Development of radionuclide therapy

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Introduction

- Define radionuclide therapy
- Look at how it has developed
- Where can it cure
- Where can it control
- Where can it delay death

What is radionuclide therapy

- Different terms used
- Unsealed sources
  - Defined for radiation protection and legal reasons
- Internal radiotherapy
  - Could be confused with radioactive seeds and wires
- Targeted (radio) therapy
  - Much liked by NM community but may be confusing

General principles

- If you can see it you can treat it
- If the patient has the right disease you can treat it
- You can image the patient to see you have targeting-gamma only
- High activity in the target tissues, low in other tissues

What can these therapies offer?

- Cure-maybe
- Tumour control-sometimes
- Symptom control-frequently
- Side effects-sometimes
- Patient intolerance-rarely
- Hope-always

Who can we cure?

- This category includes one of the oldest treatments and one of the newest
- I-131 can be used to ablate thyroid remnants and treat metastatic disease
- Y-90 Tiuxetan ibrtumumab (Zevalin) can "cure"follicular non-Hodgkins Lymphoma

Types of treatment

- P-32
- I-131
- I-131 MIBG
- I-131/Re-188 Lipiodol, Y-90 Sir spheres, Re-186/8 Ho-166 MAA
- Lu-177/Y-90 Octreotate
- I-131 Bexxar, Y-90 Zevalin, I-131 Ritux
- I-131 CHT25
- I-131 SIP
- Sm-153 EDTMP/Sr-89/Re-188/ Re-186 HEDP/Sn-177m/ Ra-223
- Y-90/Re-186/Er-169 colloids

- PCV, Cavity therapies
- Thyrotoxicosis, thyroid cancer
- NETs
- HCC
- NETs
- Follicular NHL
- Hodgkin's disease
- Solid tumours
- Palliation of bone pain, treatment of bone mets
- synevectomy

Changes in supplier

- 1988
- P-32 Amersham
- I-131Amersham
- I-131 mIBG Mallinckrodt
- Y-90 colloids Amersham
- Sr-89 Amersham

- 2010
- P-32 Polatom
- Y-90 Dotatate/toc Polatom/Perkin Elmer, Molecular imaging
- Lu-177 Dotatate AA
- Y-90 Zevalin Spectrum
- Ra-223 Bayer
- I-131 SIP Philogen

Change in attitude

- Small market
- Limited use
- Except for I-131 palliation only
- Single agent

- Small but growing market
- Use expanding to more common conditions
- Aim for cure
- Combination with chemo/immuno-therapy

Treating with I-131

- Do we do dosimetry or standard dose
- No real evidence either is superior
- Radiation protection issues
  - Staff
  - Family members
    - Partners
    - Children
    - Parents

Treatment of Grave's

- Simple equation

$$\text{Activity In MBq} = \frac{23.4 \text{ (mass of gland in g) x Absorbed dose (Gy)}}{\text{24hour uptake (\%) x T 1/2 (5 days)}}$$

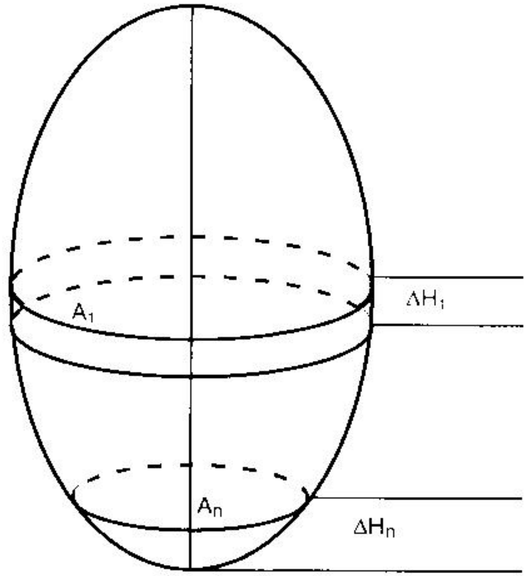
For Graves typical absorbed dose = 100 cGy

Thyroid volume

- Volume of the thyroid
  - Volume right lobe + volume left lobe + volume isthmus
- Problem not a sphere but a series of eliptoids
- How to measure nuclear medicine or ultrasound

Volume of a lobe of thyroid

- Simple method
- Works as long as thyroid is true ellipse
- Measurement best from ultrasound



$$\text{Volume} = (A_1 \times \Delta H_1 - - - - - A_n \times \Delta H_n) \times 2$$

$$= 2x \sum_{A_1 \times \Delta H_1}^{A_n \times \Delta H_n}$$

Whats the half life

- Assumed to be 5 days
- However in Graves rapid trapping and then release of I-131 without organification
- So effective half life my differ greatly and those with most aggressive disease have shorter half life.
- Need at least 2 (though 3 time points best to measure T1/2
- Normally only 4 hr or 24 hr used

What then happens

- Use ultrasound and uptake scan to calculate precise activity for treatment of Graves
- Activities given 150-800 MBq
- Re-treatment rate 10% hypothyroidism rate 60% at 12 months
- Took 3-4 hours of physics time per week which costs money

Now what we do

- New idea standard doses
- Can be pre-ordered as capsules reduced cost and radiation to staff
- 400MBq small glands in young women small toxic nodules
- 600MBq all others
- Re-treatment rate 5% hypothyroidism rate 50% at 1 year (Patel et al 2008)

Can we control disease

- P-32 in polycythaemia rubra-vera
- I-131 mIBG in neuroblastoma
- I-131 Lipiodol in HCC
- RIA in lymphoma

P-32

- Biological half life in marrow is 8 days
- Beta emitter most radiation in 3-8 mm
- Cheap isotope
- Given as 74-114 Mbq/m^2 to max 185 MBq
- Marrow dose 2.2mGy/Mbq
- No special rad proc just care with urine for 7 days
- May be given orally

Chemo vs P-32

- A few randomised studies
- Results very similar
- Some suggestion rate of strokes and MIs less with P-32 ?significance
- Cost less if treated for more than 1 year
- Rate of final leukaemic transformation same at 20% at 10 years
- Results in ET same as PCV

Can we palliate symptoms?

- The pain and swelling of Rheumatoid arthritis in the knee
- Pain from bone metastases
- Pain from liver metastases
- Reduction in carcinoid symptoms

Radiation synovectomy

- Uses radionuclides with destructive radiation to damage and destroy synovium
- Used as an alternative to chemical or operative synovectomy
- Needs to be used to treat a primary synovial problem

Indications for radiation synovectomy

- RA
- PA
- Baker's cyst
- Inflammatory OA
- Haemophiliac synovitis
- Pigmented villous synovitis
- Most need an effusion
- Normally failed at least 1 treatment with steroids

Radiation synovectomy

- Knee most common
- Shoulders
- Elbows
- Finger joints
- However important to tailor radiopharmaceutical to joint

Isotopes used

Isotope	T1/2 (days)	B-energy MeV	penetration	gamma
P-32	14.3	0.695	2.2mm	nil
Y-90	2.8	0.935	10.8 mm	nil
Re-186	3.8	0.309	4.5 mm	137keV
Er-169	9.4	0.098	1.0mm	nil
Sm-153	1.9	0.081	3.1	103keV

