# Theragnostics for bone metastases

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# Ra-223 – Biodistribution & dosimetry

Ra-223: 11.4 days half-life, range of 100 μm

Six patients with bone metastases from prostate cancer

100 kBq / kg x 2, 6 weeks apart (range 65 – 110 kg)

Faecal & urine collection (gamma spectroscopy)

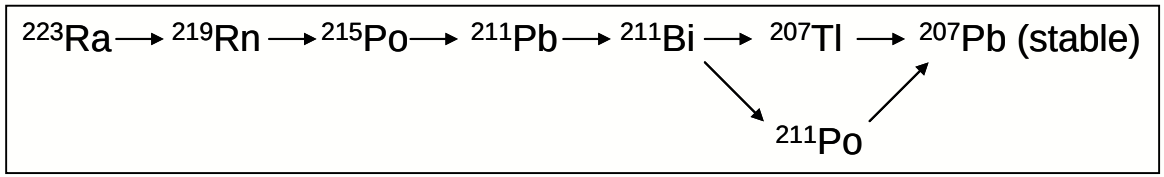
Whole-body retention (using 2 m arc external ceiling mounted counter)

Blood samples for activity retention

Planar scans – Days 0, 1, 2, 3, 7
- Insufficient counts for SPEC T, and need for whole-body imaging

*Hindorf Nuc Med Comm* 3(7) 726-732 2012

# Ra-223 – Biodistribution & dosimetry




| Radionuclide | Mode of decay | Abundance | Halflife |
|---|---|---|---|
| $^{223}Ra \rightarrow {}^{219}Rn$ | α | 100 % | 11.43 d |
| $^{219}Rn \rightarrow {}^{215}Po$ | α | 100 % | 3.96 s |
| $^{215}Po \rightarrow {}^{211}Pb$ | α | 100 % | 1.781 ms |
| $^{211}Pb \rightarrow {}^{211}Bi$ | $\beta^-$ | 100 % | 36.1 m |
| $^{211}Bi \rightarrow {}^{211}Po$ | $\beta^-$ | 0.276 % | 2.14 m |
| $^{211}Bi \rightarrow {}^{207}Tl$ | α | 99.72 % | 2.14 m |
| $^{211}Po \rightarrow {}^{207}Pb$ | α | 100 % | 0.516 s |
| $^{207}Tl \rightarrow {}^{207}Pb$ | $\beta^-$ | 100 % | 4.77 m |
| $^{207}Pb \rightarrow$ - | Stable | - | - |

# Ra-223 – Biodistribution & dosimetry

| *Mother radioisotope* | *Photon energy [keV]* | *Probability [fraction]* | *Type of photon* | *Imaging possibility* |
|---|---|---|---|---|
| $^{223}$Ra | 122.3 | 0.0121 | Gamma | Low probability of emission |
| $^{223}$Ra | 144.2 | 0.0327 | Gamma | Window 2 |
| $^{223}$Ra | 154.2 | 0.0570 | Gamma | Window 2 |
| $^{223}$Ra | 269.5 | 0.139 | Gamma | Window 3 |
| $^{223}$Ra | 323.9 | 0.0399 | Gamma | Low probability of emission |
| $^{223}$Ra | 338.3 | 0.0284 | Gamma | Low probability of emission |
| $^{223}$Ra | 83.78 | 0.251 | X-ray, K | Window 1 |
| $^{223}$Ra | 81.07 | 0.152 | X-ray, K | Window 1 |
| $^{223}$Ra | 94.90 | 0.115 | X-ray, K | Partly included in Window 1 |
| $^{223}$Ra | 11.70 | 0.229 | X-ray, L | Too low energy |
| $^{219}$Rn | 271.2 | 0.108 | Gamma | Window 3 |
| $^{219}$Rn | 401.8 | 0.0659 | Gamma | Possible |
| $^{219}$Rn | 11.10 | 0.0103 | X-ray, L | Too low energy |
| $^{211}$Pb | 404.9 | 0.0378 | Gamma | Possible |
| $^{211}$Pb | 427.1 | 0.0176 | Gamma | Possible |
| $^{211}$Pb | 832.0 | 0.0352 | Gamma | Too high energy |
| $^{211}$Bi | 351.0 | 0.129 | Gamma | Possible |
| $^{211}$Bi | 72.87 | 0.0126 | X-ray, K | Partly included in Window 1 |

# Quantitative imaging

27.8 MeV emitted per decay. 95% of energy from alpha particles. 1% gammas

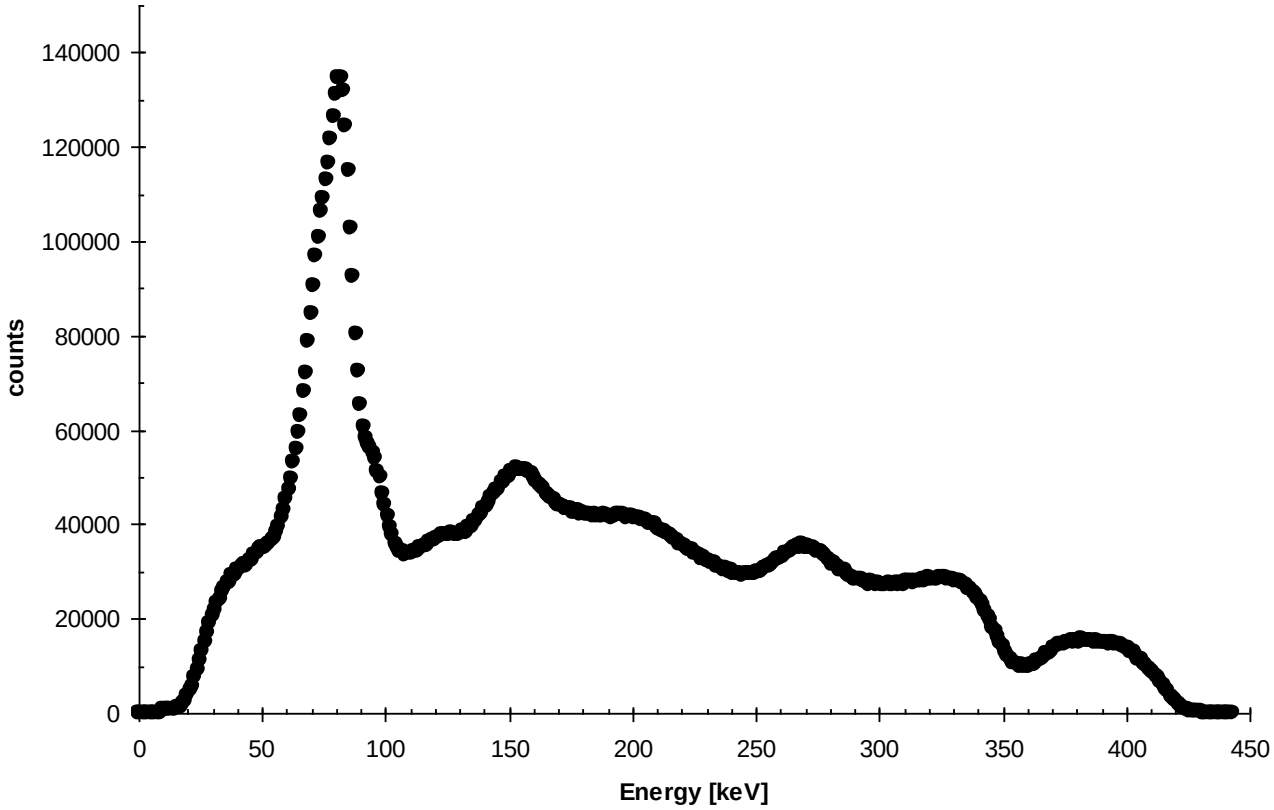
Main peak from 81 keV & 84 keV photons (15.2% & 25.1%)

Planar images obtained from Philips Forte camera with medium energy collimators (insufficient counts for SPECT)

List mode used to select arbitrary energy windows

Sensitivity, spatial resolution, effective attenuation coefficient and quantification accuracy determined from phantom studies

# Ra-223 – Energy spectrum




Energy window 1: 74 – 90 keV
Energy window 2: 142 – 166 keV
Energy window 3: 256 – 284 keV

# Results

Bladder & kidney absorbed doses from urine excretion

Bone marrow absorbed doses from blood activity and bone image data

Absorbed doses to SI, ULI, LLI calculated from image data

Absorbed doses to lesions calculated from image data

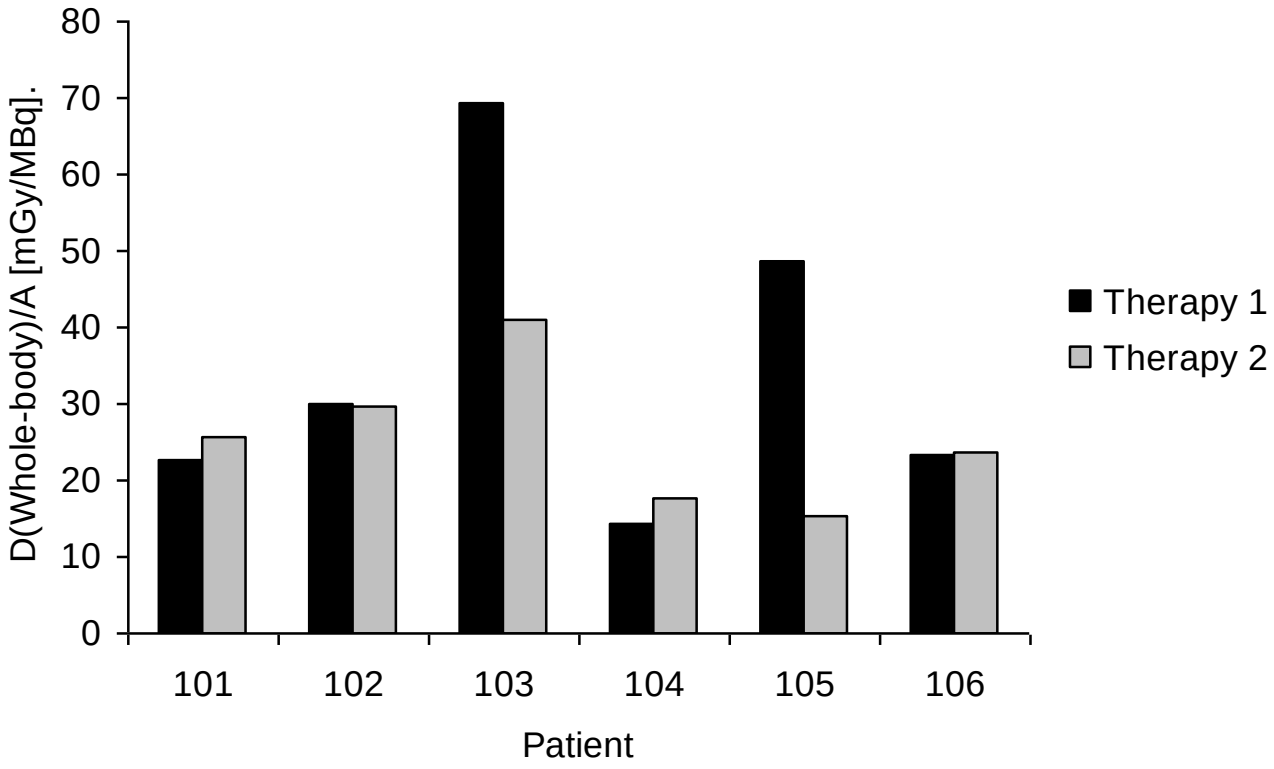
Whole-body absorbed doses from imaging, external counter, excretion

