Individualised Treatment Planning for Radionuclide therapy (Molecular Radiotherapy)

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ICRP Task Group 101

FMU/ICRP workshop 2017

Overview

- Potential for personalised treatment planning with MRT
- Treatment planning for I-131 mIBG of neuroblastoma
- Treatment planning for Ra-223 for bone metastases from CRPC
- Future directions

Treatment planning

Individualised treatment planning, based on extensive multi-centre clinical trials, is currently performed for all cancer treatments…

Population-based medicine

- I-131 NaI for thyroid remnant ablation (fixed activities):
  O'Connell *et al* (Radiother Oncol 1993) 7 – 3500 Gy
  Sgouros *et al* (J Nucl Med 2004) 1.2 – 540 Gy
  Flux et al (EJNM 2010) 6 – 570 Gy

- Y-90 Zevalin for NHL (15 mCi / kg)
  Wiseman *et al* (Cancer 2002)
  Red marrow 0.3 – 1.2 Gy
  Absorbed tumour dose 0.6 – 243 Gy

- I-131 mIBG for neuroblastoma (555 MBq / kg):
  Matthay *et al* (JNM 2002)
  Tumour absorbed doses: 3-305 Gy

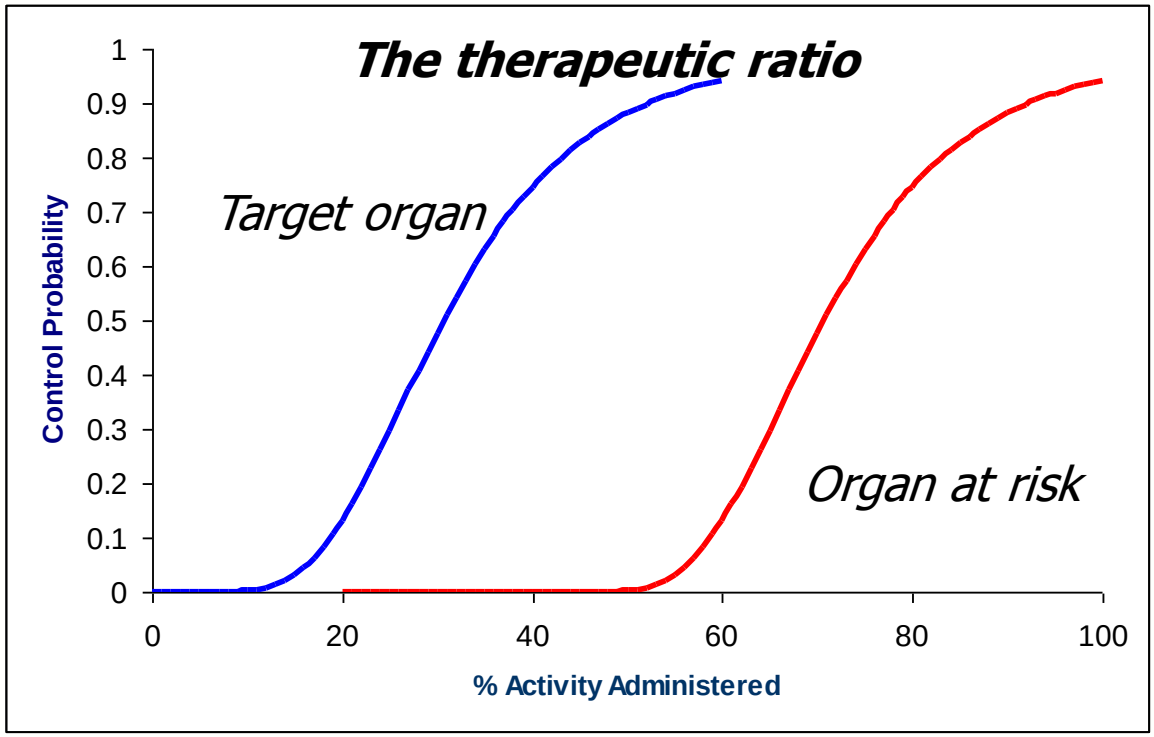
- Y-90 DOTATOC for neuroendocrine tumours
  Bodei *et al* (EJNM 2004)
  Kidneys 6 - 46 Gy
  Marrow 0.2 – 1.9 Gy

Treatment planning for MRT

If no treatment planning is performed, a wide range of absorbed doses is delivered

Can we personalise treatment in line with other cancer treatments?

Personalised MRT?



Requirements for treatment planning:

- Accurate predictions of uptake and retention of radiopharmaceutical *in vivo* for organs-at-risk and target organs (or tumour)

- Response of tissue to continual low dose irradiation

Critical organs

Various organs at risk:

- Kidney doses for peptide therapy
- Liver doses for mIBG
- Lung doses for metastatic thyroid therapy

Is it sufficient to calculate mean doses to OAR with basic assumptions and 'population' dosimetry? (Standard phantoms, mean doses etc)

Yes, if looking for rough estimate of dose for protection

No, if considering short or long term toxicity

Red marrow is the OAR for most therapies

Red marrow dosimetry

Possibly the most difficult dosimetry to perform accurately.
Can be obtained from

- Direct sampling.
- Imaging.
- Evaluation from blood doses.
- Whole-body dosimetry?

