



PRRT

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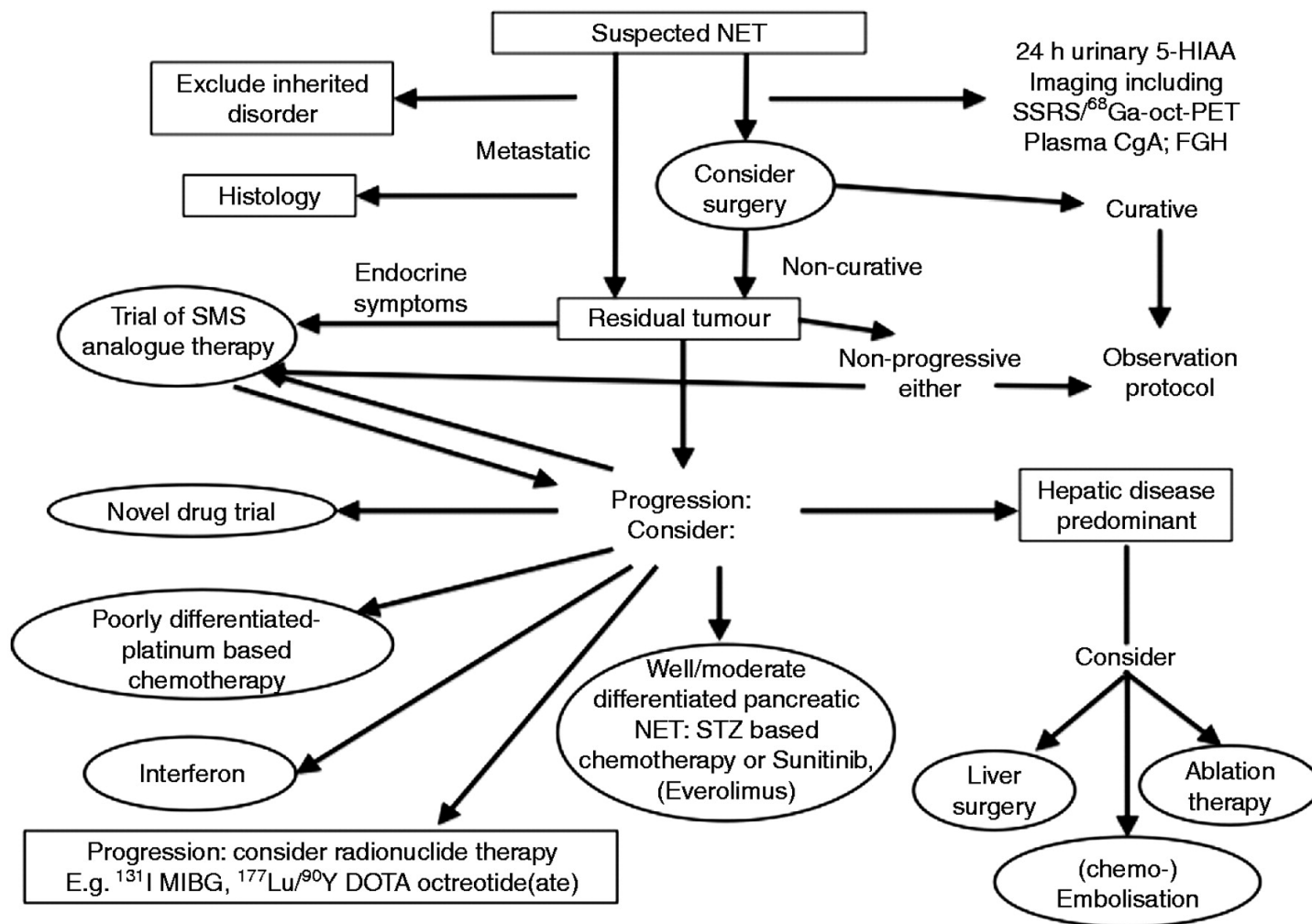
Introduction

- Why PRRT
- The factors affecting choice of treatment
- Imaging for therapy
- Types of PRRT
- Follow-up
- Outcome expectations

Why PRRT

- We know radiolabelled somatostatin localise to NETs mainly via SSR2 receptor
- If you can see tumour using gamma emitter than by changing to alpha or beta emitter can treat
- Reduced collateral damage c/w DXT
- True personalised medicine

When to give PRRT

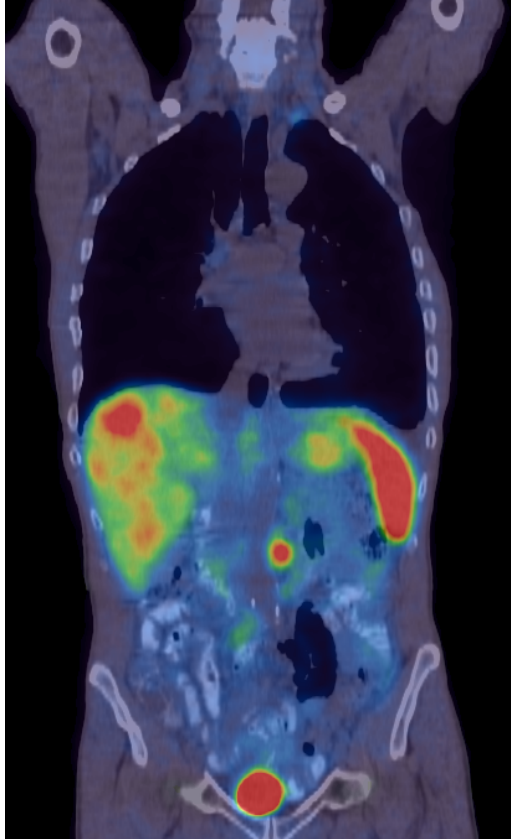


Treating NETs general principles

- Establish diagnosis
- Establish extent of disease
- Syndromic vs non syndromic
- Use of first line treatments
- Natural history of disease
- Expectations of treatment
- Quality of life
- Deciding when NOT to treat/ STOP treatment

