# Concepts of radionuclide therapy science and practice

John Buscombe

# 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

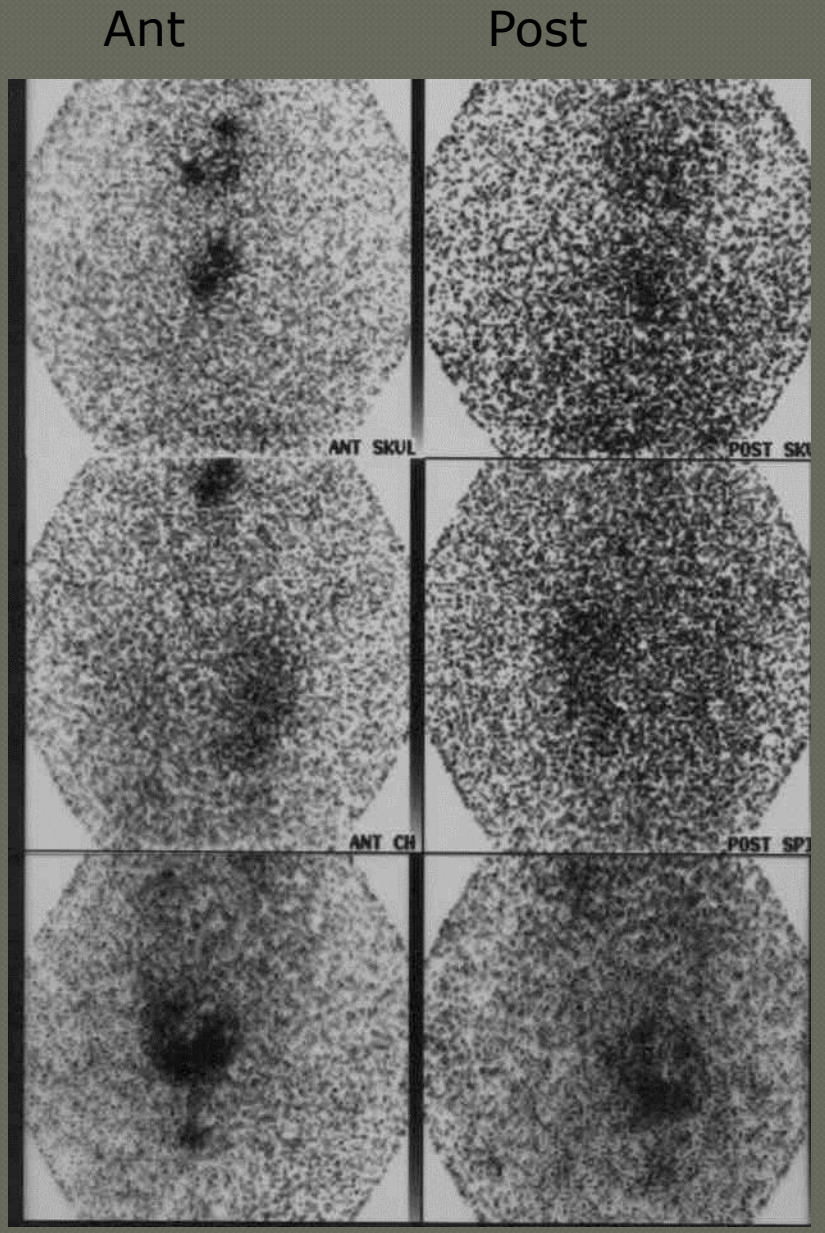
- 2010
- P-32 Polatom
- Y-90 Dotatate/toc Polatom/Perkin Elmer, Molecular imaging
- Lu-177 Dotatate Covidien
- Y-90 Zevalin Bayer
- Ra-223 Bayer
- I-131 SIP Philogen

# Change in attitude

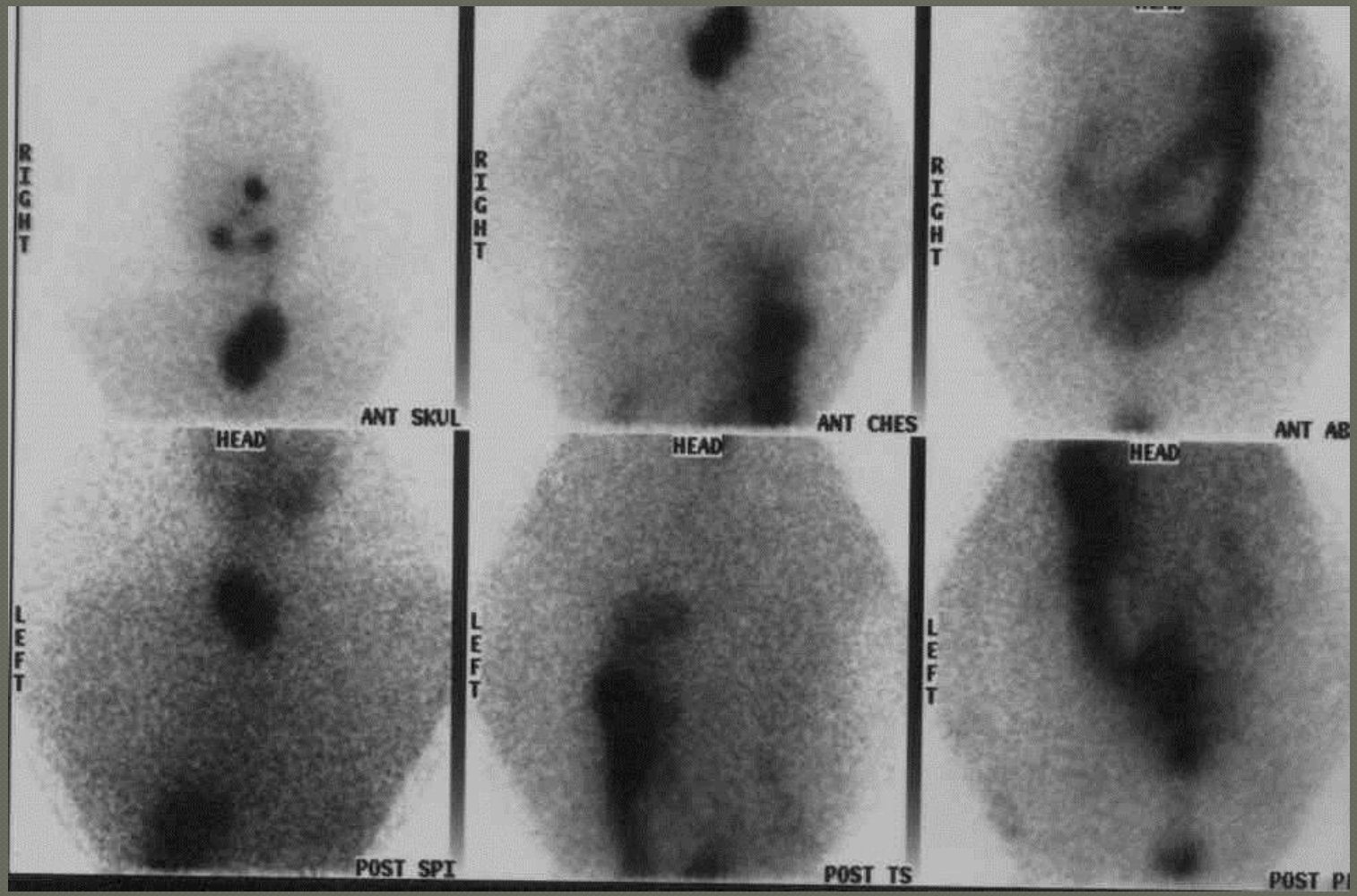
- Small market
- Limited use
- Except for I-131 palliation only
- Single agent

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

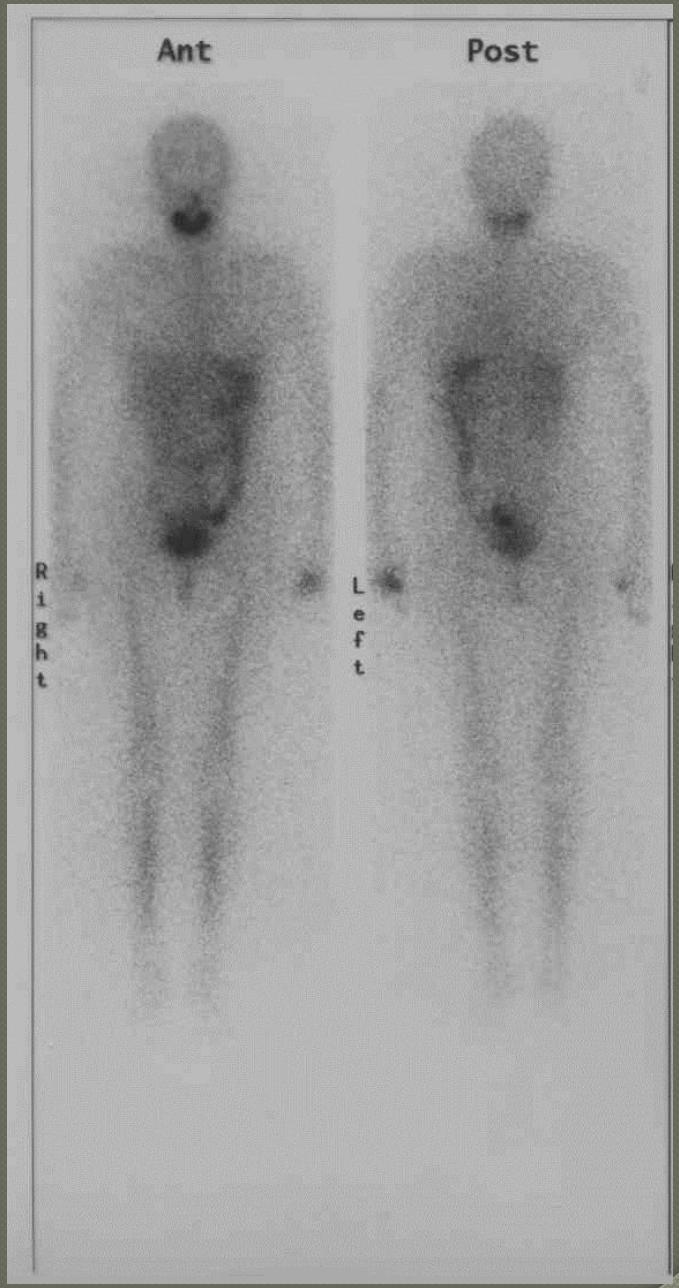
**63 year old women 6 weeks after total thyroidectomy Spot views performed 72 hours after administration of 140 MBq of I-131**



# Imaging performed 72 hours after administration of 3.5 GBq of I-131



**After 3 further treatments of 5GBq of I-131, whole body imaging with 140MBq of I-131 fails to show any uptake in tumour and TBG is normal and remains so**



# 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 | 3.1mm | 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

- Contra-indications
  - Pregnancy
  - Lactation
  - Local skin infection
  - Ruptured Baker's cyst (should be checked by ultrasound if considered possible)
- Cautions
  - Children and those under 20
  - Joint instability
  - Significant cartilage loss on x-ray

# Preparation of the patient

- Explain procedure
- Explain that a needle will be put into the joint
- Explain that their knee will be immobilised for at least 24 hours (so we can only do one)
- Response is unlikely for 14 days and there may be transient increase in pain
- Non-treated joints will  not get better!
- No surgery can be performed for 2 weeks

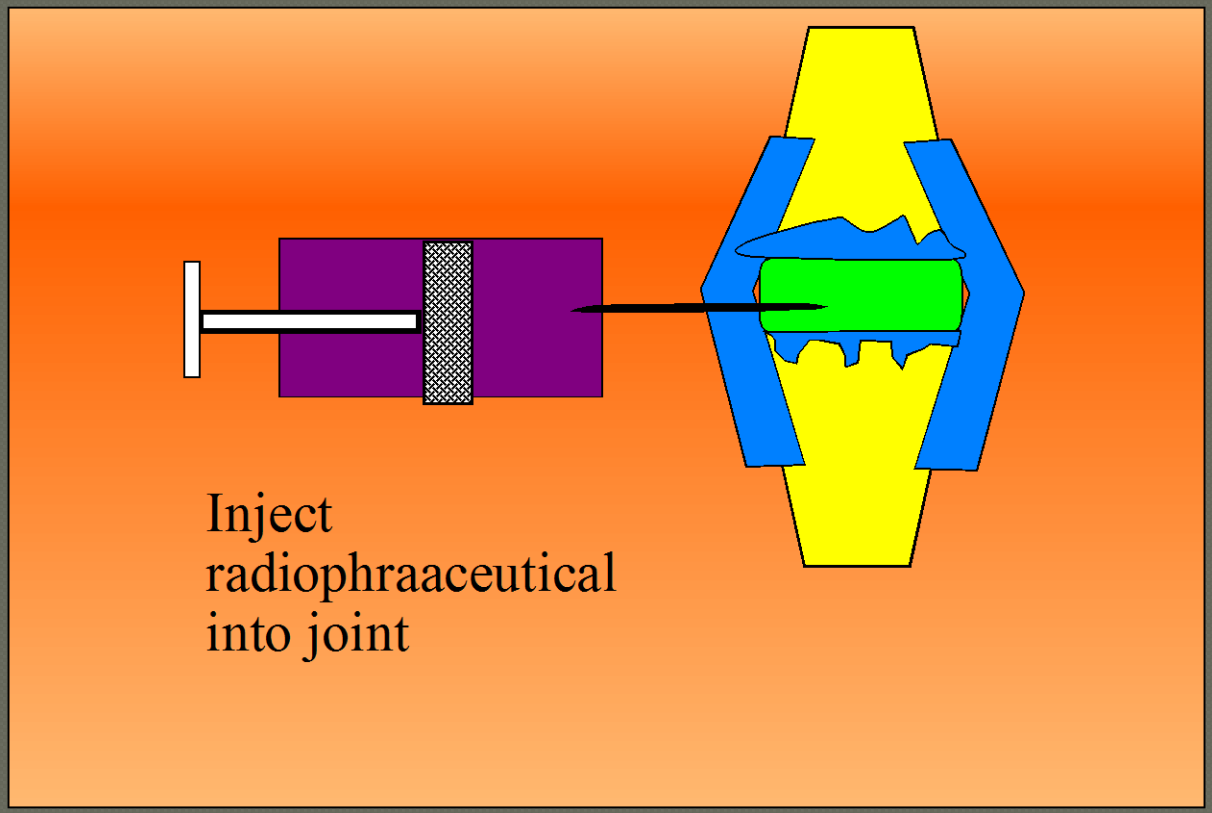
# Activity given

- Knees normally 185MBq Y-90 silicate and Y-90 colloid
- Normal volume 4 ml, may be less
- Normal minimum re-treatment rate is 6 months

# 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)

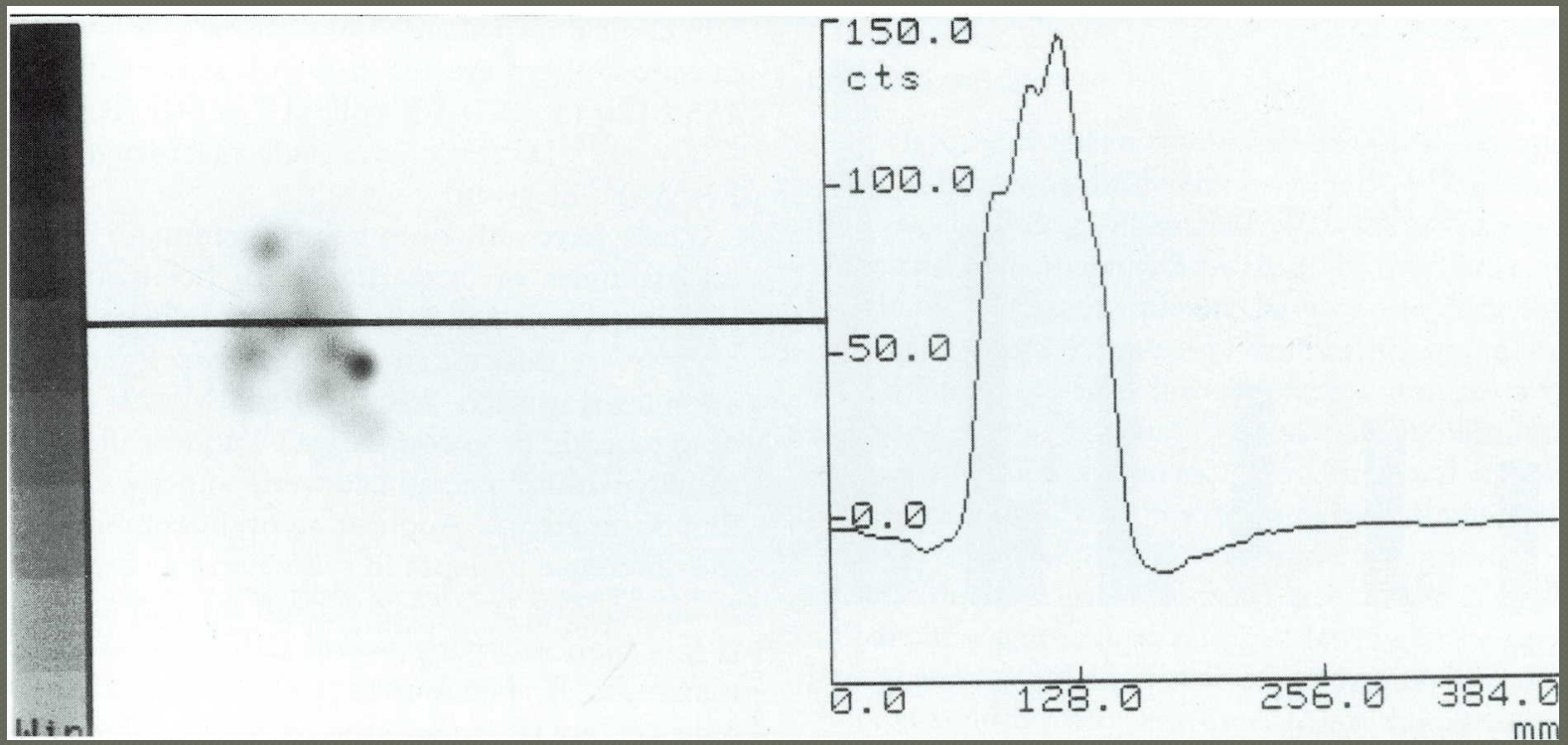
# Principles of synovectomy



# 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

# Sm-153 HYDA knee 24 hrs pi



# 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

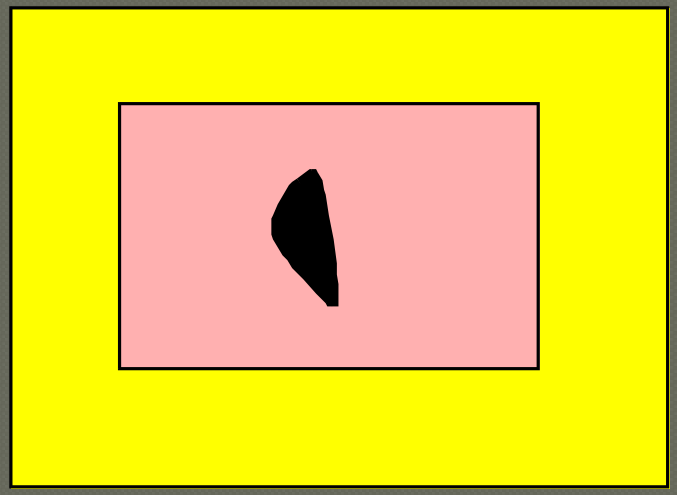
- Many cancers have cells which are present circulating in the blood
- These travel around the body and can end up anywhere with end arteries
  - Bone
  - Lung
  - Kidney
  - Brain

# 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

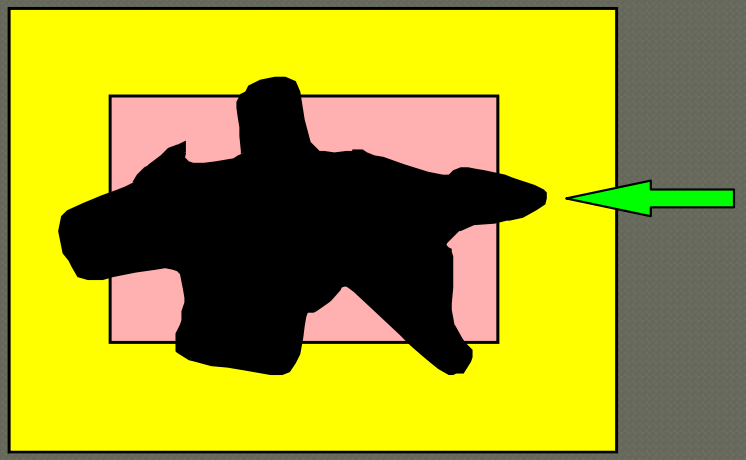
# Bone/BM metastases

- 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

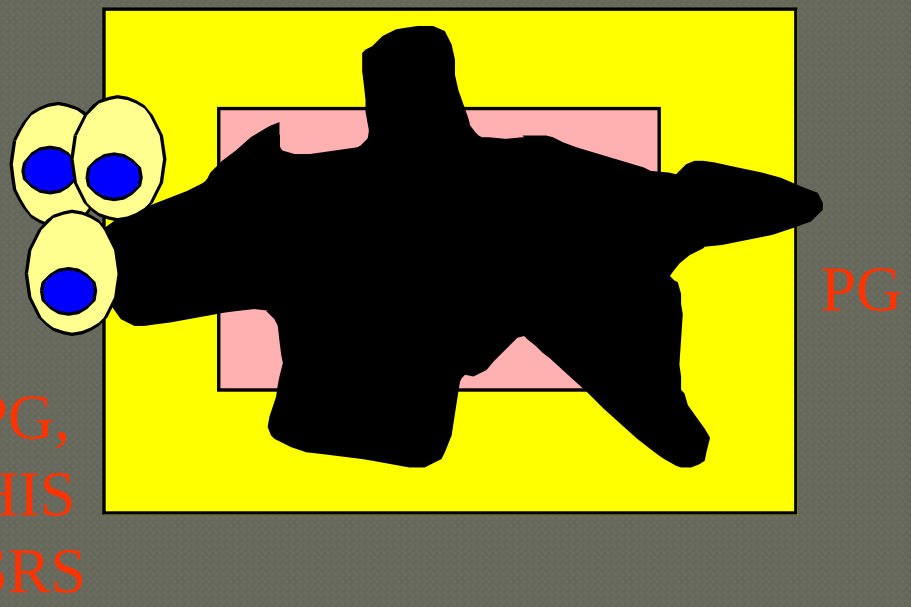
- Metastases starts to grow
- Will impinge on bone
- Bone will try to remodel
- Increased uptake of Tc-99m MDP



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

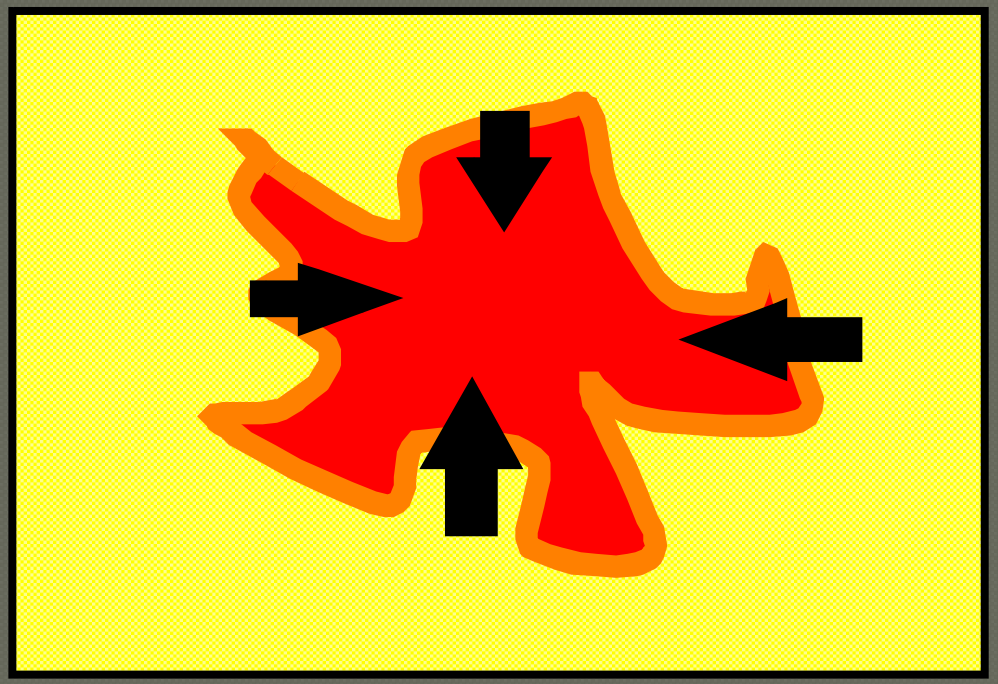
# Bone/bone marrow mets

- 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

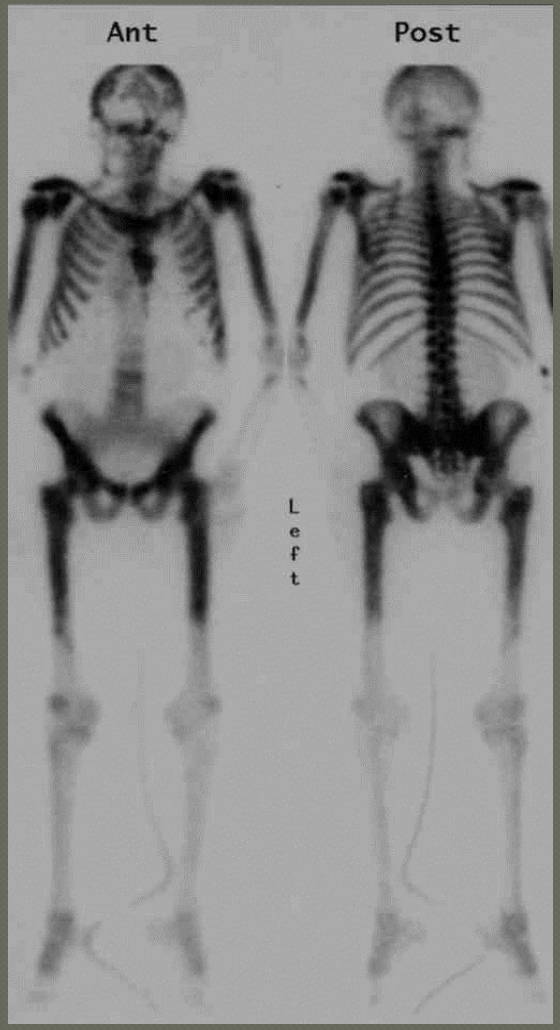
| Isotope | T1/2 | Beta energy | comments |
|---|---|---|---|
| P32 | 14.3d | 1.71 | Low TBR = 2 at most |
| Sr-89 | 50.5 | 1.46 | Fixed dose 150 MBq |