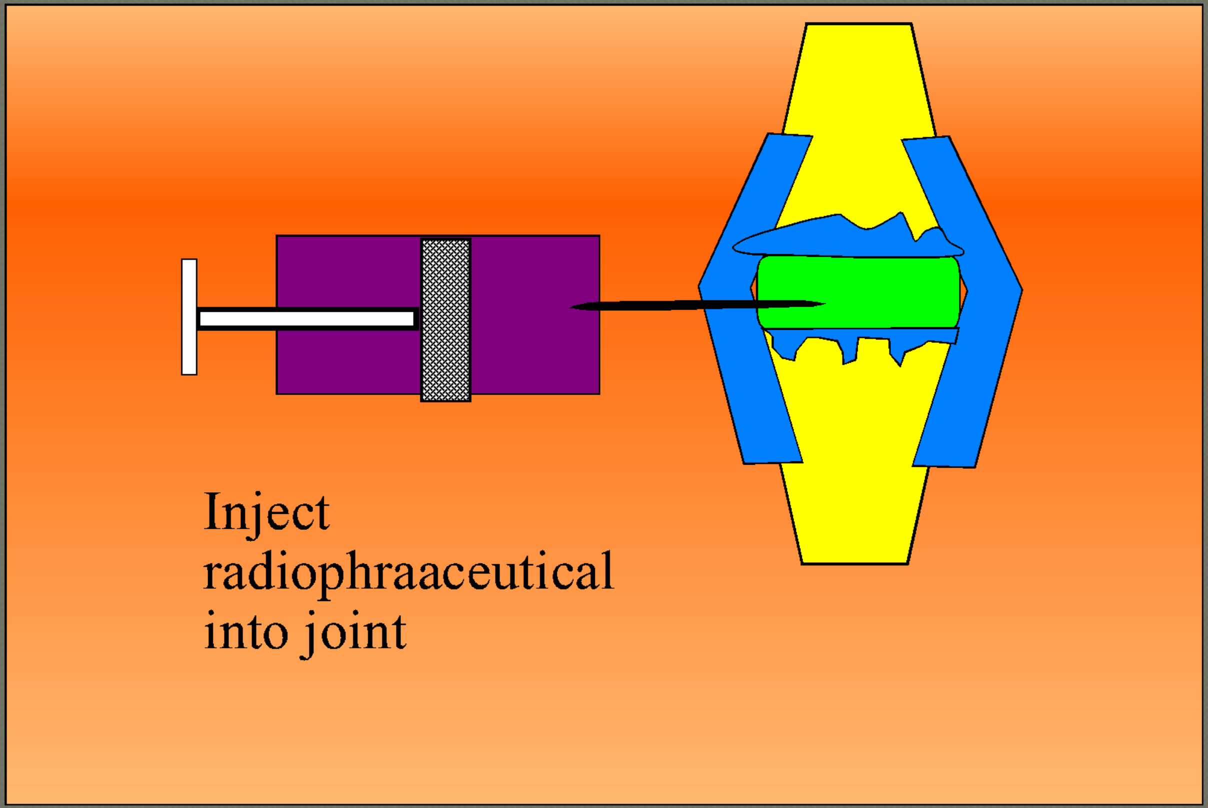
Joints and the isotopes used

Joint	Isotopes/pharms
Knee	Y-90 silicate, Y-90 colloid, Re-186 HEDP, SM-153 HYDA
Shoulder	Y-90 silicate, Y-90 colloid, Sm-153 HYDA
Elbow	Y-90 silicate, Y-90 colloid, Re-186 HEDP Er-169 colliods
Fingers	Er-169 colloids
Hip	Y-90 colloid, Y-90 silicate

Methods

- Identify effusion in joint
- Under palpation or direct vision puncture joint
- Draw any fluid in effusion from joint
- Inject radiopharm, (eg 185MBq Y-90 silicate) checking injection in joint
- Ask patient to move joint to distribute the radiopharm
- Immobilise joint, POP, splint
- Image joint (if gamma emission)

Principles of synovectomy



Methods

- At end of procedure flush needle with saline to prevent spillage of radiopharmaceutical
- Seal injection hole with a non-absorbent dressing-band-aid
- Get patient to move joint for about 5 minutes
- Then immobilise for at least 16 hours with plaster backslab

Pitfalls and problems

- Main one is not injecting into the joint
- Extravesated isotope can cause tissue and skin necrosis
- Escape of the isotope to systemic circulation
  - Y-90 colloid to liver
  - Re-186 HEDP kidney
- However systemic toxicity is theoretical
- None recorded
- Occaisional late radionecrosis

Assessment of response

- Normally made at about 6 weeks
- Should include assessment of joint clinically, use of pain killers and ultrasound of joint
- Only if no pain improvement at this point is a treatment failure defined

How well does it work?

- Though there are >70 studies
- Few randomised controlled trials
- Only 9 in full random controlled trials
- Most studies agree that 80% of patients get good pain relief
- Similar to surgical synevectomy
- Better than steroids alone Clunie et al

Bone metastses

- Often feared in cancer
- Tends to mean advanced disease
- Often painful
- Normally predict that death (possibly unpleasant) will come soon

Which cancers?

- The 5 Bs go to bones
  - Breast
  - (B)rostate
  - Bronchus
  - (B)ryroid
  - (B)idney

How do they occur

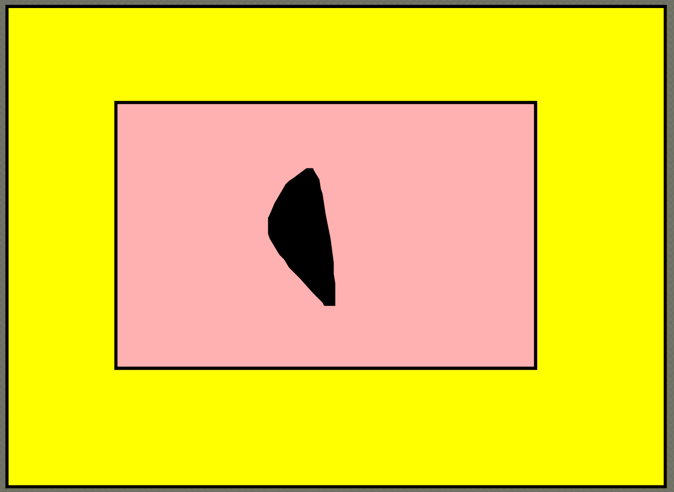
- Many cancers have cells which are present circulating in the blood
- These travel around the body and can end up anywhere with end arteries
  - Bone
  - Lung
  - Kidney
  - Brain

Growing metastases

- Mechanism of why certain sites favoured is not clear
- May be related to blood supply and oxygen levels
  - Kidney prefers lung and bone
  - Breast prefers bone and brain
- Cells survive and start to grow into new clumps of cancer cells-a metastases

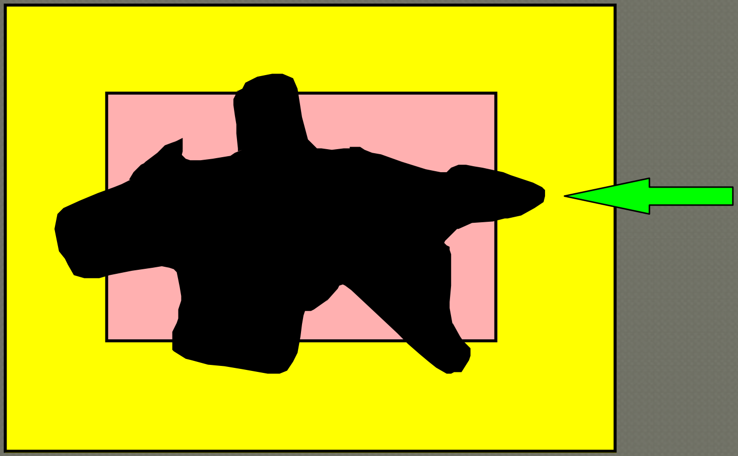
Bone/BM metastases

- Though we call them bone mets
- Really bone marrow mets
- Nearly always need red marrow
- Adult-axial skeleton & prox humerus/femur
- Neg bone scan
- MRI, PET positive



Bone/bone marrow mets

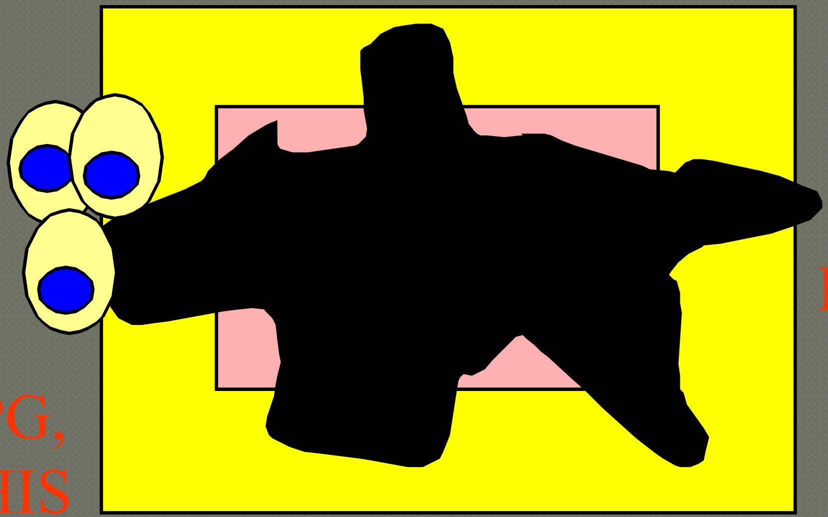
- Metastases starts to grow
- Will impinge on bone
- Bone will try to remodel
- Increased uptake of Tc-99m MDP



As bone affected Osteoclasts breakdown damaged bone, osteoblasts and fibroblasts try to reform bone

