Terapia radiorecettoriale

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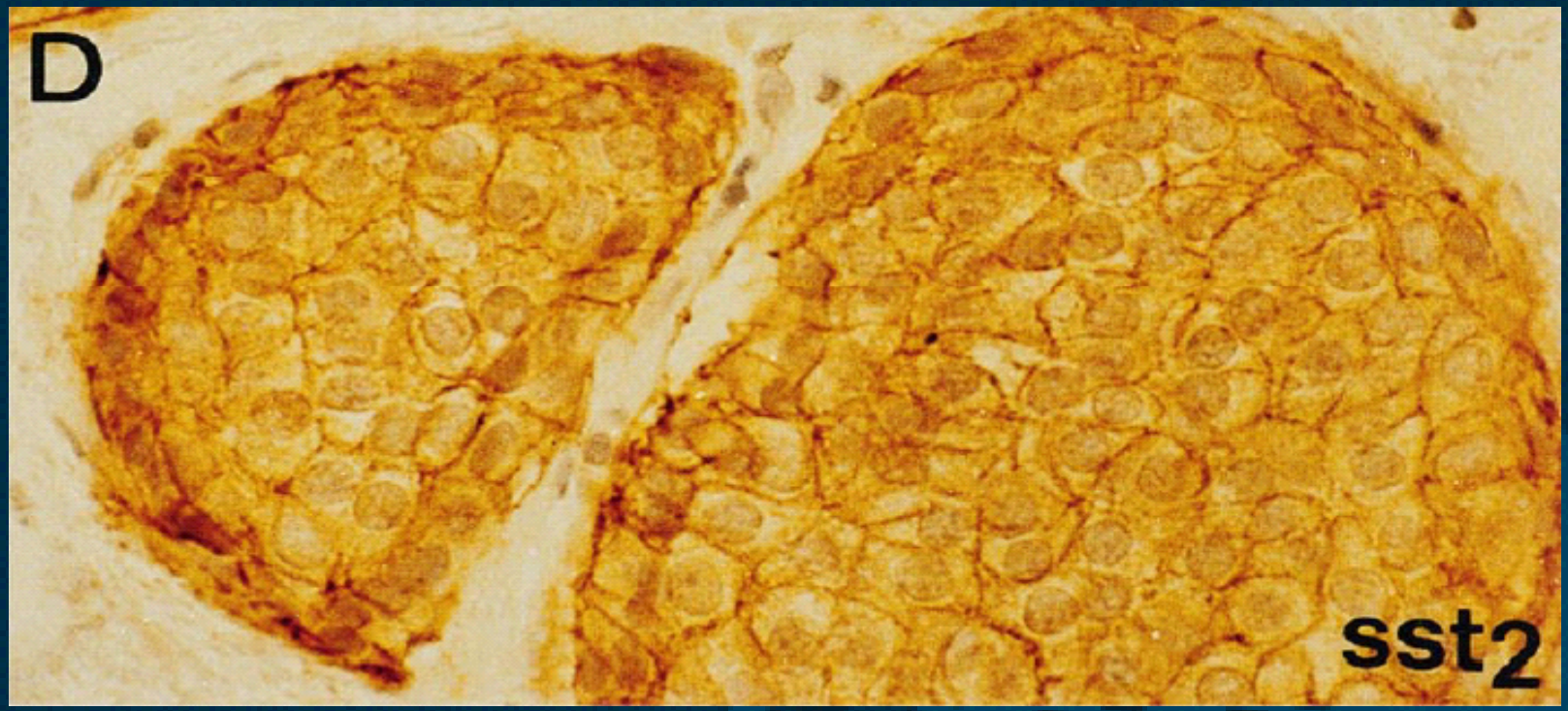
Peptide therapy: rationale basis receptor over-expression

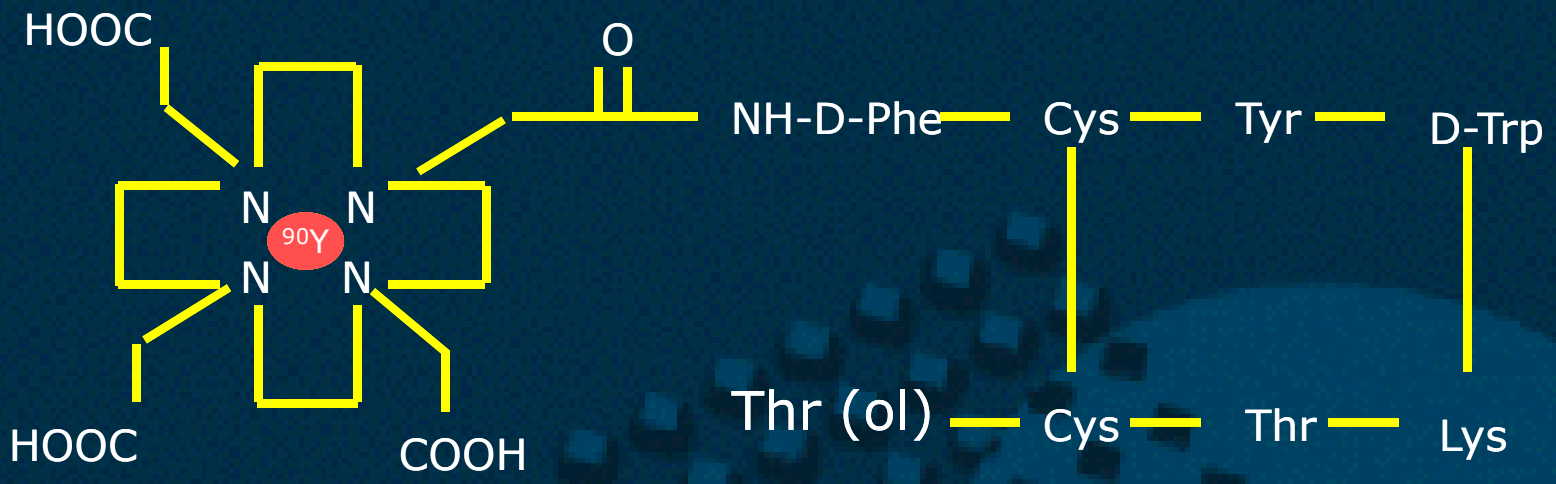


IHC for sst2 in human gastrinoma

Hofland LJ et al. JCE&M 1999

[^{90}Y-DOTA^{0}-Tyr^{3}]-octreotide

^{90}Y-DOTATOC

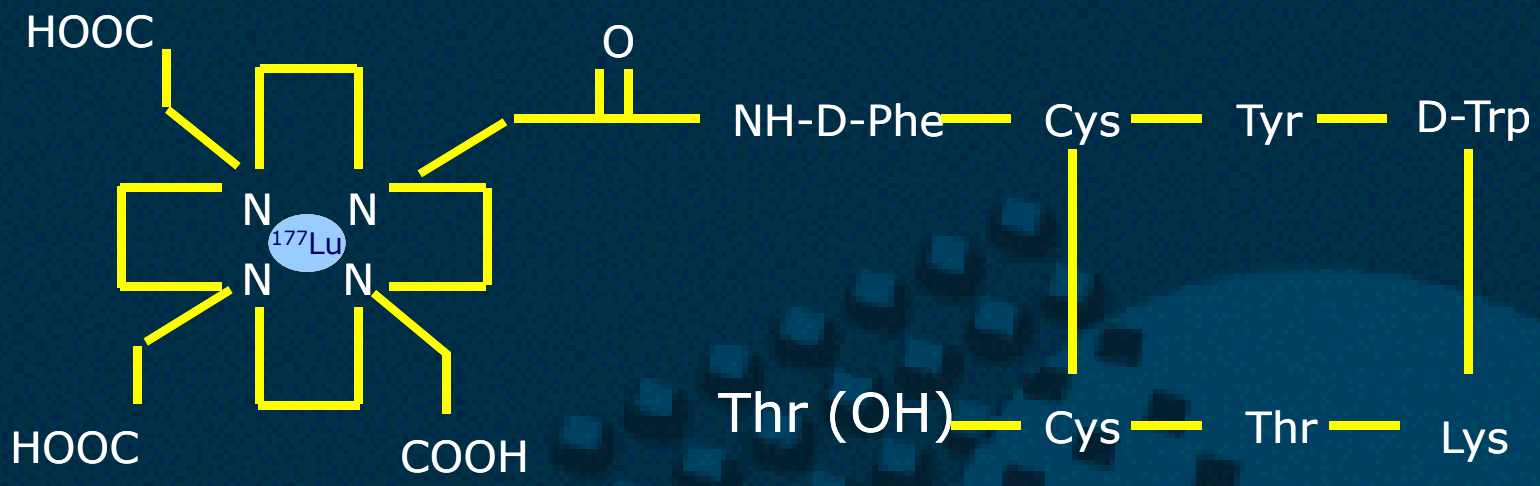


Affinity (IC_{50}, nM)

***sst*$_1$**	***sst*$_2$**	***sst*$_3$**	***sst*$_4$**	***sst*$_5$**
>10,000	**11** ± 1.7	**389** ± 13	**>10,000**	**114** ± 29

[^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate

^{177}Lu-DOTATATE



Affinity (IC_{50}, nM)

***sst*$_1$**	***sst*$_2$**	***sst*$_3$**	***sst*$_4$**	***sst*$_5$**
>10,000	**1.6** ± 0.4	**>1,000**	**523** ± 239	**187** ± 50

Radionuclides for therapy (electrons)

^{177}Lu	$T_{1/2}$	6.7 d	
	$E\gamma$	0.11 (3%) ; 0.21 (7%) MeV	
	$E_{max}\ \beta^-$	0.50 MeV	
	R_{max}	~ 1.8 mm	
^{90}Y	$T_{1/2}$	2.7 d	
	$E\gamma$	-	
	$E_{max}\ \beta^-$	2.3 MeV	cross-fire
	R_{max}	~ 11 mm	

Receptor radionuclide treatments at IEO -Milano

Patients treated from April 1997 to November 2008:

- ^{90}Y-octreotides:
  - Neuroendocrine tumours: 817 patients (70 in protocols):
    - 457 with ^{90}Y-DOTATOC; 360 with ^{90}Y-DOTATATE;
  - Non neuroendocrine tumours: 295 patients
    - 140 with ^{90}Y-DOTATOC; 155 with ^{90}Y-DOTATATE;
- ^{177}Lu-DOTATATE:
  - Neuroendocrine tumours : 157 patients (51 in protocol)
  - Non neuroendocrine tumours : 49 patients
- ^{90}Y-DOTA-lanreotide:
  - Non neuroendocrine tumours : 12 patients

