APPLICABILITY OF PRRT IN THE „REAL WORLD“

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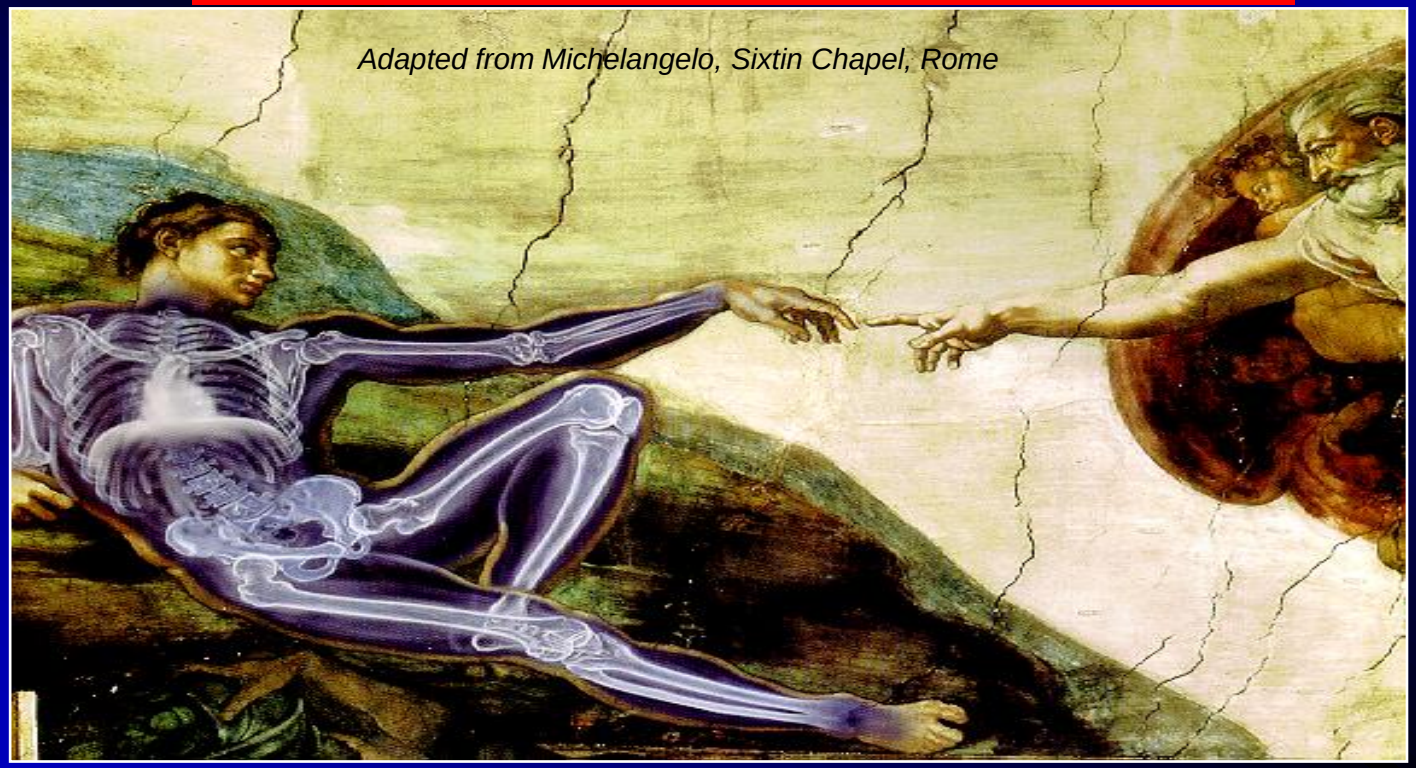


X Simposio Internacional GETNE

Madrid 10th October 2014

Disclosures

- **Conflicts of Interest - None**
- Consultant/Advisor: OctreoPharm Sciences GmbH
- Research Grants: ITM, Novartis, Ipsen, Covidien, Shaanxi, Inc.
- Scientific Study/Trial: ImaginaAb, AAA
- Scientific Meetings Support:

• http://www.itr8.com/hosted/badberka/jun2011

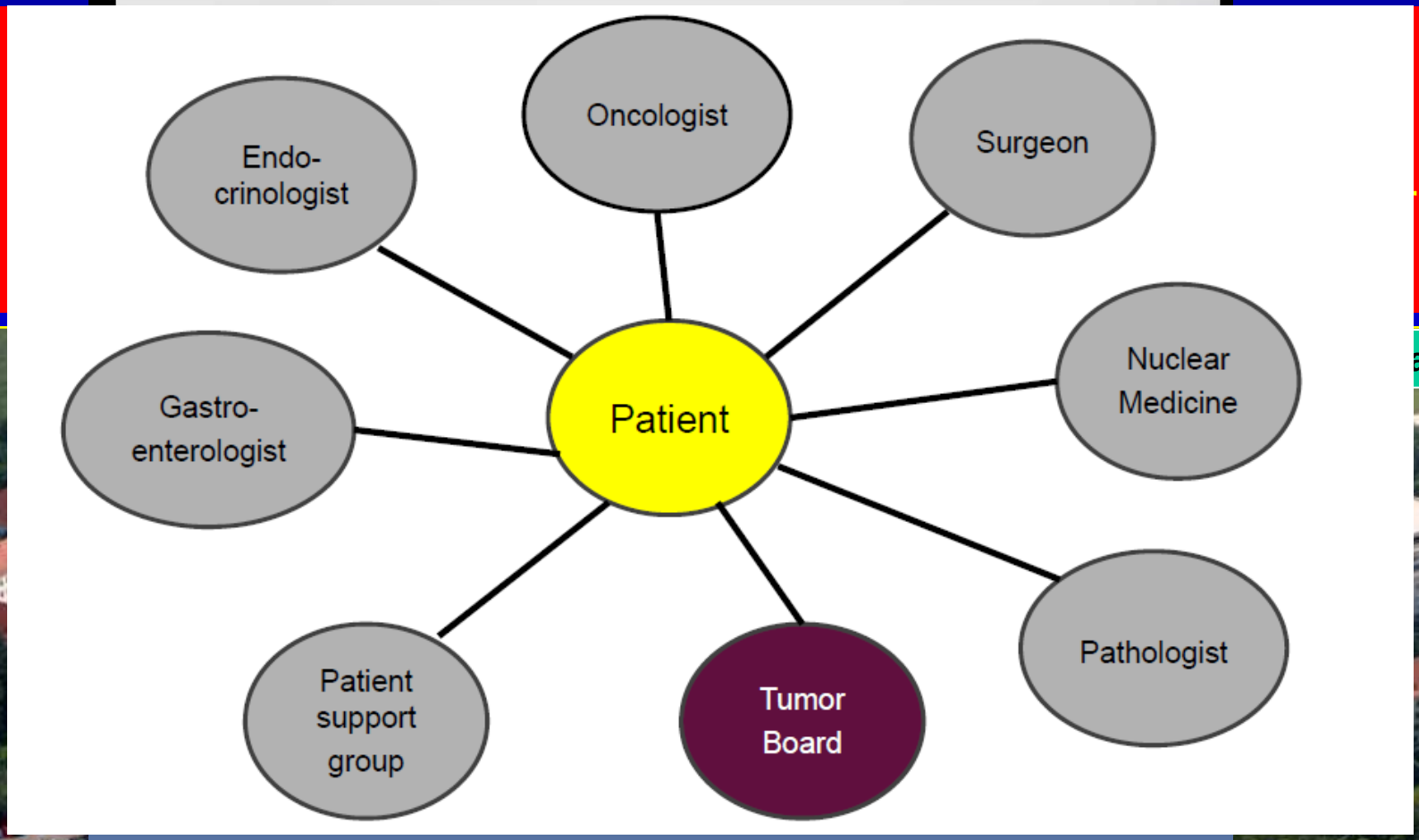
• http://itr8.com/hosted/chandighar

Zentralklinik Bad Berka - ENETS Center of Excellence since 2011

Molecular Radiotherapy & Imaging (PET/CT Center)

including a specialized nuclear medicine ward, medical physcis
and GMP radiopharmaceutical facilities/radiopharmacy center

Int. Medicine, Endocrinology, Gastroenterology, Oncology,
Abdominal, Thoracic, Spinal and Heart Surgery
Radiology, Interventional Radiology



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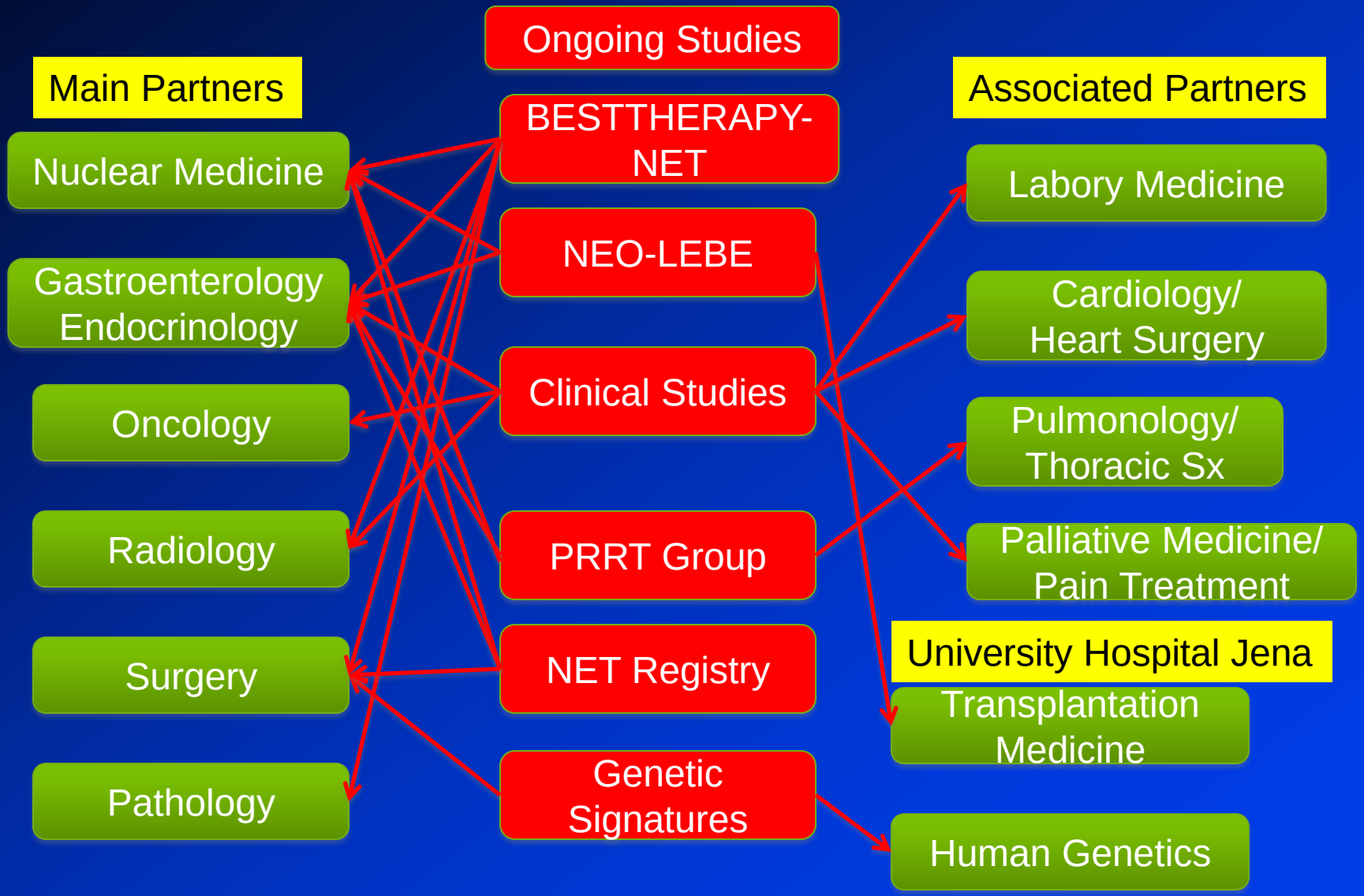
ENETS Center of Excellence Structure

Zentralklinik Bad Berka



PRRT – The Bad Berka Concept

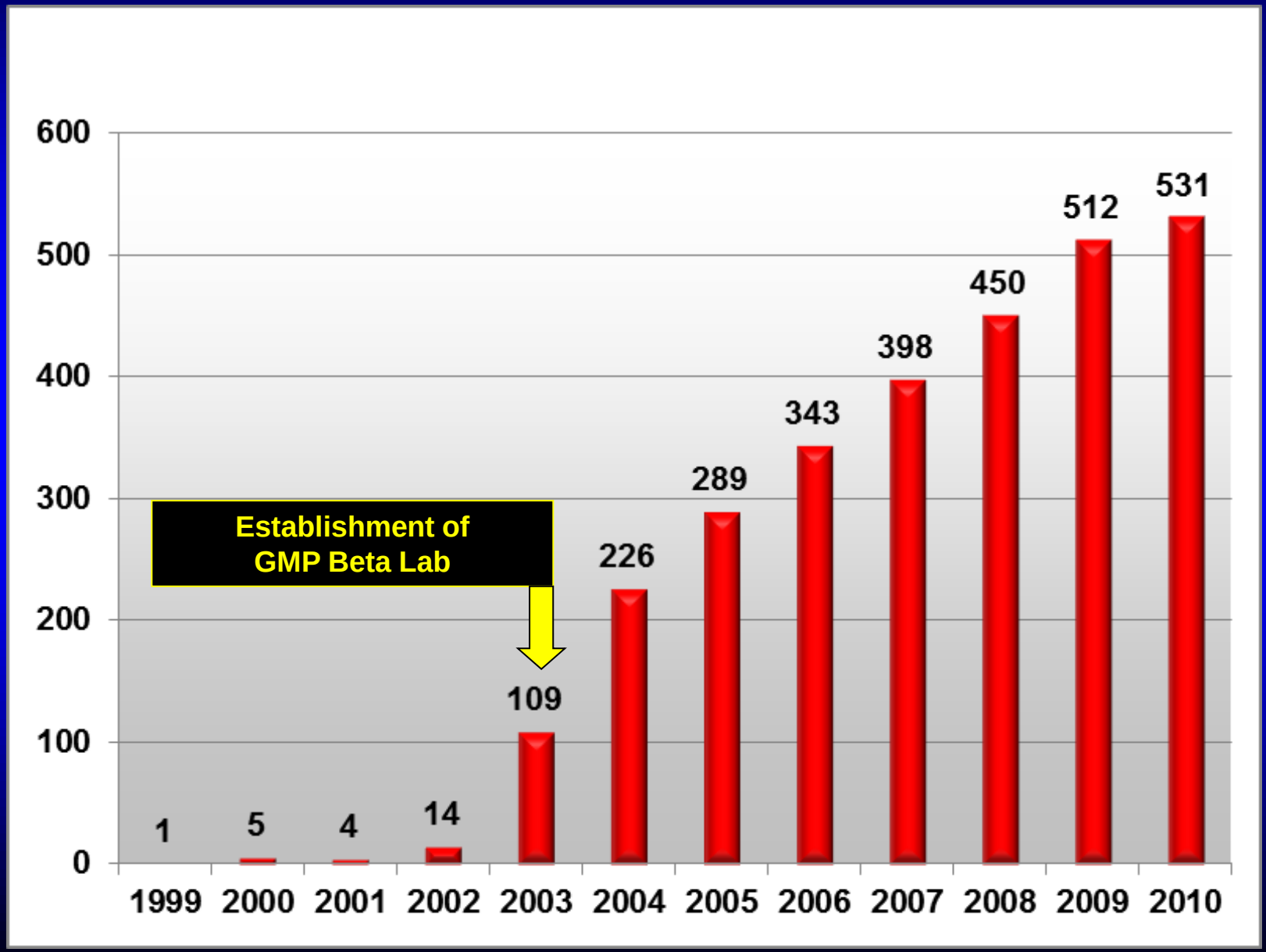
- Dedicated **multidisciplinary team** of experienced NET specialists
- **Selection of patients** for PRRT based on Bad Berka Score (BBS) i.e. clinical aspects / molecular features: progressive tumors, uncontrolled symptoms despite maximum conventional therapy / high SMS-receptor expression (as determined by **receptor PET/CT**)
- **Individualized therapy plan** for each patient **by tumor board consensus**

- **Frequent cycles** (4-6, up to 10) applying **low/intermediate doses of radioactivity: long term low dose, not short term high dose concept**
- **Combined use** of Y-90 and Lu-177 (in sequence, in few concurrent)
- **Intra-arterial PRRT** (for liver metastases & inoperable primary tumors)

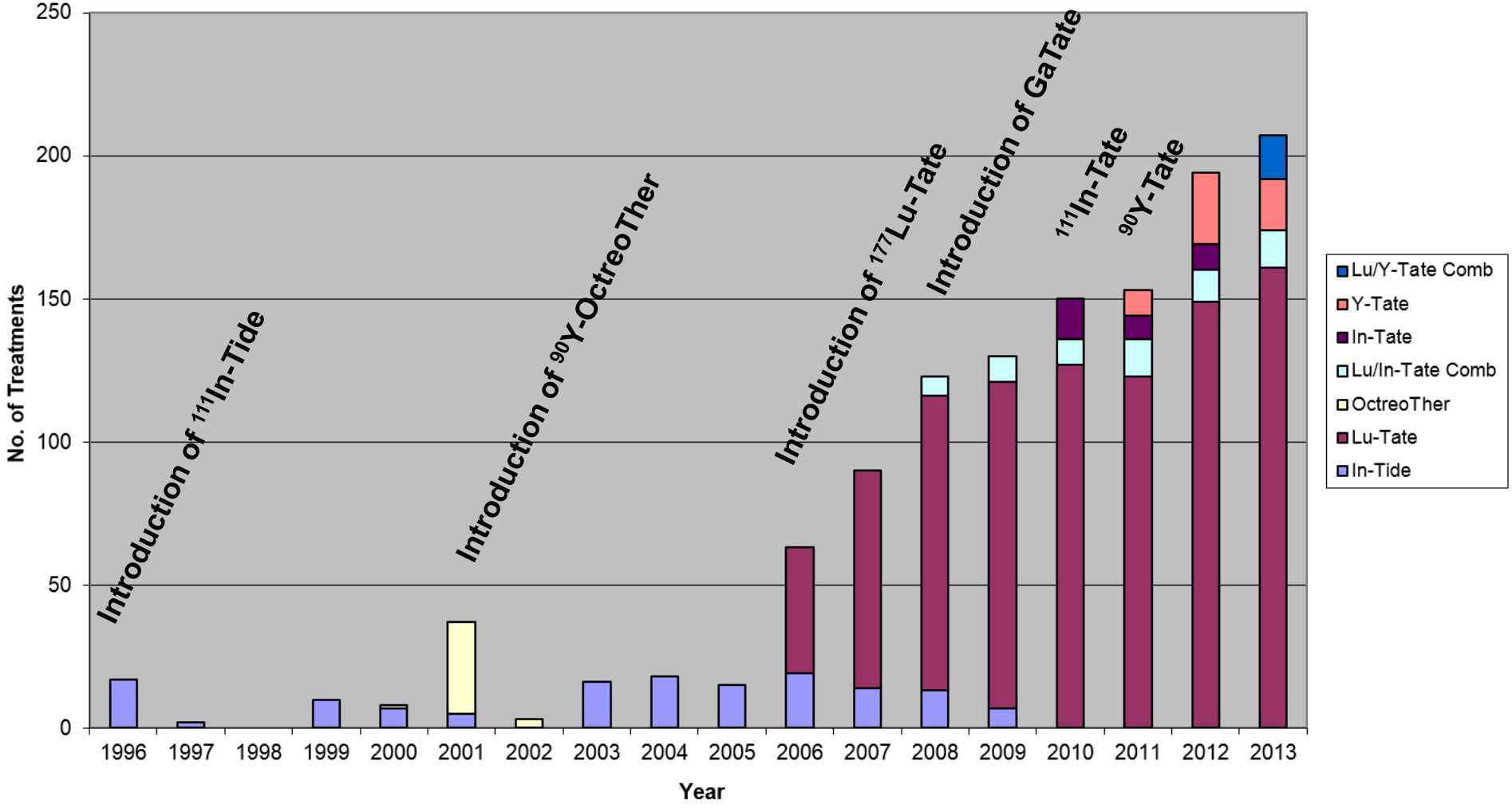
- **Standardized evaluation** before therapy and **systematic restaging**
- All clinical data are entered into a **prospective clinical database**

Radiopeptide Therapy Cycles

Zentralklinik Bad Berka 1999 - 2010

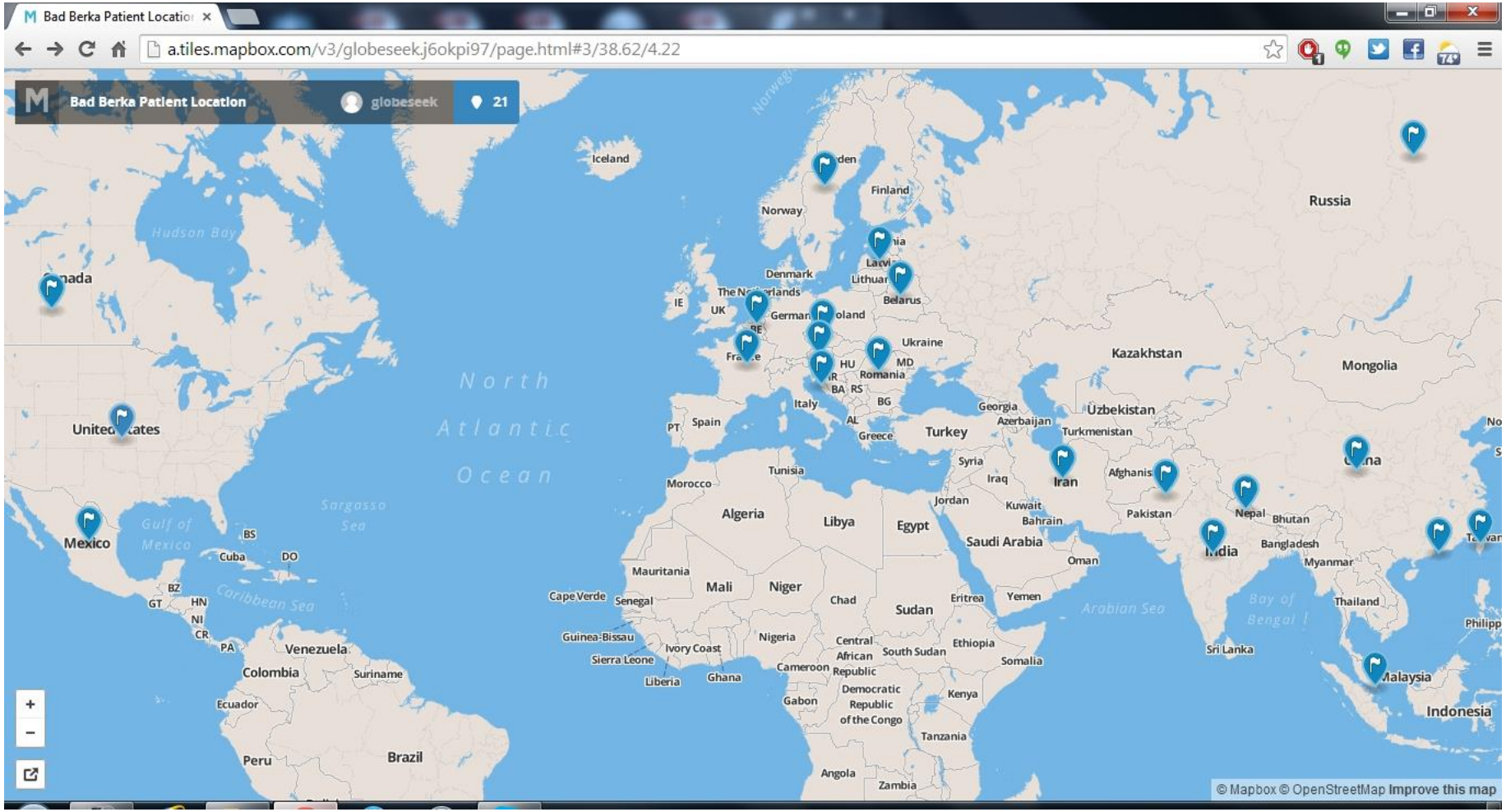


PRRT @ PeterMac (Melbourne, Australia)



Foreign Patients treated by PRRT at Zentraklinik Bad Berka

APPLICABILITY OF PRRT IN THE REAL WORLD



RADIOPEPTIDE THERAPY (ZKL BAD BERKA)

As of August 15th, 2014

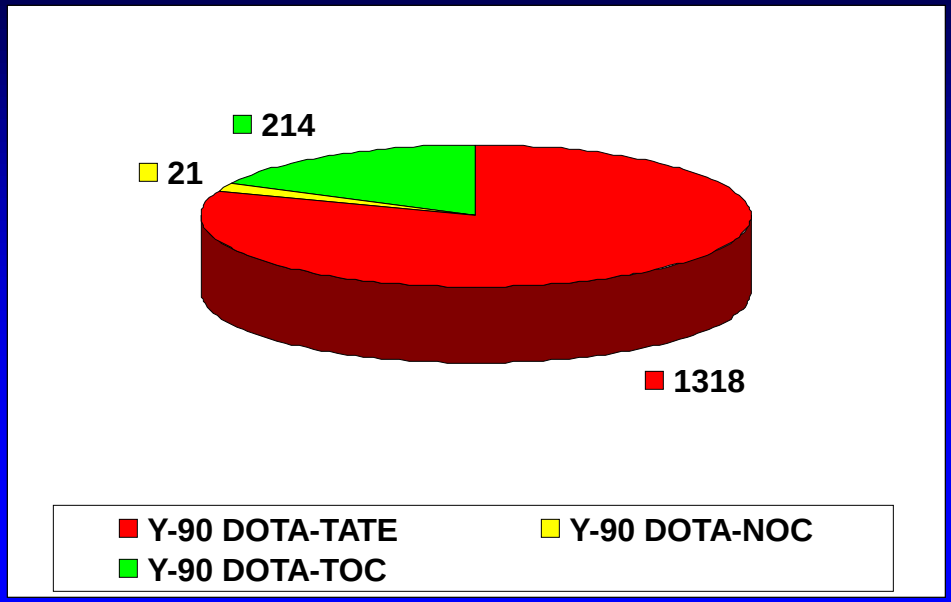
Patients treated	**n = 1251**
Therapy cycles	**n = 4323**