No specific uptake seen in kidneys or liver

Dosimetry calculated with to Olinda EXM (also RADAR and alternative methods)

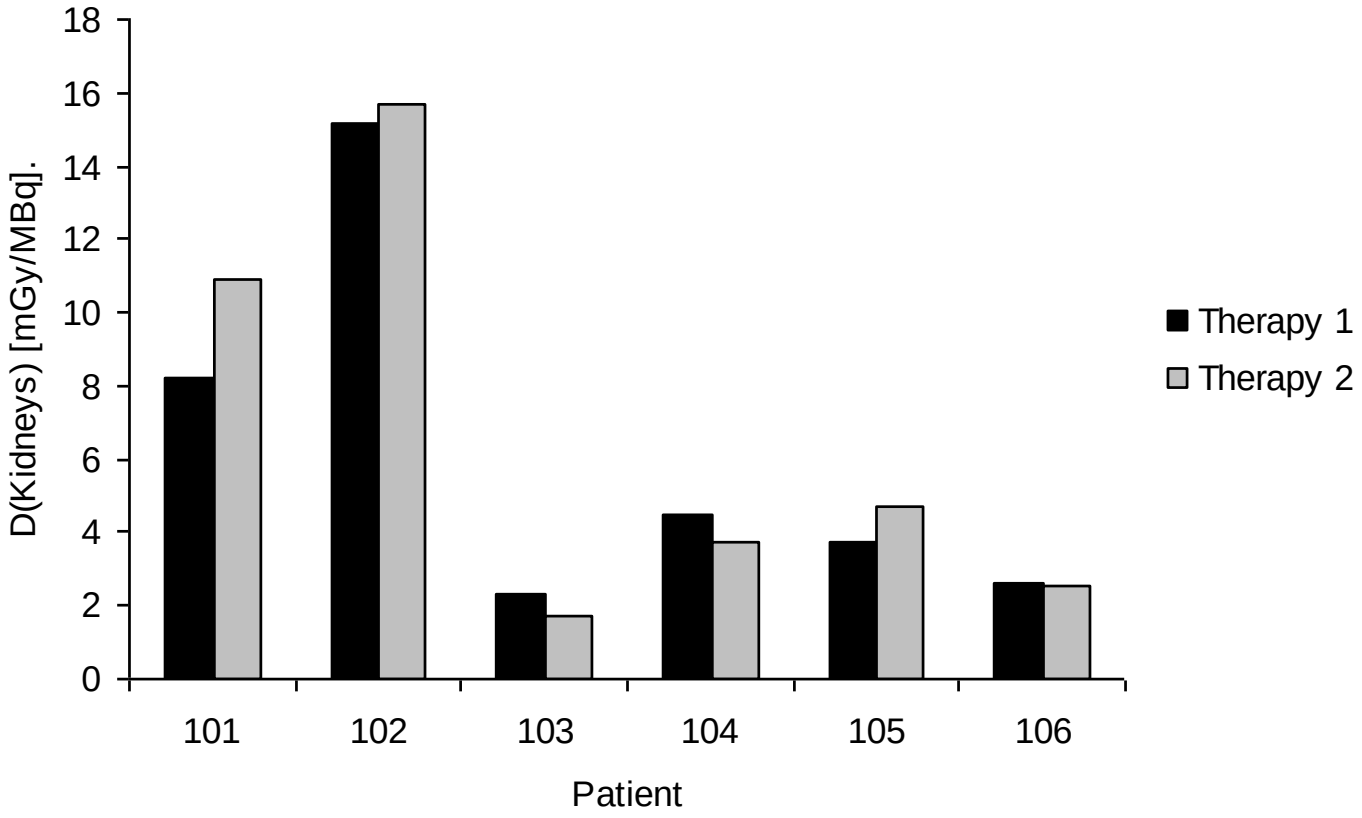
# Absorbed dose to whole body

Differences due to faecal excretion



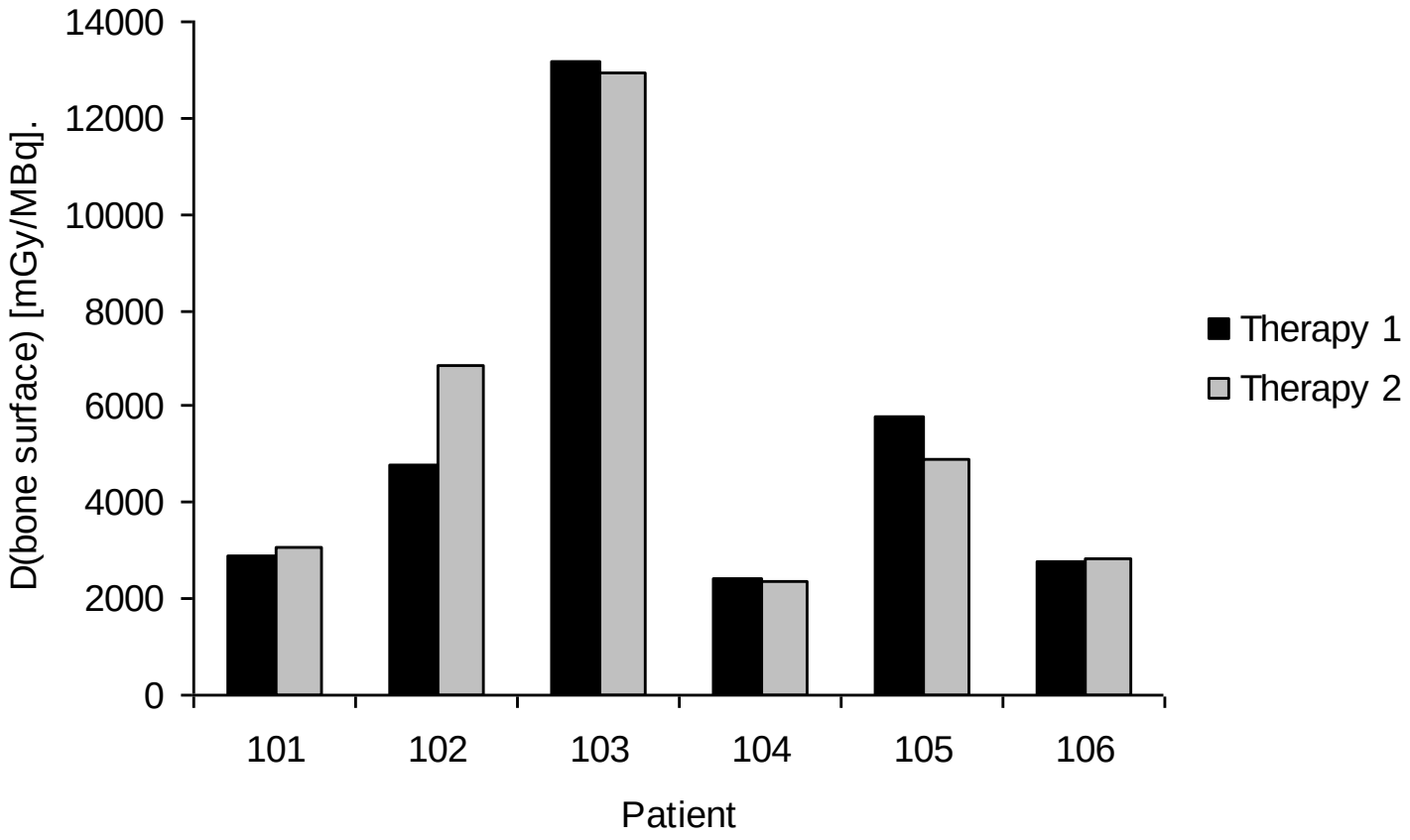
# Absorbed doses to kidneys

From urine excretion: Range 14-101 mGy



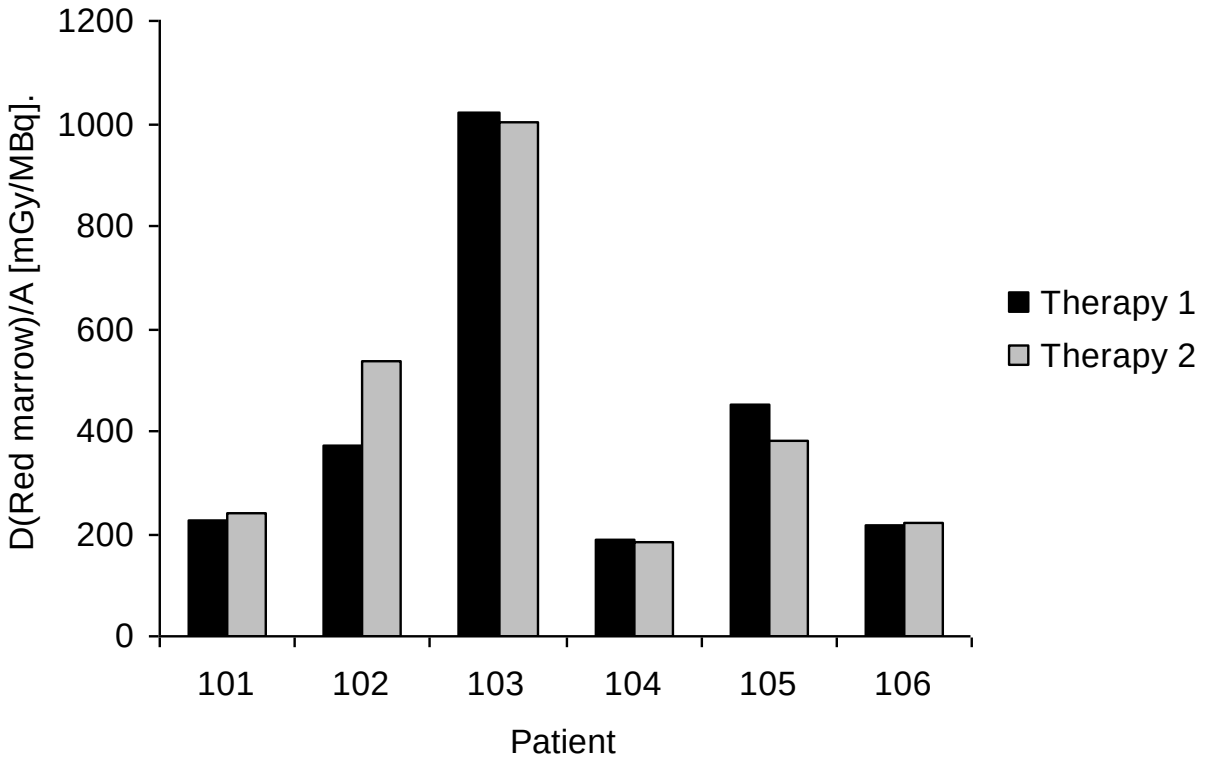
# Bone surfaces

Assumption: all activity concentrates on bone surfaces
- rather than uniform distribution. Range 20 Gy – 102 Gy