# 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 | 3.7d | 1.07 MeV | 137 |
| Sn-117m DTPA | 14d | EC only | 158 |

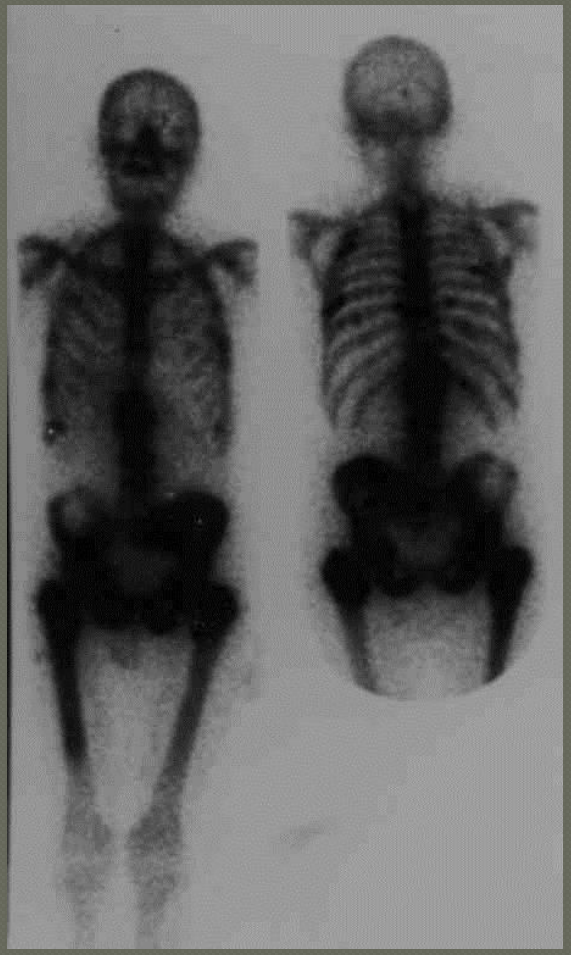
# Gamma emitters

- 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

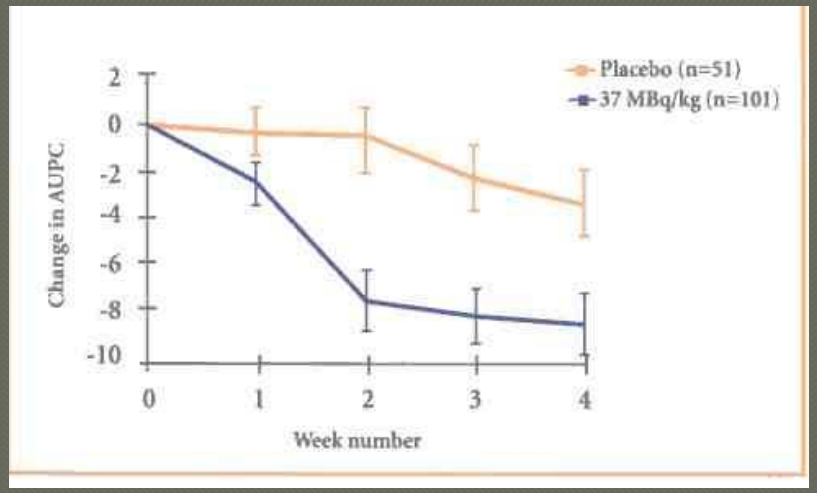
Images not so clear as low energy reduces count rate.

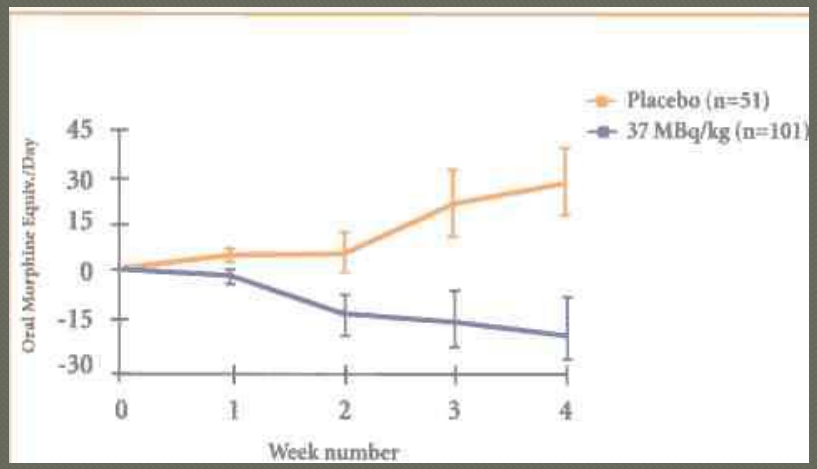
Note at 24 hours no renal or bladder activity seen but this is not a superscan



# 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



# Limitations to trials

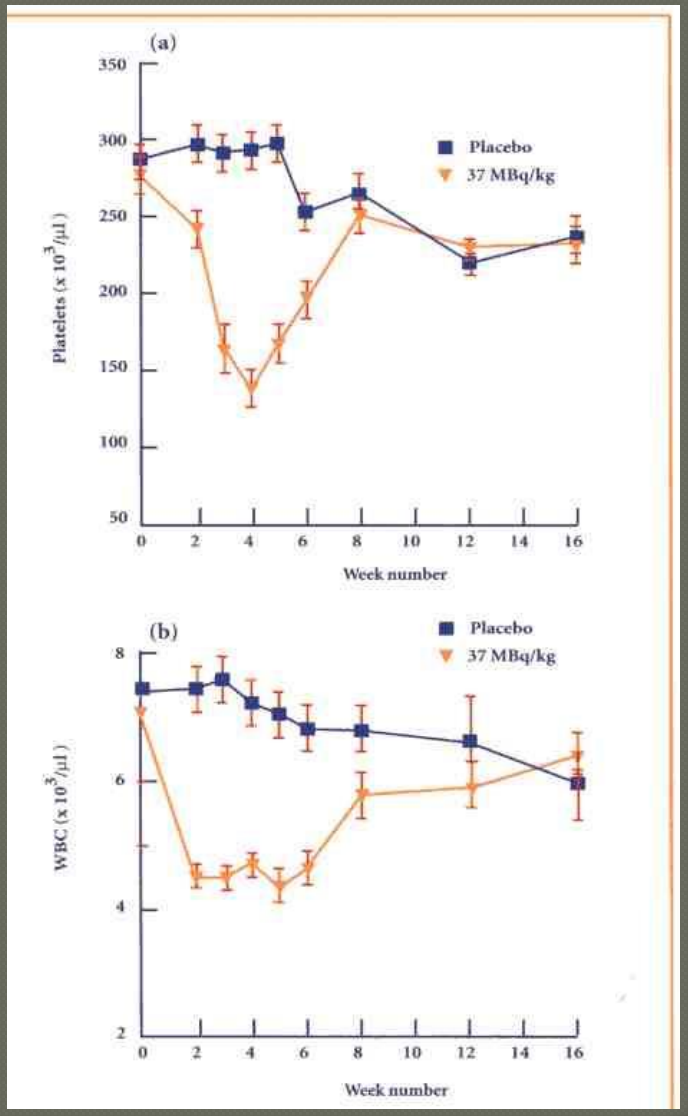
- Primary aim has been pain relief
- However could there be an advantage in combing treatments
  - Longer pain relief
  - Anticancer effect
- Drugs that can be added
  - Bisphosphonate
  - Chemotherapy

# Concerns

- The primary organ for toxicity in radionuclide therapy with bone palliation therapy is bone marrow
- Often compromised by previous treatment or disease
- Would additional treatment jut result in greater toxicity

# Sm-153 EDTMP

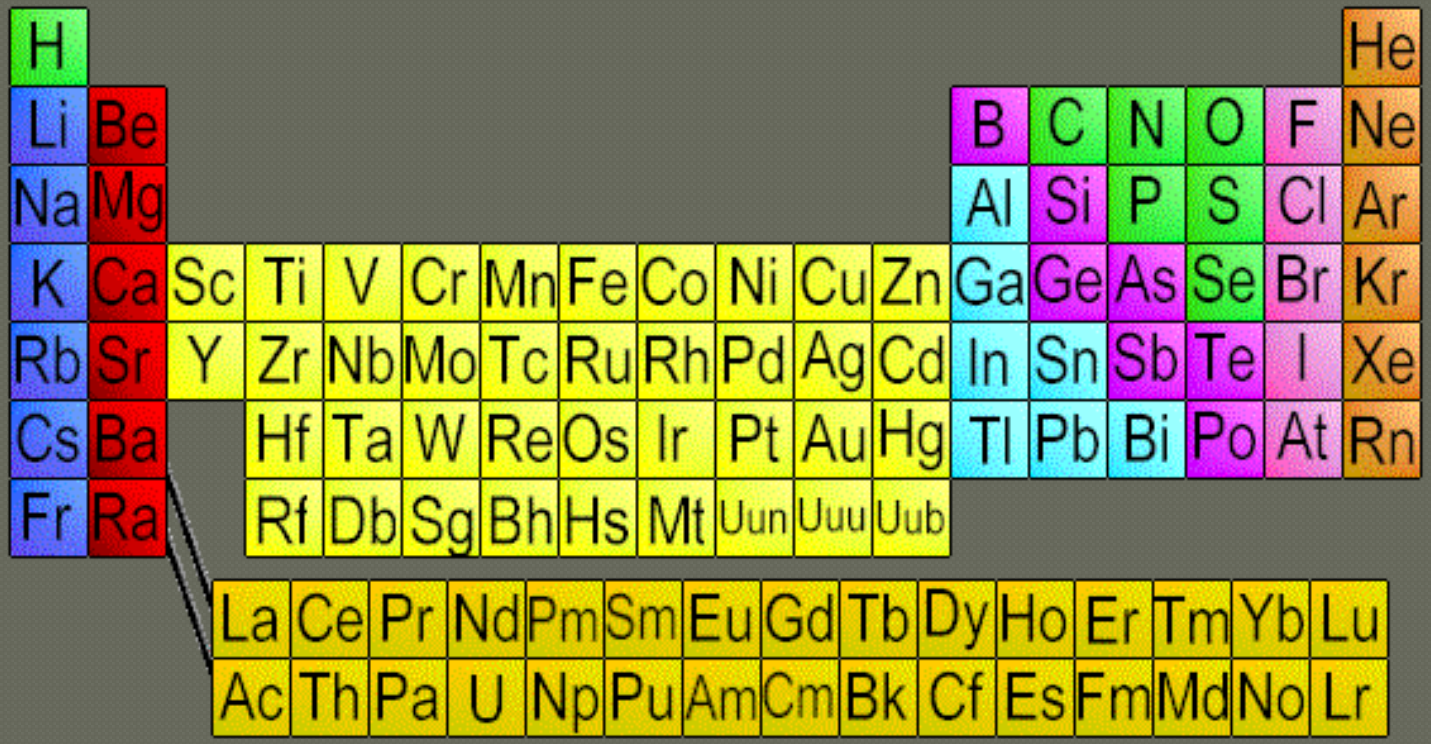
- Effect on Pts and WBC
- Related to radioactivity not lexidronam
- Recovered by 6 weeks



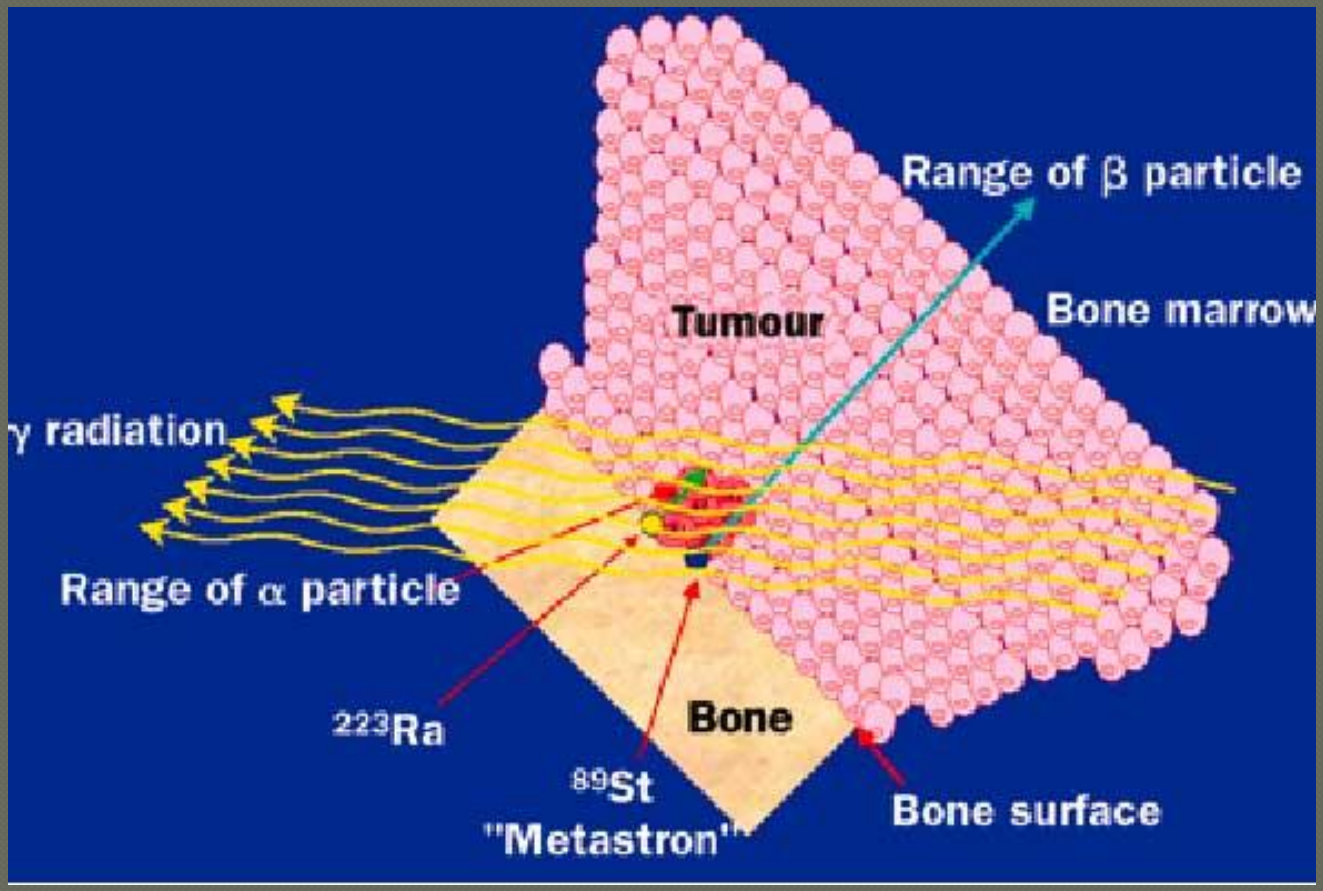
# Bone mets and radium

- At site of bone mets increased turnover of bone matrix
- Increased uptake of calcium
- As Sr is also a group II metal Sr-89 (metastron) used to treat painful bone metastases
- Radium below Sr in group II also has uptake in bone matrix
- Ra-223 an alpha emitter

# The periodic table



# Ra-223


Range of β particle
Tumour
Bone marrow
γ radiation
Range of α particle
223Ra
Bone
89St
"Metastron"
Bone surface

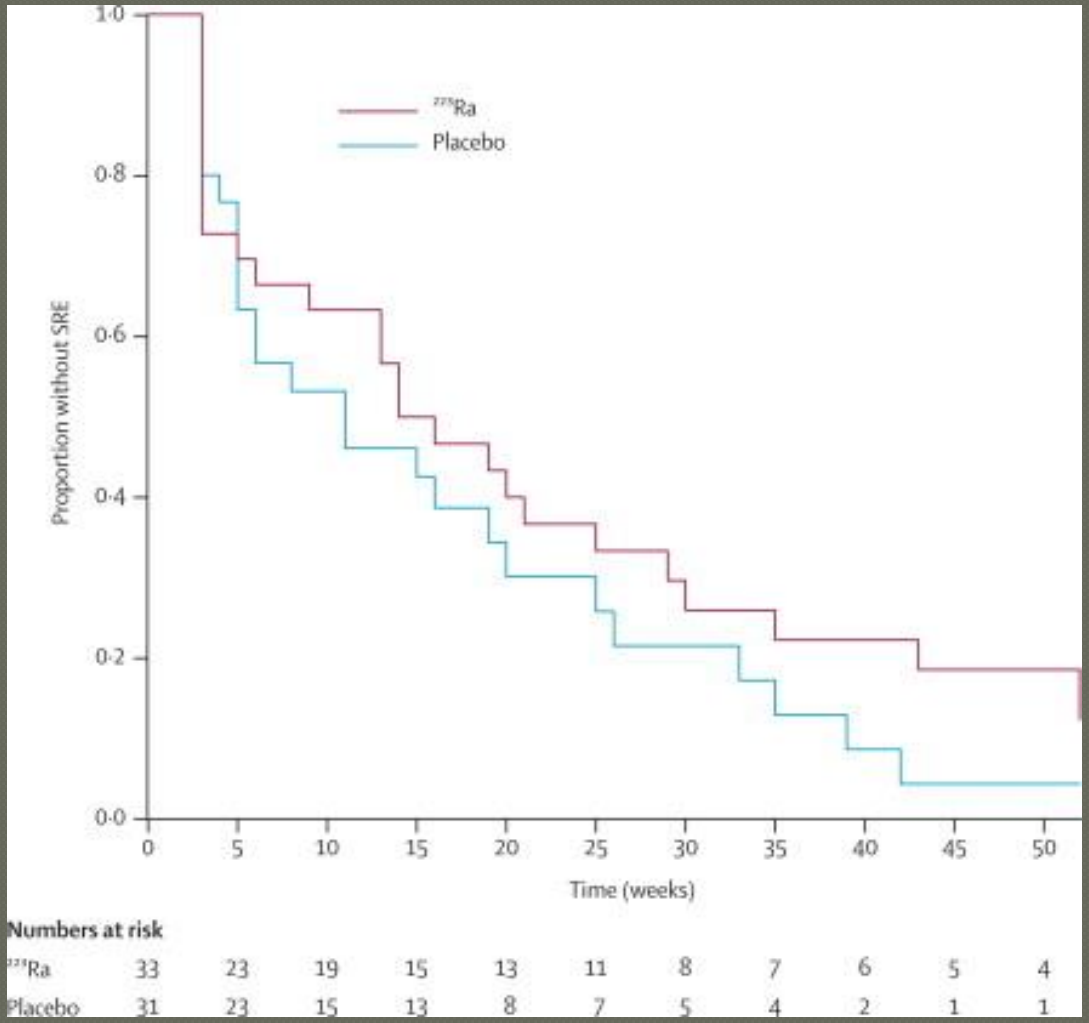
# Ra-223 vs placebo

- Multi-centre phase II trial
- Patients with symptomatic bone metastases treated with placebo or Ra-233 given 4 weekly
- 33 patients received Ra-233 and 31 placebo
- Activities 50KBq/kg (mean 3.5MBq)

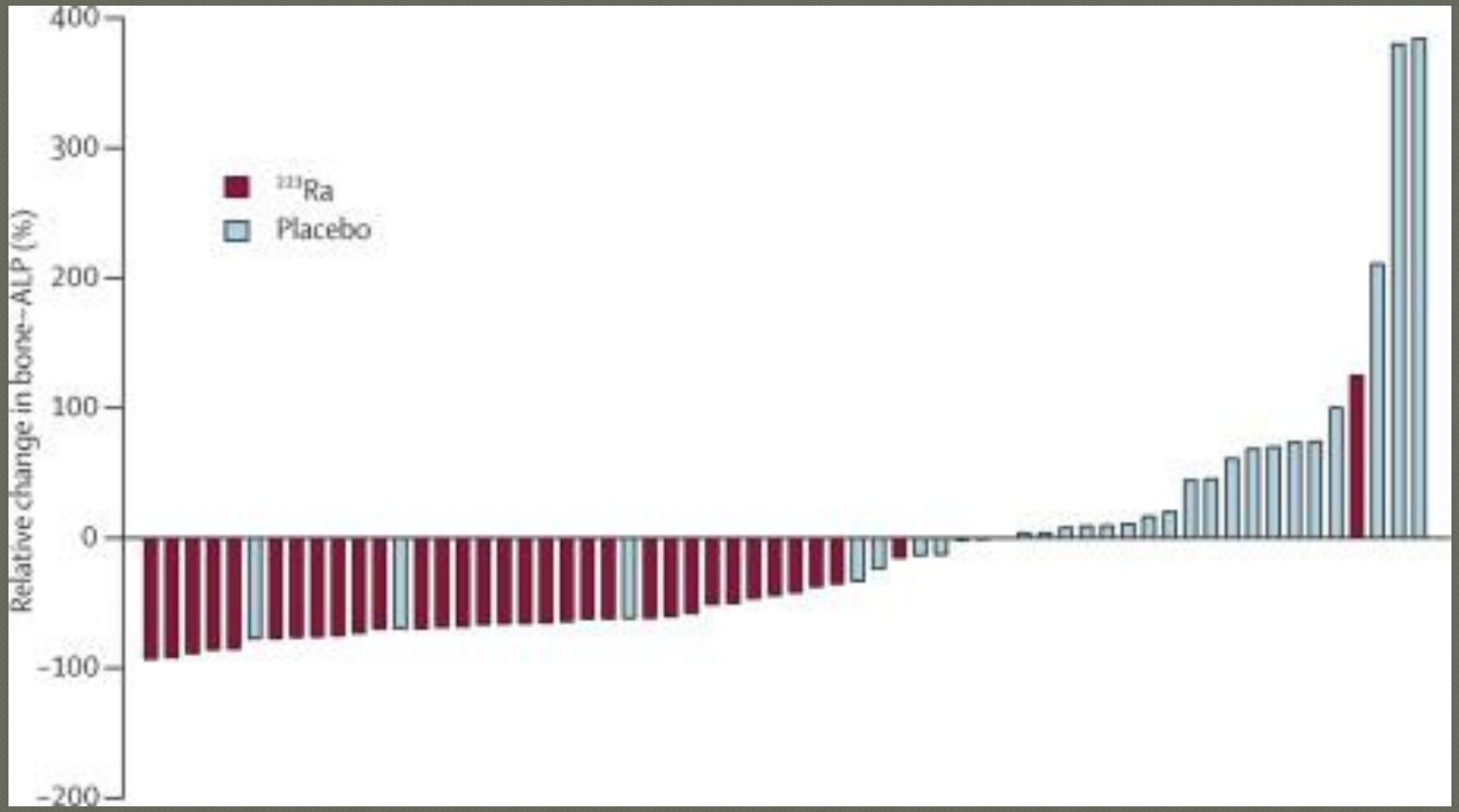
# Ra-233 vs placebo

- Well tolerated no significant BM toxicity
- Some diarrhoea in treatment group
- Mean Alk phos change over 6 months was -65% in treated group and +9% in placebo
- Mean overall survival was significantly longer (65 weeks) c/w placebo (46 weeks)