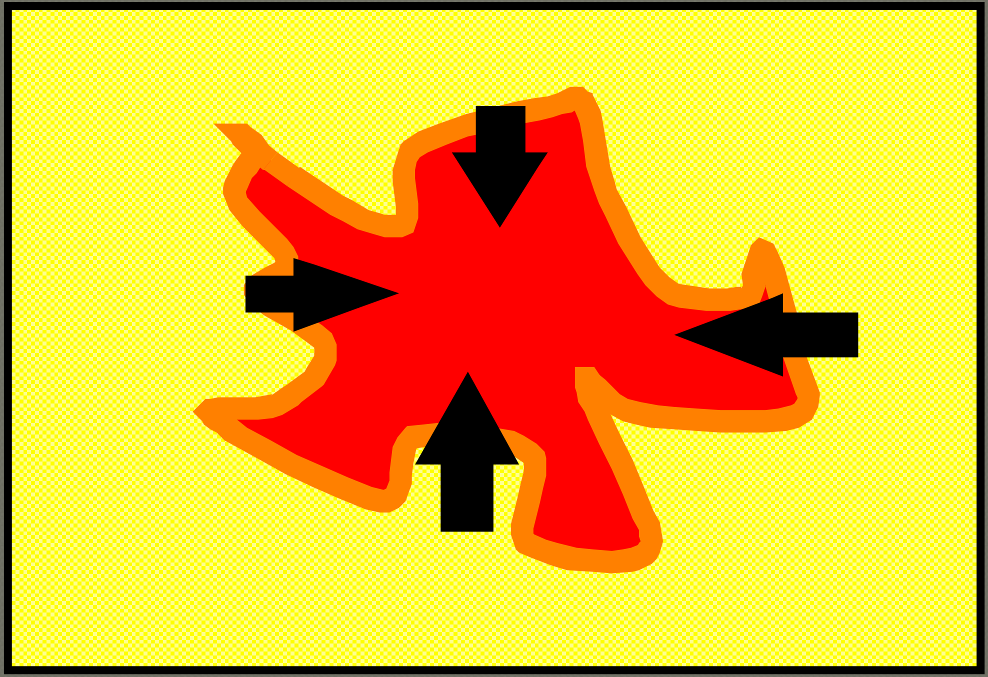
Bone/bone marrow mets

- The bone may be breached-#s
- Fibroblasts release PGs
- These PGs produce local pain
- Other inflammatory cells involved
- Other pain mediators may be released
- Direct involvement of nerve fibres



Therapy of bone metastases

Uptake of radionuclide in sclerotic zone (orange) with irradiation within that zone and some into the tumour



Development of radionuclide therapy for bone pain

- Early work with P-32
- Efficacy good and low cost but increased toxicity (?) especially to bone marrow has limited its use
- Sr-89, first true bone seeking agent, also has significant toxicity in widespread mets

Pure beta emitters

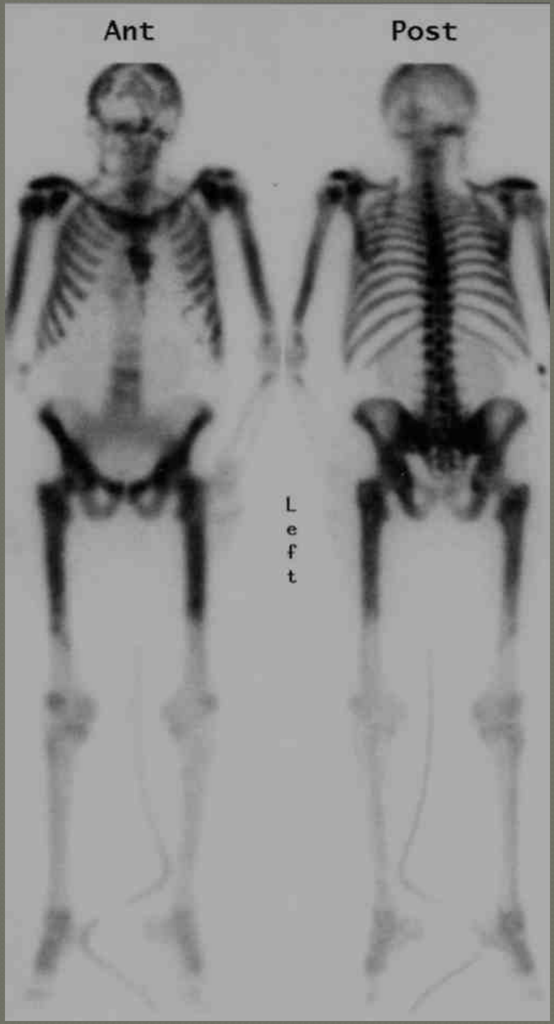
Isotope	T1/2	Beta energy	comments
P32	14.3d	1.71	Low TBR = 2 at most
Sr-89	50.5	1.46	Fixed dose 150 MBq

Metastron

- Well tolerated
- Up to 80% patient will have fall in Pts of >50% at week 6, recovery normal
- G3 and G4 toxicity rare
- Some palliation in 70% of patients
- Complete pain relief in 22% (Laing et al)
- Repeat therapy at 6 months

What agent to use in this patient (62M pain in many sites, HB 10, Pts 150)

Do we wish to use an isotope with long half life which may continue to irradiate the bone marrow for up to 2 months??



Gamma emitters

Isotope	T ½	Beta energy	Gamma emission
Sm-153 EDTMP	1.93d	0.81 MeV	103
Re-186 HEDP	3.7	1.07 MeV	137
Sn-117m DTPA	14	EC only	158

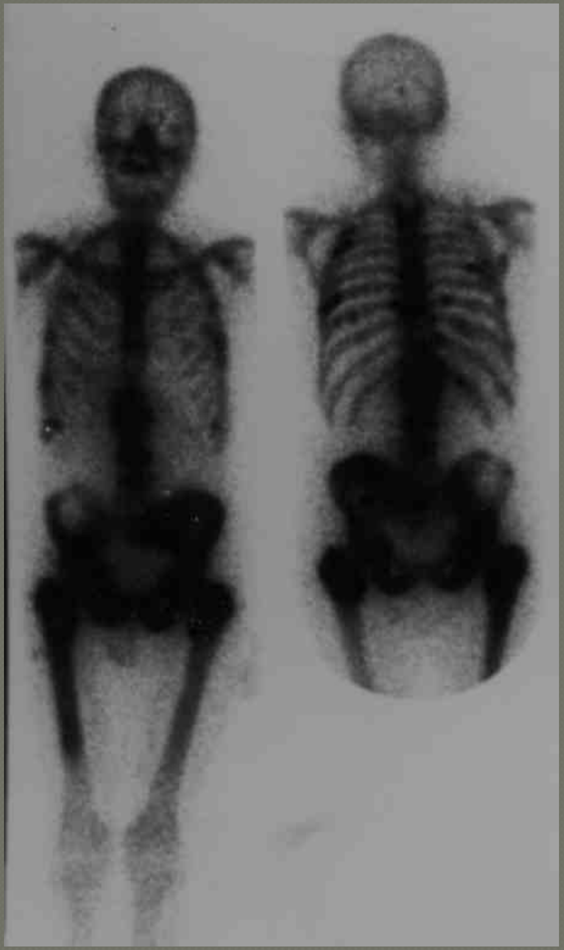
Gamma emitters

- Most experience with Samarium-153 ethyldiaminetetrametylenephosphonate
- Generally shorter T1/2 than beta emitters
- Not dependent on calcium deposition
- TBR often 10:1 or higher
- Faster onset and clearance

24 hours post 70 mCi Sm-153

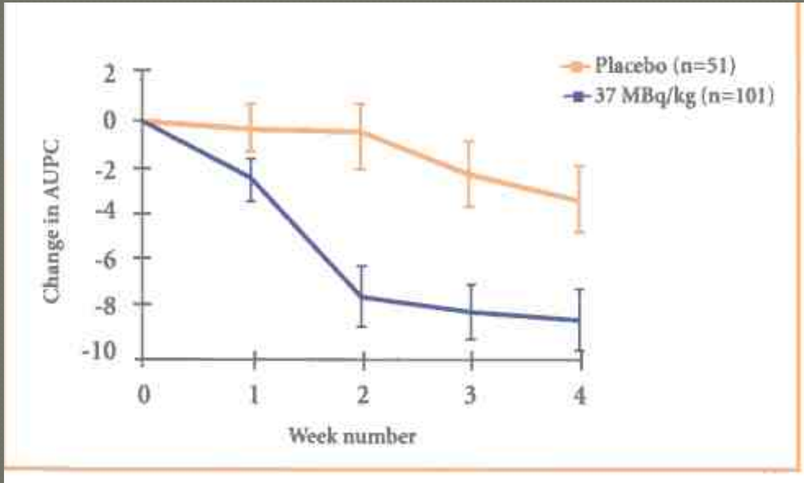
Images not so clear as low energy reduces count rate.