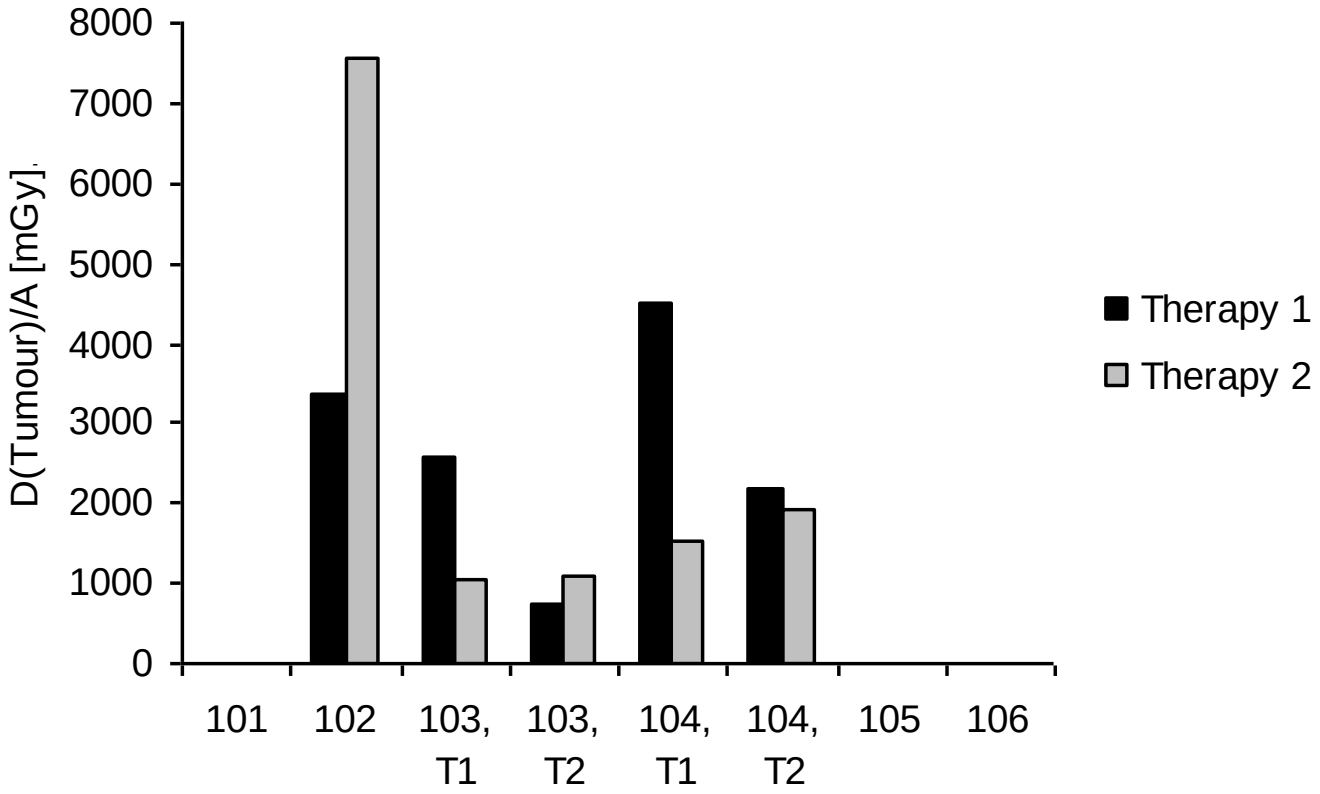
# Red marrow absorbed doses

Main contribution from activity in bone, as blood activity disappears quickly: Range 1.7 – 7.7 Gy



# Absorbed doses to tumours

Volumes range from 5 – 69 cc
Absorbed doses – 0.7 – 7.5 Gy

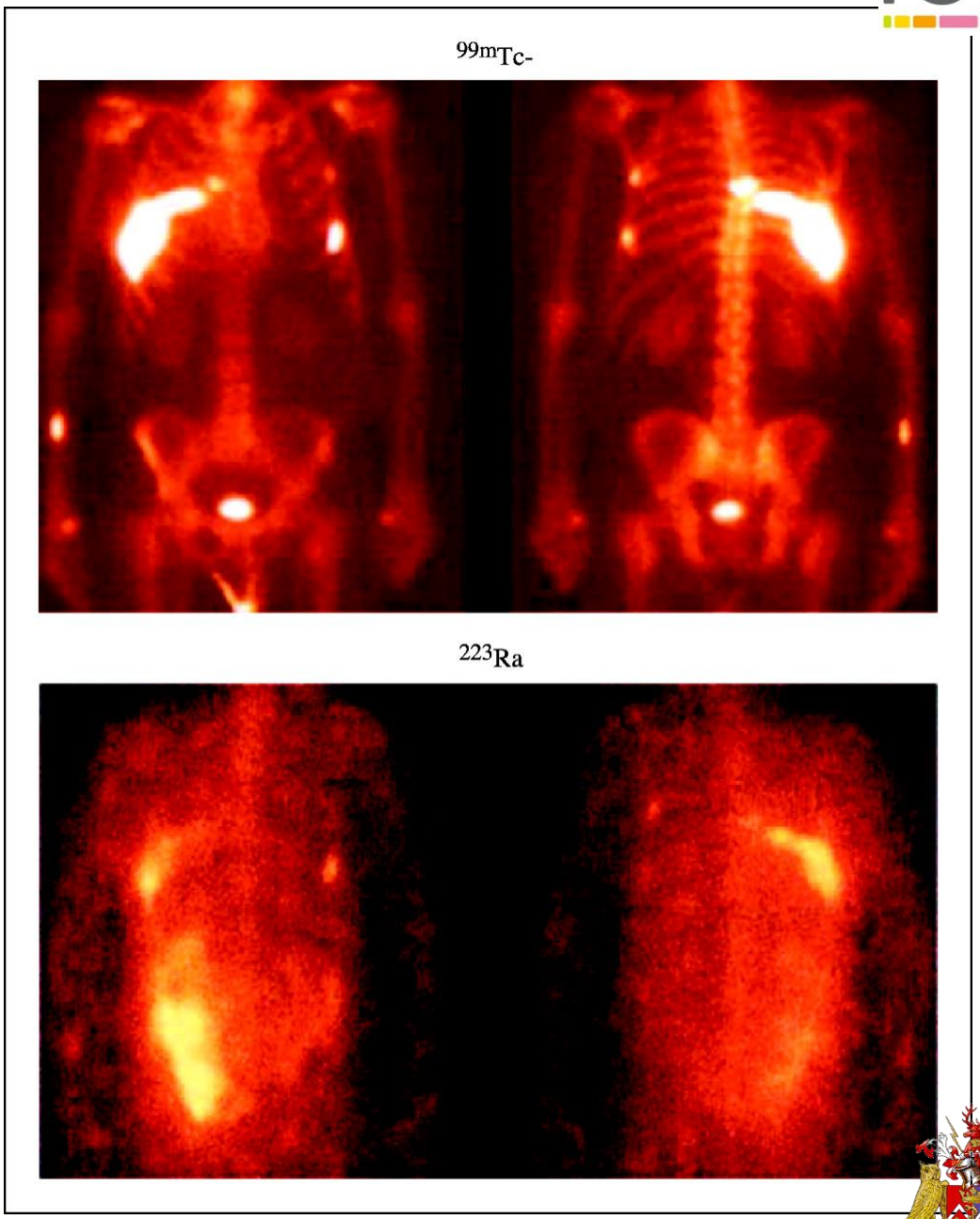


# Imaging

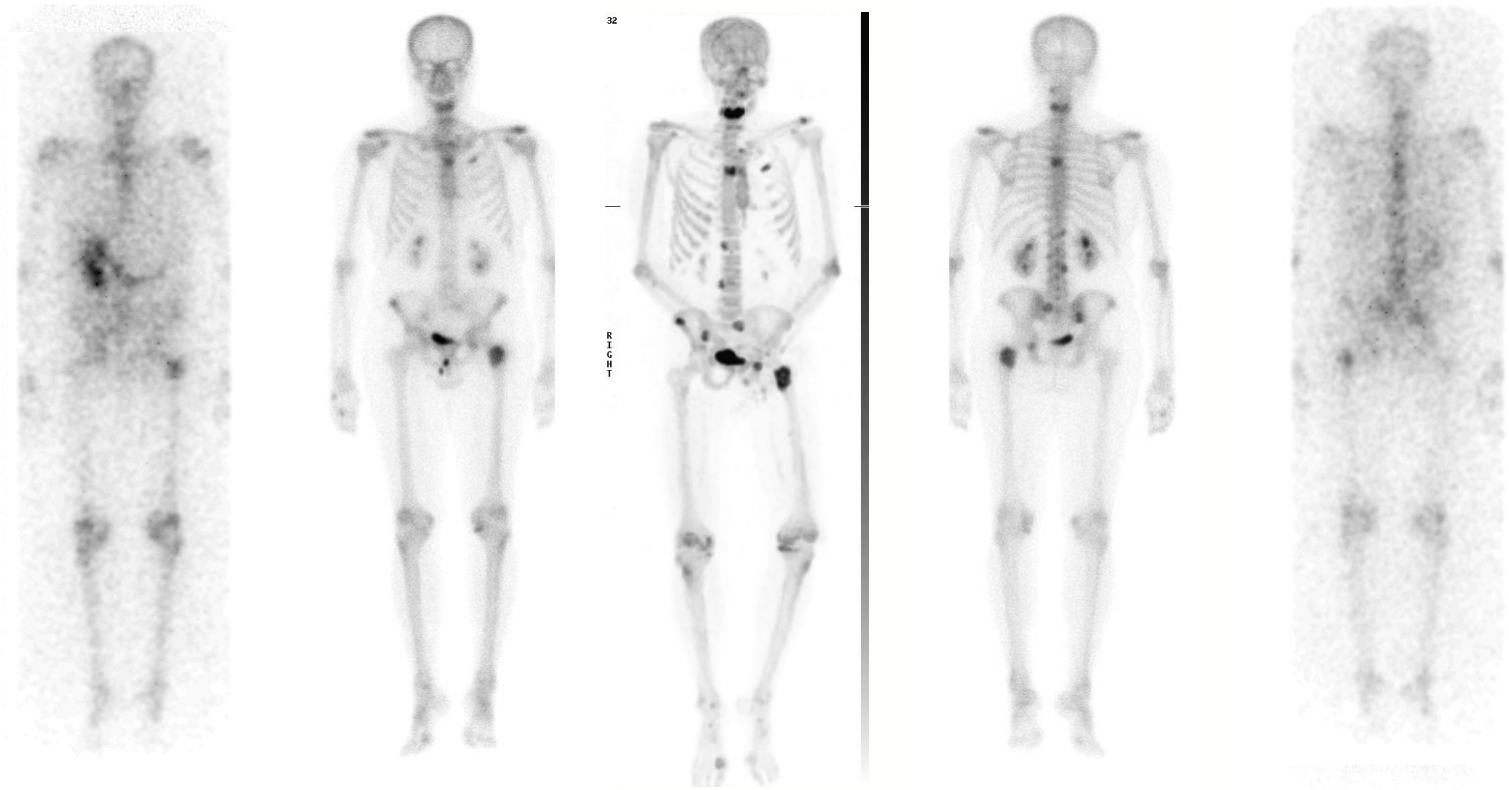
Useful to know absorbed dose to normal organs. Is personalised dosimetry needed once we have the range? Can tumour dosimetry be sufficiently accurate to impact on clinical practice?