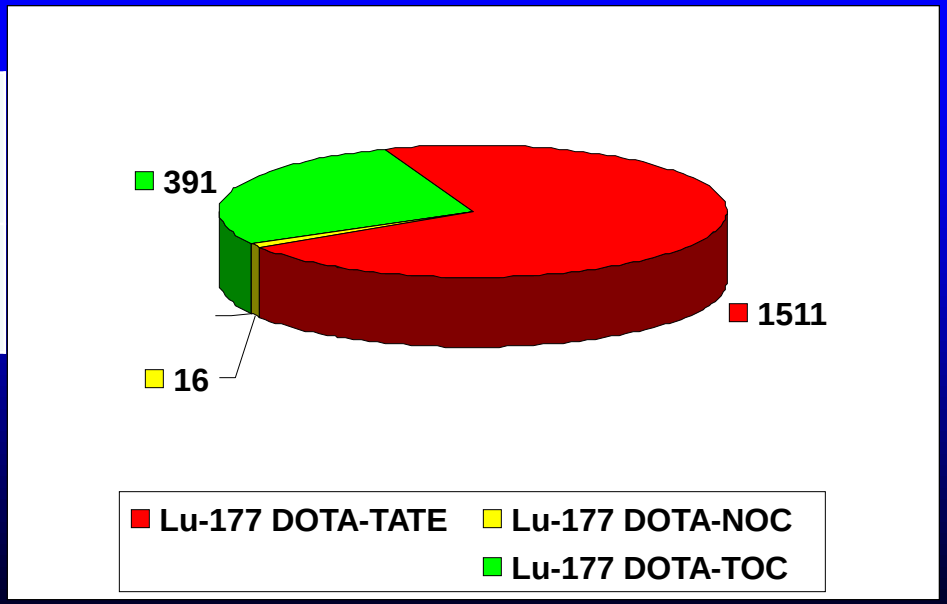
Lu-177	**n = 2745**
Y-90	**n = 1578**

	Y-90	Lu-177
Mean	3.27 GBq	6.43 GBq
Max.	7.30 GBq	12.0 GBq

Age: 4 – 85 years

Median: 59.7 years





The Bad Berka Score (BBS): Patient Selection for Personalized PRRT

- SUV on receptor PET/CT (referrals: OctreoScan K.S.)
- Renal function (GFR and TER / creatinine & BUN)
- Hematological status (blood counts)
- Liver involvement
- Extrahepatic tumor burden
- Ki-67 index / tumor grade
- FDG status (glucose hypermetabolism of tumors/mets)
- Tumor dynamics (doubling time, new lesions)
- Karnofsky performance index
- Weight loss
- Time since first diagnosis
- Functional activity of tumor
- Previous therapies

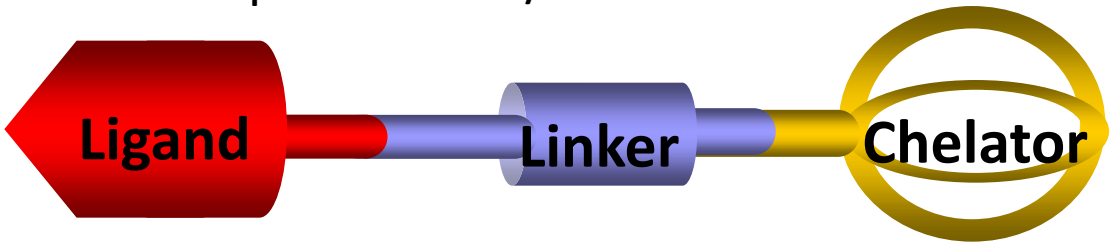
Targeted Molecular Imaging and Therapy
THERANOSTIC PAIRS
The Key-Lock Principle

Lock

Target

- Antigens (e.g. CD20, HER2)
- **GPCRs**
- Transporters
- Enzymes & inhibitors

pharmacokinetics/biodistribution modifier



Key

Molecular Address

- Antibodies, minibodies, Affibodies, SHALs, aptamers
- **Regulatory peptides (agonists & antagonists)**
- Amino Acids
- Enzymes & enzyme inhibitors

^{68}Ga, ^{90}Y, ^{177}Lu

Reporting Unit

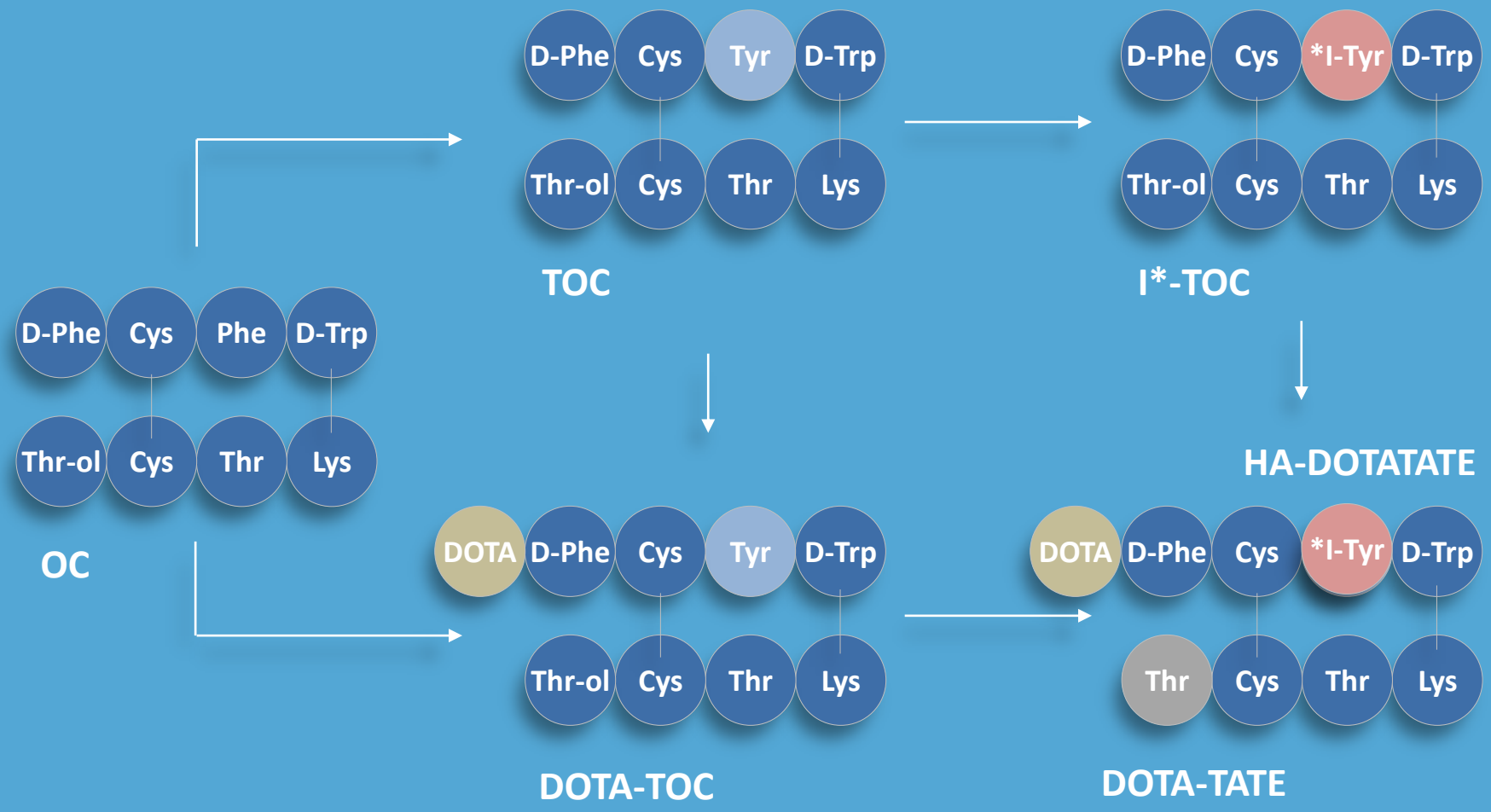
- ^{99m}Tc, ^{111}In, ^{67}Ga
- ^{64}Cu, ^{68}Ga
- Gd^{3+}

Cytotoxic Unit

- ^{90}Y, ^{177}Lu, ^{213}Bi
- ^{105}Rh, ^{67}Cu, ^{186,188}Re

Courtesy Helmut Mäcke (modified)

Somatostatin Analogs: Improvement of SST Receptor Affinity



Wester HJ, Schottelus M, Kotzerke J. et al. 2013)

Selected Compounds and their sst-Receptor Affinity

Compound	sst1	sst2	sst3	sst4	sst5
Somatostatin-28[a]	5.2 ± 0.3	2.7 ± 0.3	7.7 ± 0.9	5.6 ± 0.4	4.0 ± 0.3
OC	>10.000	2.0 ± 0.7	187 ± 55	>1000	22 ± 6
I-TOC	>10.000	1.3 ± 0.3	128± 22	867 ± 33	50 ± 12
I-TATE	>1.000	0.5 ± 0.2	187± 38	337 ± 57	50 ± 5.8
Ga-DOTA-OC	>10.000	7.3 ± 1.9	120 ± 45	>1.000	60 ± 14
Ga-DOTA-TOC	>10.000	2.5 ± 0.5	613 ± 140	>1.000	73 ± 21
Ga-DOTA-TATE	>10.000	0.20 ± 0.04	>1.000	300 ± 140	377 ± 18
Y-DOTA-OC	>10.000	20 ± 2	27 ± 8	>10.000	57 ± 22
Y-DOTA-TOC	>10.000	11.0 ± 1.7	389 ± 135	>10.000	114 ± 29
Y-DOTA-TATE	>10.000	1.6 ± 0.4	>1.000	523 ± 239	187 ± 50

Wester HJ, Schottelus M, Kotzerke J. et al. 2013 (in press)

sst-Receptor Affinities
DOTATATE versus HA-DOTATATE

	sst_1	sst_2	sst_3	sst_4	sst_5	lgP
Ga-DOTATATE	> 10.000	0.67 ± 0.25	> 1000	822 ± 327	> 1000	-3.69
Ga-HA-DOTATATE	> 10.000	0.64 ± 0.23	> 1000	> 1000	59.7 ± 15.1	-3.16
Lu-DOTATATE	> 10.000	1.21 ± 0.27	162 ± 16	> 1000	> 1000	-
Lu-HA-DOTATATE	> 10.000	0.73 ± 0.10	93 ± 0.1	> 1000	147 ± 40	-

Wester HJ, Schottelus M, Kotzerke J. et al. 2013 (in press)

Ga-68 Generator System

TiO_2 based

Developed in close collaboration between

Radiopharmacy PET/CT Center,

Zentralklinik Bad Berka

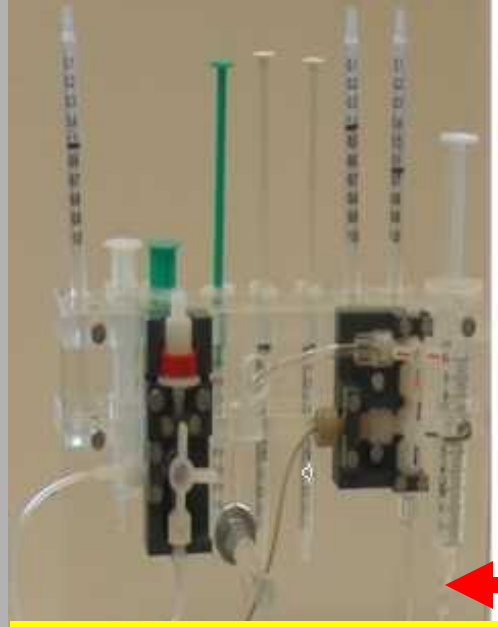
and

Institute of Nuclear Chemistry

Johannes Gutenberg-Universität, Mainz, Germany

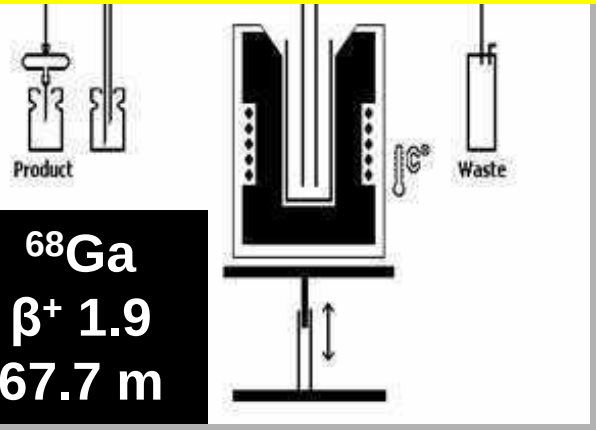
Zhernosekov K, Filosofov DV, Baum RP…. Rösch F

J Nucl Med 2007 (Oct); 48:1741-48



^{68}Ge
ε
271.0 d

Simultaneous use of several generators



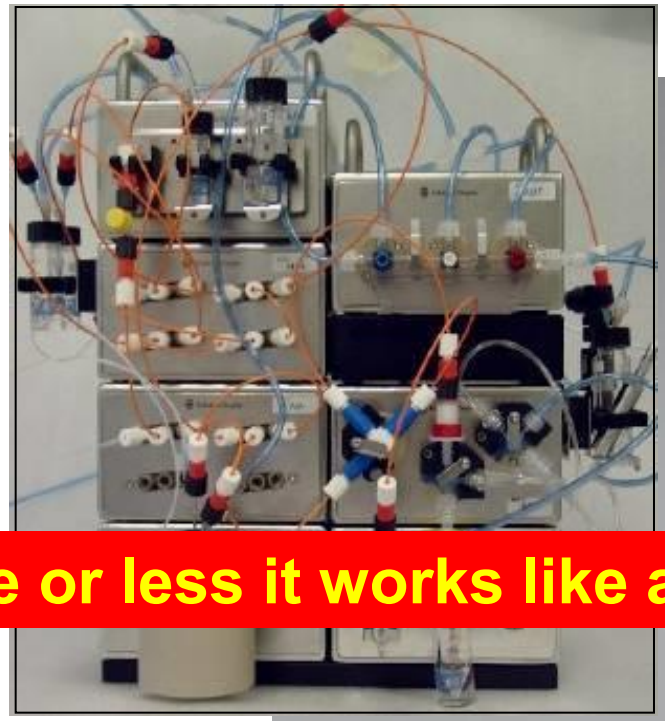
^{68}Ga
β^+ 1.9
67.7 m

^{68}Ga-elution, purificaton and synthesis module

First clinical studies in 2004, up to now over 9,000 studies done at ZKL Bad Berka.

European approval process by EMA for Gallium-68 generators successfully completed in June 2014

Eckert & Ziegler



Pre-cleaning

More or less it works like a Cappucino machine…

Modular-Lab Pharm Tracer – fully automated click‘n‘start cassette-based synthesis system for the daily routine production of radiopharmaceuticals

Made in Germany

GRP Cassette Systems with GRP User Interface

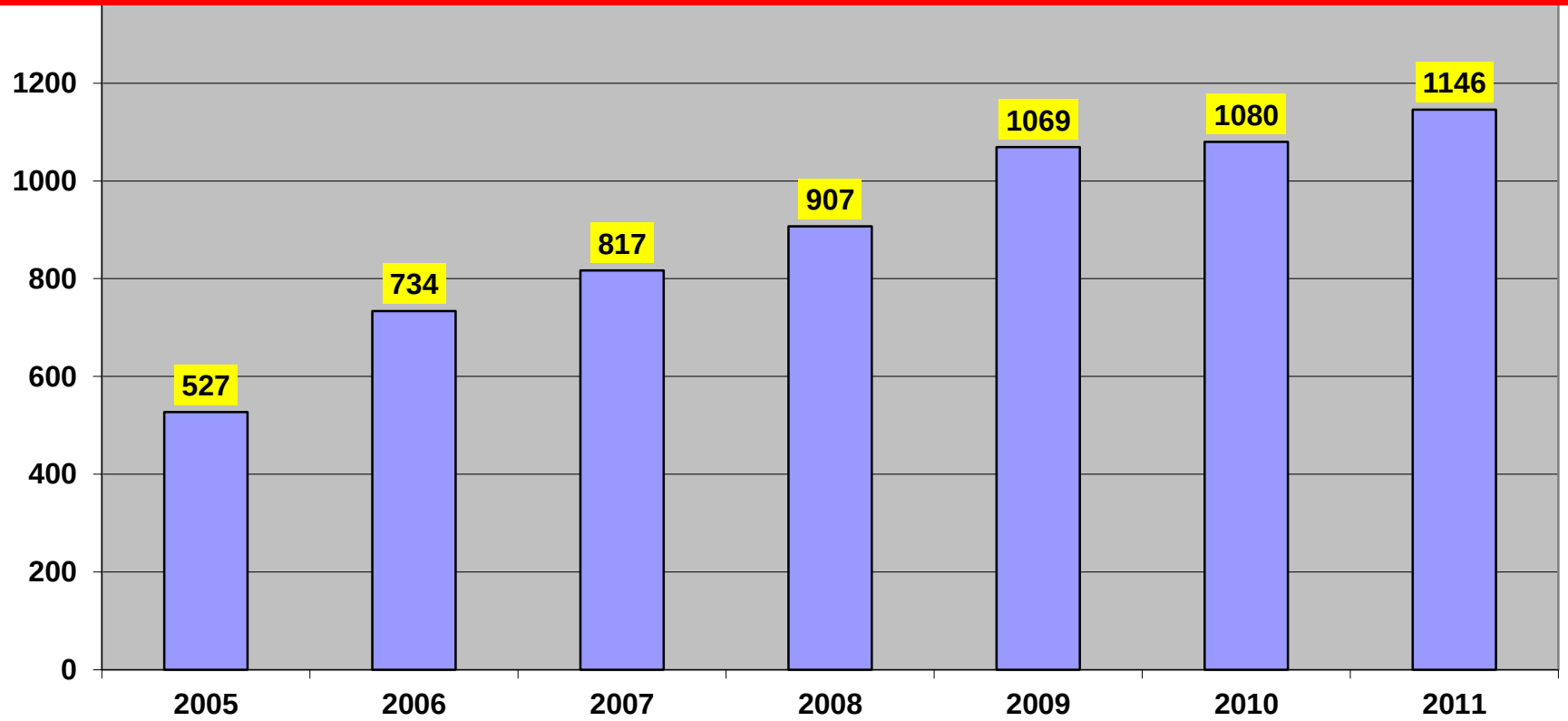
Two GRP Cassette Systems in one Hot Cell

GRP Capillary Systems with GMP Reagent and Disposable Kit

Automated cassette-based synthesis for the daily routine production of radiopharmaceuticals, e.g. Ga-68 DOTATATE, PSMA, CXCR4, RGD…..

Gallium-68 has the potential to become the Tc-99m for PET/CT! *

In 2014, we have 8 different Ga-68 labeled radiopharmaceuticals in clinical use!



Ga-68 PET/CT Studies Zentralklinik Bad Berka

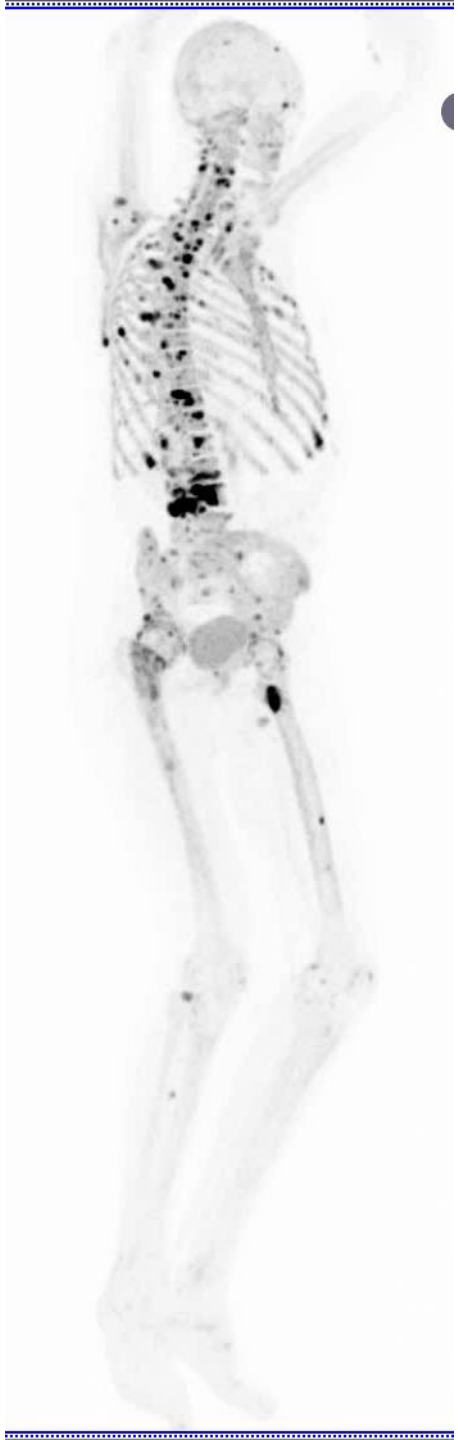
Center for Molecular Radiotherapy / Department of Molecular Imaging (PET/CT) Zentralklinik Bad Berka

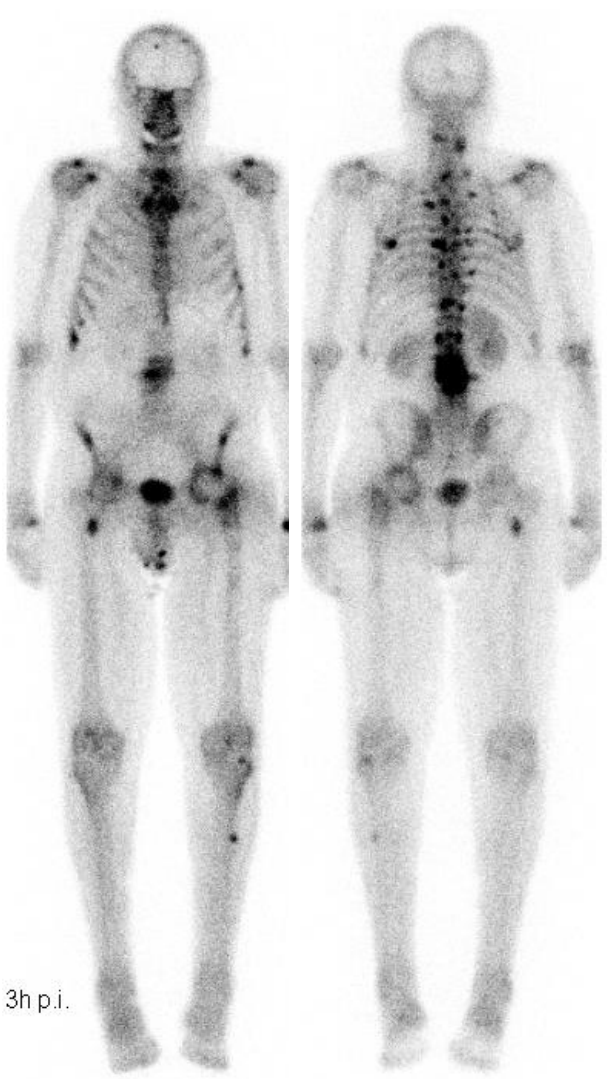
Dept. of Molecular Imaging, Zentralklinik Bad Berka

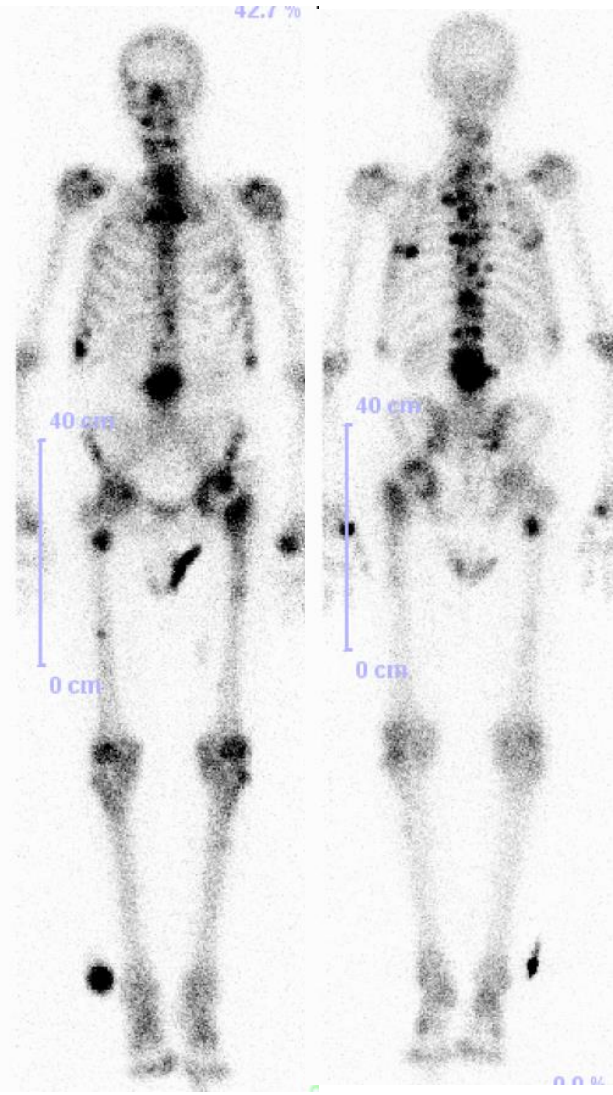
Installation Biograph mCT Flow on February 24, 2014

>90% oncological studies (fast WB)

NET: 2nd most frequent indication







Tc-99m MDP Scintigraphy

Lu-177 BPAMD Therapy Scan

Biograph mCT Flow – 15 min whole body scan using Ga-68 NO2A-BP for measuring osteoblastic activity in bone metastases. Treatment of the same patient by Lu-177 BPAMD – another pair of Theranostics