Total: 1330 patients

Tumor types treated

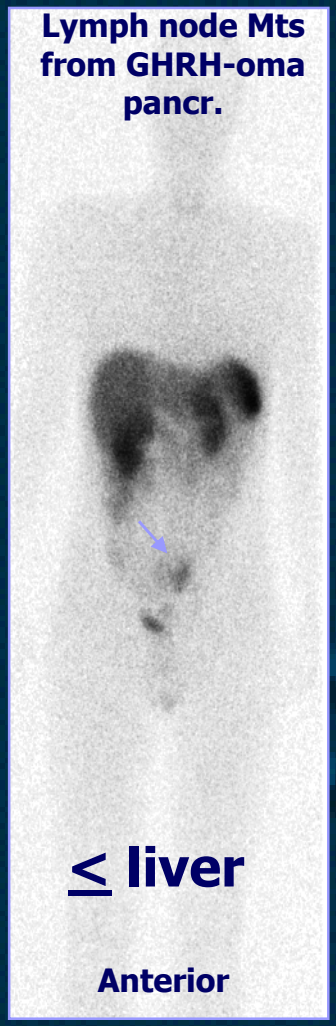
Skin	
Aggressive fibromatosis	2
Merkel cell carcinoma	1
Brain	
Meningioma	11
High-grade glioma	4
Ependymoma	1
Oligodendroglioma	1
Lungs	
Bronchial NET	11
SCLC	1
Stomach	
Gastric NET	3
Small Intestine	
Ileal NET	27
Pancreas	
Non-functioning NET	14
Gastrinoma	4
Insulinoma	3
Glucagonoma	2
VIPoma	1
Somatostatinoma	1
GH-RH secreting NET	1
Rectum	
Rectal NET	2
Unknown	
NET of unknown origin	13
Breast	
Infiltrating ductal carcinoma	2
Thyroid	
Medullary thyroid carcinoma	23
Papillary thyroid carcinoma	2
Ganglia	
Paraganglioma	1
Phaeochromocytoma	2
Pituitary	
GH/PRL-oma	1
GH-oma	1
PRL-oma	1
Non-functioning adenoma	2
Unusual NET sites	
Retroperitoneal NET	1
Testicular NET	1
Thyroid NET	1
Total number	141

NET, Neuroendocrine tumour; SCLC, small cell lung cancer; GH, growth hormone; PRL, prolactin

Bodei L et al. Eur J Nucl Med Mol Imaging 2004

Inclusion Criteria: receptor scintigraphy

Grade 1



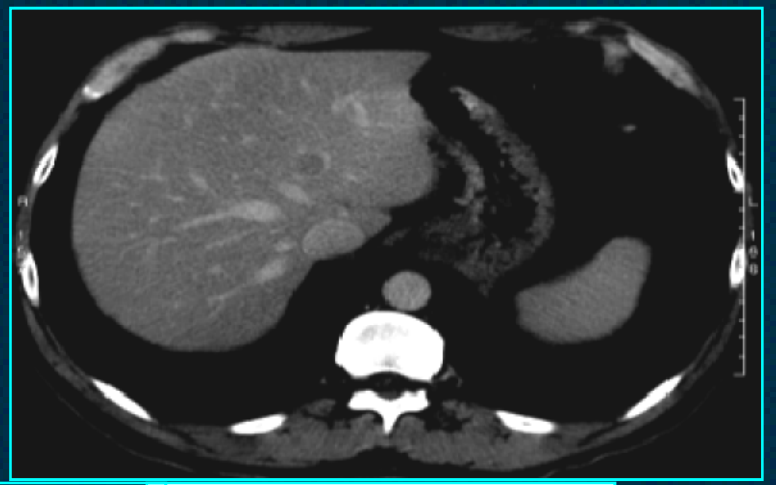
Grade 2

Grade 3

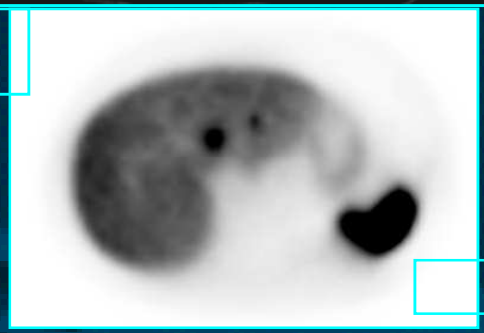
Grade 4

^{111}In-Octreotide (OctreoScan®)

^{68}Ga-DOTATOC



Axial cCT (portal phase)



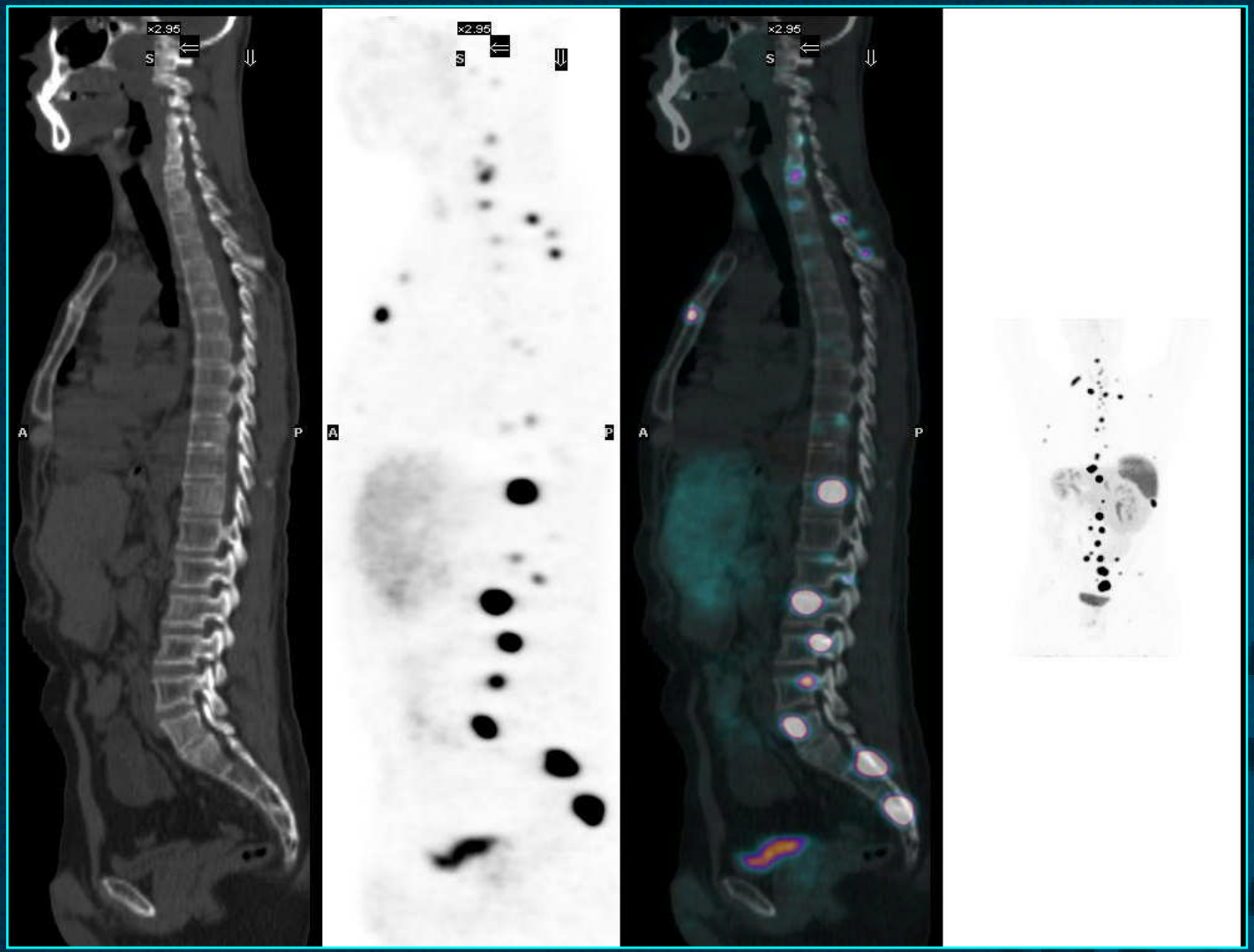
68Ga-PET

T. P. 54 y

Liver metastases from
well-differentiate neuro-endocrine carcinoma of Ileum

- Surgery on primary

- Cromogranine-A: 100% positive
- NSE: 100% positive
- sst_2-receptor: 100% positive
- Ki-67: 5%