Is there a role for imaging?

What image quality is necessary to be of clinical benefit?

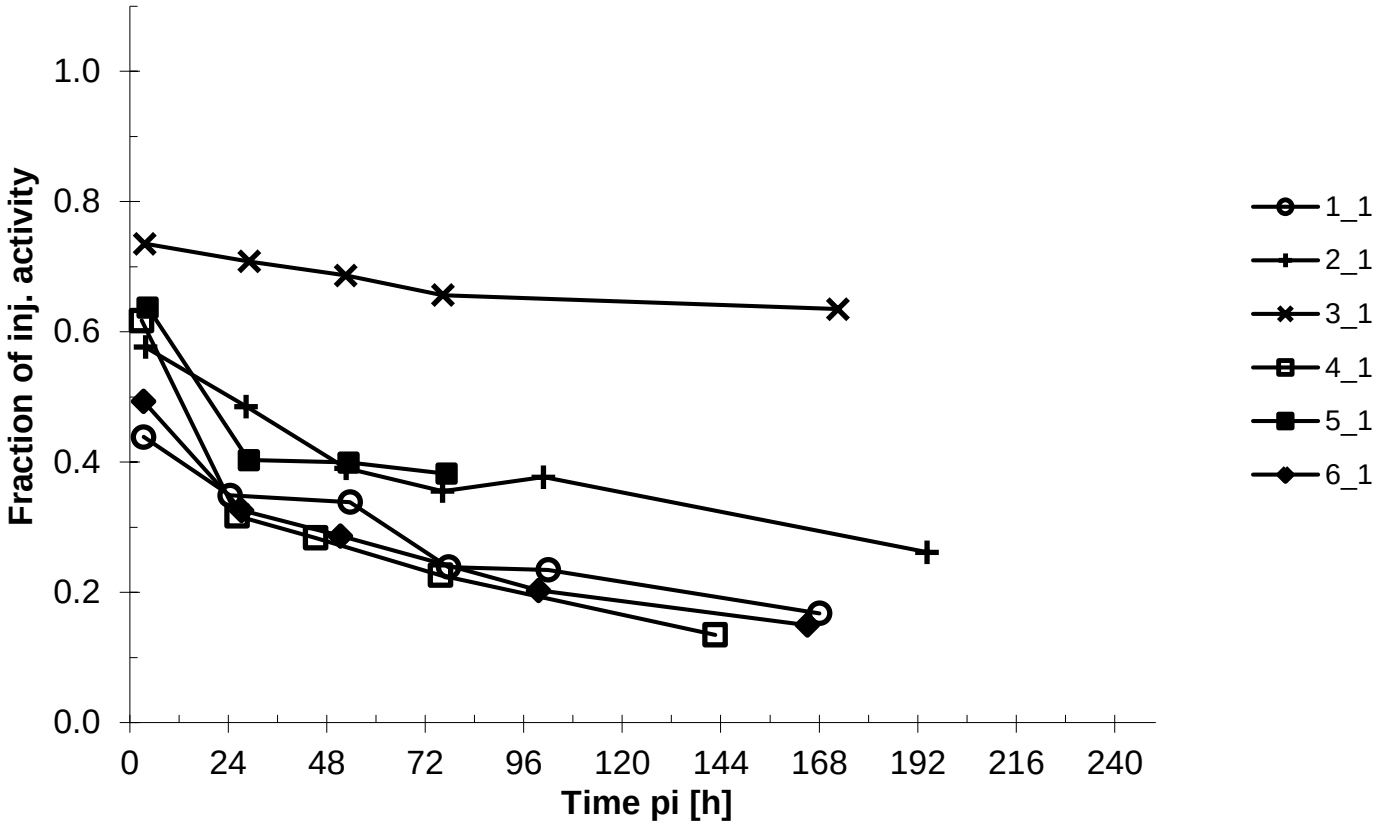


# Radium / Fluoride Uptake




Iain Murray, RMH/ICR

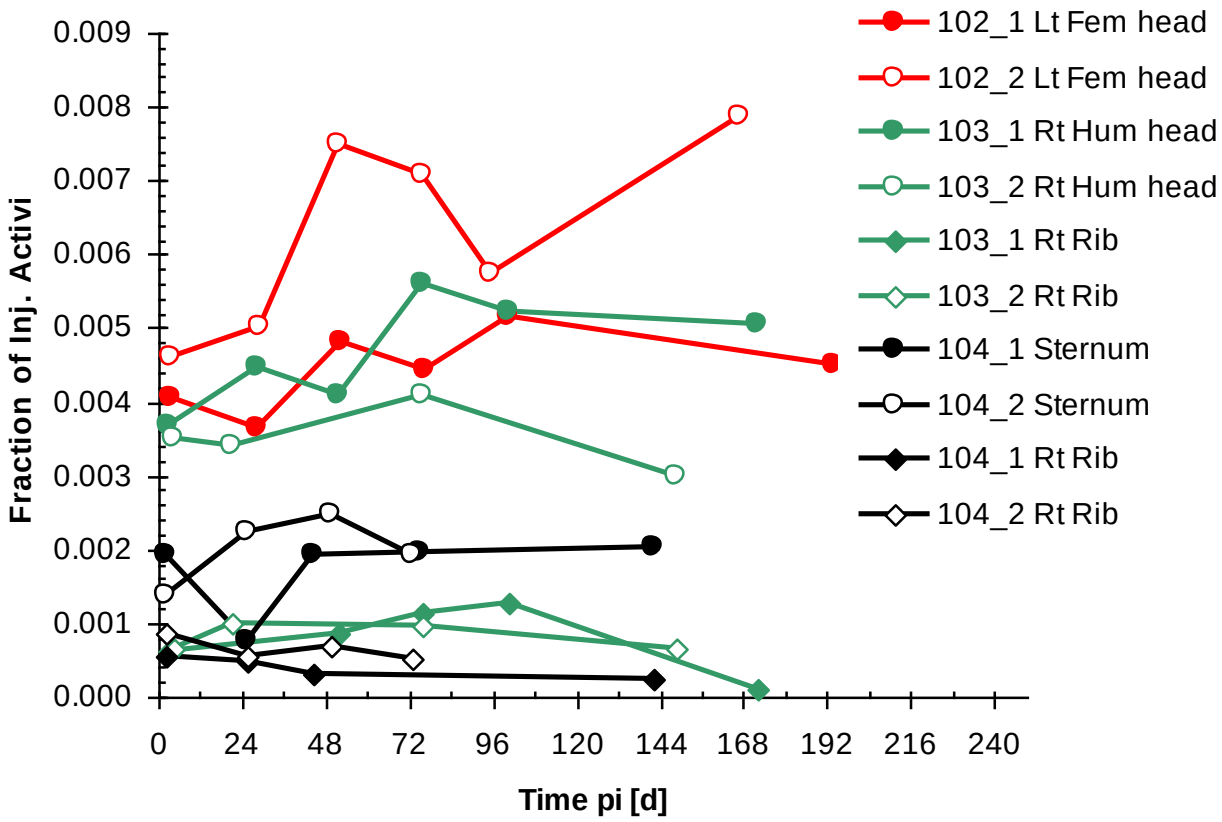
# Bone




'Smooth line' indicates reproducibility

Generally physical half-life

# Tumour




Uptake seen in 5 sites in 3 patients. Also physical half-life.

But greater (probably) uncertainty in measurements. Can we use PET data?

Cook et al. EJNMMI Research 2011, 1:4
http://www.ejnmmires.com/content/1/1/4

EJNMMI Research
a SpringerOpen Journal

PRELIMINARY RESEARCH Open Access

# $^{18}$F-fluoride PET: changes in uptake as a method to assess response in bone metastases from castrate-resistant prostate cancer patients treated with $^{223}$Ra-chloride (Alpharadin)

Gary JR Cook[1*], Chris Parker[2], Sue Chua[1], Bernadette Johnson[2], Anne Kirsti Aksnes[3] and Val J Lewington[1]

**Abstract**

**Background:** A qualitative assessment of conventional bone scintigraphy with $^{99m}$Tc methylene diphosphonate is perceived as an insensitive method for monitoring the treatment response of bone metastases, and we postulated that semi-quantitative $^{18}$F-fluoride positron emission tomography (PET) might serve as a suitable alternative biomarker of the treatment response.

**Methods:** Five patients with castrate-resistant prostate cancer and bone metastases with no known soft tissue disease received 100 kBq/kg of radium-223 ($^{223}$Ra)-chloride (Alpharadin) therapy at 0 and 6 weeks and had whole body $^{18}$F-fluoride PET scans at baseline, 6 and 12 weeks with concurrent prostatic-specific antigen (PSA) and alkaline phosphatase (ALP) measurements. A qualitative comparison of the PET scans was performed blinded to the PSA and ALP results. A semi-quantitative comparison was made by measuring the maximum standardised uptake values (SUVmax) in five bone metastases in each patient. The means of the five SUVmax measurements in each subject were used as a quantitative measure of global metastatic activity at each time point.

**Results:** Three patients showed a PSA decline at 12 weeks (-44%, -31%, -27% reduction) whilst two patients showed PSA increases (+10%, +17%). All five patients showed a reduction in ALP of greater than 25%. The qualitative assessment of the $^{18}$F-fluoride scans recorded a stable disease in each case. However, the semi-quantitative assessment showed agreement with the PSA decline in three patients (-52%, -75%, -49%) and minimal change (+12%, -16%) in two patients with increased PSA at 12 weeks. Four patients showed similar reductions in mean SUVmax and ALP at 12 weeks.