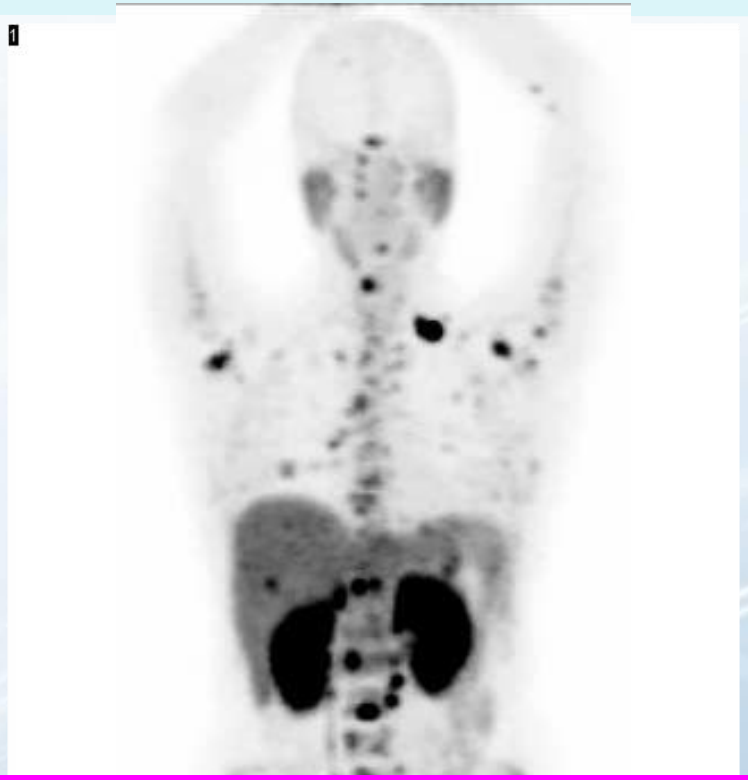
Molecular Imaging of NET

by SMS-Receptor-PET/CT

- **Whole-body diagnosis („one-stop shop“)**
- **Detection of unknown primary tumors (CUP)**
- **Evaluation of receptor status before and after PRRT**

Dr Michael Hofman

Gatate PET/CT vs ^{111}In-Octreotide

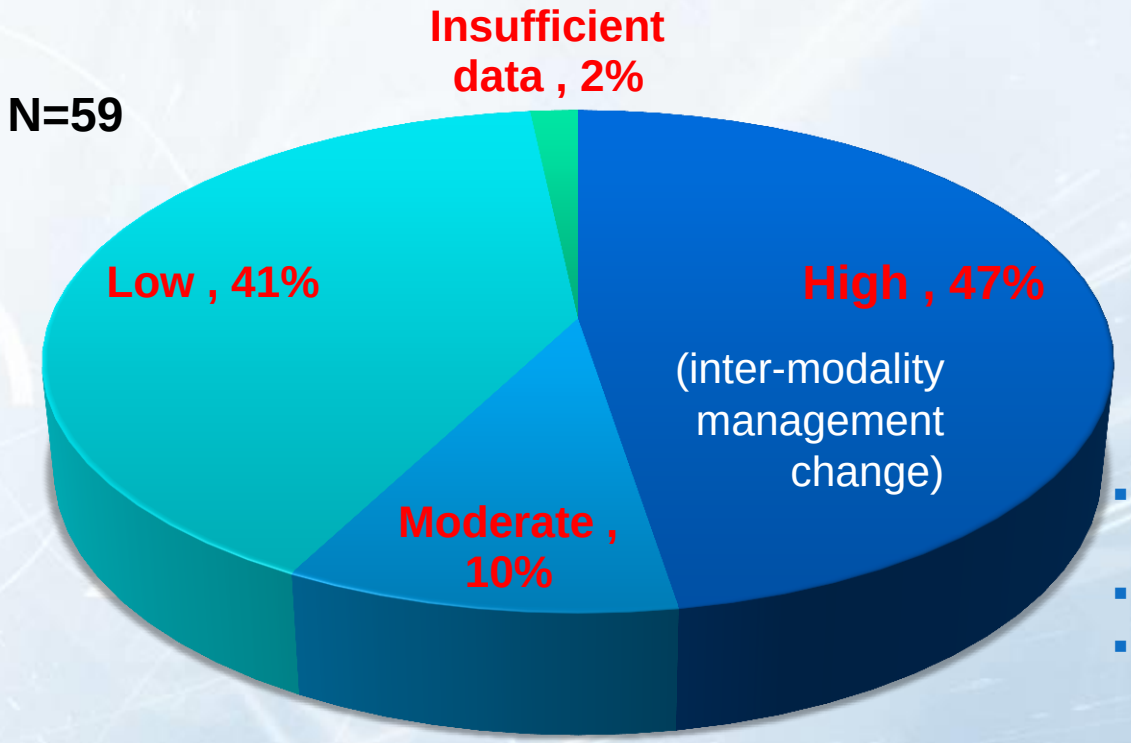


NUCLEAR = UNCLEAR

From „unclear“ medicine to „new clear“ medicine

High impact of GaTate PET/CT

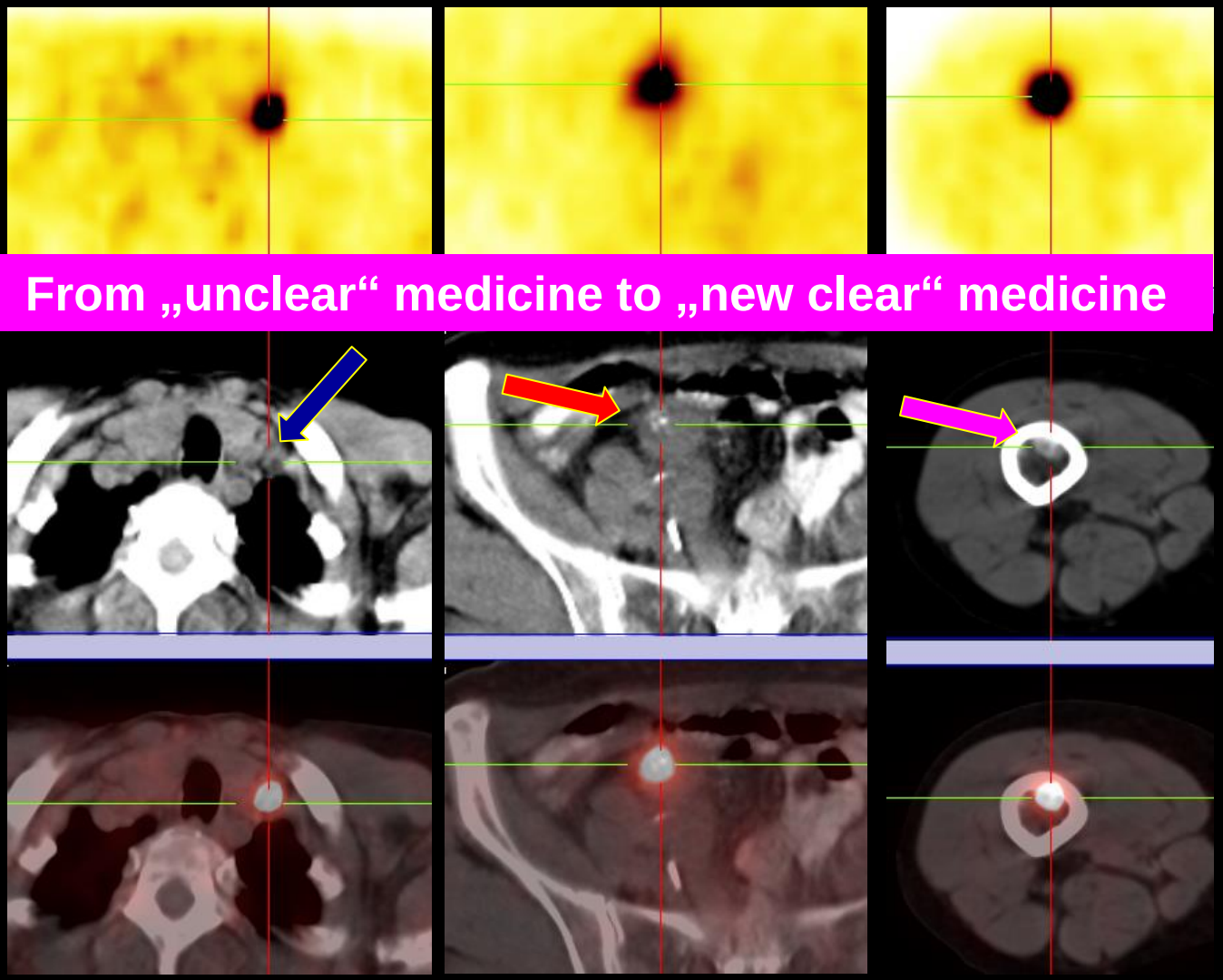
- **Additional information** compared to conventional imaging in 69 %, octreotide 83 %



- **directed to systemic therapy (19)**
- **directed to surgery (5)**
- **surgery → systemic therapy (3) or observation (1)**

Hofman MS, Kong G, Neels O, Eu P, Hicks RJ, *J Med Imaging Rad Oncol 2012,* 56(1):40-7

Whole-body diagnosis („one stop shop“)



From „unclear“ medicine to „new clear“ medicine

Receptor-PET/CT using Ga-68 DOTA-NOC

Primary tumor (ileum), liver, lymph node & bone metastases

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-009-1205-y

Eur J Nucl Med Mol Imaging 2010 Jan;37(1):67-77

ORIGINAL ARTICLE

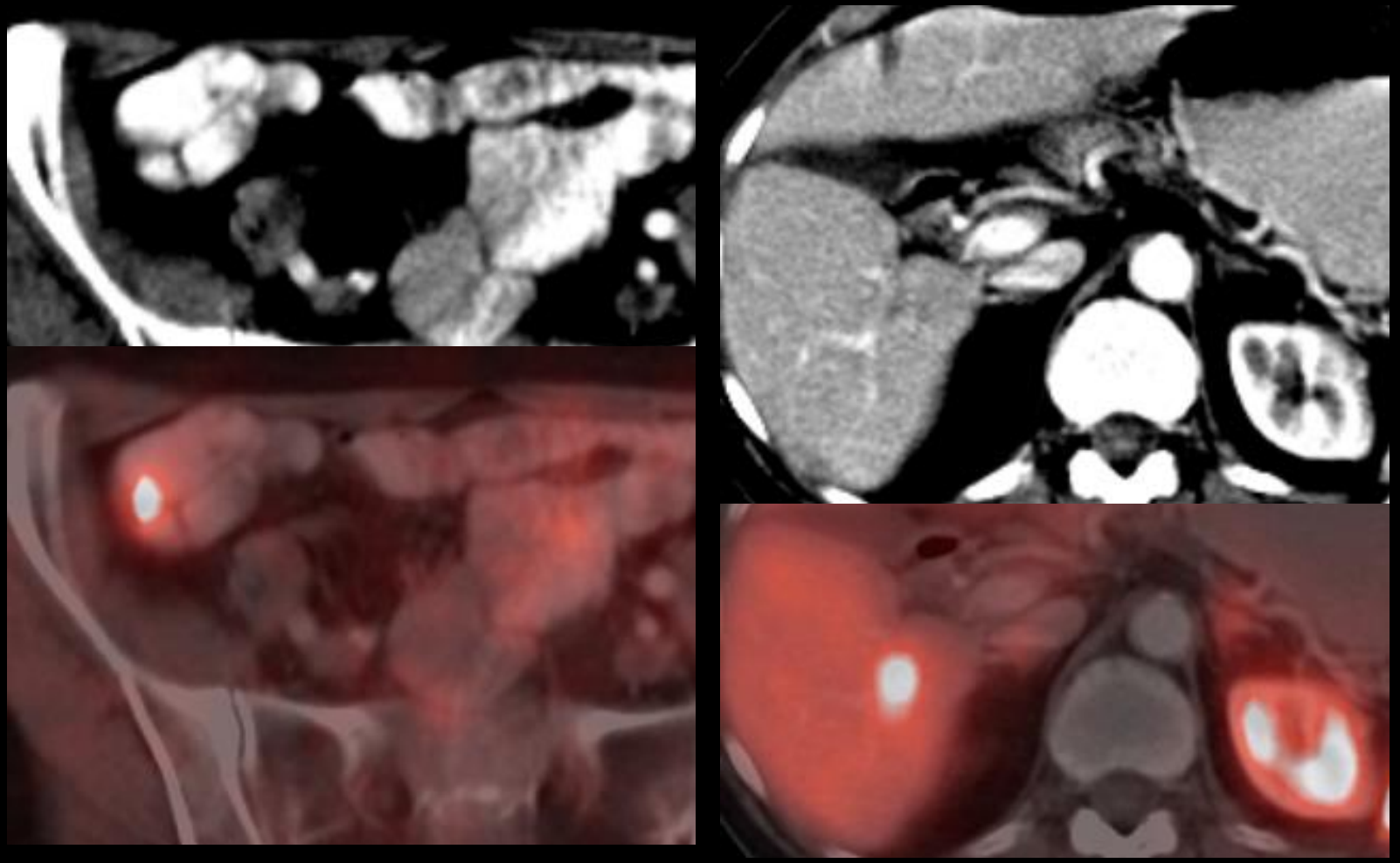
Detection of unknown primary neuroendocrine tumours (CUP-NET) using ^{68}Ga-DOTA-NOC receptor PET/CT

Vikas Prasad · Valentina Ambrosini · Merten Hommann · Dieter Hoersch · Stefano Fanti · Richard P. Baum

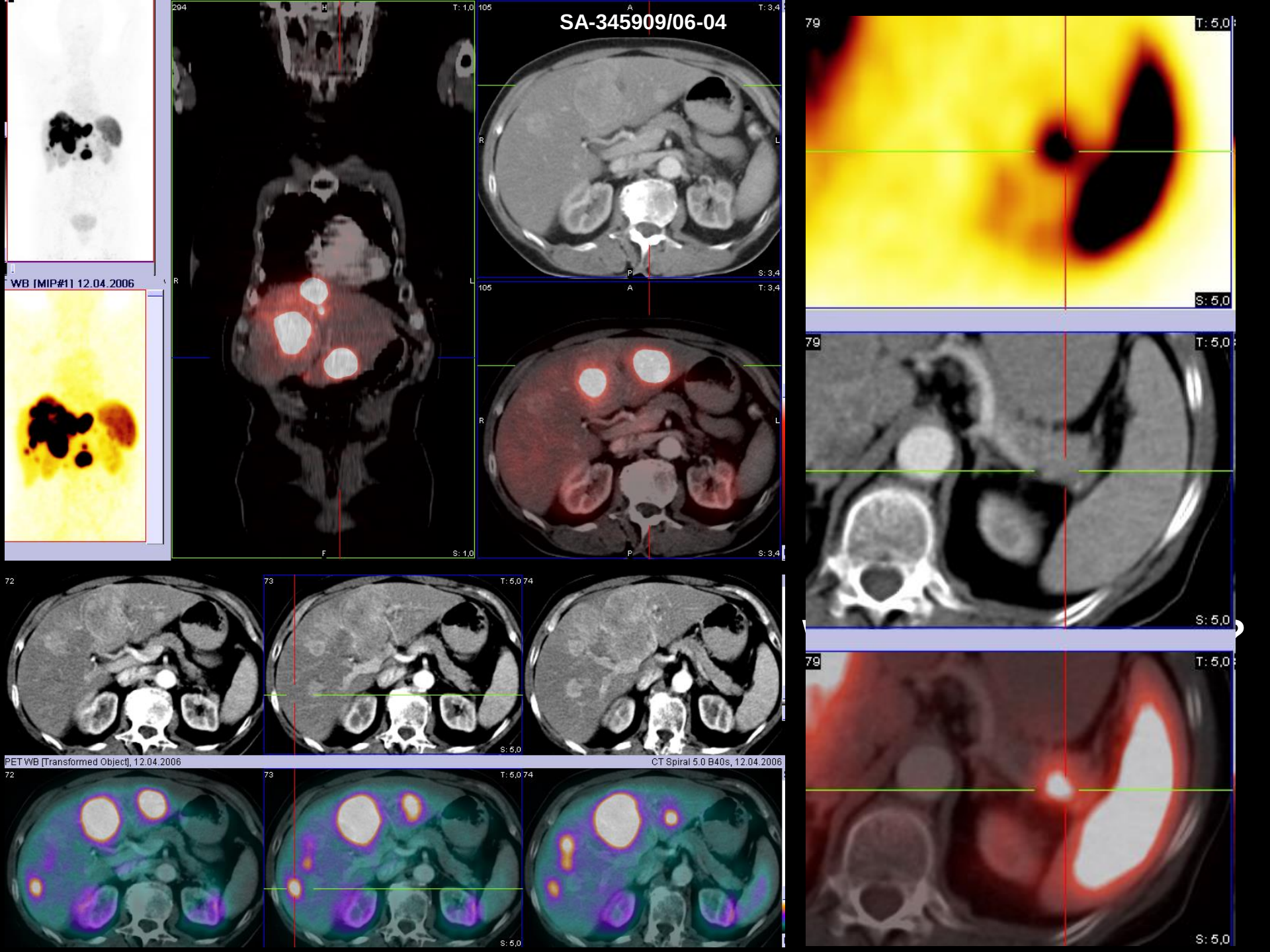
Results In 35 of 59 patients (59%), ^{68}Ga-DOTA-NOC PET/CT localised the site of the primary: ileum/jejunum (14),

Received: 30 November 2008 / Accepted: 12 June 2009

Conclusion Our data indicate that ^{68}Ga-DOTA-NOC PET/CT is highly superior to ^{111}In-OctreoScan (39% detection rate for CUP according to the literature) and can play a major role in the management of patients with CUP-NET.

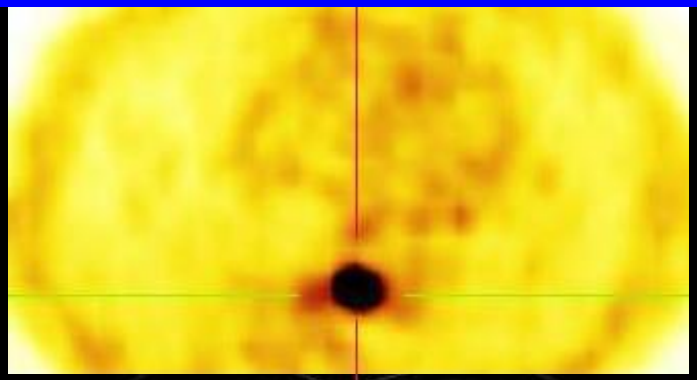


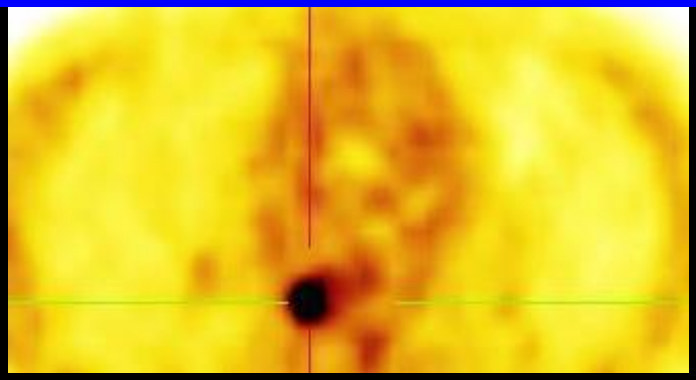
Primary tumor (ileum) and synchronous liver metastasis


SA-345909/06-04
WB [MIP#1] 12.04.2006
PET WB [Transformed Object], 12.04.2006
CT Spiral 5.0 B40s, 12.04.2006

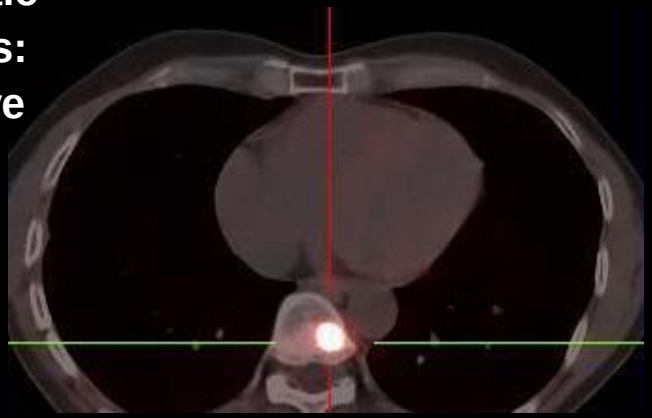
Dept. of Nuclear Medicine/P.E.T. Center, Zentralklinik Bad Berka

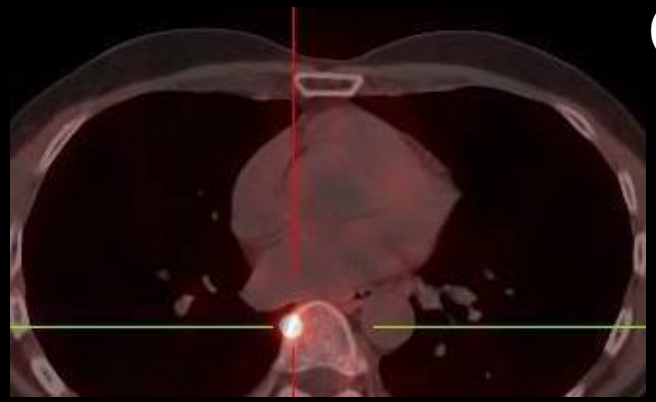
Superiority of Ga-68 DOTANOC PET/CT over conventional imaging





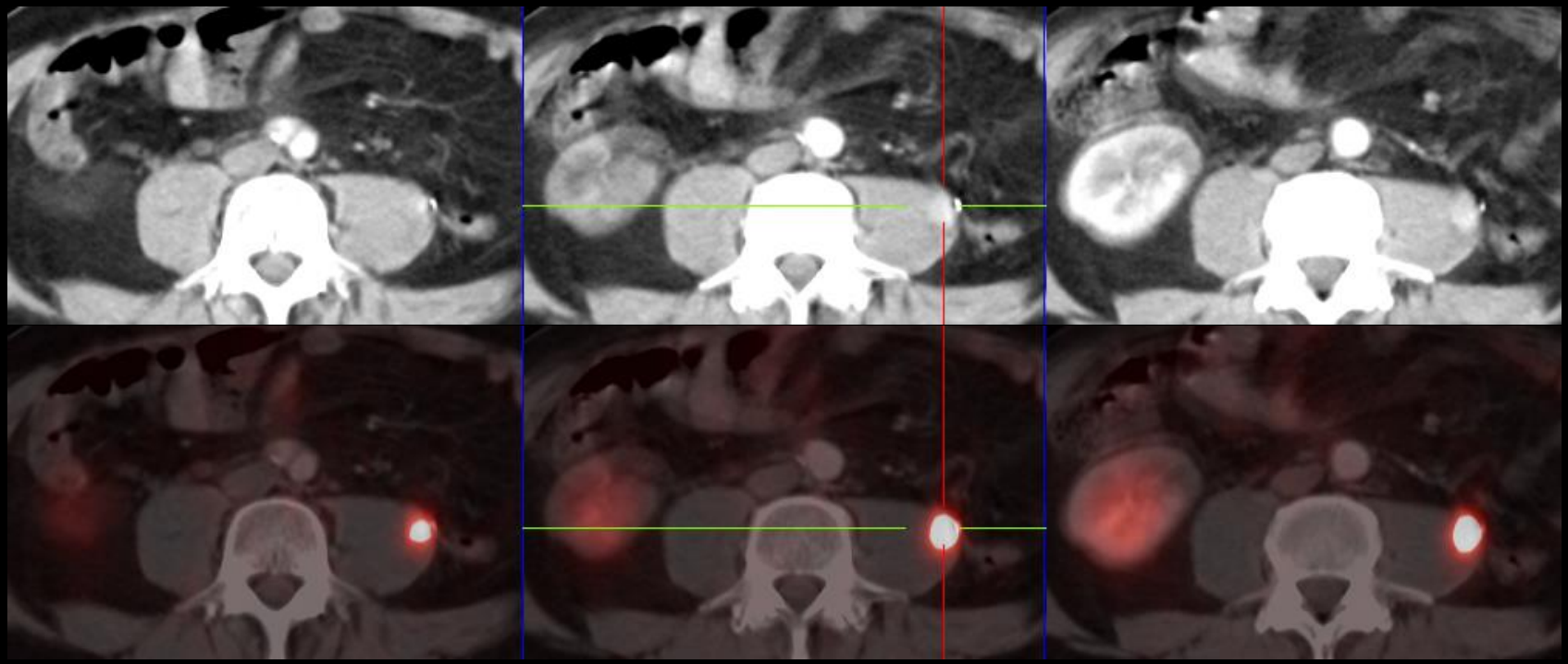
Osteoblastic metastasis: CT positive





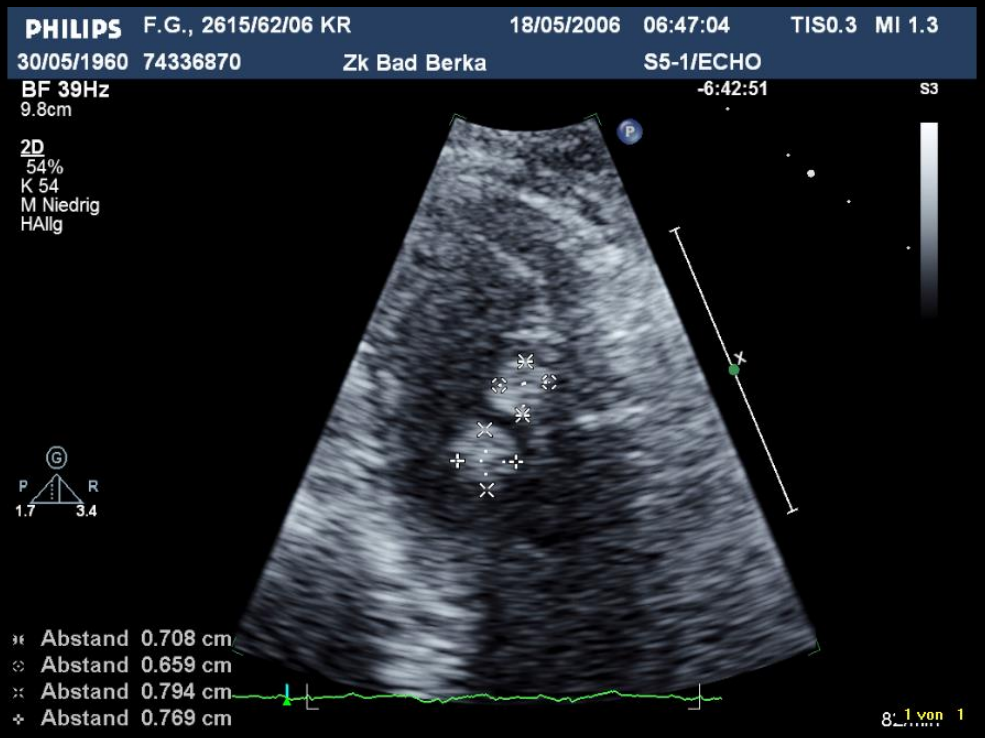
CT normal (3 mm lesion on MRI)

