

Bone targeted radionuclide therapy

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Bone malignancy

Primary bone tumours

Bone malignancy

Primary bone tumours

- chemotherapy, surgery & external beam radiotherapy

Bone malignancy

Primary bone tumours

Secondary tumours:

- **Skeleton common metastatic site**
- **80% of malignancies metastasise to bone**

Bone physiology

- **Re-modelling: resorption : formation**



Bone metabolism

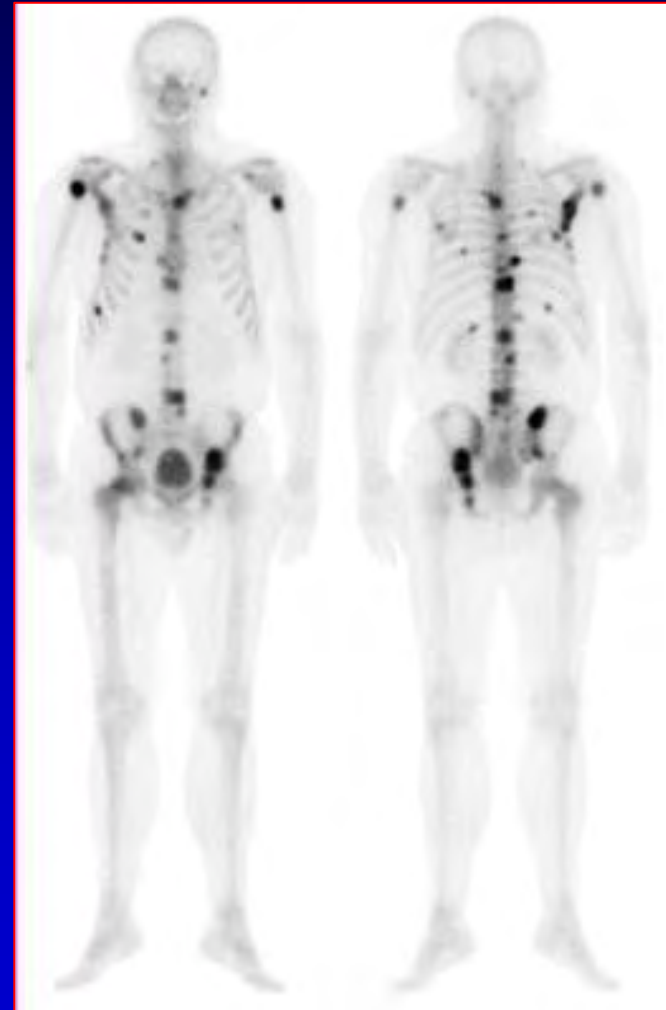
- **Re-modelling: resorption : formation**