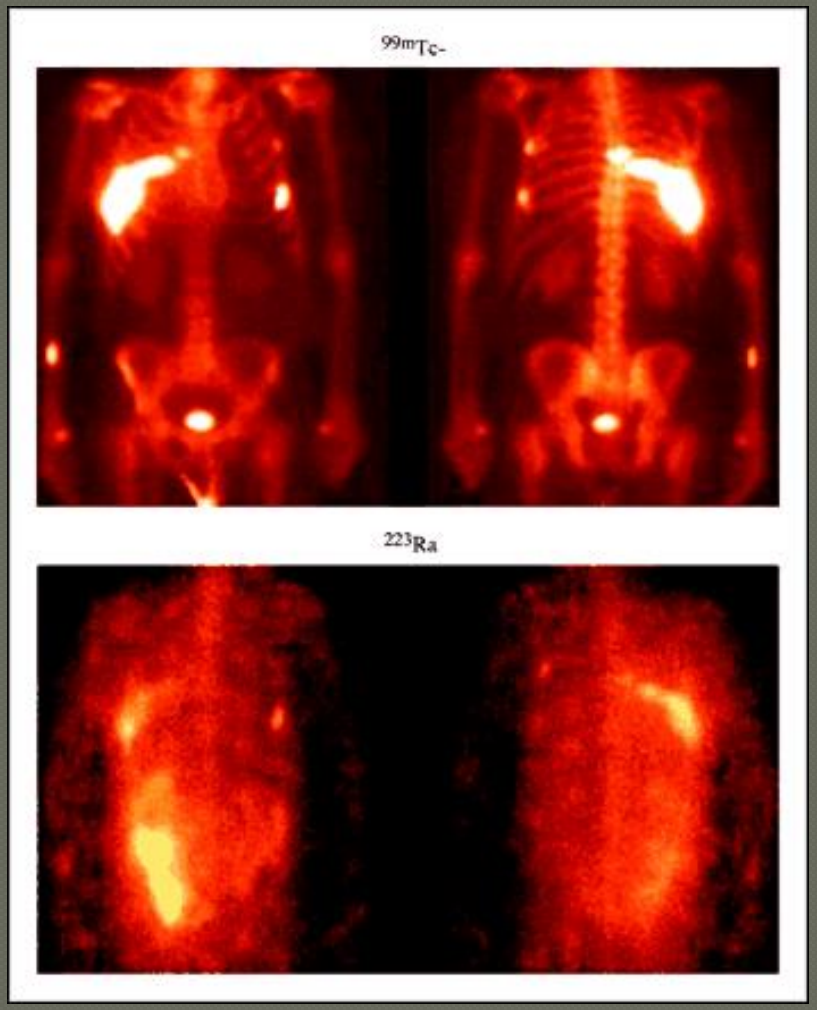
# Overall survival



# Changes in Alk Phos



# Rd-223 has 80-85keV X-ray (Nilsson at al Clin Can Res 2005



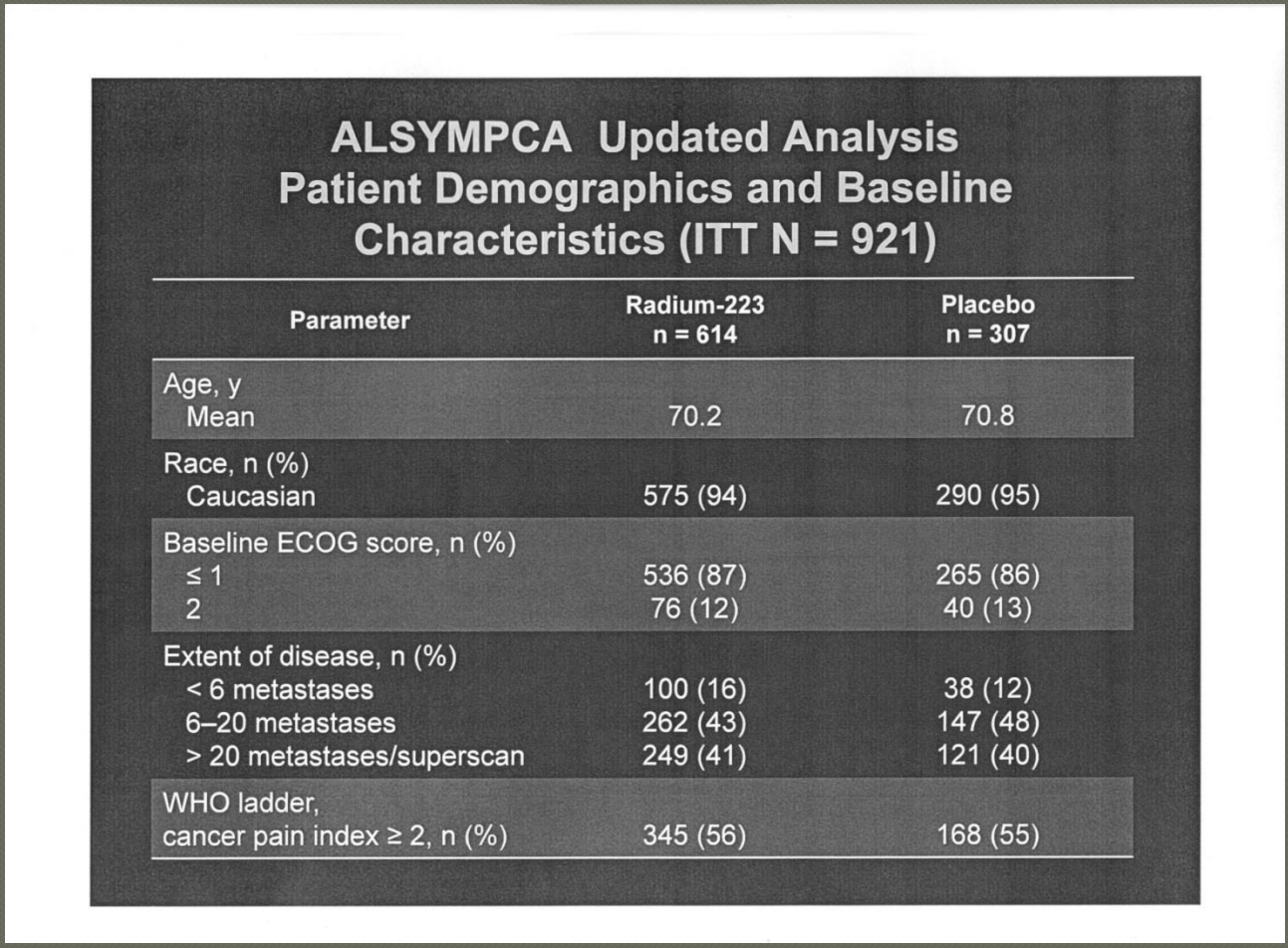
# Phase III RCT

- Set up by Algeta
- Based at Radium Hospital, Oslo
- Commercial interest from Bayer
- Plan to set up trial in 30 countries
- Powered to show survival
- Need 900 patients 2/3 to have treatment, 1/3 placebo
- No imaging to preserve blinding

# Protocol

- Patient to have proven bone metastases from Ca prostate
- Could have failed therapy such as taxanes
- After consent randomised to treatment or placebo
- Only one person at each sites know if it is active drug-must not tell patient or other docs
- 30kBq/kg 4 weekly for 6 cycles if live long enough or symptoms not worse

# Patient characteristics



**ALSYMPCA Updated Analysis**
**Patient Demographics and Baseline Characteristics (ITT N = 921)**

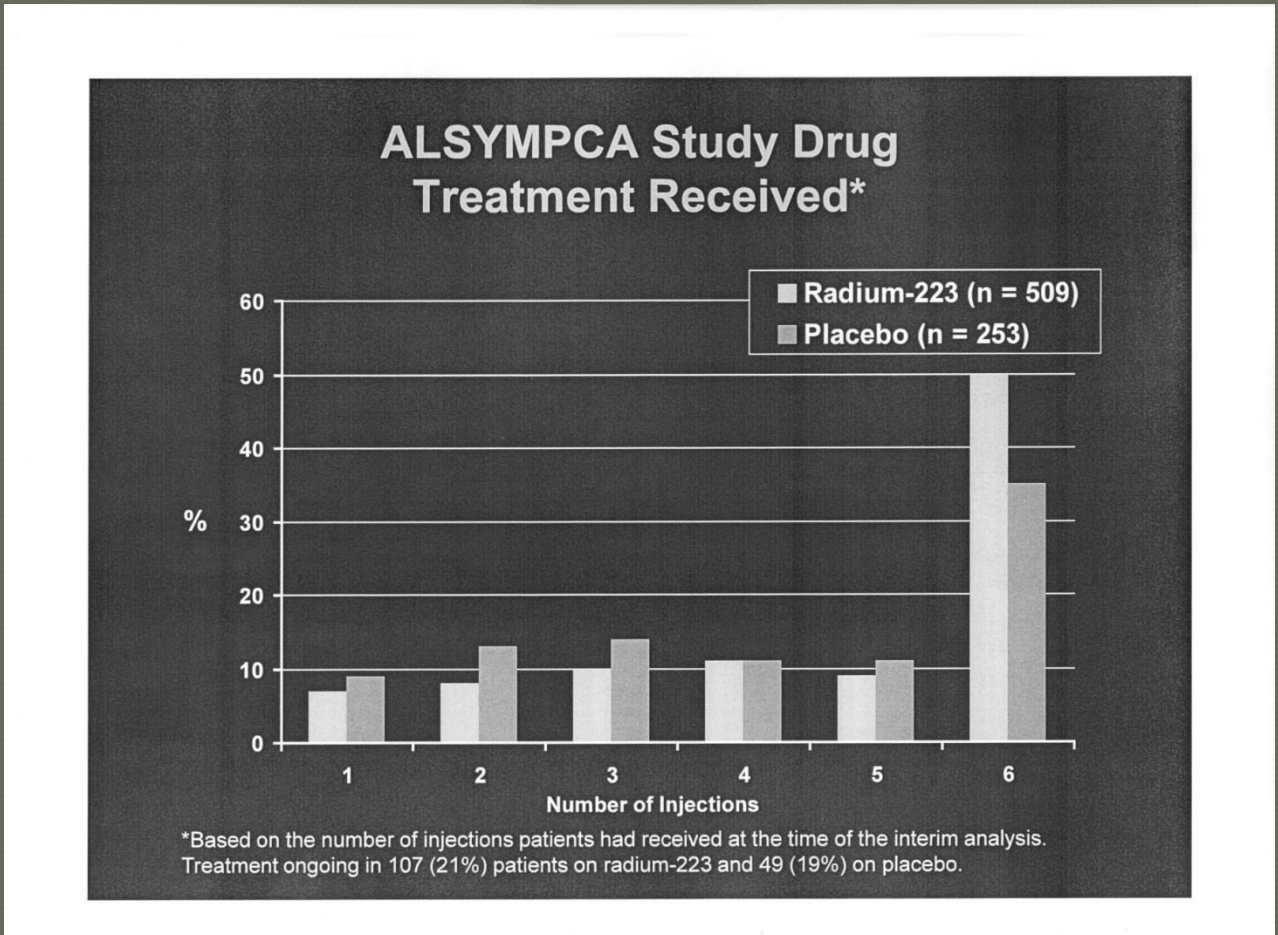
| Parameter | Radium-223 n = 614 | Placebo n = 307 |
|---|---|---|
| Age, y | | |
| Mean | 70.2 | 70.8 |
| Race, n (%) | | |
| Caucasian | 575 (94) | 290 (95) |
| Baseline ECOG score, n (%) | | |
| ≤ 1 | 536 (87) | 265 (86) |
| 2 | 76 (12) | 40 (13) |
| Extent of disease, n (%) | | |
| < 6 metastases | 100 (16) | 38 (12) |
| 6–20 metastases | 262 (43) | 147 (48) |
| > 20 metastases/superscan | 249 (41) | 121 (40) |
| WHO ladder, cancer pain index ≥ 2, n (%) | 345 (56) | 168 (55) |

# Patient characteristics

## ALSYMPCA Updated Analysis
## Patient Baseline Characteristics (ITT N = 921)

| Parameter<br>Median (min, max) | Radium-223<br>(n = 614) | Placebo<br>(n = 307) |
|---|---|---|
| Haemoglobin, g/dL | 12.2 (8.5-15.7) | 12.1 (8.5-16.4) |
| Albumin, g/L | 40 (24-53) | 40 (23-50) |
| Total ALP, µg/L | 211 (32-6431) | 223 (29-4805) |
| LDH, U/L | 315 (76-2171) | 336 (132-3856) |
| PSA, µg/L | 146 (3.8-6026) | 173 (1.5-14500) |
| Current bisphosphonates<br>Yes, n (%) | 250 (40.7) | 124 (40.4) |
| Prior docetaxel<br>Yes, n (%) | 352 (57.3) | 174 (56.7) |

# Dosing schedule



# Toxicity

## ALSYMPCA Updated Analysis
## AEs of Interest

| | All Grades | | Grades 3 or 4 | |
|---|---|---|---|---|
| **Patients with AEs n, (%)** | **Radium-223 n = 600** | **Placebo n = 301** | **Radium-223 n = 600** | **Placebo n= 301** |
| Hematologic | | | | |
| Anemia | 187 (31) | 92 (31) | 77 (13) | 39 (13) |
| Neutropenia | 30 (5) | 3 (1) | 13 (2) | 2 (1) |
| Thrombocytopenia | 69 (12) | 17 (6) | 38 (6) | 6 (2) |
| Non-Hematologic | | | | |
| Bone pain | 300 (50) | 187 (62) | 125 (21) | 77 (26) |
| Diarrhea | 151 (25) | 45 (15) | 9 (2) | 5 (2) |
| Nausea | 213 (36) | 104 (35) | 10 (2) | 5 (2) |
| Vomiting | 111 (19) | 41 (14) | 10 (2) | 7 (2) |
| Constipation | 108 (18) | 64 (21) | 6 (1) | 4 (1) |

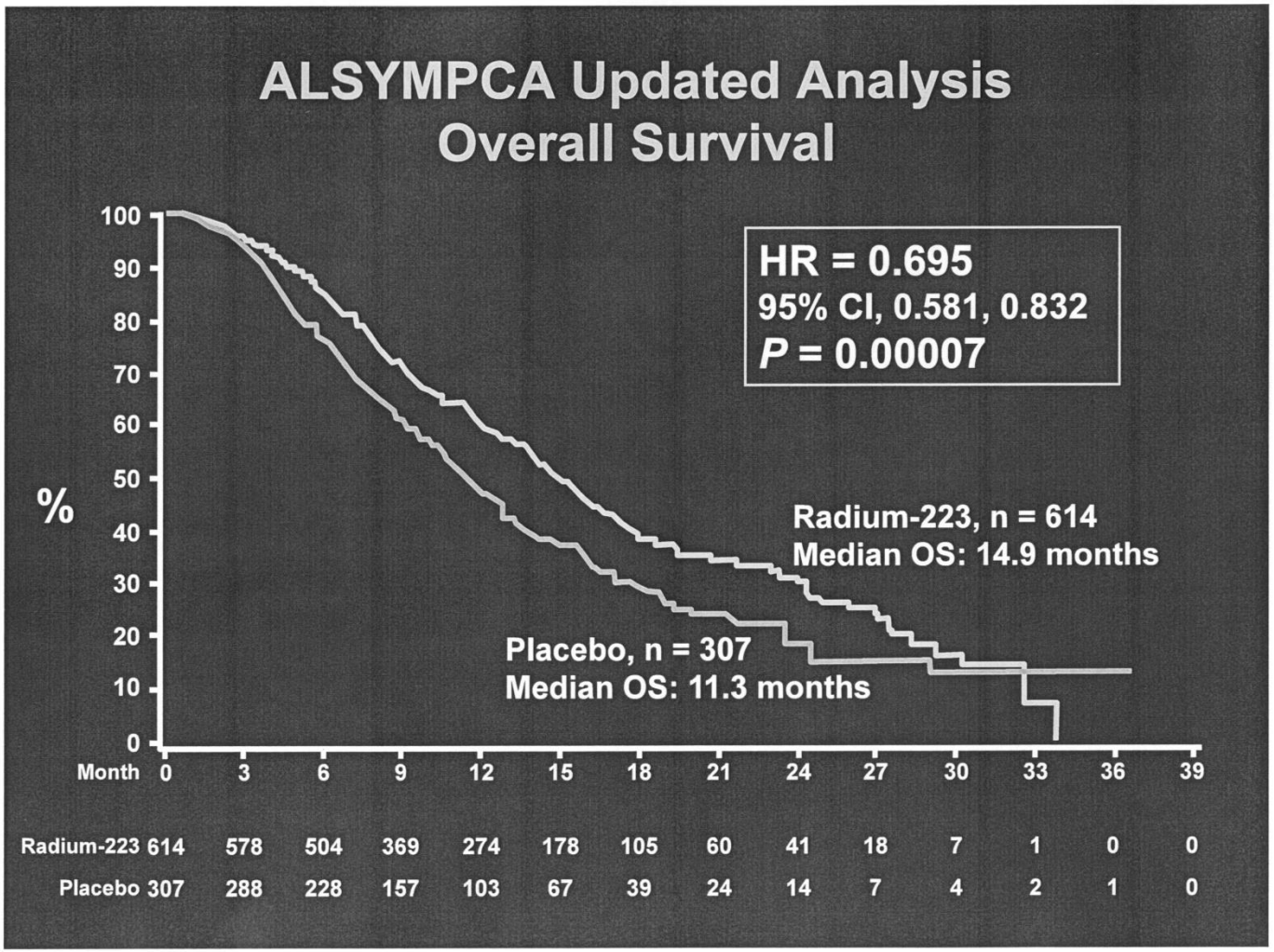
# Toxicity

## ALSYMPCA Updated Analysis Summary of Patients With Adverse Events: Safety Population*

| Patients With Adverse Events (AEs), n (%) | Radium-223 n = 600 | Placebo n = 301 |
|---|---|---|
| All grade AEs | 558 (93) | 290 (96) |
| Grade 3 or 4 AEs | 339 (57) | 188 (63) |
| Serious AEs (SAEs) | 281 (47) | 181 (60) |
| Discontinuation due to AEs | 99 (17) | 62 (21) |

*Safety population comprised patients who received at least 1 dose; 1 patient in the placebo group received one injection of Radium-223 (Week 0) and is included in the Radium-223 safety analysis.

# Does it work


ALSYMPCA Updated Analysis
Overall Survival
HR = 0.695
95% CI, 0.581, 0.832
P = 0.00007
Radium-223, n = 614
Median OS: 14.9 months
Placebo, n = 307
Median OS: 11.3 months
%
100
90
80
70
60
50
40
30
20
10
0
Month 0 3 6 9 12 15 18 21 24 27 30 33 36 39
Radium-223 614 578 504 369 274 178 105 60 41 18 7 1 0 0
Placebo 307 288 228 157 103 67 39 24 14 7 4 2 1 0

# Secondary end points

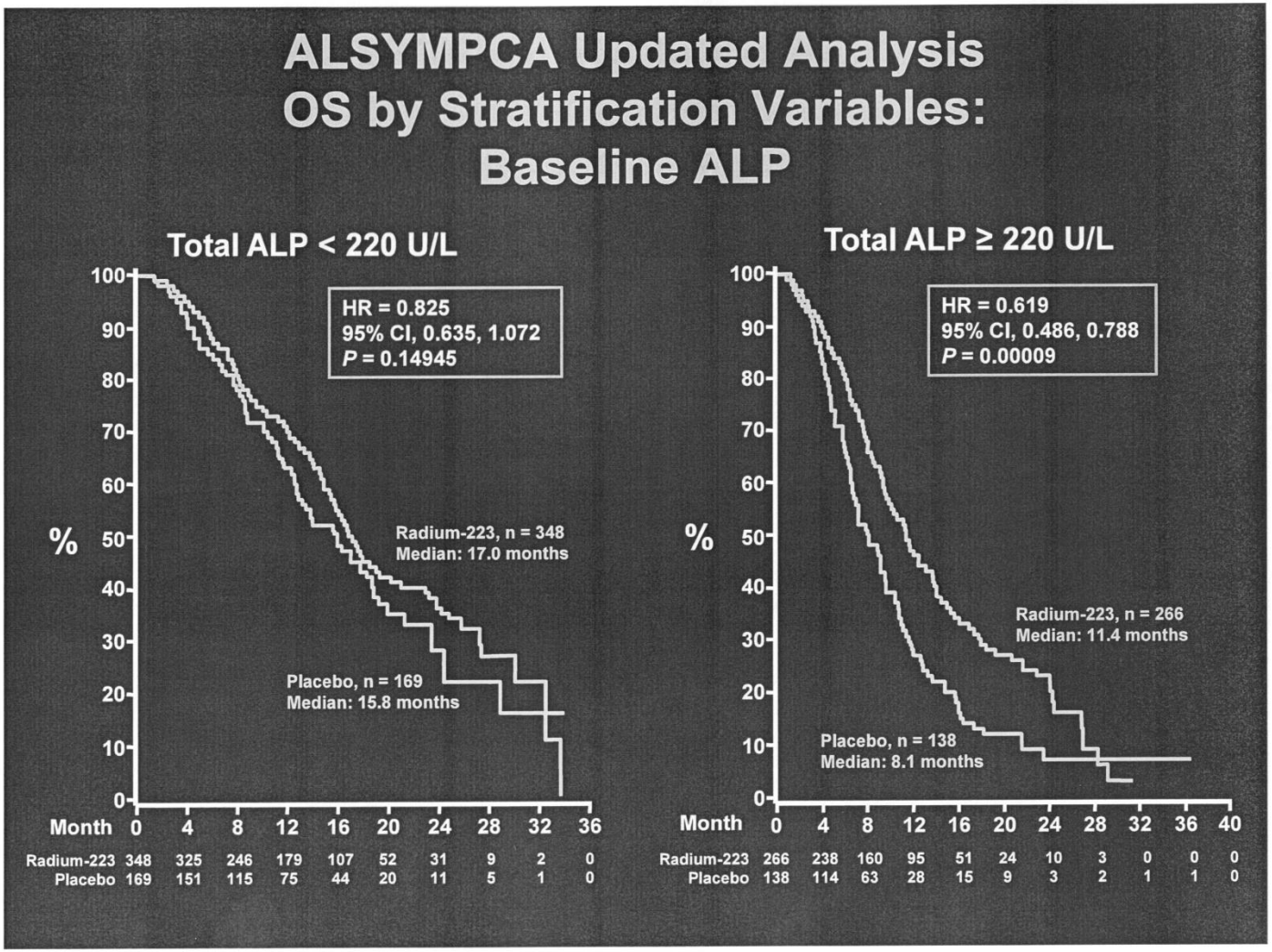
## ALSYMPCA Updated Analysis
## Secondary Endpoints: ALP and PSA

| | Hazard ratio 95% CI | *P* value |
|---|---|---|
| Time to Total ALP progression | 0.167 (0.129, 0.217) | <0.00001 |
| Time to PSA progression | 0.643 (0.539, 0.768) | <0.00001 |

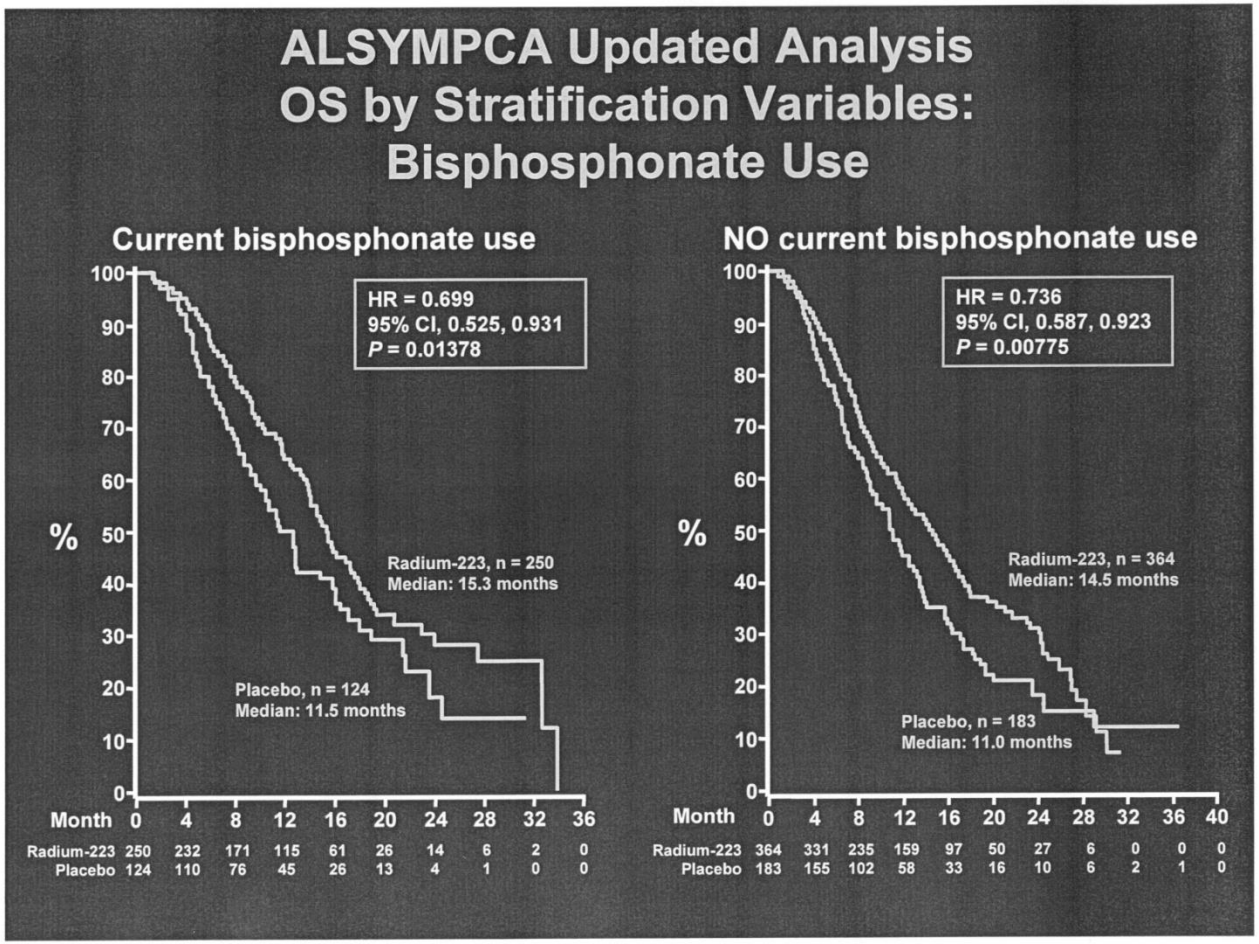
| | Radium-223 n (%) | Placebo n (%) | *P* value |
|---|---|---|---|
| Total ALP response | | | |
| 30% reduction | 233 (47) | 7 (3) | <0.001 |
| 50% reduction | 135 (27) | 2 (<1) | <0.001 |
| Total ALP normalization* | 109 (34) | 2 (1) | < 0.001 |

*In patients who had elevated total ALP at baseline.