Whole-body dosimetry

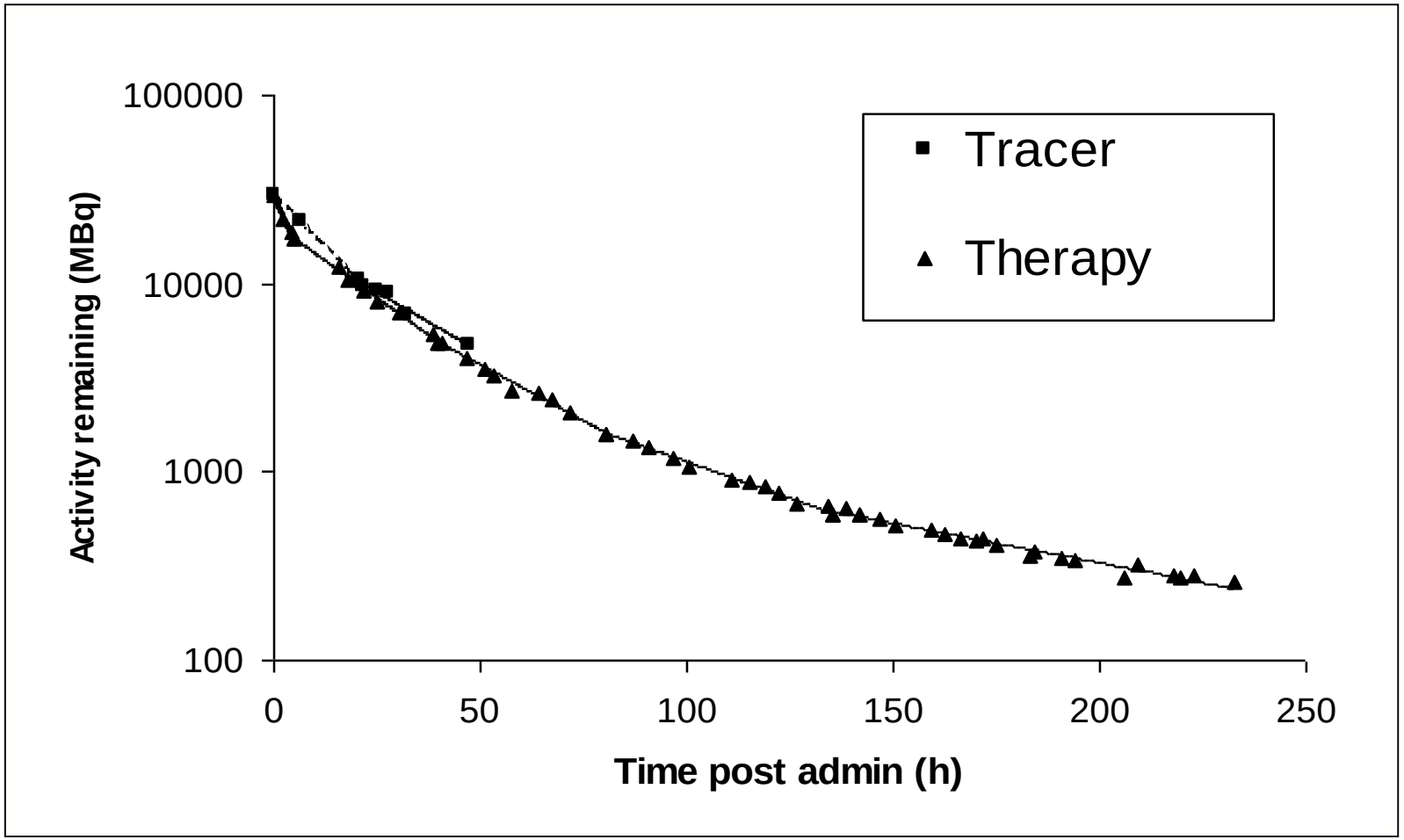
Set up: counter above patient bed.