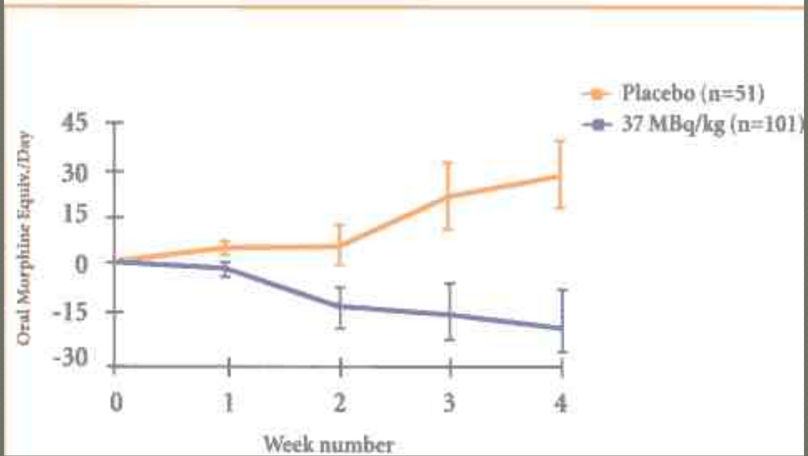
Note at 24 hours no renal or bladder activity seen but this is not a superscan



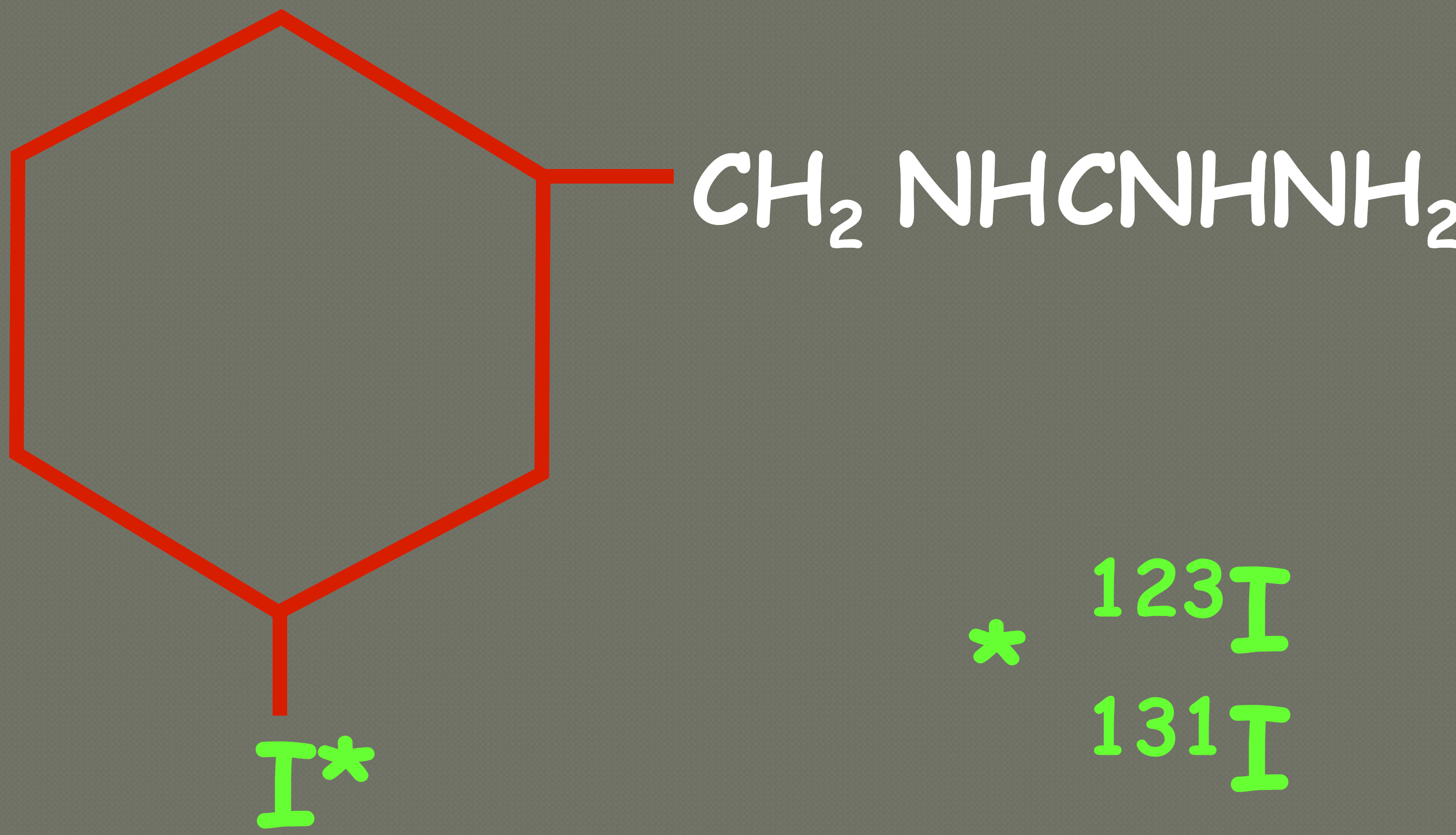
Sm-153 EDTMP (lexidronam)

- Results of US/ European MCT for Merrill Pharm
- Phase III trail in prostate cancer
- Randomised to placebo lexidronam or Sm-153 product





meta-iodobenzylguanidine



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Controversies

- Does it work
- How much do we give
- How often do we give it
- When do we stop/start treatment
- Any long term toxicity

^{131}I mIBG therapy

- Stop interfering drugs-may not be possible in Pheo may only be able to reduce phenoxybenzamine
- Quantitative tracer imaging
- Admit to isolation unit
- Block thyroid
- i.v.i. 60-90 mins

Amersham trolley

Uses a 3 way tap system

And a peadiatric burette

Behind a thick lead shield

Then system used to

washout the I-131 MIBG

into patient via pump

Giving the I-131 mIBG

Normally need to be admitted to a separate room

Can use isolated side room with mobile shields

After dose given slowly I.v (with cardiac monitoring for phaeo) Patient needs to wait until activity reduced enough for discharge