×2.95
S
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×2.95
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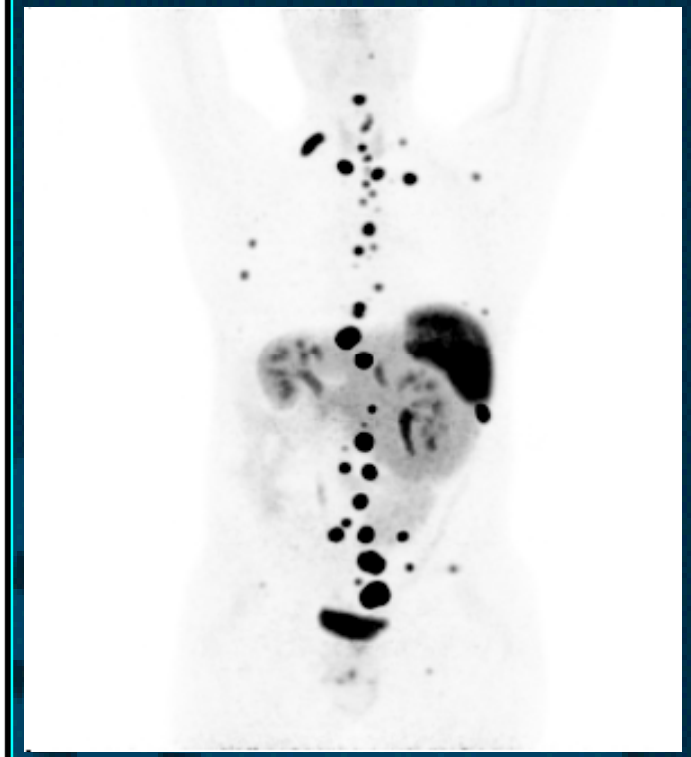
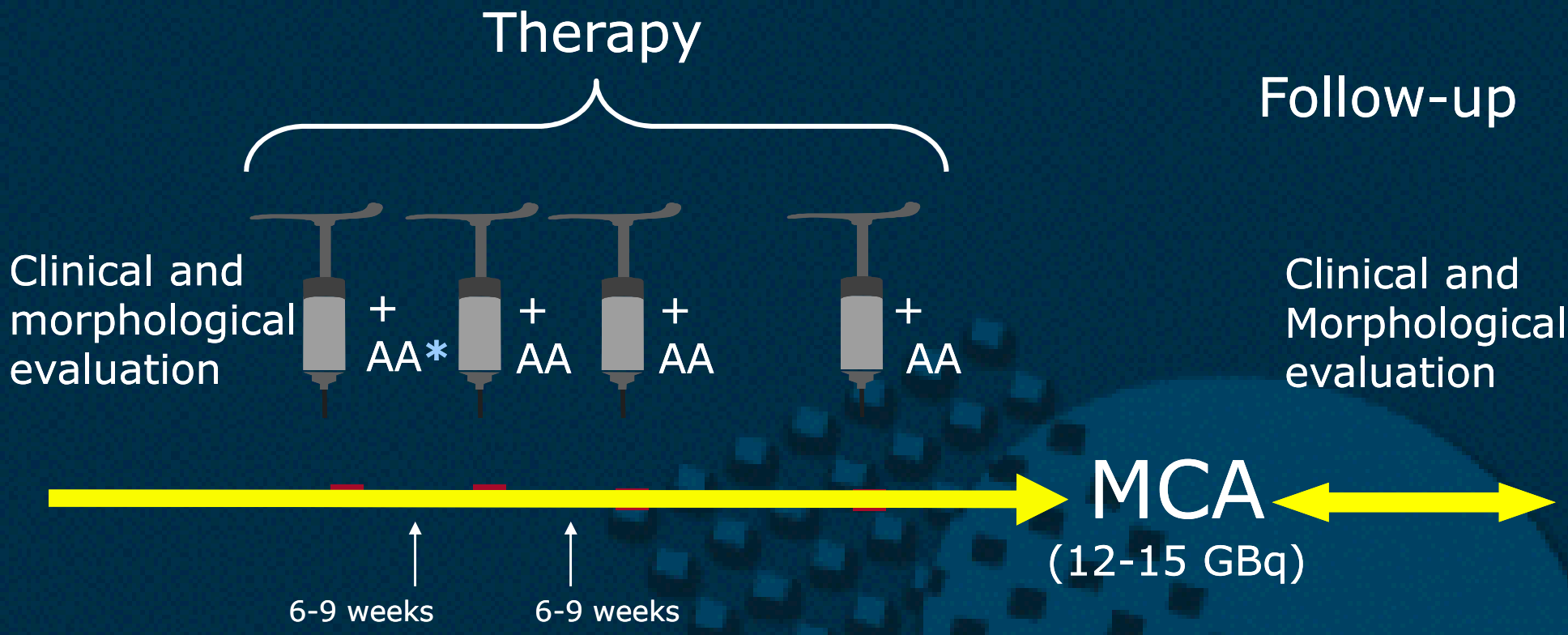
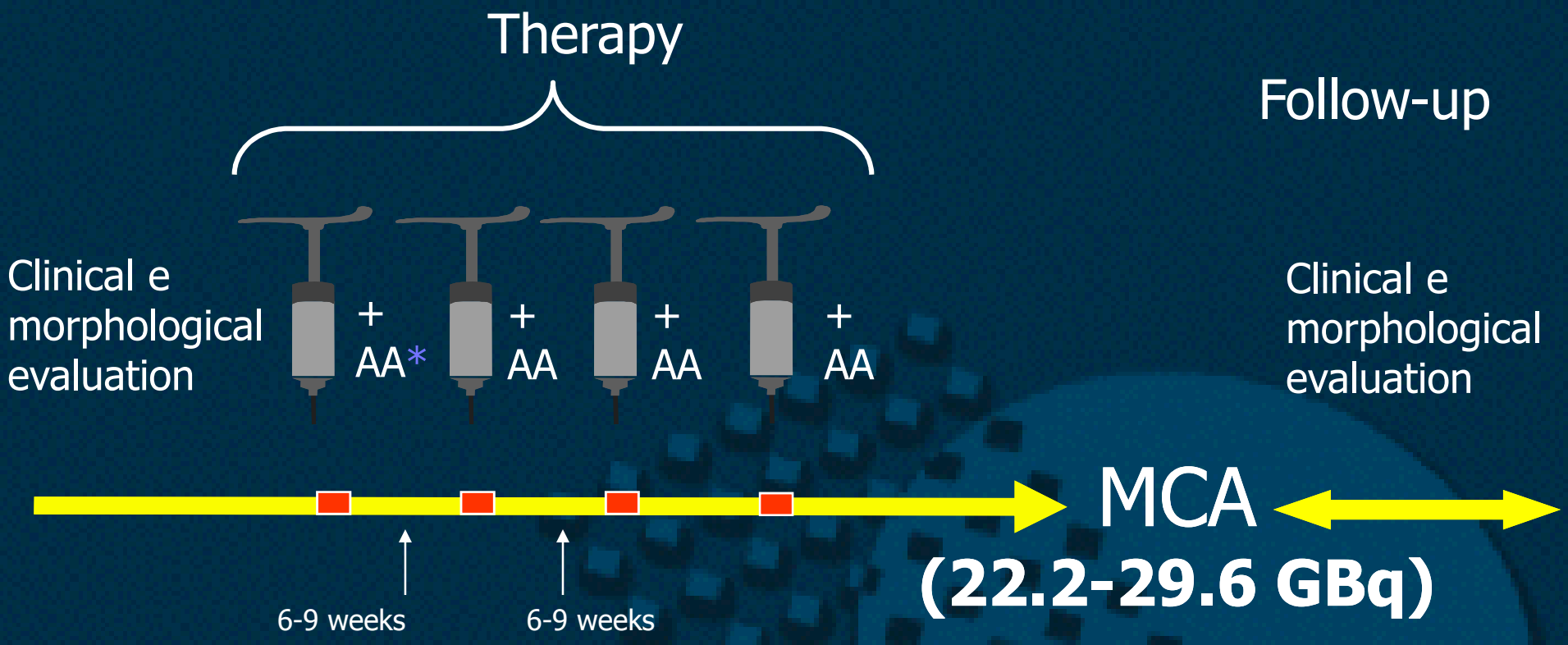


IEO –standard protocol
^{90}Y-DOTATOC



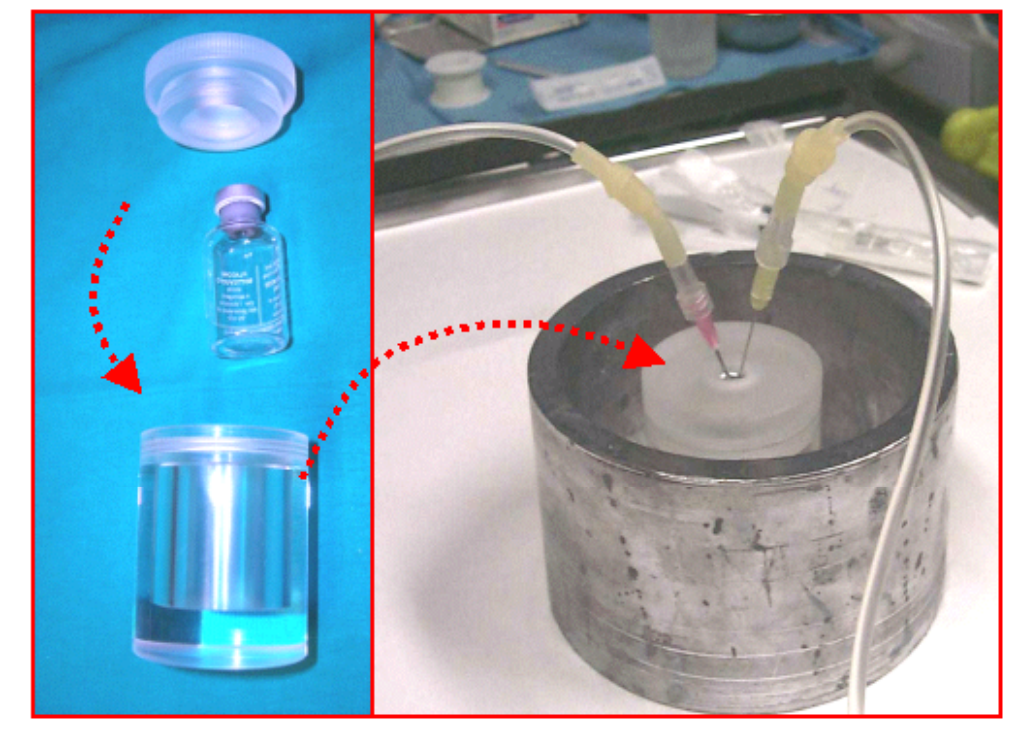
* Arginine 12.5 g in 500 ml saline before therapy
Arginine 12.5 g in 500 ml saline after therapy
Arginine 12.5 g in 500 ml saline x 2 upto two days after therapy

^{177}Lu-DOTATATE therapy schedule



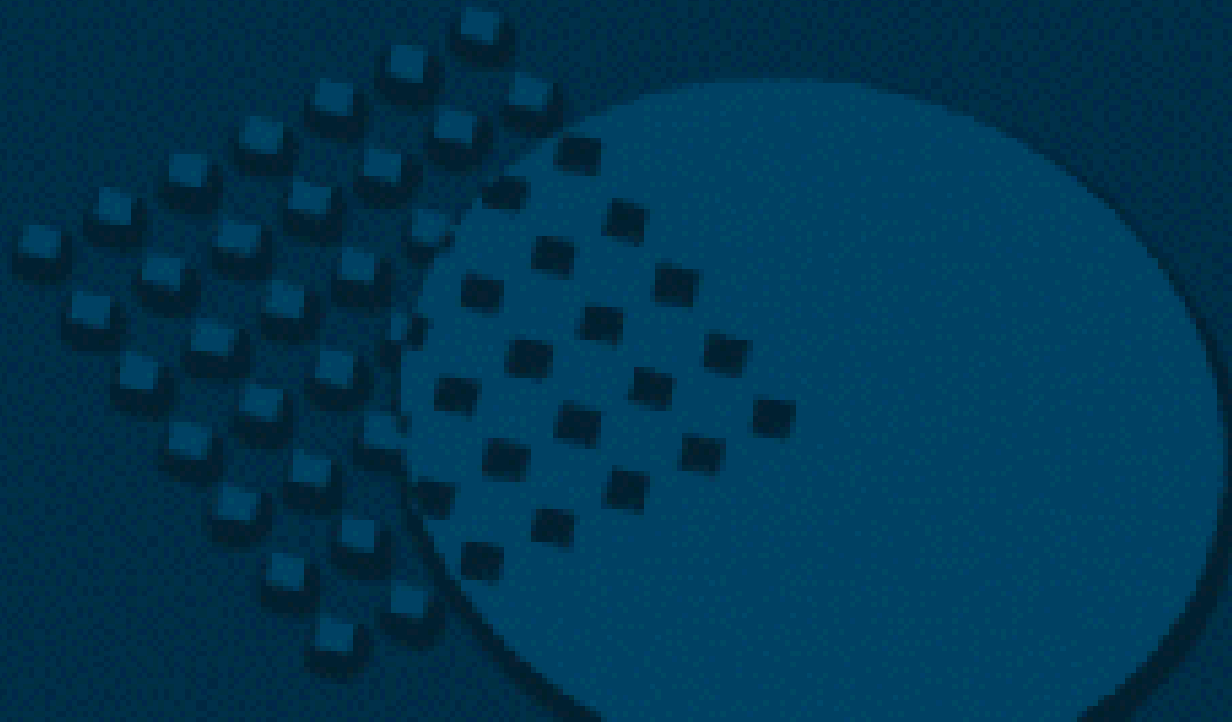
* Arginine 12.5 g in 500 ml saline before therapy
Arginine 12.5 g in 500 ml saline after therapy
Arginine 12.5 g in 500 ml saline b.i.d. up to two days after therapy