Easy to perform

Ward staff, carers can take measurements

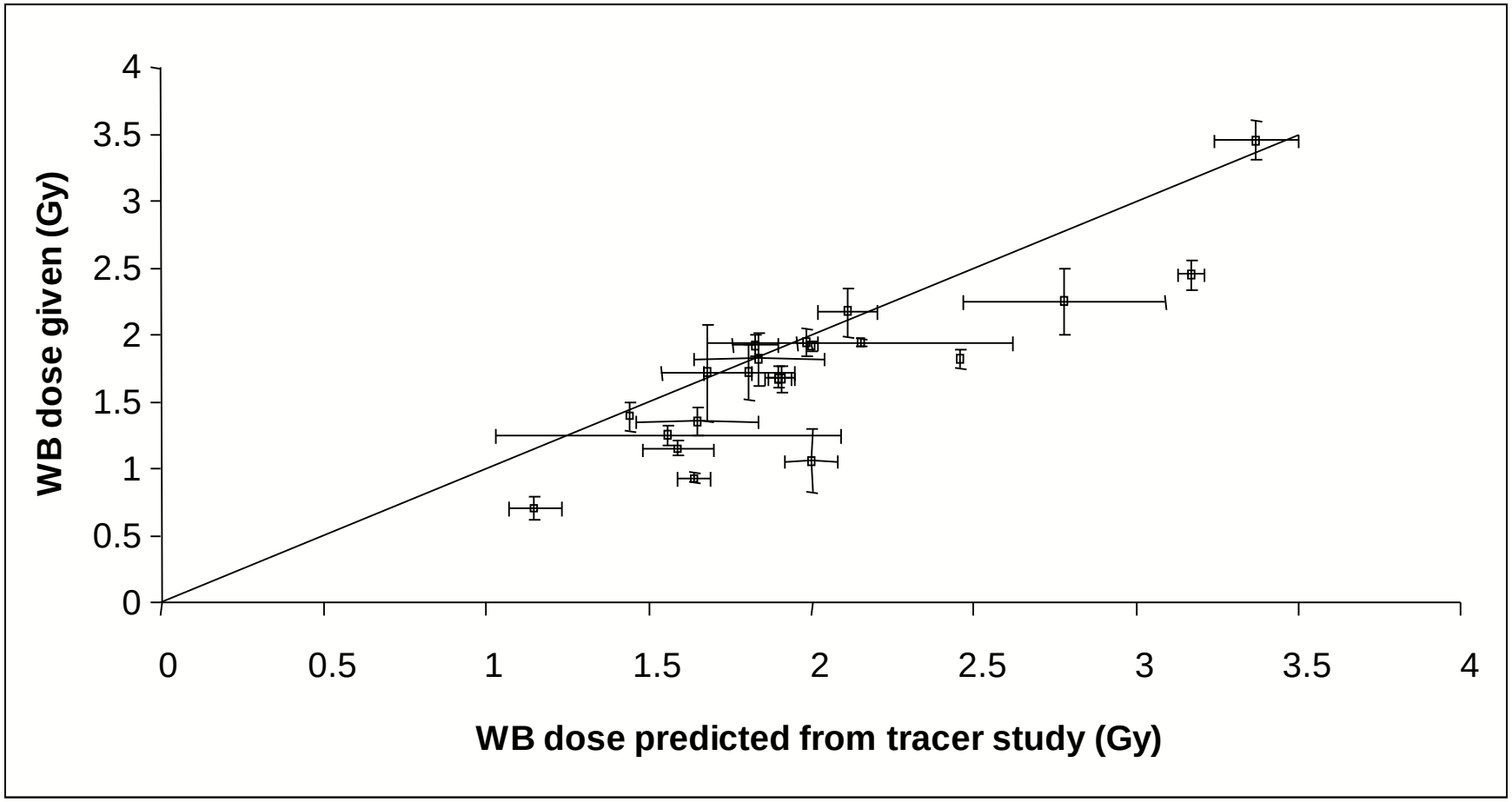
Many sample points are possible

Whole-body retention for I-131 mIBG



I-131 mIBG for neuroblastoma. Measurements acquired every 2 hours

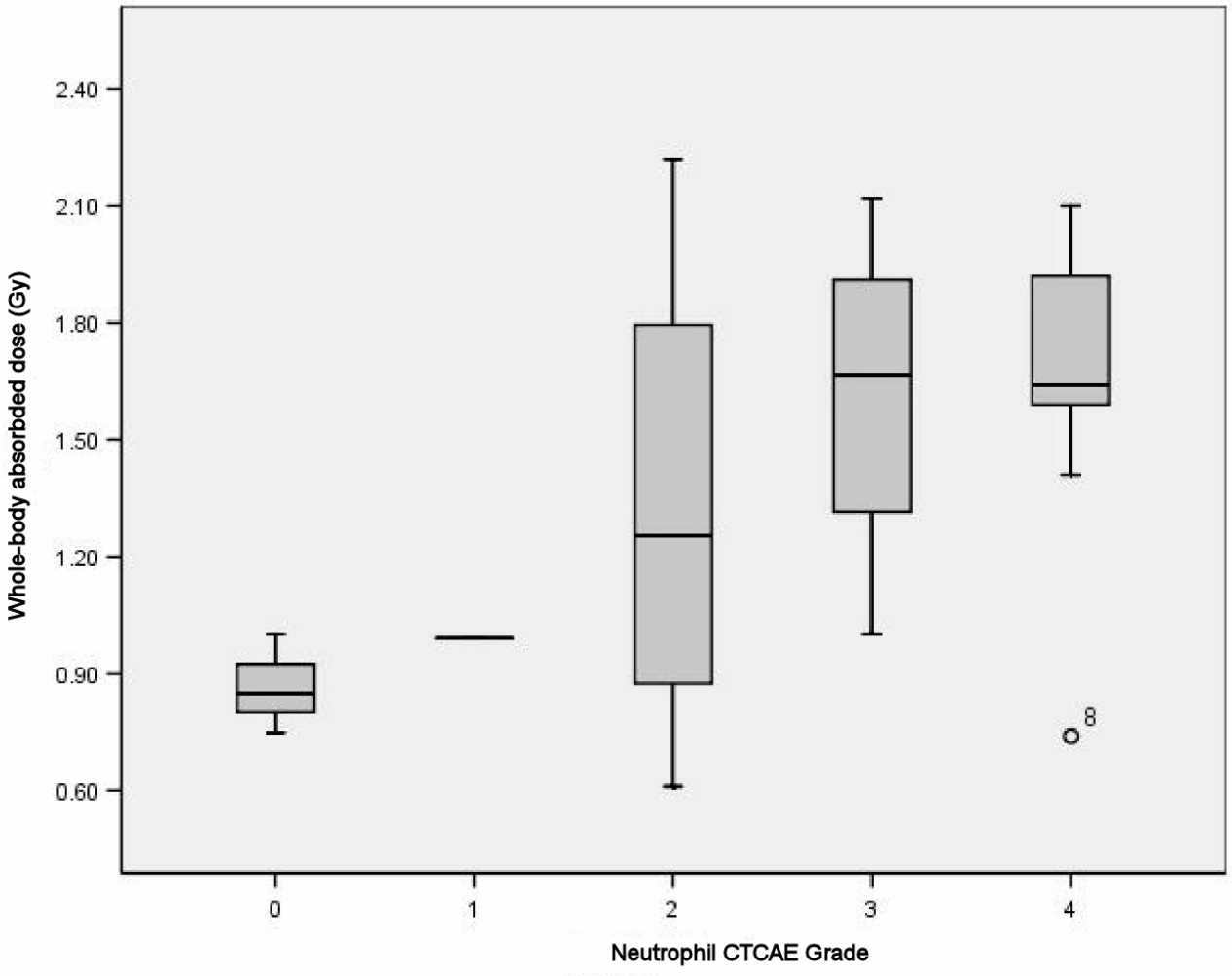
I-131 mIBG for neuroblastoma



Whole-body dose given at therapy predicted from tracer study to within 5-10%.

Buckley *et al J Nucl Med* **2010**

I-131 mIBG for neuroblastoma



Correlation of neutrophil toxicity with WB dose p=0.05

Buckley *et al JNM* **2010**

I-131 mIBG for neuroblastoma

'Feasibility of Dosimetry-Based High-Dose ^{131}I-Meta Iodobenzylguanidine with Topotecan as a Radiosensitizer in Children with Metastatic Neuroblastoma'

Aim: To deliver 4 Gy whole-body dose in two treatments

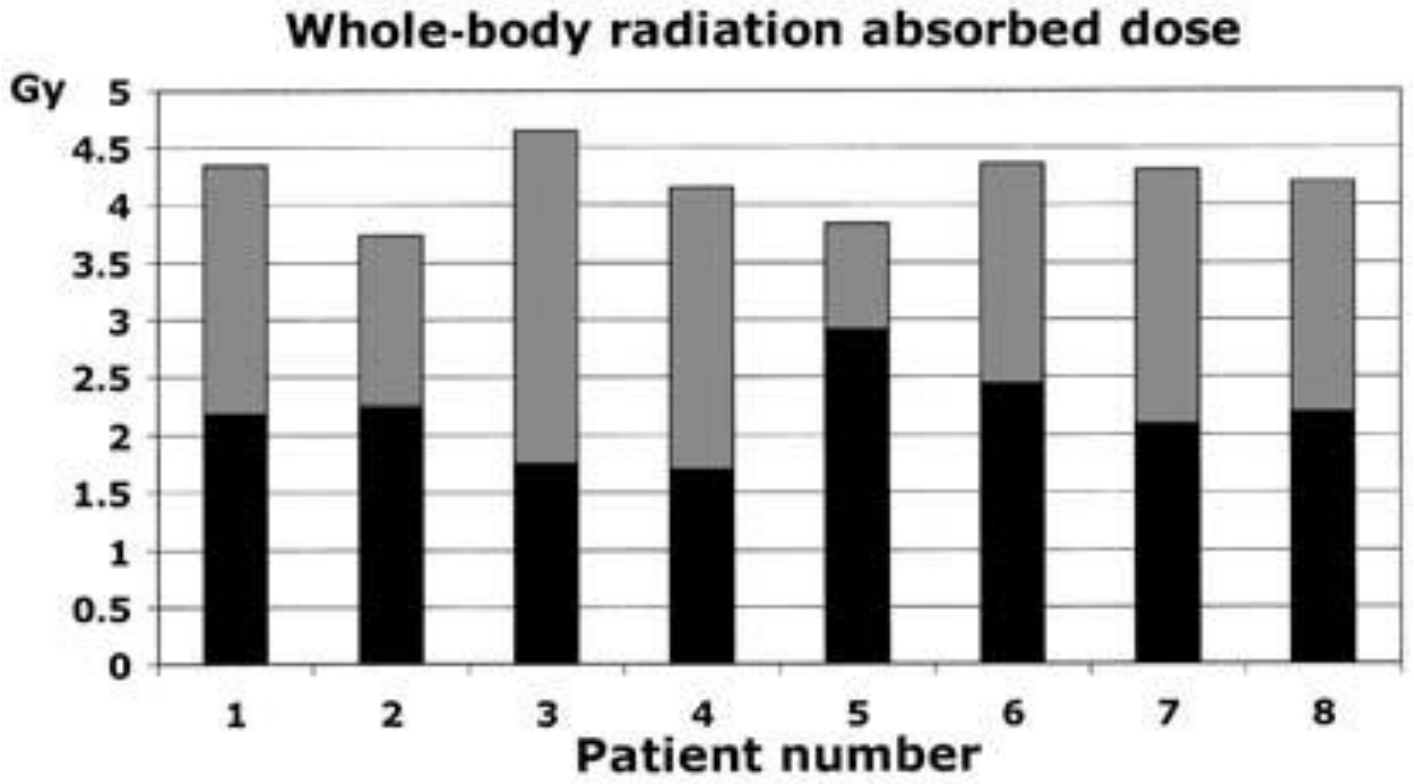
Treatment 1 – 444 MBq / kg. WB dose calculated.

