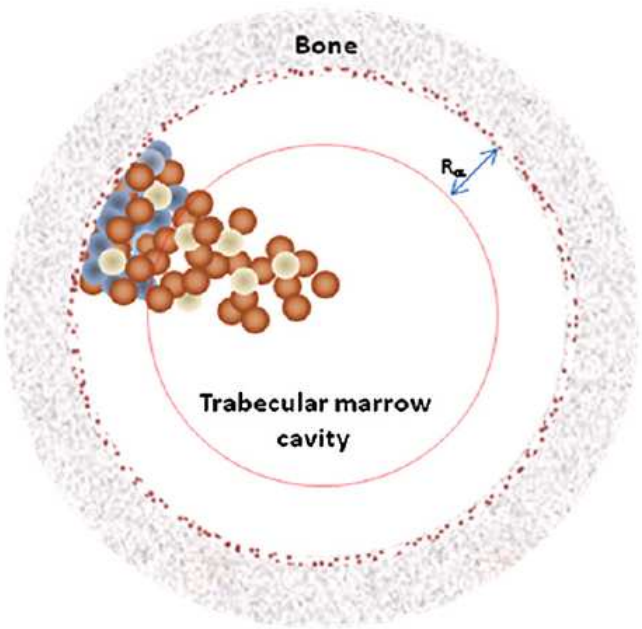

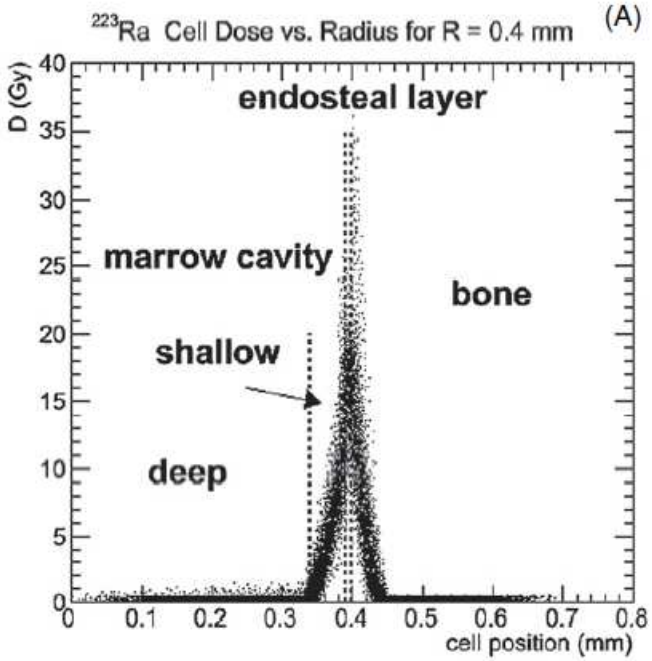

Dosimetry

Conclusions

- The absorbed dose to bone, bone endosteum and bone marrow are very dependent on the assumptions made
- The absorbed dose to liver is smaller when determined from the measured bio-distribution than from the ICRP67 compartment model

Thanks for your attention!

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