- **Metastasis:**



Bone formation - sclerosis



Bone metabolism

- **Re-modelling: resorption : formation**



- **Metastasis:**

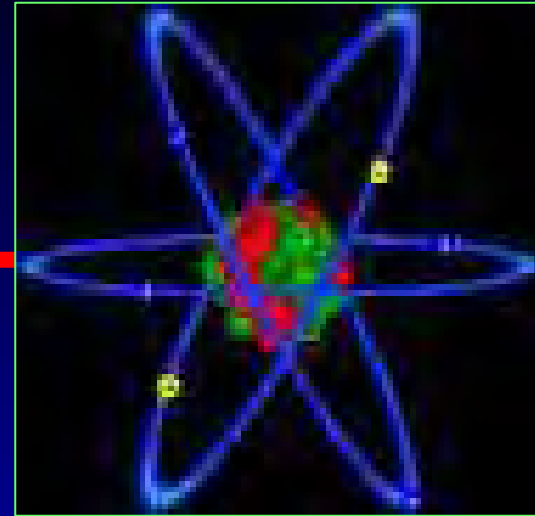


Bone destruction - lysis





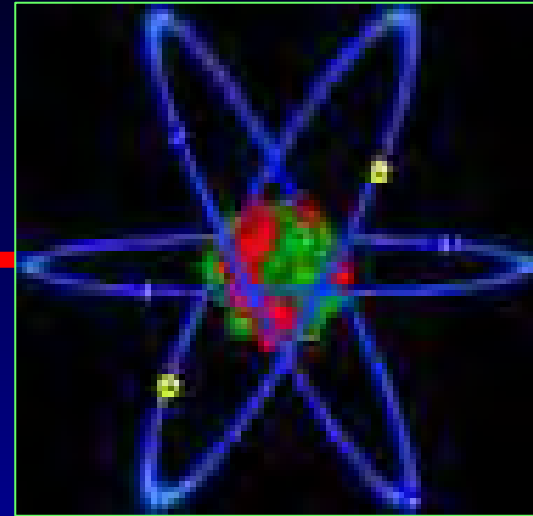
carrier



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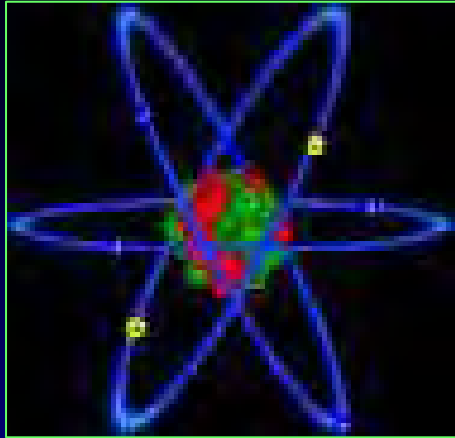
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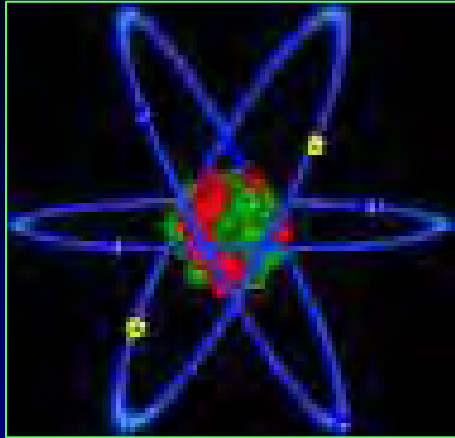
↑ **Bone mineral turnover**

- **Ca²⁺ analogue**
- **phosphate complex**



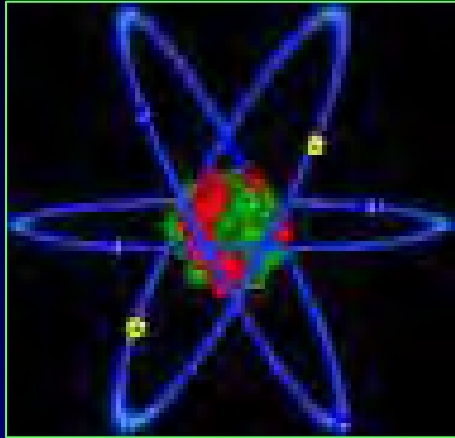
Radionuclide selection

- **Half life**



Radionuclide selection

- **Half life**
 - **Physical $t_{1/2}$ vs biological $t_{1/2}$**
 - **Dose rate**



Radionuclide selection

- **Half life**
 - Physical $t_{1/2}$ vs biological $t_{1/2}$
 - Dose rate
- **Particle range**