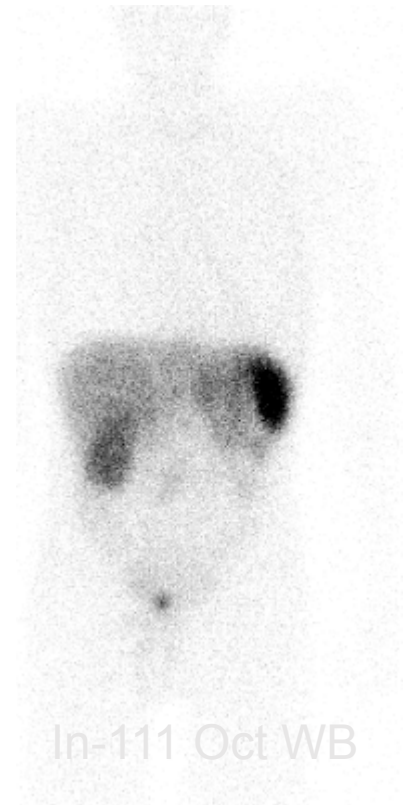
Practical points

- Patient selection
- Positive study on In-111 oct, Tc-99m DOTANOC or Ga-68 DOTATATE
- Must have progressive disease on CT or MRI or symptoms not controlled by sandostatins
- WHO performance status 0,1
- If on LAR time treatment for week before or after injection
- If sub cut stop 24 hours

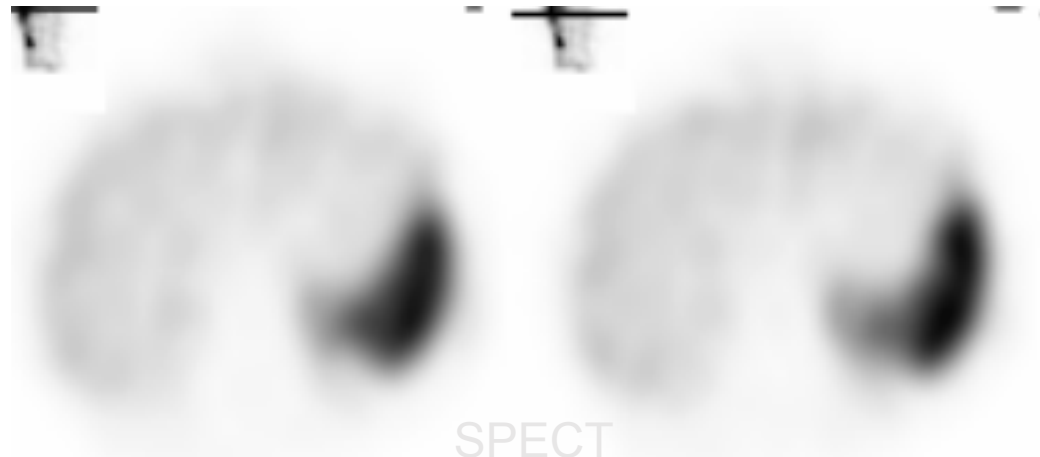
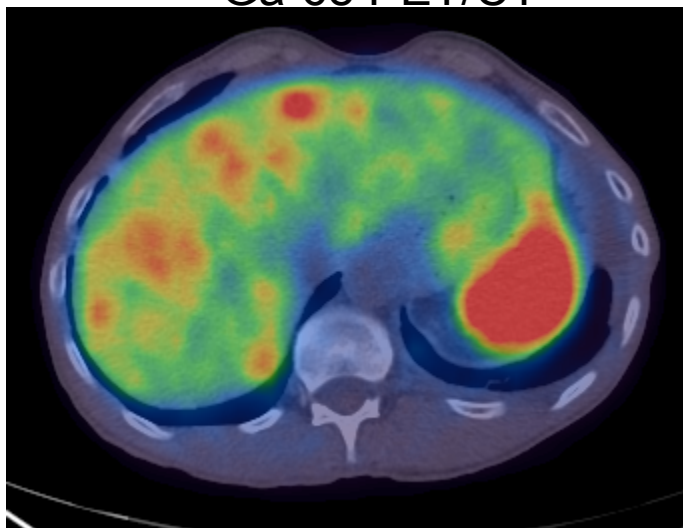