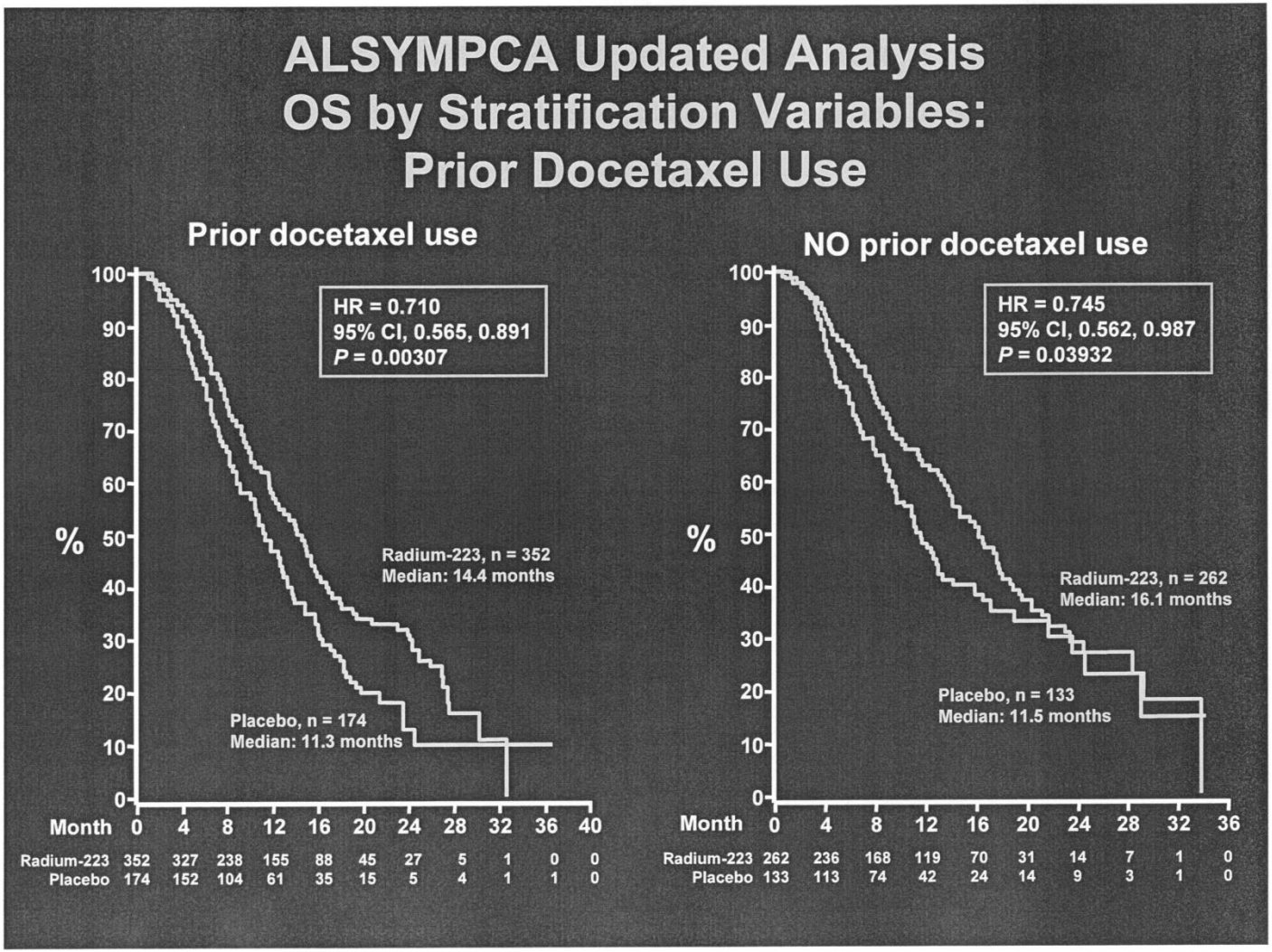
# Effect of extent of bone disease



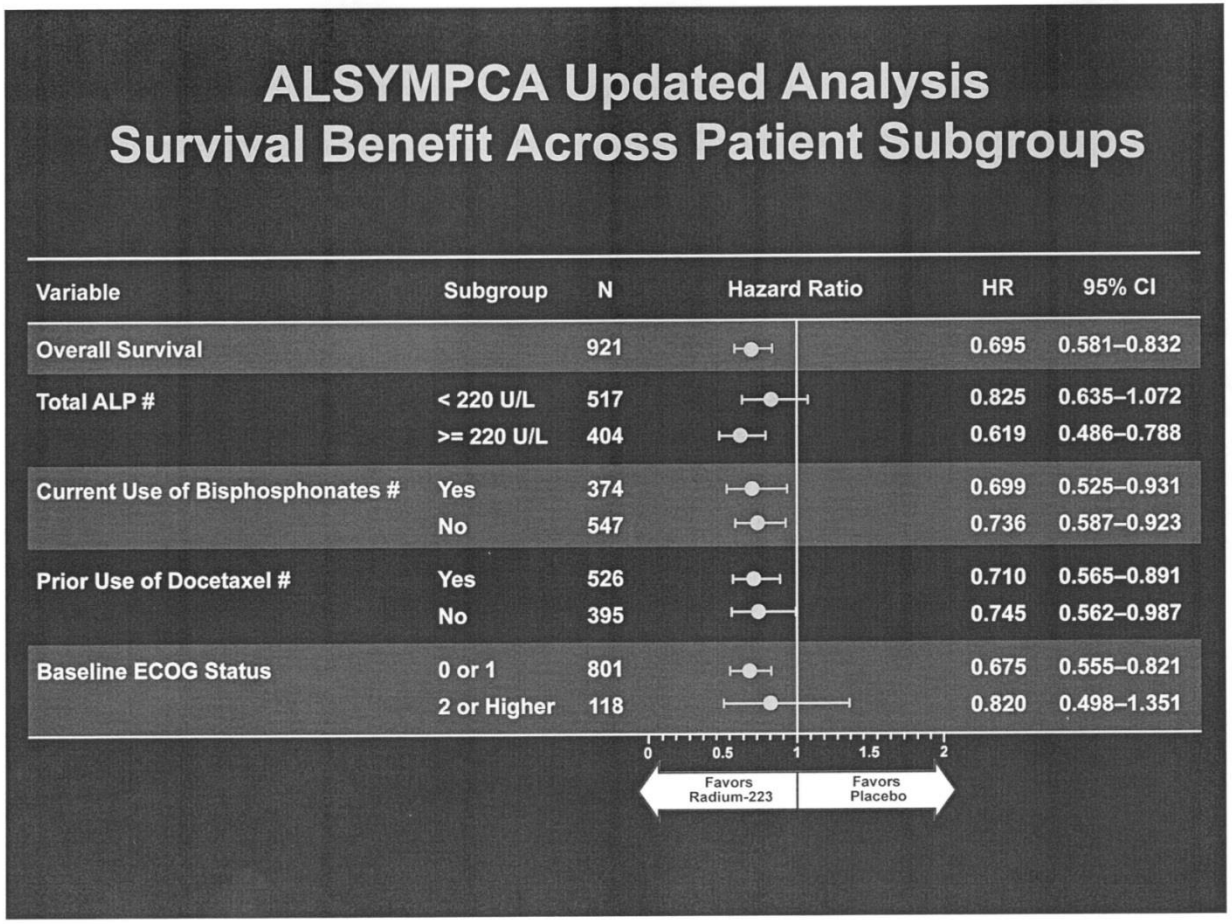
# Effect of previous treatment



# Effect of previous treatment



# Summary of results



# How does Ra-223 compare

## Overall Survival Benefit in Recent CRPC Trials

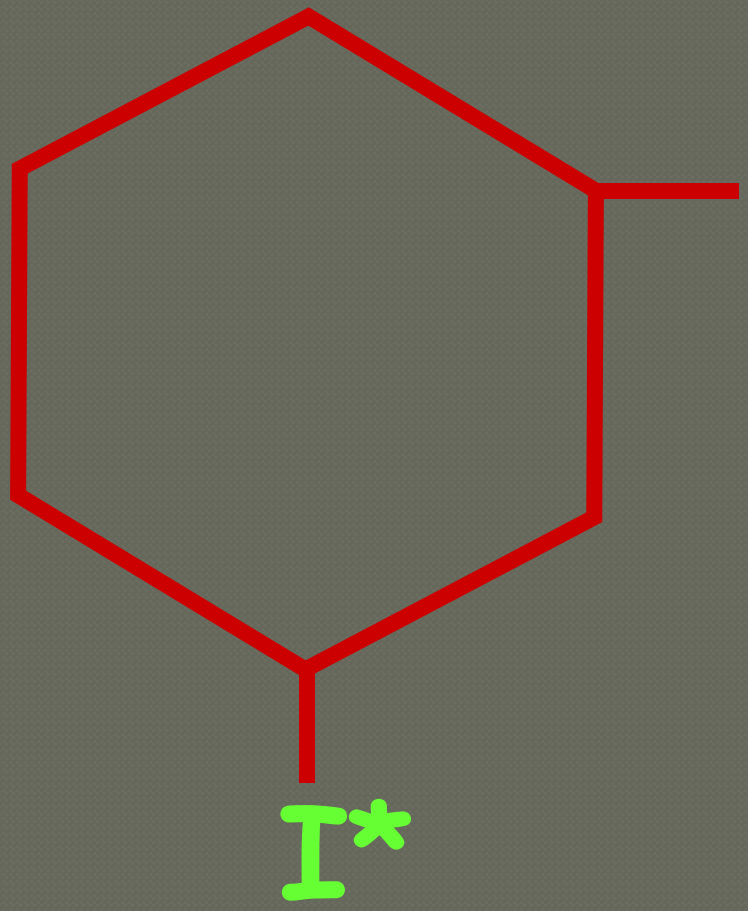
| Agent (trial, year) | Disease State | Comparator | Hazard Ratio | *P* value |
|---|---|---|---|---|
| Radium-223/Alpharadin (ALSYMPCA 2011) | Bone metastases CRPC | Placebo + best standard of care | 0.695 | 0.00185 |
| Docetaxel/Taxotere[1] (TAX327 2004) | Chemo-naive CRPC | Mitoxantrone Prednisone | 0.76 | 0.009 |
| Cabazitaxel/Jevtana[2] (TROPIC 2010) | Post-docetaxel CRPC | Mitoxantrone Prednisone | 0.70 | <0.0001 |
| Sipuleucel-T/Provenge[3] (IMPACT 2010) | Chemo-naive CRPC | Placebo | 0.775 | 0.032 |
| Abiraterone/Zytiga[4] (COU-AA-301 2010) | Post-docetaxel CRPC | Placebo Prednisone | 0.65 | <0.001 |


1. Tannock et al. *N Engl J Med.* 2004;351:1502-1512.
2. de Bono. *Lancet.* 2010;376:1147-1154.
3. Kantoff et al. *N Engl J Med.* 2010;363:411-422.
4. de Bono. *N Engl J Med.* 2011;364:1995-2005.

# Where now

- Phase 1-3 cost over US$ 30 million
- Drug presented to EMA and FDA for licensing
- Will go on sale in 2013
- To re-coup costs price may be high estimated US$ 10,000 per 6 cycles
- However cost not much different from Abiratarone

# meta-iodobenzylguanidine




* $^{123}I$
$^{131}I$

# 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

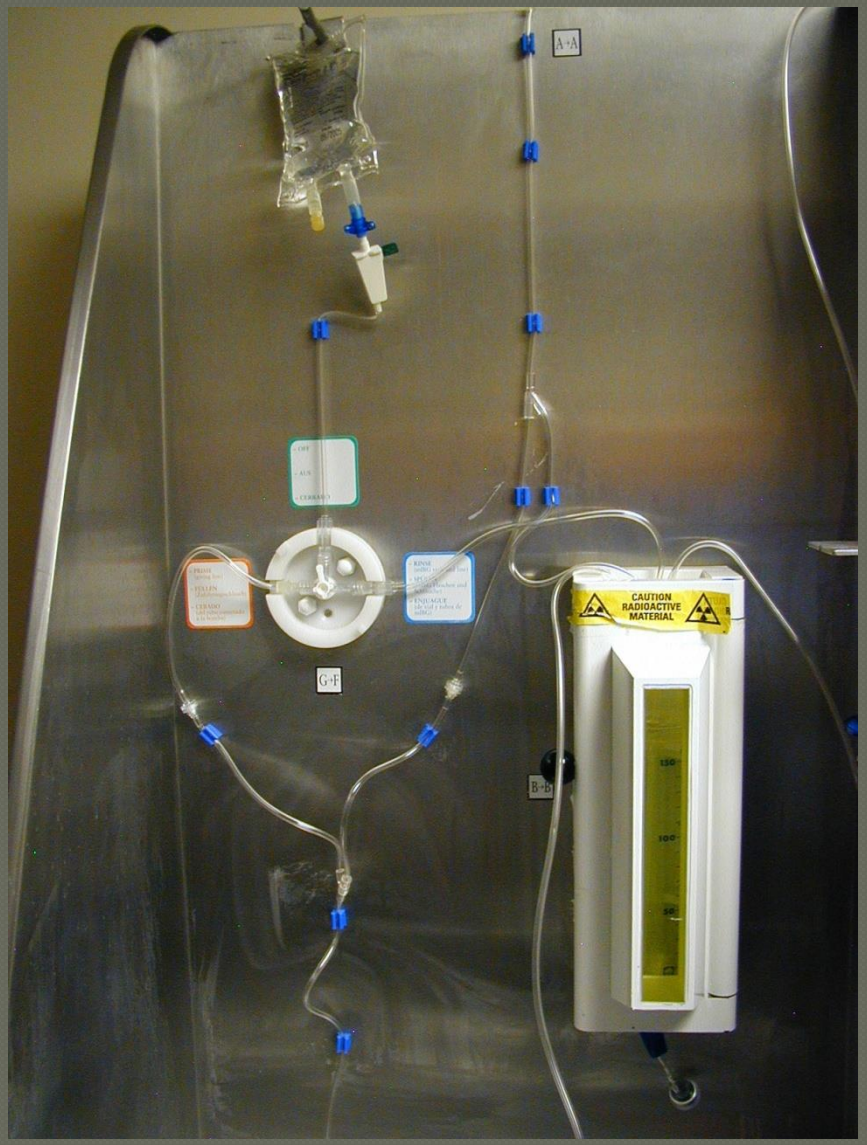
And a peadiatric burette

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

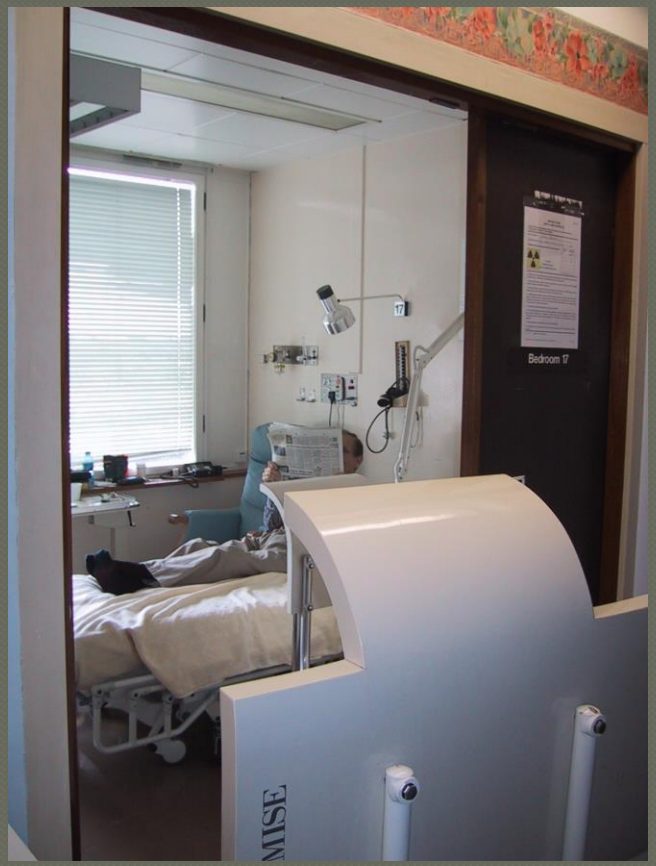
Can use isolated side room with mobile shields

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 |

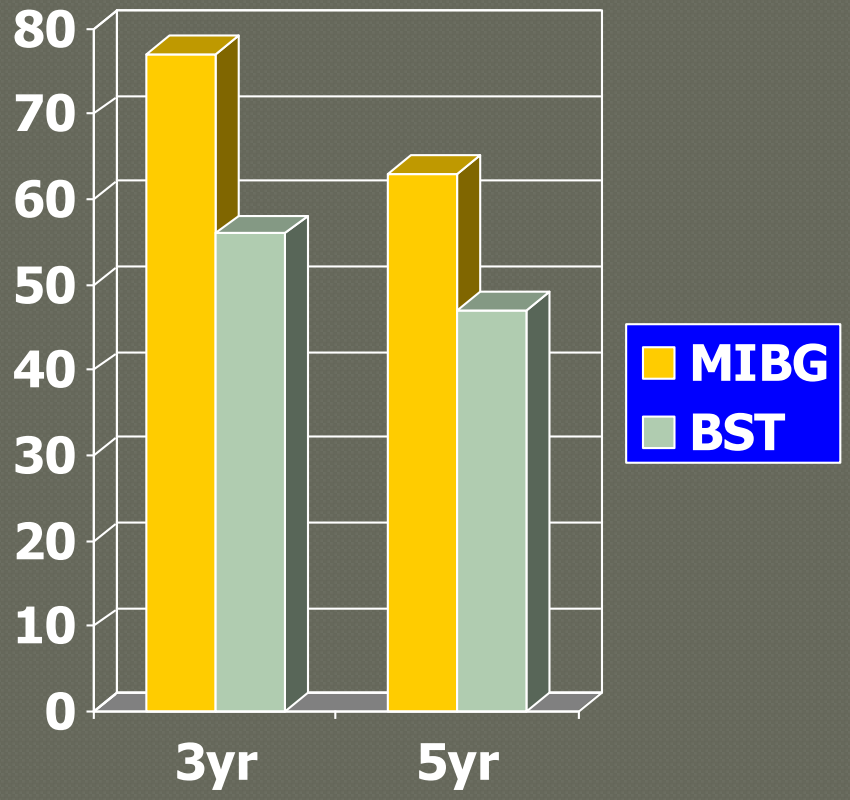
# mIBG – carcinoid-EANM survey

**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

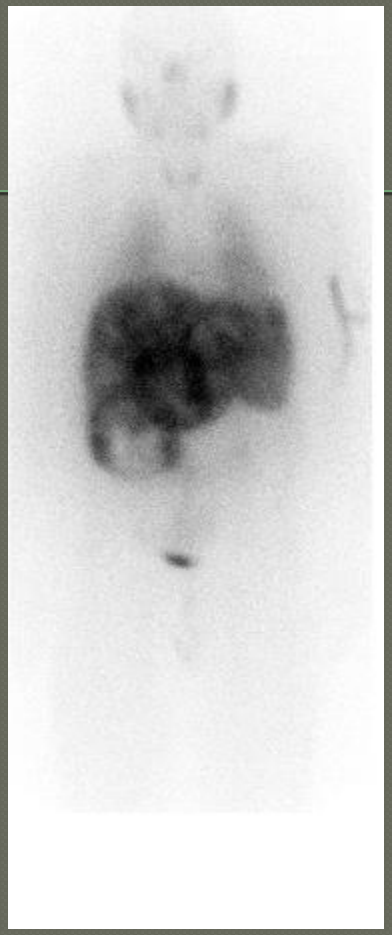
- Syweck et al WJS 2004 compared 2 centres-58 patients at each
  - 1 MIBG
  - 1 without MIBG
- % Survival noted at
  - 3 yr
  - 5 yr



# Results from other centres

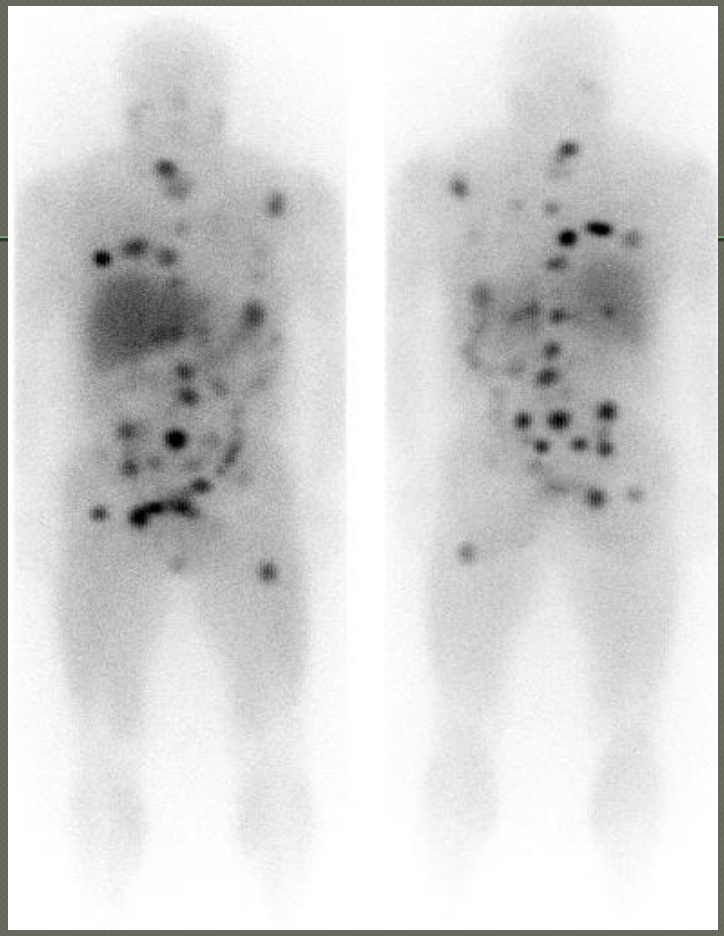
- Safford et al Cancer 2004
- 98 patients
- Median survival 24 months
- If had symptom relief with reduced flushing etc median survival 57 months
- Radiological response not predictor of survival
- Best if 15Gbq given in 2-3 doses

# 131I-MIBG therapy



Post therapy Whole body 131I-MIBG scan shows good accumulation of tracer in the

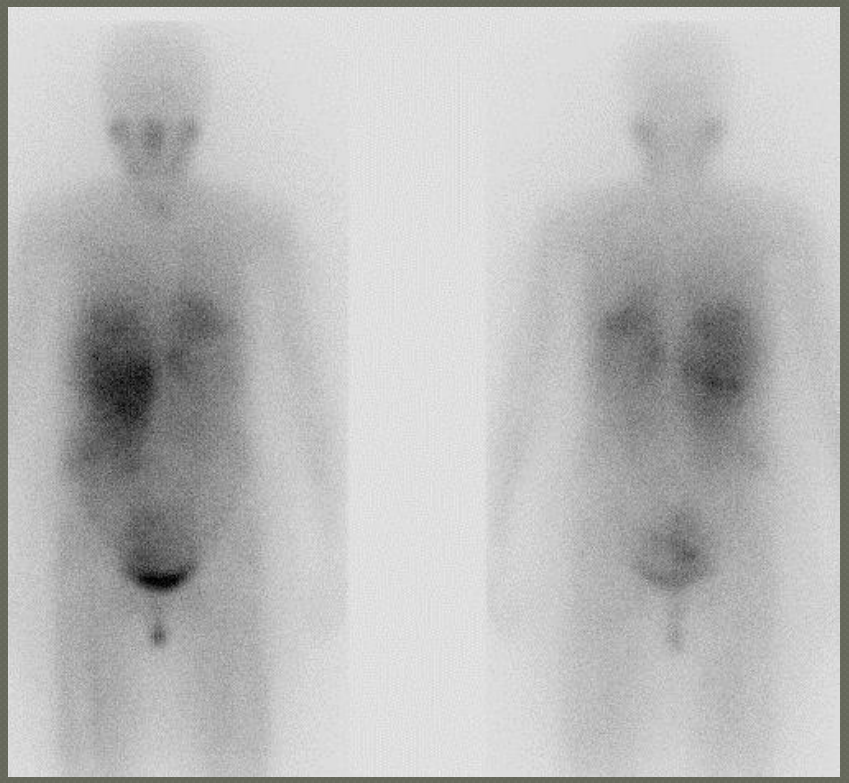
known liver metastases

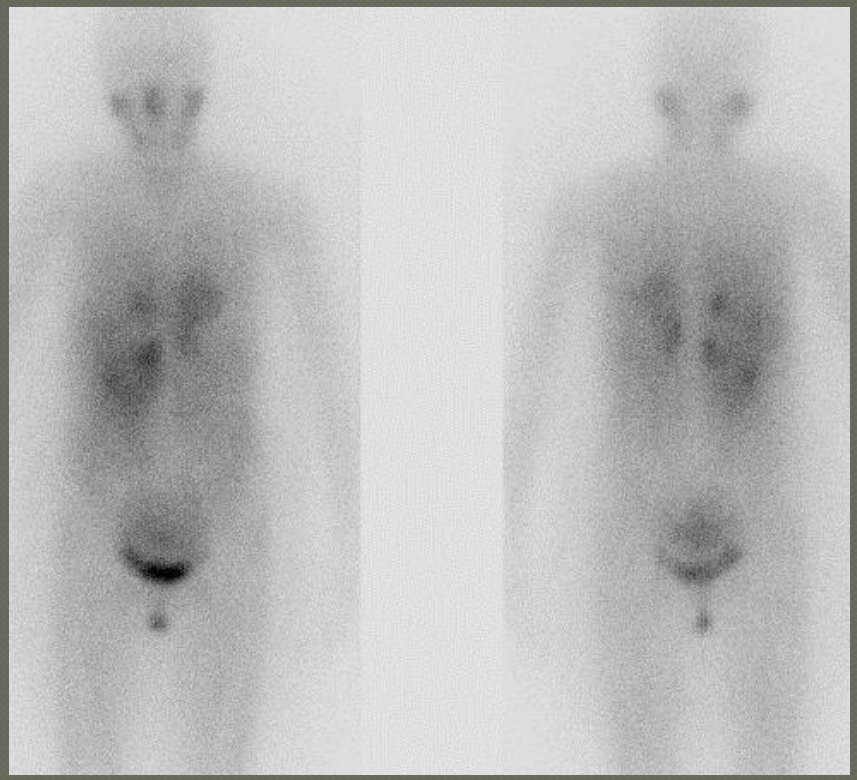


Post therapy whole body images shows multiple areas of MIBG accumulation in the neck, left shoulder, thoracic spine, lumbar spine, liver, pelvis, right hip and left upper femur consistent with therapeutic uptake in wide spread bone and soft tissue metastases