Radiolabels - Therapy

short/med range

long range

^{188}Re

^{223}Ra

Sm, ^{186}Re

Y, ^{89}Sr ,

Radiolabels - Therapy

short/med range

long range

^{188}Re

^{223}Ra

$\text{Sm}, ^{186}\text{Re}$

$\text{Y}, ^{89}\text{Sr},$

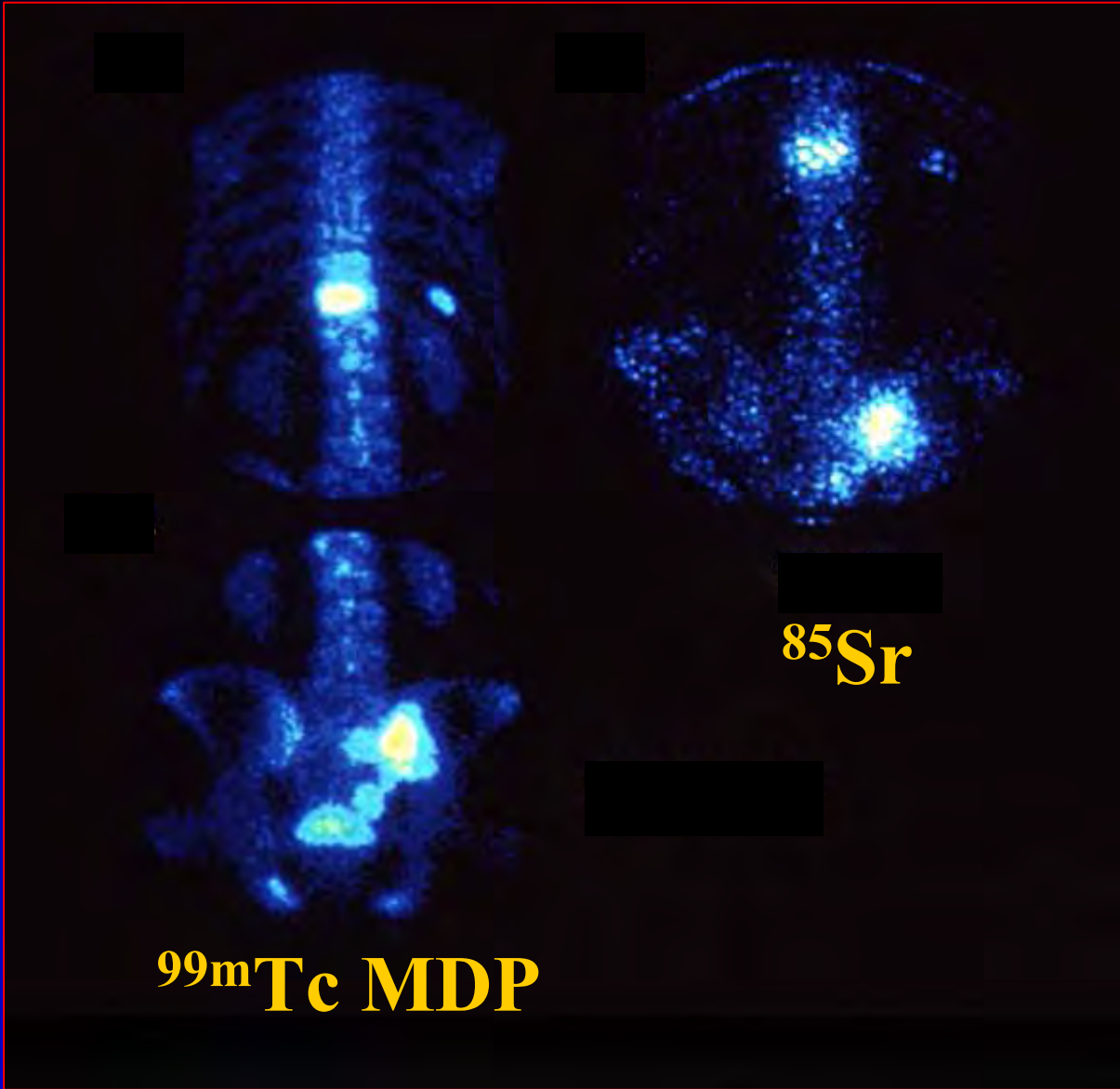


Calcium analogue

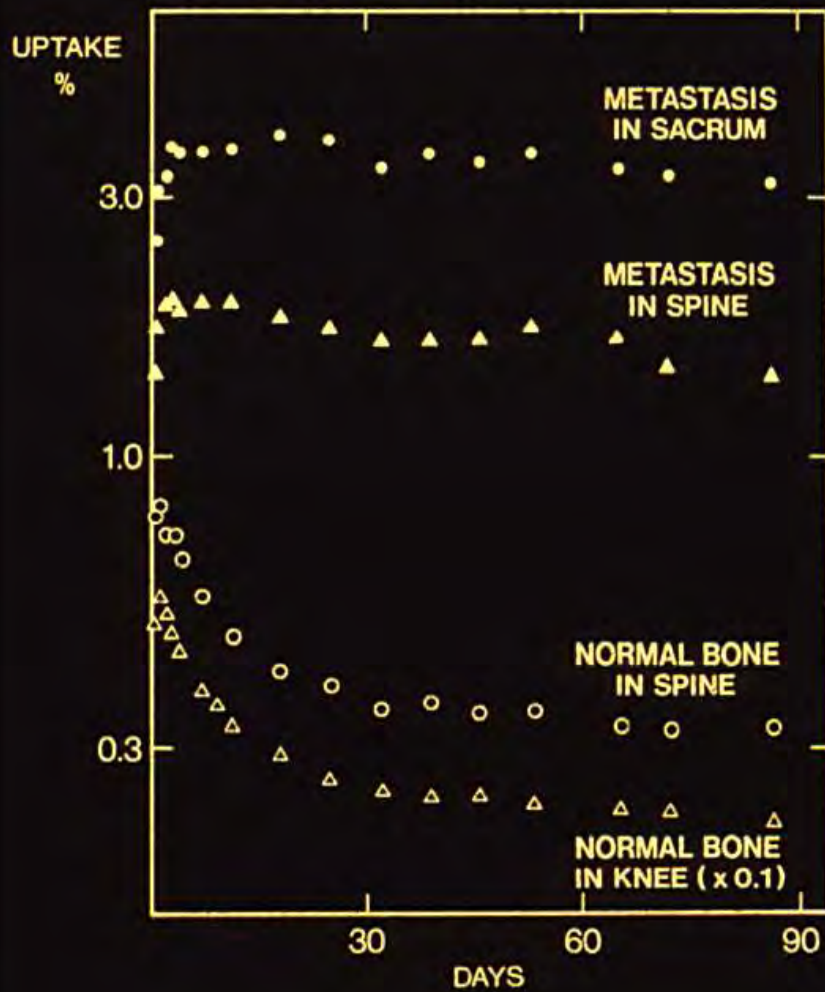
$t_{1/2}$ 50 d

max 1.46 MeV

range ~ 50 cell diameters