Ga-68 PET/CT

Ga-68 PET/CT more lesions than In-111 Oct

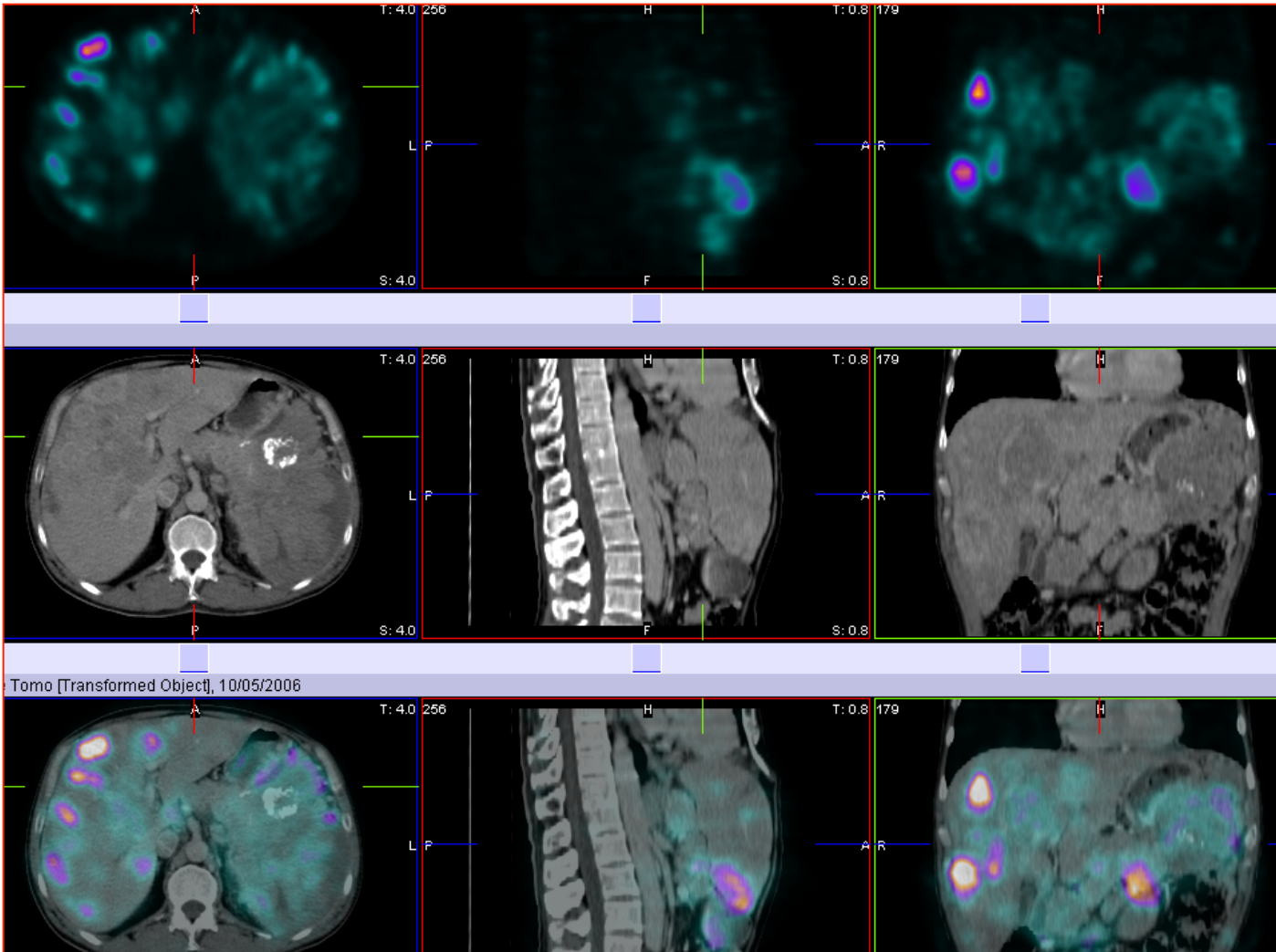


In-111 Oct WB



SPECT

Tc-99m HYNIC octreotide



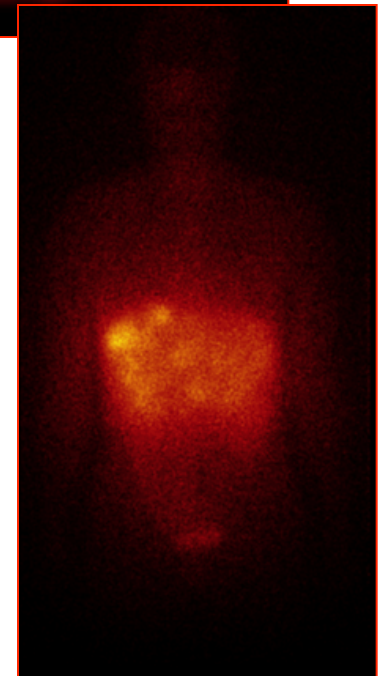
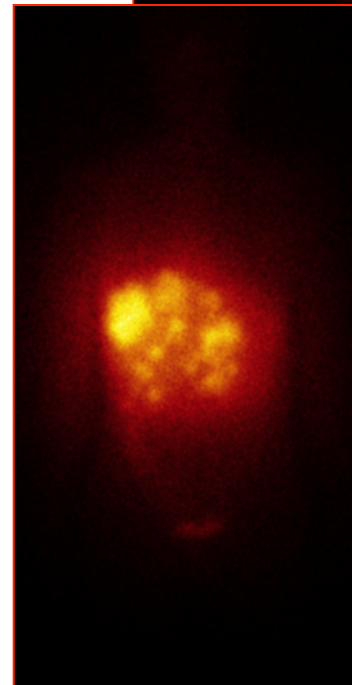
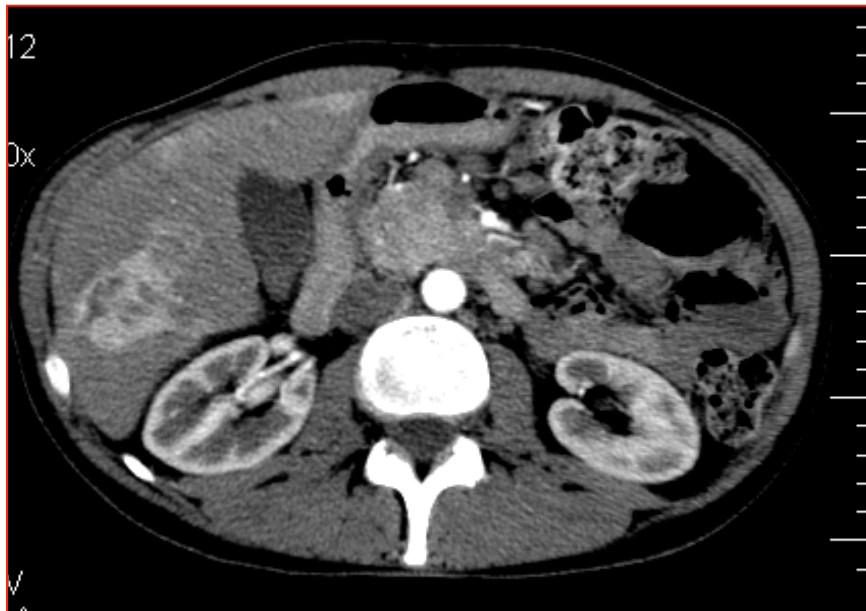
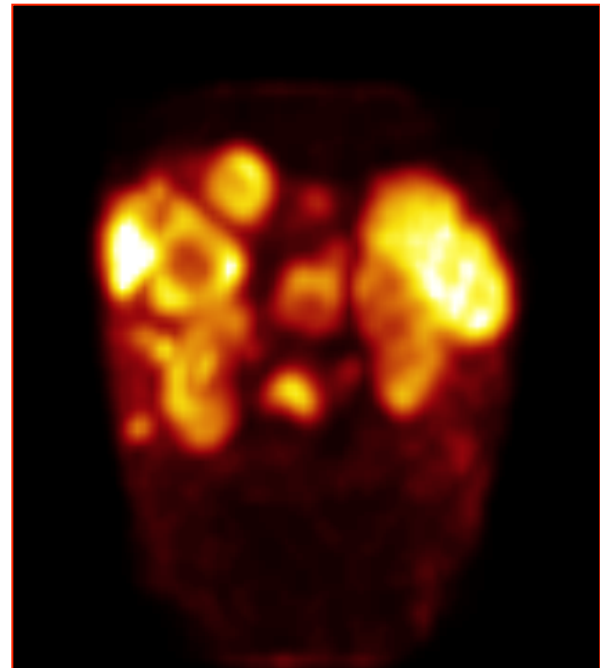
Foregut, pancreas – non-secretor, NECLM (WHO 2)

