

Alpha particle radionuclide therapies and the re-emergence of radium therapy

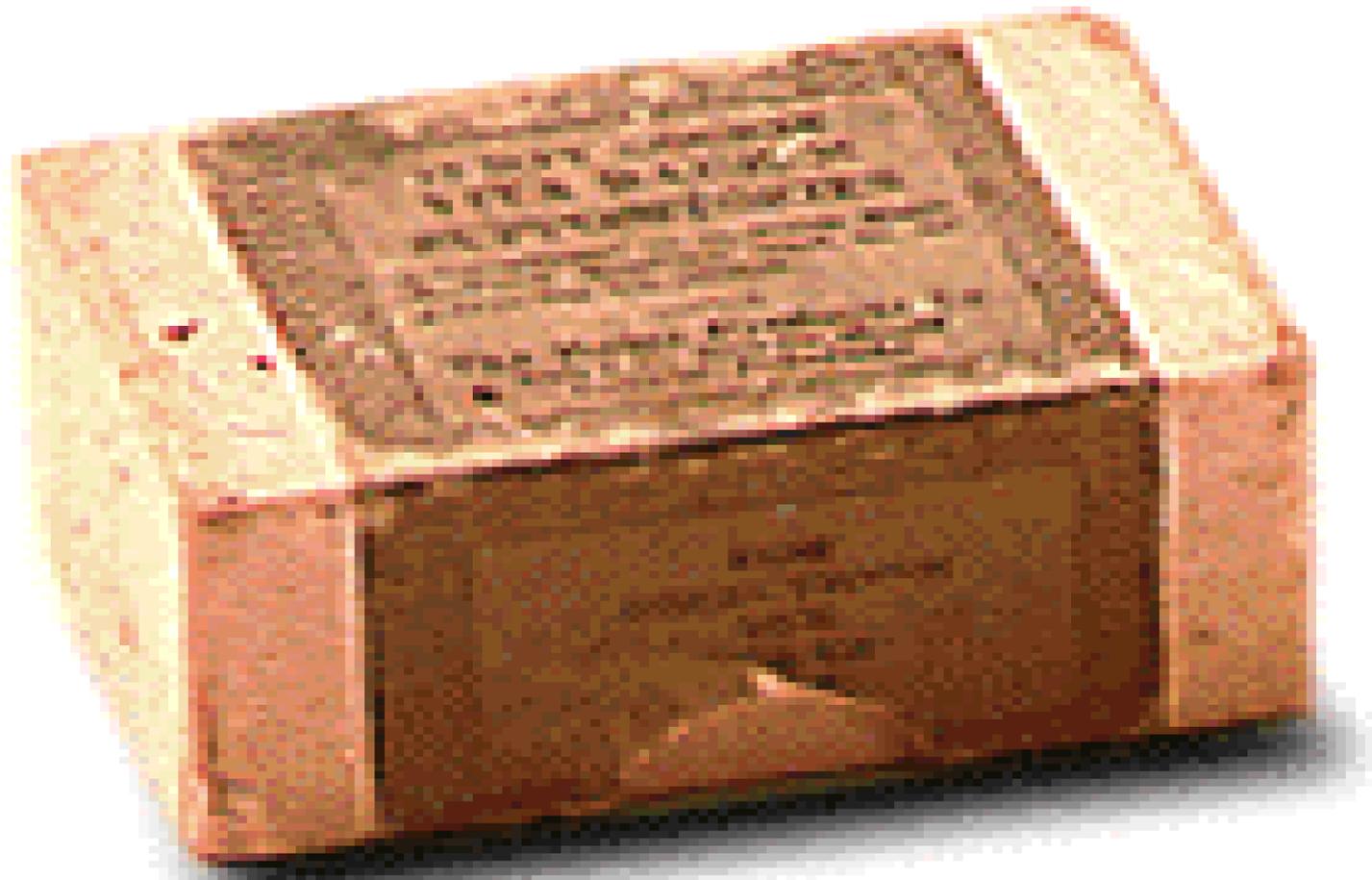
John Humm, Joe O'Donoghue & Jorge Carrasquillo
MSKCC
New York

Vita radium suppositories (1930)

Home Products Company, Denver, Colorado

For Weak Discouraged Men!

**Now Bubble Over with Joyous
Vitality through the use of Glands
and Radium~~ " properly
functioning glands make
themselves known in a quick, brisk
step, mental alertness and the
ability to live and love in the fullest
sense of the word . . . A man must
be in a bad way indeed to sit back
and be satisfied without the
pleasures that are his birthright! . .
. Try them and see what good
results you get!"**



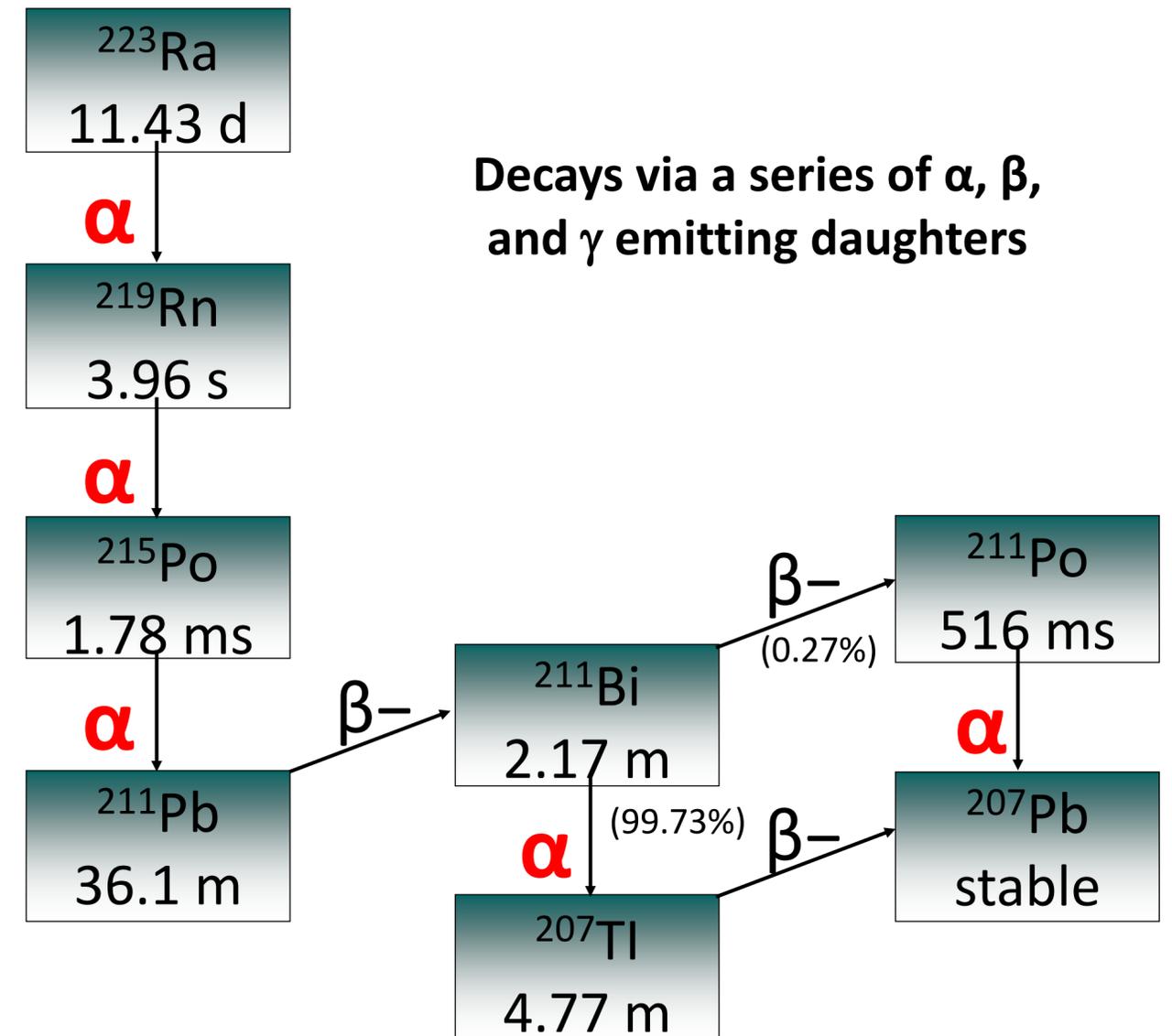
The first Viagra?

(All Home Product customer orders were shipped in a plain wrapper for confidentiality)

Radium-223

- Radium-223 chloride or Xofigo (Bayer) is an alpha-emitter
- $t_{1/2} = 11.43$ days
- Of the total decay energy
 - 93.5% emitted as 4 α particles
 - < 4% emitted as β particles
 - < 2% emitted as γ or X-rays

Radium-223 decay chain



Objectives of this Presentation

To assess pharmacokinetics and biodistribution of Ra-223 and its impact of dosimetry in patients with bone metastases.

- Ra-223 is an α -emitter decay chain for which the parent can be imaged, as well as the daughters.
- The half-lives of the daughters are more favorable relative to Ac-225 and the parent cannot be imaged.

The Ra-223 Spectrum

Ra-223

11.4 days

84 keV X-rays ~41%

154 keV (9%), 269 keV (14%)

Rn-219

4 s

271 keV

10%

Po-215

1.8 ms

Nothing
imageable

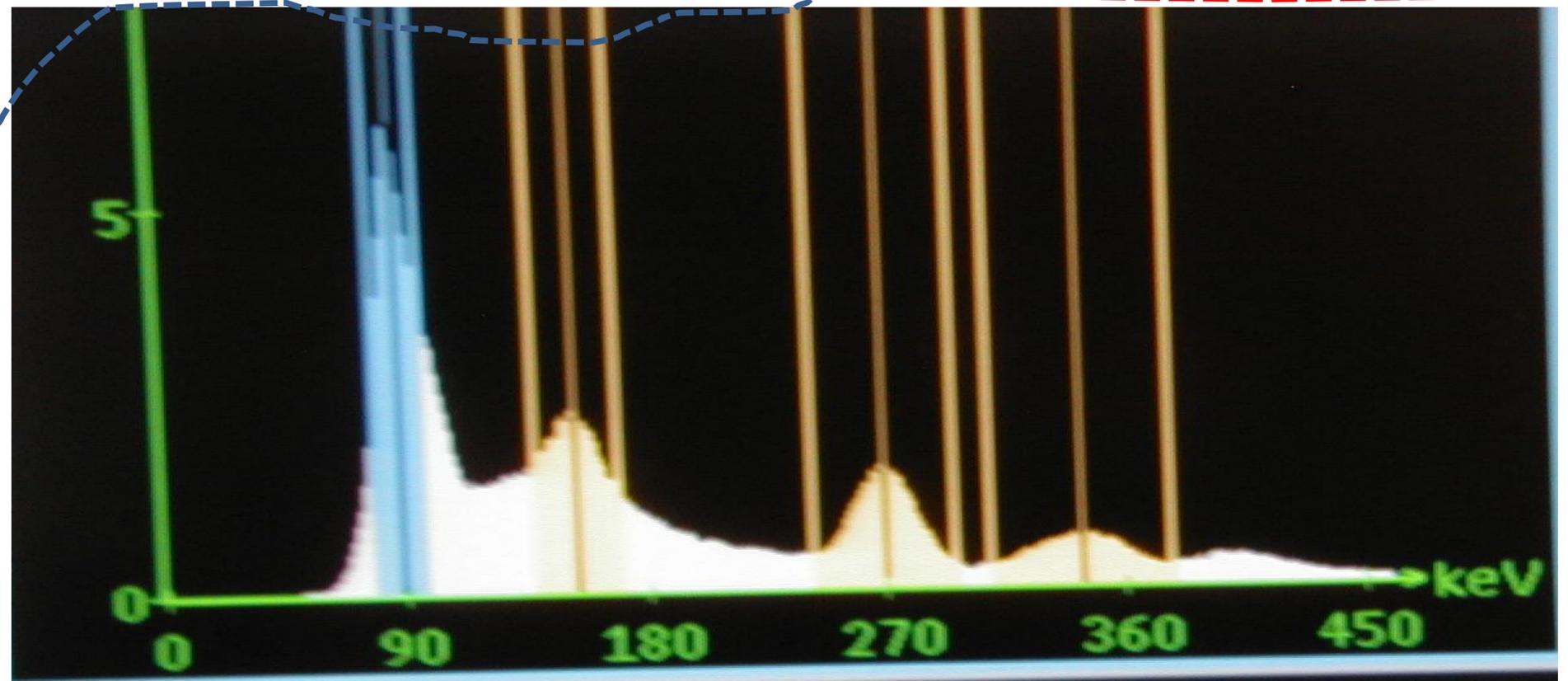
Pb / Bi-211

36m * 2.2 m

351 keV + higher

13%

5 energy windows used:
84 keV, 154, 269, 351
and 403 keV



Design

Ra-223 dose escalation

50 kBq/kg

100 kBq/kg

200 kBq/kg

Serial gamma camera images

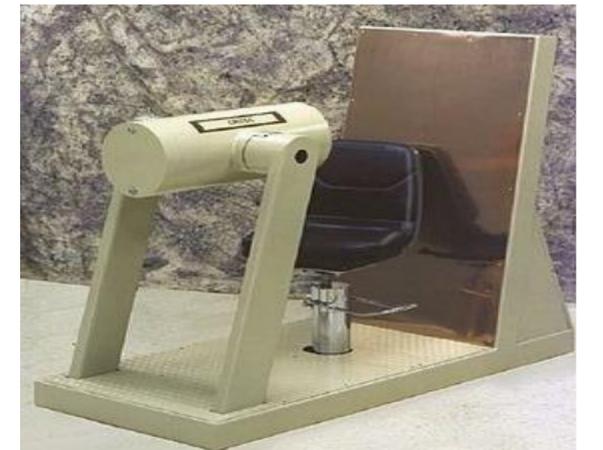
Immediately, post first void (0-6 h of treatment), and 24±6 h, 48±12 h, 96±24 h and 144±24h