**G Gnanasegaran et al**

# Response to therapy-gastrinoma

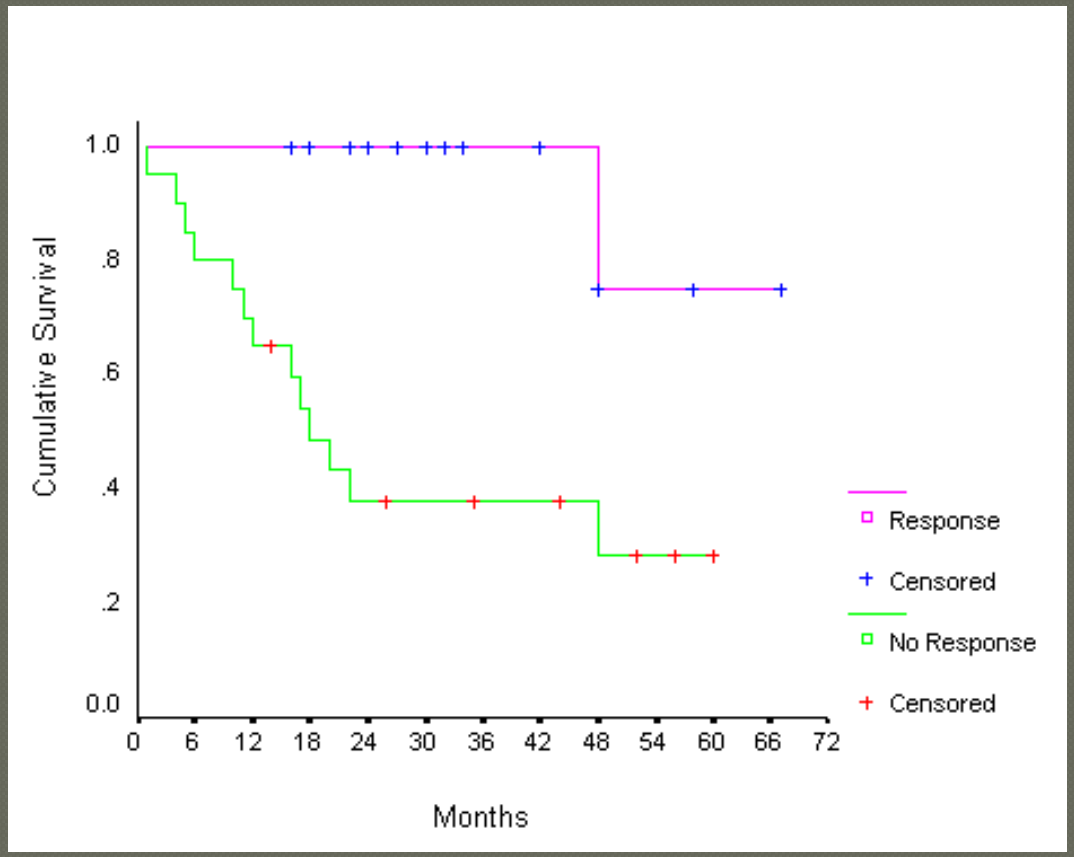




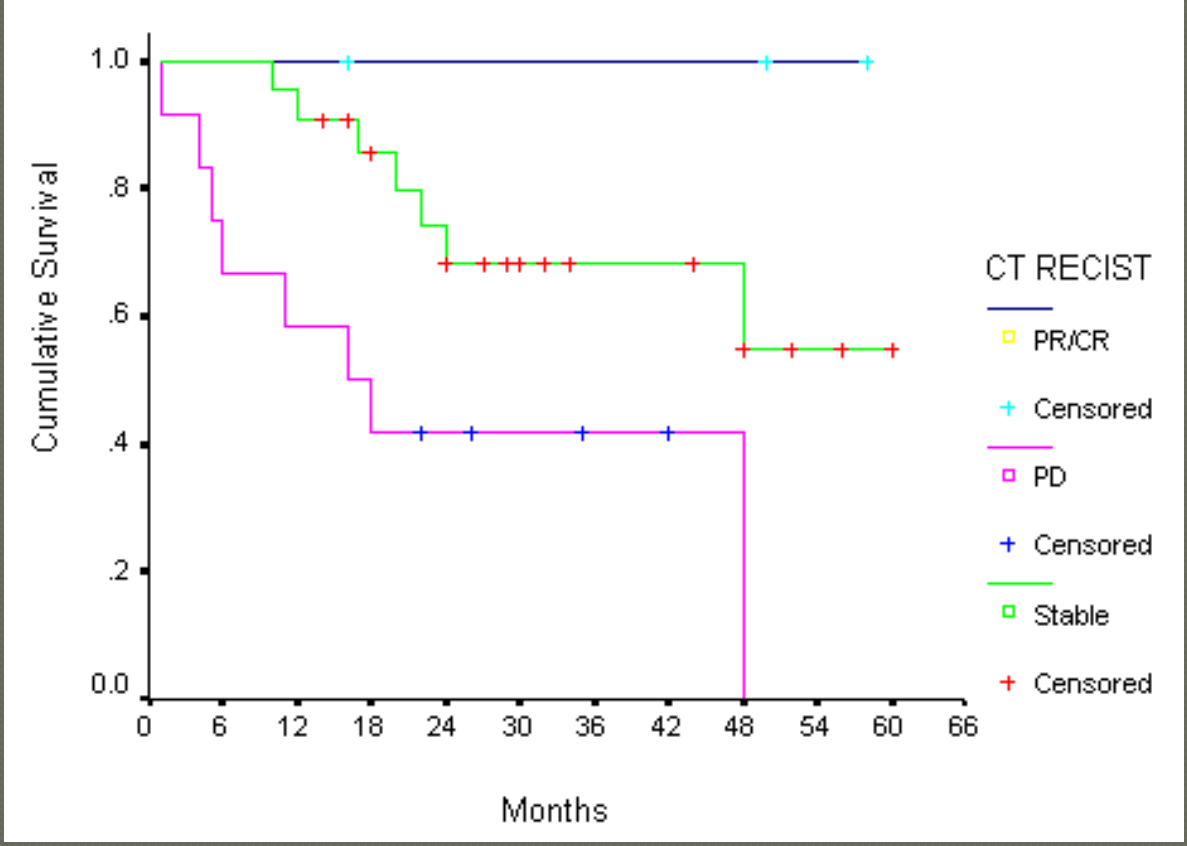
# Does CT change or symptom relief help predict survival

- RFH, review of 38 patient – completed 3x5.5GBq I-131 mIBG therapy
- All with minimum of 12 months follow-up
- Looked at PFS and OS compared to
  - CT changes
  - Symptom response

# Overall survival related to symptom response



# Overall survival related to change on CT



# Meta-analysis of MIBG therapy in NETs Navilkissoor

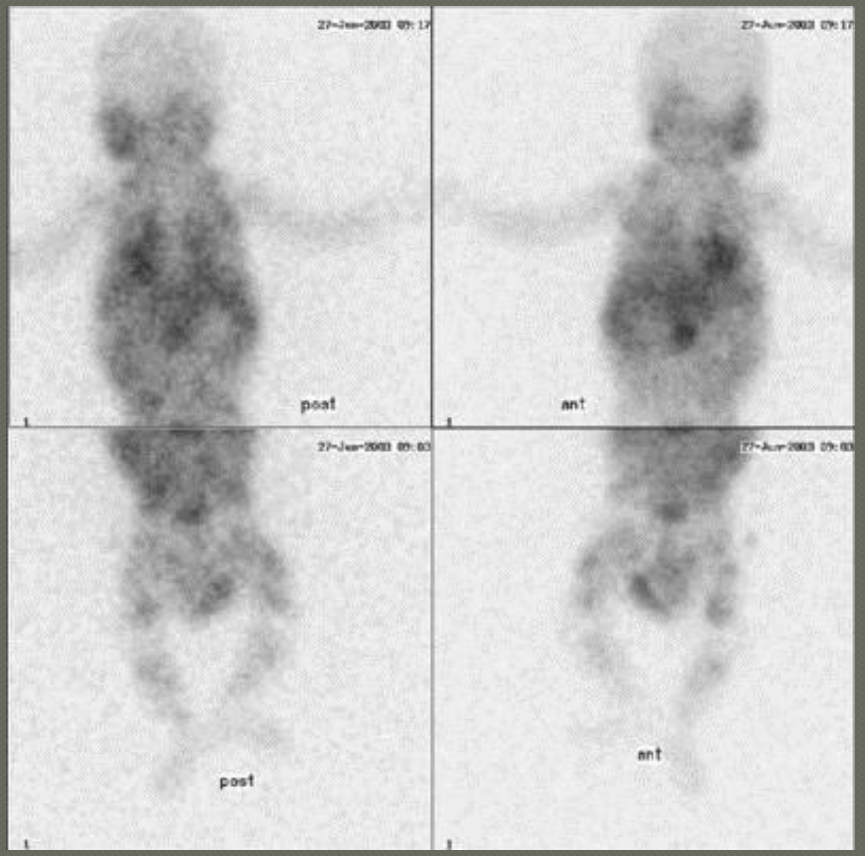
| First Author | CT Responders | CT Stable | Biochemical Responders | Symptomatic Responders | Median Overall Survival (months) | 5year survival |
|---|---|---|---|---|---|---|
| Gonias | 12/45 | 24/45 | 24/34 | n/a | - | 64% |
| Gedik | 8/17 | 6/17 | 8/12 | 16/18 | 42 | n/a |
| Nwosu | 11/40 | n/a | 11/29 | 27/48 | 46 | |
| Buscombe | 9/24 | 8/24 | n/a | n/a | - | n/a |
| Sywak | n/a | n/a | n/a | n/a | - | 63% |
| Safford | 10/75 | n/a | 15/52 | 35/72 | 28 | 22% |
| Bomanji | 12/25 | n/a | 14/25 | 20/25 | 17 | |
| Safford | 8/22 | n/a | 12/20 | 19/22 | 56 | |
| Castellani | 5/16 | 9/16 | n/a | n/a | - | |
| Fischer | n/a | n/a | n/a | n/a | - | |
| Krempf | 5/15 | n/a | 7/15 | n/a | - | |
| Shapiro | 8/28 | n/a | 12/28 | n/a | - | |
| Navalkissoor | 3/37 | 22/37 | 3/20 | 15/34 | 48 | 33% |
| **Total** | 91/344 (26%) | 69/129 (53%) | 106/235 (45%) | 132/219 (60%) | 46 | 41% |

# 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

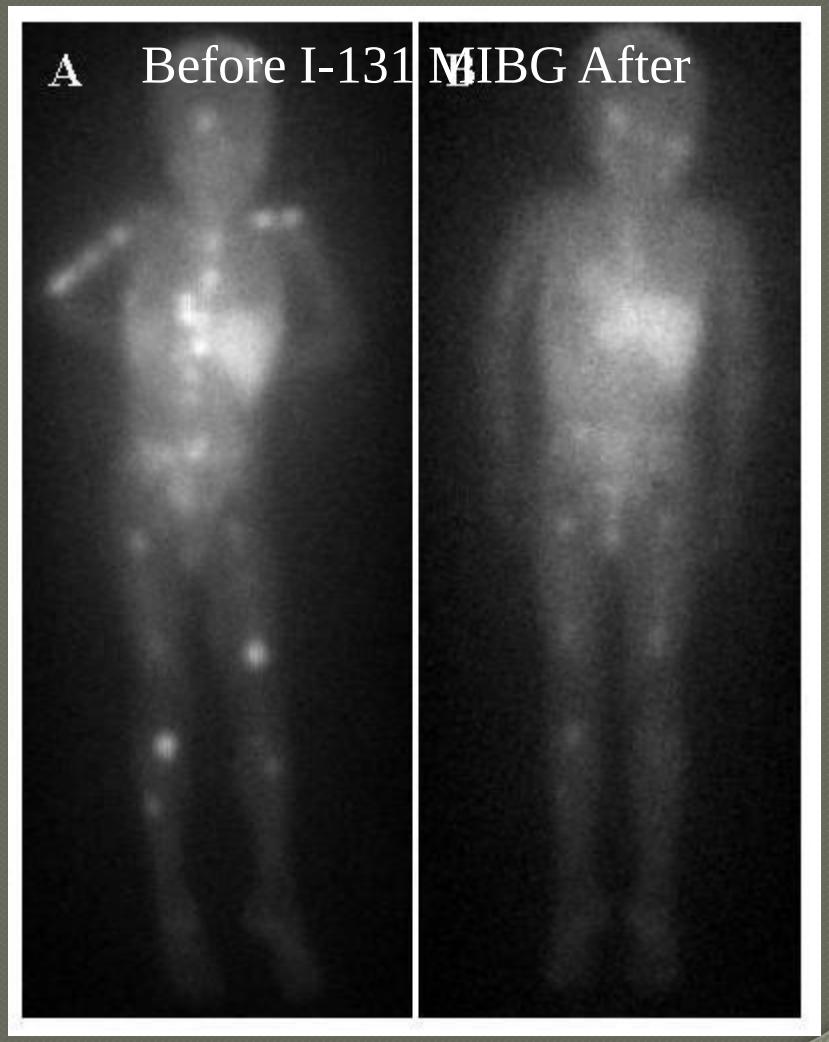


# Treatment

- 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

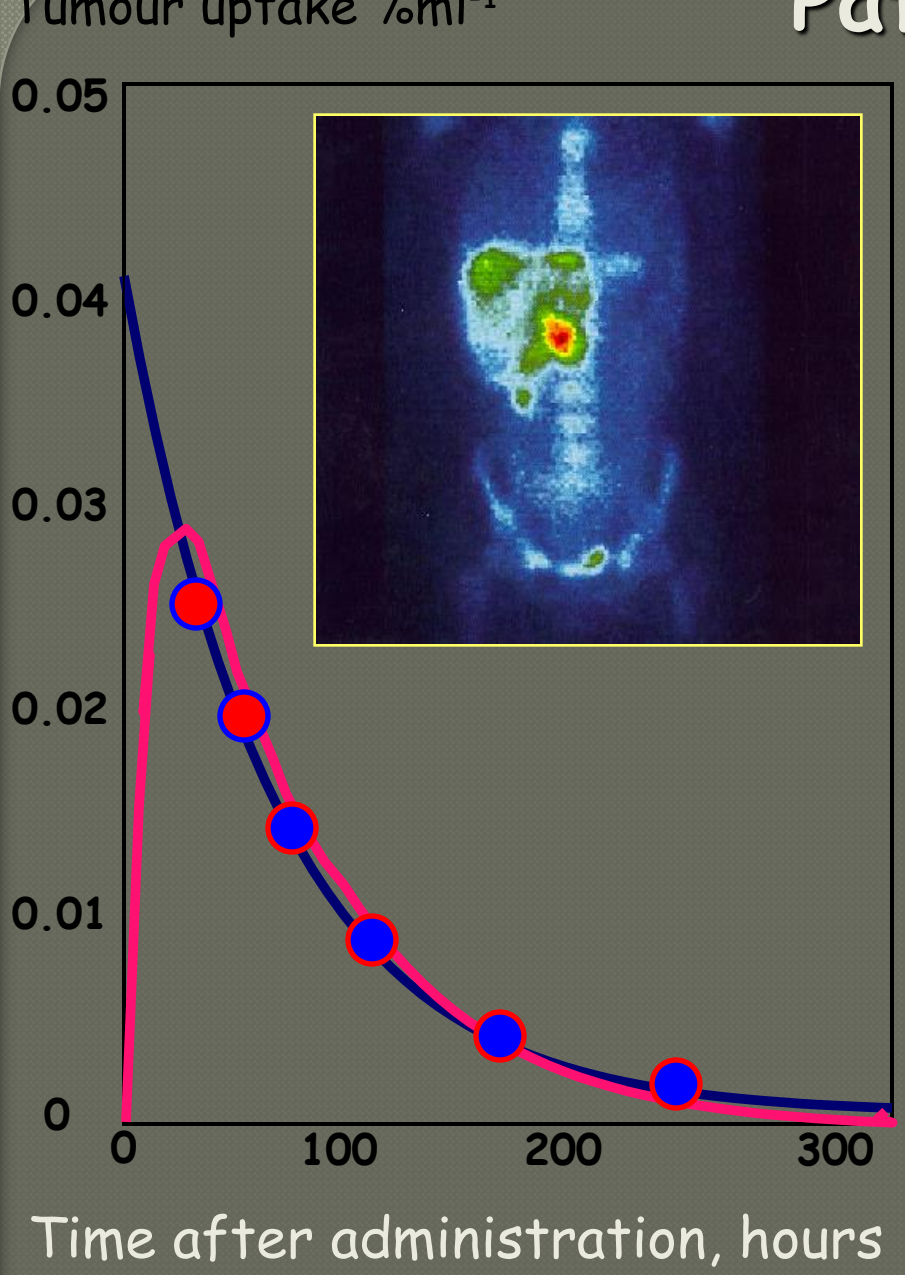
- Garaventa et al BJC 1999
- Activity based on wt 2.7GBq if <20kg, 5.5GBq if >20kg
- Of 43 patients 1xCR 12xPR, 25xDS, 6xPD
- For stage 2 few deaths, stage 4 median OS 19months



# What about dosimetry

- Approach developed by Flux et al at RMH
- Calculate how much MIBG to give for a 2Gy therapy to the patient using tracer dose and 3D dosimetry
- Activity that is required 1.8GBq to 32GBq
- This keeps toxicity down but how to give 32GBq volume problems administration issues (3BGq/hr) pharmacological issues
  - Fractionate – no evidence
  - Use carrier free- data emerging

# Patient specific dosimetry

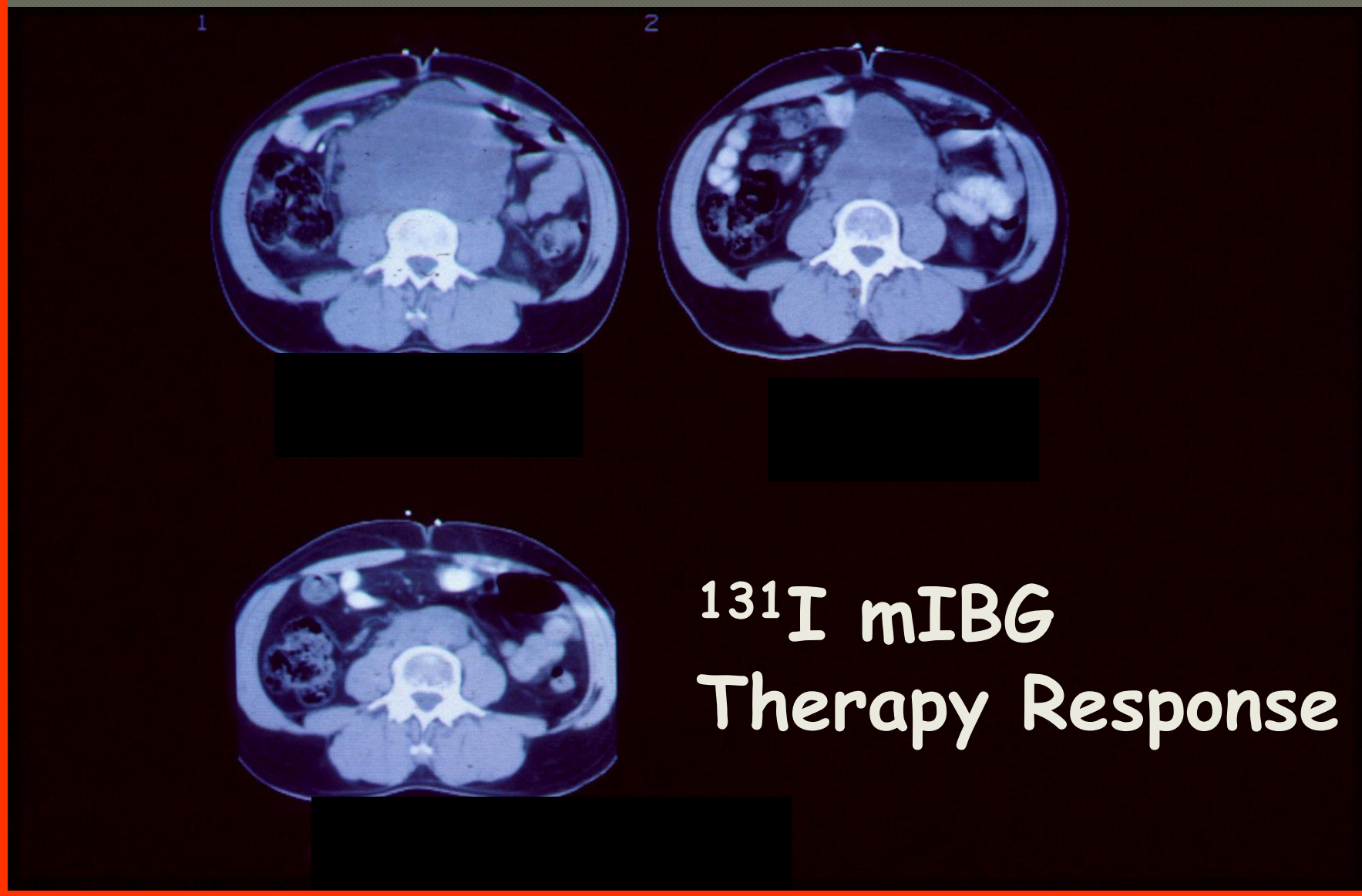



- tracer data
- post-therapy data

**Biokinetics:** T1/2 eff

**volume:** CT/MRI

**SPECT:** uptake/ml/MBq

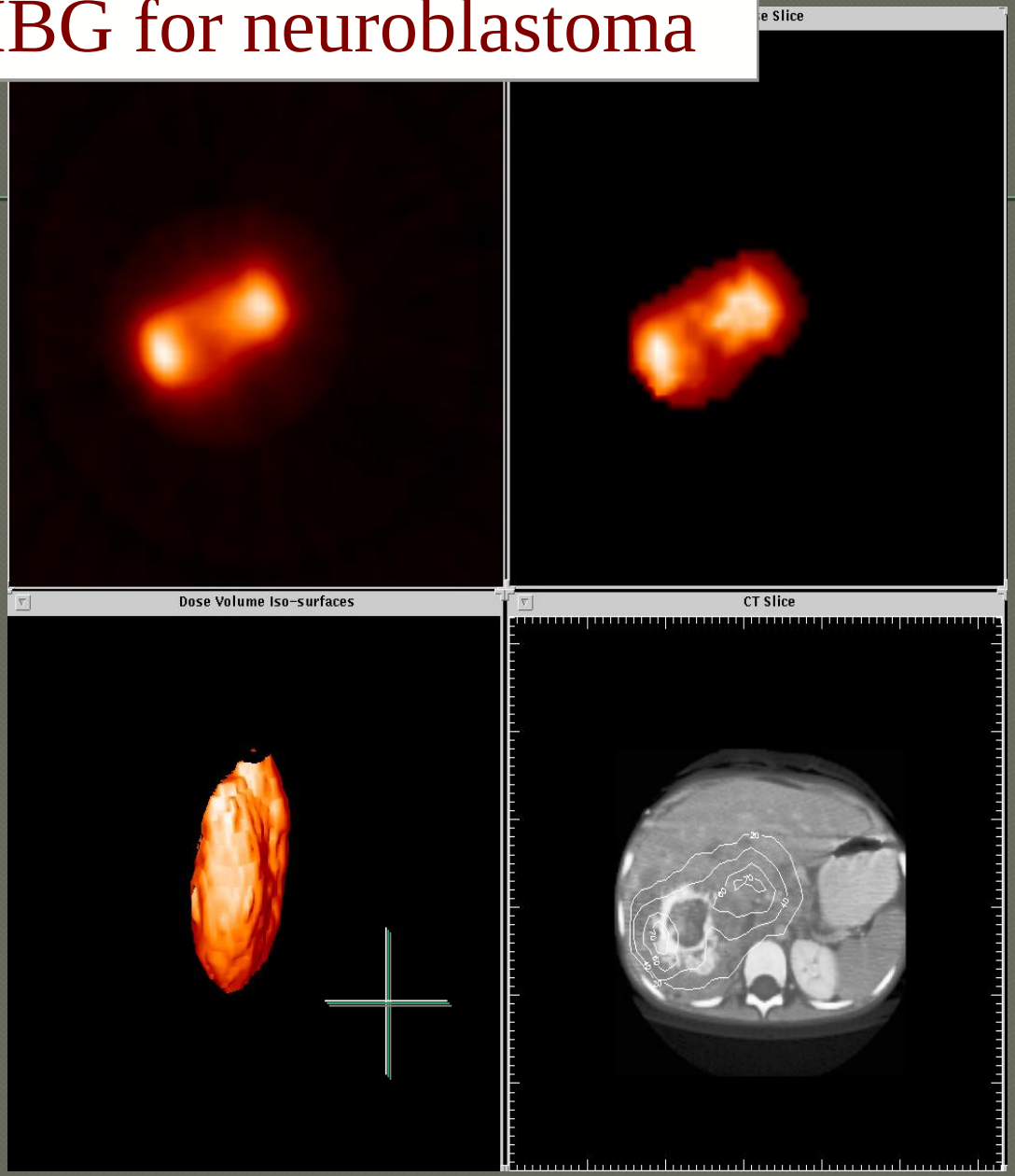



# $^{131}$I mIBG Therapy Response

# I-131 mIBG for neuroblastoma

I-131 SPECT

Absorbed dose




Dose (rendered)