^{85}Sr RETENTION FROM GAMMA CAMERA IMAGES



^{153}Sm

$t_{1/2}$ phys 2 d
max 0.81 MeV

- ^{153}Sm EDTMP

$t_{1/2}$ bio 7-12h

	t1/2_{ph}	t1/2_{bio}
⁸⁹SrCl₂	50 d	>90d
¹⁵³Sm EDTMP	2 d	12 h

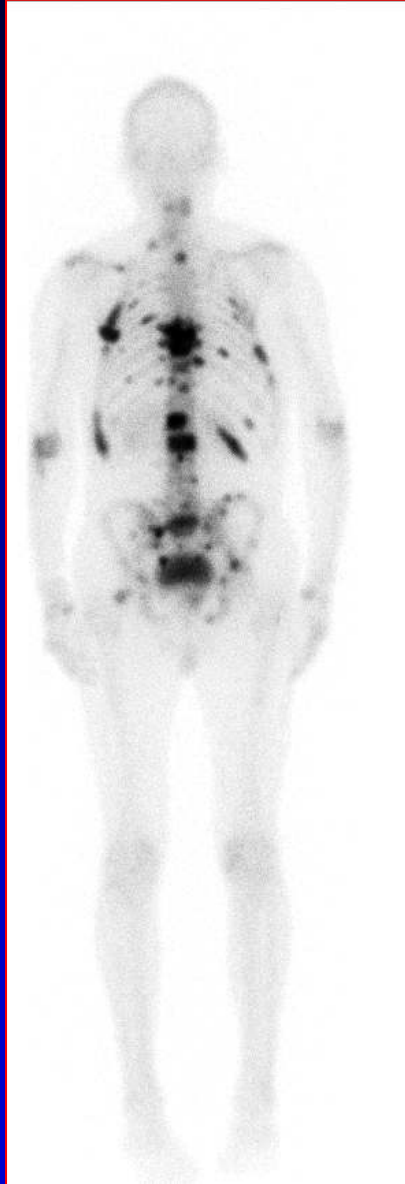


Metastatic bone pain



- **Primary tumour control**
- **tumouricidal**

Metastatic bone pain



- **Primary tumour control**
- **Pain palliation**
 - **Analgesics**
 - **Local RT**