Serial whole body counts (NaI probe)

Pre-void, post 1st void (0-6 h of treatment), and 24±6 h, 48±12 h, 96±24 h and 144±24h

Serial blood and serum counts

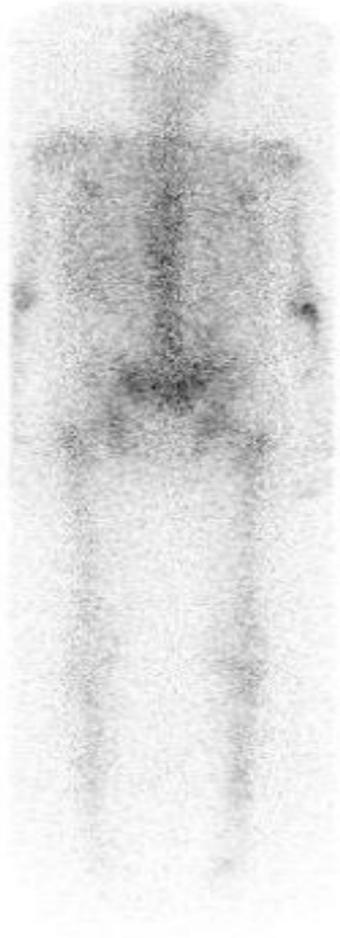
1m, 5 m, 15m, 30 m, 45m, 1 h, 24±6 h, 48±12 h, 96±24 h and 144±24 h



BC1-05 serial WB Images

APPENDIX C: Patient 103

$^{223}\text{Ra-Cl}$, Injection 1, Posterior



D0



D1



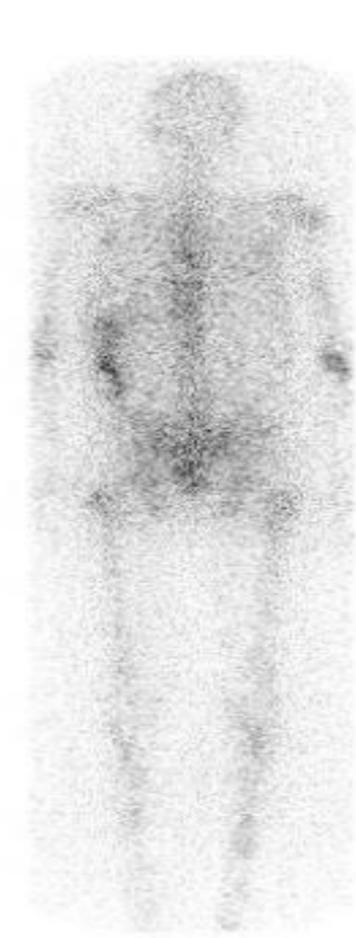
D2



D3



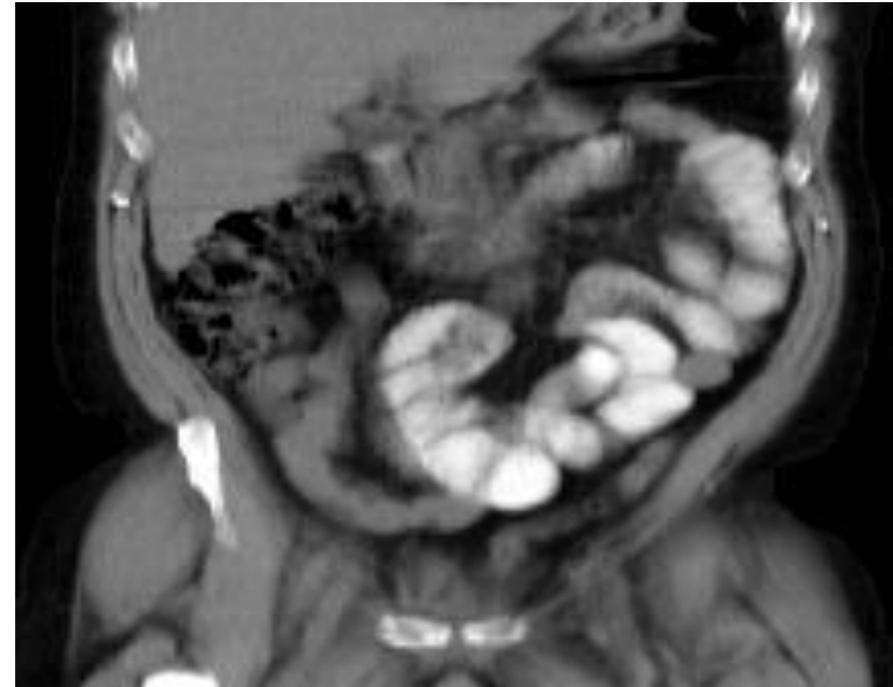
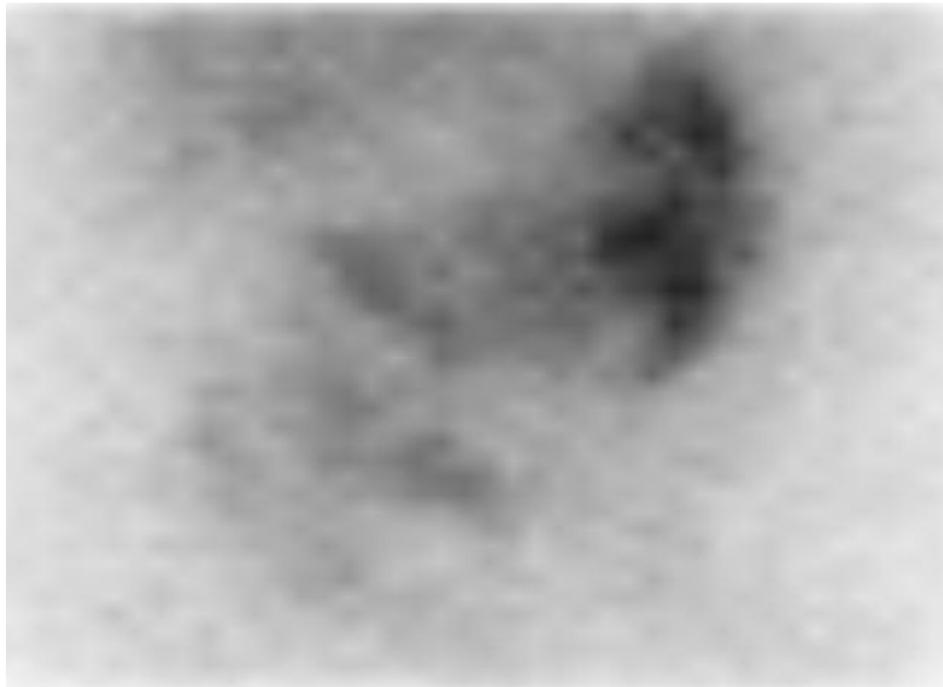
D4



D7

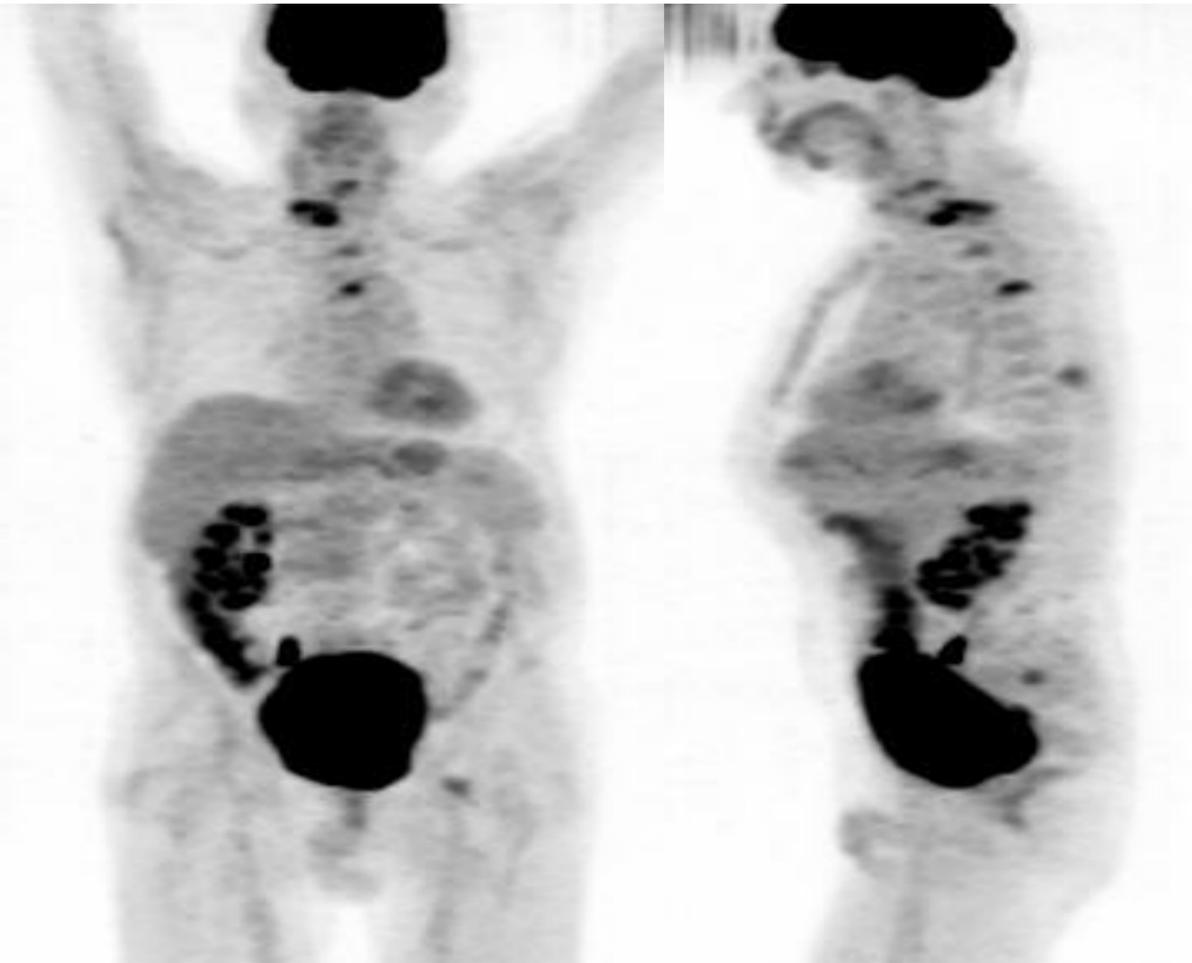
Pharmacokinetic Data

- Since BC1-05 had already acquired serial whole body scan data, our philosophy was to try to get early organ data.
- Relevant organs would be vertebrae, kidney, liver, G.I. tract.
- Serial ant & post spot views of the abdomen and pelvis.
- Images are noisy due to the low administered activity (50 – 200 kBq/kg).