Treatment 2 – Activity to make up a total of 4 Gy WB dose

'Veritas' trial now starting in Europe (ESIOP)

Gaze *et al CBR* **20** (2) (2005)

I-131 mIBG for neuroblastoma



Results (8 patients): Mean total dose of 4.2 Gy (range 3.7 – 4.7 Gy)

Range of administered activities: 10 GBq – 25 GBq

Gaze *et al CBR* **20** (2) (2005)

Potential for further developments

Administrations of I-131 mIBG, tailored to the individual patient according to dosimetry, can have remarkable success.

Unfortunately, patients often relapse due to the growth of micrometastases that are not targeted by I-131 due to its relatively long path length.

Astatine-211 (mABG) would target micrometastases well.

Combination therapy with I-131 mIBG and At-211 mABG could be very promising

Ra-223 – Biodistribution & dosimetry

Half-life: 11.4 days

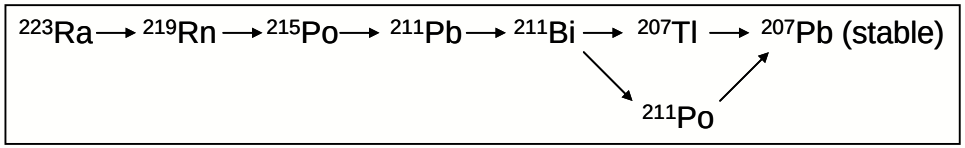
Range < 100 μm

High LET

Belongs to same group of elements as calcium & strontium so accumulates in bone

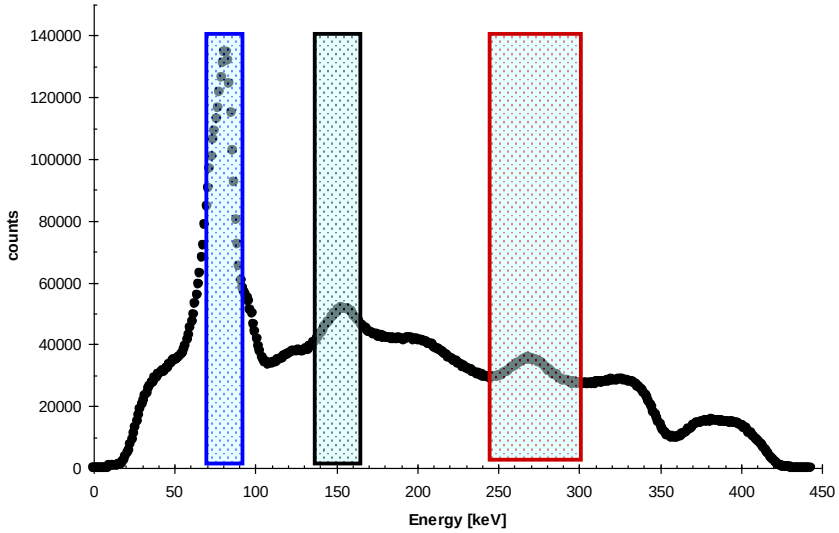
Decays to stable lead (Pb-207) through a complicated decay scheme with alpha, beta and gamma emissions.

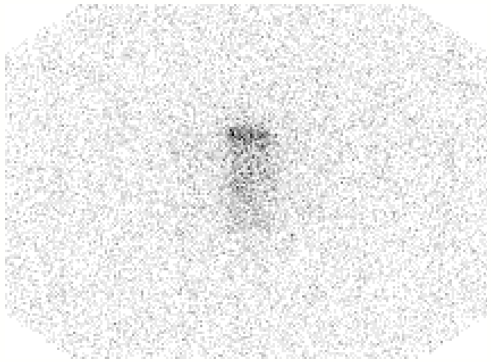
27.8 MeV per decay (95% alphas, 1% gammas)



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
$^{211}Pb \rightarrow {}^{211}Bi$	β^-	100 %	36.1 m
$^{211}Bi \rightarrow {}^{211}Po$	β^-	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
$^{207}Tl \rightarrow {}^{207}Pb$	β^-	100 %	4.77 m
$^{207}Pb \rightarrow$ -	Stable	-	-

Ra-223 – Imaging





Phantom scans

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

Hindorf Nucl Med Commun 2012

Ra-223 – Biodistribution & dosimetry

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 WB scans over 7 days

Hindorf Nucl Med Commun 2012

Dosimetry

Absorbed doses to gut, bone surfaces and lesions calculated from image data

Bone marrow (DLT) absorbed doses from bone image data and blood activity (not possible to measure directly)