Metastatic bone pain



- **Primary tumour control**
- **Pain palliation**
 - analgesics
 - Local RT
 - Wide field RT
 - bisphosphonates

Metastatic bone pain



- **Primary tumour control**
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Targeted Radionuclide Therapy

- **Systemic**
- **Tumour specific**

Patient Selection

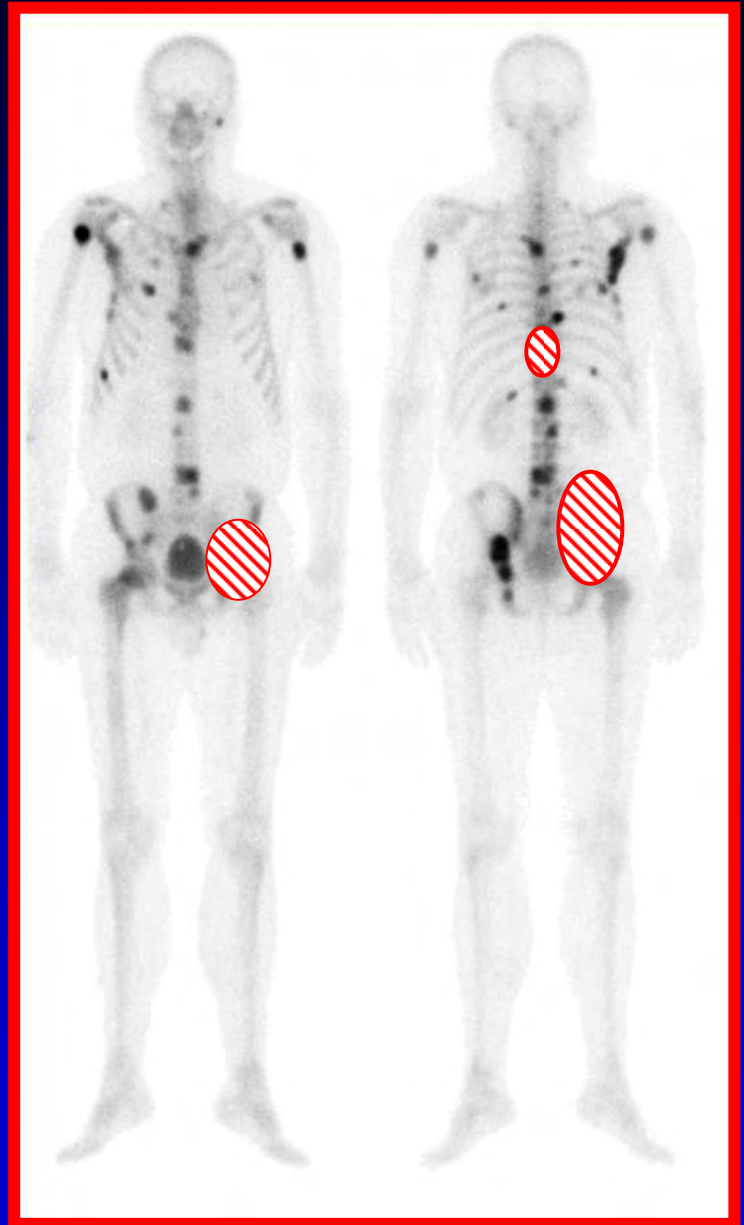
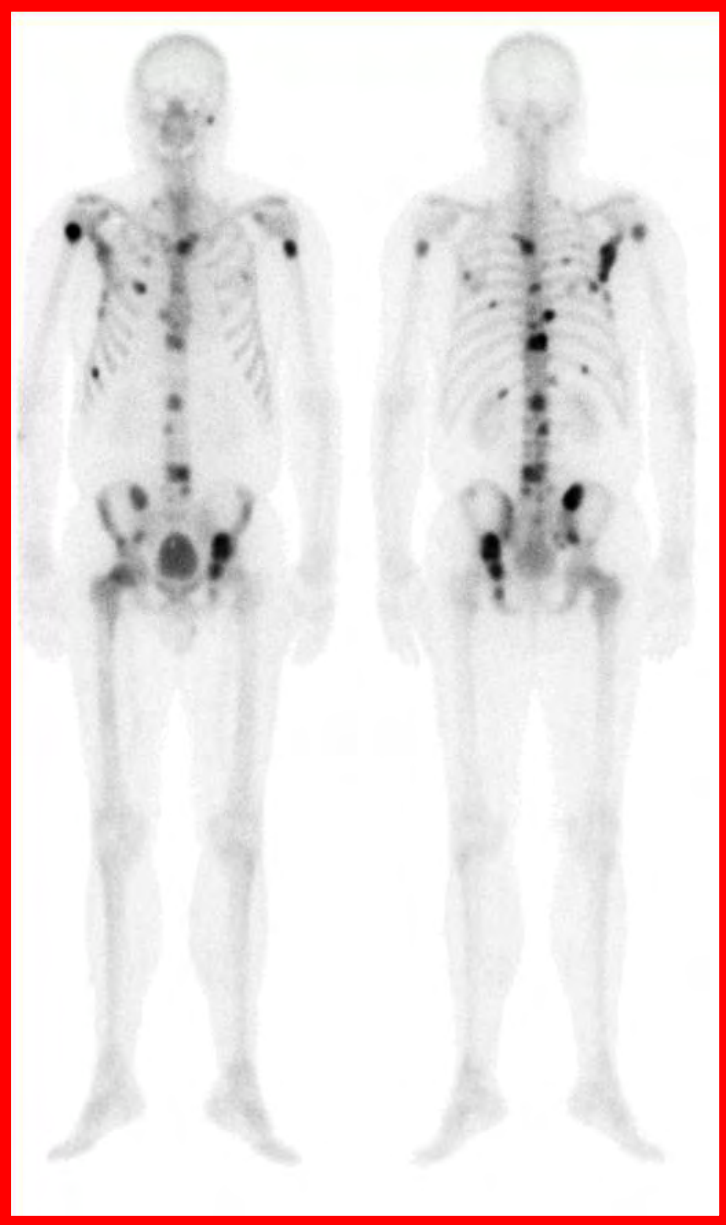
- **Refractory bone pain**
- **+ve bone scan**