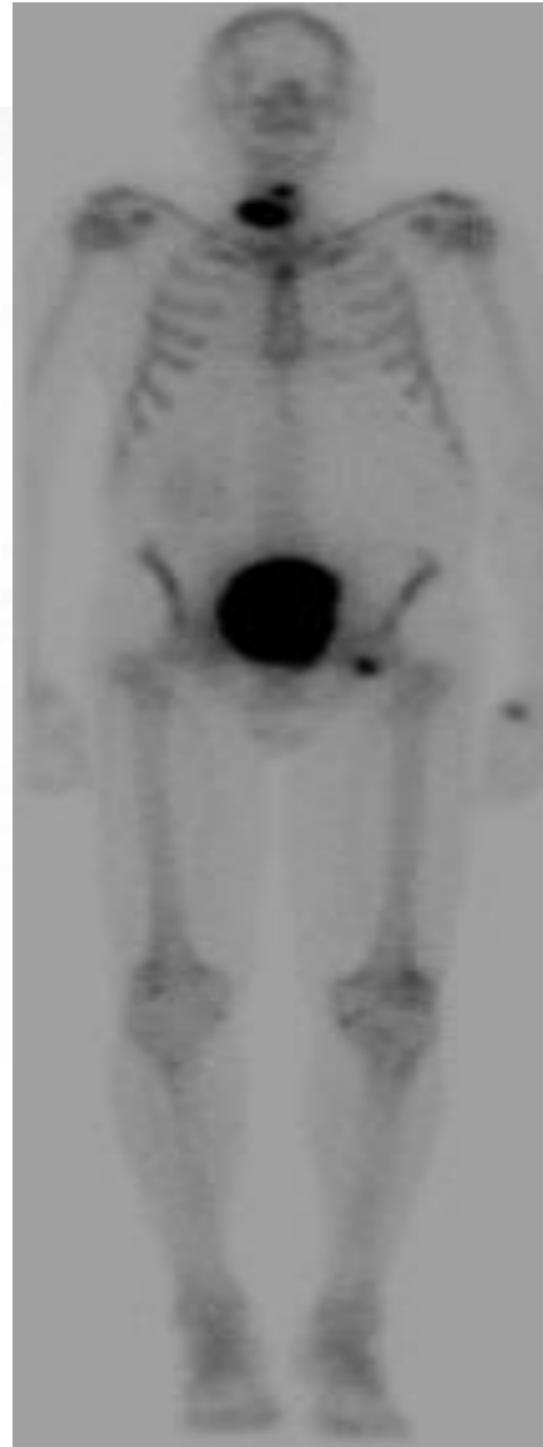


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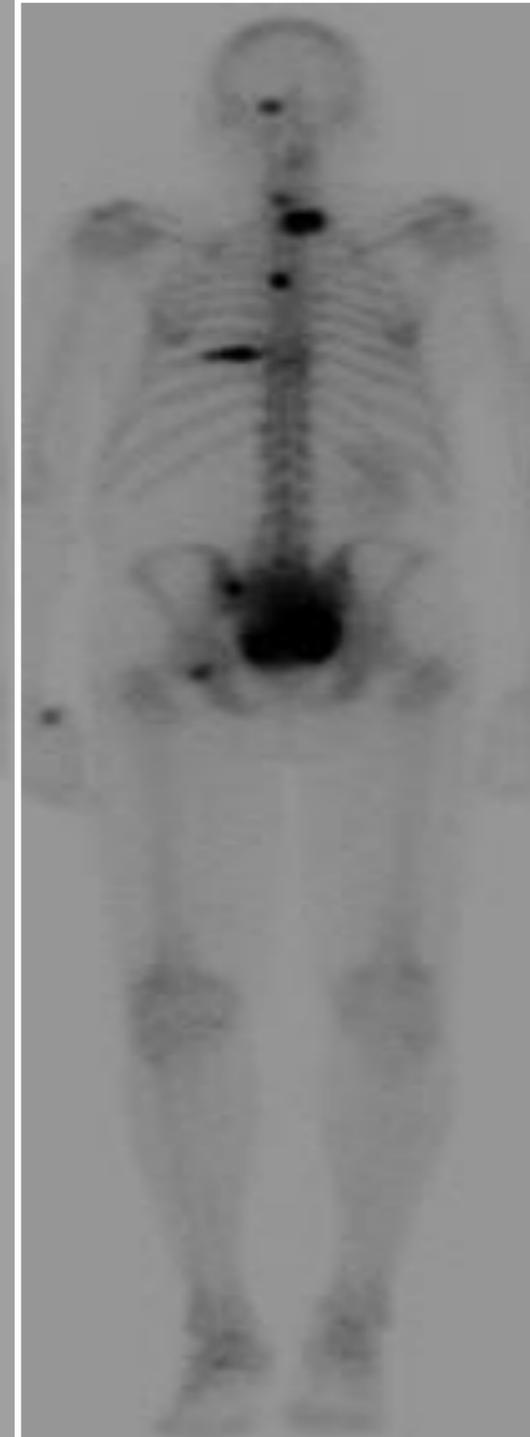
Upper spine 1.41
Lt acetabulum 1.14
Colon 37.5%