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

Bladder & kidney absorbed doses from urine excretion

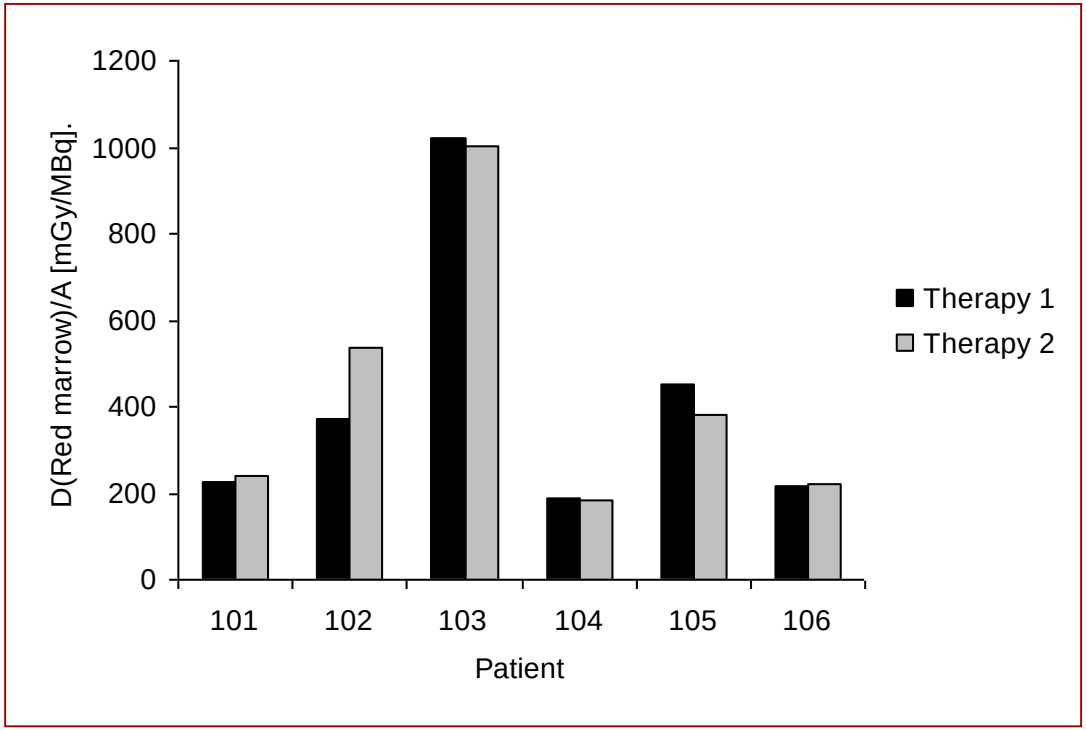
No specific uptake seen in kidneys or liver

Dosimetry calculated with Olinda/EXM software

Chittenden J Nucl Med 2015

Red marrow absorbed doses

Absorbed dose range 1.7 – 7.7 Gy

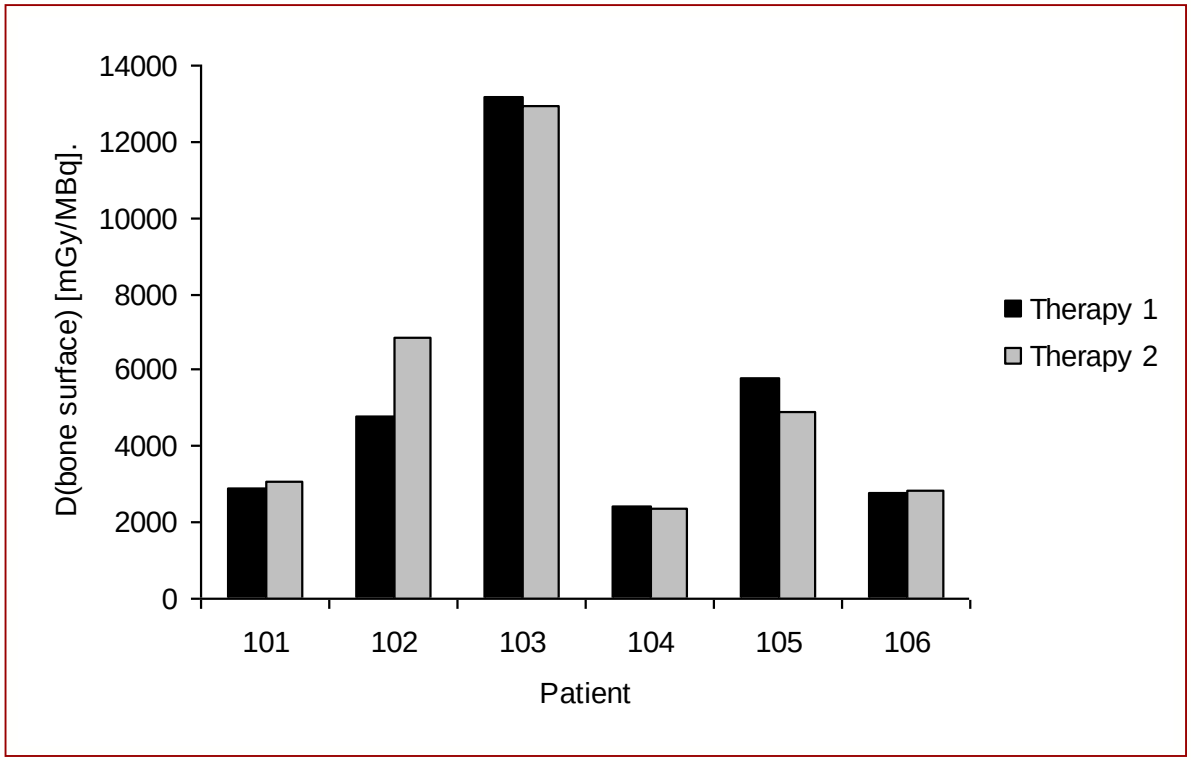


- 1. Large range of absorbed dose delivered to all organs

Chittenden J Nucl Med 2015

Bone surfaces

Range 20 Gy – 102 Gy

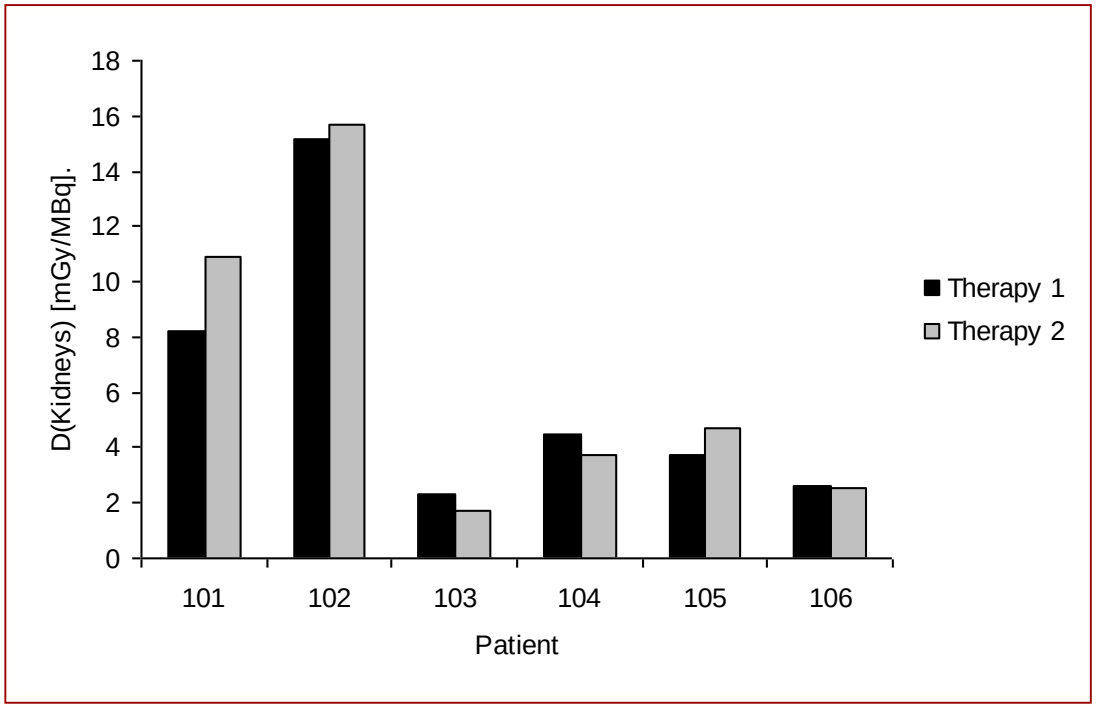


- 2. The intra-patient variation is small – the absorbed dose delivered from the second treatment is as for the first.