Radiopeptides

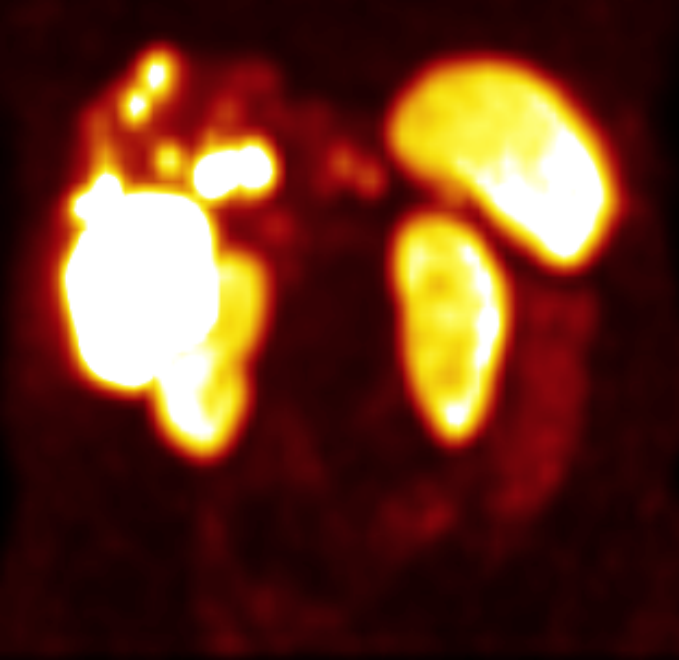
- Based on somatostatin system
- Peptides converted from commercial sources:
 - Lanreotide
 - Octreotide
 - Octreotate
- Normally DOTA linker
- Isotopes In-111, Y-90, Lu-177

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)



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

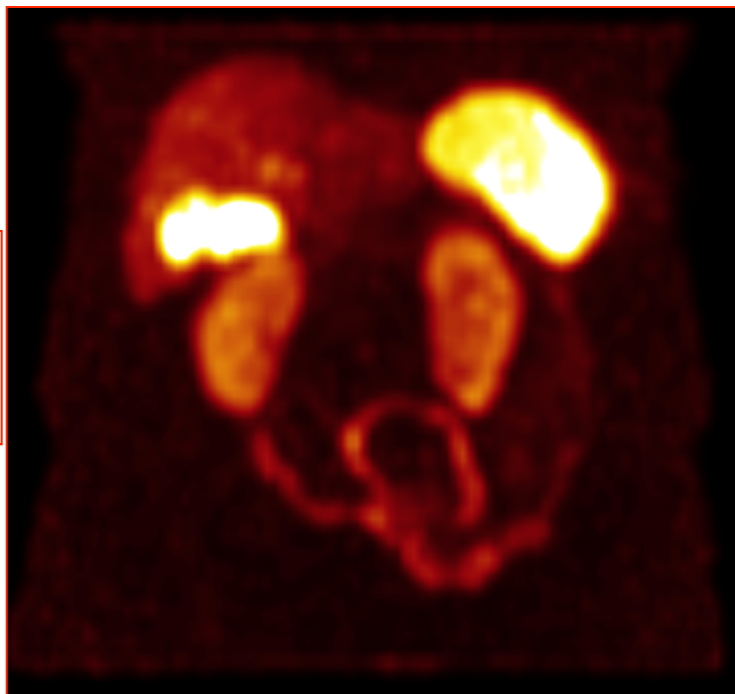
Initial SRS (⁹⁹Tc TOC)

Initial CT



CT 12 M
after PRRT

SRS 12 M
after PRRT,
(⁹⁹Tc TOC)

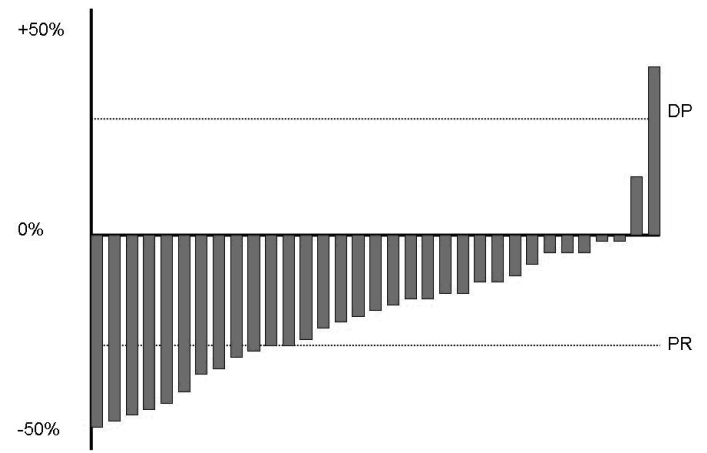
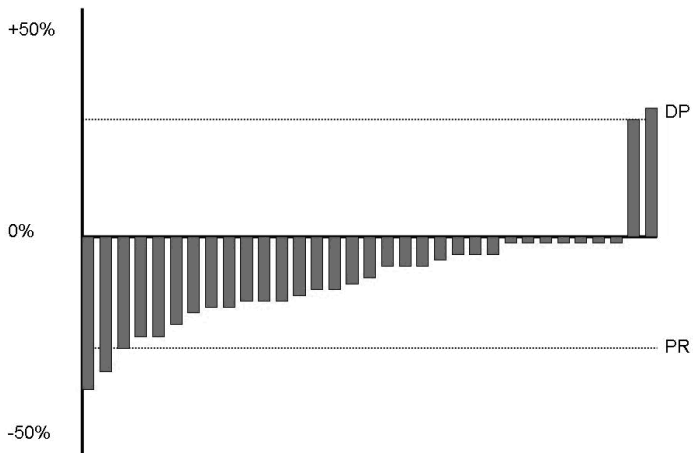