Administration System

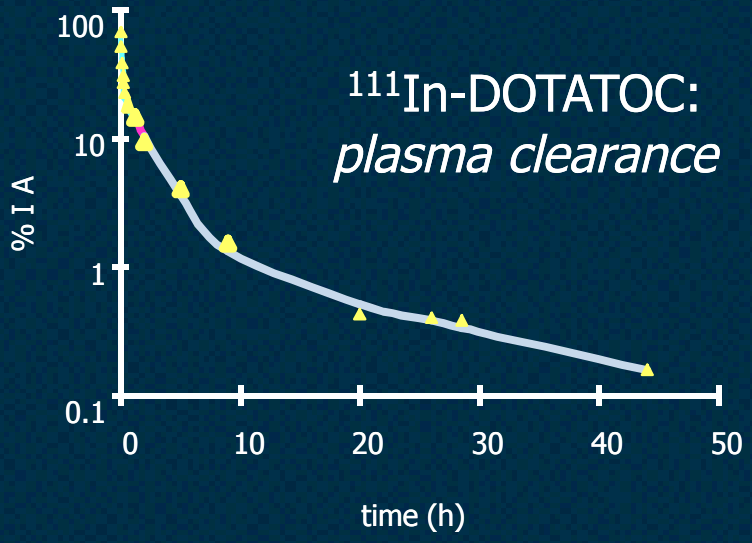


I.E.O. infusion system: the radiopharmaceutical is provided in a vial shielded by a PMMA sleeve (1 cm thick), further surrounded by lead (1 cm thick). A double catheter system is used, one coming from a saline bag located on a pole to the ^{90}Y vial, and the one from the ^{90}Y vial to the patient