2.7GBq = 3 days

5.5 GBq = 5 days

7.7 GBq= 7 days

Toxicity of mIBG-EANM survey

Haematological toxicity children and adults

Grade	%
I	4
II	23
III	4
IV	0

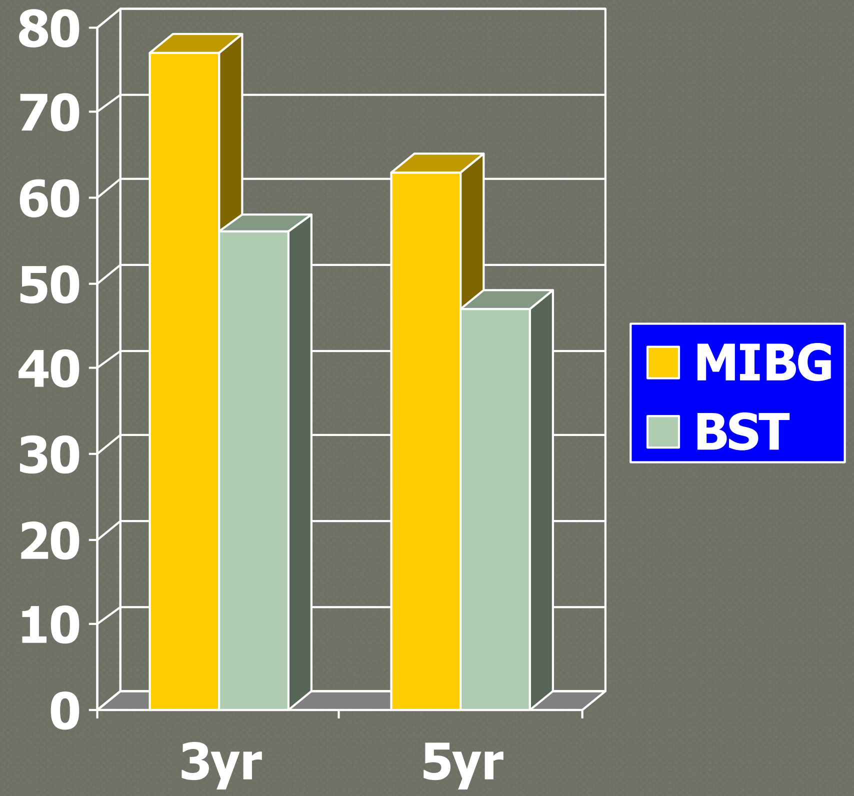
mIBG – carcinoid- EANM survey

N = 157   96% Stage III/IV

%	Tumour	Marker	Palliation
CR	0	17	10
PR	16	39	61
SD	65	36	27
PD	19	8	2

Results from other centres

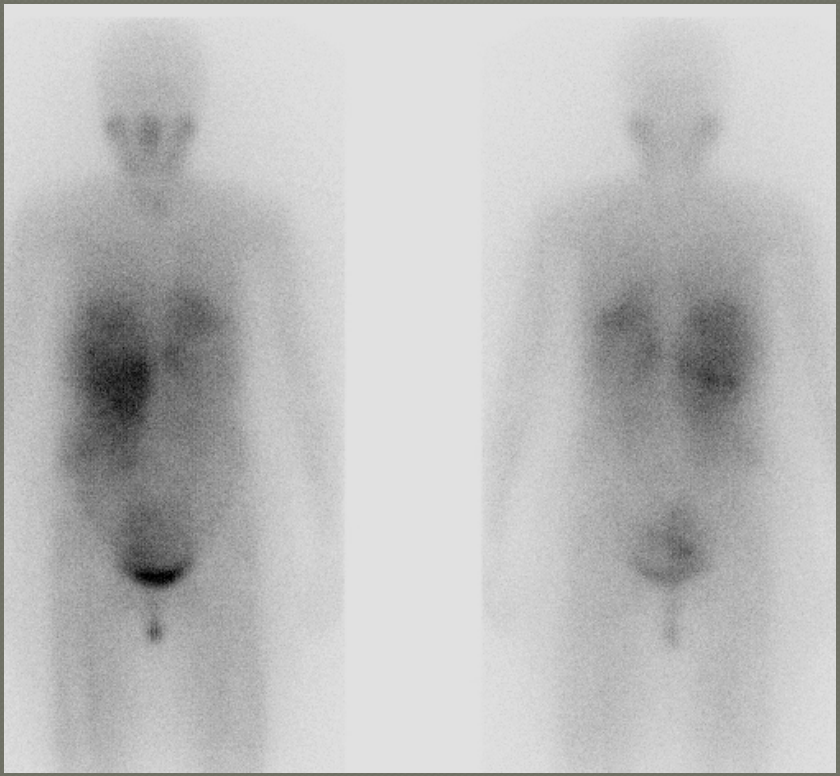
- Syweck et al WJS 2004 compared 2 centres-58 patients at each
  - 1 MIBG
  - 1 without MIBG
- % Survival noted at
  - 3 yr
  - 5 yr

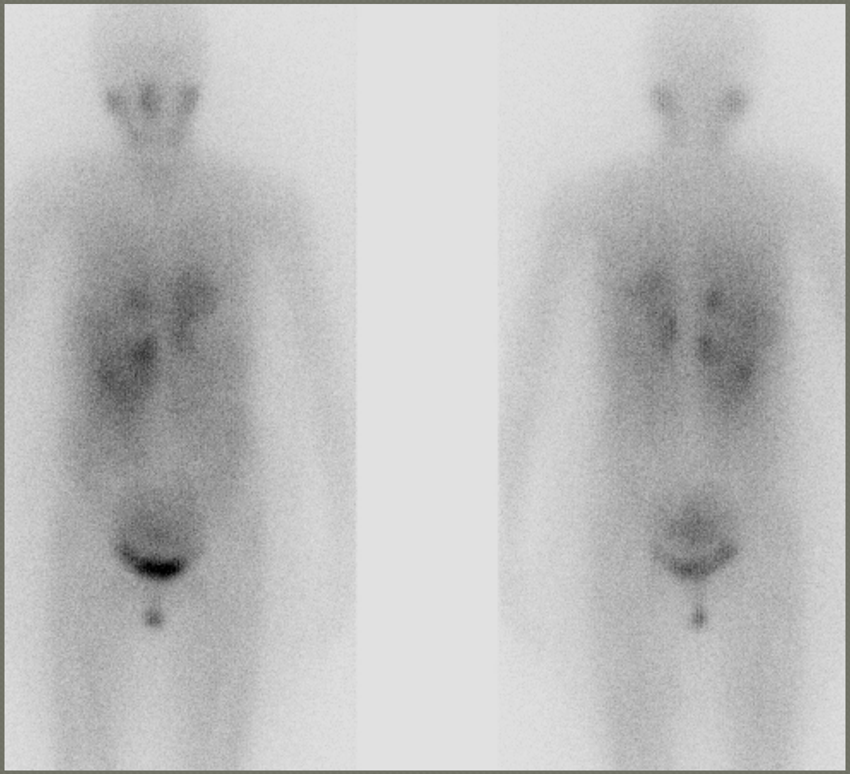


Results from other centres

- Safford et al Cancer 2004
- 98 patients
- Median survival 24 months
- If had symptom relief with reduced flushing etc median survival 57 months
- Radiological response not predictor of survival
- Best if 15Gbq given in 2-3 doses

Response to therapy-gastrinoma



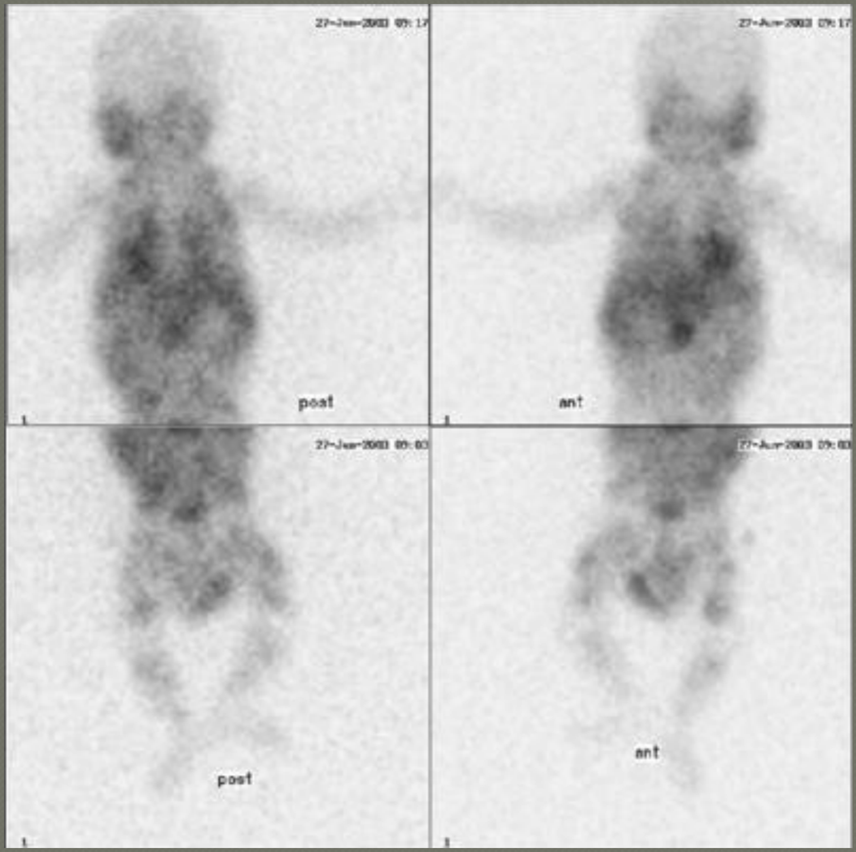


I-131 in neuroblastoma

- Tumour of childhood
- Most common extra-cranial solid tumour in children
- As many as 150 new cases per annum in UK
- 50% in children under 2
- Neural crest origin
- May develop anywhere along sympathetic NS
- Often metastasises especially to bone and liver

MIBG and neuroblastoma

- 85-90% of neuroblastomas have uptake of MIBG
- Can be used to look for unexpected sites of disease
- Remember children often very young so image quality may be an issue