CT + isodose contours

# Radiopeptides

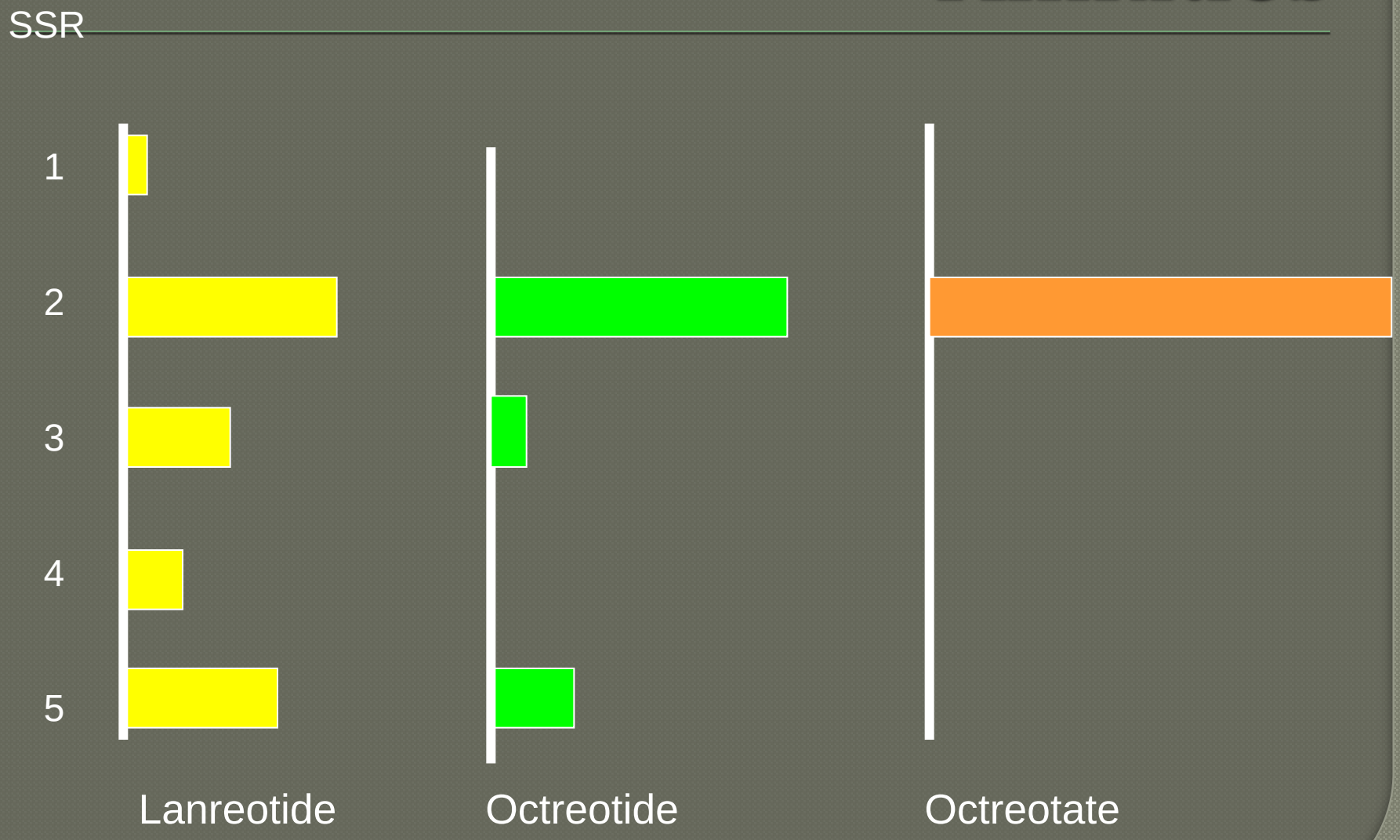
- Based on somatostatin system
- Peptides converted form commercial sources:
  - Lanreotide
  - Octreotide
  - Octreotate
- Normally DOTA linker
- Isotopes In-111, Y-90, Lu-177

# It is all getting complex

- RADIOISOTOPES
- In-111
- Y-90
- Lu-177
- Re-188

- PEPTIDES
- Octreotide
- Lanreotide
- Depreotide
- Octreotate
- OctreoNOC

# Affinities



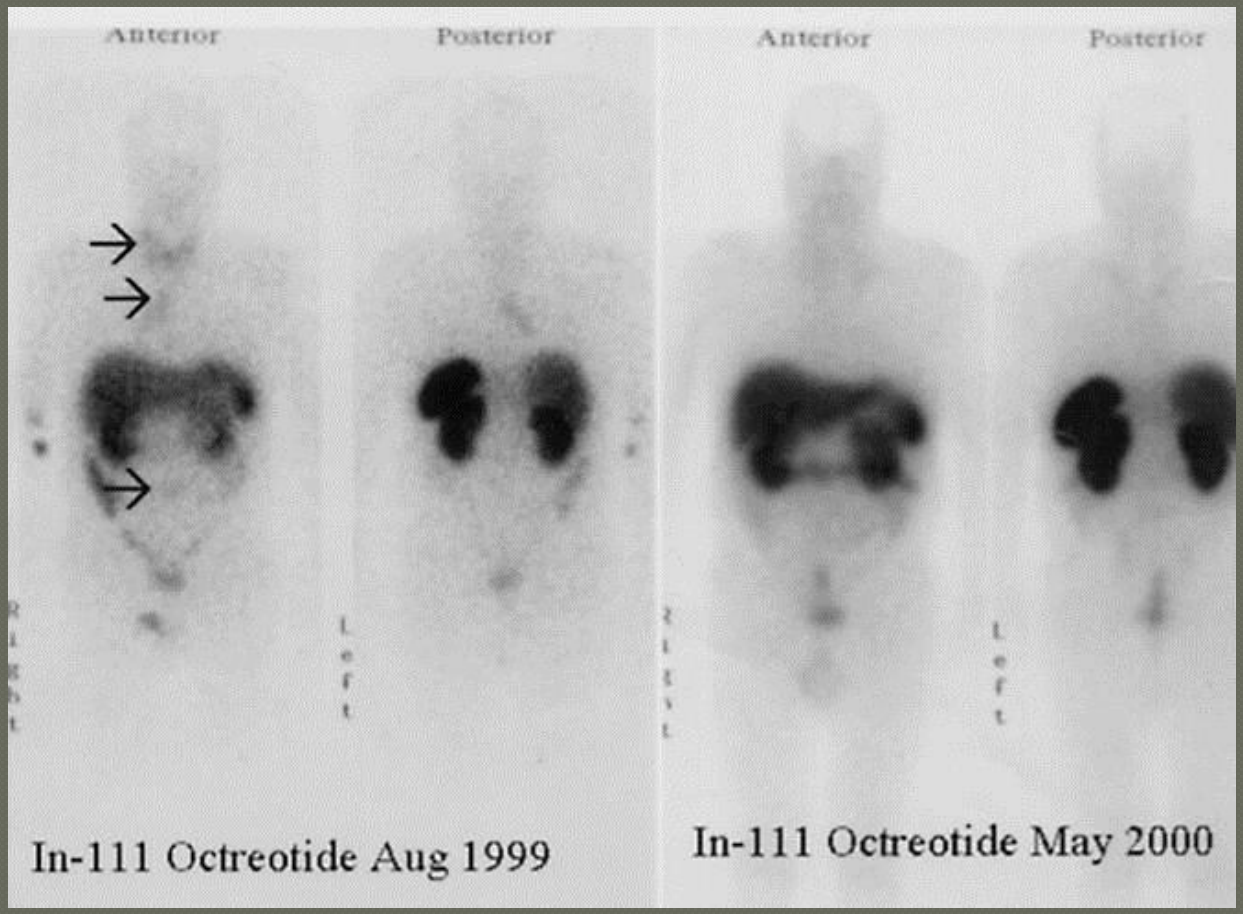
# High activity In-111 oct

- Based on Auger electron of In-111
- Penetration 1-2 cells
- Fortunately localises within cell
- Up to 7GBq can be given
- After 35GBq some bone marrow toxicity noted
- Expensive

# Results

- Main groups reported
- Krenning over 100 patients
- RFH 18 patients
- Lowe, Louisiana 24 patients
- About 15% CR/PR
- 60% symptom relief especially carcinoid
- Minimal toxicity under 35GBq cumulative activity

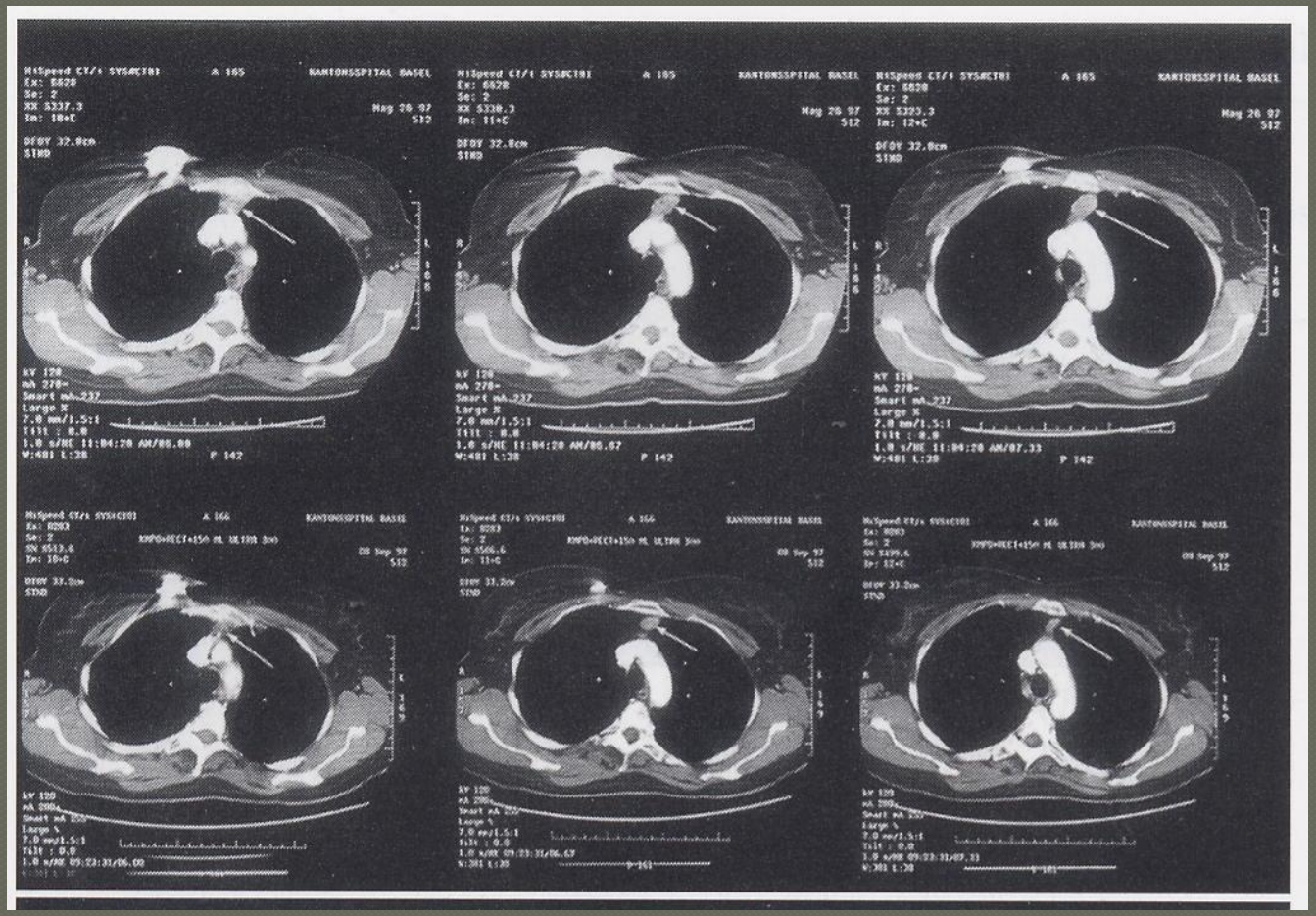
# Patient with MCT



# Y-90 DOTATOC first results Otte et al EJNM 1999; 26; 1439

- Results of first 29 patients who had received 4 or more cycles of >4 GBq of Y-90 DOTATOC
- Toxicity at cumulative doses of approx 15GBq in 5 pts
- Stability in 20 pts, PR 6 Prog in 3
- 10 patients marked improvement in pain
- Now extended to >200 patients

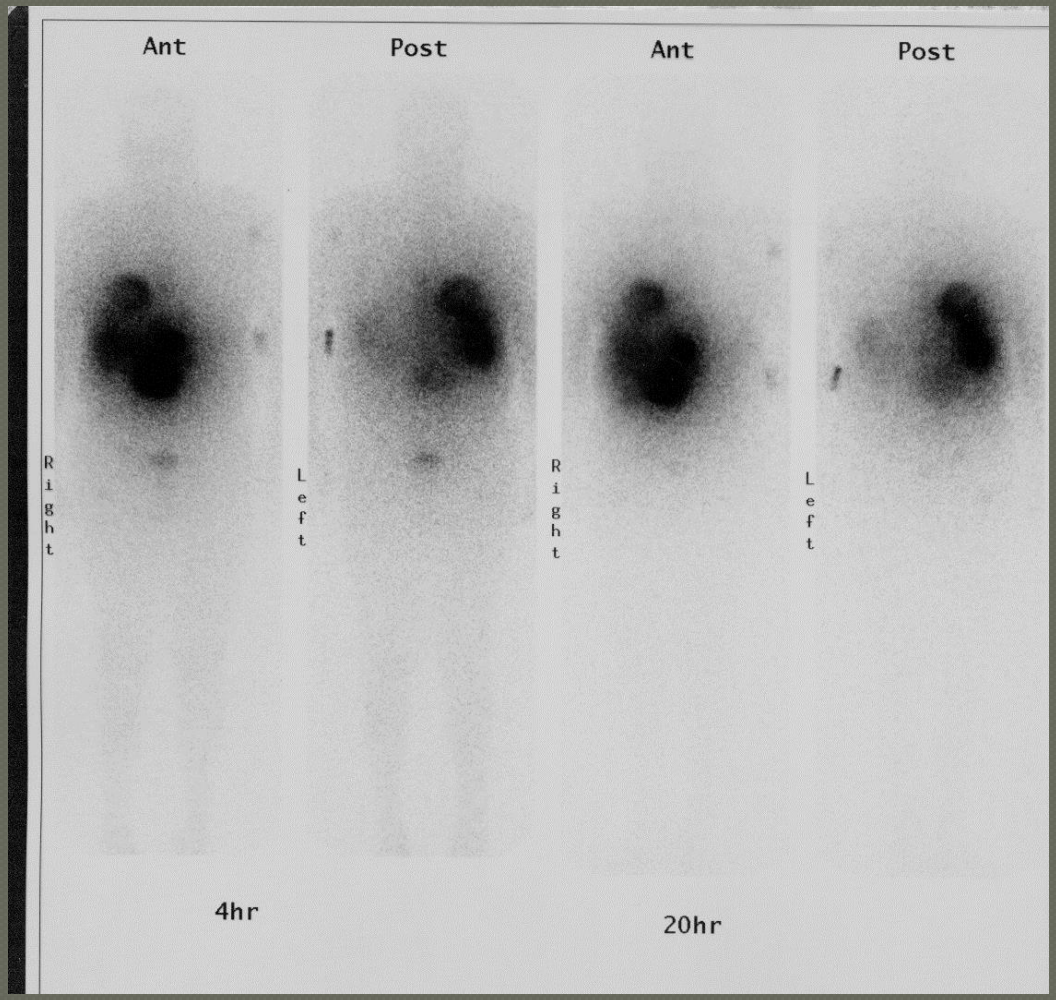
# Response to Y-90 Octreotide Otte et al EJNM 1999



# Y-90 SMT 487

- Phase II study completed
- Noted little renal toxicity under 4.4 GBq given in 3 cycles
- Use of amino acids to protect kidney with at least 10g lysine/cystine
- Use In-111 product or Y-86 DOTATOC for dosimetry
- Over 160 patients in 10 countries studied
- Better results if less tumour present
- Worked better in foregut tumours

# Insulinoma 4.4 GBq with aa



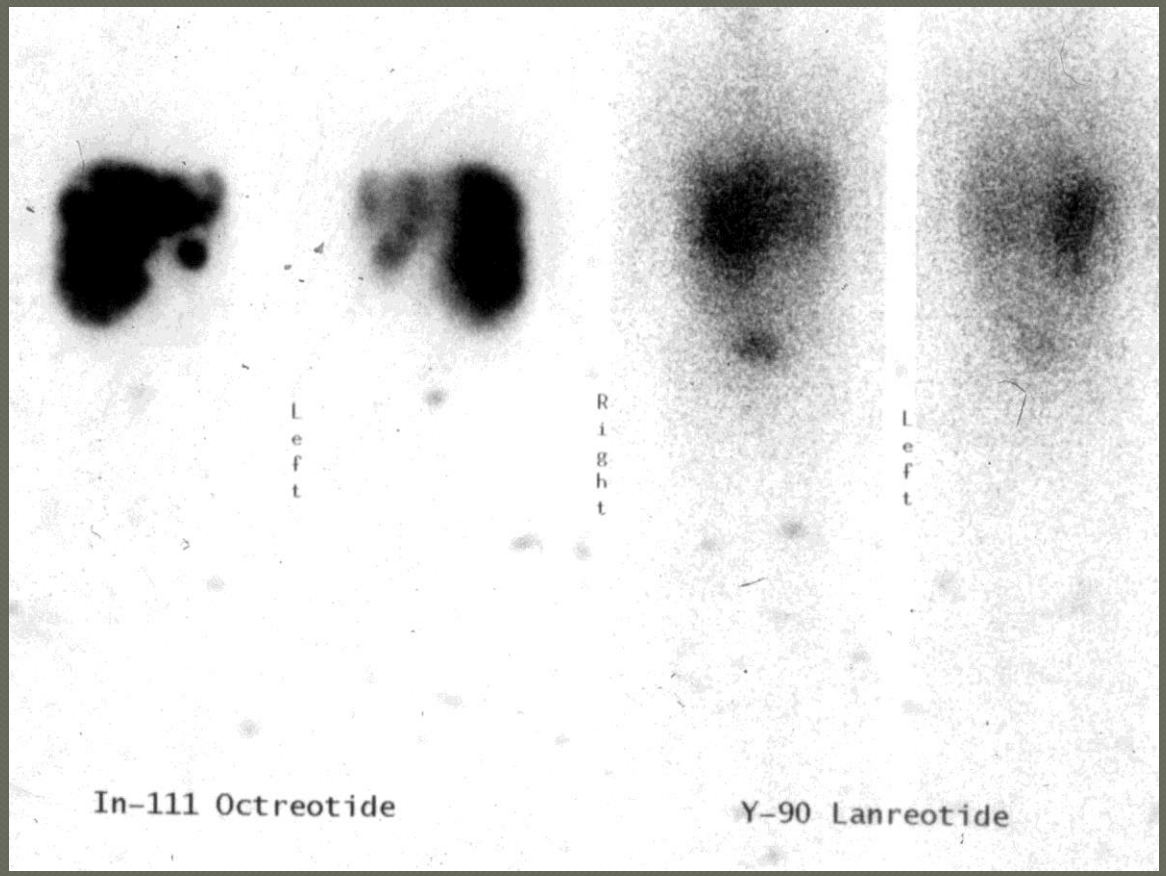
# Use of Y-86 octreotide Jamar et al 2003 EJNMMI

- 24 patients studied
- Look at Y-86 PET as predictor of Y-90
- Aim to look at renal toxicity and tumour dosimetry
- PET 4-48 hours pi MIRD3
- Use of amino acids reduced renal dose form 4.4mGy/MBq-1.7mGy/MBq
- Therefore to stay under 23Gy limit max 12GBq to be given
- Tumour dose variable 0.4-16mGy/MBq not affected by amino acids and not related to tumour response

# Y-90 Lanreotide

- Patients selected if:
  - SSR positive tumour on In-111 Octreotide
  - Uptake in lesions greater than normal liver (Krenning grade 3&4)
  - No other treatment successful or appropriate
  - Symptomatic or growing disease
  - Consent to experimental nature of treatment

# Biodistribution of In-111 Octreotide and Y-90 Lanreotide

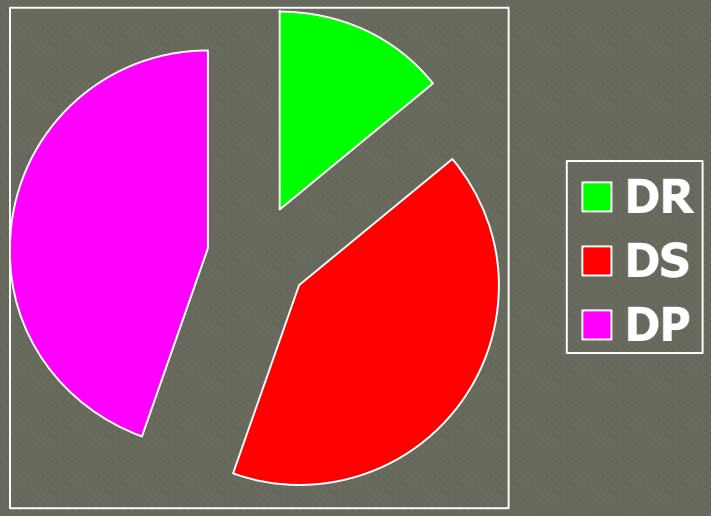


# Y-90 Lanreotide

- Lanreotide additional tyrosine increase biding to SSR 5
- 154 patients in multi-centre trial
- 3 cycles of 1 GBq of Y-90 lanreotide
- Repeated one if some response
- 54% have sustained response
- Tumour shrinkage in 14%

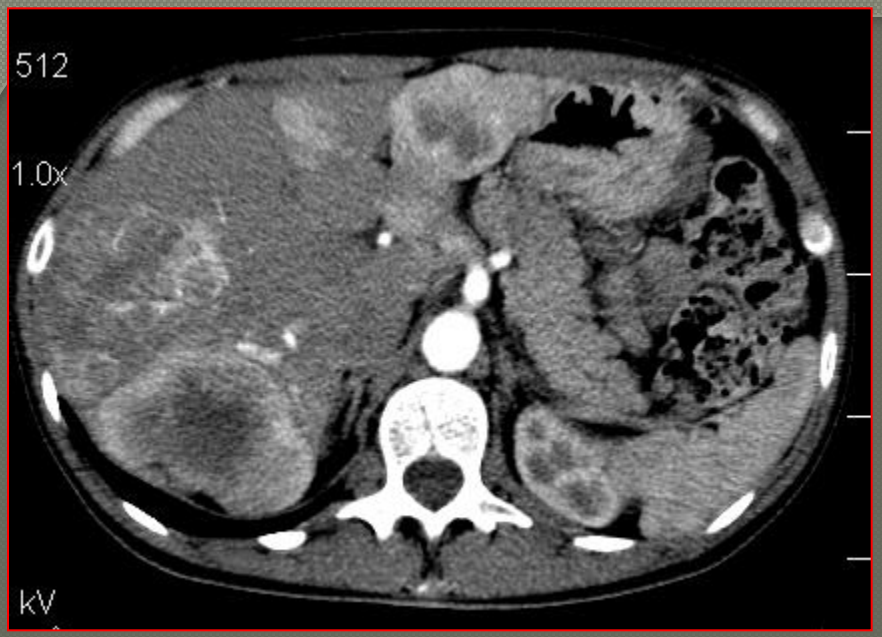
# Results of Lanreotide multi-centre trial (n=154)