Treatment with Y-90 DOTATATE

Cwikla et al (Ann Oncol 2010)

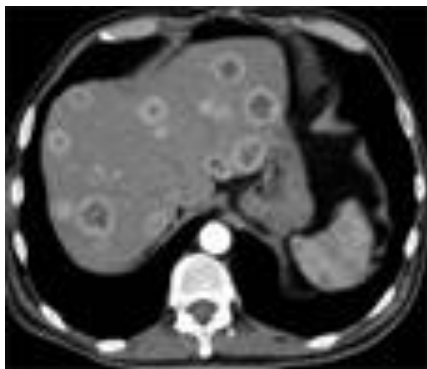
- 35 patients with proven GEP-NET
- All treated patient had evidence of PD before therapy
- 4x3-4GBq Y-90 DOTATATE with amino-acid cover 12 weeks apart
- Response measure by CT and symptom relief
- Good correlation between symptom relief and survival
- Correlation with imaging less clear

What is a response with Y-90 Cwikla et al



Waterfall plot at 6 weeks

Waterfall plot at 6 months



Pre-therapy

6 months post last cycle

12 months after last cycle

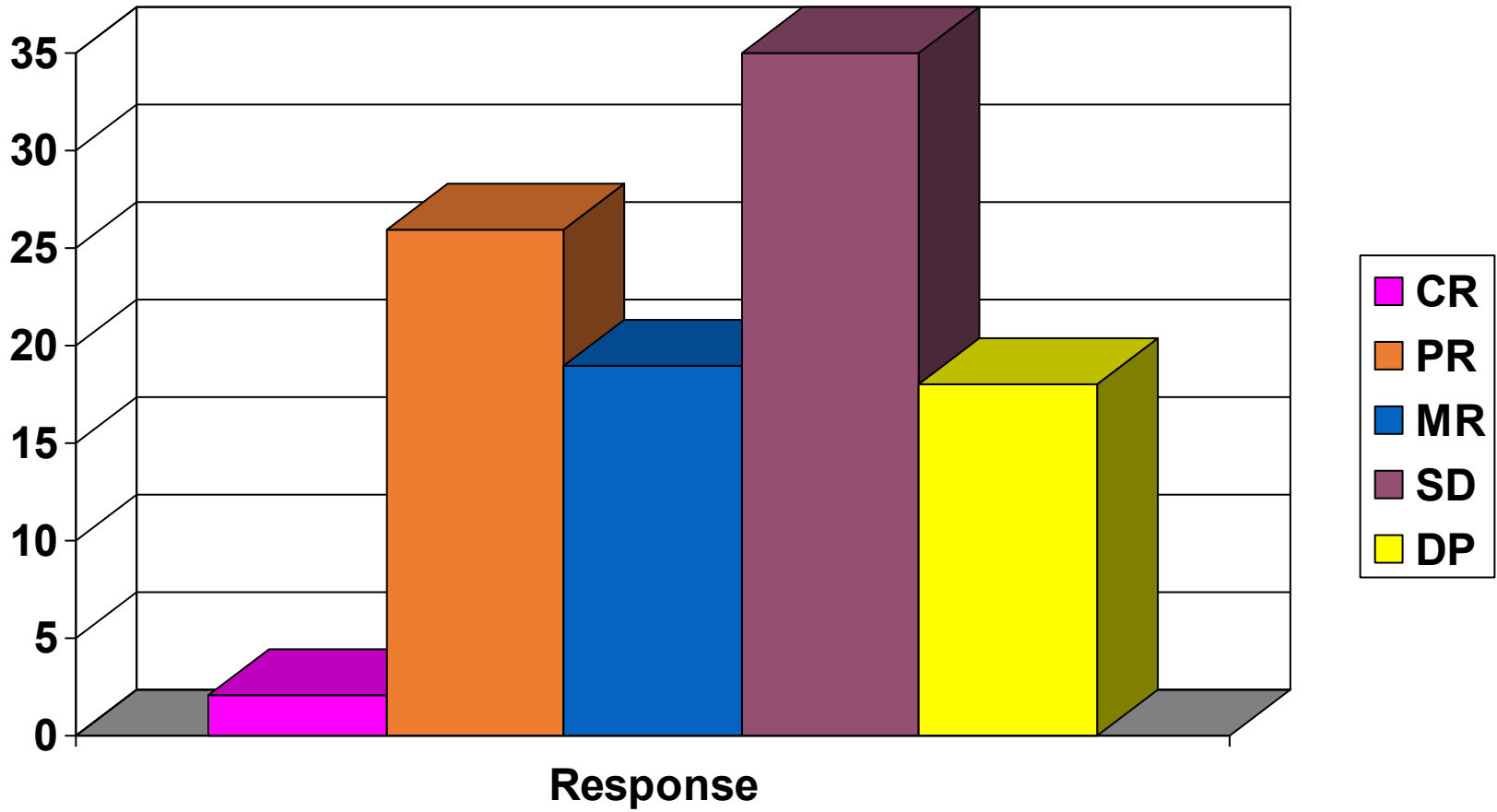
Y-90 DOTATATE

- 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%

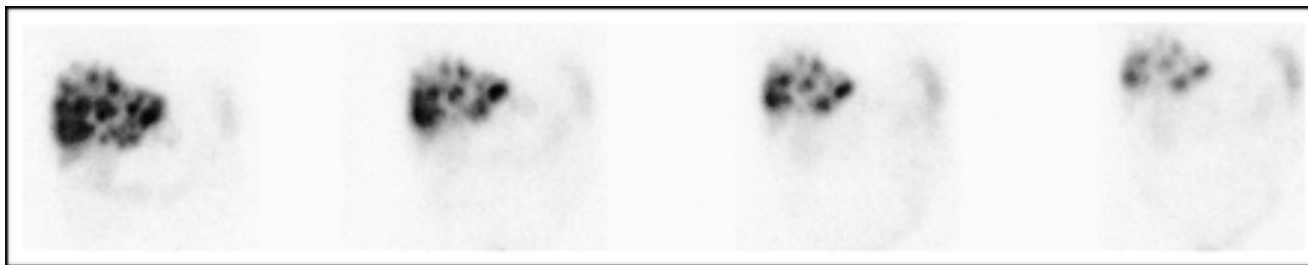
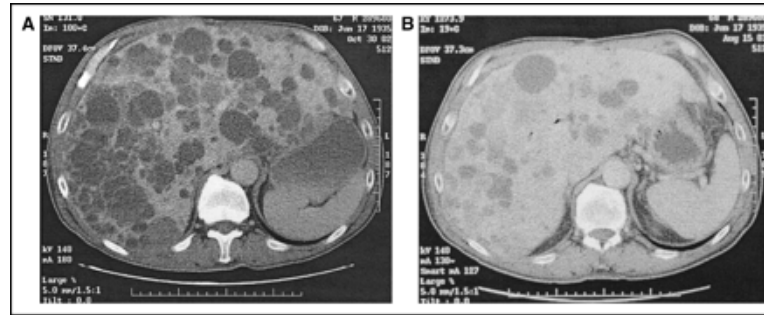
Lu-177 Octreotate

- 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)