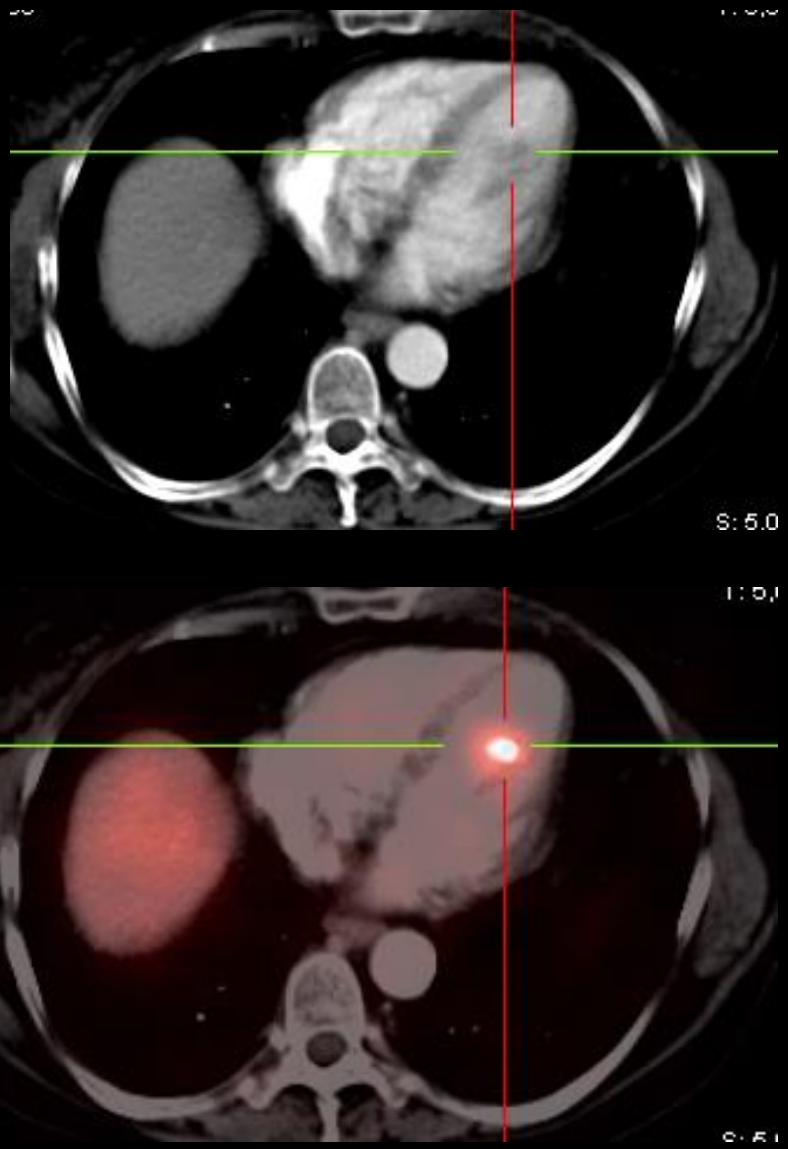
Rare localizations detected by PET/CT



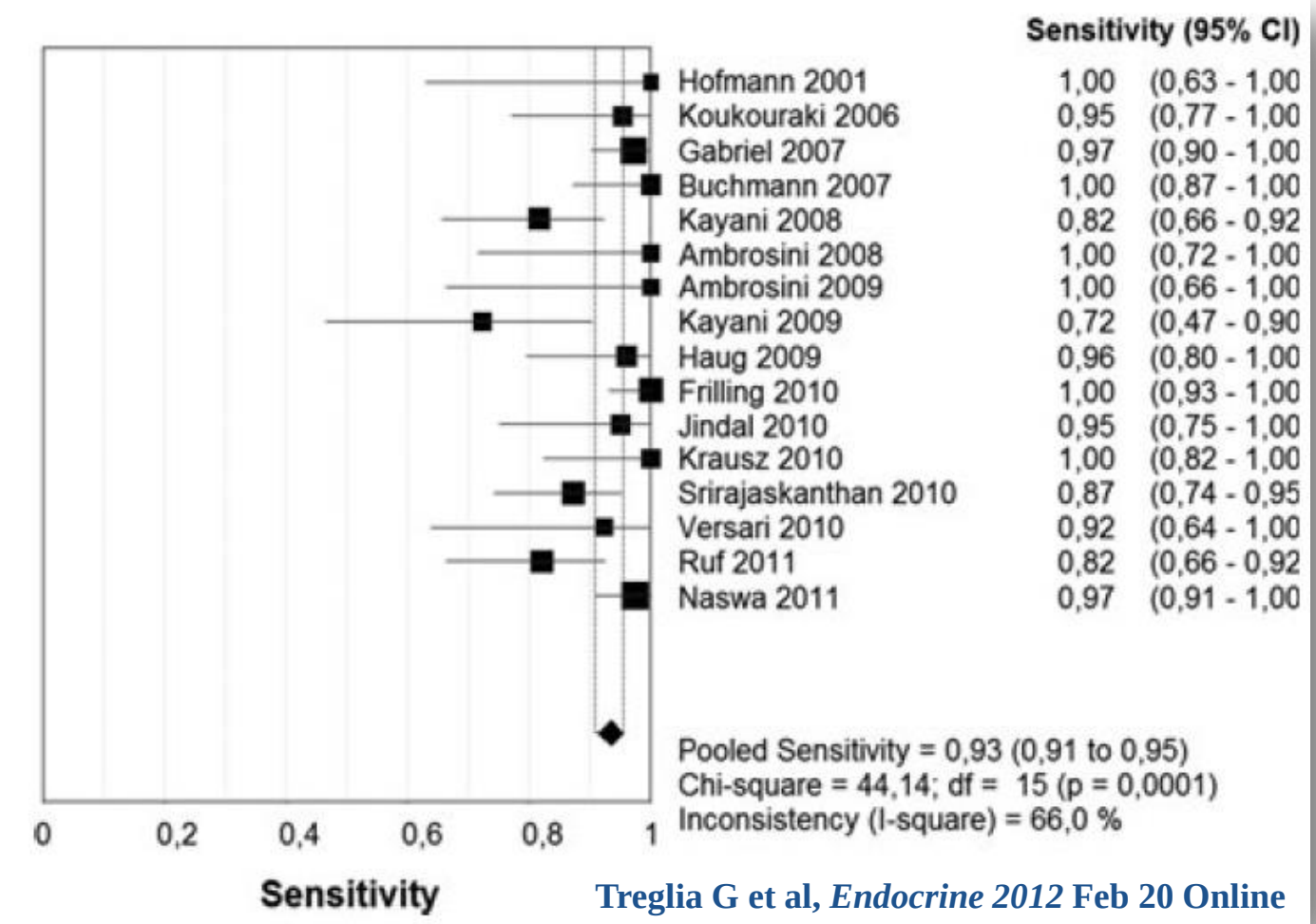
Intramuscular metastasis (psoas muscle)

INTRACARDIAC METASTASIS (SEPTUM)





Meta-analysis: Accuracy of SSTR PET/CT ~93 %



Treglia G et al, *Endocrine 2012* Feb 20 Online

"False –ve"

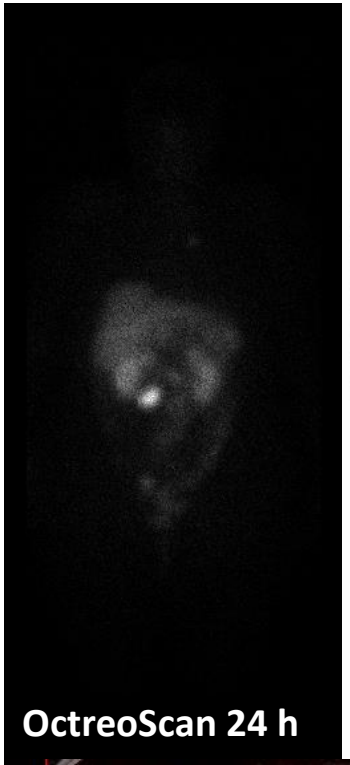
- <3 to 5 mm
- at physiologic uptake site (pancreatic head, pituitary, adrenal)
- low SSTR expression

"False +ve"

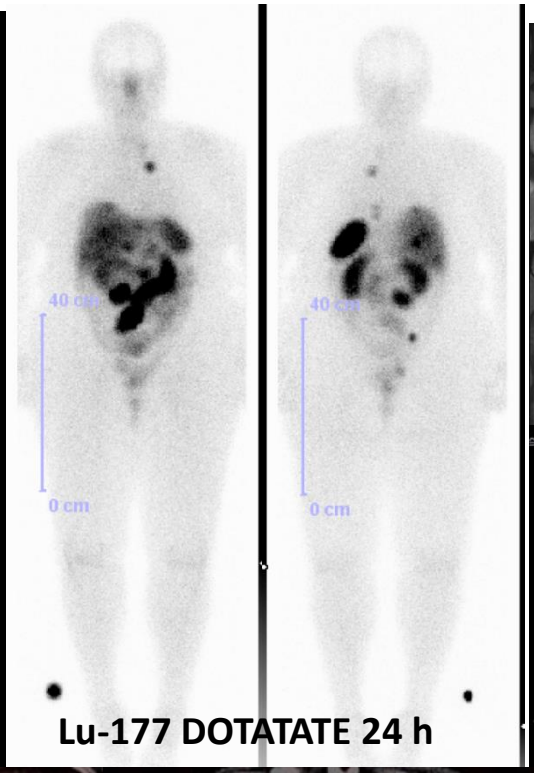
Rare (v. specific)

- reactive nodes
- uncinate process

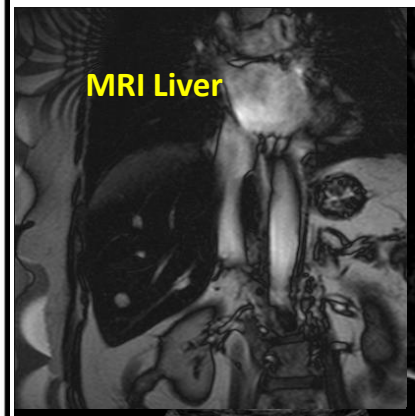
"Should be considered first line diagnostic imaging methods in patients with thoracic / GEP-NETs"

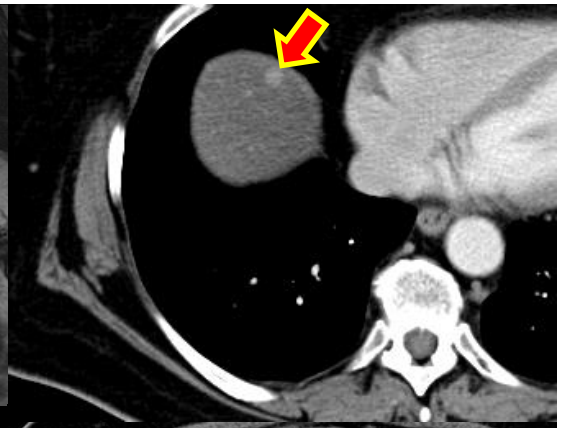


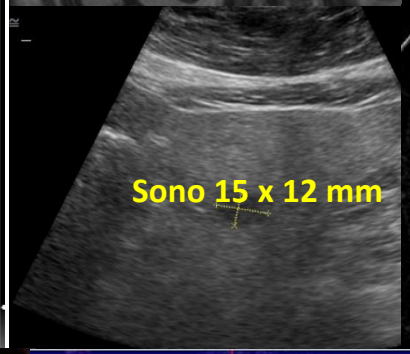
OctreoScan 24 h

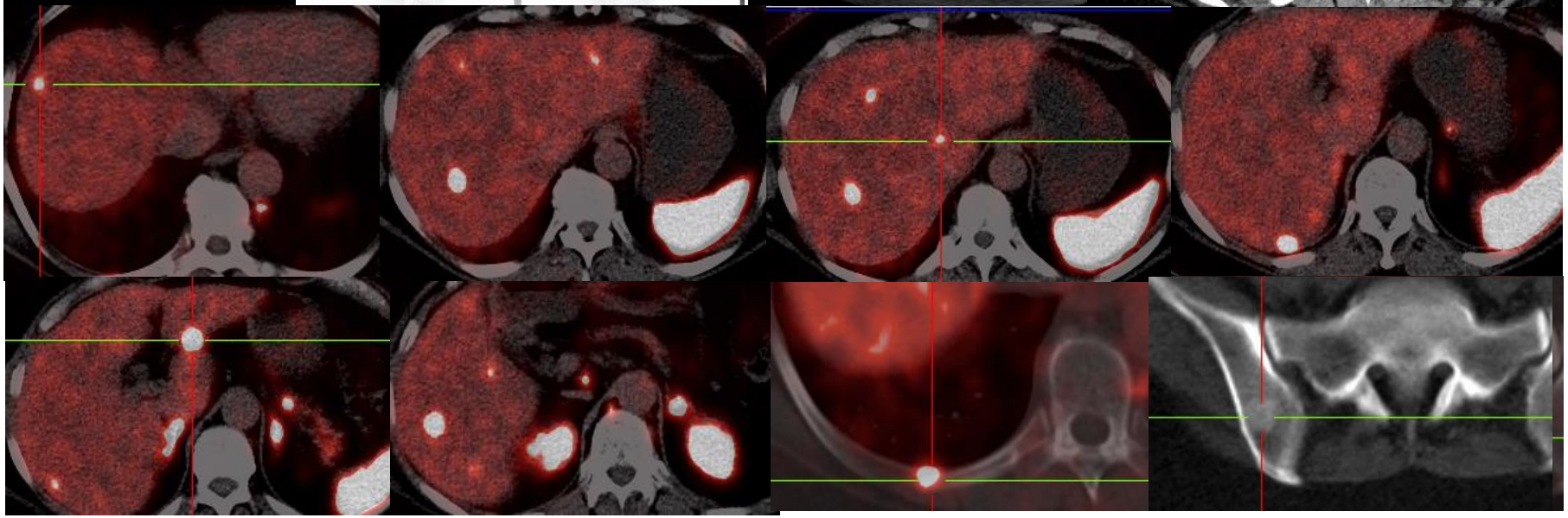


Lu-177 DOTATATE 24 h









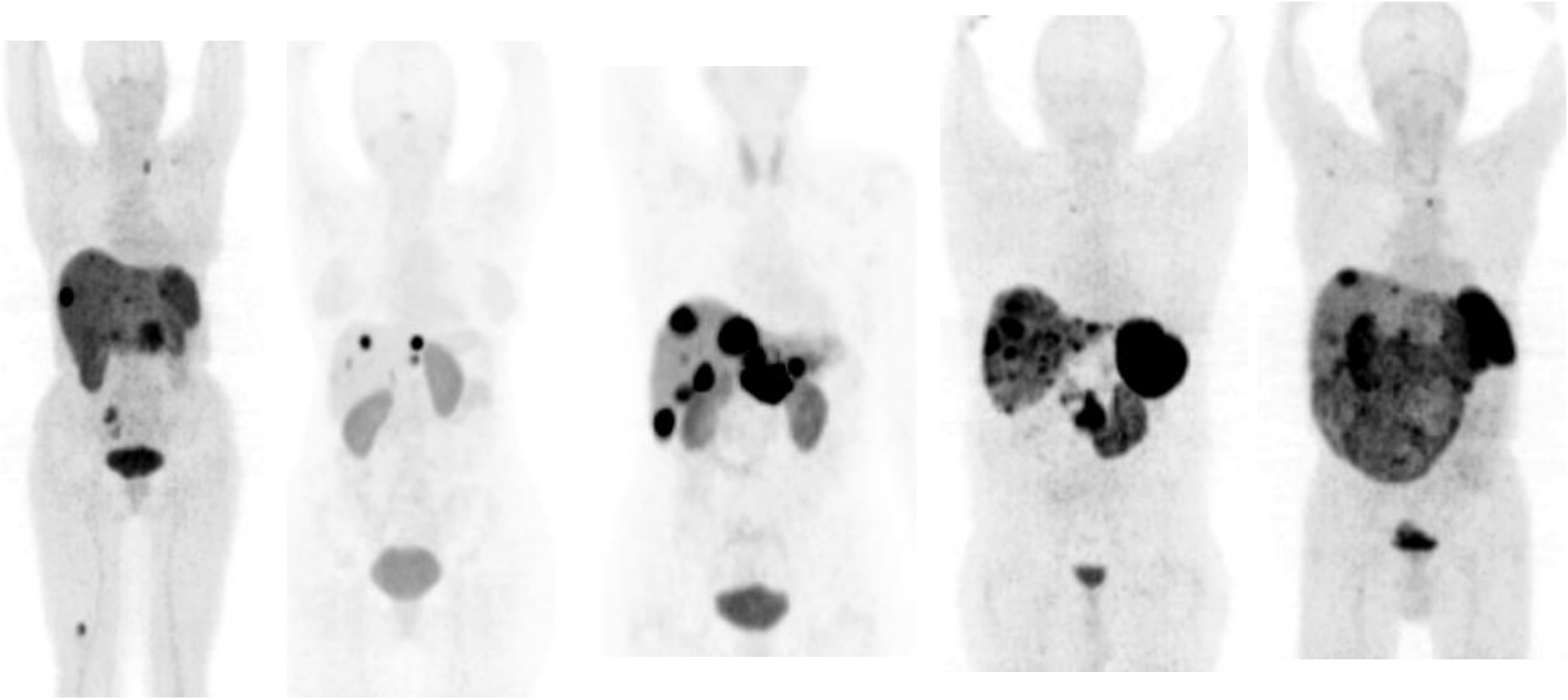
THERANOSTICS OF NET

Receptor density determined by Ga-68 receptor PET/CT:

semiquantitative measurement by

SUV (Standardized Uptake Values)

More than just looking at images..



Patient Evaluation Before Peptide Receptor Radionuclide Therapy = PRRT

Treatment decisons based on Ga-68 SMS receptor PET/CT: Bad Berka scoring system is based on SUVs – not on visual analogue scales as previously derived from OctreoScans

Ga-68 DOTA-NOC receptor PET/CT: SUV of primary tumors and metastases

V. Prasad, R.P. Baum Q J Nucl Med Mol Imaging 2010; 54:61-67

SUV in primary tumors and metastases (n = 1,400 studies)	Mean	Range
Primary tumors	19.2	8.2 – 109
Liver mets	20.9	3.3 - 156
Lymph node mets	9.5	4.2 – 152
Bone mets	13.6	3.0 – 20.4
Brain mets	12.3	4.6 – 17.2
Lung mets	2.3	1.6 – 5.6
Abdominal mets	14.8	5.8 – 34.1

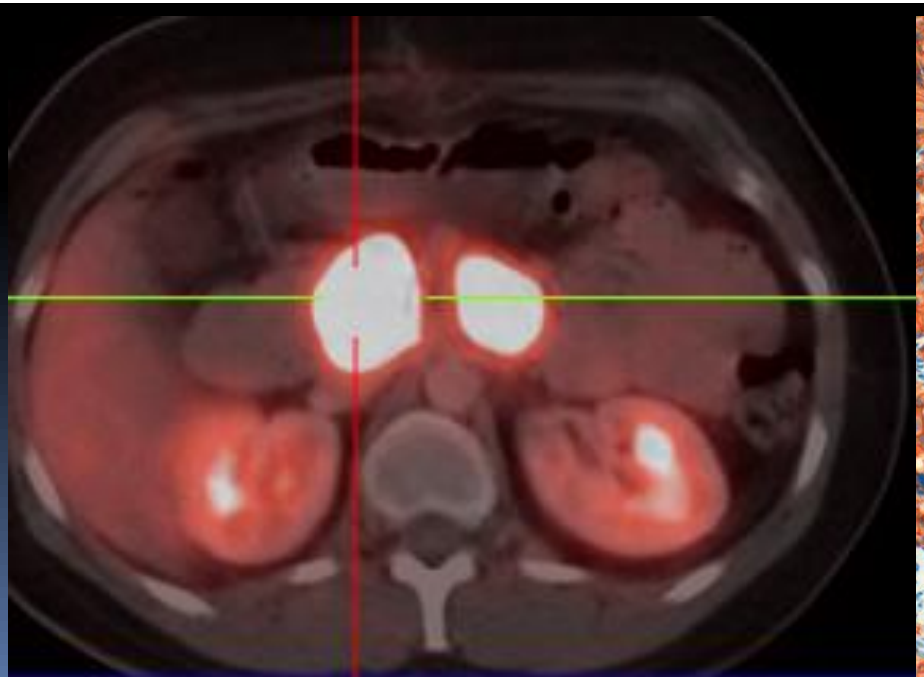
Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-011-1846-5

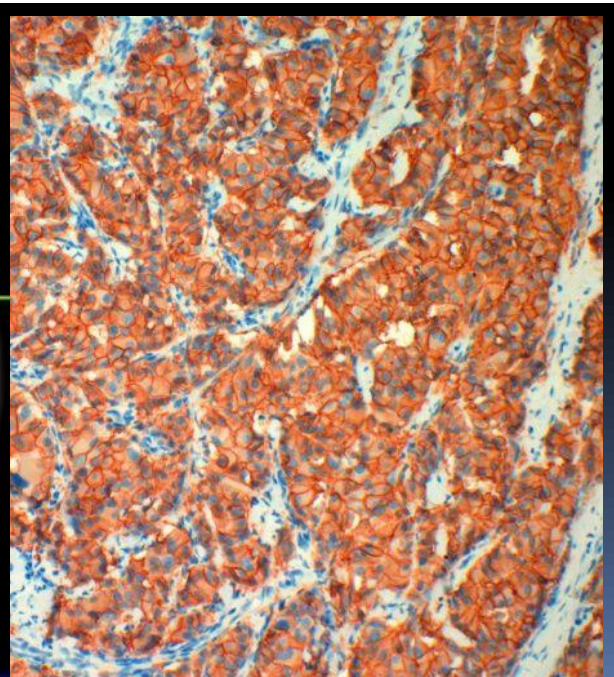
Eur J Nucl Med Mol Imaginge 2011 Sep;38(9):1659-68

ORIGINAL ARTICLE

Molecular imaging with ^{68}Ga-SSTR PET/CT and correlation to immunohistochemistry of somatostatin receptors in neuroendocrine tumours

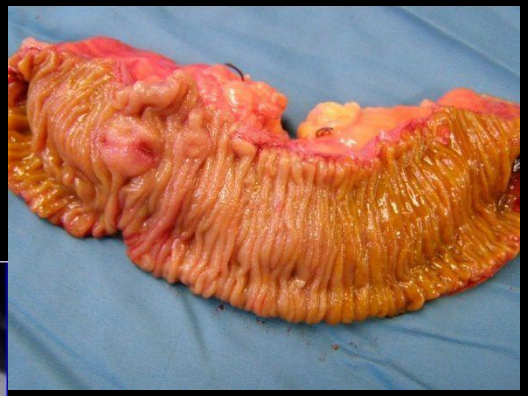
Daniel Kaemmerer · Luisa Peter · Amelie Lupp · Stefan Schulz · Jörg Sänger · Vikas Prasad · Harshad Kulkarni · Sven-Petter Haugvik · Merten Hommann · Richard Paul Baum



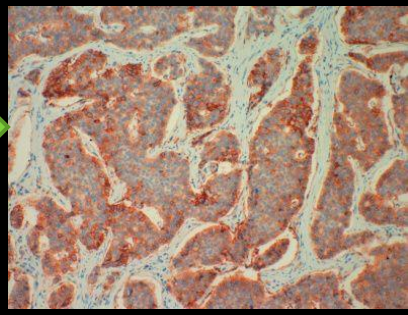


From Molecular Imaging to Therapy

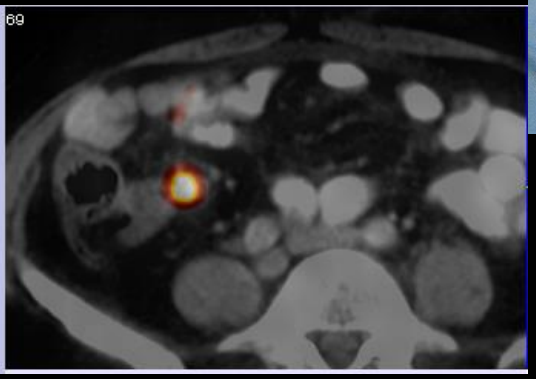
Ileum NET, size 4 mm



Ileum NET



IHC Scoring for SSTR1-5



Ga-68 DOTA-SMS PET/CT in 34 histologically documented GEP NET patients

44 surgical specimens generated

Only lesions > 1.5 cm on PET/CT were selected to avoid partial volume effect on the semi-quantitative parameters

Somatostatin receptor imaging using Ga-68 DOTA-NOC PET/CT results in accurate estimation of the receptor density.