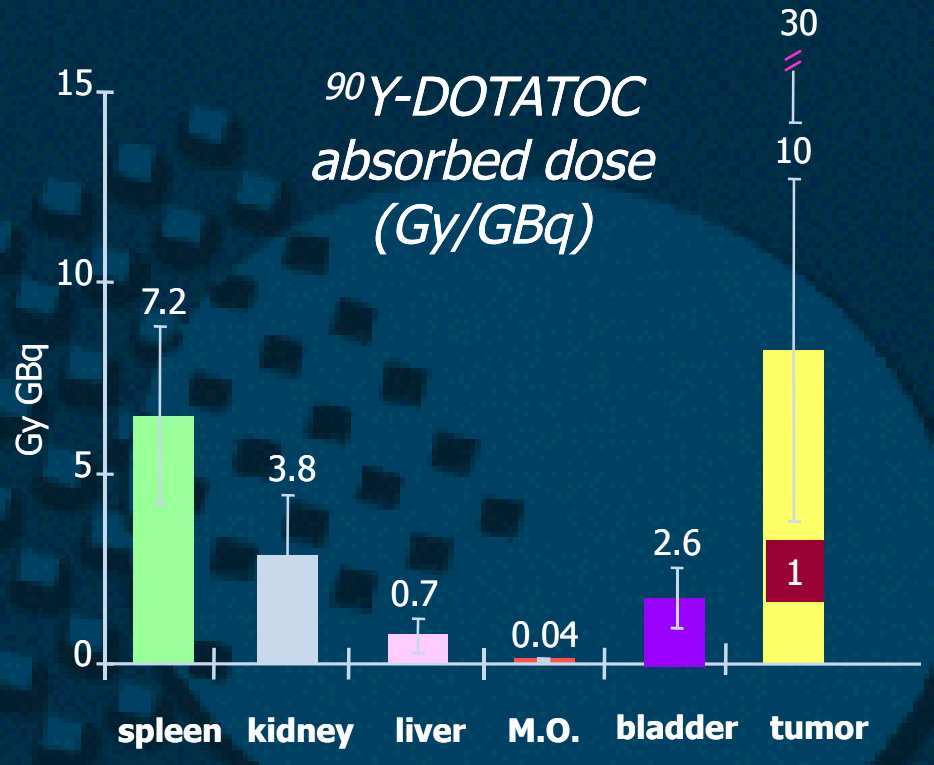
PHARMACOKINETICS AND DOSIMETRY



^{90}Y-DOTATOC: biodistribution and dosimetry



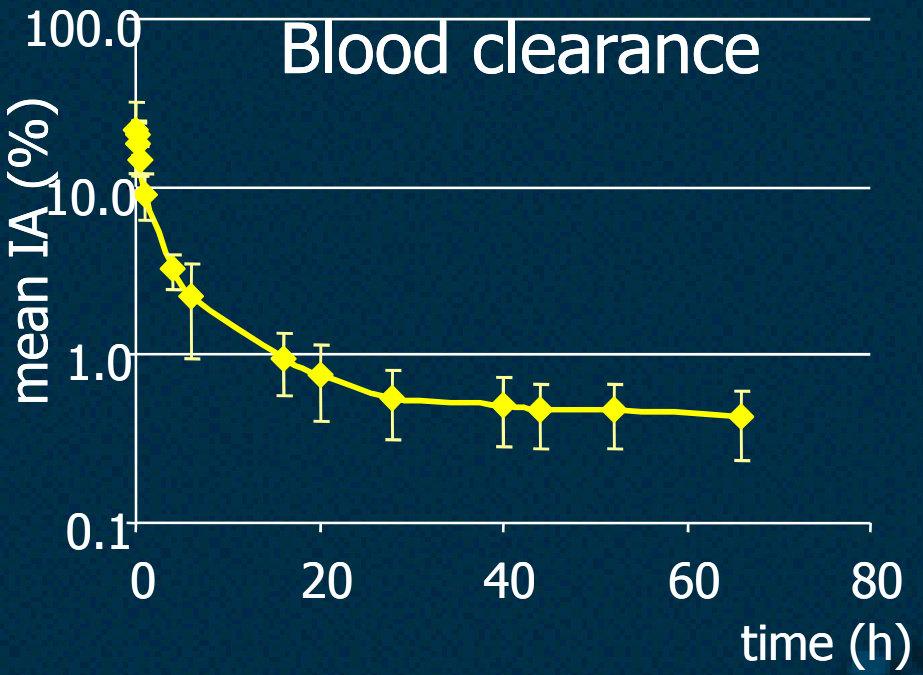
^{111}In-DOTATOC:
plasma clearance



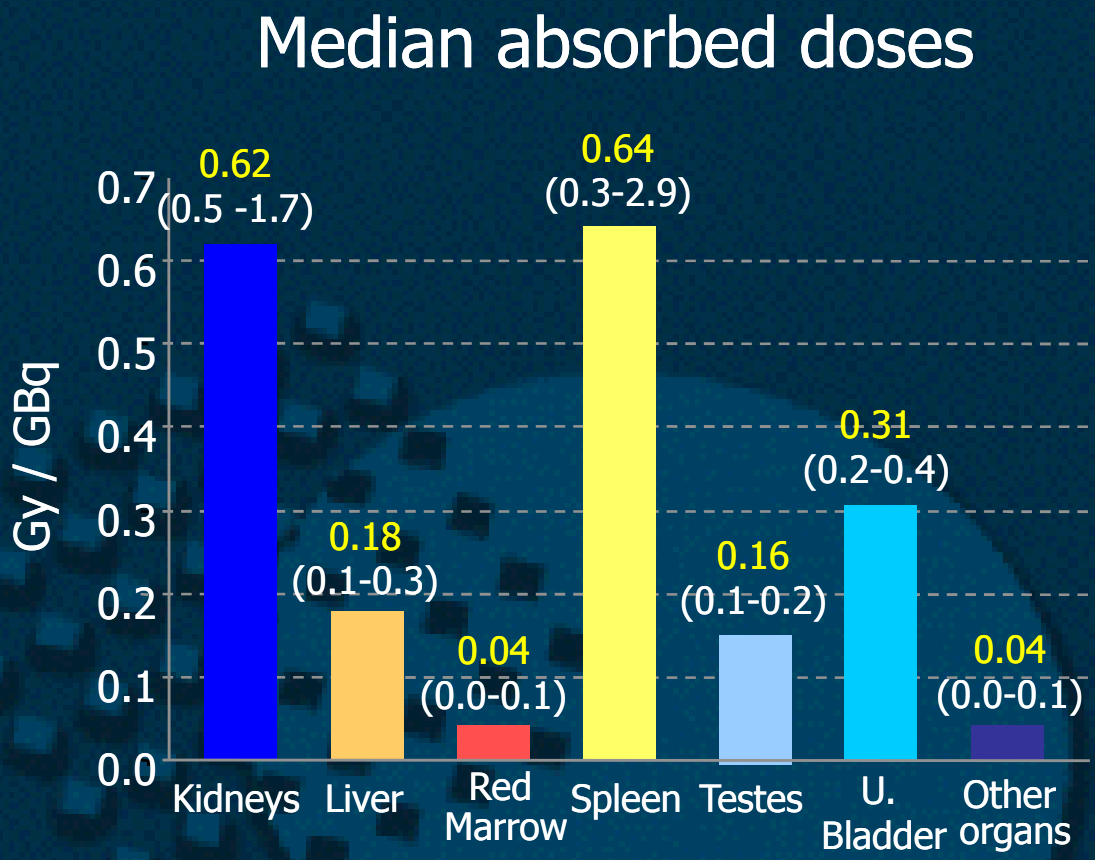
Cremonesi M et al. Eur J Nucl Med 1999

Cremonesi M et al. J Nucl Med 2006

^{177}Lu-DOTATATE: biodistribution and dosimetry



Tumours (0.6 – 56) Gy/GBq

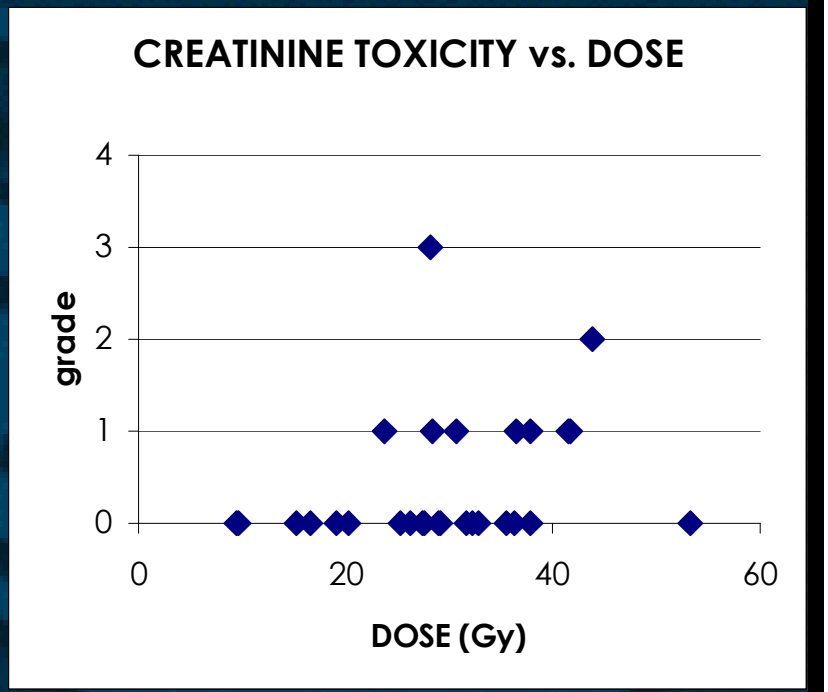


90Y-DOTATOC and 177Lu-DOTATATE

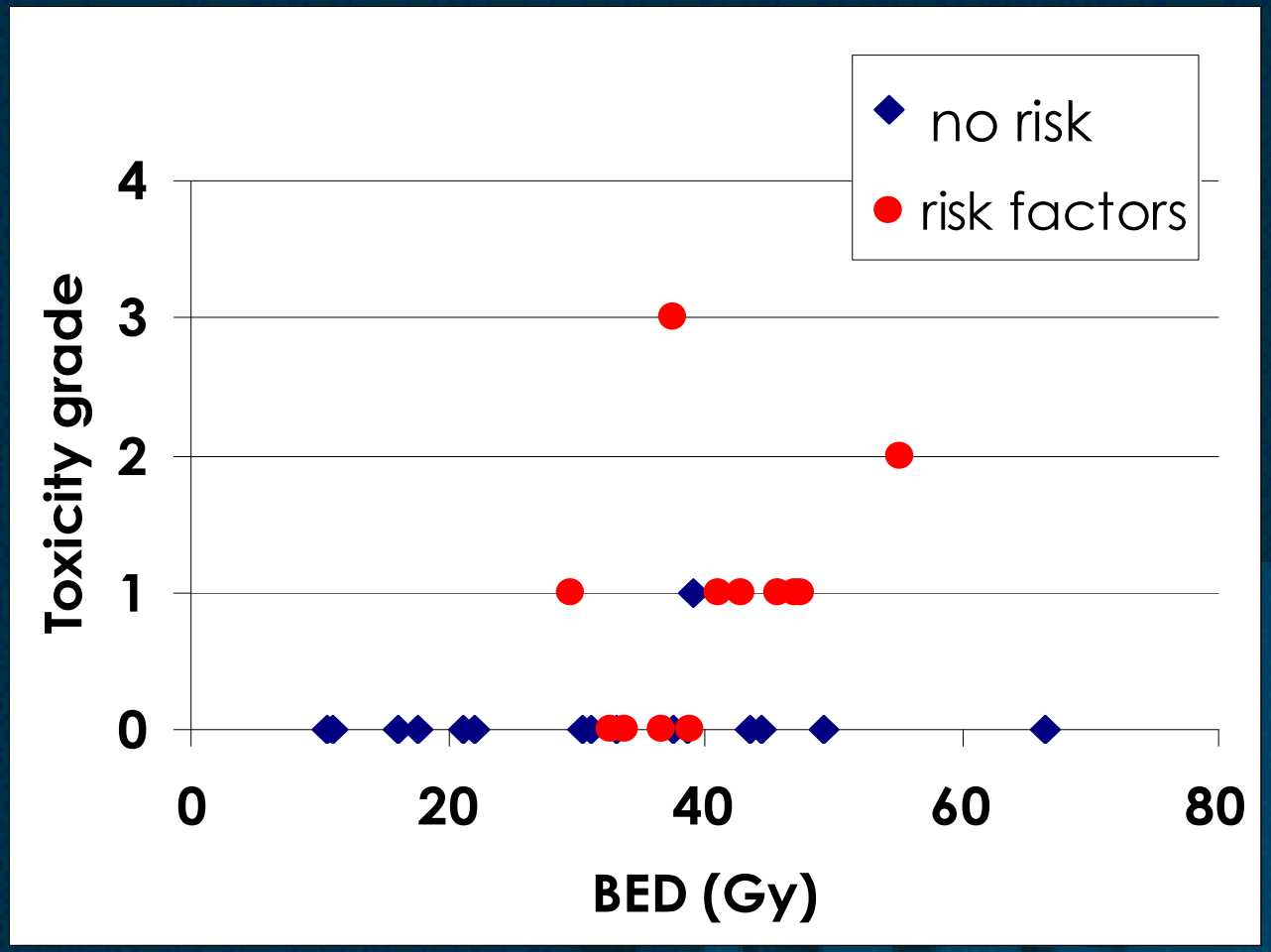
Kidney Toxicity

Results: renal parameters

- Patients treated with ^{90}Y-DOTATOC had:
  - creatinine clearance loss >10% at 1 year in 14 cases
  - creatinine toxicity in 9 cases
    - 7 grade 1
    - 1 grade 2
    - 1 grade 3



Creatinine toxicity vs BED and risk factors



BED threshold of 28 Gy (22 dose) in patients with risk factors
BED threshold of 40 Gy (30 dose) in patients without risk factors

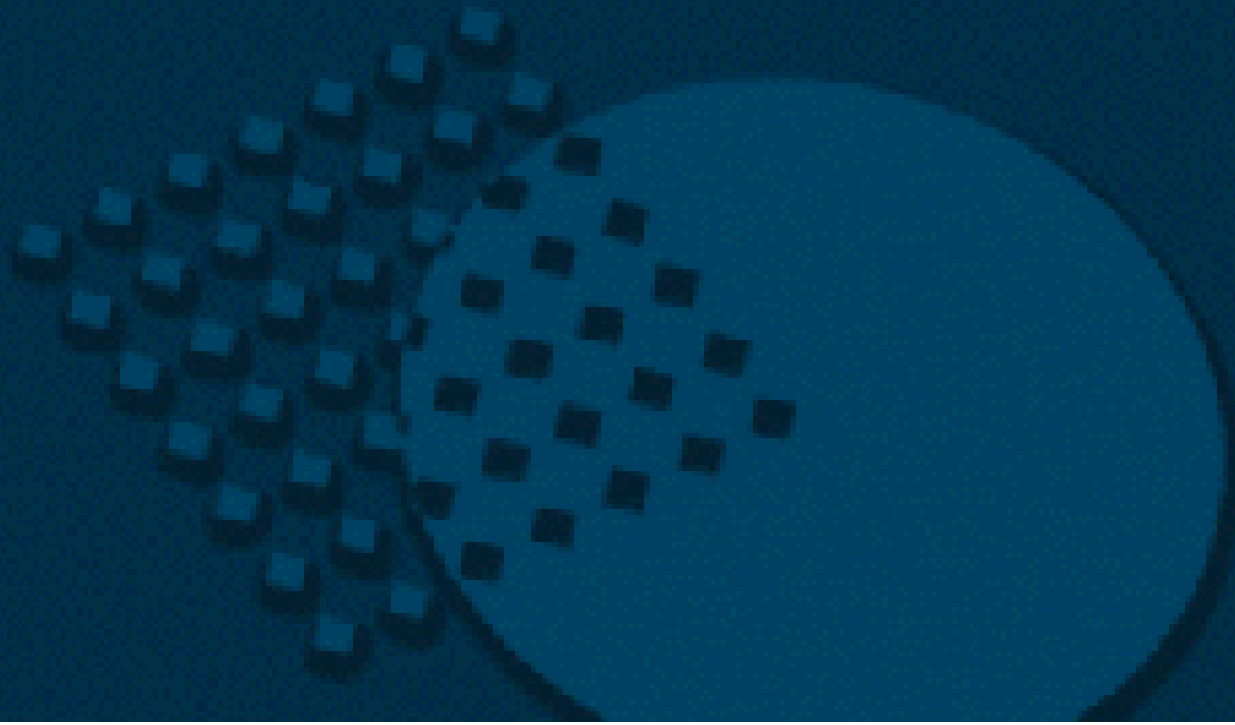
Results: renal parameters

- None of the patients treated with ^{177}Lu-DOTATATE had any toxicity for the moment (FuP: 2-11 m)

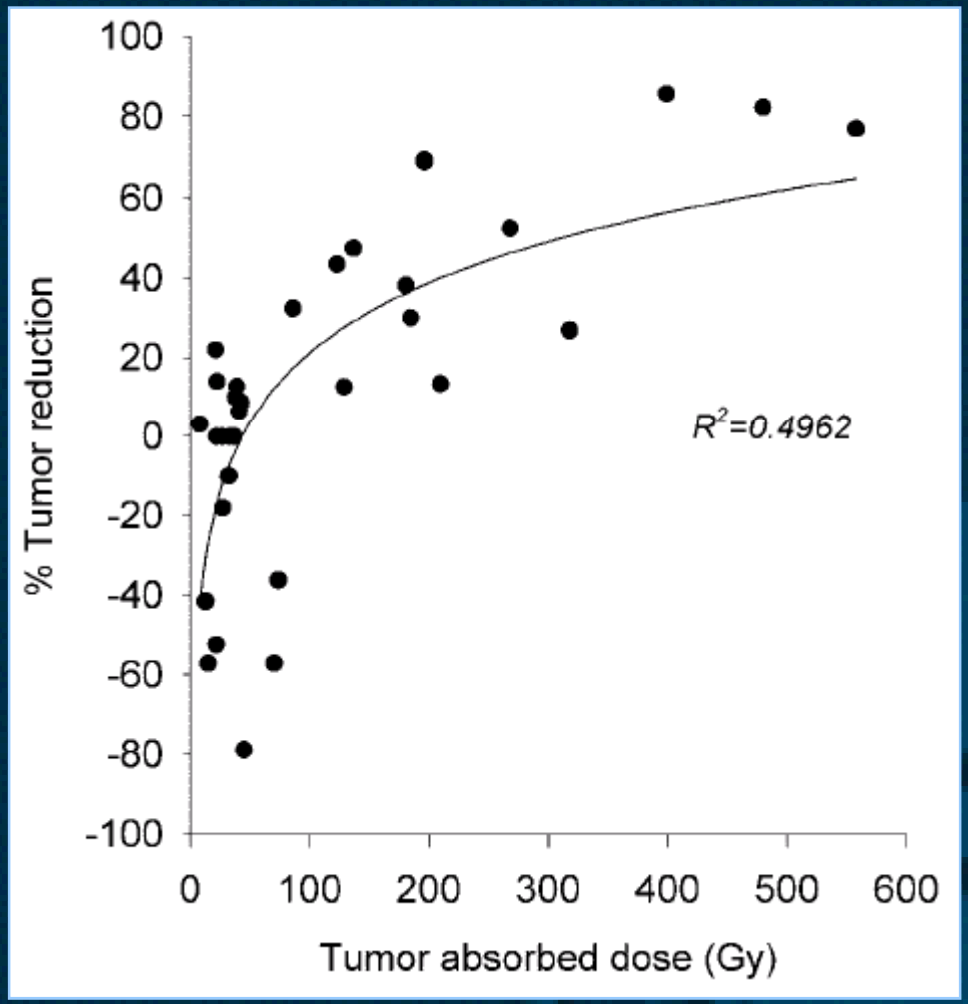
Kidney dose	0.62 (0.5-1.7) Gy/GBq
Median	15 (10-39) Gy cumulative