**Conclusions:** The semi-quantitative $^{18}$F-fluoride PET is more accurate than the qualitative comparison of scans in assessing response in bone metastases, correlating with the PSA response and ALP activity and offering a potential imaging biomarker for monitoring treatment response in bone metastases following treatment with $^{223}$Ra-chloride.

## Background

Prostate cancer is the commonest cancer in men in the UK and is the second most common male cancer worldwide [1]. Bone metastases are common in patients with prostate cancer, and approximately 70% of patients have evidence of skeletal disease at post-mortem [2]. Bone metastases are associated with significant morbidity including pain, pathological fracture and cord compression, and the median survival is 20 months [2]. The demands on health care resources can be great, and it is therefore important that accurate methods are available to monitor therapy which can give an indication of success or failure early in the course of treatment as part of routine clinical management or within the context of clinical trials.

However, bone metastases are notoriously difficult to monitor during treatment, and in practice a combination of clinical, biochemical (e.g. prostate-specific

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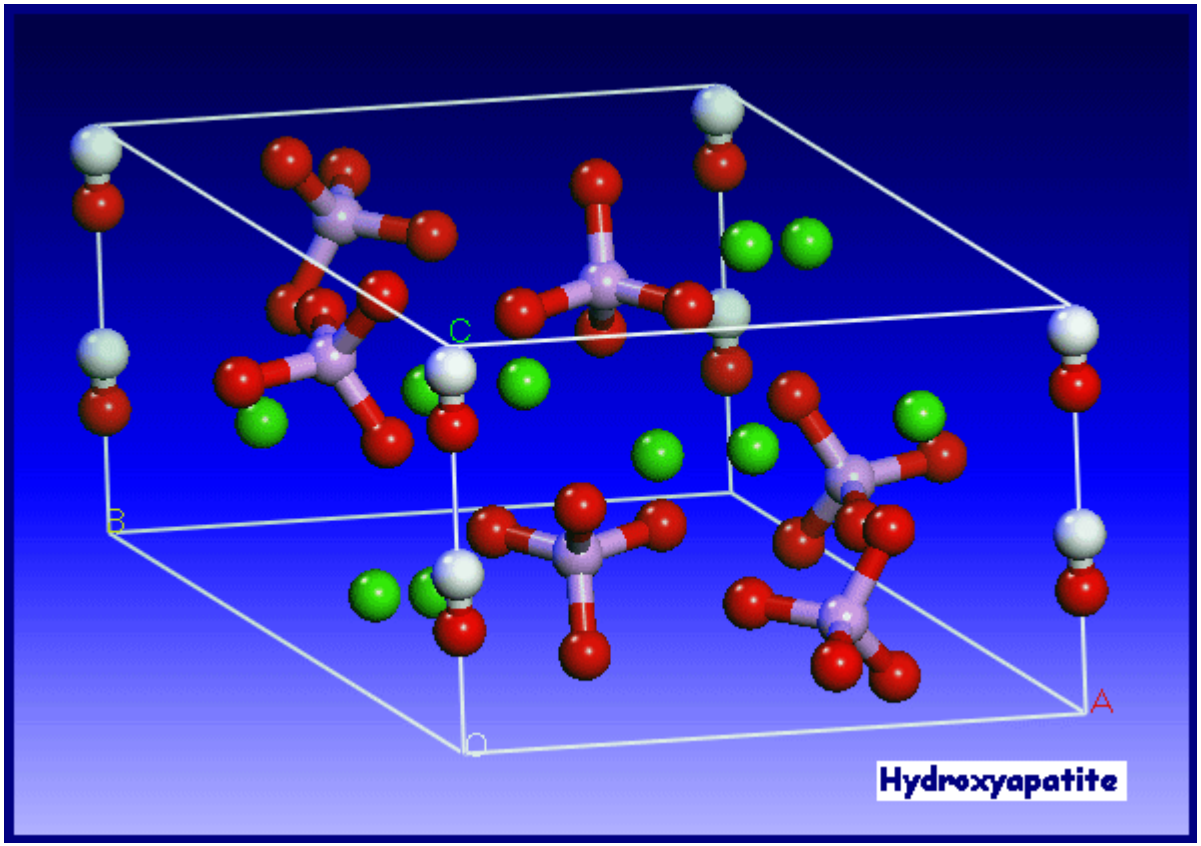
"The semi-quantitative 18F-fluoride PET is" … "a potential imaging biomarker for monitoring treatment response in bone metastases following treatment with 223Ra-chloride"

# Hydroxyapatite

$Ca_{10}(PO_4)_6(OH)_2$

- oxygen
- calcium
- phosphorus
- hydrogen

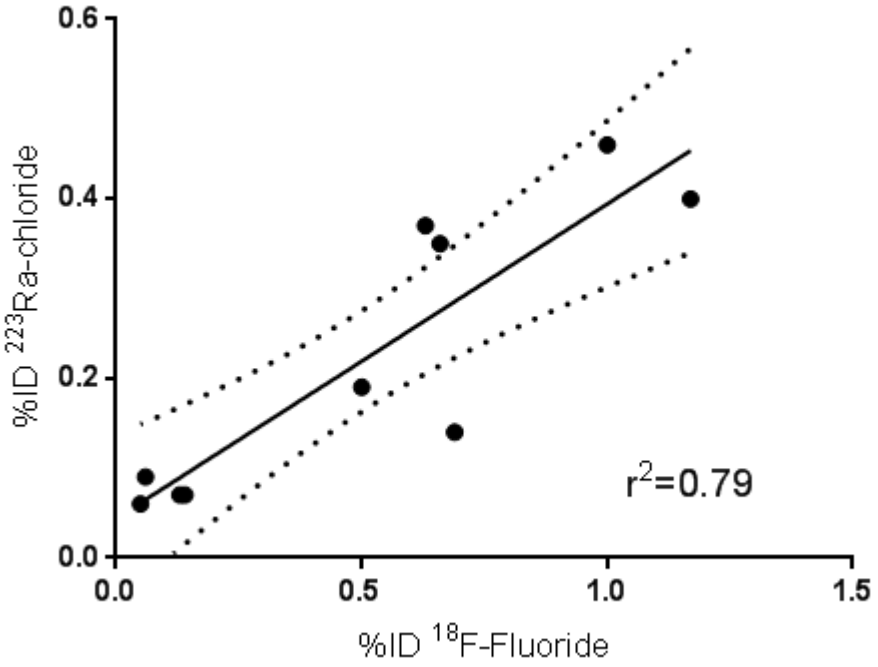



Radium undergoes ionic exchange with the calcium ions

Fluoride ions substituted for hydroxyl ions

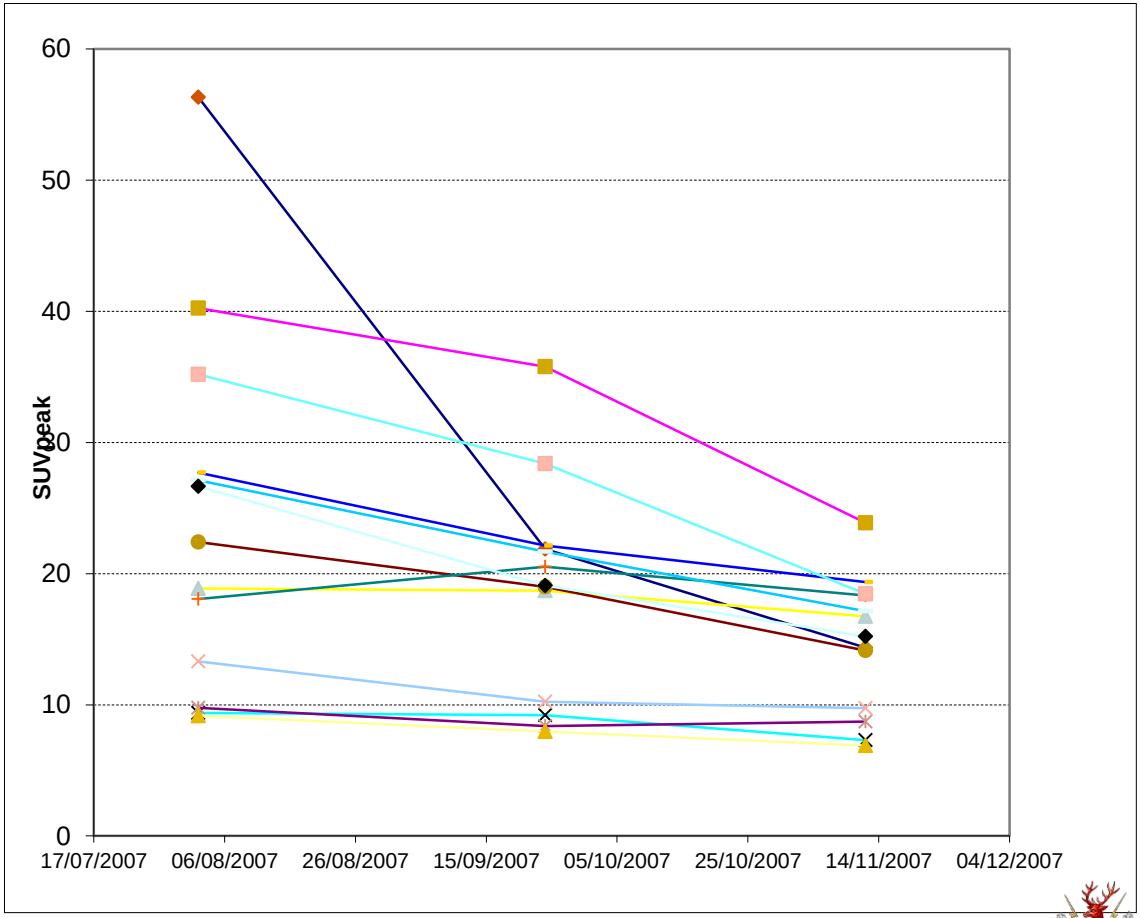
# Does $^{18}$F uptake reflect $^{223}$Ra uptake?

Limited number of lesions available for analysis on planar $^{223}$Ra, but reasonable correlation.