Image Analysis Results SSTR-2	Correlation	Liver Mets SUVmax PET/CT
N1	Correlation Coefficient	-0,733
	P Value	0.02
N2	Correlation Coefficient	-0.750
	P Value	0.0158

Number of Patients : 9

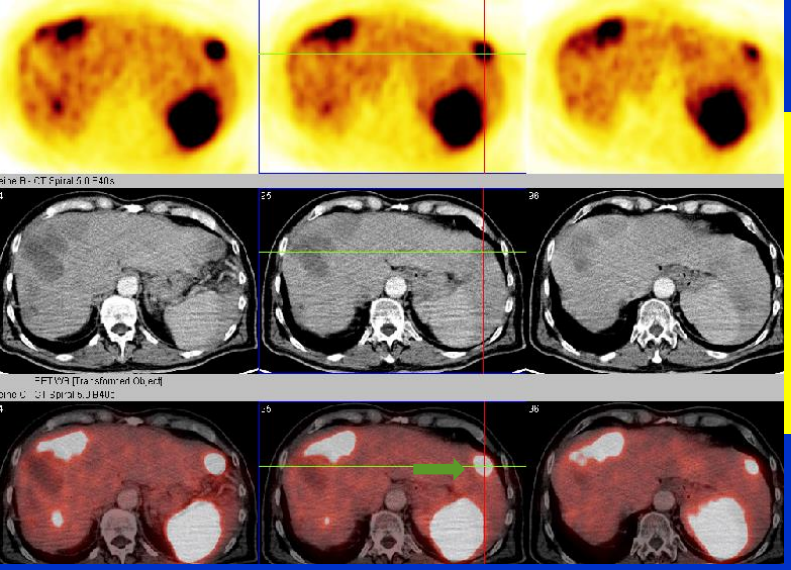
Results

The correlation coefficients for SUV max, SUVmean, and MTV ranged from 0.83 to 0.99 ($p<0.005$).

The tumor SUVmax showed a significant correlation with immunohistopathology scores.

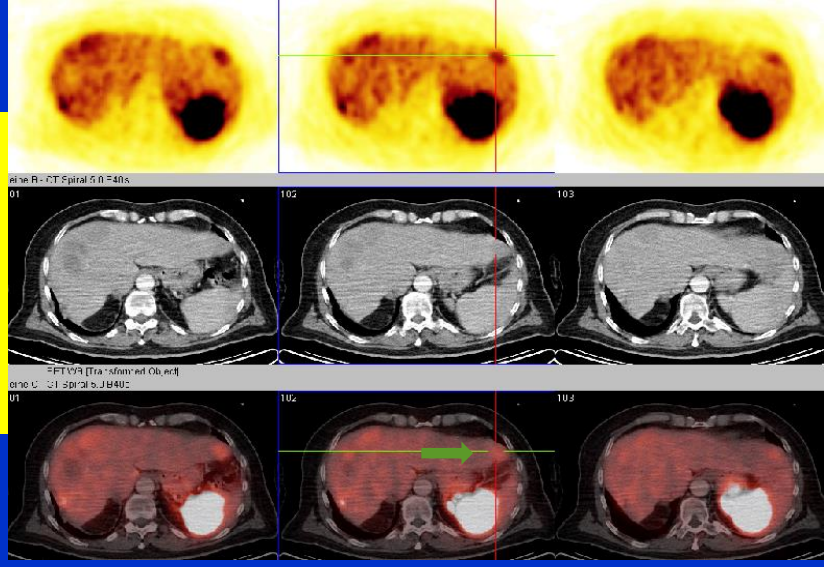
A correlation was also found between SSTR1-5 staining and the corresponding pathology grading.

Ga-68 DOTA-SSTR PET/CT provides *in vivo* histopathology!

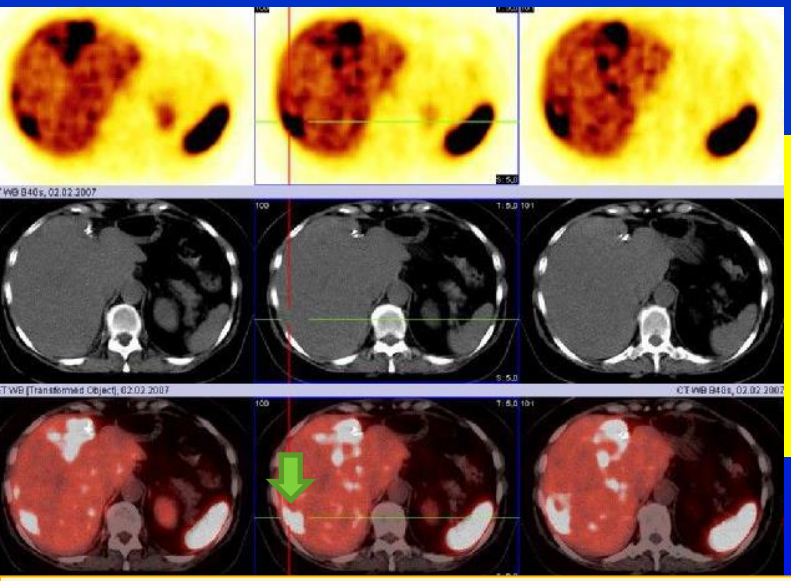


Responder – 42% reduction in SUV_{max}

Dose to tumor – 371 Gy

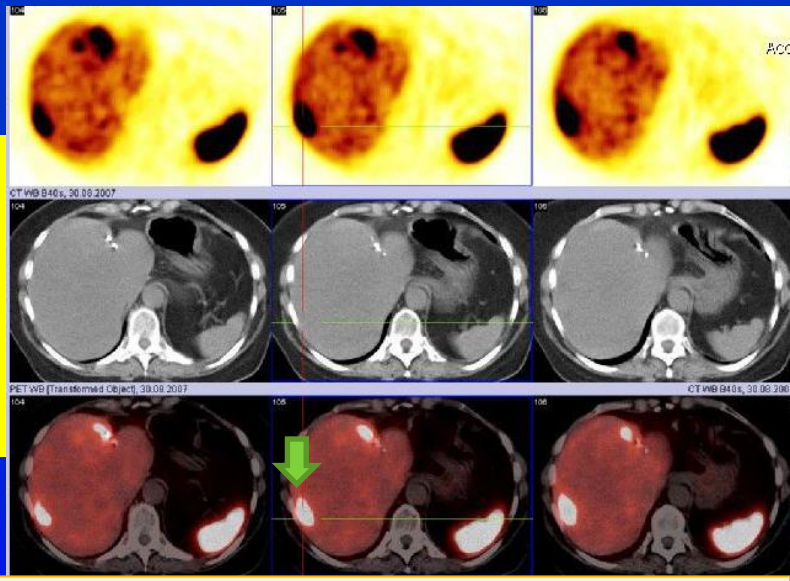


Ga-68 DOTATOC PET/CT



Non – responder 125% increase in SUV_{max}

Dose to tumor – 25 Gy

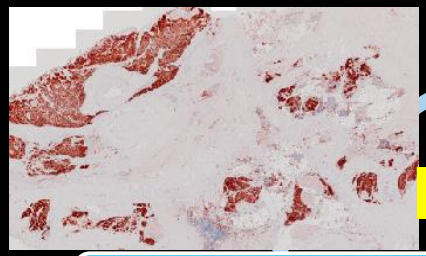


This study confirmed - for the first time - that there is a relationship between the radiation dose delivered to liver metastases and the molecular response post PRRNT as measured by somatostatin receptor PET/CT.

Digitalized Histopathology Combined with Somatostatin Receptor PET/CT

From Tissue to Molecular Imaging to Therapy

Surgical specimen ileum NET



Digital pathology - virtual microscopy

PET/CT - ileum NET, Ø 4 mm

- Tissue Sampling
- Tissue Staining

Definiens XD Image Analysis

Histopathological Grading

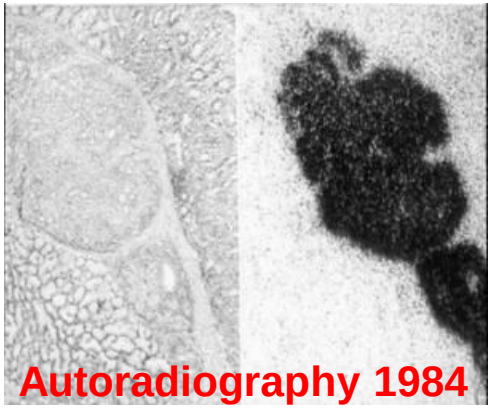
- SMS-R density on tumor cells
- Proliferation rate (Ki-67 / MIB1)
- Chromogranin A / Synaptophysin

- Prognosis
- Selection of most appropriate peptide (DOTATOC, DOTATATE, DOTANOC, SOMscan etc. for SMS-R PET/CT
- Therapy guidance – peptide receptor radionuclide therapy (PRRT) versus chemotherapy vs localised therapy vs molecular therapy etc.

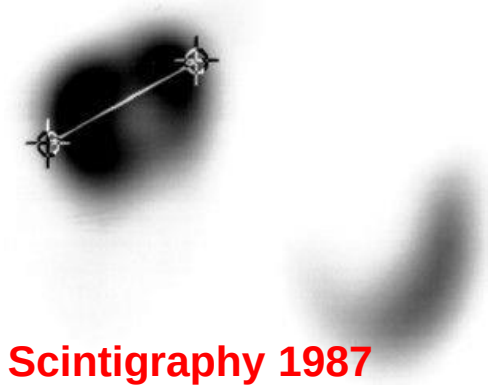
Management Strategy

On the Way to Precision Medicine

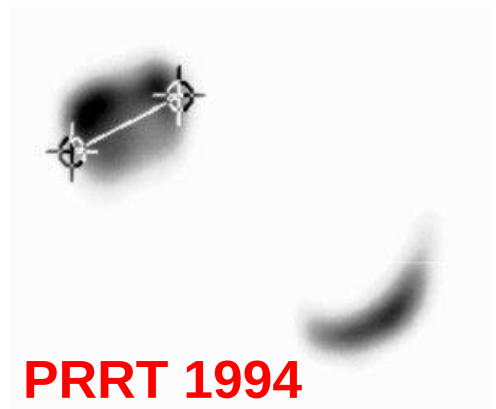
PRRT: a long story…



Autoradiography 1984



Scintigraphy 1987



PRRT 1994

1972	• somatostatin first isolated
1987	• octreotide synthesis • scintigraphy with ^{123}I-octreotide
1991	• ^{111}In-octreotide first employed
1992	• five G-protein coupled somatostatin receptors (sst1–5), identified and cloned
1993	• ^{111}In-octreotide registered
1994	• **First PRRT with high-dose ^{111}In-octreotide**
1996	• **First ^{90}Y-octreotide PRRT**
2000	• **First ^{177}Lu-octreotate PRRT**
2012	• Phase III registration trial of ^{177}Lu-octreotate

Erasmus MC
University Medical Center Rotterdam

PRRT
"Present Status and Future"

EP Krenning, MD, PhD, FRCP

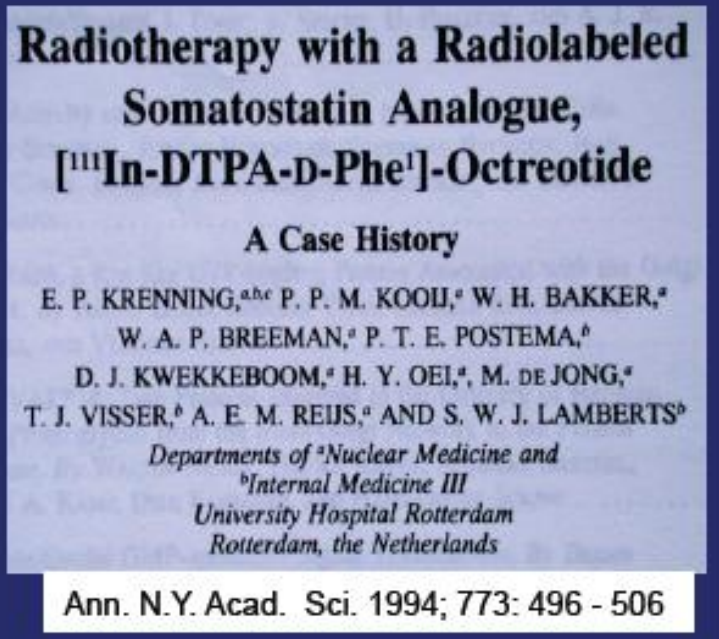
Keynote Lecture ENETS 2014

Barcelona

2014 – 20th Anniversary of PRRT!

ERASMUS MC, ROTTERDAM , NL

Center of Excellence for GEP-NET Patients (ENETS)



Radiotherapy with a Radiolabeled Somatostatin Analogue, [^{111}In-DTPA-D-Phe^{1}]-Octreotide

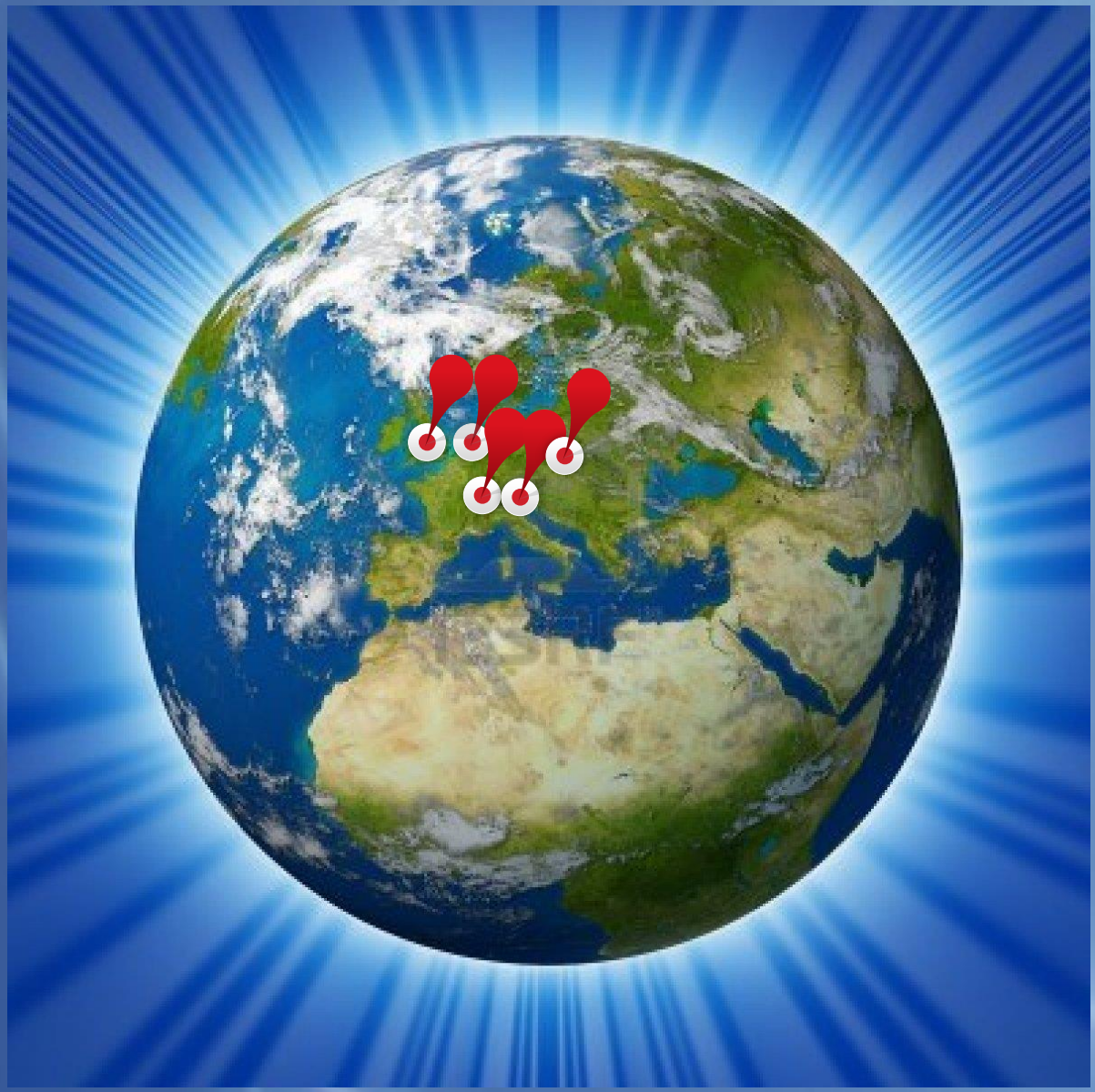
A Case History

E. P. KRENNING,[a,b,c] P. P. M. KOOIJ,[a] W. H. BAKKER,[a] W. A. P. BREEMAN,[a] P. T. E. POSTEMA,[b] D. J. KWEKKEBOOM,[a] H. Y. OEI,[a], M. DE JONG,[a] T. J. VISSER,[b] A. E. M. REIJS,[a] AND S. W. J. LAMBERTS[b]

Departments of [a]Nuclear Medicine and [b]Internal Medicine III University Hospital Rotterdam Rotterdam, the Netherlands

Ann. N.Y. Acad. Sci. 1994; 773: 496 - 506

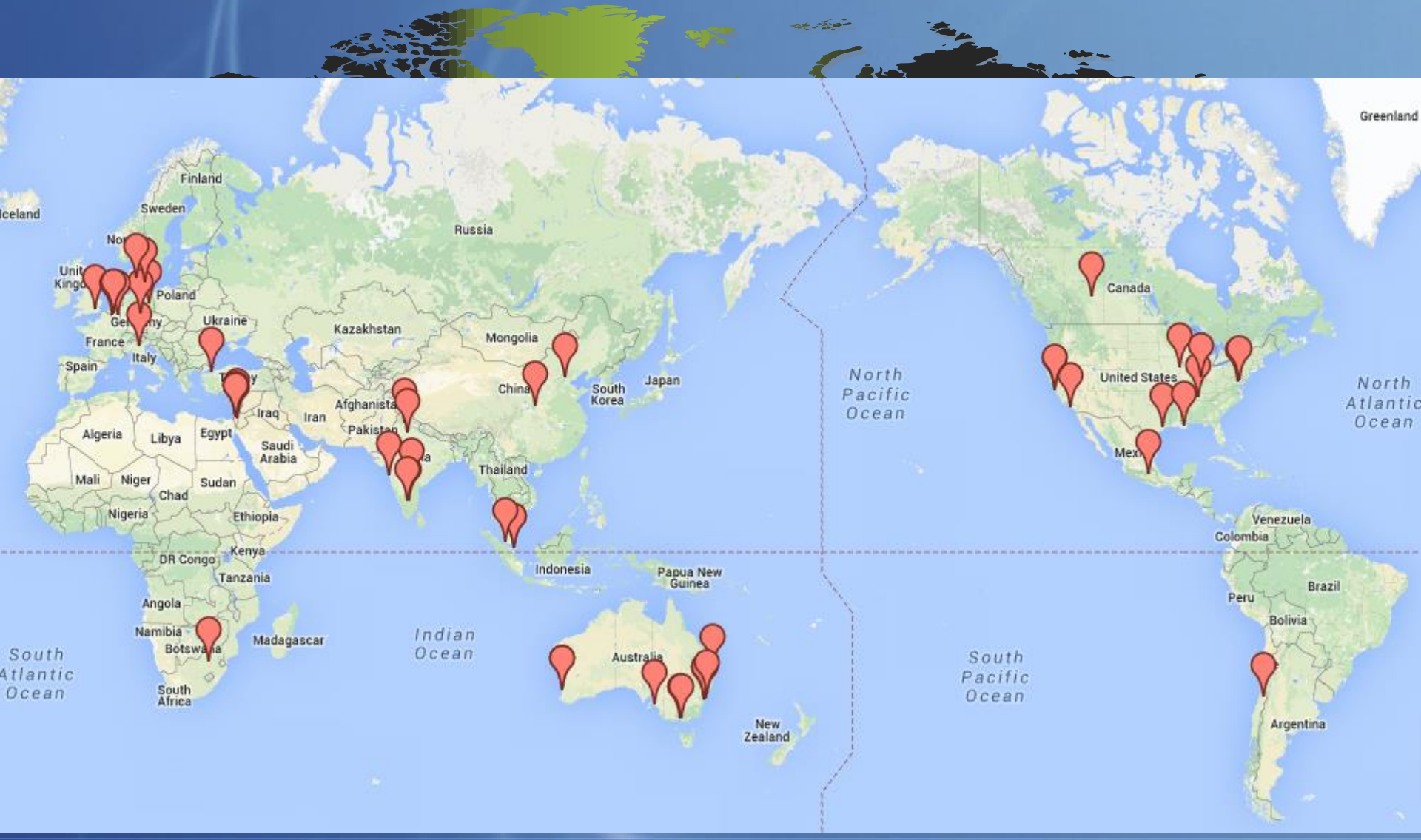
PRRT at the beginning



IEO
Istituto Europeo di Oncologia

Courtesy Lisa Bodei

PRRT: expansion of a concept to the real *WORLD*



What we learned in 18 yrs of Clinical Trials of PRRT

despite the lack of homogeneity among studies

EFFICACY

- ✓ Tumor shrinkage
- ✓ Symptom relief and QoL improvement
- ✓ Biomarker reduction
- ✓ Impact on survival

TOLERABILITY

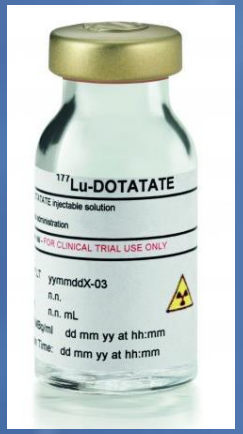
- ✓ Generally well tolerated
- ✓ Generally mild acute side effects:
  - AA-related: nausea, vomiting
  - PRRT-related: fatigue, mild hair loss (Lu-tate), rare exacerbation of syndromes
- ✓ Chronic and permanent effect on kidney, BM, (testes)
  - Generally mild if necessary precautions are taken

Kwekkeboom DJ et al. JNM 2005
Bodei L et al. Eur J Nucl Med Mol Imaging 2004
Bodei et al. J Endocrinol Invest 2009
Kwekkeboom DJ et al. Endocrine Rel Cancer 2010
Brans B et al. Eur J Nucl Med 2007
Cremonesi M et al. Q J Nucl Med Mol Imaging 2011

NETTER-1 Trial (AAA-III-01)

multicentre, stratified, open, randomized, phase III study

R



^{177}Lu-DOTATATE:

- 200 mCi x 4 cycles at q8 wks + Octreotide LAR 30 mg q4 wks

Compare PFS

Octreotide LAR:

- Octreotide LAR 60 mg q4 wks

Over 20 years from first clinical use in patients to drug approval !

Courtesy Lisa Bodei

How to perform

***Peptide Receptor Radionuclide Therapy (PRRT)* – in daily practice in the *real* world?**

Is there any guidance?

PRRT is part of the ENETS Consensus GL

Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumours

A Consensus Statement on Behalf of the European Neuroendocrine Tumour Society (ENETS)

Neuroendocrinology 2006; 84: 155-215

Neuroendocrinology 2008; 87 (1): 8-39

---

www.neuroendocrine.net

The IAEA Practical Guidance Document on PRRT for NETs

Panel of Experts
joint international effort under the auspices of the Division Human Health of the IAEA

Purpose
to enable multidisciplinary teams in IAEA Member States to implement PRRT safely and effectively

Consultant meetings
Vienna, Austria:
7–11 December 2009,
15–19 March 2010,
23–27 May 2011

IAEA
International Atomic Energy Agency

1st time for a joint effort in PRRT!

http://www-pub.iaea.org/MTCD/Publications/PDF/P1560_web.pdf

Courtesy Lisa Bodei

The IAEA Doc on PRRT: Contributors

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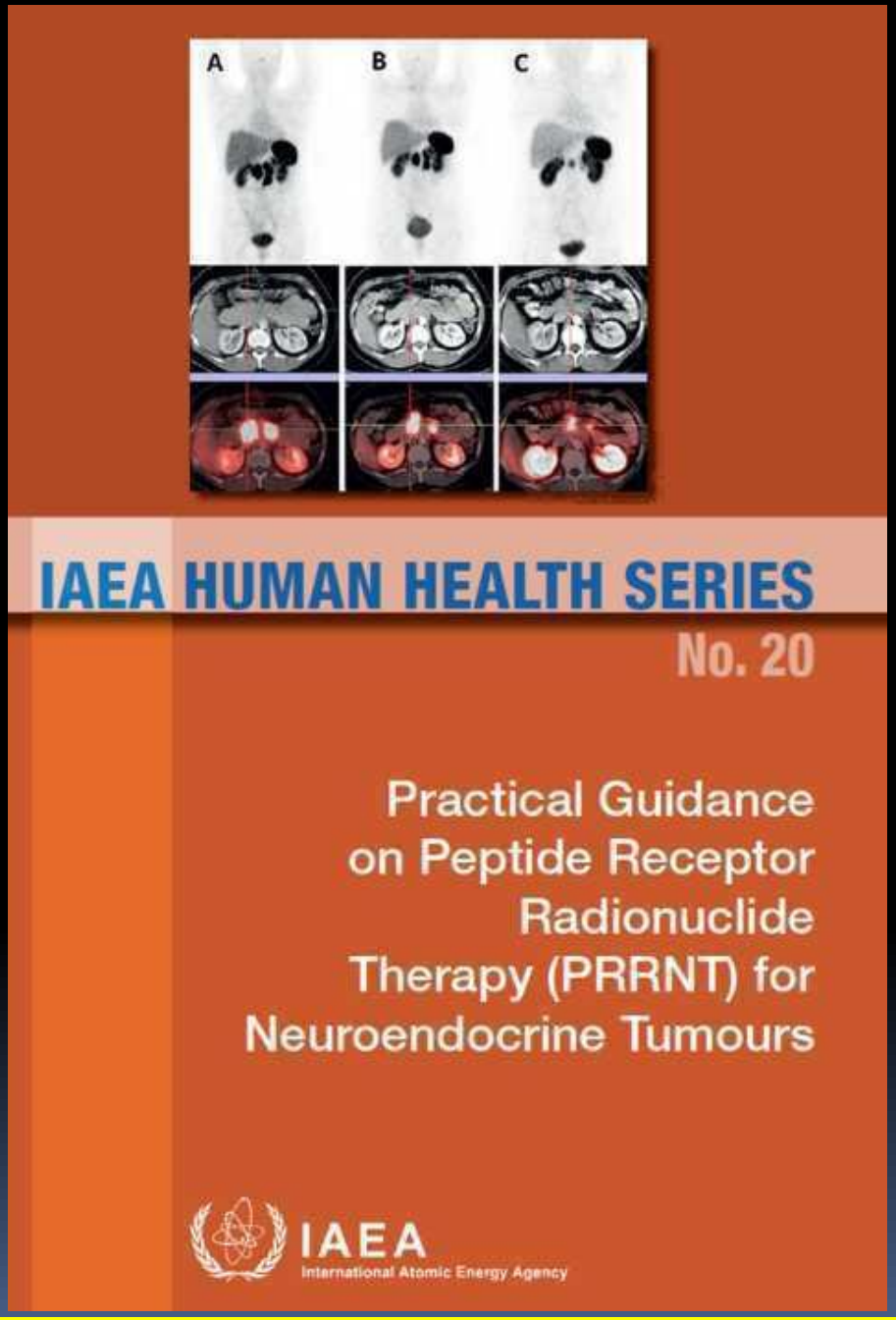
Walter, M.	Universitätsspital Basel, Switzerland
Zaknun, J.J.	International Atomic Energy Agency