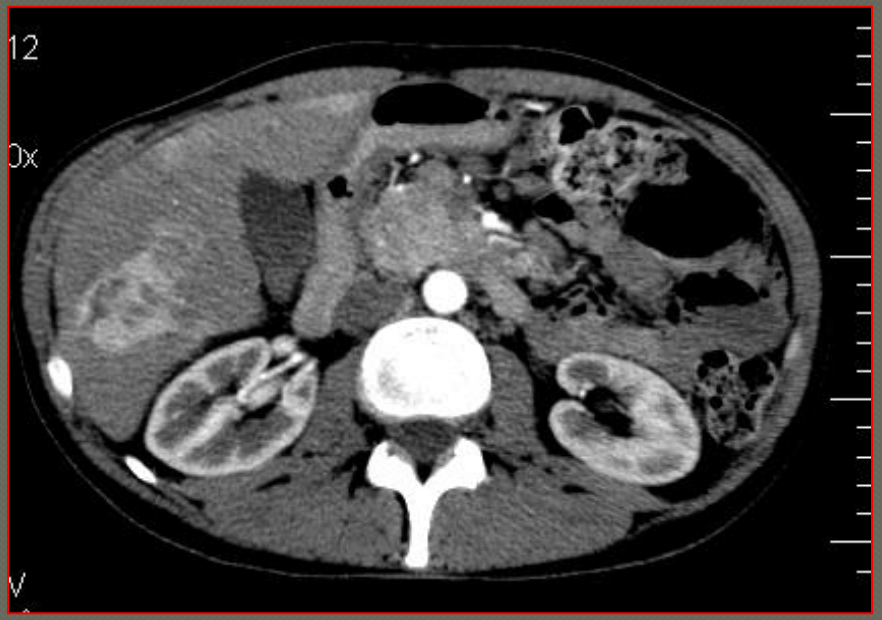
- Patients from UK, Switzerland, Austria and Italy
- All responses by SWOG criteria
- Also 17 patients had improved QALY

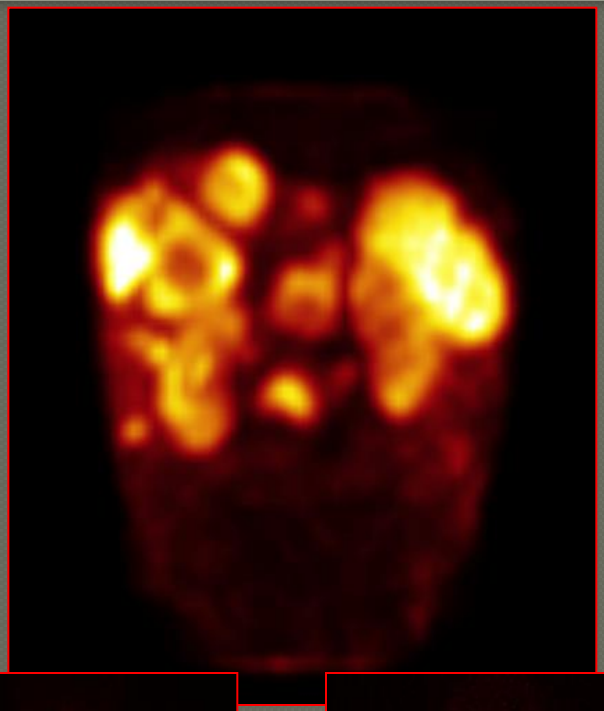


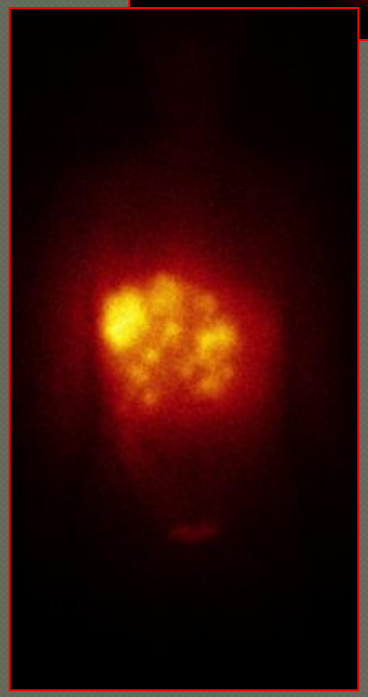
# Y-90 octreotate

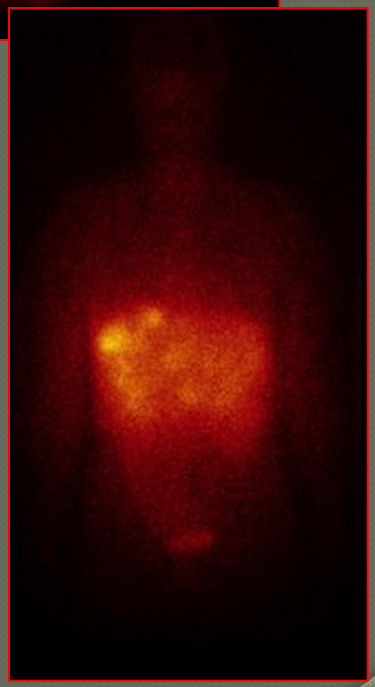
- Newer peptide
- Higher affinity for SSR2
- Minimal side effects as renal and bone marrow uptake low
- Patients treated in Poland, UK and Germany



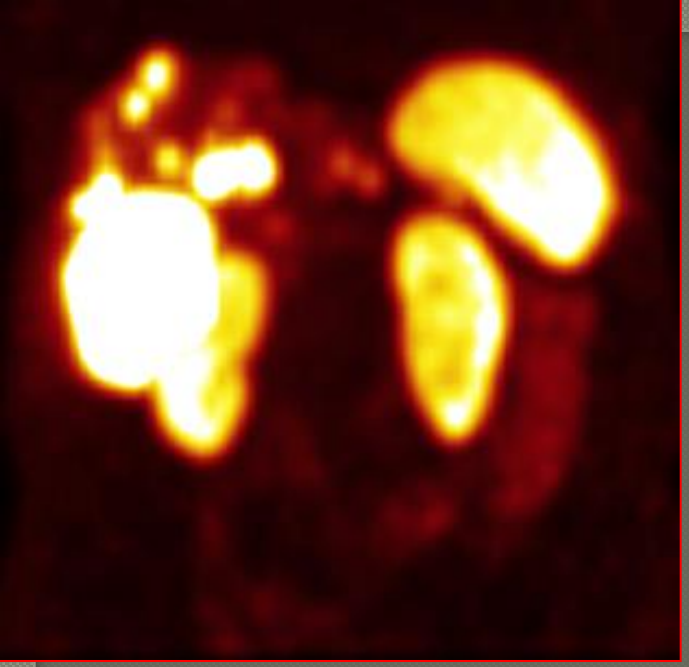




Foregut, pancreas – secretor (gastrinoma)
NECLM (WHO 2)

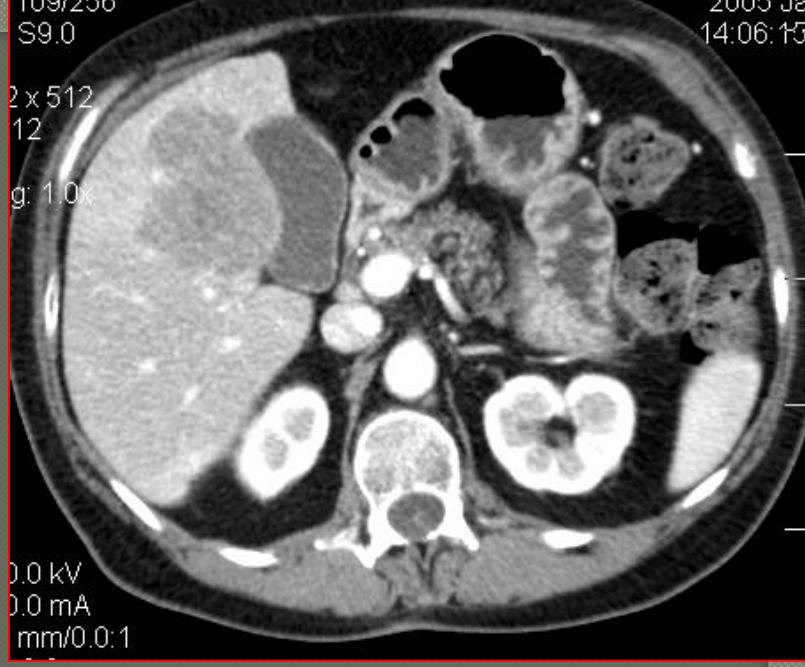
# Results Cwikla et al

- At 6 months 12 patients PR, 1 only PD
  - 23 patients had good symptomatic response
- Median PFS was 20 months with Median OS of 22 months
- 6 patients mild renal toxicity (WHO grade 1,2)
- 1 patient reduced platelets grade3

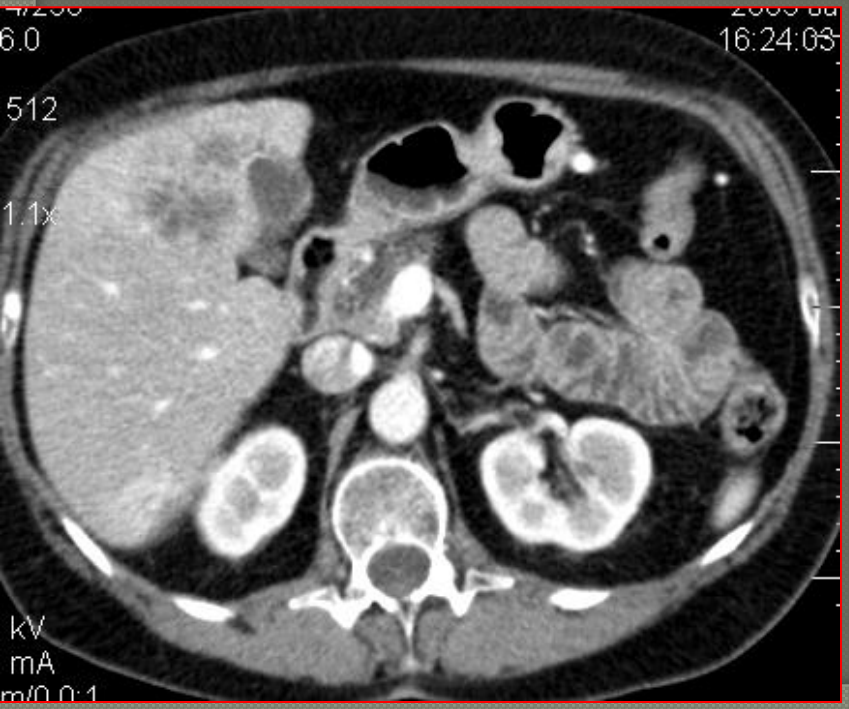


61 yrs old female;
FPI, WHO 2, G2;
CS IV, nonsecretor

Initial SRS ($^{99}$Tc TOC)

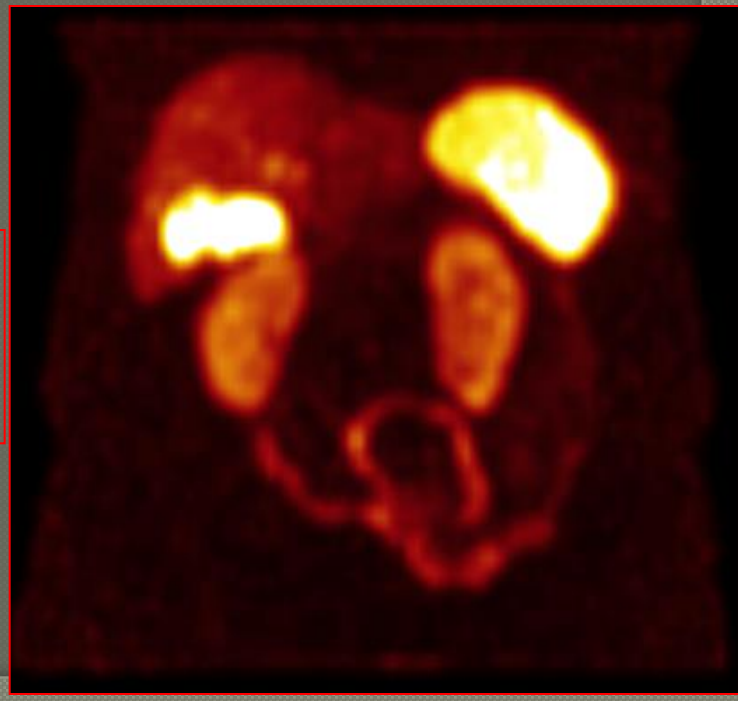



Initial CT




CT 12 M
after PRRT

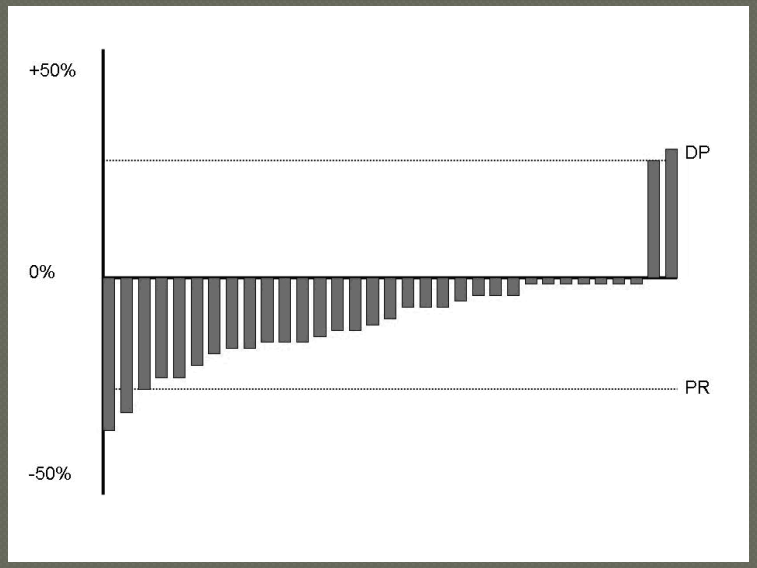
SRS 12 M
after PRRT,
($^{99}$Tc TOC)



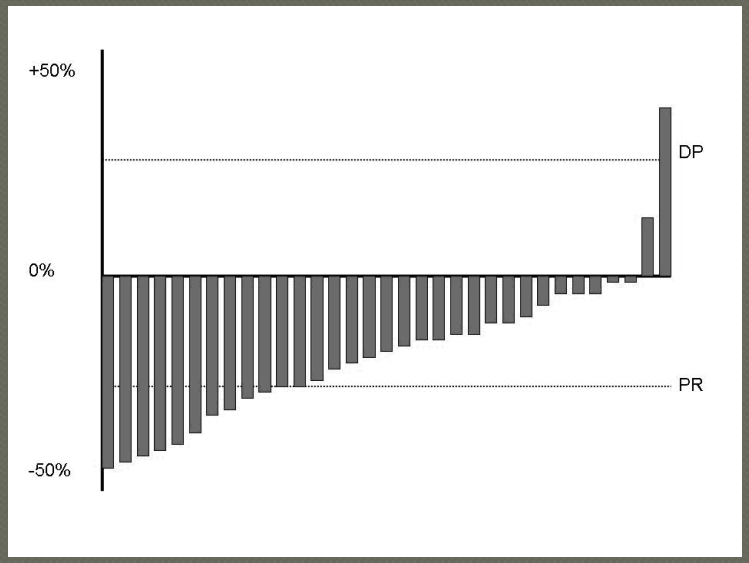
# Treatment with Y-90 DOTATATE Cwikla et al (Ann Oncol 2010)

- 35 patients with proven GEP-NET
- All treated patient had evidence of PD before therapy
- 4x3-4GBq Y-90 DOTATATE with amino-acid cover 12 weeks apart
- Response measure by CT and symptom relief

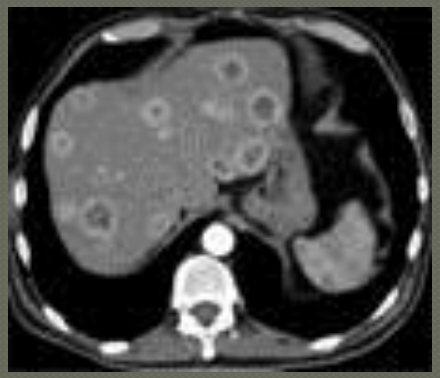
# What is a response with Y-90



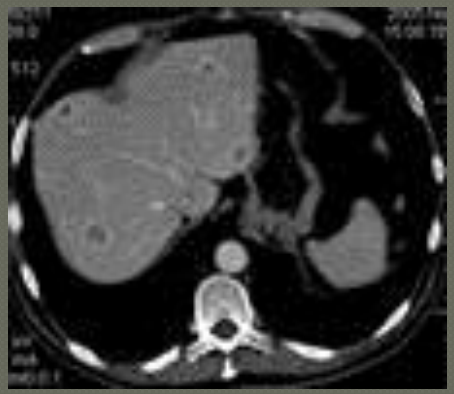

Waterfall plot at 6 weeks



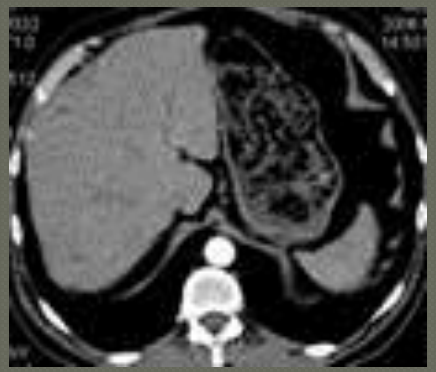

Waterfall plot at 6 months



Pre-therapy



6 months post last cycle



12 months after last cycle

# Y-90 DOTATATE

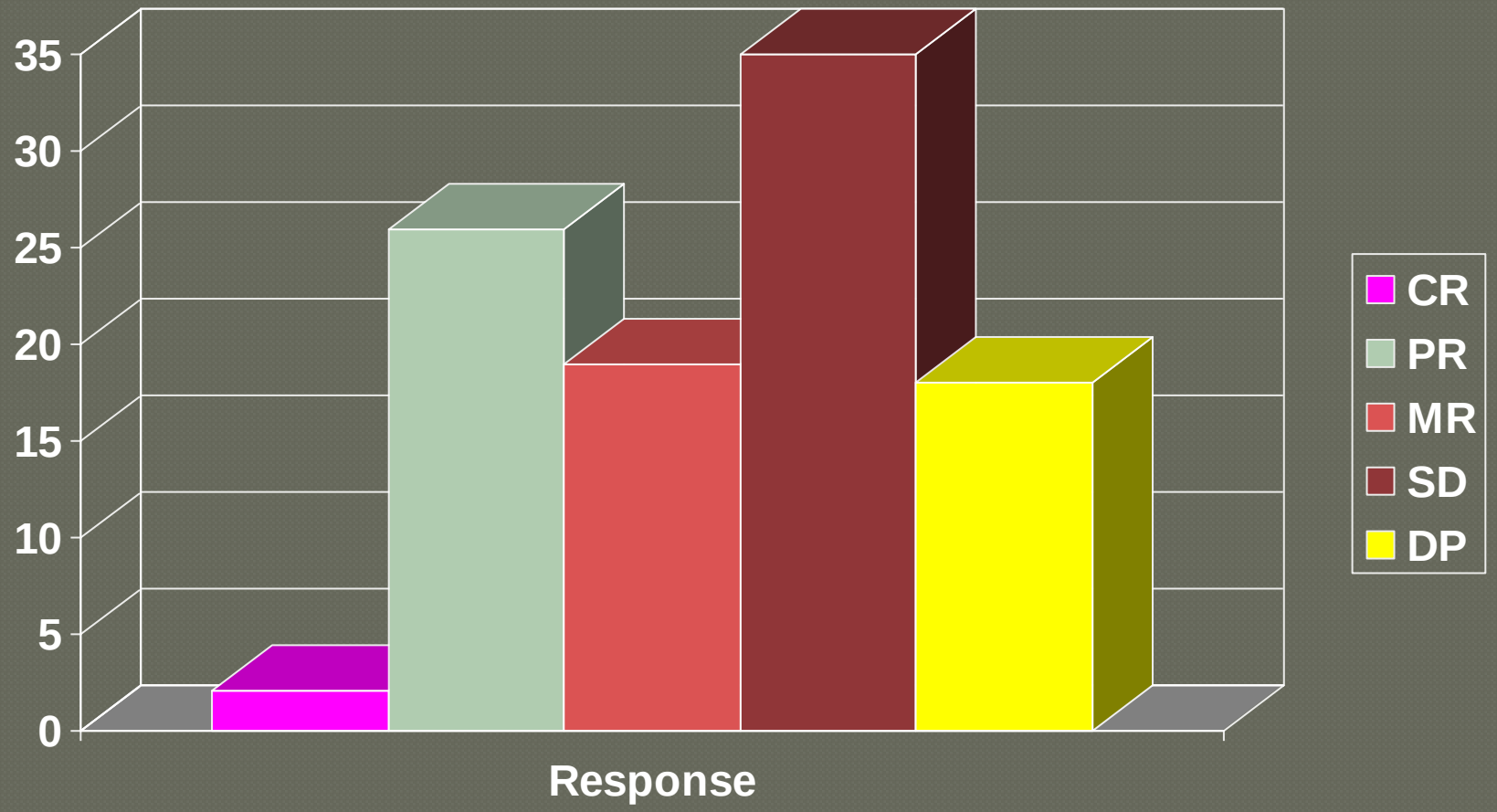
- Latest RFH figures
- **Total patient survival** (all 82 patients):

  mean patient survival: 39 +/- 3 months
- Patient survival rate at:
- 1 year: 95+/-3%
- 2 year: 91+/- 4%
- 3 year: 84+/- 5%
- 5 year: 55+/-7%

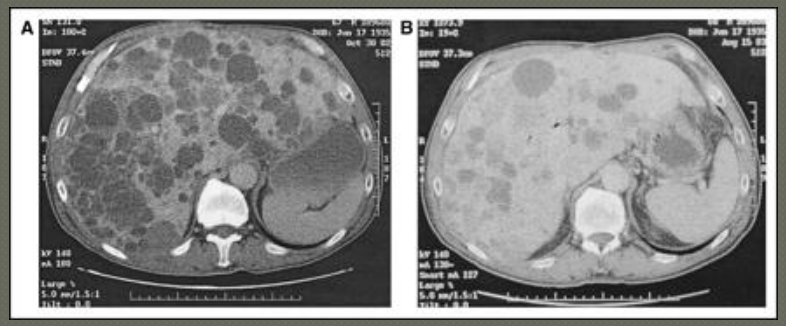
# Lu-177 Octreotate

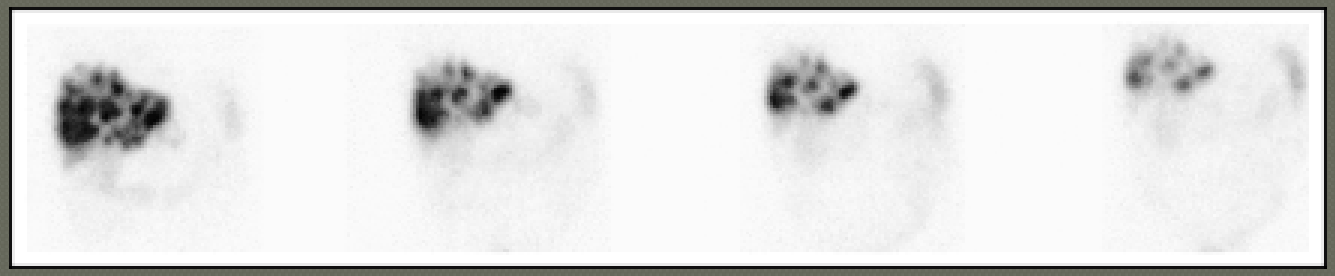
- Developed by Krenning
- JCO 2005
- 151 patients treated with cum activities of 22-30 GBq of Lu-177 octreotate
- Given with renal protection
- Toxicity bone marrow and in some men reduction in testosterone
- Follow up data in 125 patients

# Lu-177 in GEP (Krenning-JCO 2005)



# Krenning et al JCO 2005



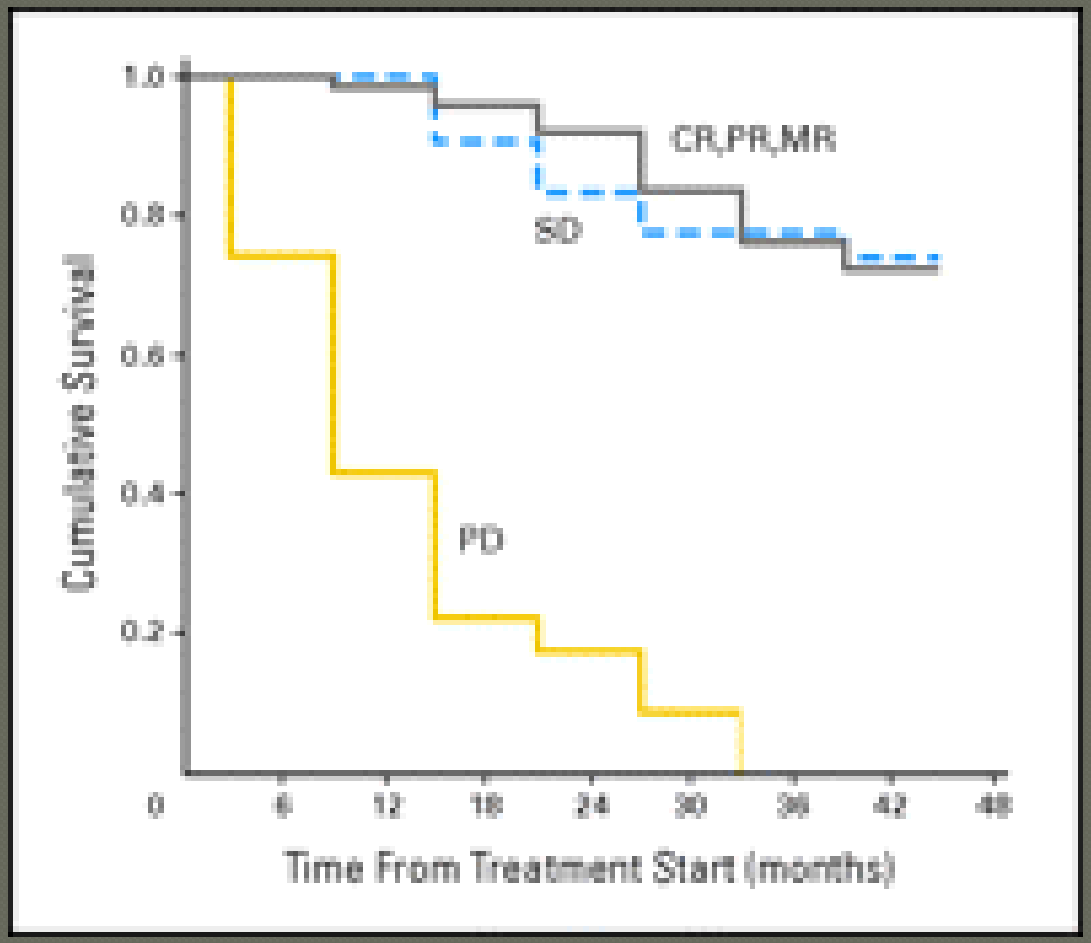
# Lu-177 dosimetry Baum et al Cancer Bio & radiopharm 2007