Chittenden J Nucl Med 2015

Absorbed doses to kidneys

From urine excretion: Range 14-101 mGy



- 3. The range of absorbed doses and lack of toxicity implies that most patients could be administered higher activities.

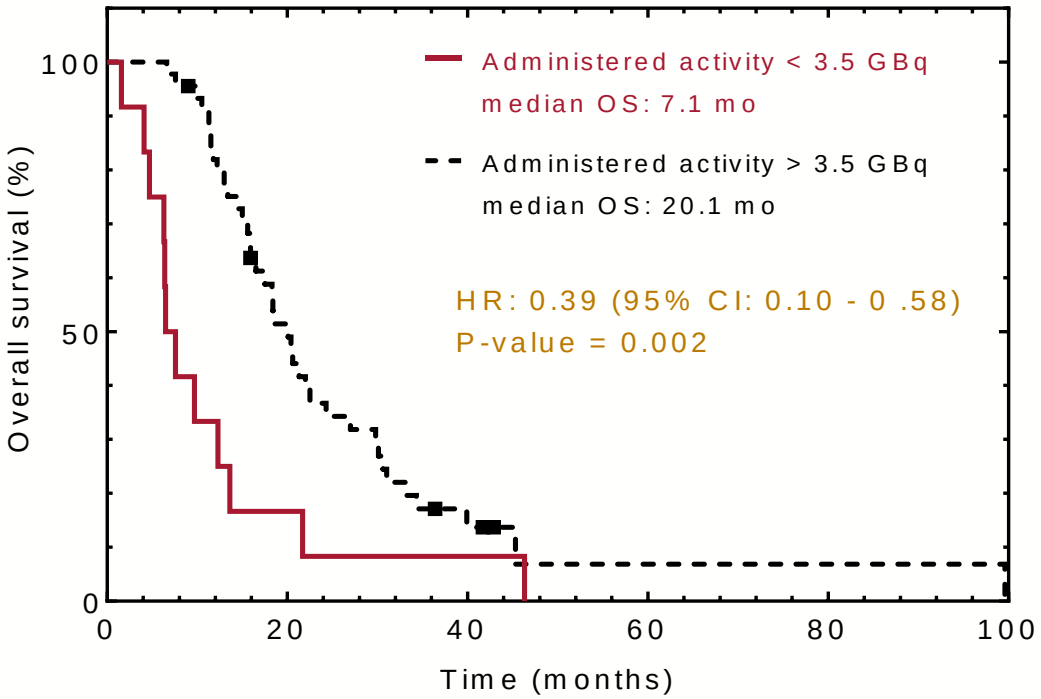
- Would higher activities be more effective?

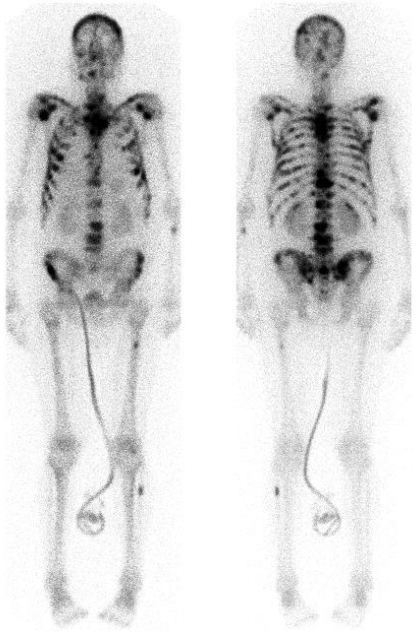
Chittenden J Nucl Med 2015

^{186}Re-HEDP for bone metastases from CRPC

Activity/outcome data not available for Ra-223

Patients received ^{186}Re-HEDP in an activity escalation phase I/II trial (NIH). Long term follow up:





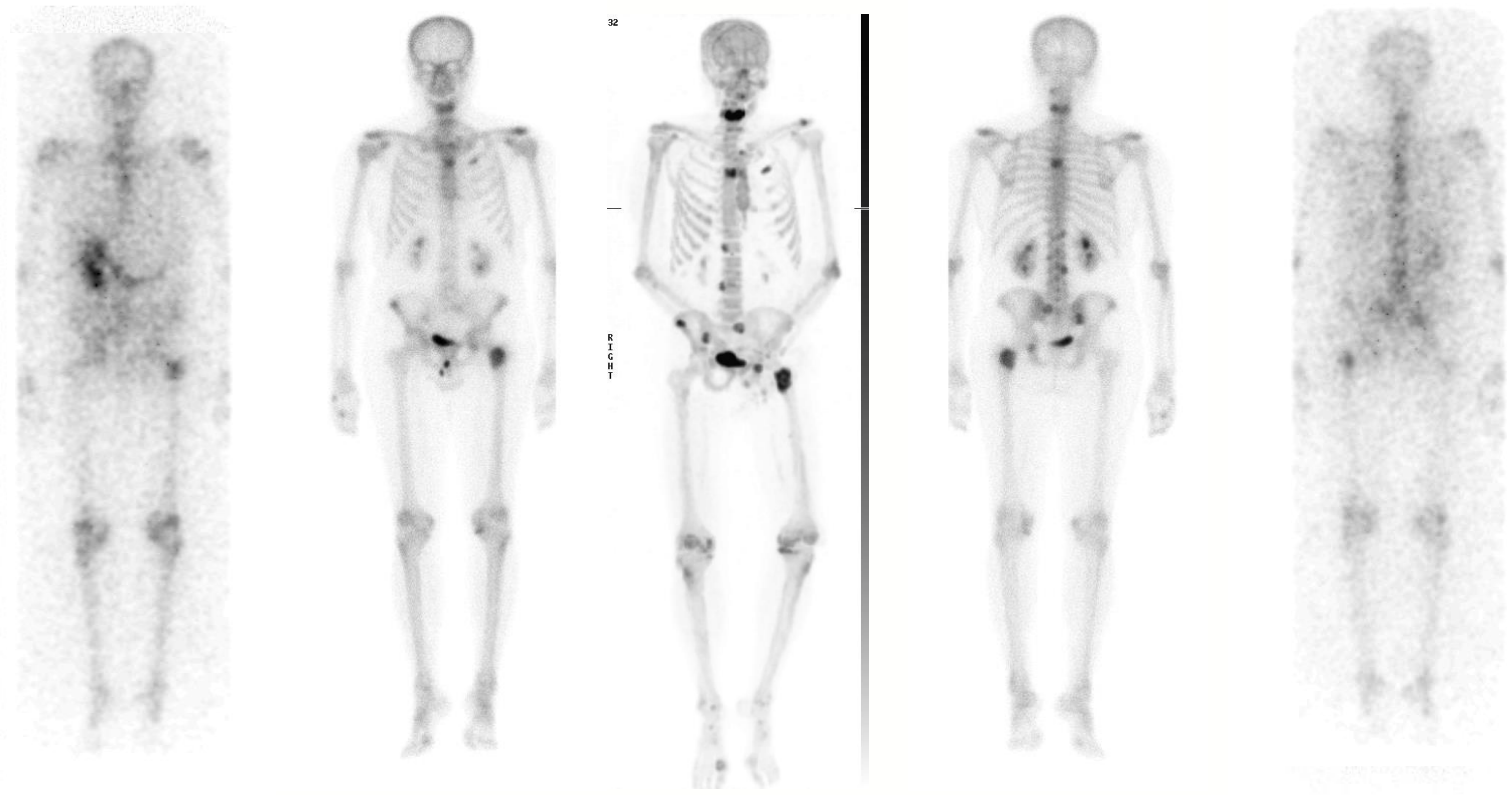
O'Sullivan *et al,* Eur J Nuc Med (2006)