The IAEA Doc on PRRT: CONTENTS

- Neuroendocrine Tumors and PRRT
- Special Consideration of PRRT in Children and Adolescent
- Anatomical Imaging
- Molecular Imaging
- Options for the Care of NET Patients
- Peptide Receptor Radionuclide Therapy (PRRT)
  - Multidisciplinary approaches to PRRT
  - Patient eligibility
  - Implementing PRRT
- Evaluation of Response
- Practical Aspects of PRRT
- Dosimetry

http://www-pub.iaea.org/MTCD/Publications/PDF/P1560_web.pdf



http://www-pub.iaea.org/MTCD/Publications/PDF/P1560_web.pdf

The IAEA – EANM - SNMMI Practical Guidance Document on PRRT in NETs

IAEA International Atomic Energy Agency

EANM European Association of Nuclear Medicine

SNMMI Society of Nuclear Medicine and Molecular Imaging

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-012-2330-6

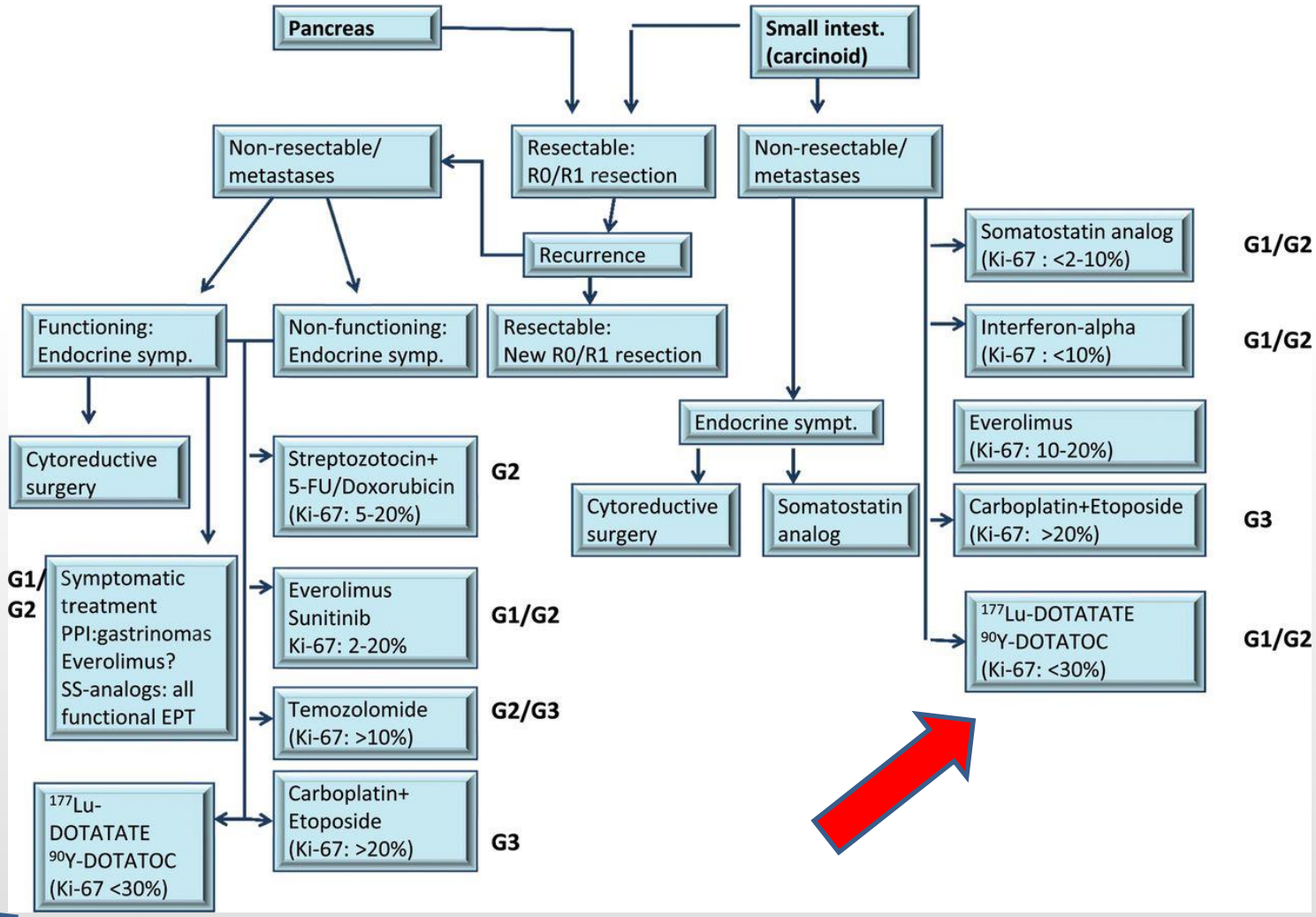
GUIDELINES

The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours

John J. Zaknun · L. Bodei · J. Mueller-Brand · M. E. Pavel · R. P. Baum · D. Hörsch · M. S. O'Dorisio · T. M. O'Dorisiol · J. R. Howe · M. Cremonesi · D. J. Kwekkeboom

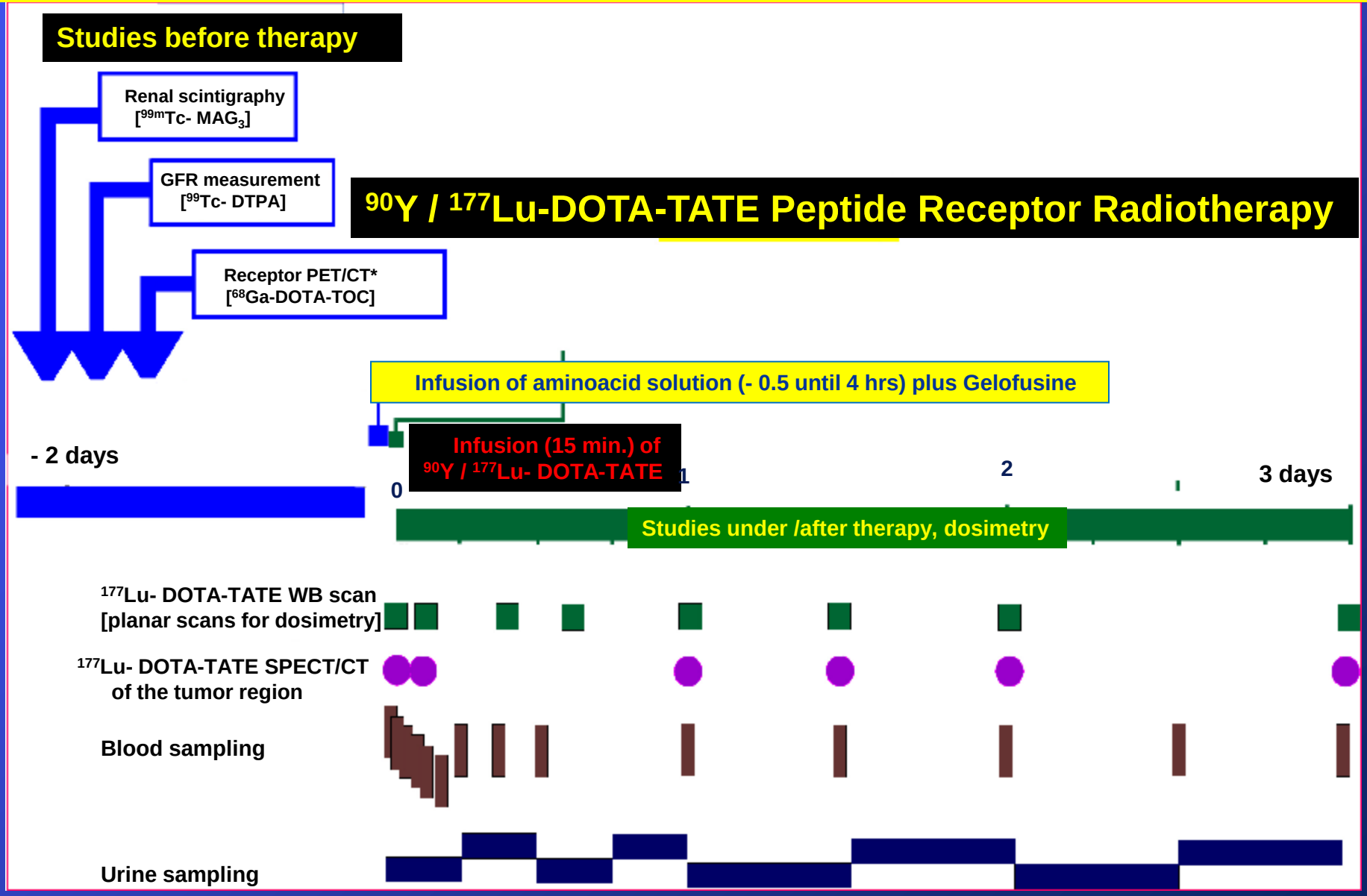
EJNMMI February 2013

Treatment algorithm ESMO guidelines 2012



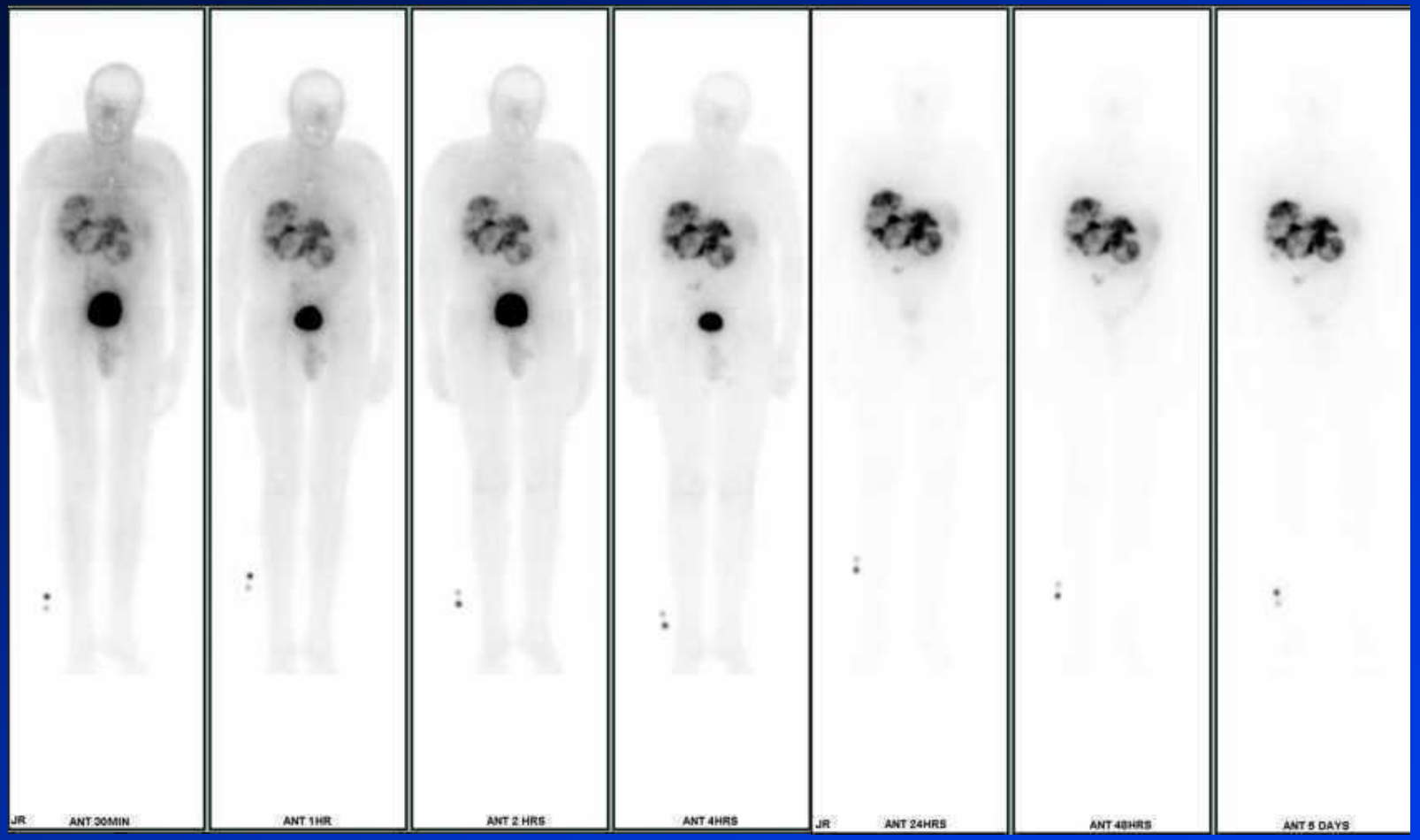
Öberg K et al. Ann Oncol 2012;23:vii124-vii130

BAD BERKA PROCEDURE FOR PRRT



* Since July 2004. Previously, Tc-99m EDDA Hynic TOC (planar & SPECT) was performed.
In selected patients, also F-18 FDG and / or F-18 fluoride PET/CT is performed as well as MRI of the liver / bones

Lutetium-177 DOTATATE
PHARMACOKINETICS



30m 1h 2h 4h 24h 48h 5d

Zentralklinik Bad Berka

Dosimetry in Targeted Radionuclide Therapy:

The Bad Berka Dose Protocol

Experience after more than 550 Evaluations

Christiane Schuchardt

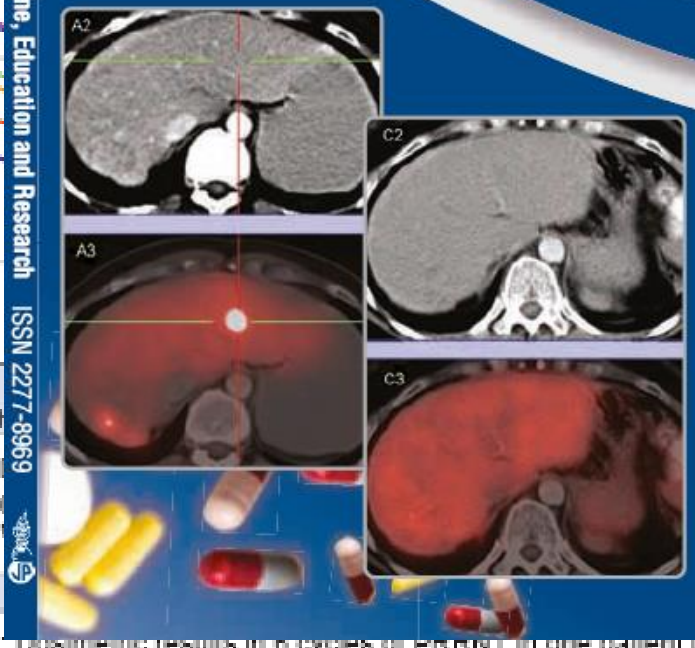
THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging
ENETS Center of Excellence
Zentralklinik Bad Berka, Bad Berka, Germany

January-March 2013 Volume 47 Number 1
ISSN 2277-8969
eISSN 2278-0262

Journal of Postgraduate Medicine Education and Research

The Official Journal of Postgraduate Institute of Medical Education and Research, Chandigarh, India

The pdf of this issue is available on our website www.prrtinfo.org and on the congress website http://www.2ndworldcongress-ga-68.de/



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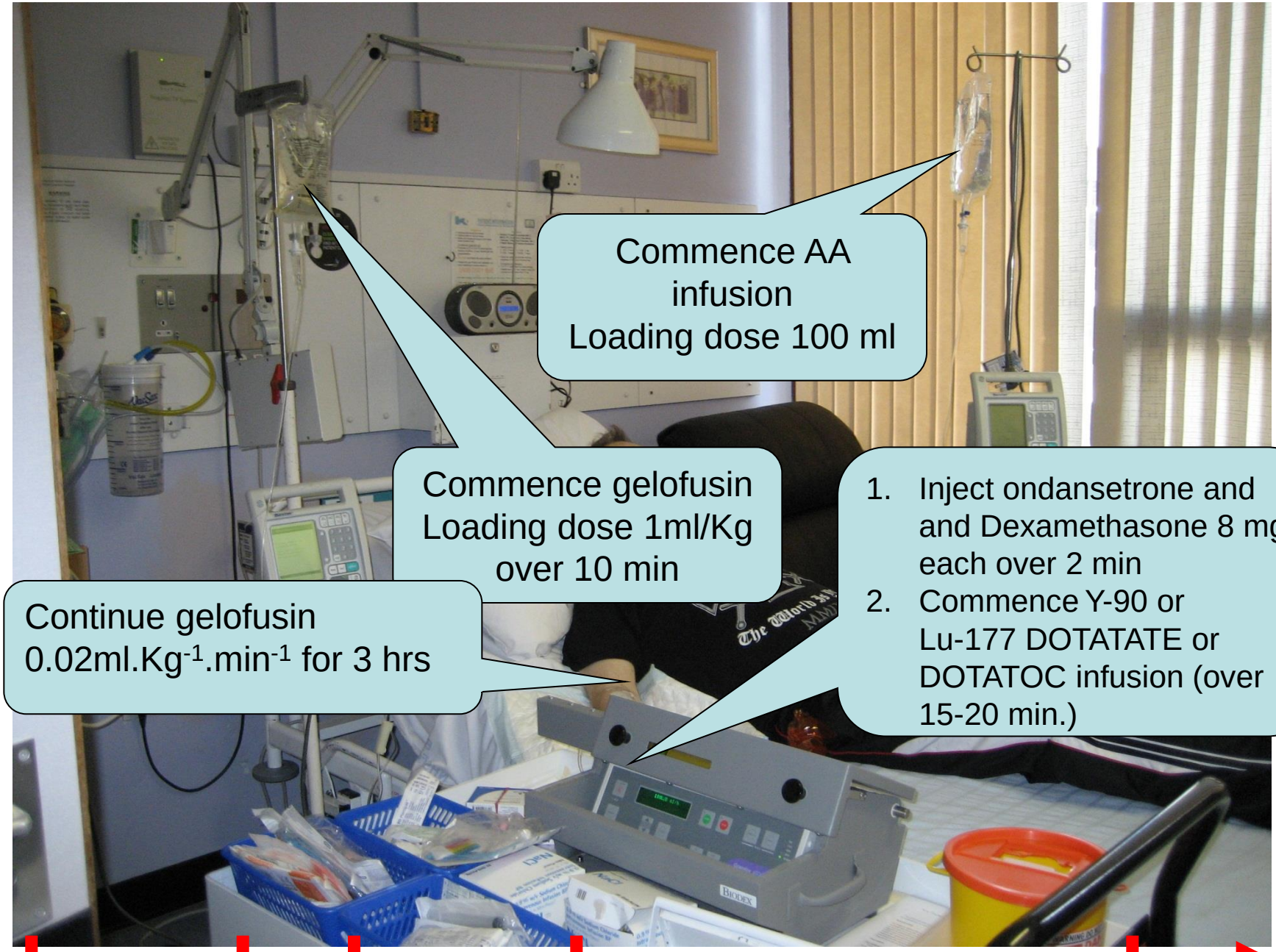
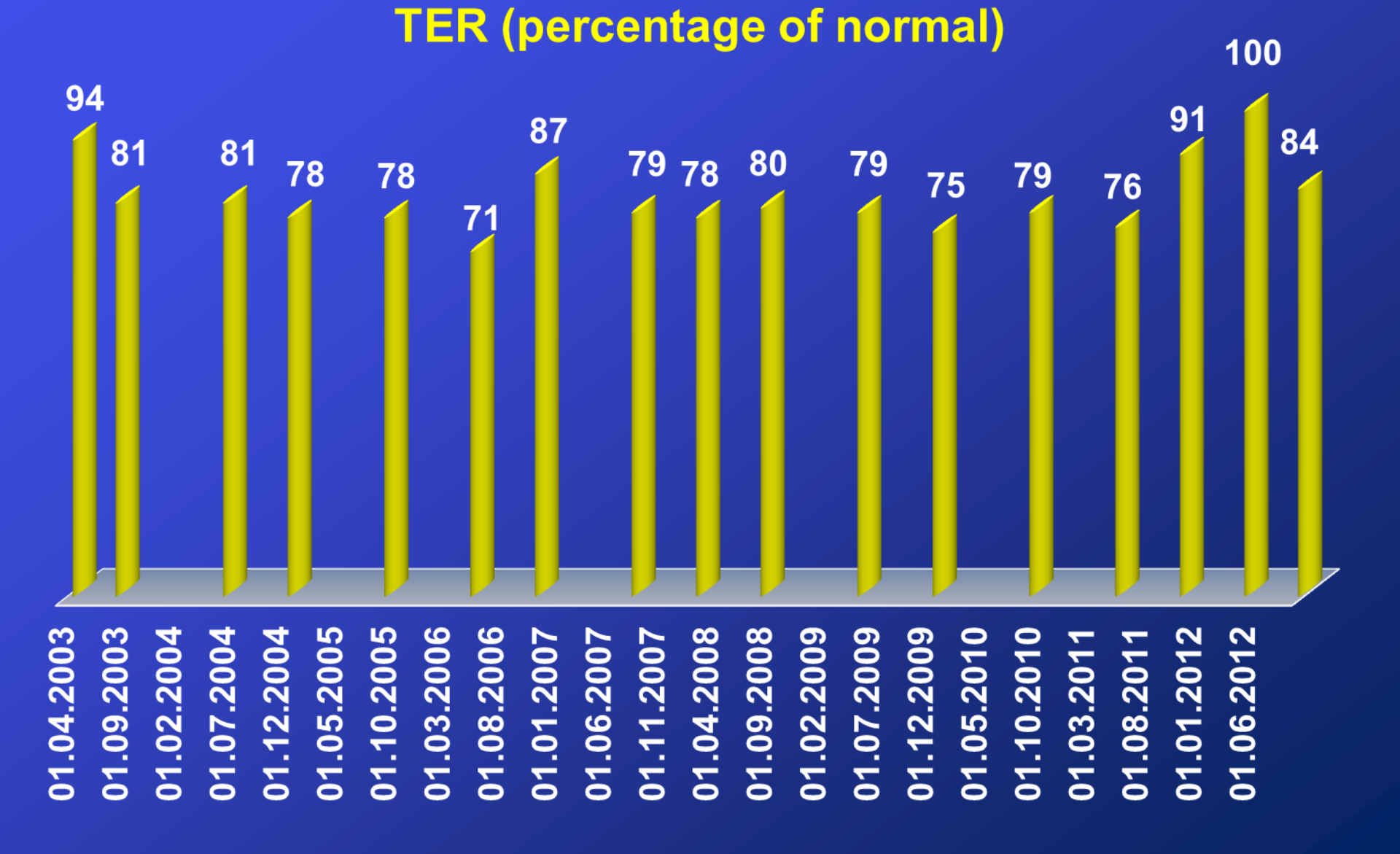
January-March 2013 Vol. 47 No. 1 Journal of Postgraduate Medicine, Education and Research ISSN 2277-8969

Graph 4: Dosimetric results in 6 cycles of PRRNT in one patient using three different peptides


Commence AA infusion
Loading dose 100 ml
Commence gelofusin
Loading dose 1ml/Kg over 10 min
1. Inject ondansetrone and and Dexamethasone 8 mg each over 2 min
2. Commence Y-90 or Lu-177 DOTATATE or DOTATOC infusion (over 15-20 min.)
Continue gelofusin
0.02ml.Kg-1.min-1 for 3 hrs
-30 min
-10 min
0 min
+20 min
+3 hrs

7 patients receiving PRRT on one day…

Serial renal function assessment in a patient treated with 9 PRRNT cycles over 9 years by measurement of the tubular extraction rate (TER) using Tc-99m MAG3.



JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adverse events – Basel data

Hematological toxicity 3 or 4: **12.8 %**
(transient)

Renal toxicity

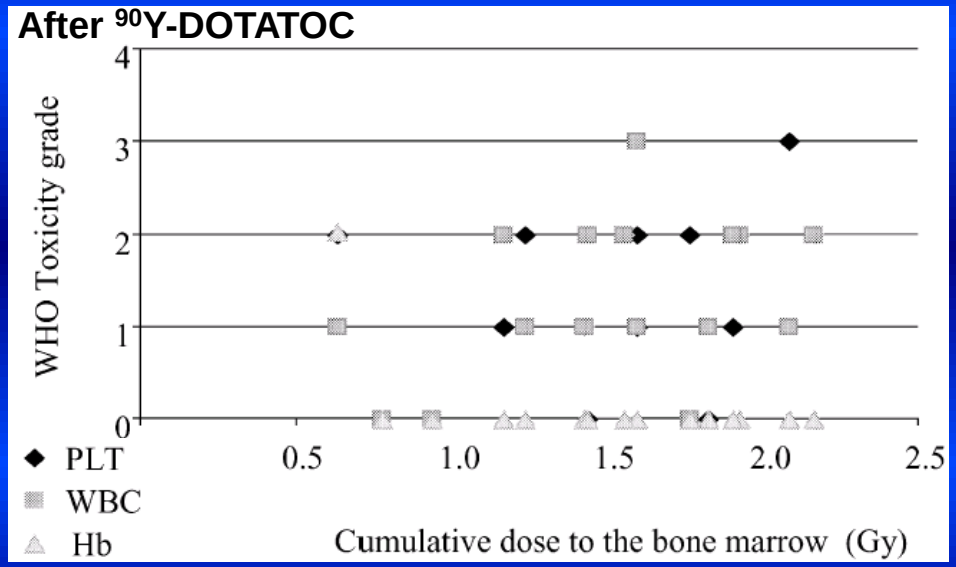
grade 4 (n = 67 pts)
grade 5 (n = 35 pts): **9.2 %**

Bad Berka (DUO-PRRT): 1/1002 patients (0.1 %) on dialysis

Safety: Bone Marrow & Kidney

Center (reference)	Ligand	No. of patients	Toxicity: Grade 3 or 4 hematologic* Platelets	Hb	WBC	Other†
Rotterdam (2)	[^{111}In-DTPA^0]octreotide	50	10	15	2	3 AML or MDS
New Orleans (3)	[^{111}In-DTPA^0]octreotide	27	7	11	7	3 liver, 1 renal
Milan (10)	[^{90}Y-DOTA^0, Tyr^3]octreotide	40	7	3	7	
Basel (4)	[^{90}Y-DOTA^0, Tyr^3]octreotide	29	3	7	0	4 renal‡
Basel (6)	[^{90}Y-DOTA^0, Tyr^3]octreotide	39	0	3	0	1 renal
Rotterdam (11)	[^{90}Y-DOTA^0, Tyr^3]octreotide	60	12	8	13	1 MDS, 1 liver, 1 renal
Rotterdam (18)	[^{177}Lu-DOTA^0, Tyr^3]octreotate	200	9.5% after at least one cycle			1 MDS, 1 renal

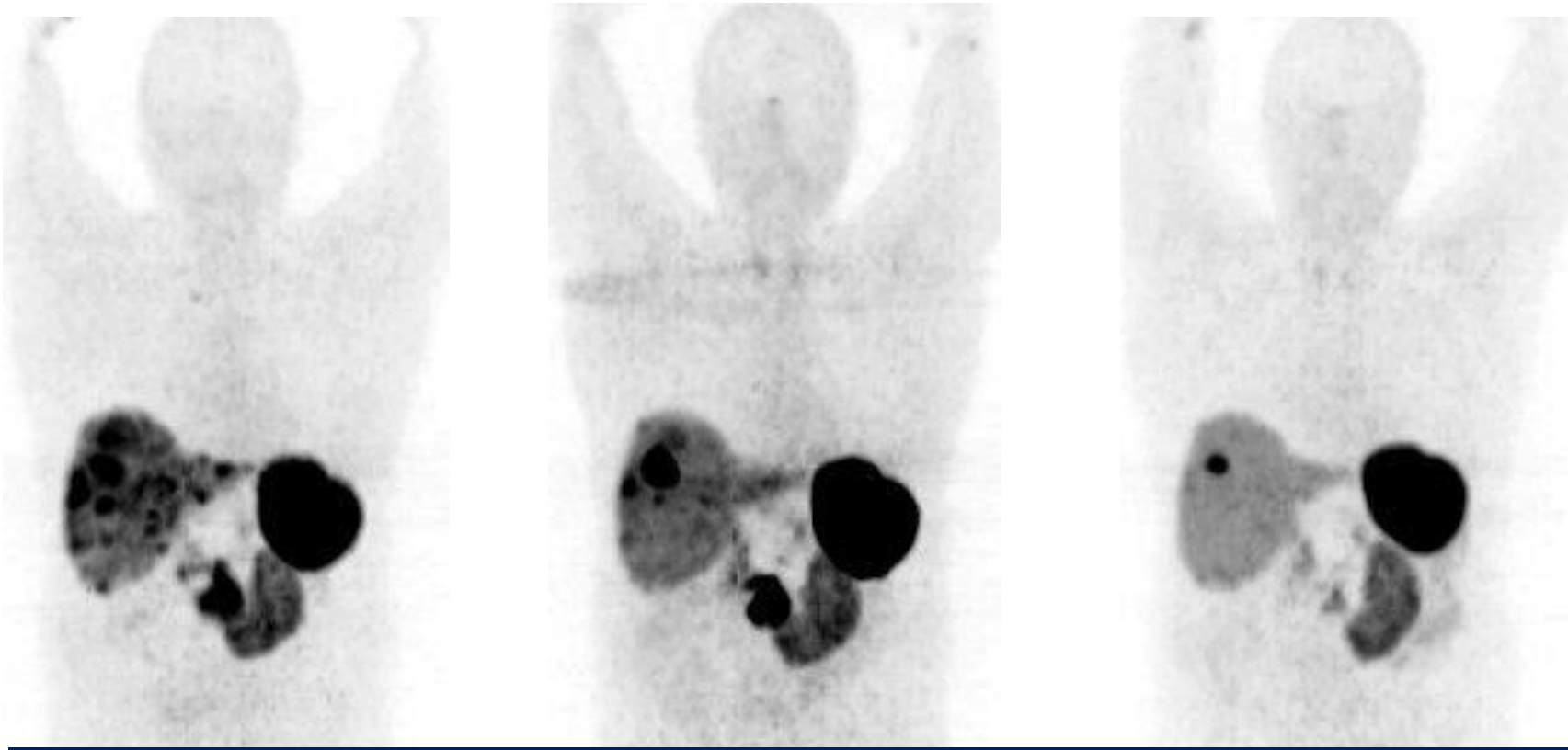
Kwekkeboom DJ et al, J Nucl Med 2005
Kwekkeboom DJ et al. Endocrine Rel Cancer 2010



Bodei L et al, Eur J Nucl Med 2004

Dept. of Nuclear Medicine/P.E.T. Center, Zentralklinik Bad Berka

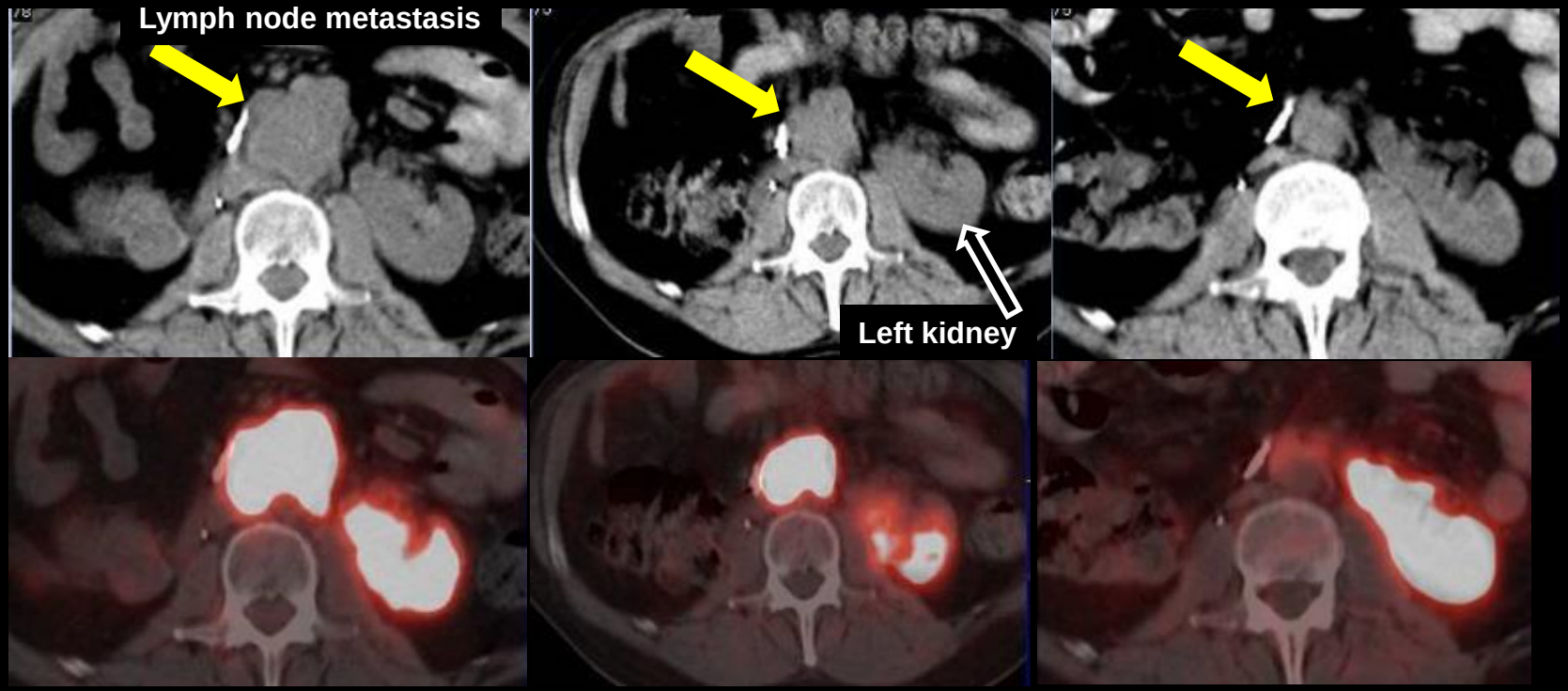
Neuroendocrine cancer of the right kidney with extensive bilateral liver metastases (size 3.7 cm in S7) and retroperitoneal lymph node (size up to 6.5 cm) and bone metastases.



MOLECULAR RESPONSE BY ^{68}GA DOTA-TOC PET/CT
IMPROVEMENT OF KIDNEY FUNCTION IN A PATIENT WITH A SINGLE KIDNEY

May 2009 – before PRRT	Sept. 2009 - after 1st PRRT	Jan. 2010 - 4mo after 2nd PRRT
TER 97 ml/min (35 %)	*TER 147 ml/min (54 %)*	*TER 202 ml/min (74 %)*

ANATOMIC (CT, UPPER ROW) AND MOLECULAR (GA-68 DOTA-TOC PET, LOWER ROW) RESPONSE



May 2009

Before PRRT-1
Using
7 GBq Lu-177 DOTA-TATE

Diameter 6.5 cm on CT

Sept. 2009

Before PRRT-2
7.5 GBq Lu-177 DOTA-TOC
SUV 41.6

Diameter 4.8 cm on CT

Jan. 2010

Restaging
4-mo after PRRT-2
SUV 11.2

Diameter 2.6 cm on CT

Online Submissions: wjg.wjgnet.com
wjg@wjgnet.com
doi:10.3748/wjg.15.5867

World J Gastroenterol 2009 December 14; 15(46): 5867-5870
World Journal of Gastroenterology ISSN 1007-9327
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CASE REPORT

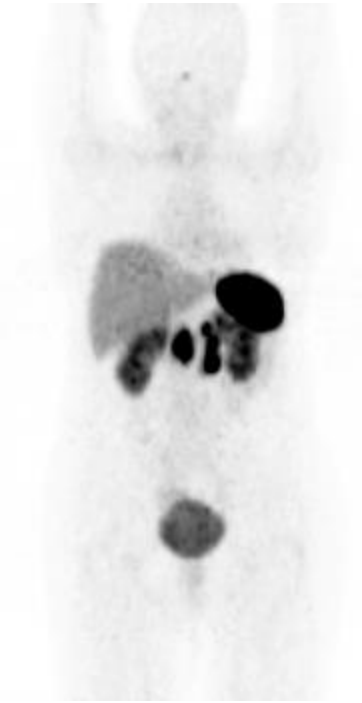
Neoadjuvant peptide receptor radionuclide therapy for an inoperable neuroendocrine pancreatic tumor

Daniel Kaemmerer, Vikas Prasad, Wolfgang Daffner, Dieter Hörsch, Günter Klöppel, Merten Hommann, Richard P Baum

World Journal Gastroenterol 2009

Neoadjuvant sequential PRRT (Y-90 DOTA-TATE) of inoperable progressive pancreatic NET. 32-y-o female, refused chemotherapy.

Before PRRT-1
6 GBq Y-90
SUV 29.4

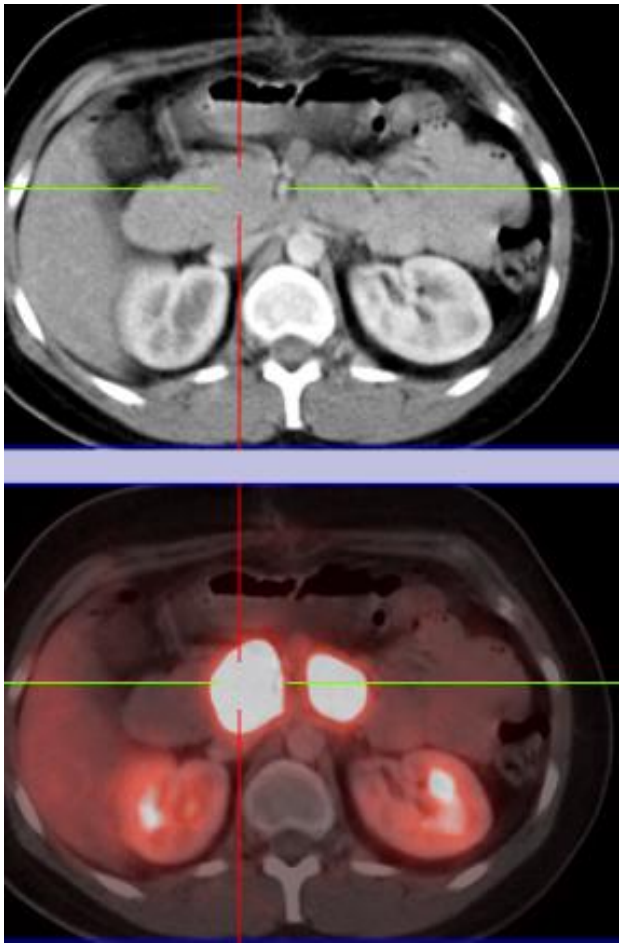


Before PRRT-2
4.5 GBq Y-90
SUV 25.4

5-mo after PRRT-2
pre Op.
SUV 12.5

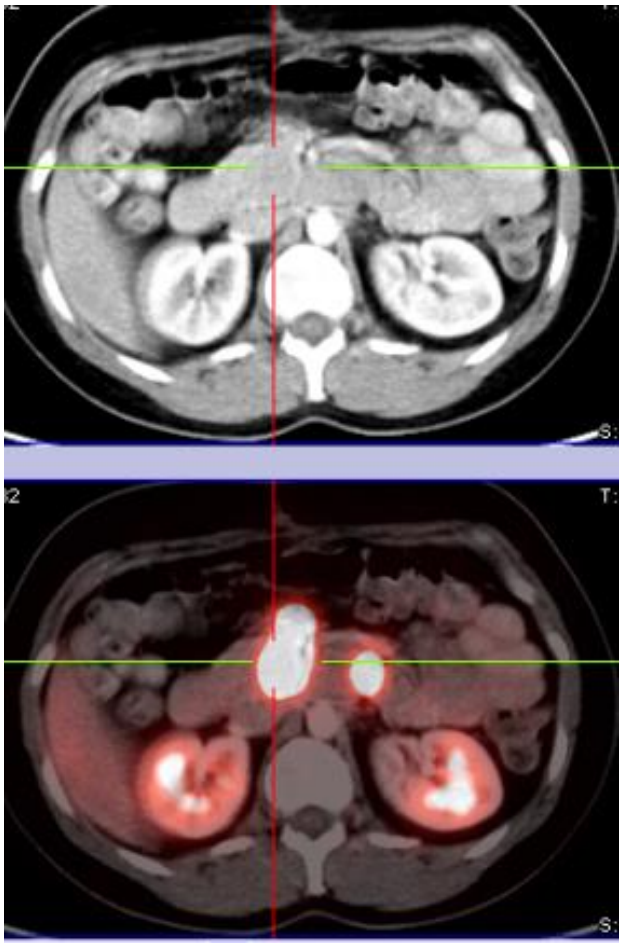
Laparotomy (PE): Highly differentiated NET, Ki-67 8%, CgA +/ NSE +

Sequential PRRT (Y-90 DOTA-TATE) of Inoperable Pancreatic NET



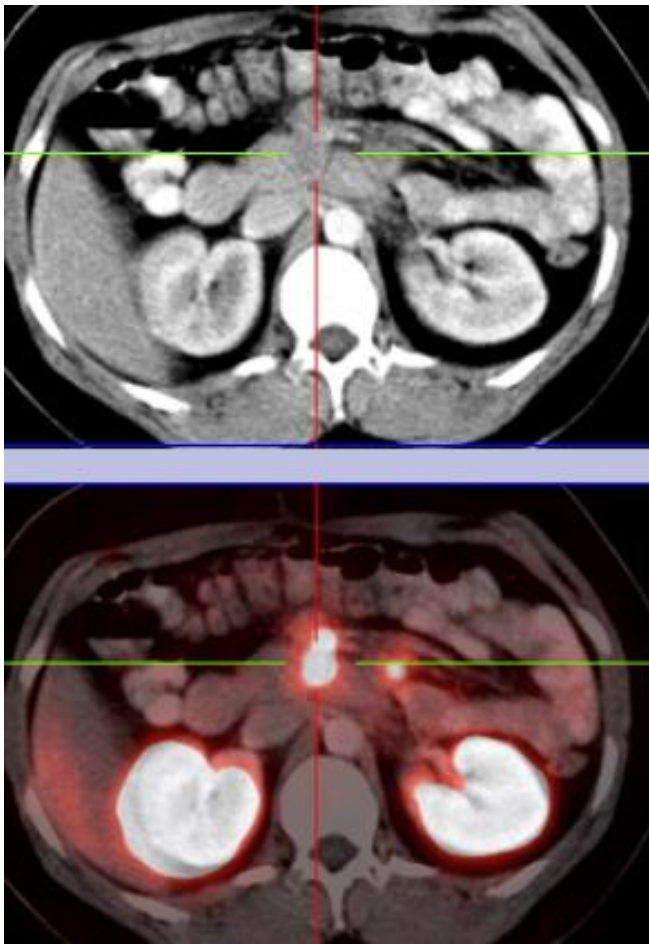
Before PRRT-1
6 GBq Y-90
SUV 29.4

Jan. 2007



Before PRRT-2
4.5 GBq Y-90
SUV 25.4

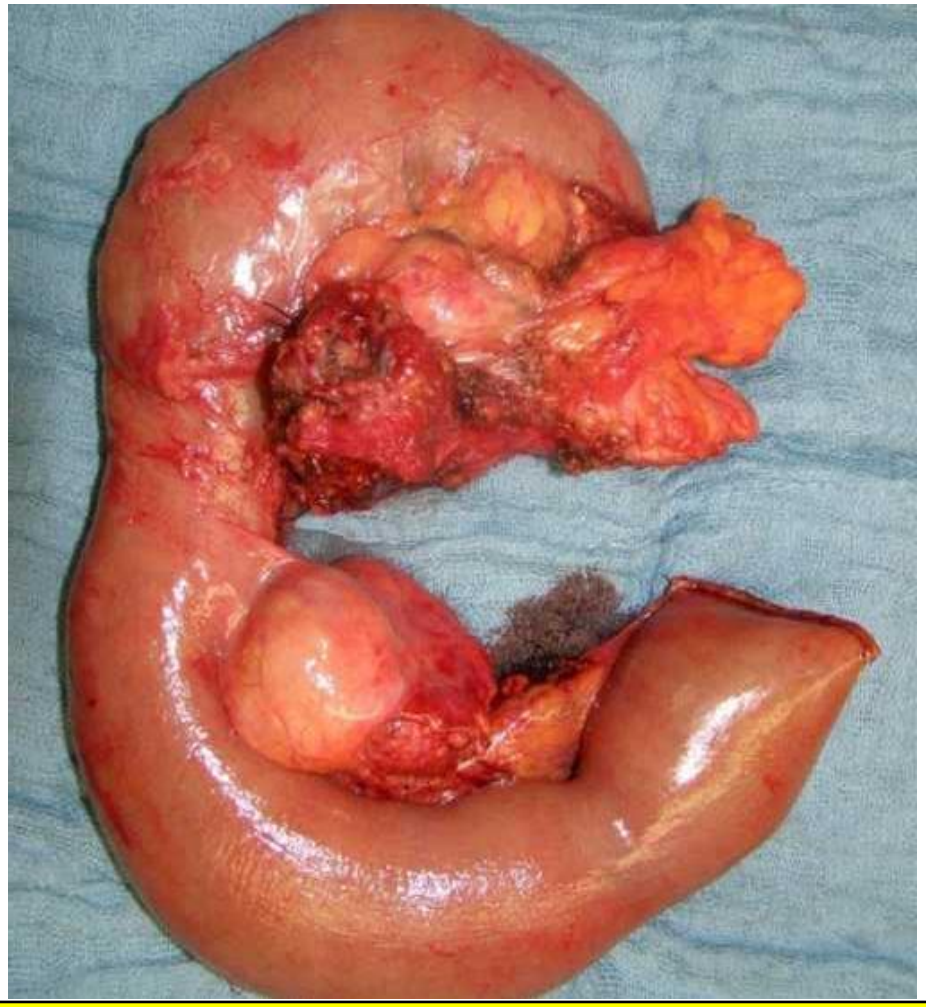
May 2007

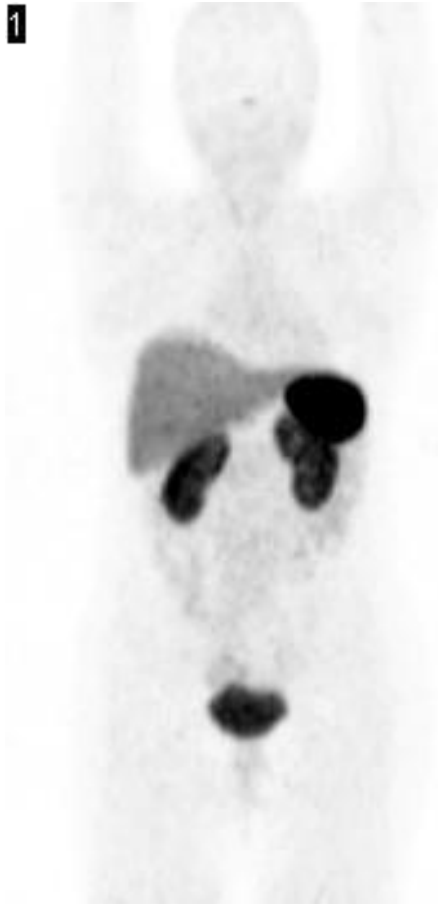


5-mo after PRRT-2
pre Op.
SUV 12.5

Oct. 2007

Whipple‘ Operation – Complete Resection of Pancreatic NET after Neoadjuvant PRRT





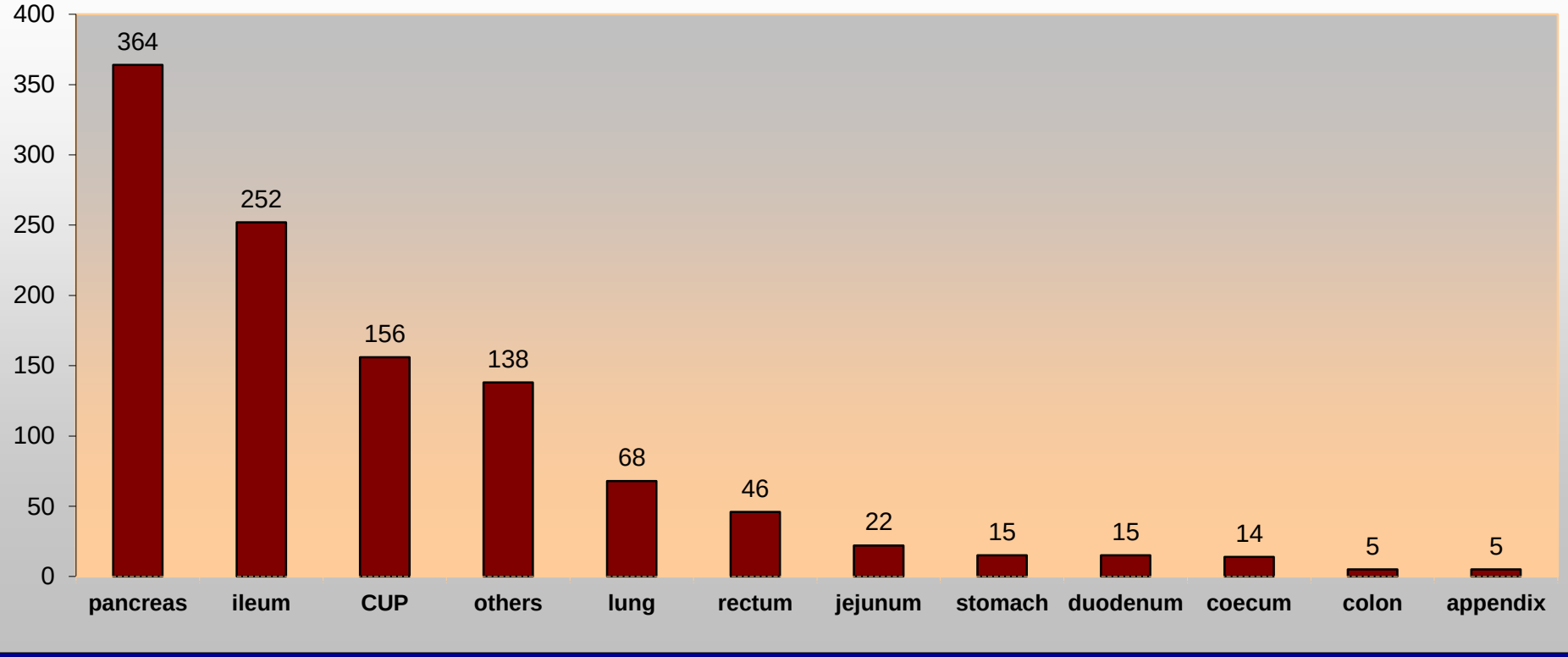
Histology revealed nearly total tumor necrosis typical for radiation necrosis

Follow-up at 54 months: Complete Remission

And the Results?