FDG – D20



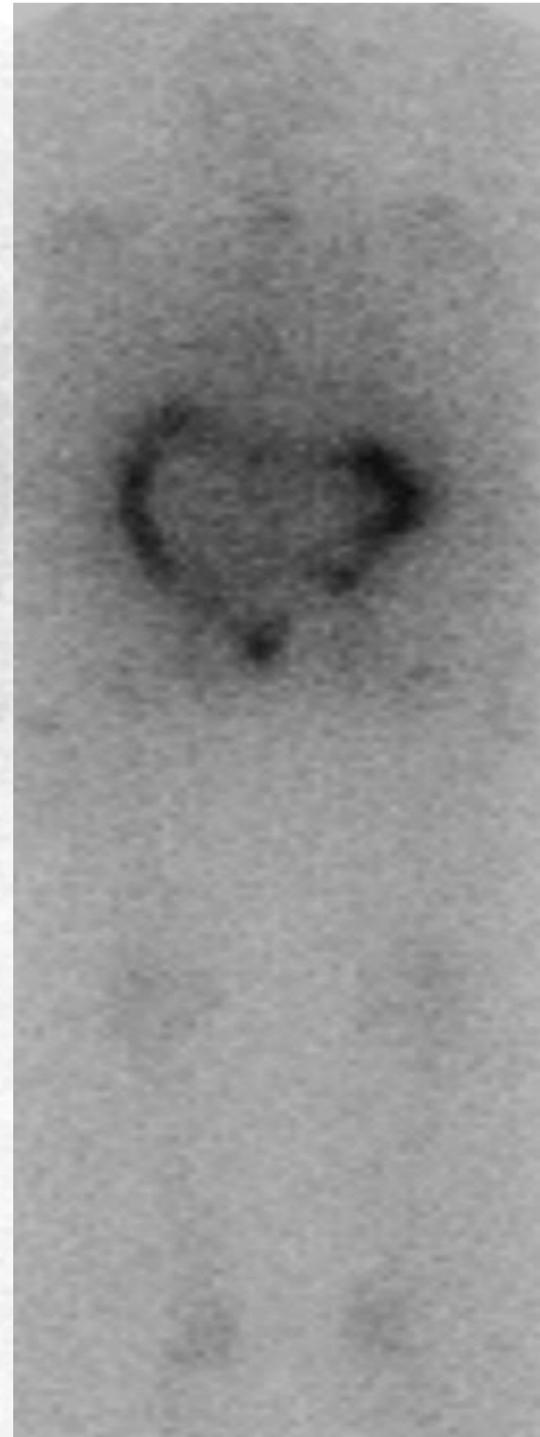
Tc-99m MDP –D7 ant



Tc-99m MDP –D7 pos



Ra-223 24hr



Ra-223 24hr

Ra-223

its temporal history



0-10 m



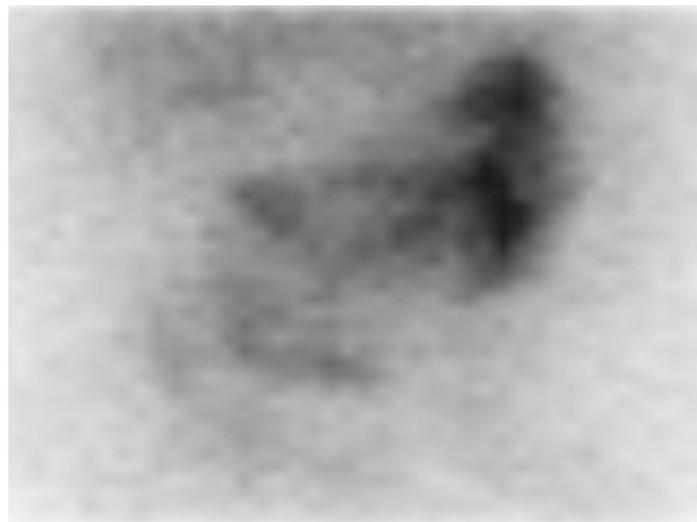
10-20 m



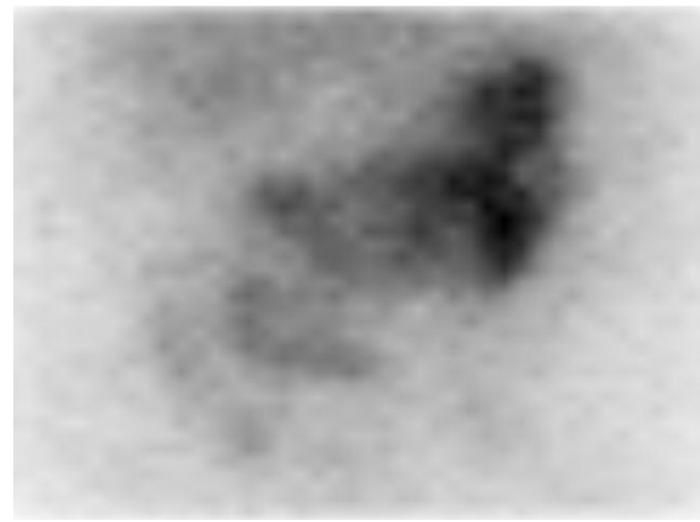
20-30 m



30-40 m



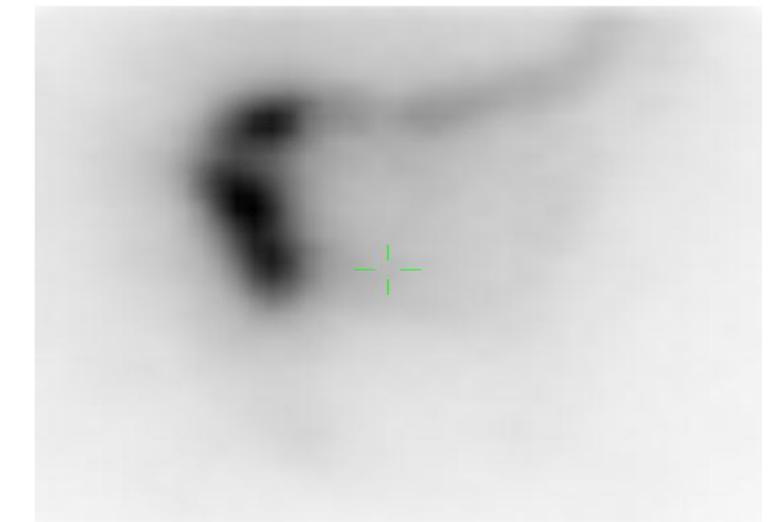
40-50 m



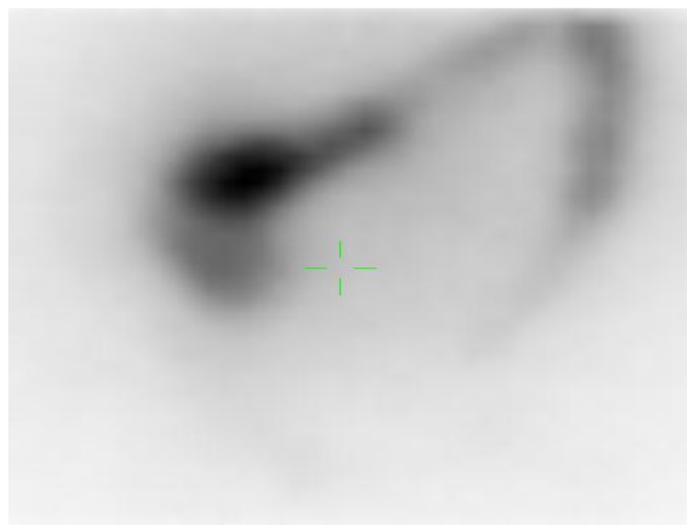
50-60 m



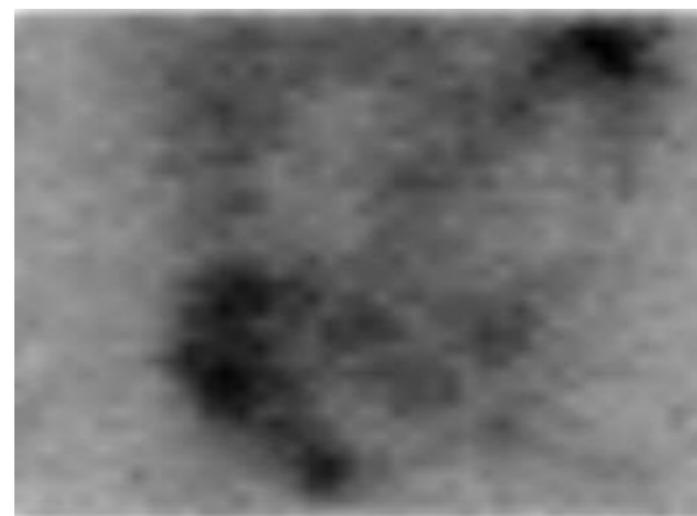
232 min post



1 d



2 d

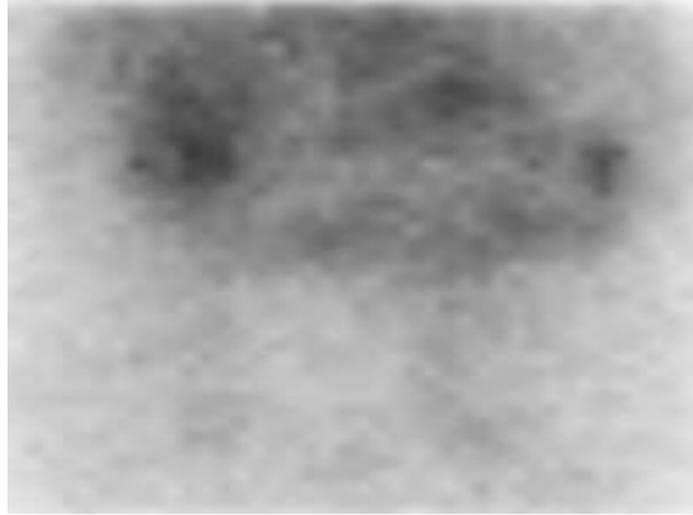


6 d

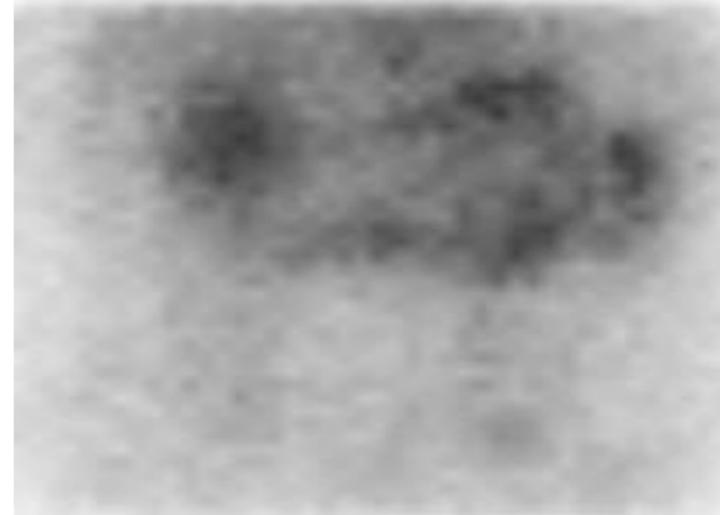


Bone scan -D13

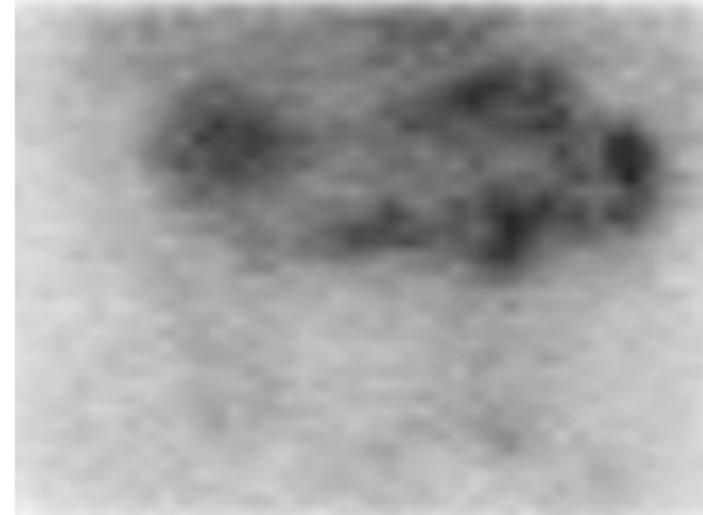




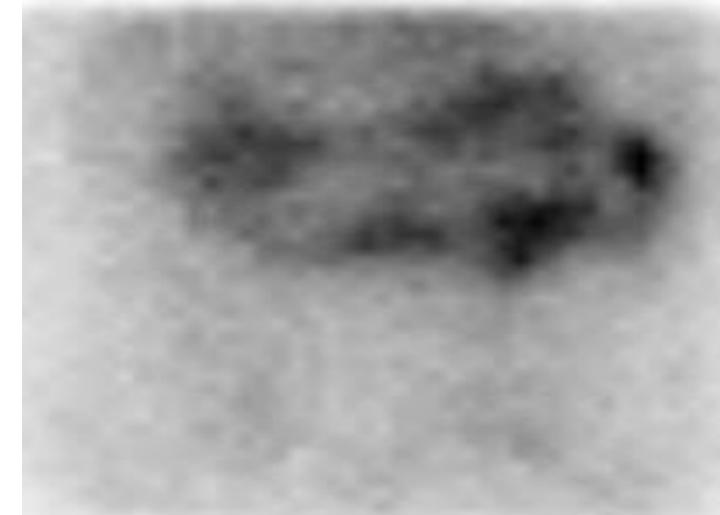
0-10 m



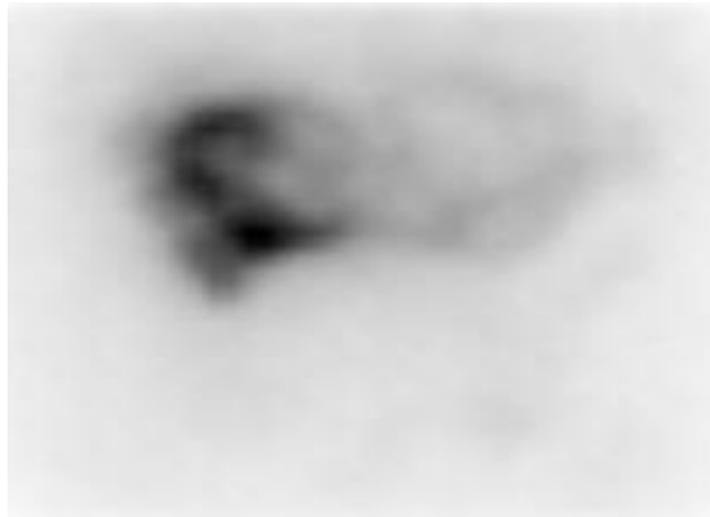
10-20 m



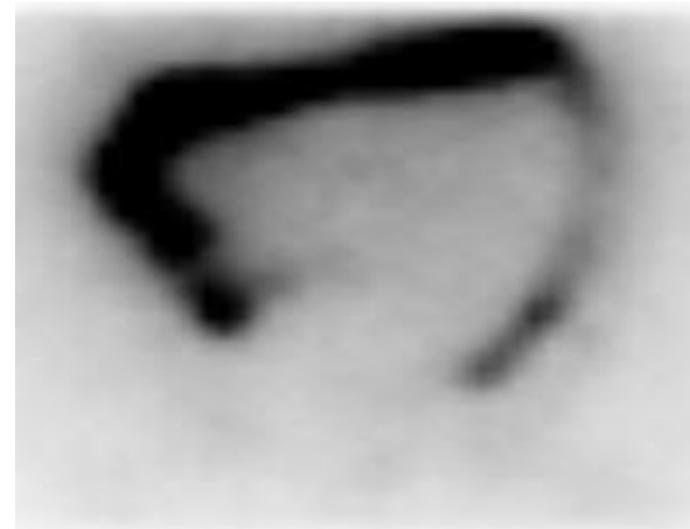
20-30 m



30-40 m



187 min post



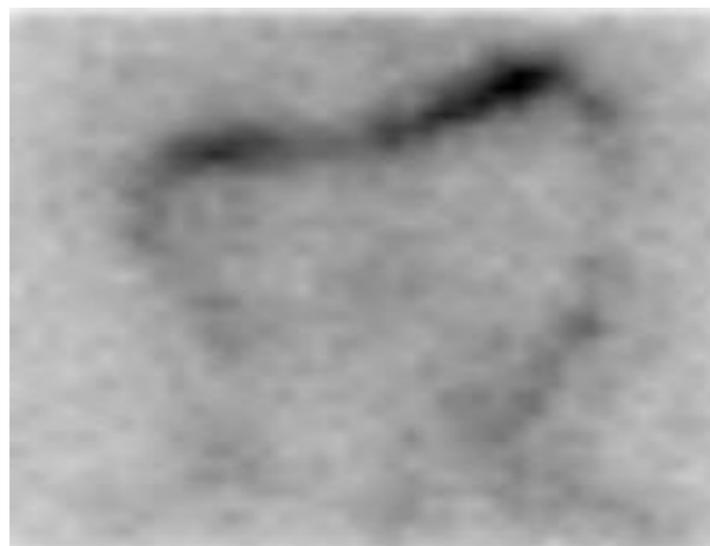
1 d



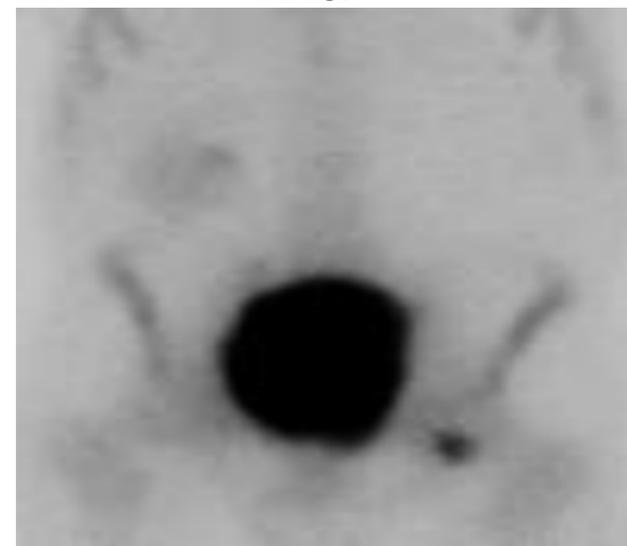