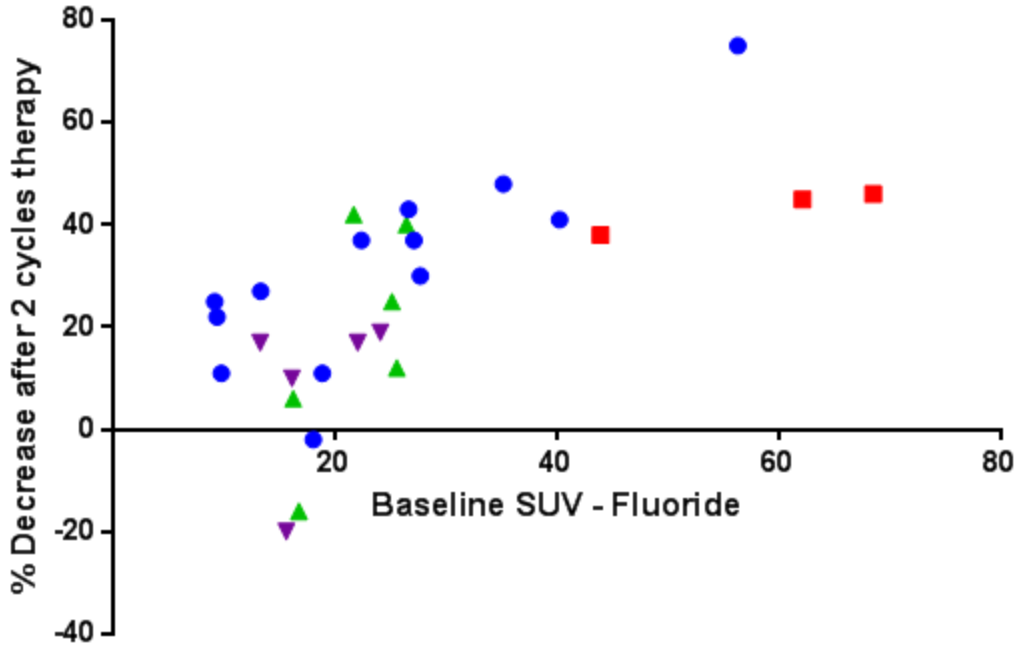


# $^{18}$F as marker of response

- Define change in $SUV_{peak}$ as measure of response.
- If F-18 uptake correlates with Ra-223 uptake, and absorbed dose (physical half-life should mean that 1 scan is sufficient), it should also be a predictive biomarker of response.



# $^{18}$F as predictor of response

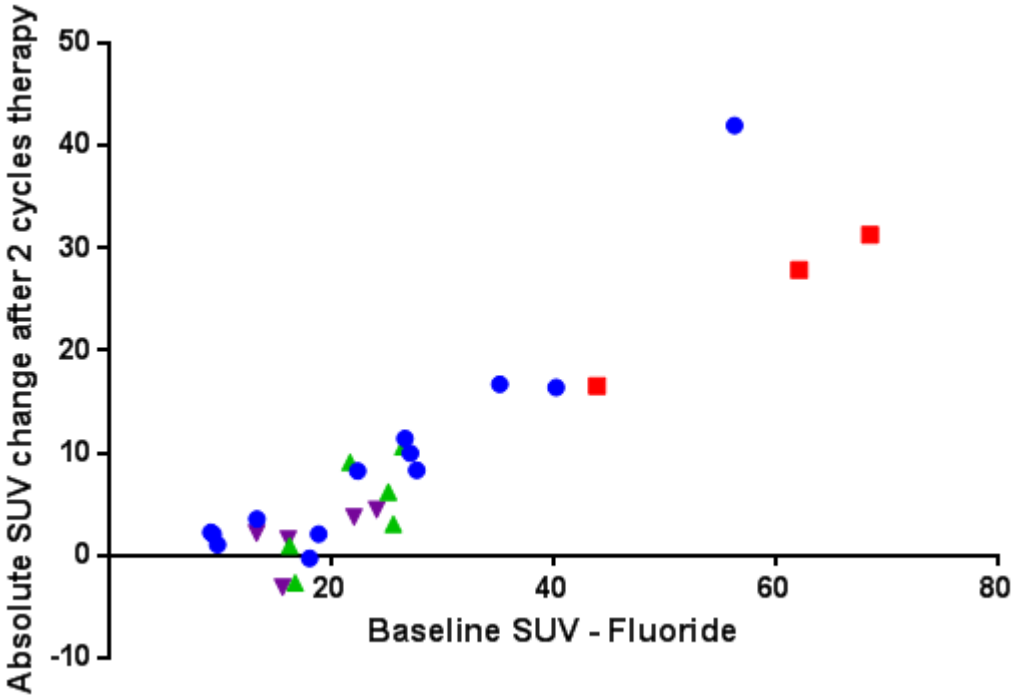



$r^2 = 0.44$

Conventionally responses to therapy are presented as %changes in SUV.

Consider absolute response?

# $^{18}$F as predictor of response

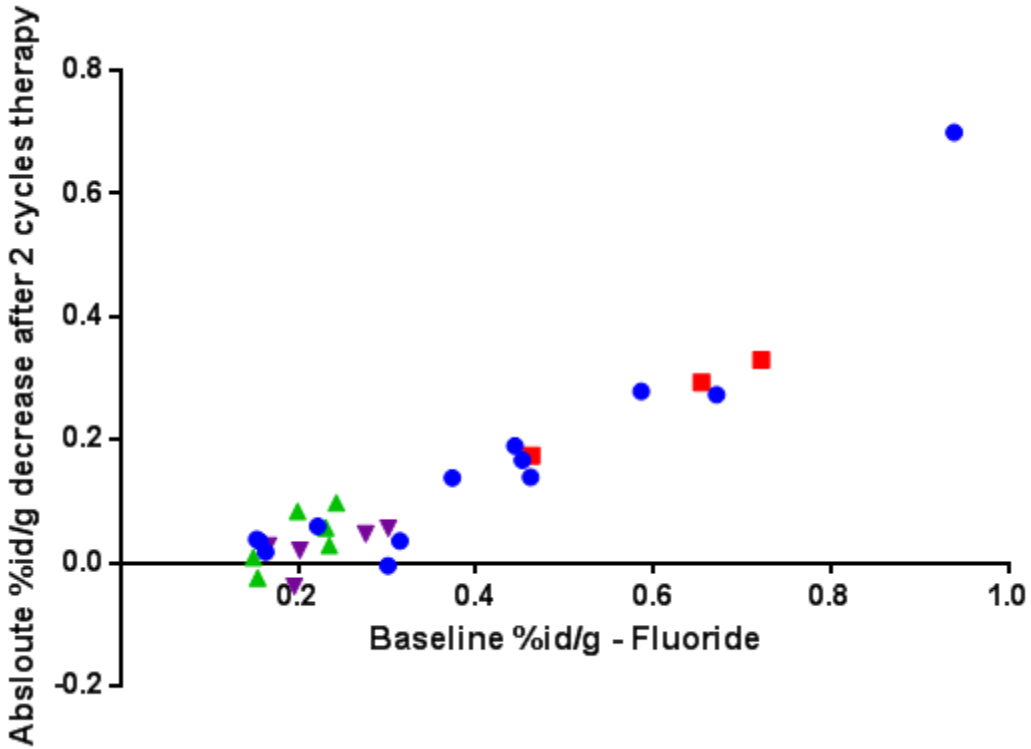



$r^2 = 0.85$

Should we be normalising to body mass for $^{18}$F-Fluoride?

Consider just absolute uptake.

# $^{18}$F as predictor of response

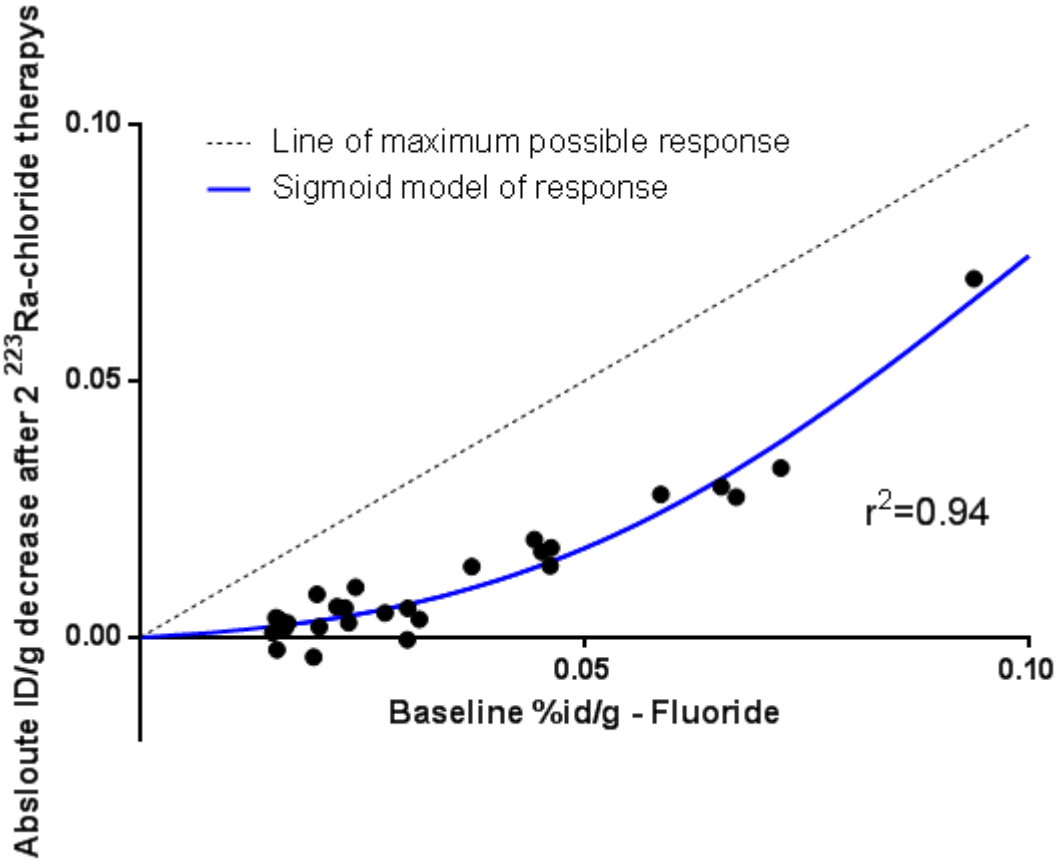



$r^2 = 0.88$

Maximum possible response is defined by y = x

Threshold dose indicated. Response should be sigmoidal.