Patient Selection

- **Refractory bone pain**
- **+ve bone scan**



Pain map



Patient Selection

- Refractory bone pain
- +ve bone scan
- **Stable haematology** Platelet $> 100 \times 10^9/l$

Patient Selection

- Refractory bone pain
- +ve bone scan
- Stable haematology
- **Stable renal function** **GFR > 40 ml/min**

Patient Selection

- Refractory bone pain
- +ve bone scan
- Stable haematology
- **Stable renal function**

Administration

- **Outpatient**
- **i.v. bolus**

- **Continue analgesics**

Response

- **Symptom benefit**
 - Pain severity/frequency
 - No.of pain sites
- **Analgesic intake**
- **Performance status**
- **Quality of life**

Efficacy

60 - 75 % benefit

25 % pain free

- **Multi-site palliation**
- **Response ~ tumour extent** Laing 1989

$t_{1/2}$

Response
time

Duration

^{153}Sm

2d

2 – 7 d

2 – 4 m

^{89}Sr

50d

2 – 4 w

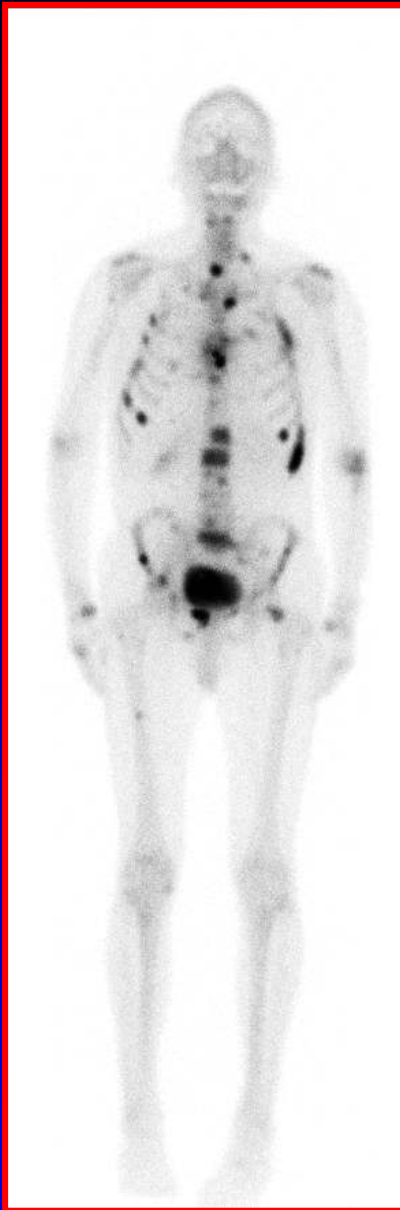
3 – 6 m

Systemic effect

- **Equal efficacy with EBRT**
- **Delays new pain**

Quilty Radiother Oncol 1994

Porter Int J Radiat Oncol Biol Phys 1993



**Systemic TRT
delays new pain**

Toxicity

Toxicity

- **Temporary myelosuppression**
 - ~ 30% platelet fall at 4- 6 w
 - Recovery over 8 – 12 w
- **Recovery reflects marrow reserve**

Recovery vs marrow reserve



Toxicity

$t_{1/2}$ Myelosuppression

^{89}Sr

50d

++

^{153}Sm

2 d

+

Mechanism of action

- **Radiation effect – active Rx v placebo**

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- **EBRT 8Gy single fraction effective**

Mechanism of action

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Pain palliation not dependent on cell kill

Mechanism of action

- **Radiation effect – active Rx v placebo**
- **EBRT 8Gy single fraction effective**
- **EBRT Efficacy independent of primary tumour histology** **Hoskin PJ Clin Oncol 1989**

Mechanism of action

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Tumour:normal bone interface target

Myelotoxicity

$t_{1/2}$ Myelosuppression

^{89}Sr	50d	++
^{153}Sm	2 d	+

Cumulative myelotoxicity

- radiation absorbed dose
- advancing underlying disease

The future

1. Integrated therapy

- chemotherapy + isotope

Chemo/isotope combination

- **^{89}Sr + low dose cisplatin** Sciuto J Nucl Med 2002
- **doxorubicin /estramustine/vinblastine + ^{89}Sr**
Tu Lancet 200
- **estramustine + vinblastine + ^{89}Sr**
Ackerley Cancer 2002
- **docetaxel + ^{153}Sm** Massard Abs. 227 ASCO 2007

**Combined Rx superior to isotope or
chemo alone**

The future

1. Integrated therapy

- chemotherapy + isotope
- bisphosphonate + isotope



The future

1. Integrated therapy

- chemotherapy + isotope
- bisphosphonate + isotope
- **EBRT + isotope**

Porter Int J Radiat Oncol Biol Phys 1993

Smeland Int J Radiat Oncol Biol Phys 2003

The future

1. Integrated therapy

2. Isotope combination

short $t_{1/2}$ + long $t_{1/2}$

The future

1. Integrated therapy
2. Isotope combination
eg short $t_{1/2}$ + long $t_{1/2}$
3. **Activity escalation**

The future

1. Integrated therapy

2. Isotope combination

eg short $t_{1/2}$ + long $t_{1/2}$

3. Activity escalation

^{153}Sm EDTMP Collins J Nucl Med 1993

^{186}Re HEDP [+ PBSC] O'Sullivan Br J Cancer 2002

The future

1. Integrated therapy
2. Isotope combination
eg short $t_{1/2}$ + long $t_{1/2}$
3. Activity escalation
4. New radiopharmaceuticals
eg $^{223}\text{RaCl}_2$