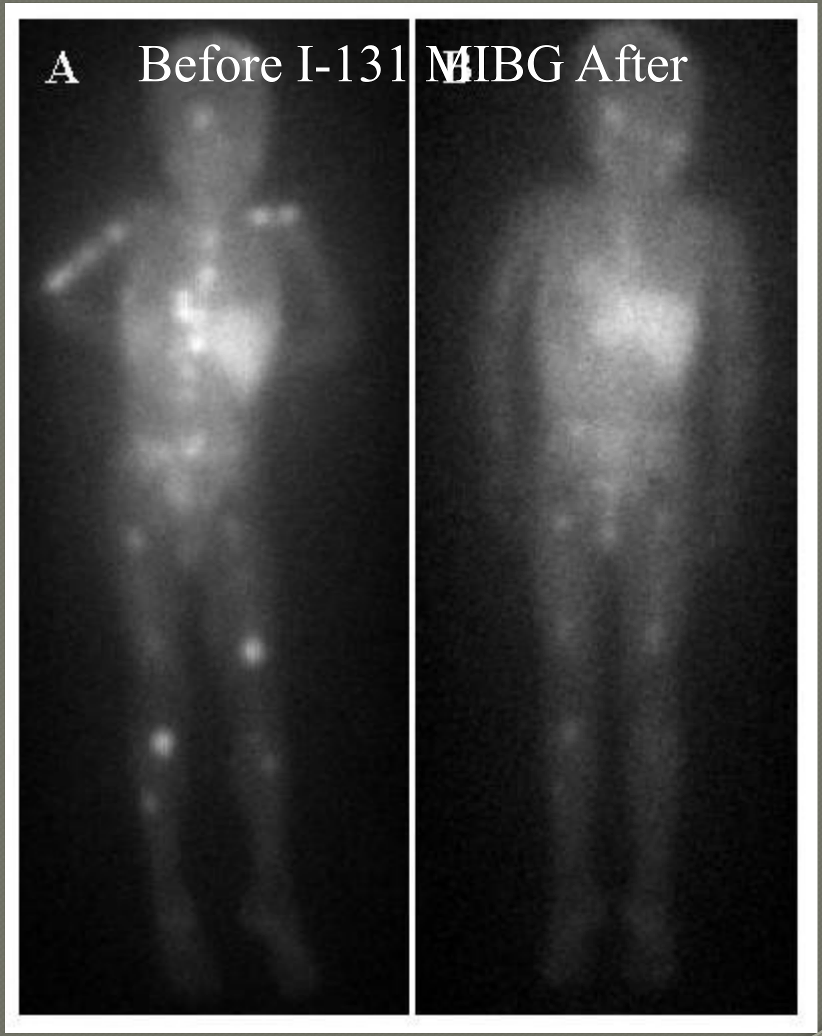


Treatment

- Primary treatment is surgery if possible
- Second line treatment now accepted as chemotherapy and or radiotherapy
- Chemotherapy based on temozolamide and irinotecan
- If fail then palliative treatment with I-131 MIBG (maybe with chemotherapy) can extend survival

I-131 MIBG results

- Garaventa et al BJC 1999
- Activity based on wt 2.7GBq if <20kg, 5.5GBq if >20kg
- Of 43 patients 1xCR 12xPR, 25xDS, 6xPD
- For stage 2 few deaths, stage 4 median OS 19months



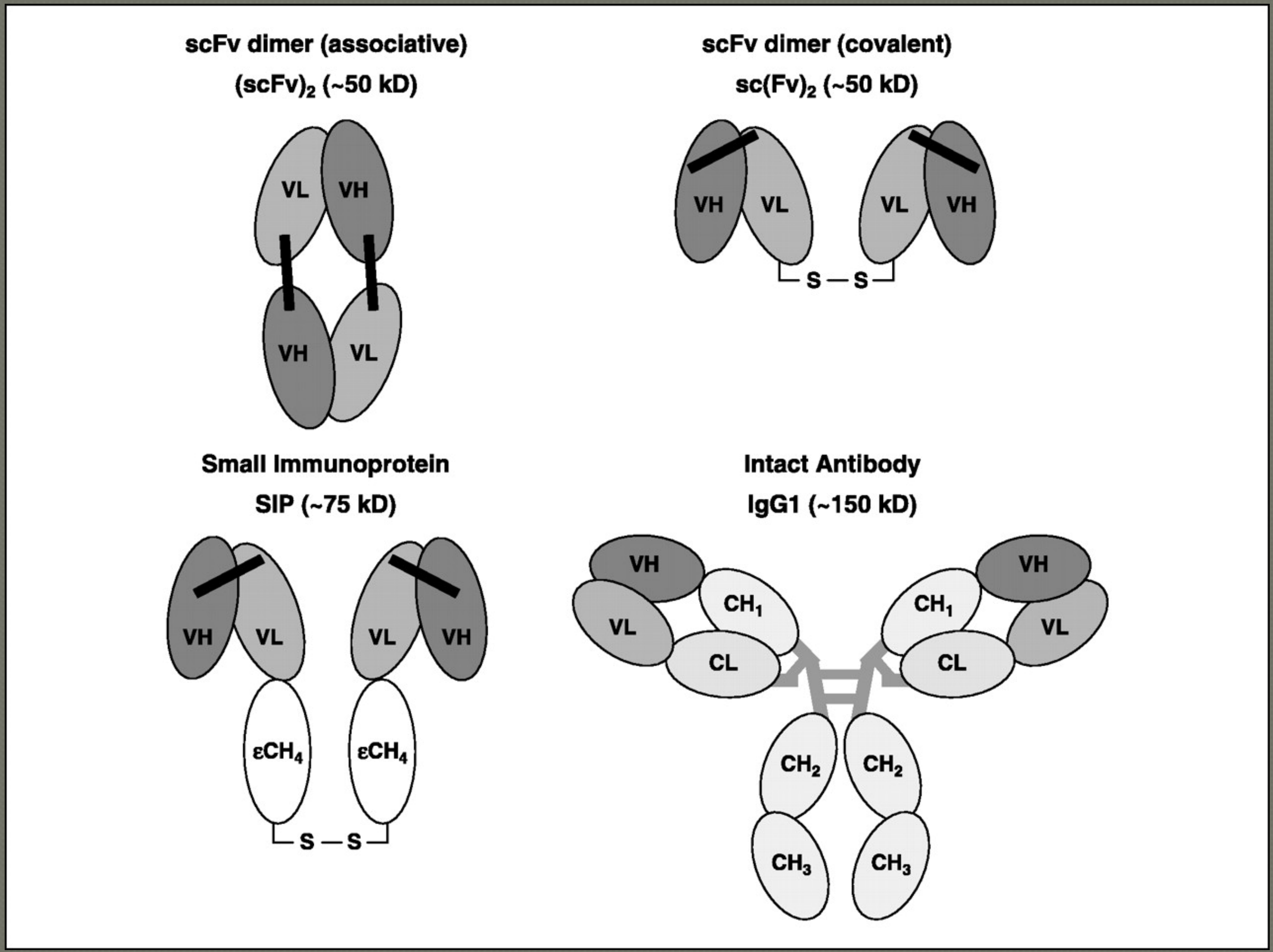
New ideas

- Use of pan tumour targeting – SIP
- Use of alpha emitters
  - Maybe delivered locally to tumour