Dosimetric results would suggest an acceptable dose for the kidneys with cumulative IA up to 30 GBq

EFFICACY



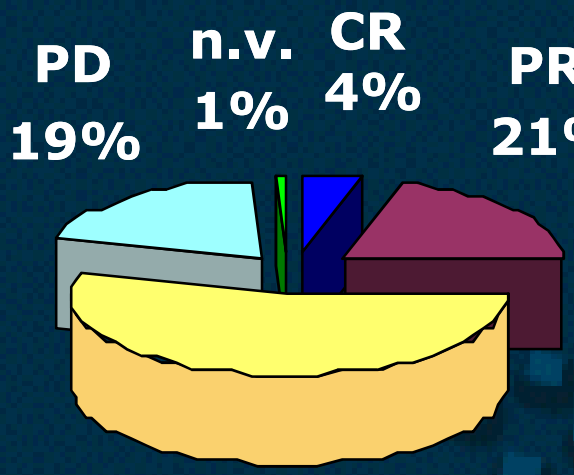
DOSE-EFFECT RELATIONSHIP



Pauwels S et al. J Nucl Med 2005

^{90}Y-DOTATOC: objective response in patients treated with ≥7.4 GBq

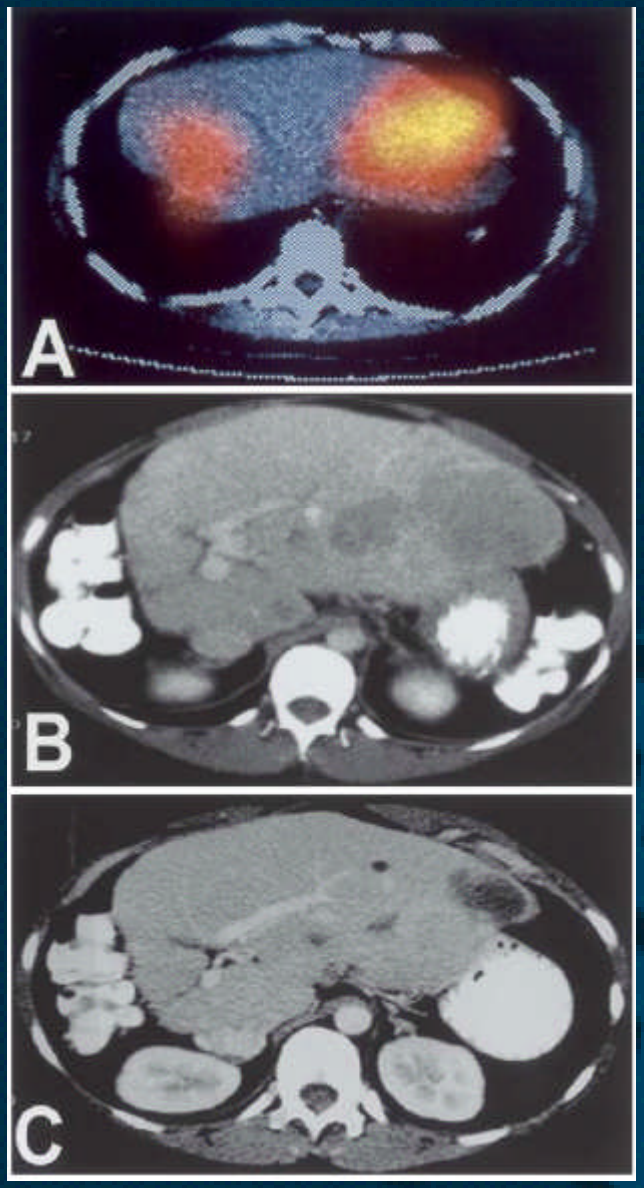
141 pts



Duration
2 - 59 m (m 18)

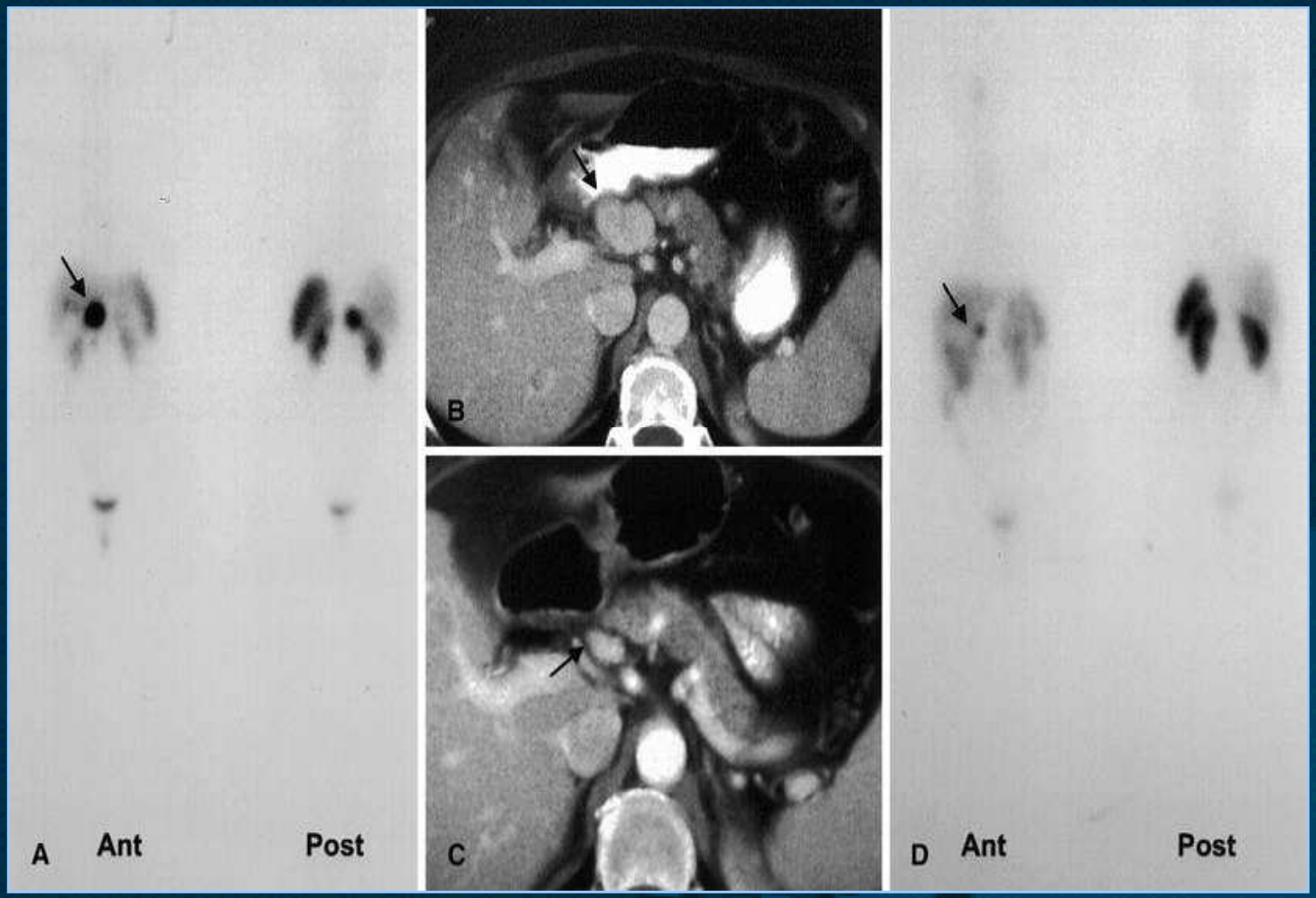
L. Bodei et al. Eur J Nucl Med Mol Imaging 2004