2 d



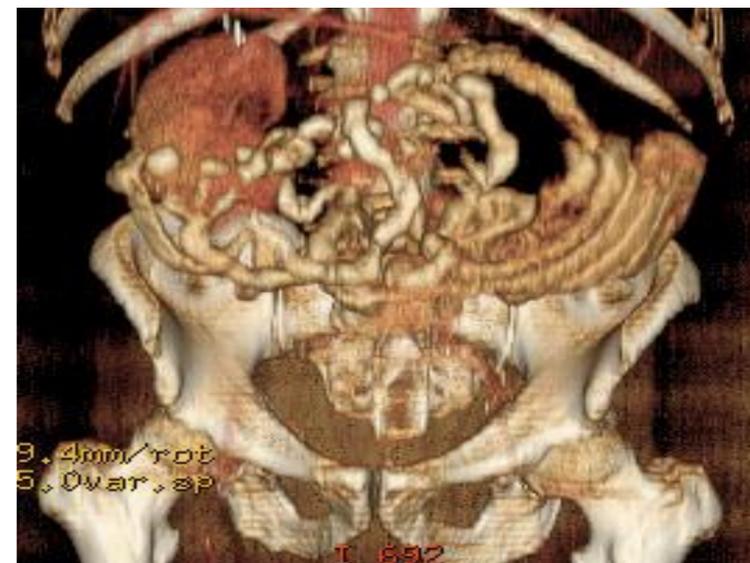
4d



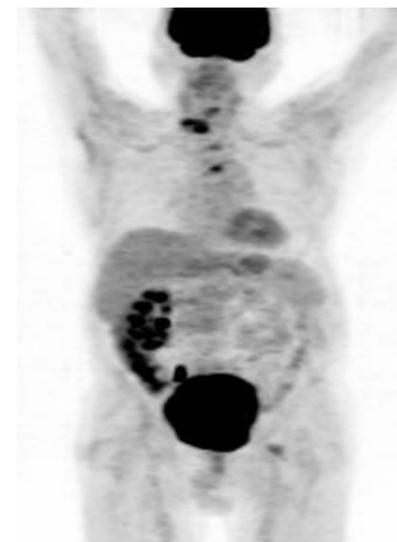
7 d



Bone scan -D7

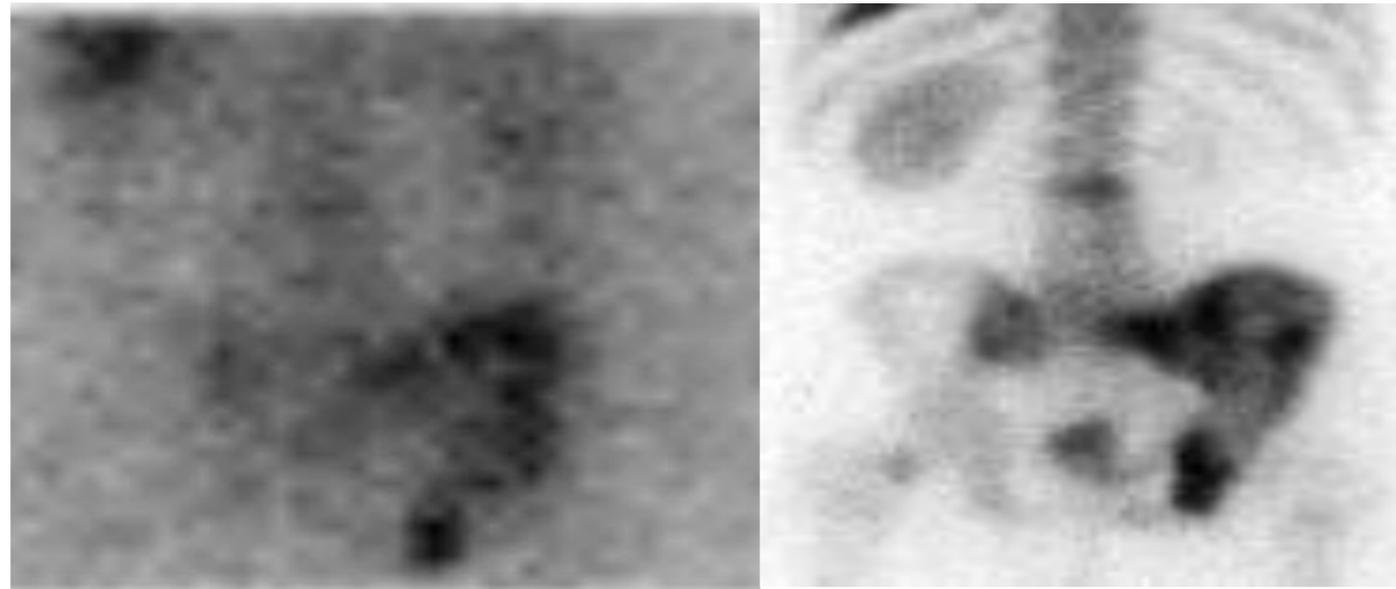


Ant View
107
Not much
disease



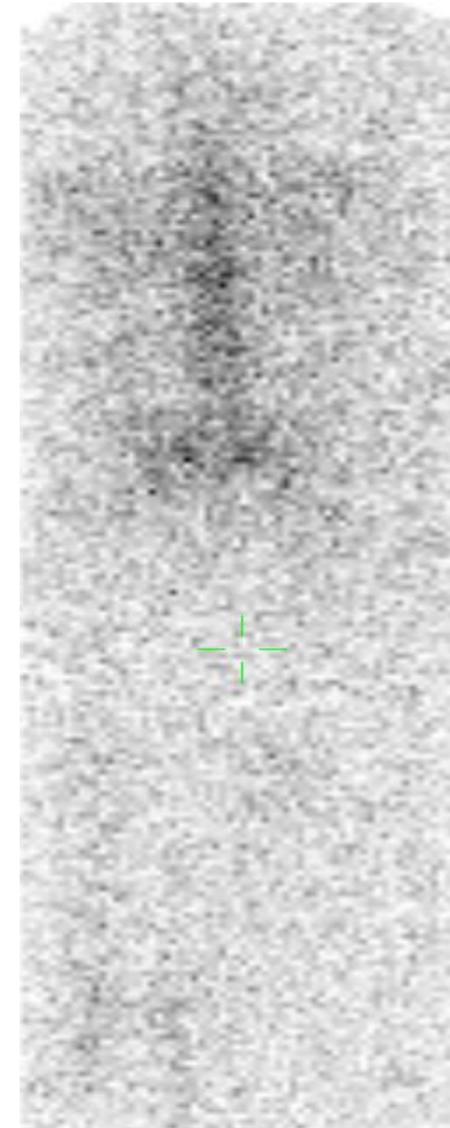
Bone Retention is very long

Posterior View Pelvis
204 μCi

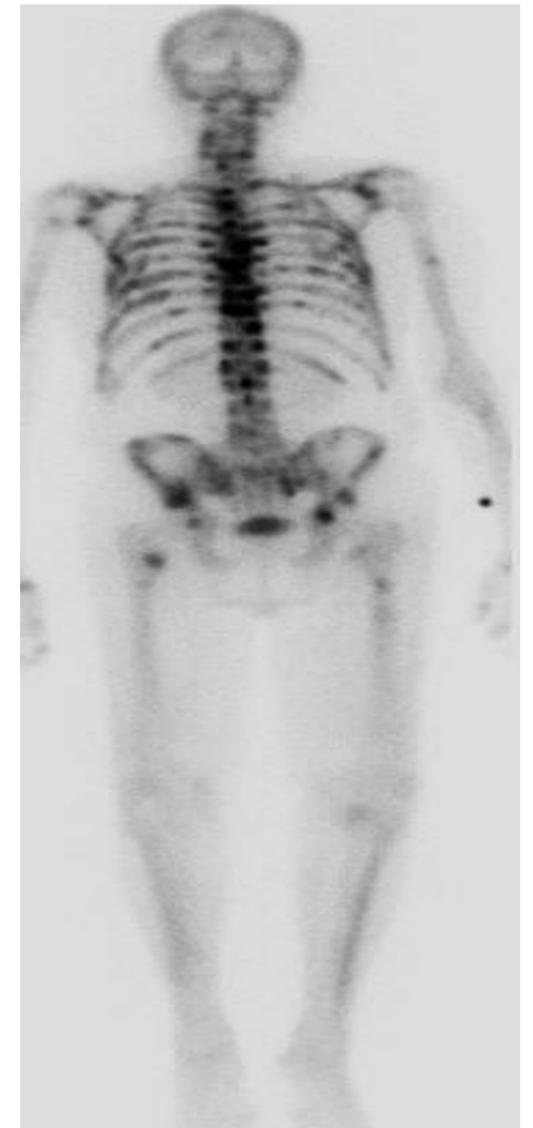


Ra-223 6 d

Bone scan



Ra-223 14 d



Bone scan

108 (240 μCi)

Whole Body Excretion

Where does the Ra-223 go?

| Urinary Excretion First void (%) | Amount in bowel at 1d (%) | Amount Excreted from Whole Body at 7d (range 6 - 8) %ID |
|--|---------------------------------|--|
| 4% (range -3.9 - 11%) | 30% (range 20 - 44%) | 68% (range 44 -78%) |

Residual Activity at 7d is mostly in bone

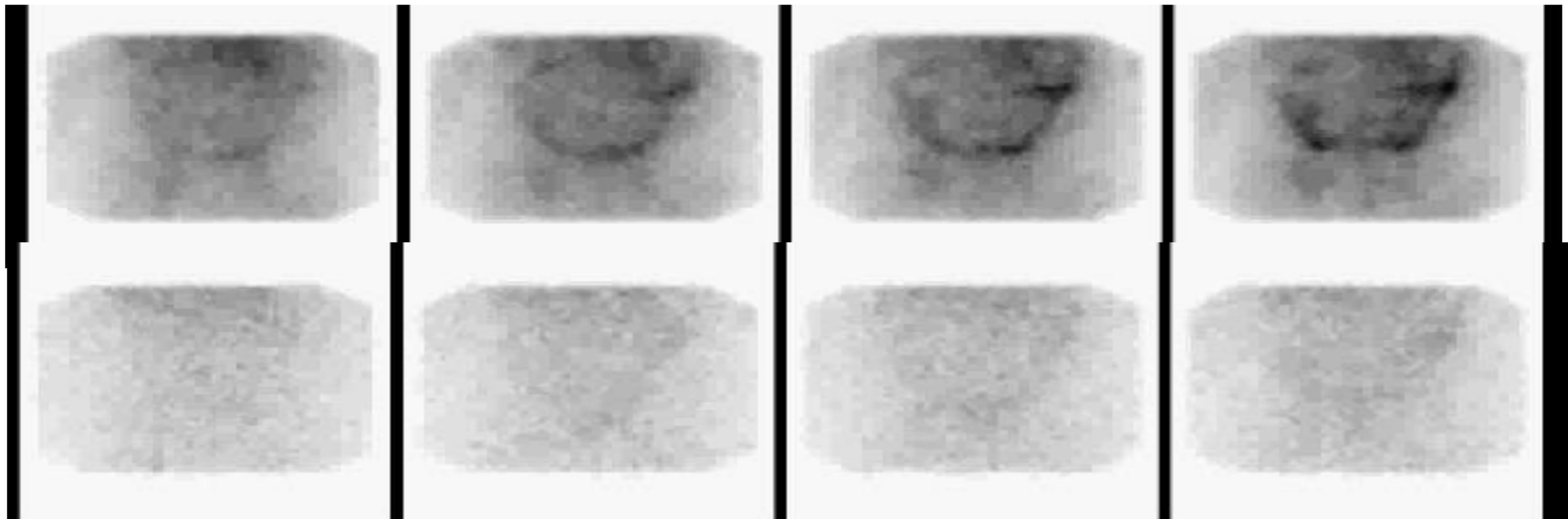
There appears to be some unattributable Ra-223 activity in the rest of body

What happens to the Daughters?