SIP

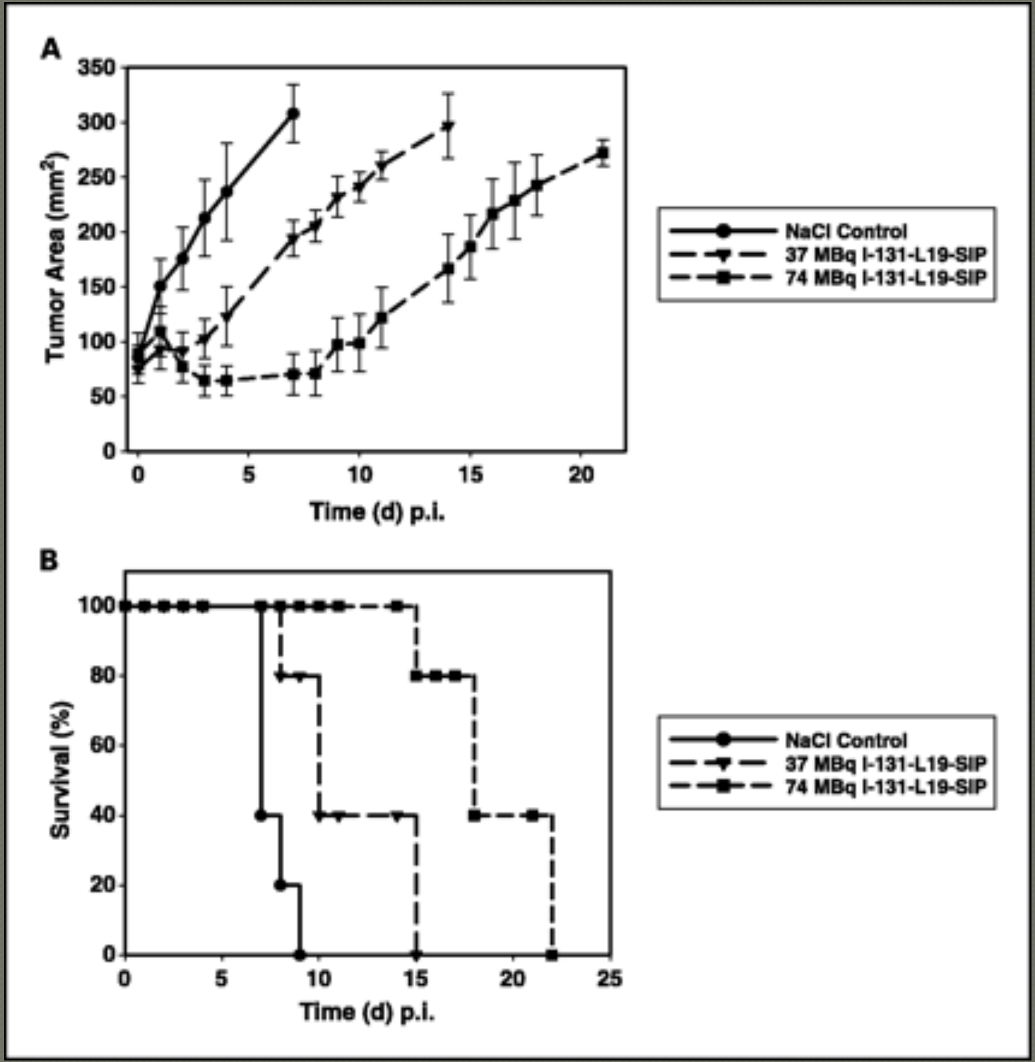
- Work in Germany Italy and USA
- Common cancer antigen fibronectin
- Present on solid tumours and Hodgkin's
- L-19 SIP dimeric antibody like structure with high affinity and low antigenicity has high levels of affinity for tumours

L19-SIP

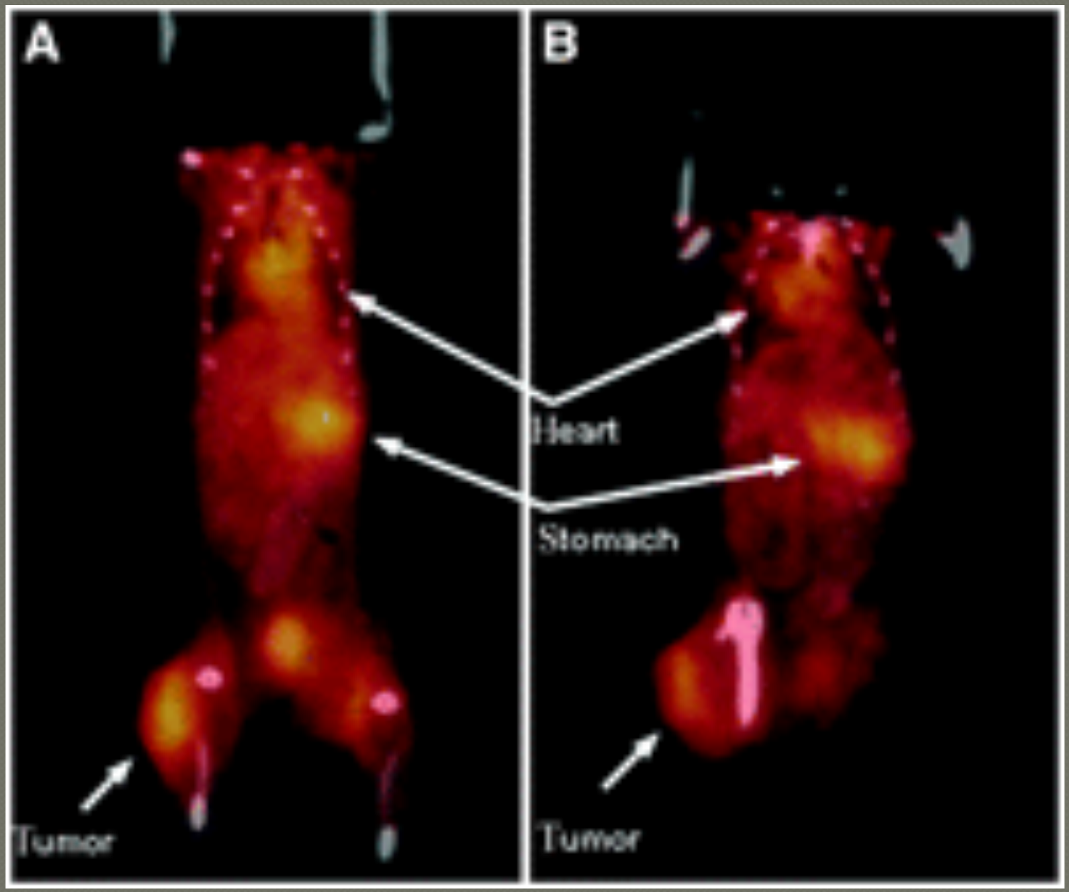


scFv dimer (associative)
(scFv)2 (~50 kD)
VL
VH
VH
VL
scFv dimer (covalent)
sc(Fv)2 (~50 kD)
VH
VL
VL
VH
S — S
Small Immunoprotein
SIP (~75 kD)
VH
VL
VL
VH
εCH4
εCH4
S — S
Intact Antibody
IgG1 (~150 kD)
VH
VL
CH1
CL
VH
VL
CH1
CL
CH2
CH2
CH3
CH3

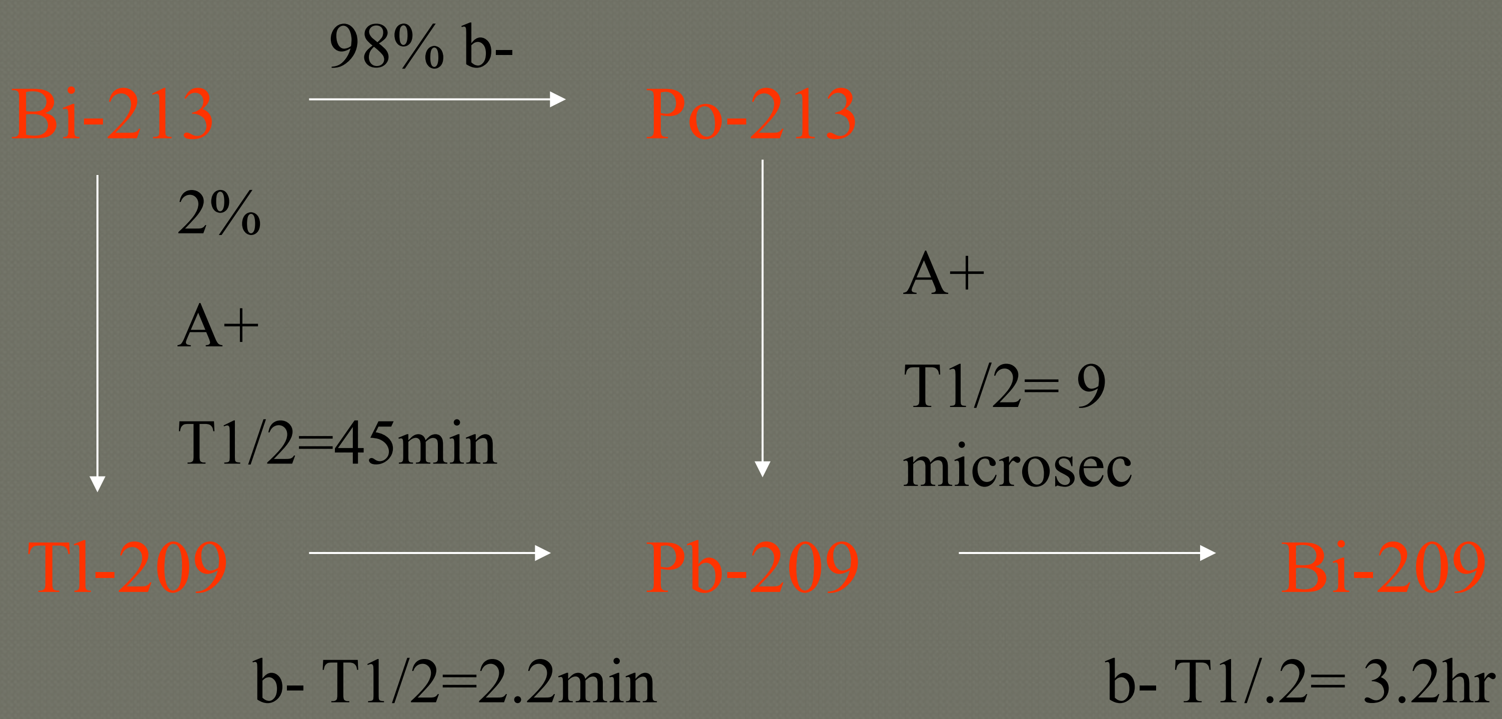
Berghoff et at Cancer Research 2005 showed dose response with I-131 L19-SIP