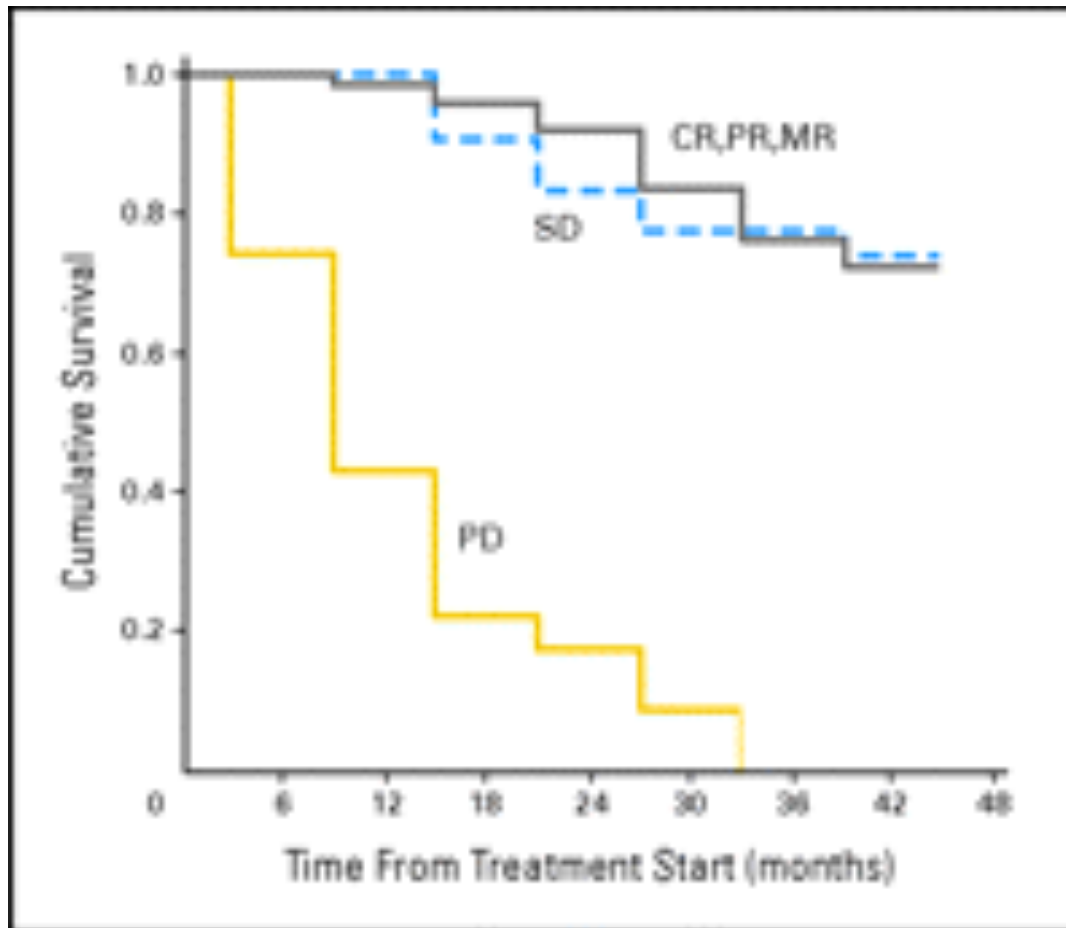
Krenning et al JCO 2005



Lu-177 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



Post therapy with Lu-177tate

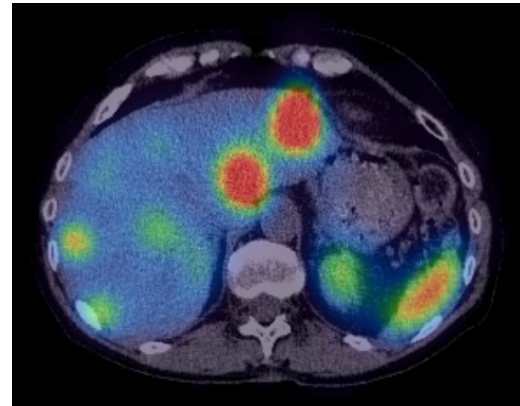
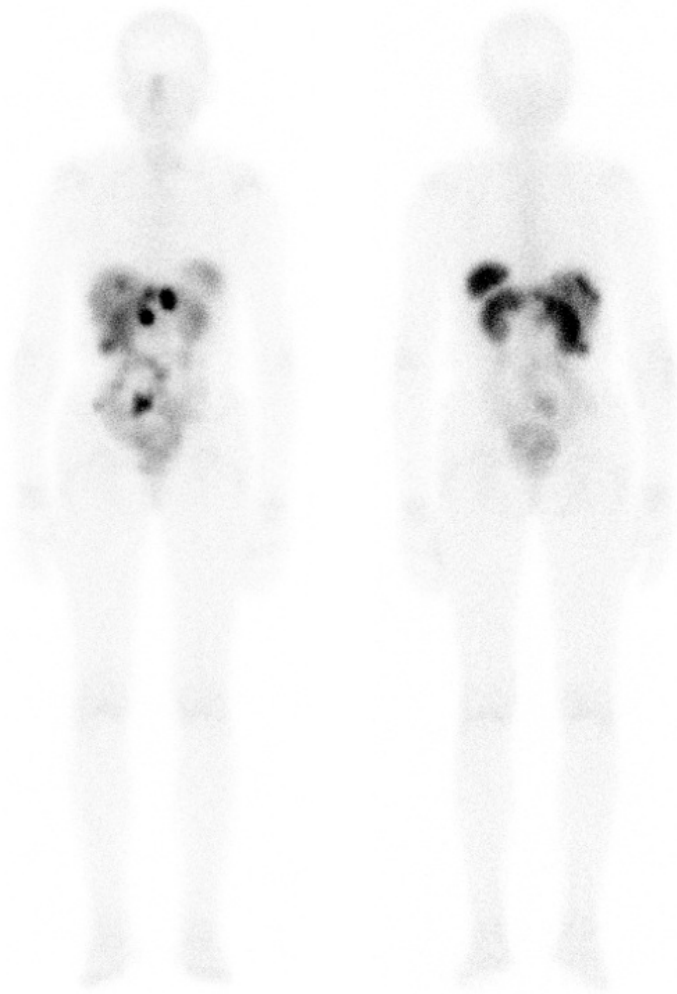


Image courtesy of Dr S Navalkisoor
Royal Free Hospital London

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 dosimetry in NETs

- Garkavij et al Cancer 2010
- 21 patients treated with 3-4 cycles of Lu-177 DOTATATE studied
- Whole body imaging with SPECT-CT of the kidneys used after treatments 1 and 2
- Standard 7GBq Lu-177 DOTATATE with amino acid cover for 1st 2 cycles
- Subsequent activities altered to keep renal dose to <27 Gy

Lu-177 dosimetry contd..

- Used MIRD dosimetry on whole body imaging