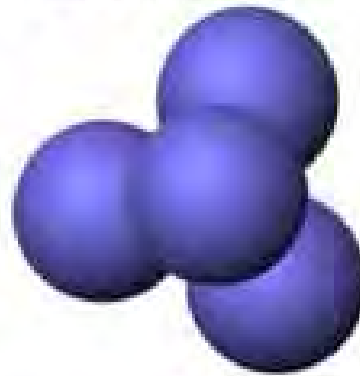
^{223}Ra

Ca^{2+} analogue

$t_{1/2}$ 11 d

emitter

Alpha Emitters: The Core Platform



Alpha particle

Beta particle



The alpha particle

- Helium nucleus: two protons plus two neutrons
- Emitted during decay of many radionuclides with high atomic weights

Properties

- 7,300 times the mass of a beta particle
- **High energy**
- **Short path length:** only 2-10 cell diameters

Why use alpha emitters?

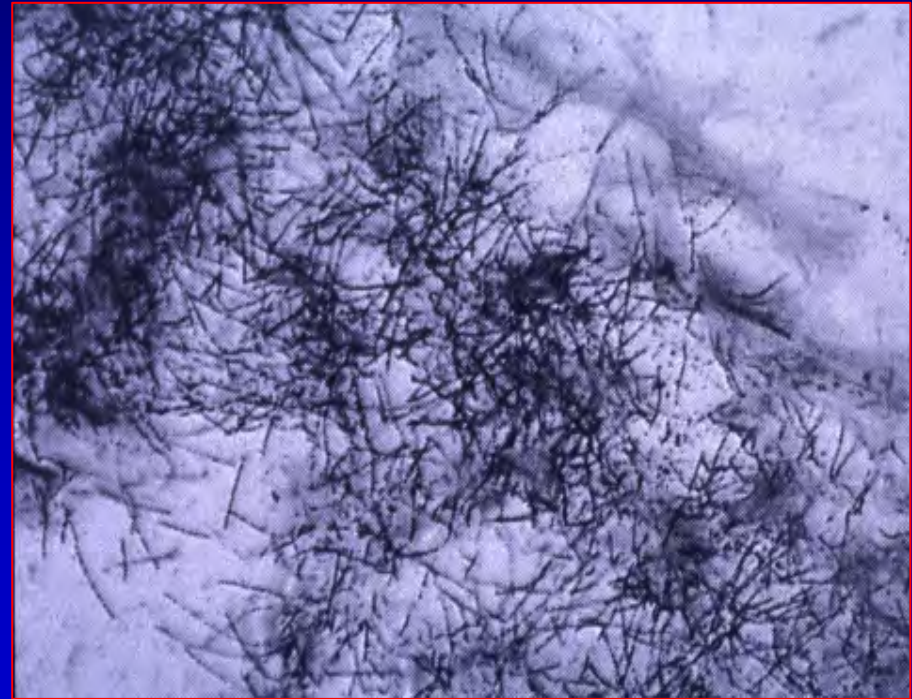
	Alpha	Beta
Range in tissue	40 – 90 m	500– 6000 m
Linear Energy Transfer	60 – 230 keV/ m	0.015 - 0.4 keV/ m
DNA hits to kill a cell	1 - 5	100 – 1000
Relative particle mass	7000	1

Canine Model Micro-autoradiography

Normal bone



Bone metastasis



^{223}Ra

- Ca^{2+} analogue
- $t_{1/2}$ 11 d α emitter
- Short range α i.e. Low toxicity

Phase I & II trials - dose limiting
toxicity not reached

Repeated Rx – for sustained response

Conclusions

- **Simple, safe, effective palliative Rx**
- **Well tolerated**
- **Best response in early disease**

- **Integrated, multi modality regimen**
- **^{223}Ra in clinical trials**