Buffa *et al*
Eur J Nucl Med (2003)

Higher activities → longer overall survival

Denis-Bacelar EJNMMI 2016

Personalised treatment with functional imaging

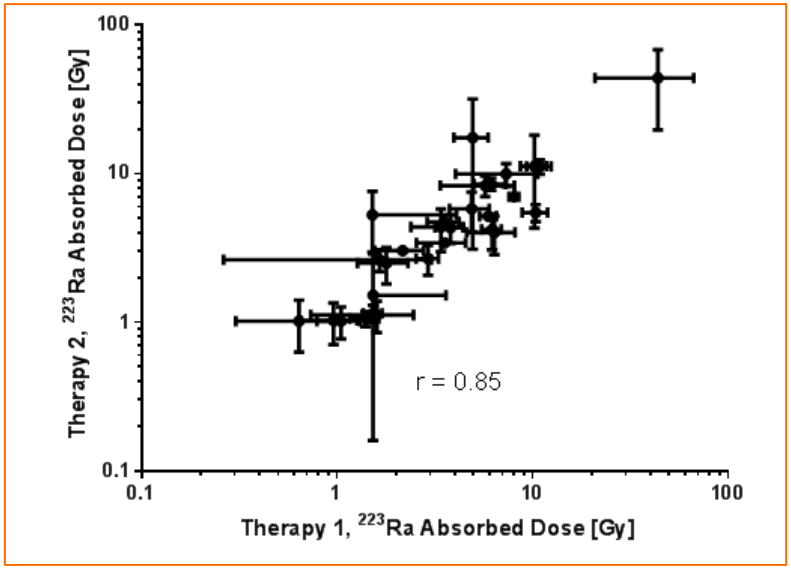


Ra-223 | Tc-99m MDP | F-18 Fluoride | Tc-99m MDP | Ra-223

(Murray EJNMMI in press)

Lesion dosimetry

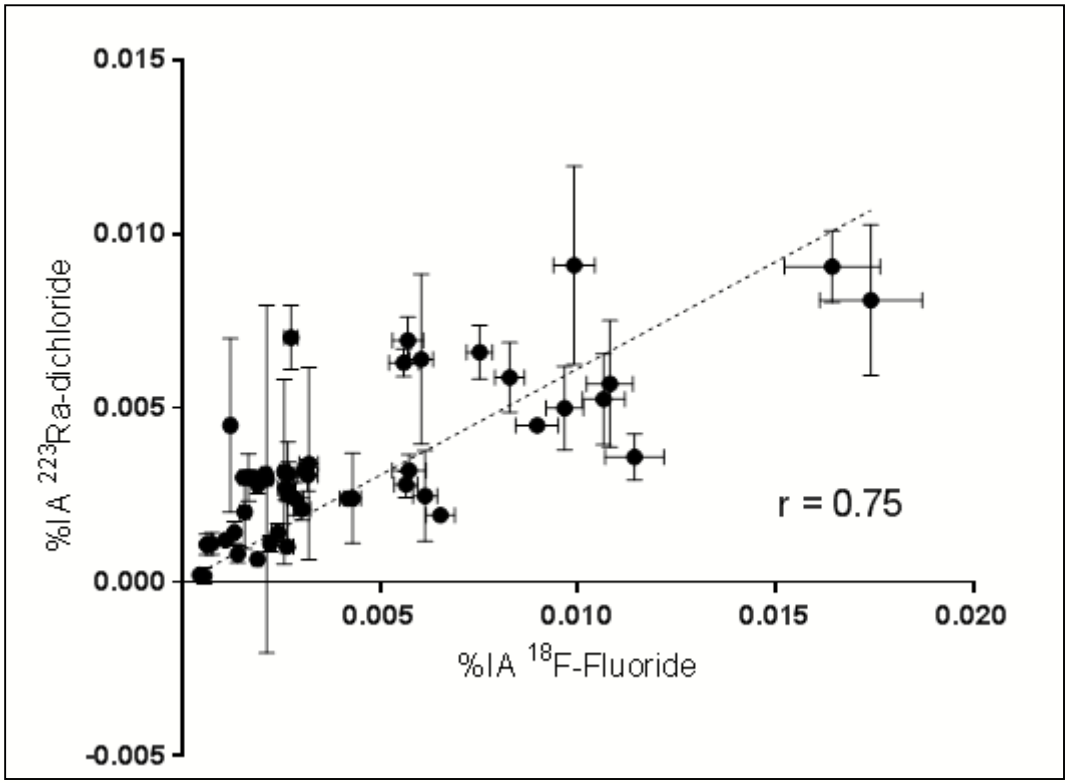
- Lesion delineation and volume aided by fluoride-18 PET images.
- Lesion absorbed doses also consistent for both treatments, with a very wide range
- Radium uptake and washout assessed by radium-223 γ-camera images
- Response assessed by changes in fluoride-18 uptake (SUV)



(Murray EJNMMI 2017)