Anterior View – Dynamic Scan 0-40mins

All peaks – top

Final Daughters - bottom



10 min

20 min

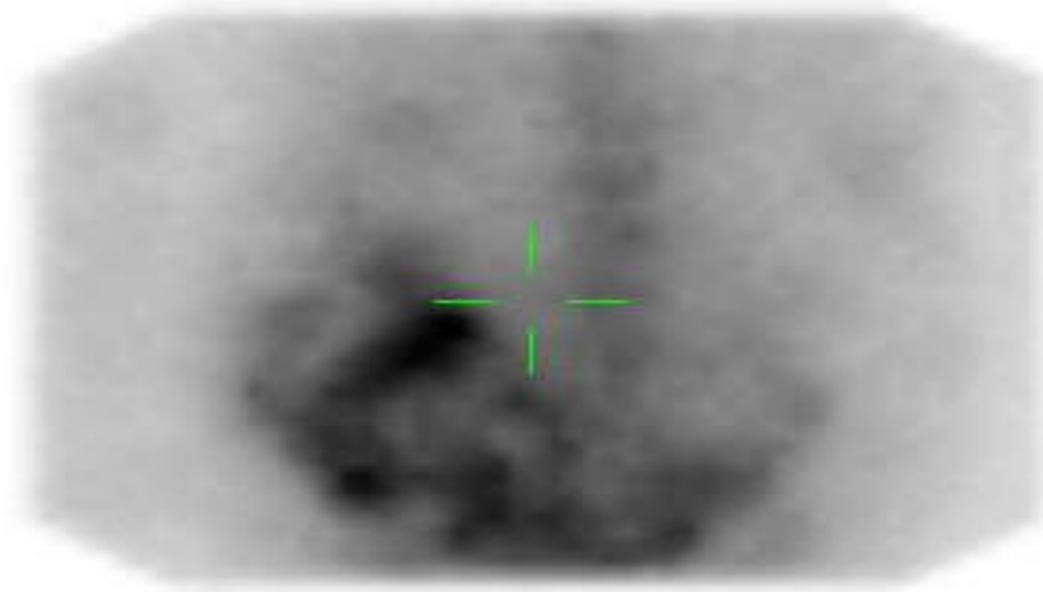
30 min

40 min

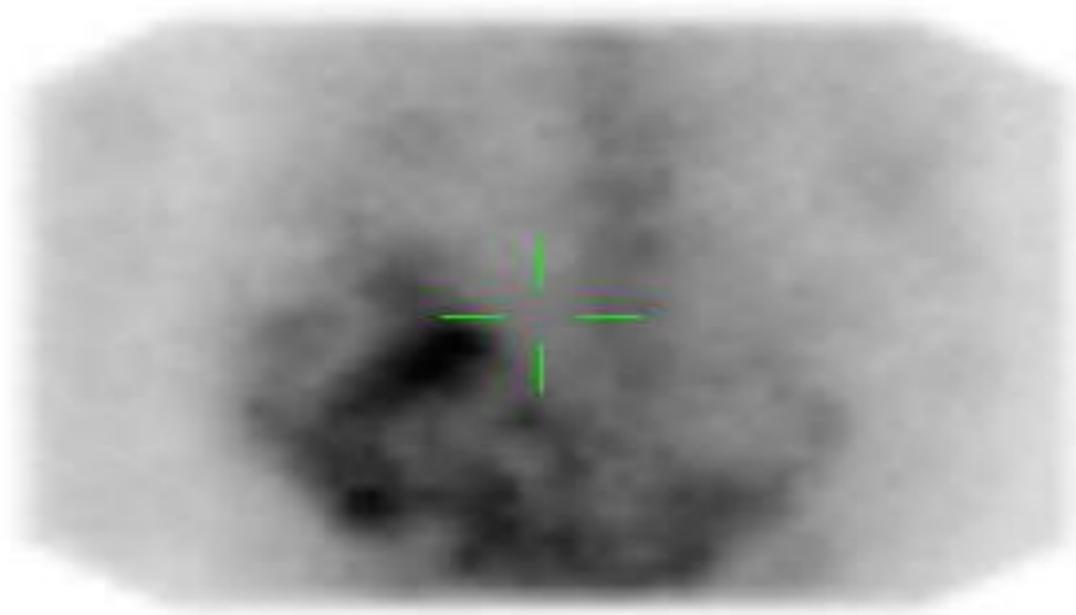
Parent and Daughter Sequence

Day 0 Post-void

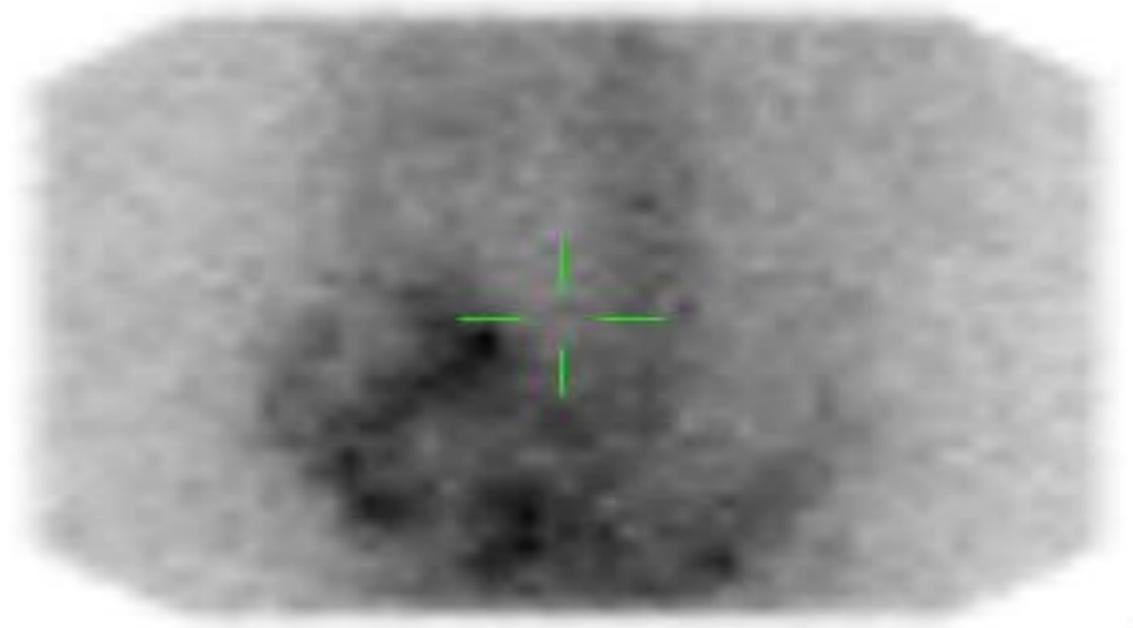
All Counts



Parents



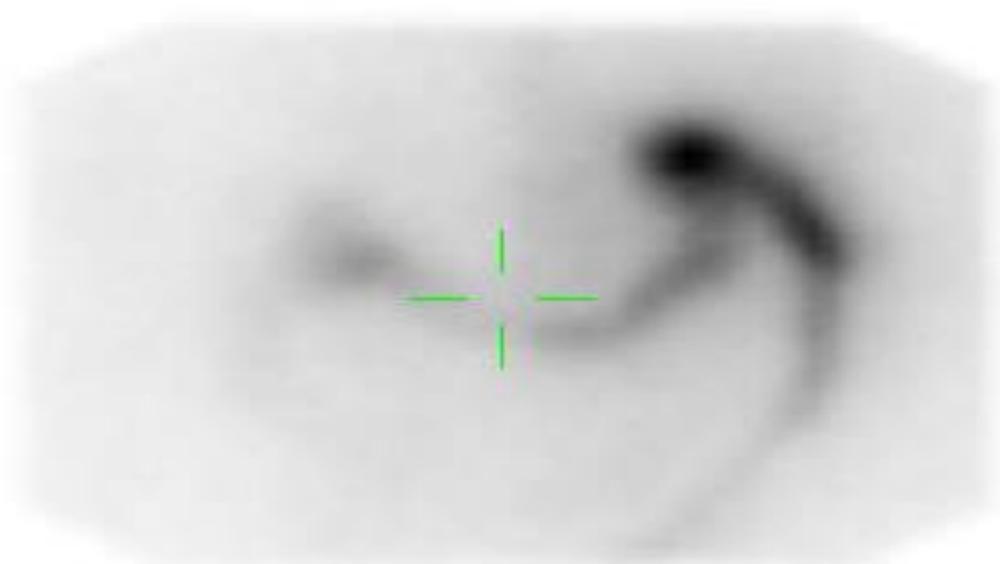
Final Daughter



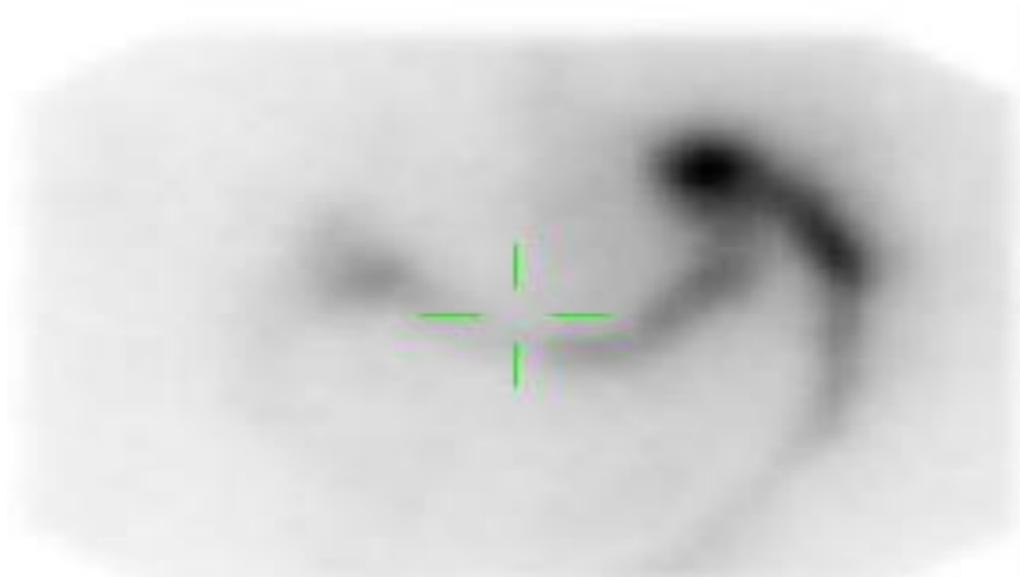
Parent and Daughter Sequence

Day 3

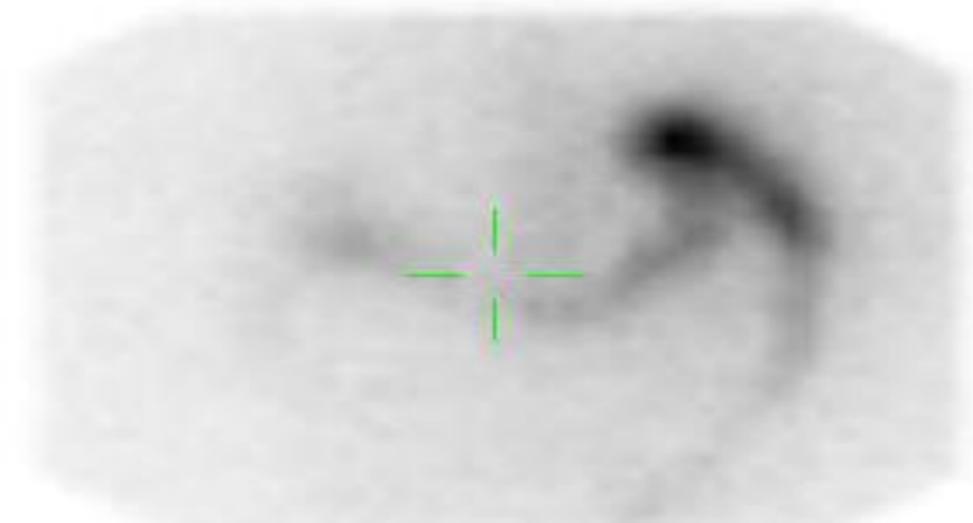
All Counts



Parents



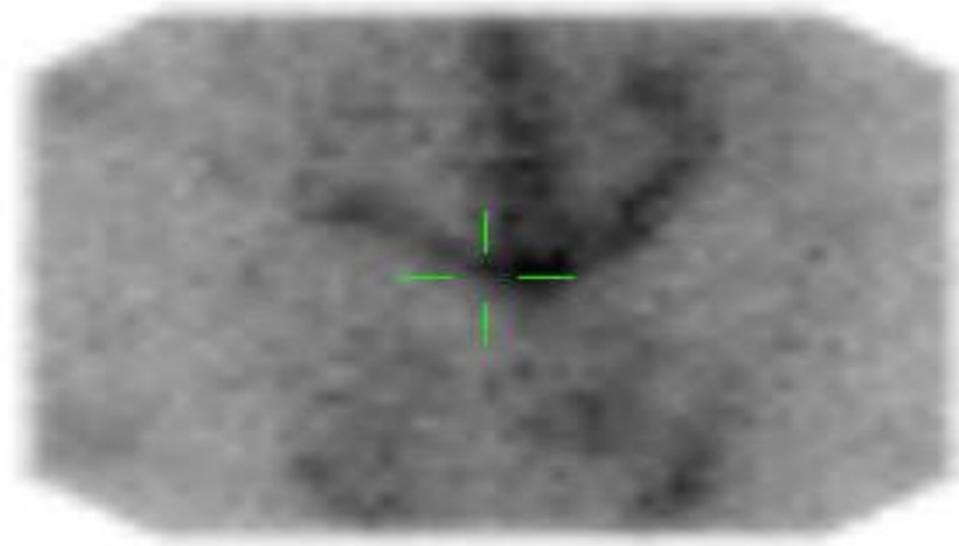
Final Daughter



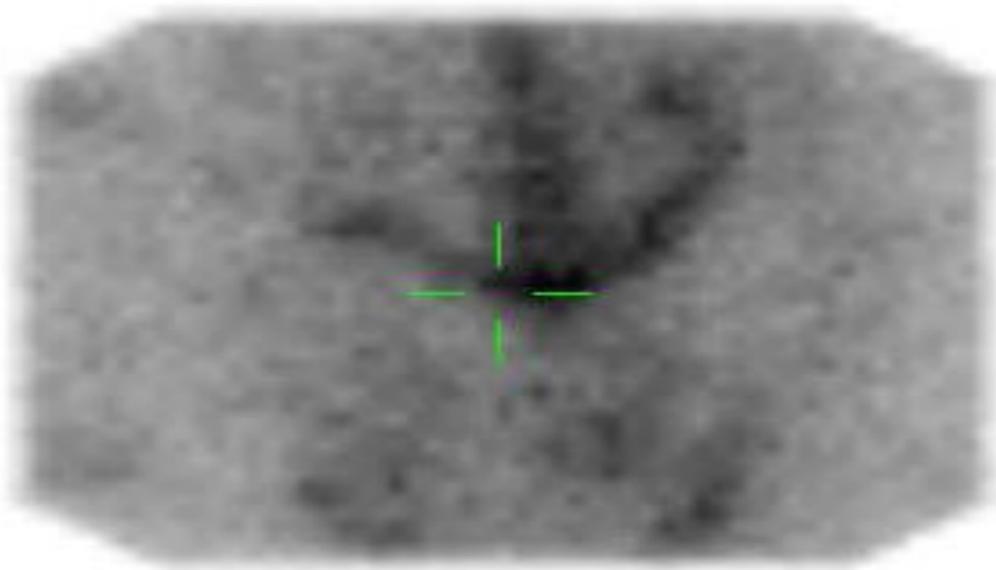
Parent and Daughter Sequence

Day 6

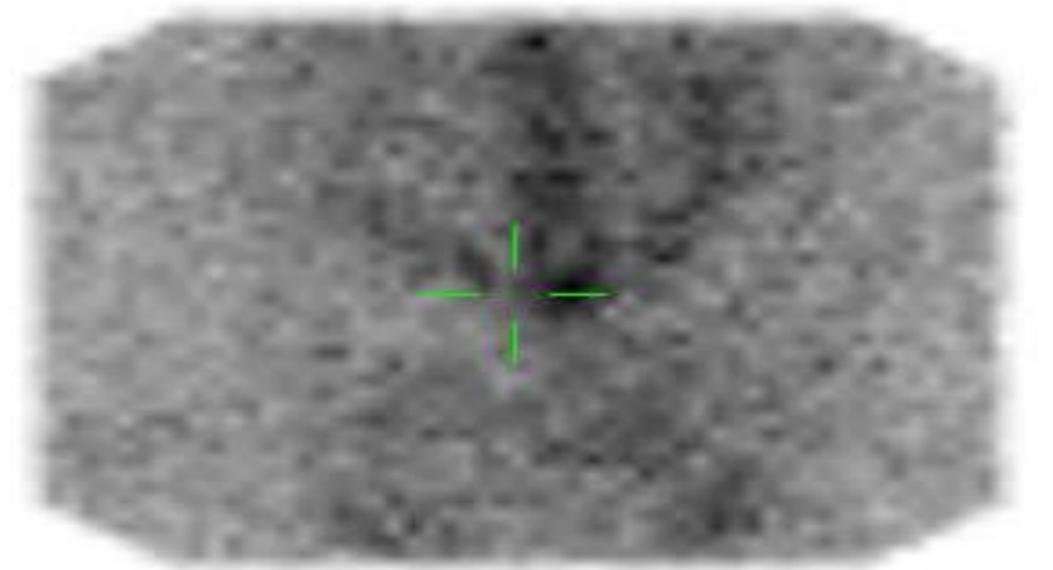
All Counts



Parents



Final Daughter



BC1-05

Absorbed doses (Gy/MBq) to different organs

| Target organ | Individual emission contributions (Gy/MBq) | | | Total | Total | SD | Organ Dose in a 73-kg Adult given 50 kBq/kg | |
|----------------------|--|----------|----------|----------|-----------|-----|---|--------|
| | Alpha | Beta | Photon | (Gy/MBq) | (rad/mCi) | (%) | Gy | rad |
| Adrenals | 0.00E+00 | 2.35E-05 | 9.41E-05 | 0.00012 | 0.44 | 56 | 0.0004 | 0.04 |
| Brain | 0.00E+00 | 2.35E-05 | 7.52E-05 | 0.00010 | 0.37 | 80 | 0.0004 | 0.04 |
| Breasts | 0.00E+00 | 2.35E-05 | 2.53E-05 | 0.00005 | 0.18 | 120 | 0.0002 | 0.02 |
| Gallbladder wall | 0.00E+00 | 2.35E-05 | 2.05E-04 | 0.00023 | 0.85 | 14 | 0.0008 | 0.08 |
| LLI Wall | 0.00E+00 | 4.56E-02 | 8.49E-04 | 0.04645 | 171.88 | 83 | 0.1696 | 16.96 |
| Small intestine wall | 3.19E-03 | 3.60E-03 | 4.71E-04 | 0.00726 | 26.87 | 45 | 0.0265 | 2.65 |
| Stomach wall | 0.00E+00 | 2.35E-05 | 1.15E-04 | 0.00014 | 0.51 | 22 | 0.0005 | 0.05 |
| ULI wall | 0.00E+00 | 3.15E-02 | 8.24E-04 | 0.03232 | 119.58 | 50 | 0.1180 | 11.80 |
| Heart wall | 1.61E-03 | 7.07E-05 | 4.67E-05 | 0.00173 | 6.40 | 42 | 0.0063 | 0.63 |