[^{90}Y-DOTA^{0},Tyr^{3}]-octreotide: response



Bodei L et al. Eur J Nucl Med 2003

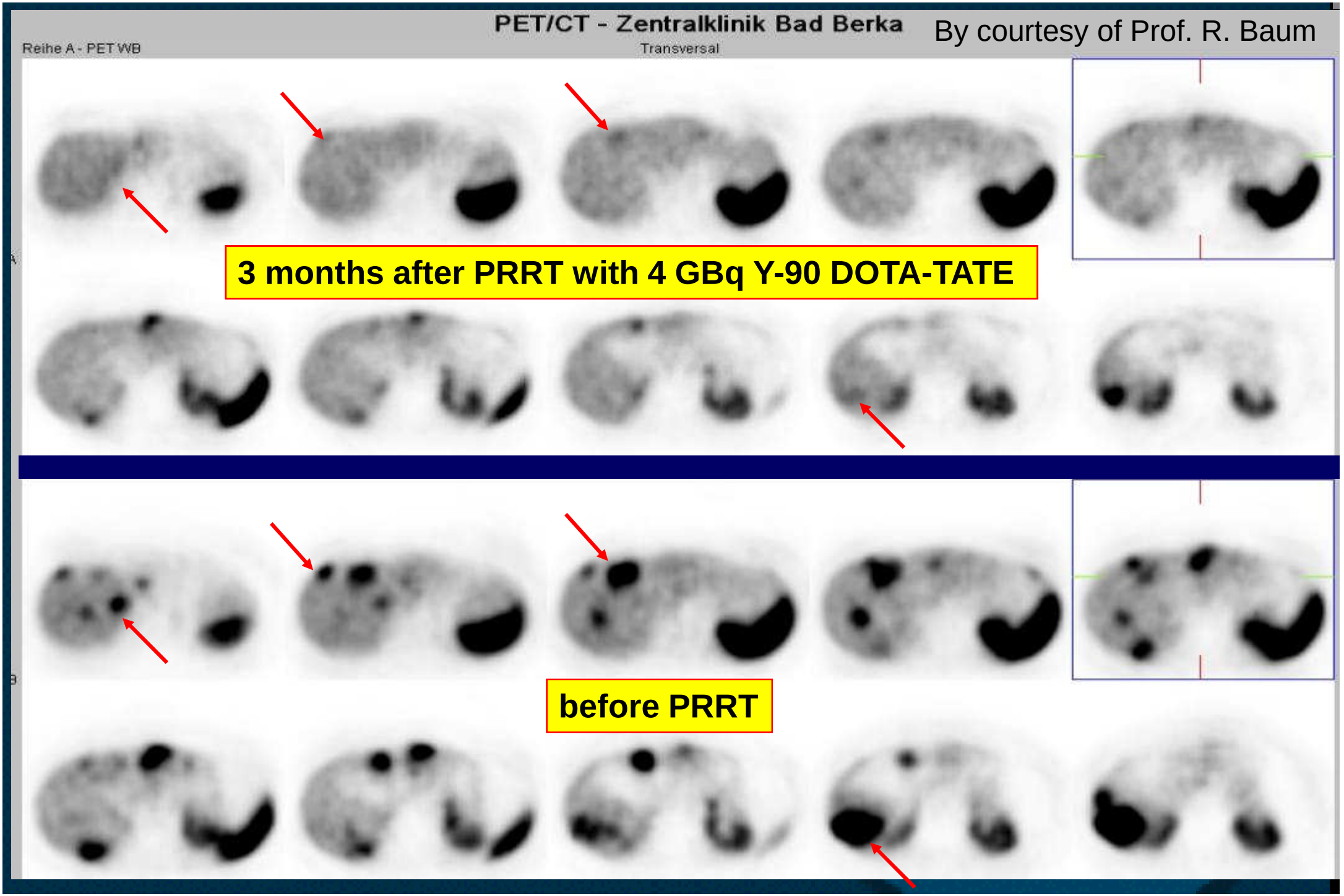
Endocrine pancreatic carcinoma



basal

after ^{90}Y-DOTATOC

Paganelli G, Eur J Nucl Med 2001

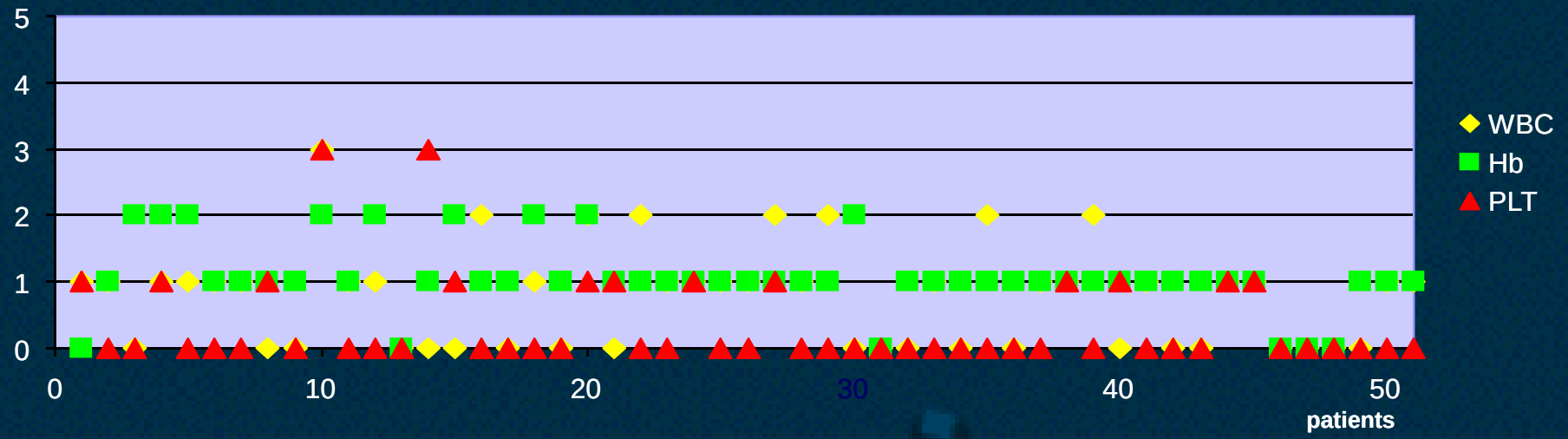

PET/CT - Zentralklinik Bad Berka
Reihe A - PET WB
Transversal
By courtesy of Prof. R. Baum
3 months after PRRT with 4 GBq Y-90 DOTA-TATE
before PRRT

^{177}Lu-DOTATATE
IEO S189/104: a phase I-II study

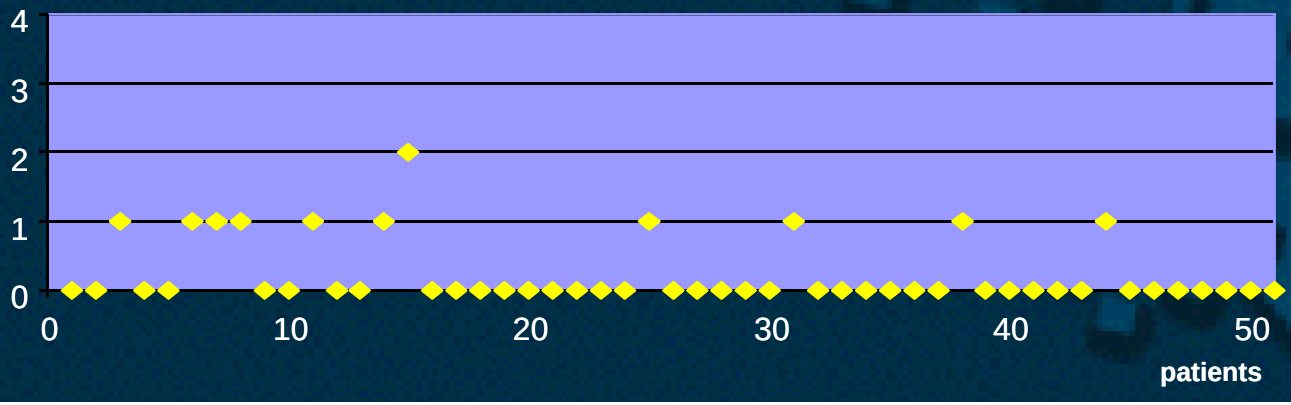
- 51 patients (26 m, 25 f, 30-79 y, median 54)
- 38 / 51 (75%) in PD at enrolment
- treated with 3.7 - 7.4 GBq/cycle, MCA 3.7 - 28.9 GBq in 1-7 cycles
- *Treatments completed Sept. 2008 -> evaluation ongoing*

bronchial endocrine carcinoma	**5**
duodenum endocrine carcinoma	**3**
ileum endocrine carcinoma	**19**
appendix endocrine carcinoma	**1**
rectum endocrine carcinoma	**1**
pancreatic endocrine carcinoma	**13**
endocrine ca. of unknown origin	**5**
paraganglioma	**3**
meningioma	**1**

Haematological toxicity



Renal toxicity
(creatinine)



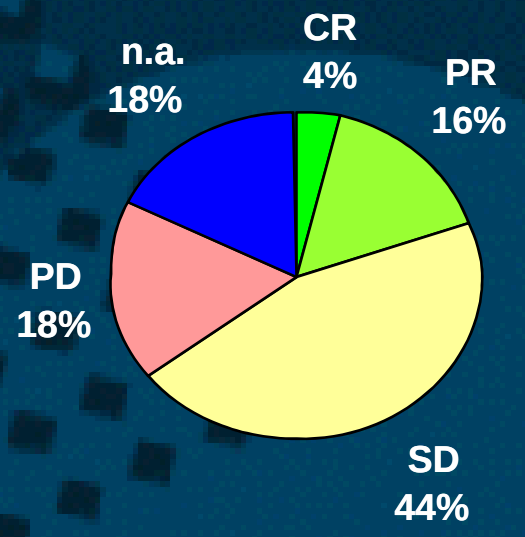
IEO S189/104

Objective response

51 patients (75 % PD)

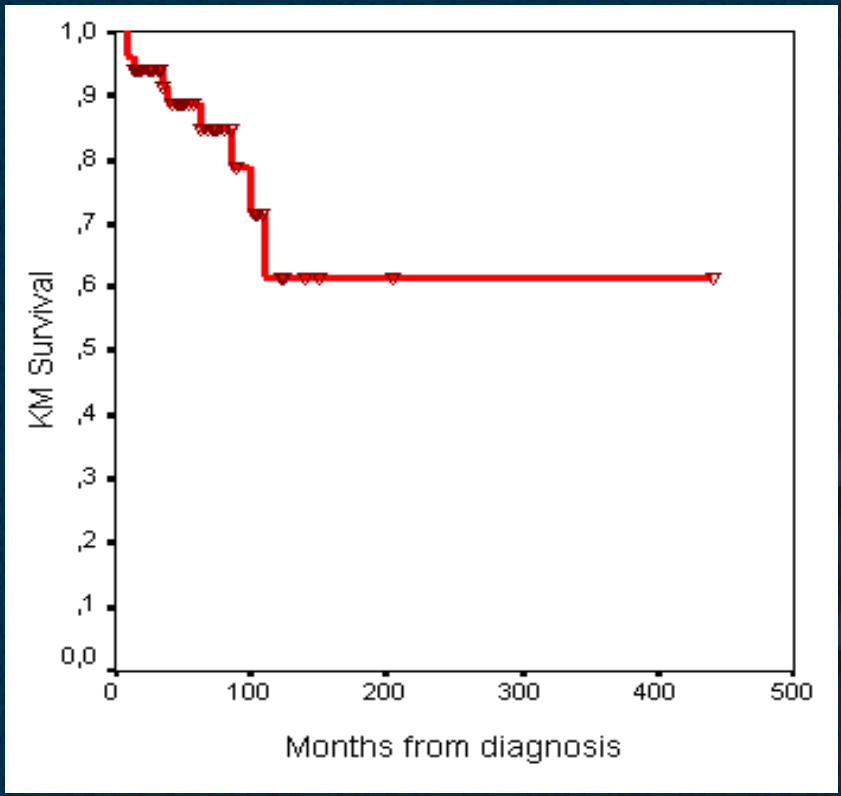
- 6 pts OFF protocol
  for massive progression/other ca.
- 8 pts still to be evaluated (last treatment few days ago)

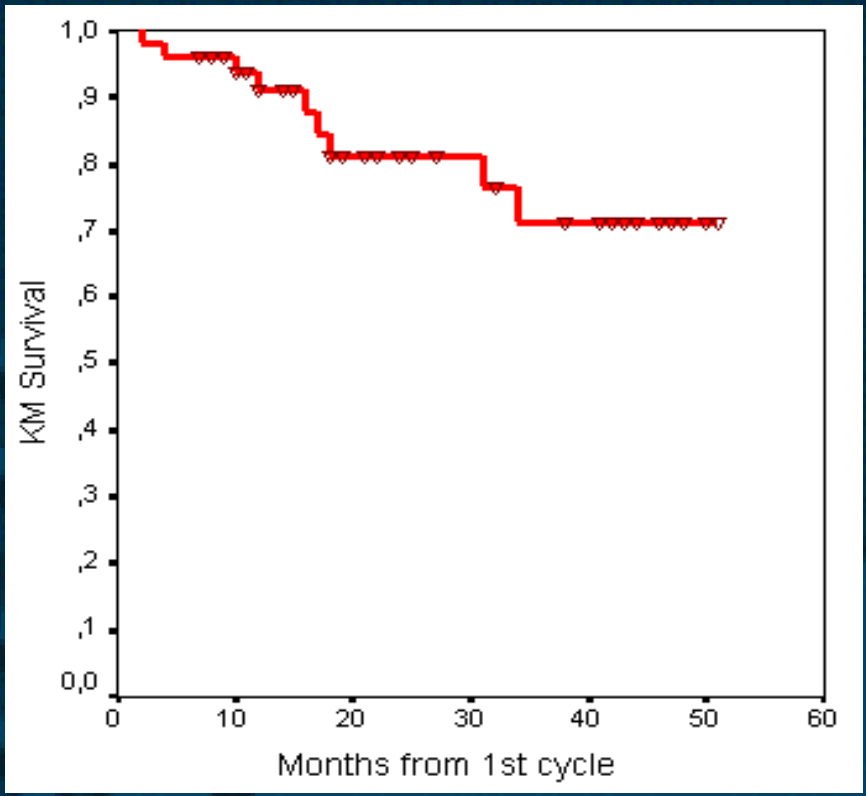
43 patients (MCA: 22.2 - 28.9 GBq)