- Or used CT corrected SPECT data to find kidney doses
- Planar methods over estimated renal dose
- Cumulative tumour doses calculated as high as 207Gy but no comment on relationship of tumour dose and response

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 0%	49 23%	149 69%	19 8%	167 77%

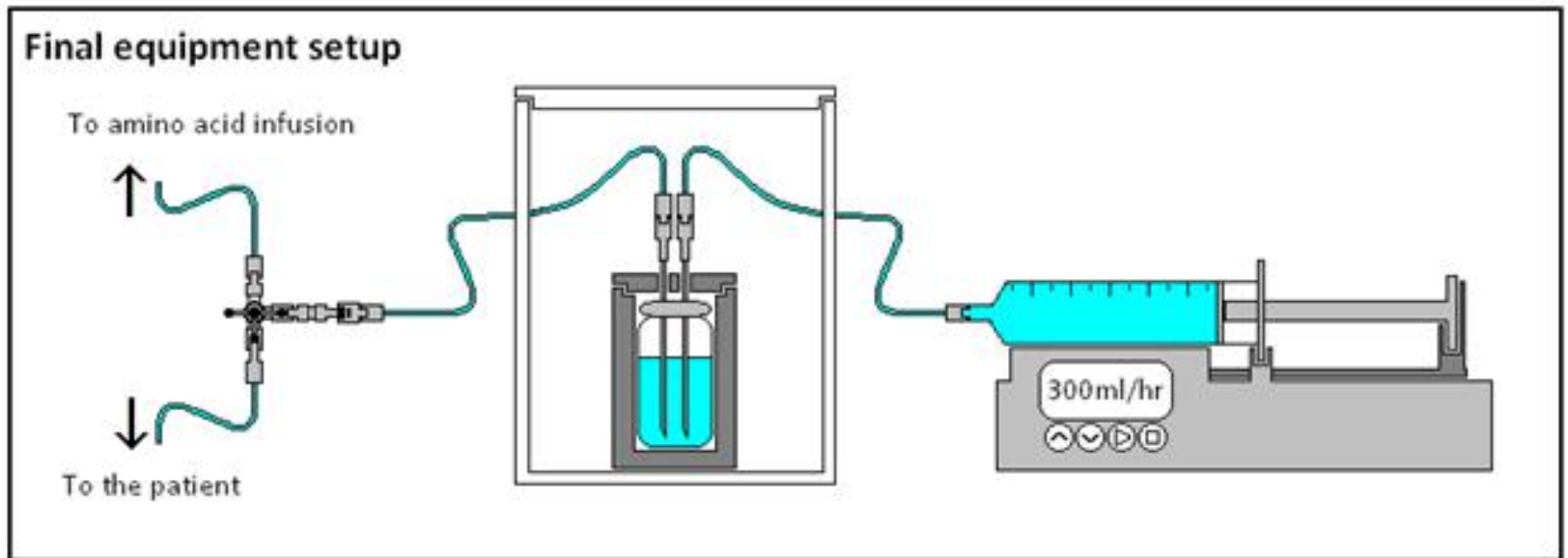
Lu-177

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 2%	101 27%	185 51%	74 20%	58%

Giving PRRT-general principles

- Discuss treatment with patient
- Obtain consent
- Give anti-emetic eg odansetron 8mg
- 15 minutes later start amino acid + fluids to give 30g lysine and 2 litres over 6 hours
- 45 minutes after amino acids start give Lu-177 DOTATATE over 20-30 minutes
- Repeat 3 more times 8 weeks apart