Fluoride PET as a surrogate for Ra-223

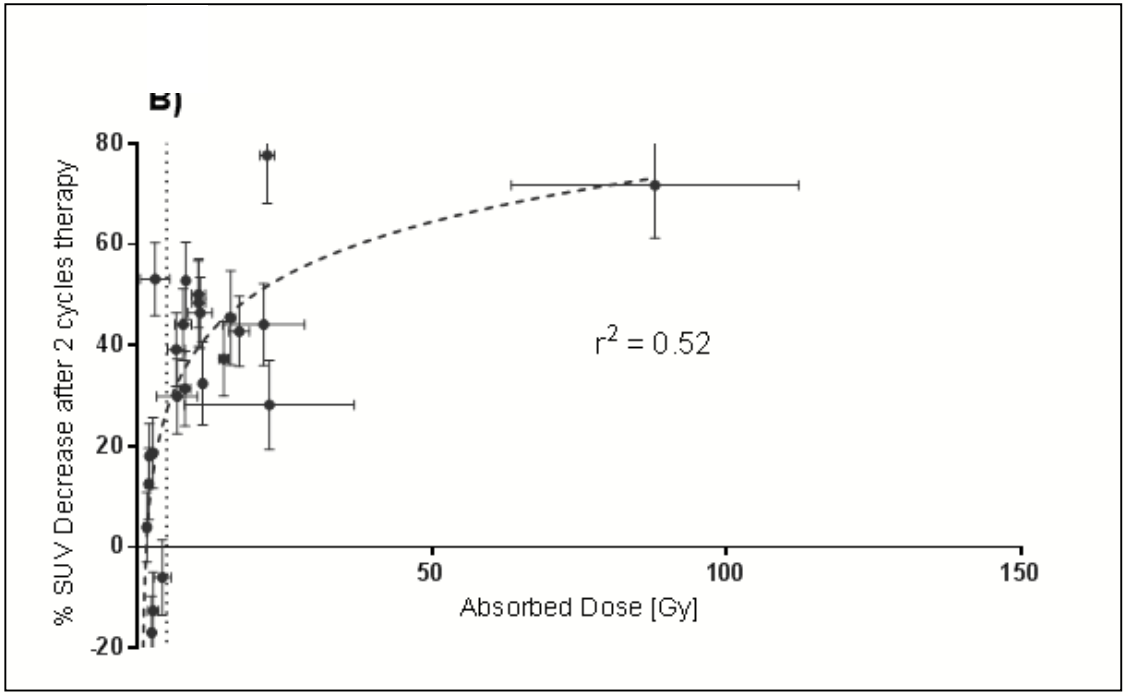
- Significant correlation between uptake fraction of injected radium and uptake fraction of injected fluoride at each lesion.
- Does the F-18 then predict the absorbed dose?



Murray EJNMMI 2017

Absorbed dose relationship

- Relationship between lesion absorbed dose and % change in fluoride-18 SUV

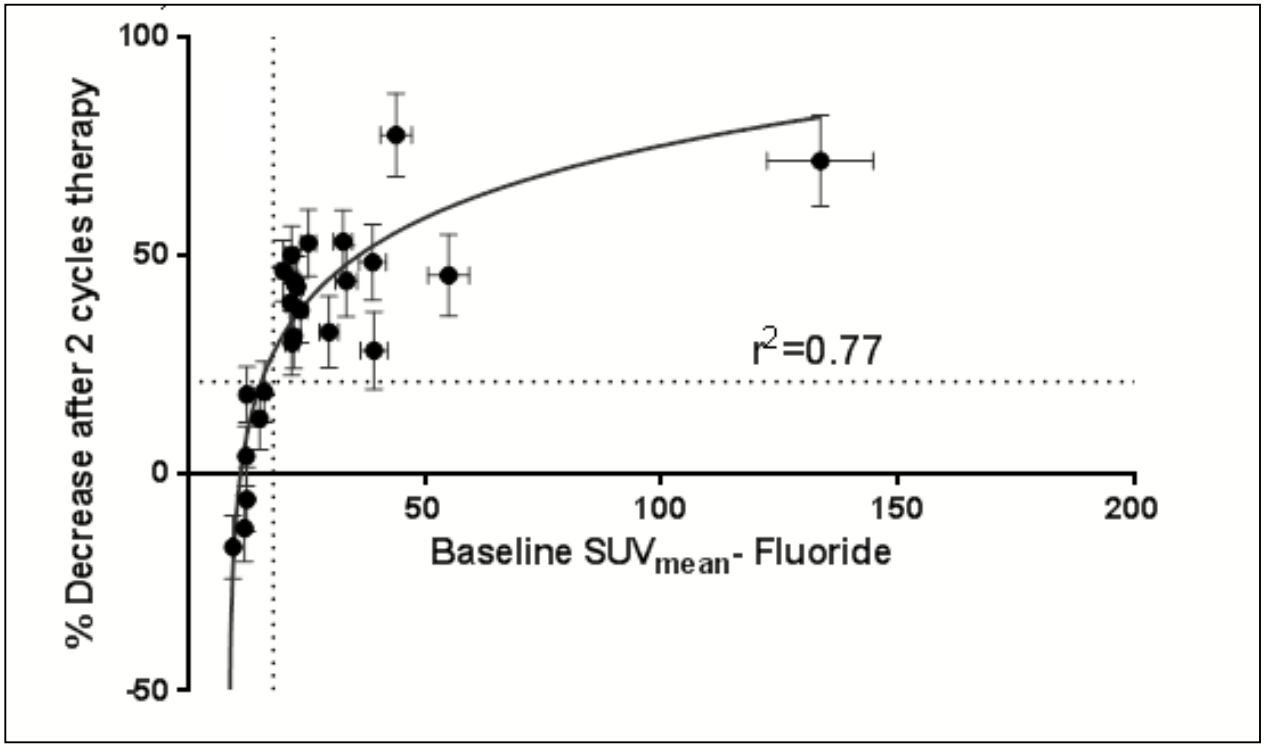


- Baseline PET could predict response and be used for initial treatment planning

Murray EJNMMI 2017

PET – response relationship

- Relationship between baseline PET and % change in SUV



- If baseline PET SUV is below ~30, we could increase administration or look for alternative treatment.

Murray EJNMMI 2017

Future directions & conclusions

Many new radiotherapeutics are emerging. The market is expected to grow by 30% per year for the foreseeable future.

Dosimetry allows higher activities for most patients (if all patients are given the same activity, they are treated according to the most vulnerable) Higher activities lead to longer survival.

Therefore, personalised therapy using patient-specific dosimetry has the potential to significantly improve effectiveness both clinically and in terms of cost.

Further treatment options can be explored, including combinations of alpha and beta emitting radionuclides, and combinations with external beam radiotherapy and chemotherapy.

The development of the radionuclide therapy facility at FMU highlights the potential for a new era of dosimetry to personalise treatment for patients.

Thank you for listening.

ご聴取ありがとうございました