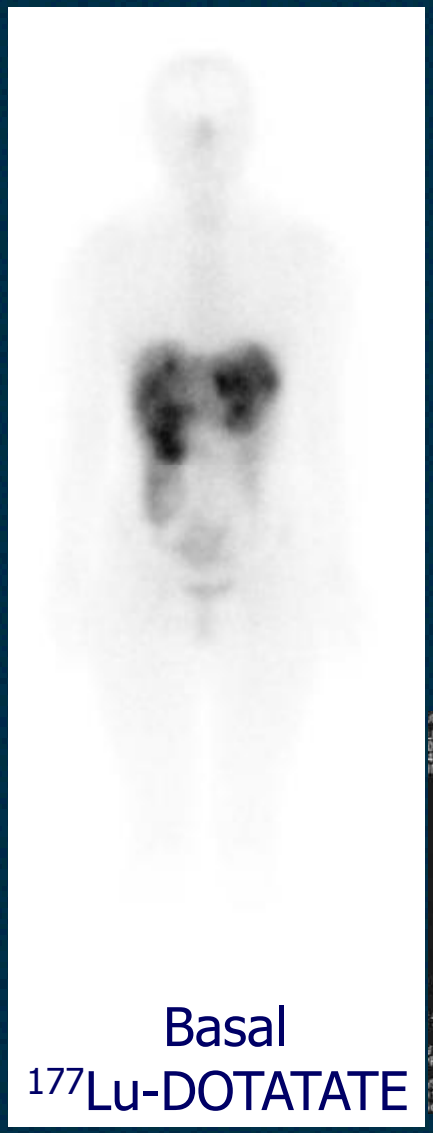
Duration of response
3-39 months
(median 14)

PRRT with ^{177}Lu-Octreotate
Survival in 51 NET patients (IEO S189/104)





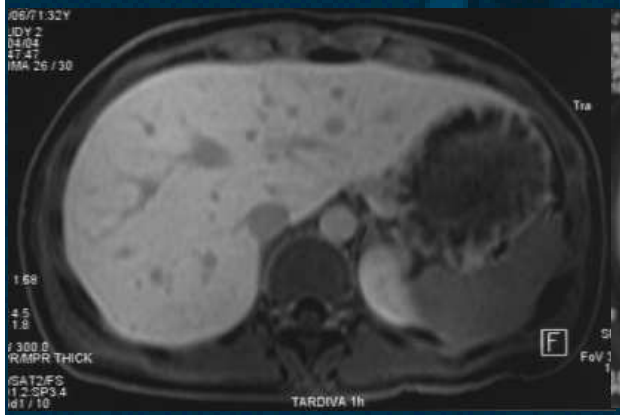
Objective response: pt #20



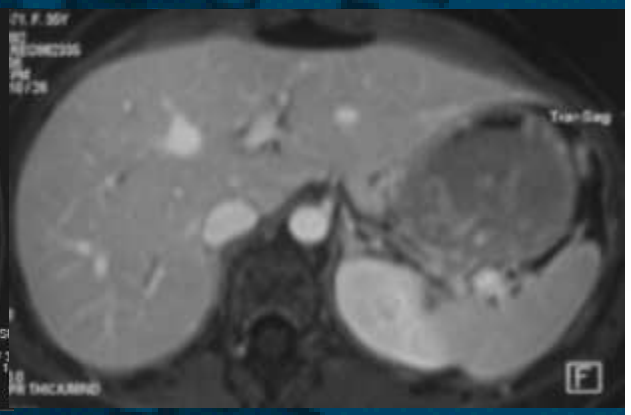
Basal
^{177}Lu-DOTATATE

Basal arteriograpy

Basal MR

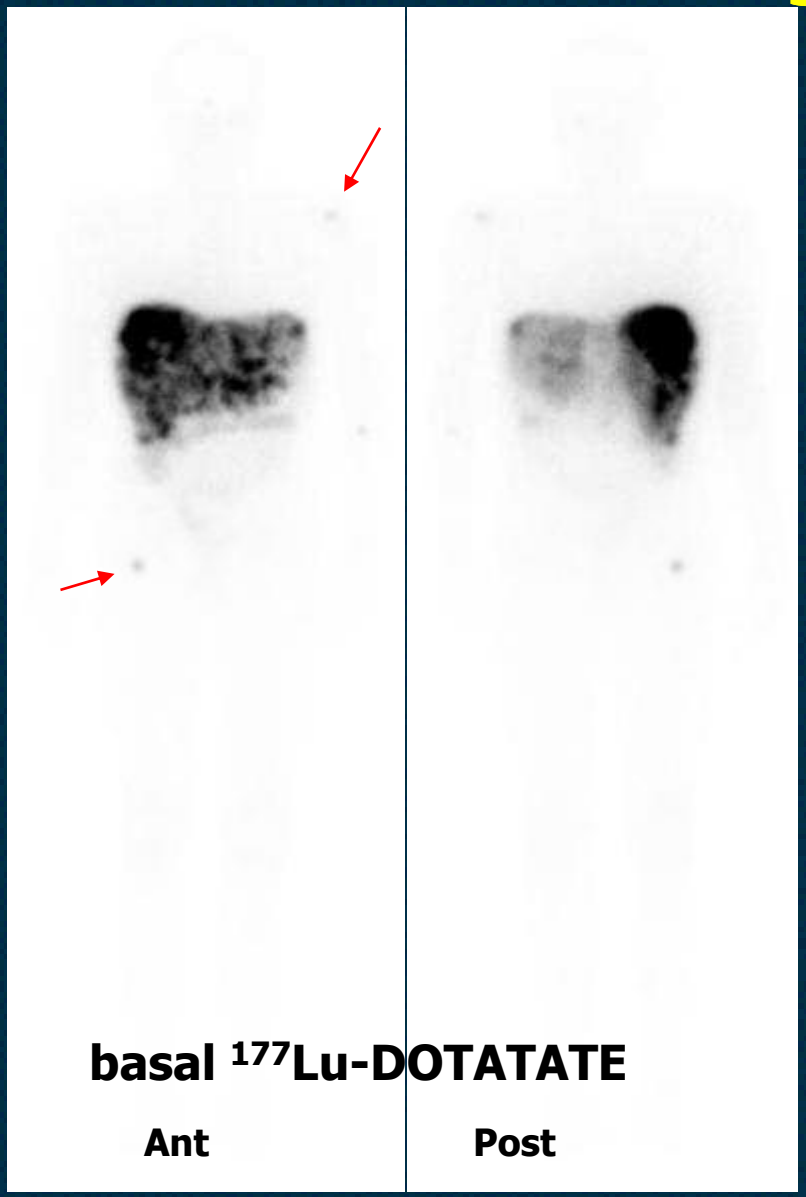


Final MR



Final
^{177}Lu-DOTATATE

Favourable factors: high uptake, small tumor volume



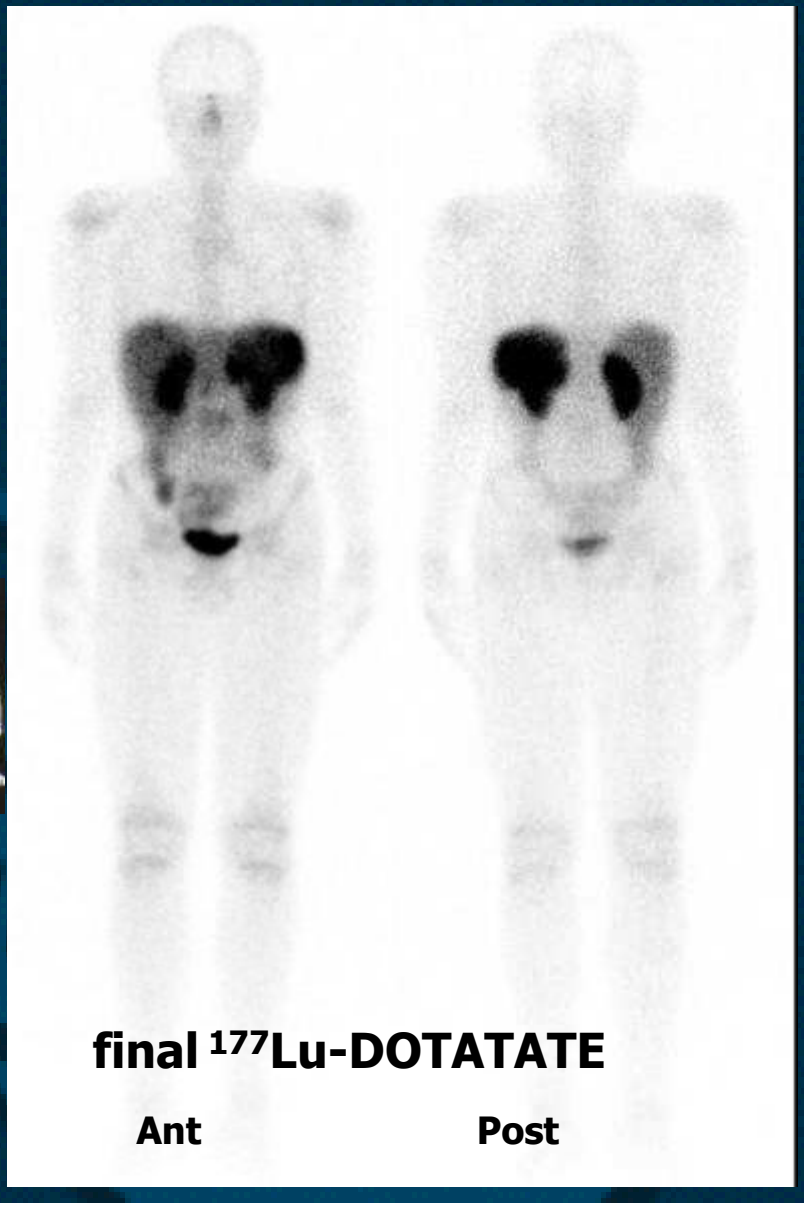
basal ^{177}Lu-DOTATATE

Ant Post

basal MR

final MR

IEO S189/104



final ^{177}Lu-DOTATATE

Ant Post

WHAT NEXT?

UNIFORM STUDIES NEEDED

- phase II studies on single classes of diseases
- comparison studies between ^{90}Y and ^{177}Lu

FURTHER DEVELOPMENTS

- GMP CENTRALIZED PRODUCTION AND DELIVERY OF RADIOPEPTIDES
  - to overcome the difficulties of legislation in various countries on experimental studies
  - to pass from experimental to standardized therapy

Receptor radionuclide therapy in Italy

- IEO Milano: since 1997
- Others: since 2002
- Ready to start

CONFIDENTIAL

Acknowledgements