| Kidneys | 2.99E-03 | 1.08E-04 | 1.06E-04 | 0.00320 | 11.86 | 36 | 0.0117 | 1.17 |
| Liver | 2.79E-03 | 1.02E-04 | 8.22E-05 | 0.00298 | 11.01 | 36 | 0.0109 | 1.09 |
| Lungs | 0.00E+00 | 2.35E-05 | 4.85E-05 | 0.00007 | 0.27 | 90 | 0.0003 | 0.03 |
| Muscle | 0.00E+00 | 2.35E-05 | 9.54E-05 | 0.00012 | 0.44 | 41 | 0.0004 | 0.04 |
| Ovaries | 0.00E+00 | 2.35E-05 | 4.62E-04 | 0.00049 | 1.80 | 40 | 0.0018 | 0.18 |
| Pancreas | 0.00E+00 | 2.35E-05 | 8.82E-05 | 0.00011 | 0.41 | 43 | 0.0004 | 0.04 |
| Red marrow | 1.32E-01 | 6.42E-03 | 2.02E-04 | 0.13879 | 513.51 | 41 | 0.5066 | 50.66 |
| Osteogenic cells | 1.14E+00 | 1.49E-02 | 2.98E-04 | 1.15206 | 4262.60 | 41 | 4.2050 | 420.50 |
| Skin | 0.00E+00 | 2.35E-05 | 4.86E-05 | 0.00007 | 0.27 | 79 | 0.0003 | 0.03 |
| Spleen | 0.00E+00 | 2.35E-05 | 6.65E-05 | 0.00009 | 0.33 | 54 | 0.0003 | 0.03 |
| Testes | 0.00E+00 | 2.35E-05 | 5.96E-05 | 0.00008 | 0.31 | 59 | 0.0003 | 0.03 |
| Thymus | 0.00E+00 | 2.35E-05 | 3.35E-05 | 0.00006 | 0.21 | 109 | 0.0002 | 0.02 |
| Thyroid | 0.00E+00 | 2.35E-05 | 4.80E-05 | 0.00007 | 0.26 | 96 | 0.0003 | 0.03 |
| U. bladder wall | 3.71E-03 | 1.61E-04 | 1.56E-04 | 0.00403 | 14.90 | 63 | 0.0147 | 1.47 |
| Uterus | 0.00E+00 | 2.35E-05 | 2.32E-04 | 0.00026 | 0.94 | 28 | 0.0009 | 0.09 |
| Whole body | 2.22E-02 | 8.08E-04 | 1.19E-04 | 0.02311 | 85.50 | 16 | 0.0843 | 8.43 |

From
George Sgouros

Ra-223 dosimetry challenges

When dealing with patient radionuclide dosimetry, we always have to consider:

- the macro-dosimetry based upon what can be practically measure in the clinic using imaging devices and counting equipment.
- the micro-dosimetry which can have a significant impact on organ toxicity or tumor response which depends upon the microscopic relationship between the source and target.

In the case of Ra-223, the major unresolved questions are:

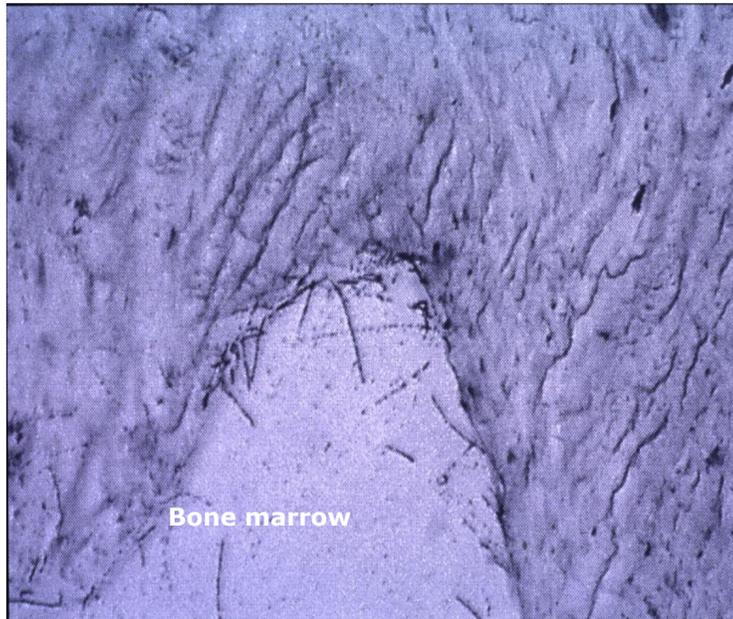
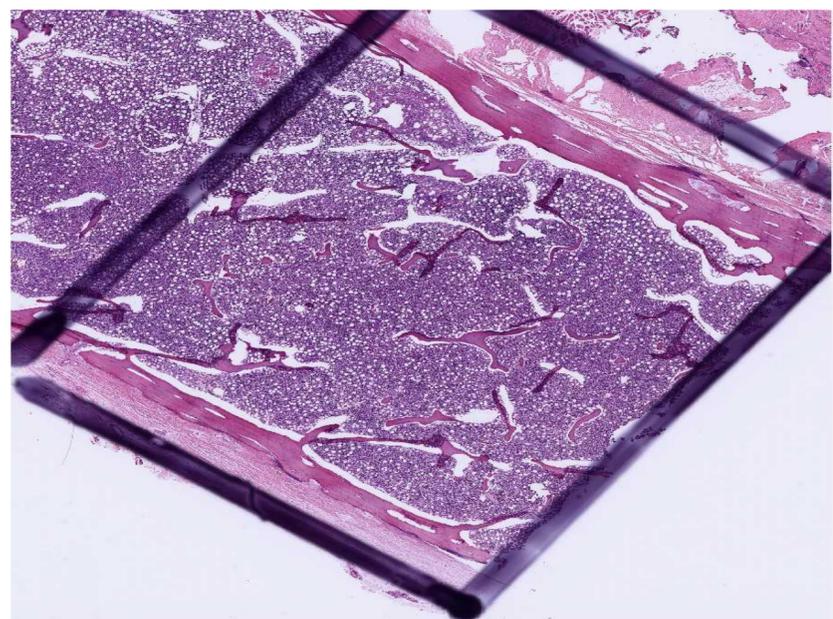
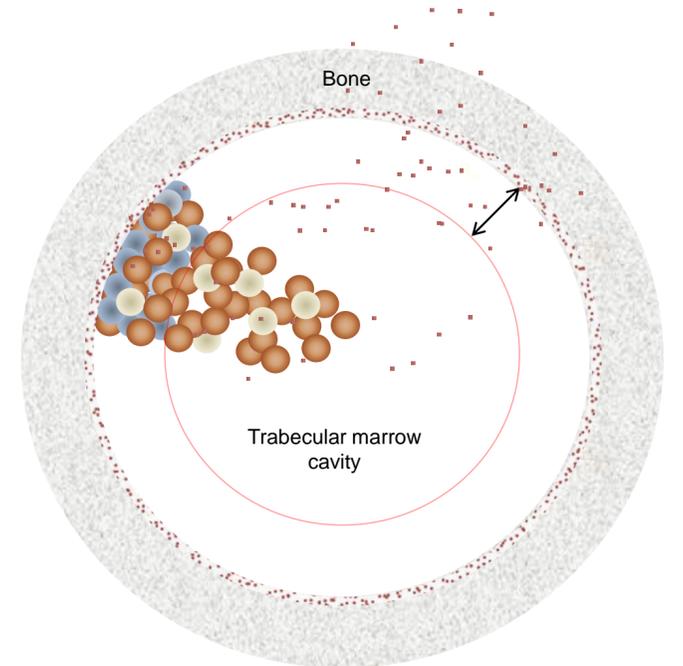
- Dose to the marrow
- Dose to the intestine
- Dose to the lesions

Ra-223 dosimetry challenges

- **Dose to the marrow**
- Dose to the intestine
- Dose to the lesion

Less than 1% of 292 patients treated in phase I & II trials receiving up to 250 kBq/kg of ^{223}Ra had CTC grade 4 hematological toxicity; 2%-4% had grade 3 toxicity.

Cheetham & Petrylak, **Alpha Particles as Radiopharmaceuticals in the Treatment of Bone Metastases: Mechanism of Action of Radium-223 Chloride (Alpharadin) and Radiation**, ONCOLOGY. Vol. 26 No. 4, 2012.



- α -emitters mostly on bone surface and more concentrated at diseased sites
- **Mean dose to marrow cavity won't predict effect**

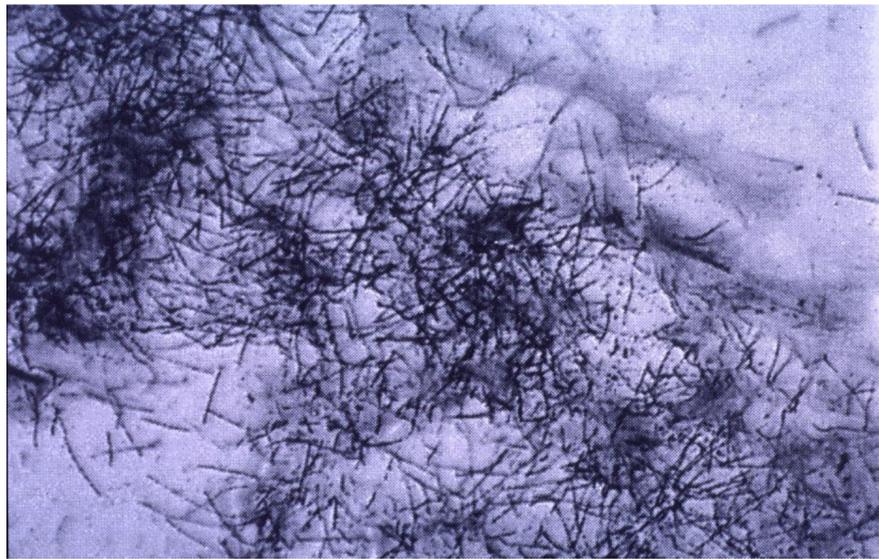
Courtesy of Oyvind Bruland

From Hobbs, et al. Phys Med Bio '12

Ra-223 dosimetry challenges

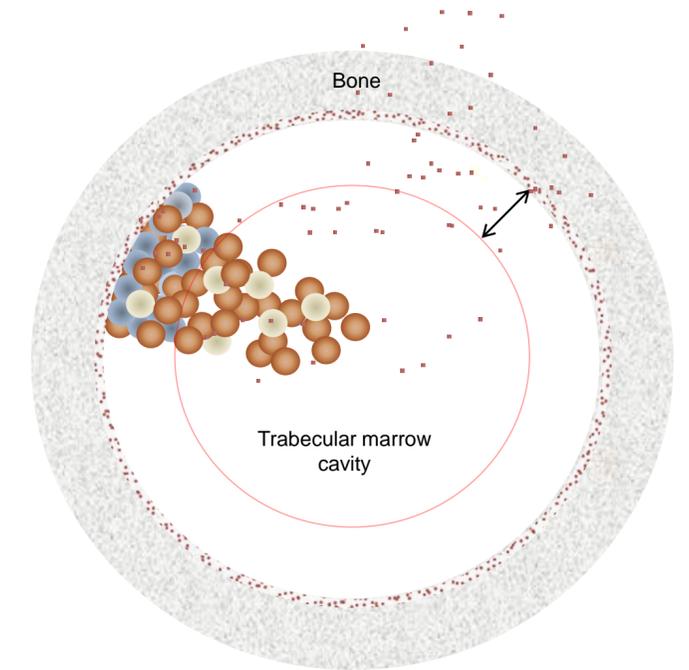
- Dose to the marrow
- Dose to the intestine
- **Dose to the lesion**

Bone Met surface



Courtesy of Oyvind Bruland

Rt humerus
1.74 →

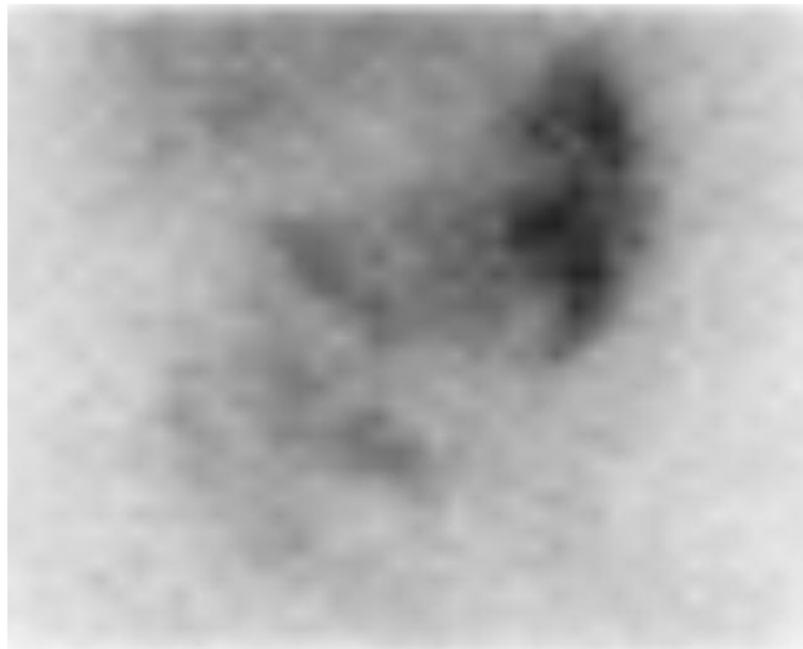


- α -emitters mostly on bone surface and more concentrated at diseased sites
- How do we determine mass of tumor deposits?
- Microdosimetry modeling key

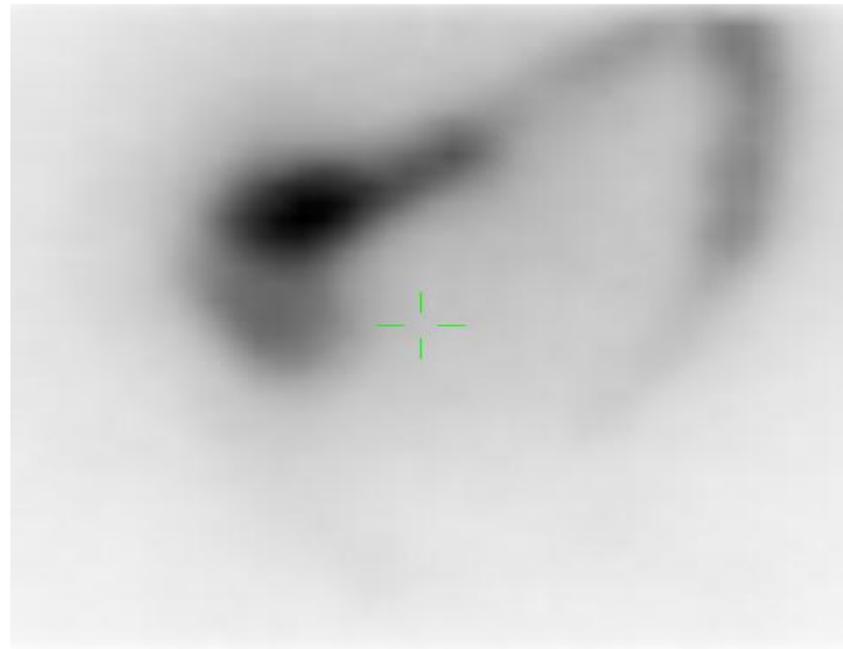
From Hobbs, et al. Phys Med Bio '12

Ra-223 dosimetry challenges

- Dose to the marrow
- **Dose to the intestine**
- Dose to the lesion



At early times Ra-223 activity transits small bowel (10 mins – 4hr)



At later times Ra-223 activity in stools and slowly clears over several days.

Need models to determine the dosimetry and microdosimetry to the small intestine.

Dose to critical targets in the large bowel are probably out of range of the Ra-223 α -emissions.

CONCLUSIONS

- Imaging demonstrated bone targeting, and excretion through small bowel (rapid) with transit through large bowel.
- No significant redistribution of daughters to dose limiting organs such as the kidney detected.
- There are challenges to performing marrow, G.I. and lesion dosimetry due to difficulty in obtaining knowledge regarding the microdistribution of the sources to the target cells.
- Theoretical modelling based on histological and autoradiographic data to perform microdosimetry will help to drive the field forward.

Dose Rates to the Public from Patients Administered Alpharadin



Since we are not giving activities that are significantly lower than those used for diagnostic nuclear medicine scans, there is a much smaller hazard than with radioiodine for thyroid therapies for which 30-200 mCi are typically administered.

Dose rate are in $\mu\text{Sv/hr}$ below - compare to 90 $\mu\text{Sv/hr}$ (contact) after a bone scan

| | | Time after administration | | ~0 h | | | ~24 h | | | T~48 h | |
|------|-------------------|---------------------------|-------|-------|---------|-------|-------|---------|-------|--------|--|
| | | Contact | 0.3 m | 1 m | Contact | 0.3 m | 1 m | Contact | 0.3 m | 1 m | |
| | Activity (MBq) | | | | | | | | | | |
| Mean | 5.93 (160uCi) | 3.122 | 1.316 | 0.500 | 5.50 | 0.925 | 0.343 | 6.375 | 1.138 | 0.300 | |
| Max | 23.20 (627uCi) | 11.00 | 2.400 | 1.500 | 10.00 | 2.700 | 1.000 | 13.00 | 2.500 | 1.500 | |