Tumour uptake (Welch JNM 2007)



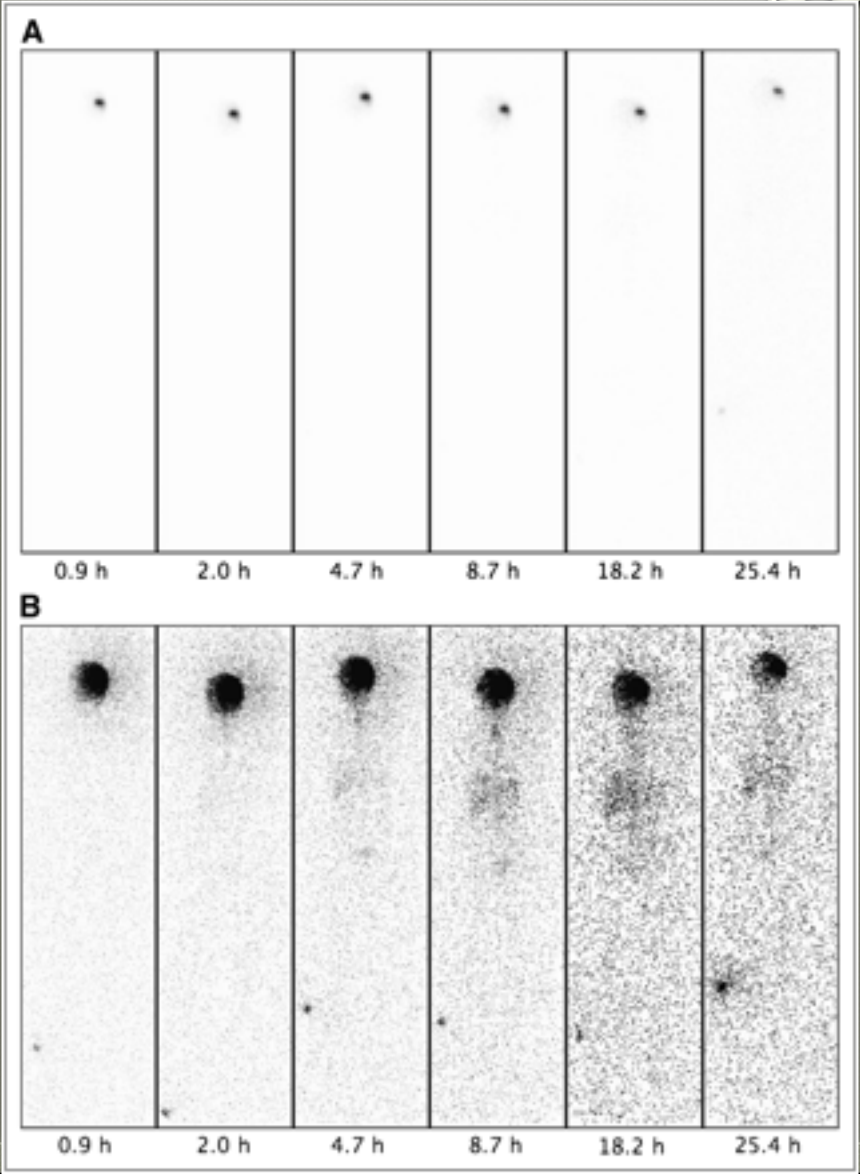
Complex decay



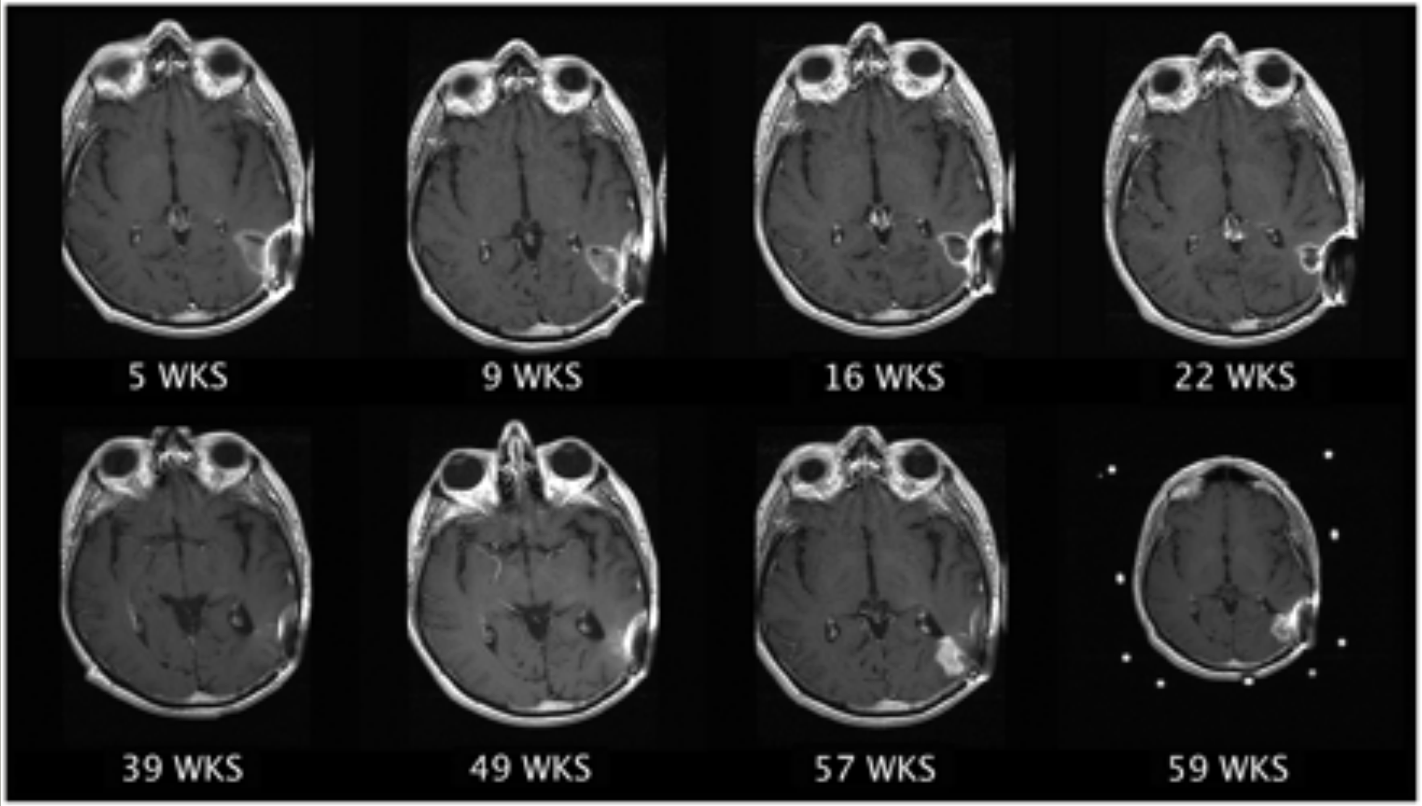
Recent developments

- Zalutsky et al JNM 2008
- At-211 anti-tenascin antibody
- To treat malignant gliomas
- 18 patients with untreatable glioma treated with
- 74-108 MBq of At-211-ch81C6 given to 9 patients via intra-thecal catheter
- Imaging of Xrays from Po recorded

Polonium images at differnet ime points



Responses to At-211



Summary

- Radionuclide therapy can treat a range of benign and malignant conditions
- Beginning to be involved in more common tumours
- Area of research which is active
- Radiologists do not do therapy