# Dose-Response Model

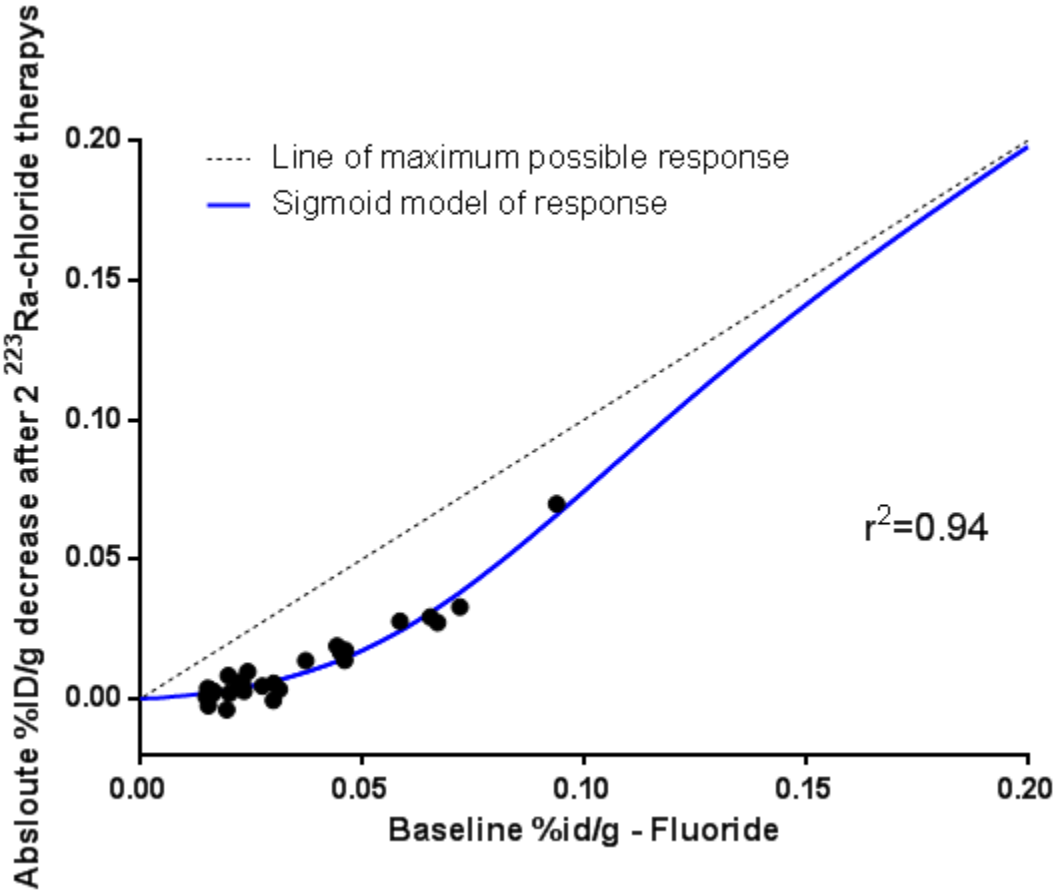



$$y = c + x\left(\frac{1}{1 + e^{(m(T-x))}}\right)$$

Sigmoidal fit

Ideal therapy would aim at the line of maximum response

# Dose-Response Model




Could predict uptake to achieve high TCP?

# Conclusions and questions

Currently, Ra-223 treatment is ‘safe’

Are higher activities warranted?

Could we make more use of PET/CT for dosimetry?

The potential for ‘theragnostics’?

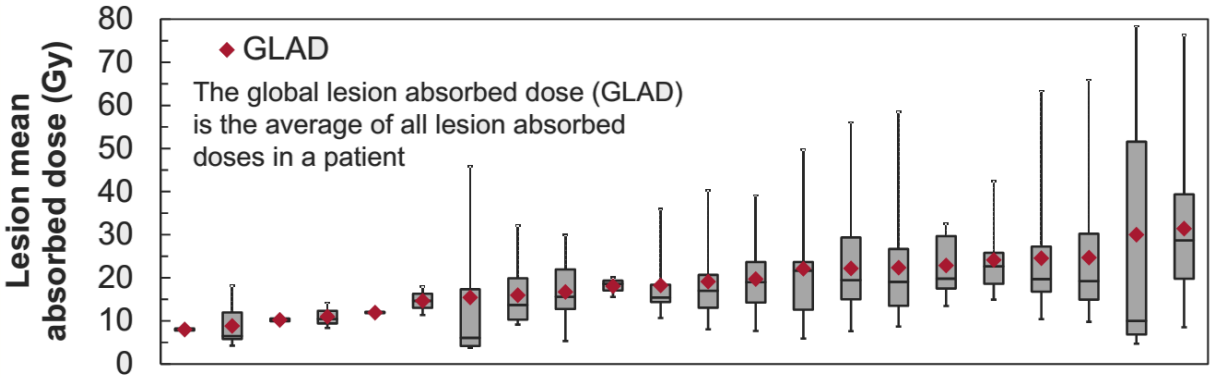
# Thanks to:

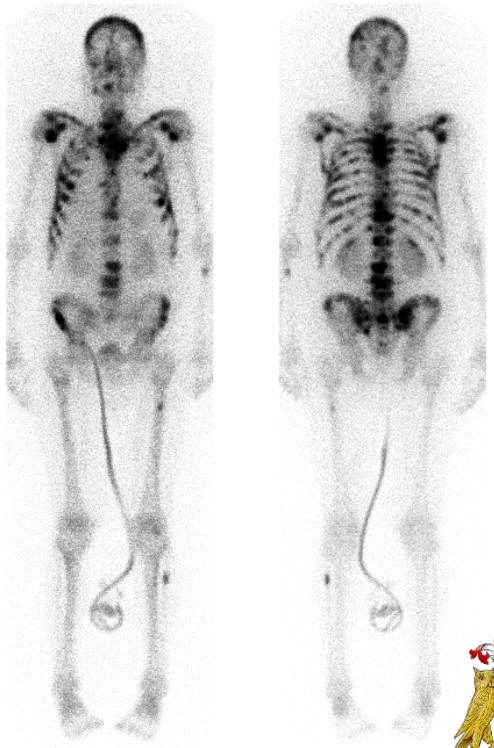

- Cecilia Hindorf
- Ana Denis-Bacelar
- Iain Murray
- Sarah Chittenden
- Antigoni Divoli
- Jon Gear
- Becky Gregory
- Matt Gray
- Charlotte Barker
- Dominic Rushforth

# Retrospective dosimetry in palliative molecular radiotherapy with $^{186}$Re-HEDP for bone pain in patients with CRPC

Ana M Denis-Bacelar

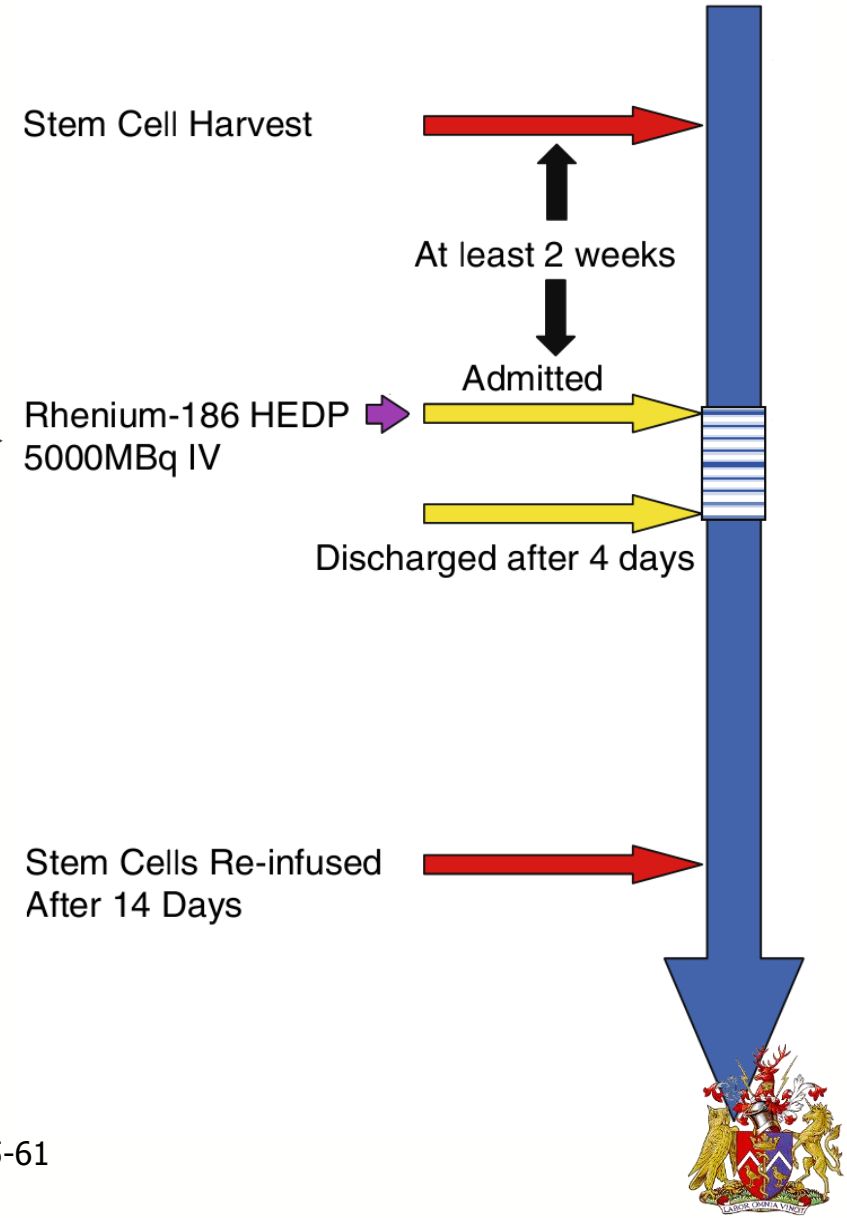
- Prostate cancer is the 2nd most common cause of cancer death among men in the United Kingdom
- 90% of patients with castrate resistant prostate cancer (CRPC) develop bone metastases
- Aim: retrospective dosimetry, intra- and inter-patient absorbed dose variation
- 22 patients treated with 5 GBq of $^{186}$Re-HEDP showed a range of absorbed dose delivered to lesions