Infusion system



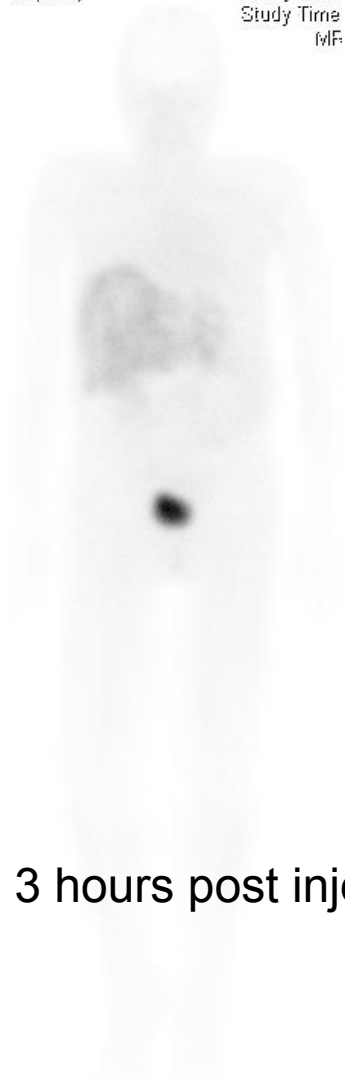
Infusion system



Lu-177 DOTATATE- post therapy imaging

0 (F3/4)

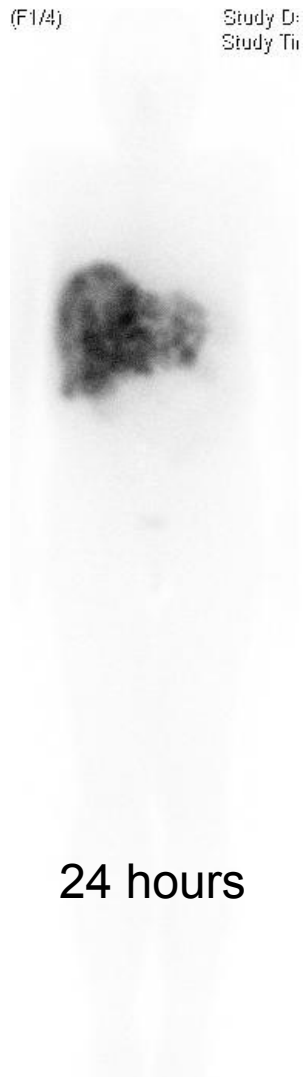
Study Date
Study Time
MF



3 hours post injection

(F1/4)

Study D:
Study Ti



24 hours

(F3/4)

Study 1
Study 1



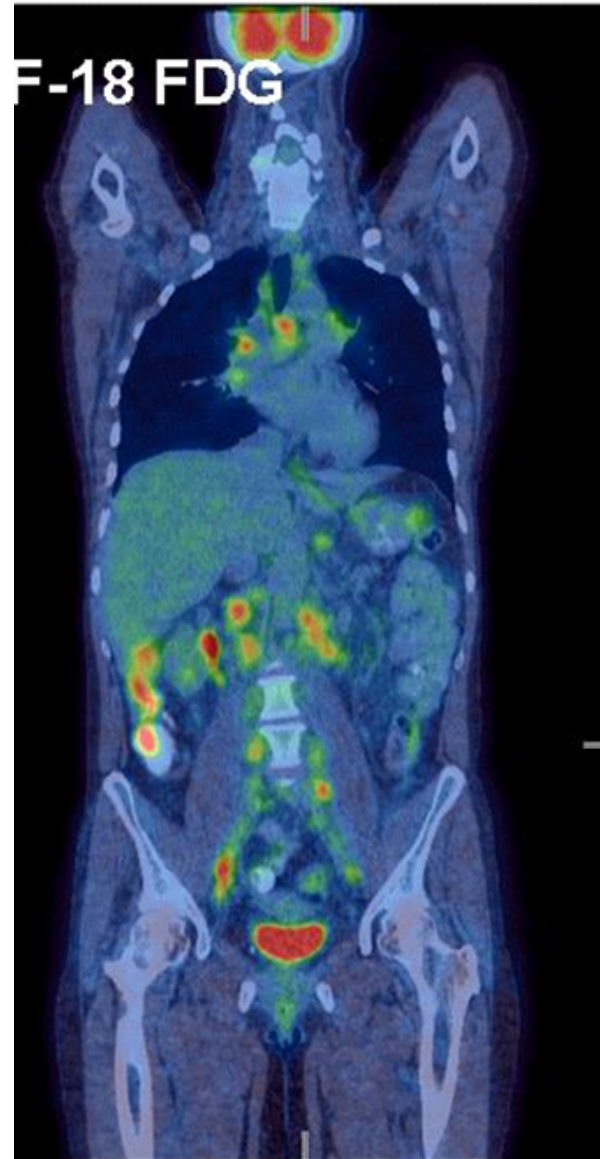
7 days

Controversies

- How can we reduce treatment failures – the role of F-18 FDG imaging
- Could Y-90 and Lu-177 PRRT be combined – Warsaw group
- Should we use a fixed activity if so what should that activity be
- Should PRRT be combined with other treatments
- How often can PRRT be administered

What does this tell us?

Though generally we assume NETs are negative on F-18 FDG this may not always be the case. A reasonable proportion of fore-gut and mid gut NETs can be F-18 FDG positive



F-18 FDG predicting response to Lu-177 DOTATATE

- Severi et al EJNMMI 2013
- F-18 FDG imaging in 52 NET patients WHO grade 1 and 2.
- F-18 FDG positive in 57% grade 1 patients, 66% grade 2 patients
- SD and PR/CR in 100% FDG neg vs 76% pos (P=0.02)
- Median PFS 33 months (FDG neg) vs 20 months (FDG pos)- p=0.03

Conclusions

- Surgery if possible
- If not palliative therapy only
- Mid gut SSR analogues
- Fore gut chemo
- Then consider PRRT
- Review and reconsider