- Easier as can use tracer dose or after first therapy as Lu-177 has a low yield 103keV gamma emission
- 69 patients treated with Lu-177 DOTATATE Lu-177 DOTANOC
- Radiation dose calculated using MIRD3
- Lower dosimetry to kidneys and spleen with and higher dose to tumour with DOTATATE
- No correlation between tumour dose and clinical or radiological response

# Lu-177 octreotate (n=310) Kwekkeboom JCO 2008

- Carcinoid n=188
  - 1% CR, 22% PR, 17% MR, 42% SD, 20%DP
- PET non func n=72
  - 6% CR, 36% PR, 18%MR, 26% SD, 14% DP
- PET func n=19
  - 0% CR 60% PR, 20% MR, 30% DS, 10% PD

# Survival post Lu-177 oct n=310



Navilkissor et al 2011

# PPRT DOTATATE

Y-90

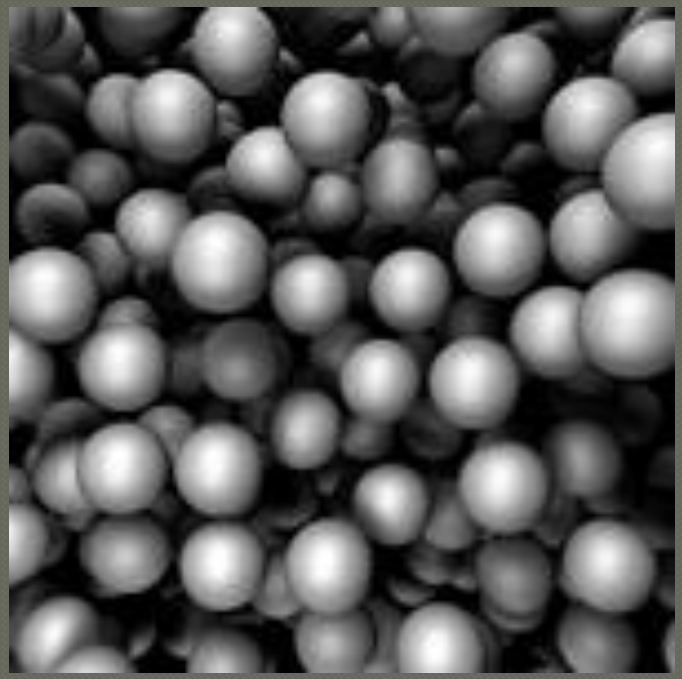
| Author (n) | CR | PR | SD | DP | Symptom relief |
|---|---|---|---|---|---|
| Baum (75) | 0 | 28 | 39 | 8 | 64 |
| Cwikla (57) | 0 | 14 | 44 | 0 | 51 |
| Toupanakis (85) | 0 | 11 | 66 | 11 | 62 |
| TOTAL (217) | 0<br>0% | 49<br>23% | 149<br>69% | 19<br>8% | 167<br>77% |

Lu-177

| Author (n) | CR | PR | SD | DP | Symptom relief |
|---|---|---|---|---|---|
| Kwekenboom (310) | 5 | 86 | 158 | 61 | 21/36 |
| Gabriel (55) | 0 | 15 | 27 | 13 | |
| Total (365) | 5<br>2% | 101<br>27% | 185<br>51% | 74<br>20% | 58% |

# Y-90 particulates

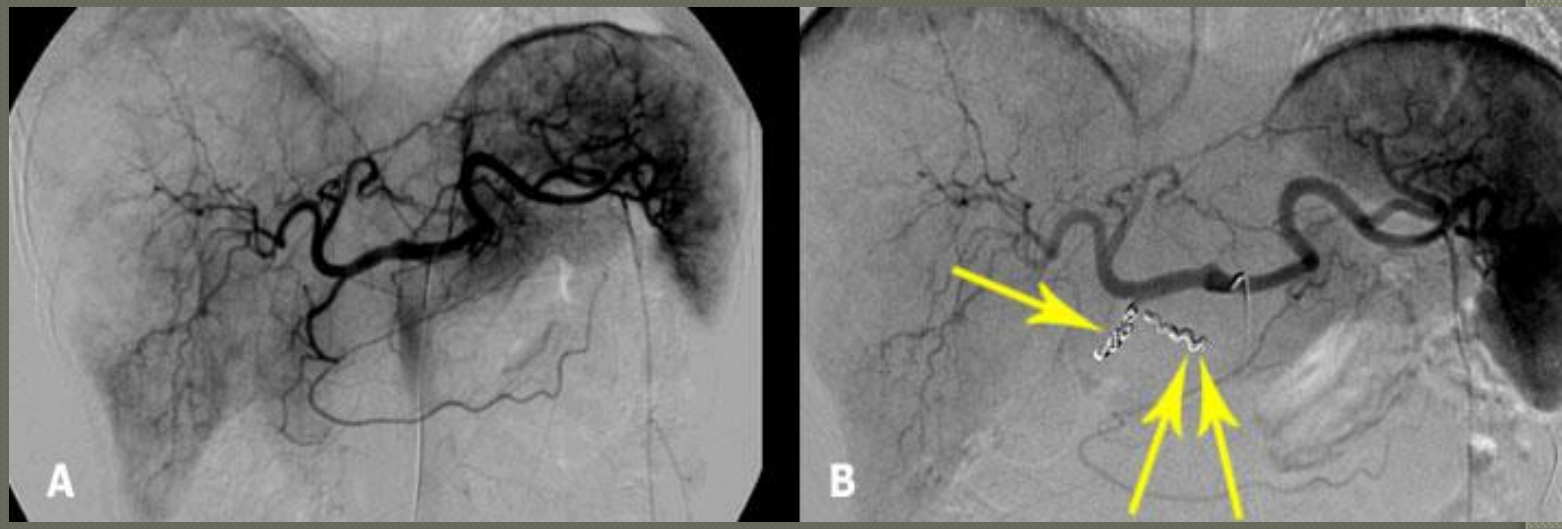
2 main types
From Australia Y-90 resin balls SIRspheres
From Canada Y-90 imptegnated glass balls Therasphers



# How do you give SIR spheres

- Day 1
- Need to block off collaterals including GDA with coils
- Prevents Sir spheres going to stomach or pancreas
- Inject 80-100MBq Tc-99m MAA into radiological catheter and flush line
- Image to determine shunt

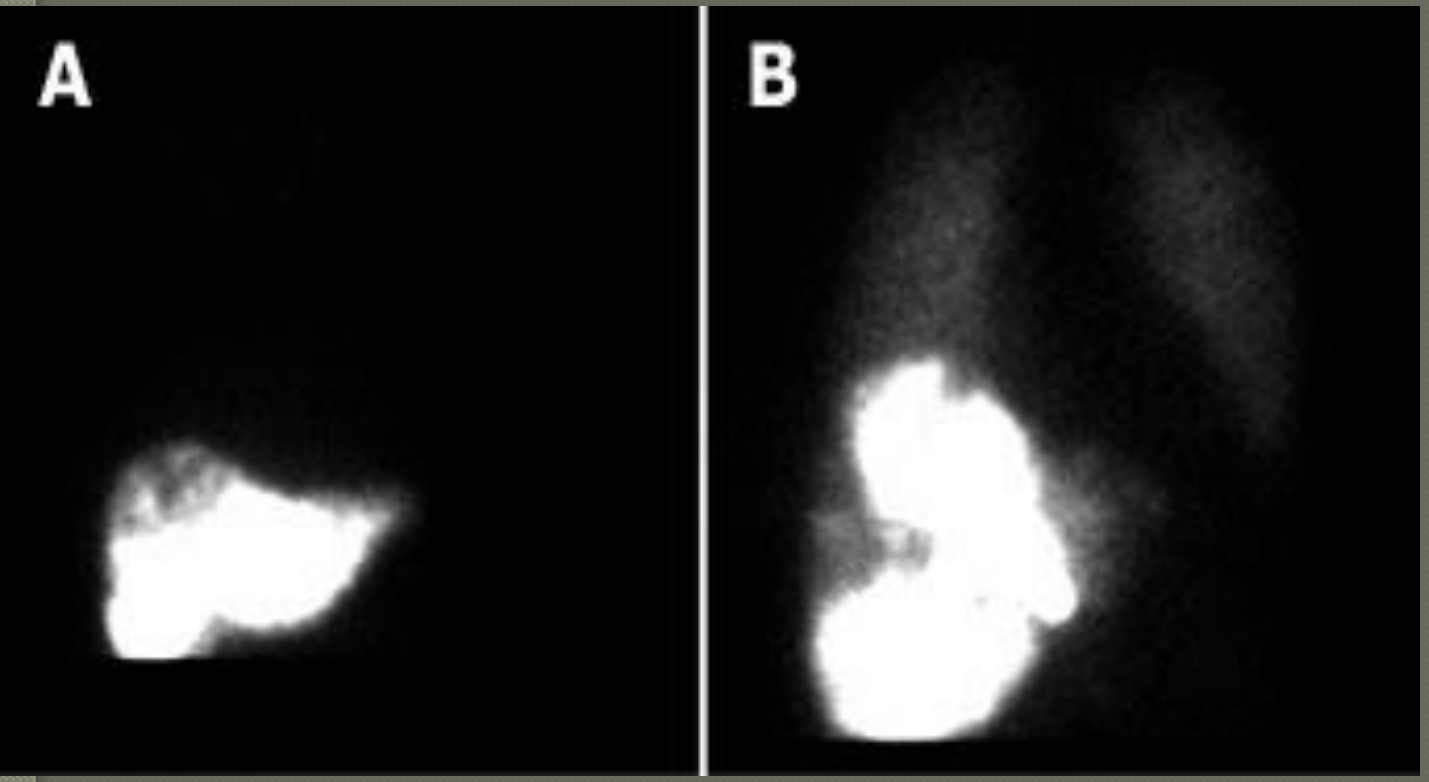
# Removing collaterals



# Shunting

- 2 main problems with SIR spheres
- If too much (more than 20%) shunt to lung leads to lung fibrosis
- Also in some patients shunting to small bowel
- All can be calculated from MAA scan

# Shunting




No shunting

27% shunting

# Dosing

- 3 methods
  - Individual dosimtry based on MAA scan +/- SPECT keep lung dose below 30Gy
  - Semi empirical
    - Degree of shunting
    - Size of patient
    - % liver full of tumour
  - Fully empirical Give 2-3GBq
- No good evidence which is best

# Dose reduction and shunting

| Lung shunt | Change in Y-90 SIR sphere dose |
|---|---|
| <10% | No change |
| 10-15% | Reduce by 20% |
| 15-20% | Reduced by 40% |
| >20% | Do not give |

# Dosing SIR spheres

- Use weight and height
- Calculate BSA using du Bois method
- Use CT/MRI to determine % liver involvement
- Calculate activity in GBq as (BSA-0.2) + (% tumour involvement)
- Correct for shunt if needed

# Dosing empirical

- Use estimated activity as described in table
- Adjust for shunting

| Estimate of tumour-liver involvement | Activity of Y-90 Sir spheres |
|---|---|
| >50% | 3GBq |
| 25-50% | 2.5GBq |
| <25% | 2 GBq |

# MIRD method

- Use Tc-99m MAA scan to calculate the distribution
- Try to give tumour 70-90 Gy
- Keep normal liver to 20-25Gy
- Lung ALARA but must be <30Gy

| Liver activity | Lung activity | Liver dose mGy/Mq | Lung dose mGy/Mq |
|---|---|---|---|
| 100% | 0% | 0.101 | 0.006 |
| 95% | 5% | 0.096 | 0.012 |
| 90% | 10% | 0.091 | 0.017 |
| 80% | 20% | 0.82 | 0.028 |
| 70% | 30% | 0.072 | 0.039 |

# Giving SIR sphere

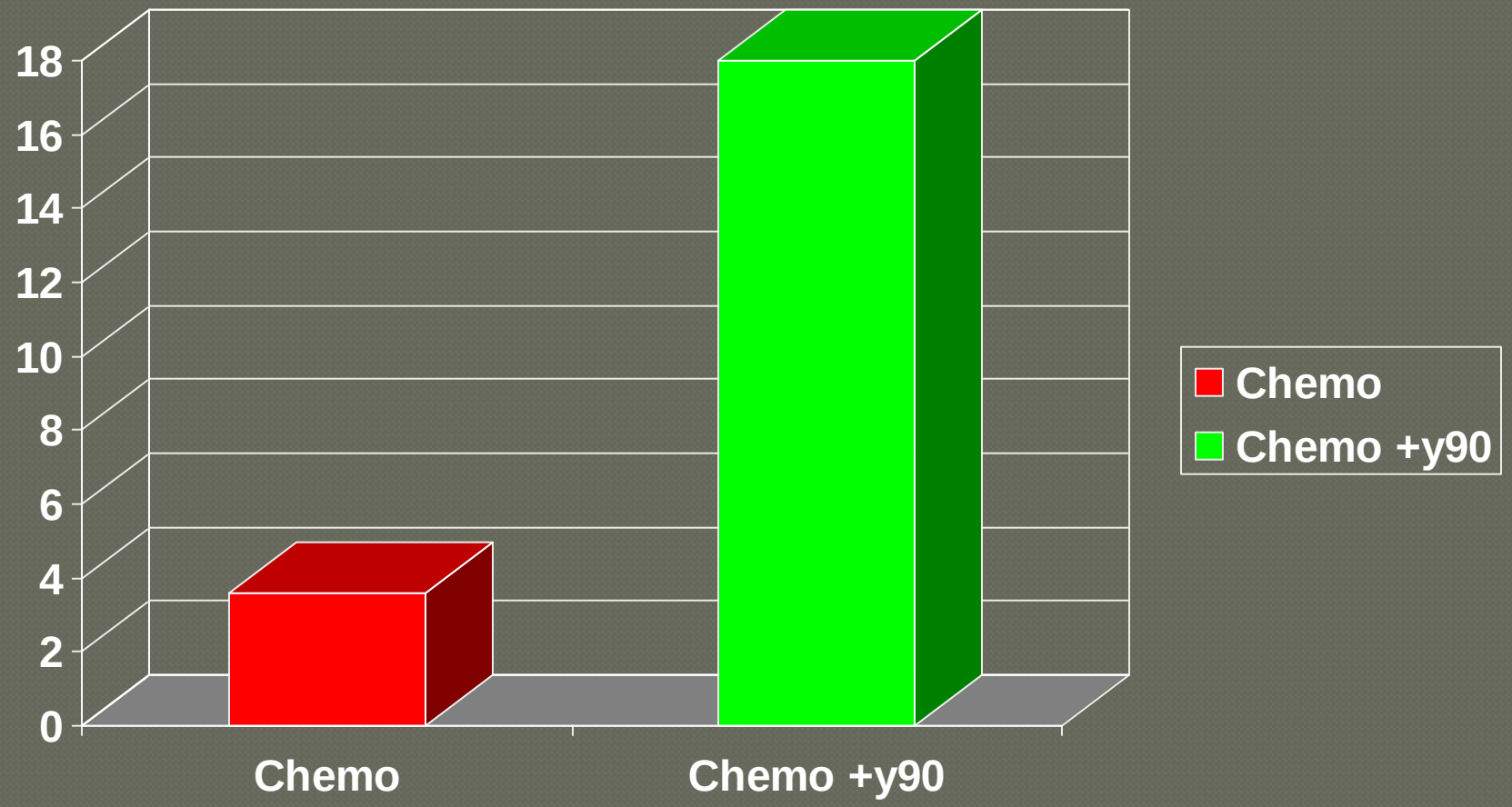
- Day 8
- Check no re-cannulisation
- Place cannula at same site as where MAA infused
- Give slowly using WATER as driver
- Need to give in small allaquots to prevent liver embolisation
- As heavy need to agitate spheres as inject

# Administration kit

# Pivotal study
## van hazel JSO 2004

- Phase II RCT from Australia
- 21 patients metastatic CRC
- <25% liver mets >80% mets in liver
- All patients received 4 cycles of 5F-U and leucovorin
- Half randomised to additional Y-90 Sir spheres

# van Hazel et al 2004
# Median PFS (p=0.005)



# One patient's result

Cambridge News

Wednesday, August 31, 2011 cambridge-news.co.uk 45p

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# My cancer miracle

## Doctors who gave Brian just 12 months to live are amazed as tumours vanish under trial treatment

JORDAN DAY

IN REMISSION: Brian Brooks at home with his wife Nicky. Picture: Richard Patterson 765835

ALMOST a year ago today, 72-year-old Brian Brooks was given just 12 months to live.

It was discovered that the beloved father and grandfather had massive tumours in both his colon and liver.

Even with gruelling chemotherapy, doctors at Addenbrooke's feared the tumours would not clear.

But Mr Brooks is now alive to tell the tale and in remission – after taking part in a ground-breaking trial launched by Cancer Research UK.

Speaking from their home in Nornea Lane, near Stuntney, Ely, Mr Brooks and his wife, Nicky, both committed Christians, described it as a "miracle".

Mr Brooks said: "To be told you have 12 months to live and then to have completely healed 12 months down the line, we believe, is a miracle.

"Obviously there is always the risk that cancer can come back but I am now in remission and that is something that doctors did not believe was possible."

It was on September 6 last year that Mr Brooks, a retired boarding kennel owner, was diagnosed with cancer of the colon and liver after he had randomly decided to undergo a bowel screening test at Addenbrooke's. It showed there was a huge tumour in his colon.

Further scans then showed the cancer had spread to Mr Brooks's liver. He was given just 12 months to live.

But it was when Mr Brooks was about to start his chemotherapy that a nurse mentioned a special trial, called Foxfire, had been launched.

The trial, spearheaded by Cancer Research UK and the Bobby Moore Fund, was testing a new treatment called Radioembolisation, a form of internal radiotherapy that uses the tumour's blood supply to target multiple sites of disease within the liver.

Mr Brooks put his name forward – and to his shock, was one of hundreds of people to be picked to take part.

Mrs Brooks, 67, said: "Again, it was completely random – Brian's name was picked and he underwent the trial alongside his chemotherapy.

"We've just had the results back and Addenbrooke's can't believe

Turn to page 5

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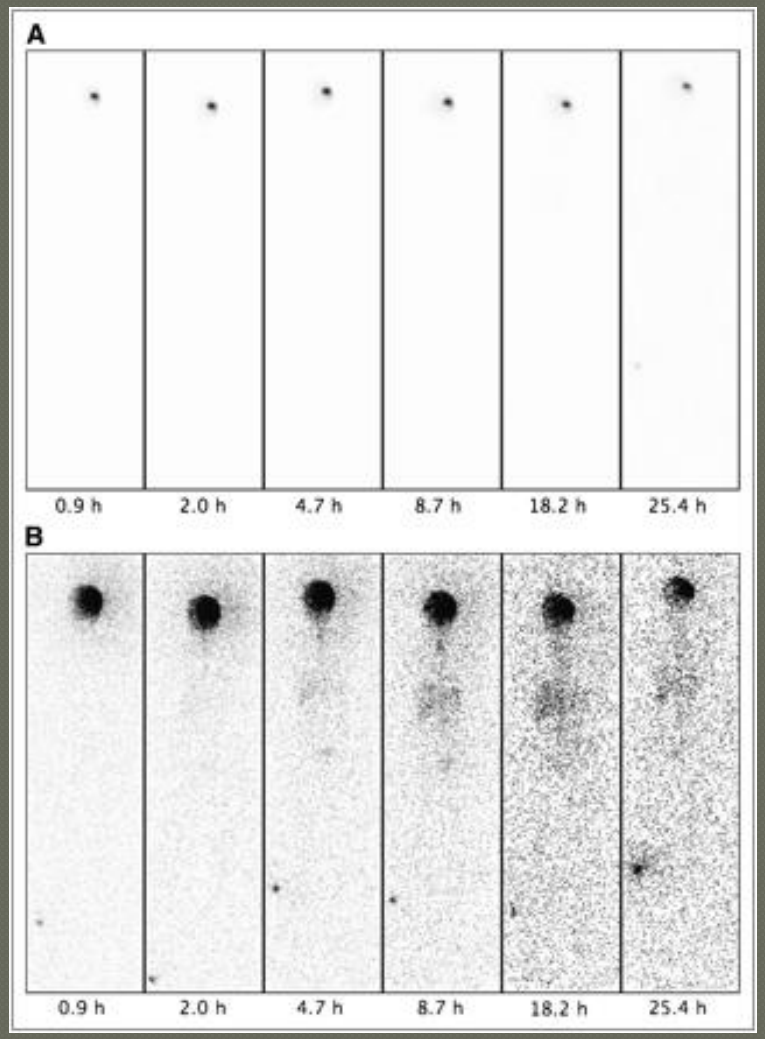
# Recent developments

- 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

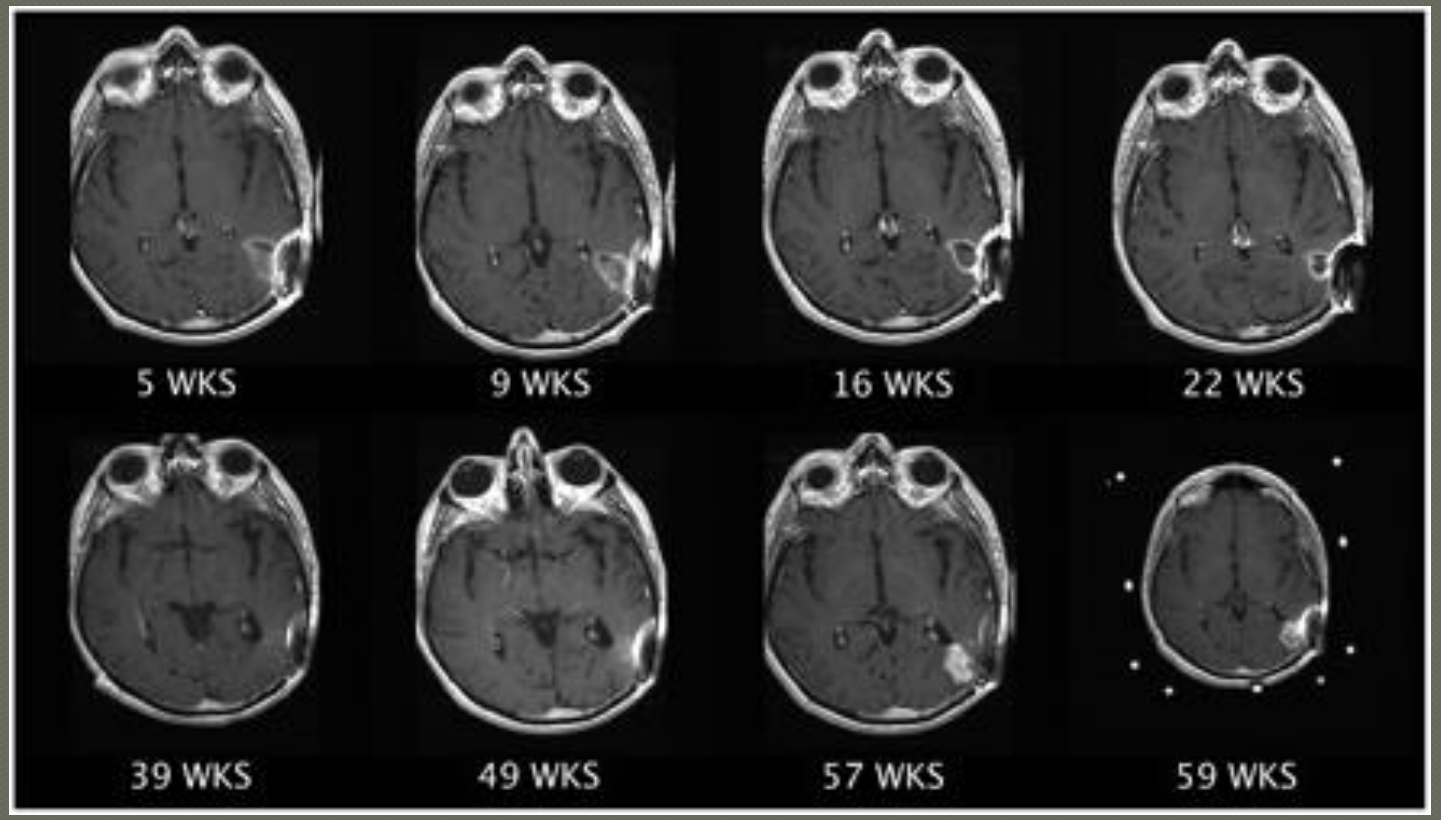
# Polonium images at different time points




Patient A Given via Omyha resevoir

Patient B Given via catheter into CSF in lower lumber spine

# 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