# Methods: Study details

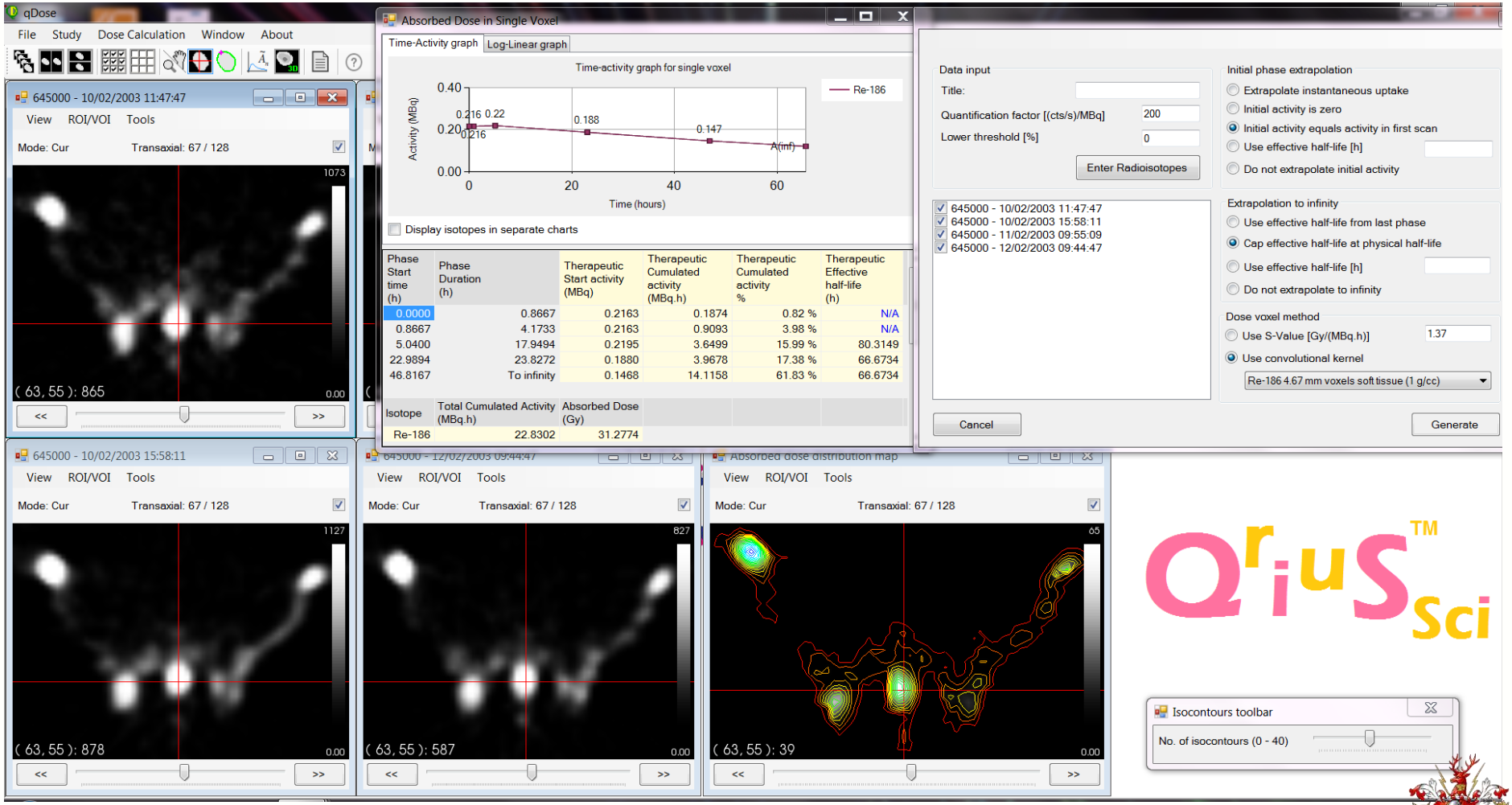
- 22 patients received 4.8–5.1 GBq of $^{186}$Re-HEDP part of a phase II trial[1]
- Stem cell transplantation enabled higher activities to be administered
- Sequential SPECT imaging:
  - Scans of thorax and pelvis
  - Acquired at 1, 4, 24, 48 and 72 hours following administration
- Scans reconstructed using FBP
- Scatter and attenuation corrected (CT was not available)



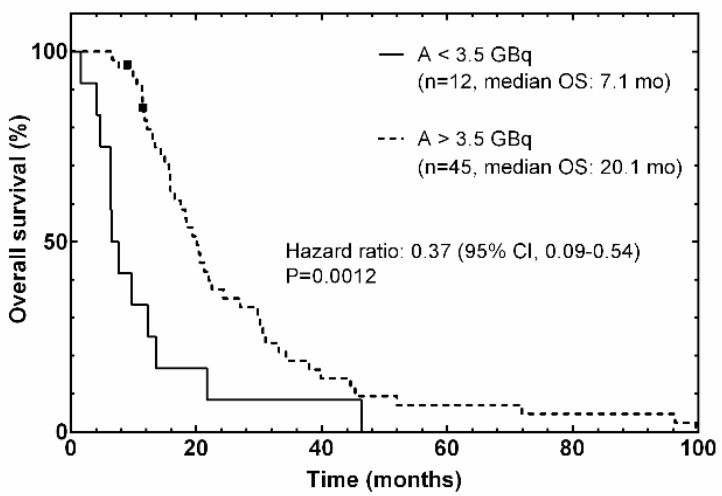

[1]J M O'Sullivan *et al,* Eur J Nuc Med Mol Imaging (2006) 33(9), 1055-61

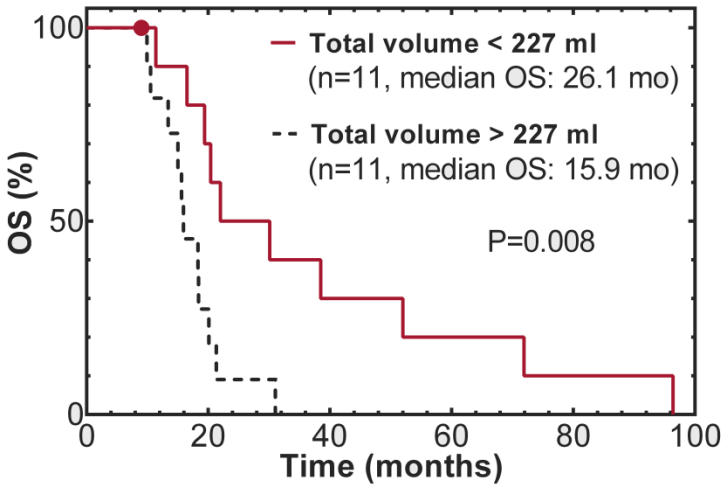
# Methods: 3D voxel dosimetry

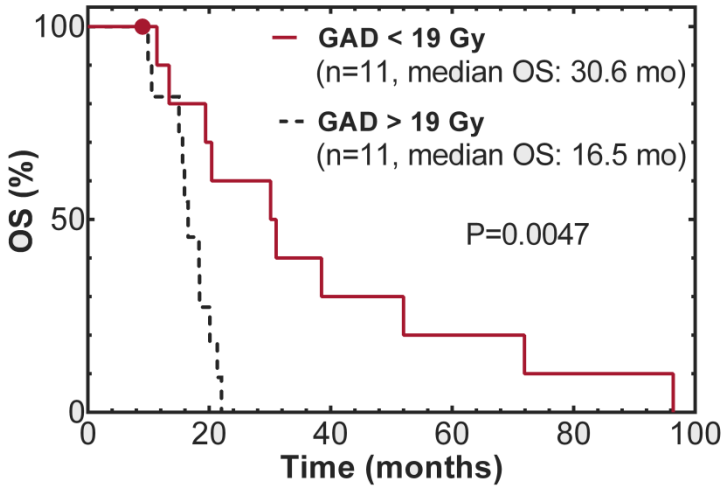
- In-house dosimetry software: Qrius™, (OP270, Monday 20th, 13:11)

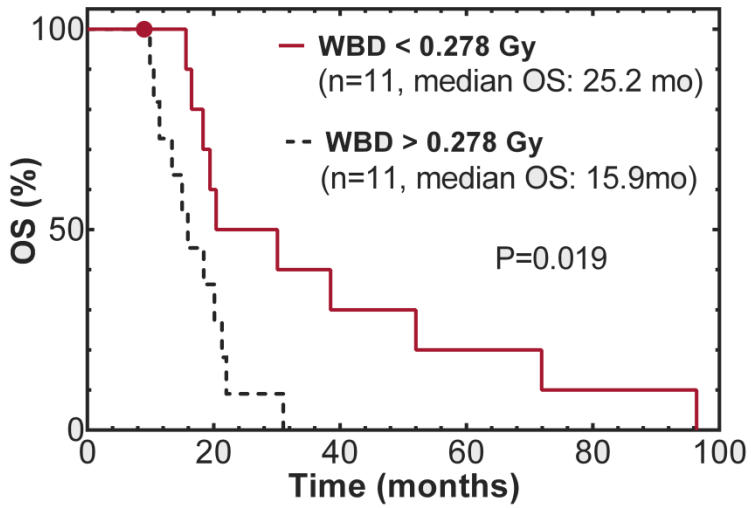


# Kaplan-Meier

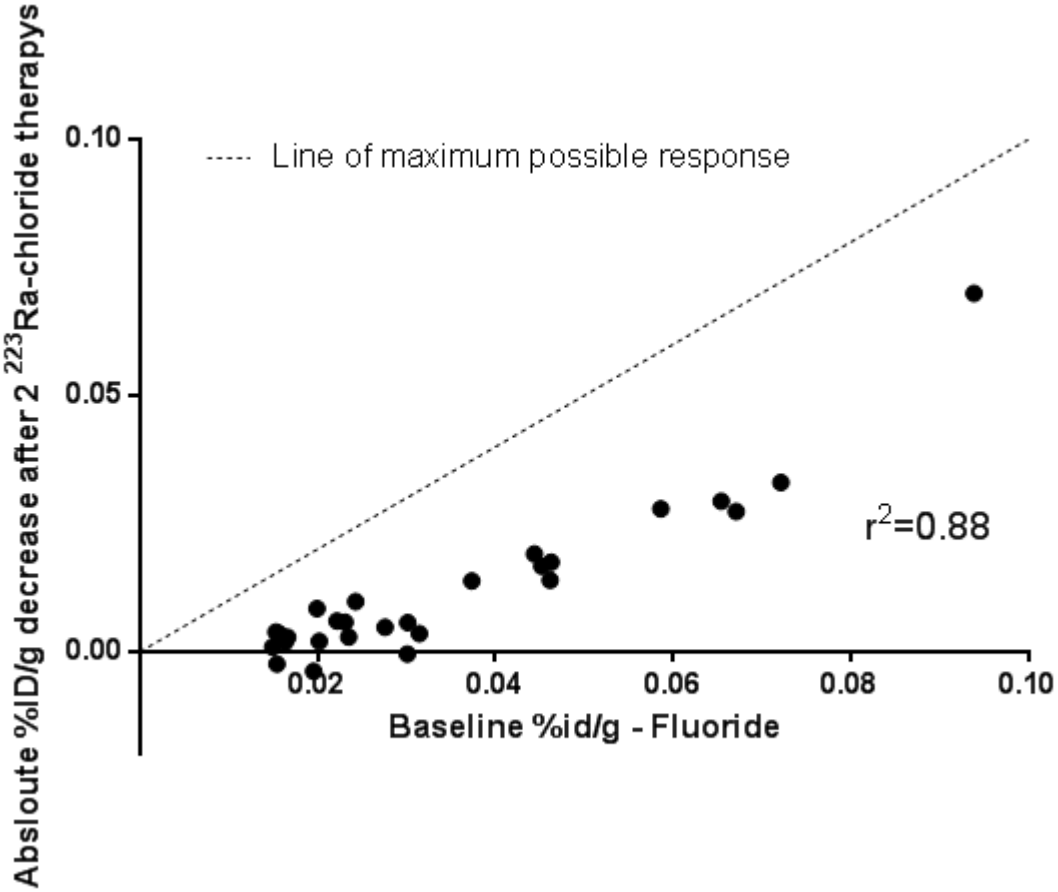


# $^{18}F$ as predictor of response




Maximum possible response is defined by y = x

Threshold dose indicated. Response should be sigmoidal.