Center for Molecular Radiotherapy, Zentralklinik Bad Berka

Primary tumors of patients with metastatic NETs treated by PRRT
n=1100 patients



IMPACT ON THE CLINICAL STATUS OF THE PATIENT

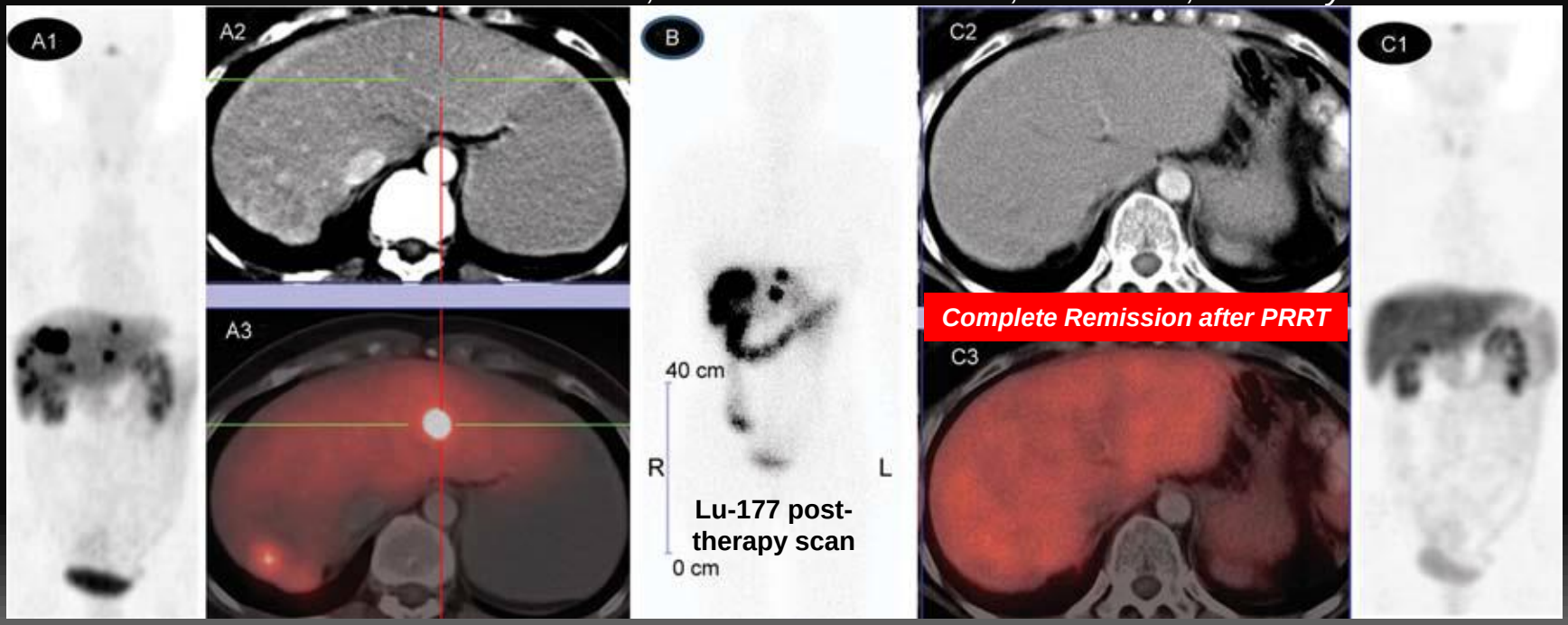
- **Improvement of clinical symptoms in 85 %**
  - **diarrhea**
  - **flushing**
  - **pain**
- **Octreotide doses before/after PRRT: 75 % less or no Oct**
- **Weight gain of 5 % or more in underweight pts. in 95 %**
- **Improvement in Karnofsky performance scale**
- **Improvement of health state score**

Efficacy of Single- or Duo-Radionuclide Peptide Receptor Radionuclide Therapy (PRRT) in 1000 Patients with Neuroendocrine Neoplasms (NENs): Analysis from a Single Center over More than 10 Years

Harshad Kulkarni[1], Richard Baum[1], Daniel Kaemmerer[2], Alexander Petrovitch[3], Merten Hommann[2], Dieter Hörsch[4]

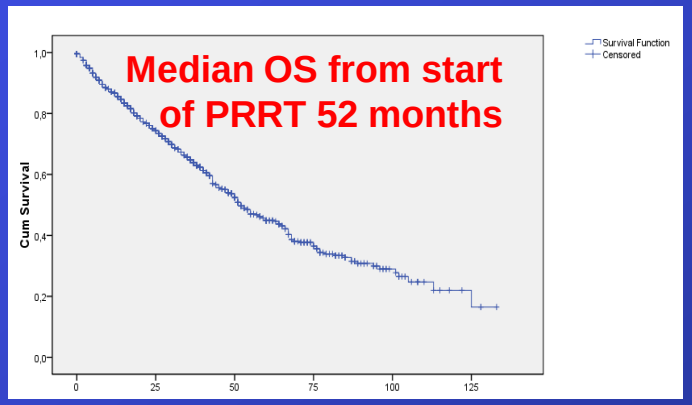
[1]Theranostics Center for Molecular Radiotherapy and Molecular Imaging, [2]General and Visceral Surgery,[3]Interventional Radiology, [4]Internal Medicine, Endocrinology and Gastroenterology,

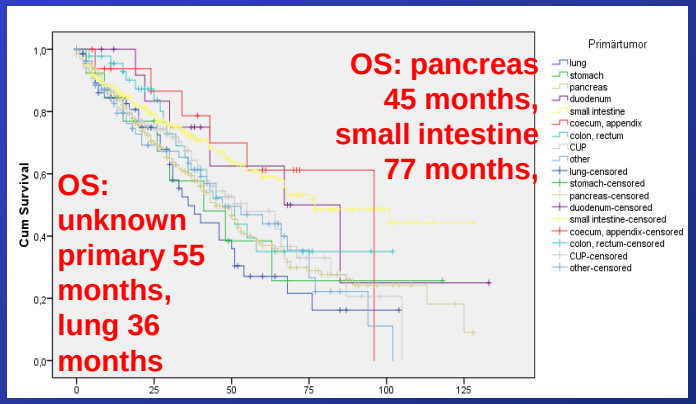
ENETS Center of Excellence, Zentralklinik Bad Berka, Bad Berka, Germany.

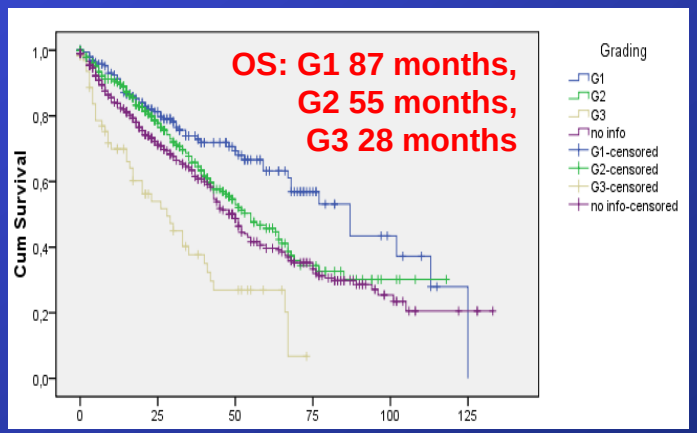


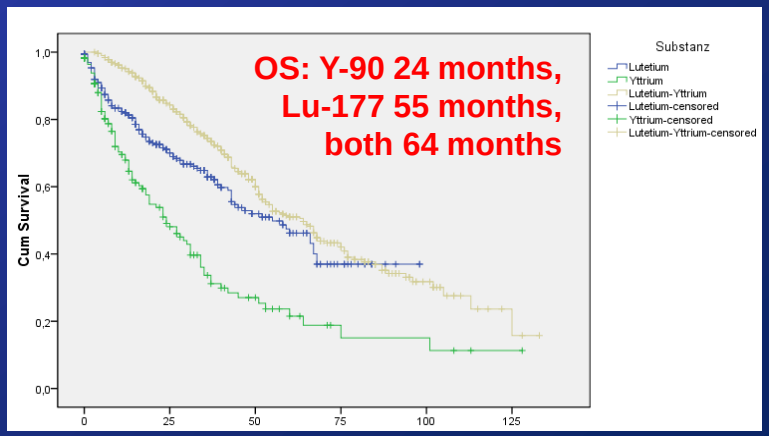
Aim: **To assess the efficacy of PRRT using a single radionuclide (SN-PRRT) approach, or a combination of both (DUO-PRRT) Lu-177 / Y-90 in the same setting (tandem) or in sequence, in 1000 patients with NENs .**

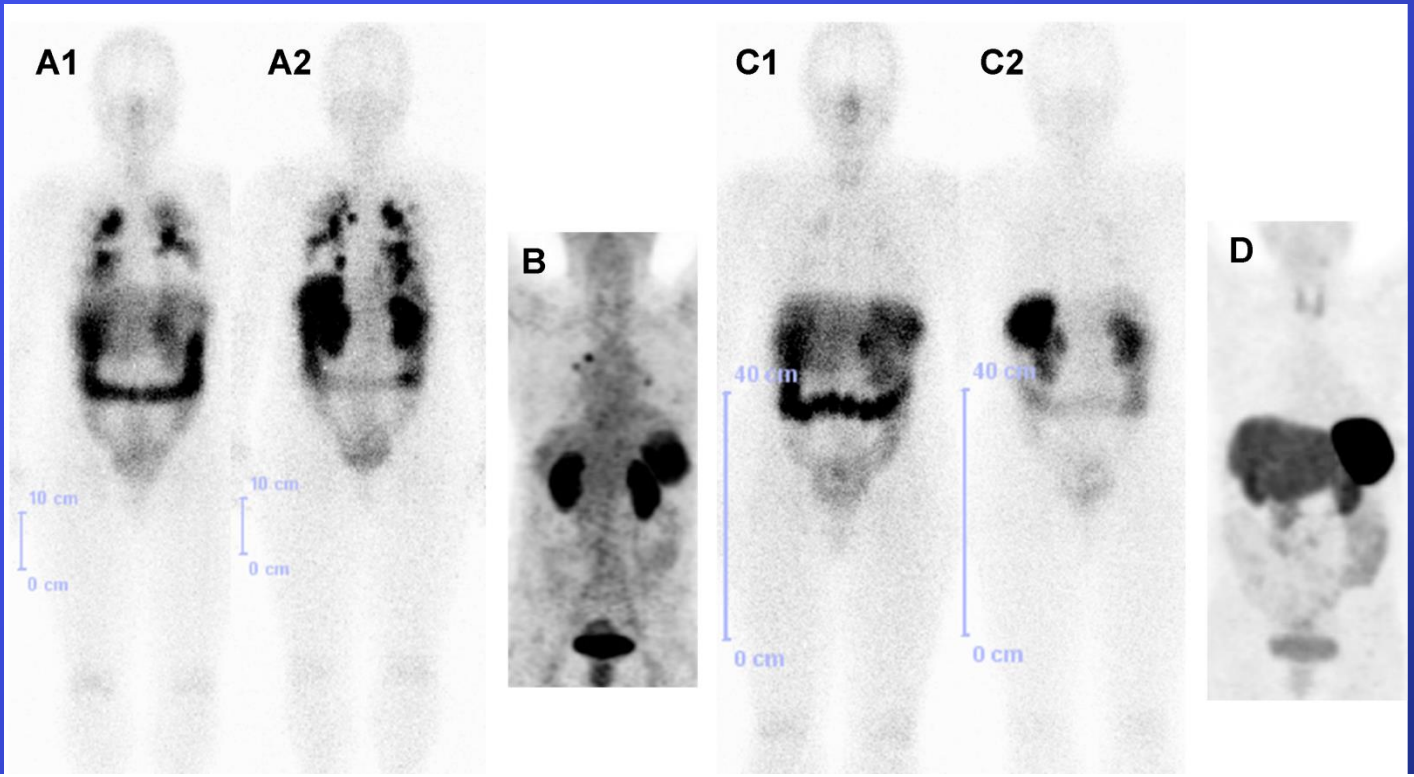
- Retrospective analysis using a database in 1000 patients with metastatic and / or progressive NENs, undergoing 1 – 9 cycles of PRRT using Lu-177 (n=331), Y-90 (n=170) or both (n=499)
- Median total administered activity was 17.5 GBq
- Patients were followed up for up to 132 months after the 1st cycle of PRRT
- Well-differentiated NETs (G1-2) accounted for >80%
- Most patients (95.6 %) had undergone at least one previous therapy (surgery 86.8 %, medical therapy 55 %, ablative therapy 14.2 % and radiotherapy 3.4 %)











A 68-year-old female with well-diffferentiated, nonfunctional NET (DD primary in the liver) with widespread metastasis in the right hepatic lobe (tumor size to 12 x 10 x 10.5 cm) and s.p. right hemihepatectomy, partial omentectomy and cold octreotide therapy presented with bilateral pulmonary metastases. She underwent 2 cycles of PRRT with a cumulative administered activity of 12.3 GBq Lu-177 DOTATATE. The post-therapy whole-body scan after the first PRRT cycle (A1, anterior view; A2, posterior view) showed extremely high uptake in the intrapulmonary metastases bilaterally. A response to PRRT was already noted after the 1st PRRT cycle (B, Ga-68 DOTATOC PET MIP) and a striking difference was noted in the post-therapy whole body scan after 2nd PRRT cycle (C1, anterior view; C2, posterior view). A complete remission was noted after the 2nd PRRT cycle (as shown in the Ga-68 DOTATOC PET MIP image, D)

PRRT lends a significant benefit in overall survival in metastasized and / or progressive G1-2 NETs as compared to other treatment modalities and regardless of previous therapy. Combination of Lu-177 and Y-90 (DUO) based PRRT may be more effective than either radionuclide alone.

Clinical Results of PRRT

^{90}Y-octreotide	number of pts	CR+PR	response criteria	outcome
Otte A (1999)	16	6%	Non specified	Not assessed
Waldherr C (2001)	37	27%	WHO	TTP>26 m
Waldherr C (2002)	36	34%	WHO	Not assessed
Bodei L (2003)	21	29%	WHO	TTP 10 m
Valkema R (2006)	58	9%	SWOG	TTP 29 m
Bushnell D (2010)	90	4%	SWOG	PFS 16 m
Imhof A (2011)	821	37%	RECIST	(Mean OS 46 m)
^{177}Lu-octreotate	number of pts	CR+PR	response criteria	outcome
Kwekkeboom D (2008)	310	30%	SWOG	(OS >48 m) PFS 33 months
Garkavij M (2010)	12	17%	RECIST	Not assessed
Bodei L (2011)	47	32%	RECIST	TTP 36 months

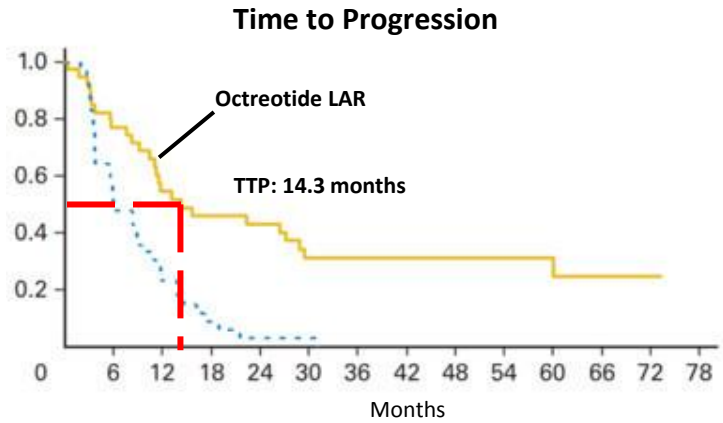
Bodei L, Kidd M, Modlin IM, Paganelli G 2013

Reported outcome in pNET – PRRT vs Afinitor

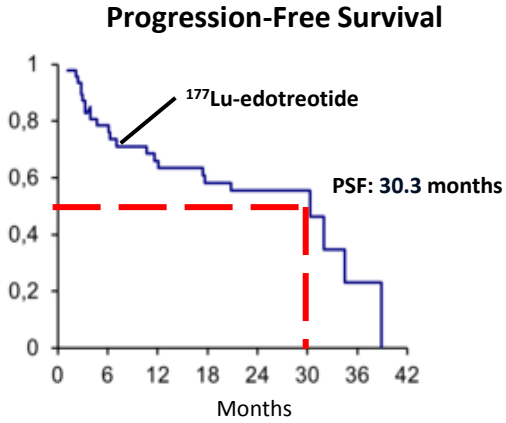
Treatment Author / Study	Comment	n=	ORR (%)	DCR (%)	SD (%)	PFS (mo)	OS (mo)
PRRT ^{177}LuTATE Kwekkeboom 2008 Retrospective Study	intended 4x 7.4 GBq	91	43	86	43	33	46+
PRRT ^{177}LuTATE Sansovini 2013 Prospective study	„full dose“ (5x 5.5 GBq)	26	39	85	46	30+	n.a. (30+)
PRRT (^{90}Y/^{177}Lu) Hörsch ASCO 2013 National registry	Personalized regimen	180	n.a.	n.a.	n.a.	39	53
PRRT ^{177}LuTATE Ezziddin 2014 Retrospective study	intended 4x 8.0 GBq	68	60	85	15	34	53
Everolimus Yao NEJM 2011 RCT	10 mg/d	207	5	78	73	**11**	28+

THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik Bad Berka

DRUG	N treated	Approved in EU or Member State(s)	Indication	Key Results (median months)
Octreotide LAR*	42	YES	Midgut NET	TTP: 14.3
^{177}Lu-edotreotide	58	NO	(GEP NET)	PFS: 30.3 95% CI: 19.2 - 41.7



*: [Rinke 2009]



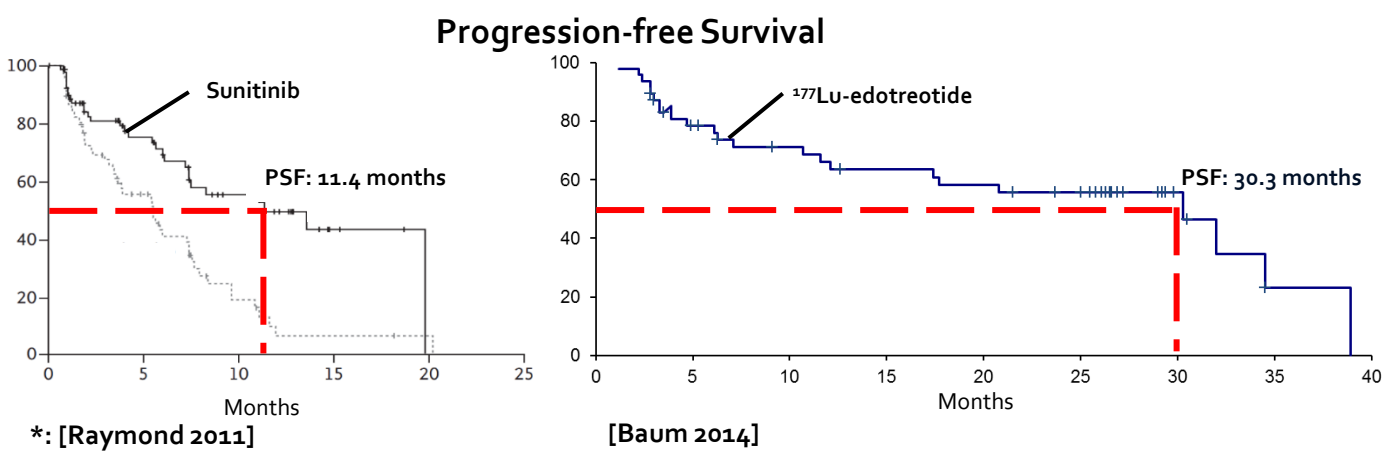
[Baum 2014]

Database Bad Berka, unpublished results

Lu-177 DOTATOC compared to Sandostatin LAR: Improvement of 16 months (PFS vs. TTP)

THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik Bad Berka

DRUG	N treated	Approved in EU or Member State(s)	Indication	Key Results (median months)
Sunitinib*	86	YES	Pancreatic NET	PFS: 11.4
^{177}Lu-edotreotide	58	NO	(GEP NET)	PFS: 30.3 95% CI: 19.2 - 41.7

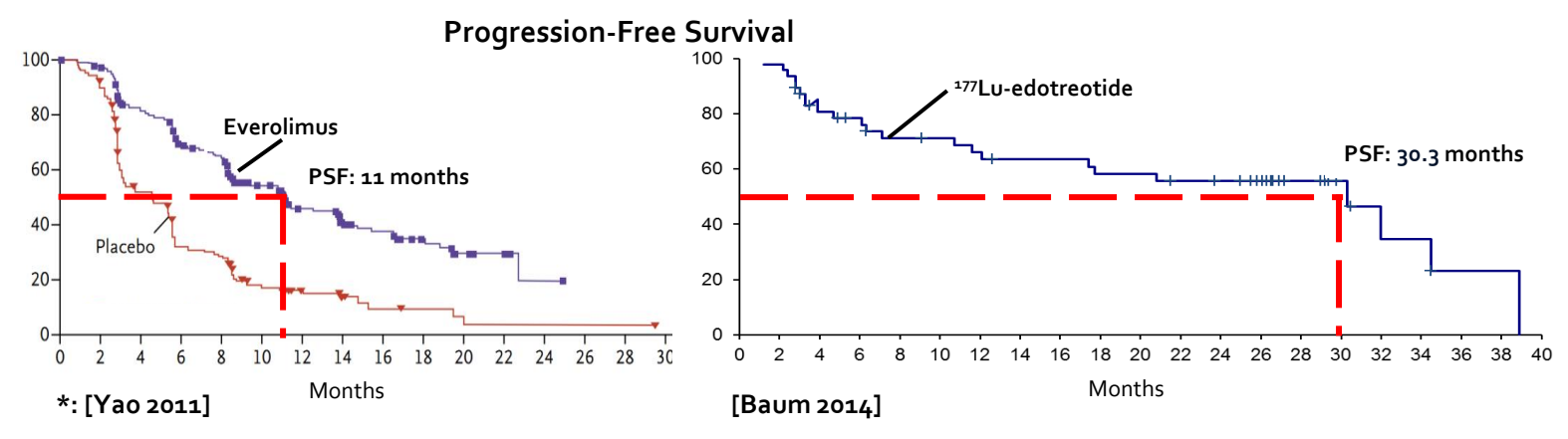


Database Bad Berka, unpublished results

Lu-177 DOTATOC compared to SUTENT: Improvement of PFS by 19 months

THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik Bad Berka

DRUG	N treated	Approved in EU or Member State(s)	Indication	Key Results (median months)
Everolimus*	207	YES	Pancreatic NET	PFS: 11.0
^{177}Lu-edotreotide	58	NO	(GEP NET)	PFS: 30.3 95% CI: 19.2 - 41.7



Database Bad Berka, unpublished results

Lu-177 DOTATOC compared to Afinitor: Improvement of PFS by 19 months

CAPECITABINE - TEMOZOLOMIDE

PANCREATIC NETS n=30

8 CYCLES OF CHEMOTHERAPY

ORR 70% CR 3% PR 67%

MEDIAN PFS 18 MONTHS

Strosberg JR et al. Cancer 2011 117:268-75

^{177}Lu-OCTREOTATE plus CAPECITABINE - TEMOZOLOMIDE

GASTRO-PANCREATIC NETS n=30

ORR 83% CR 13% PR 70%

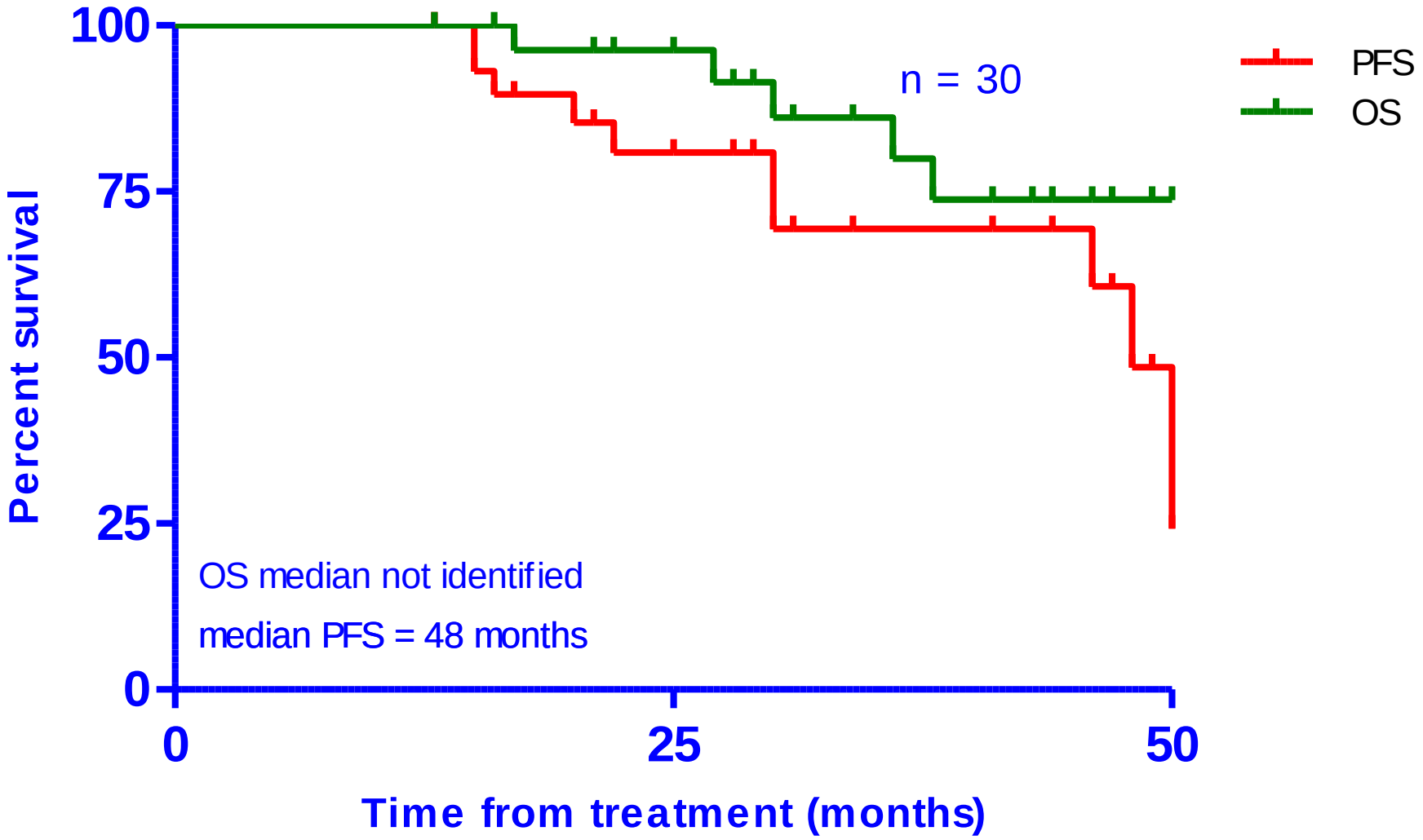
SD 17% PD 0%

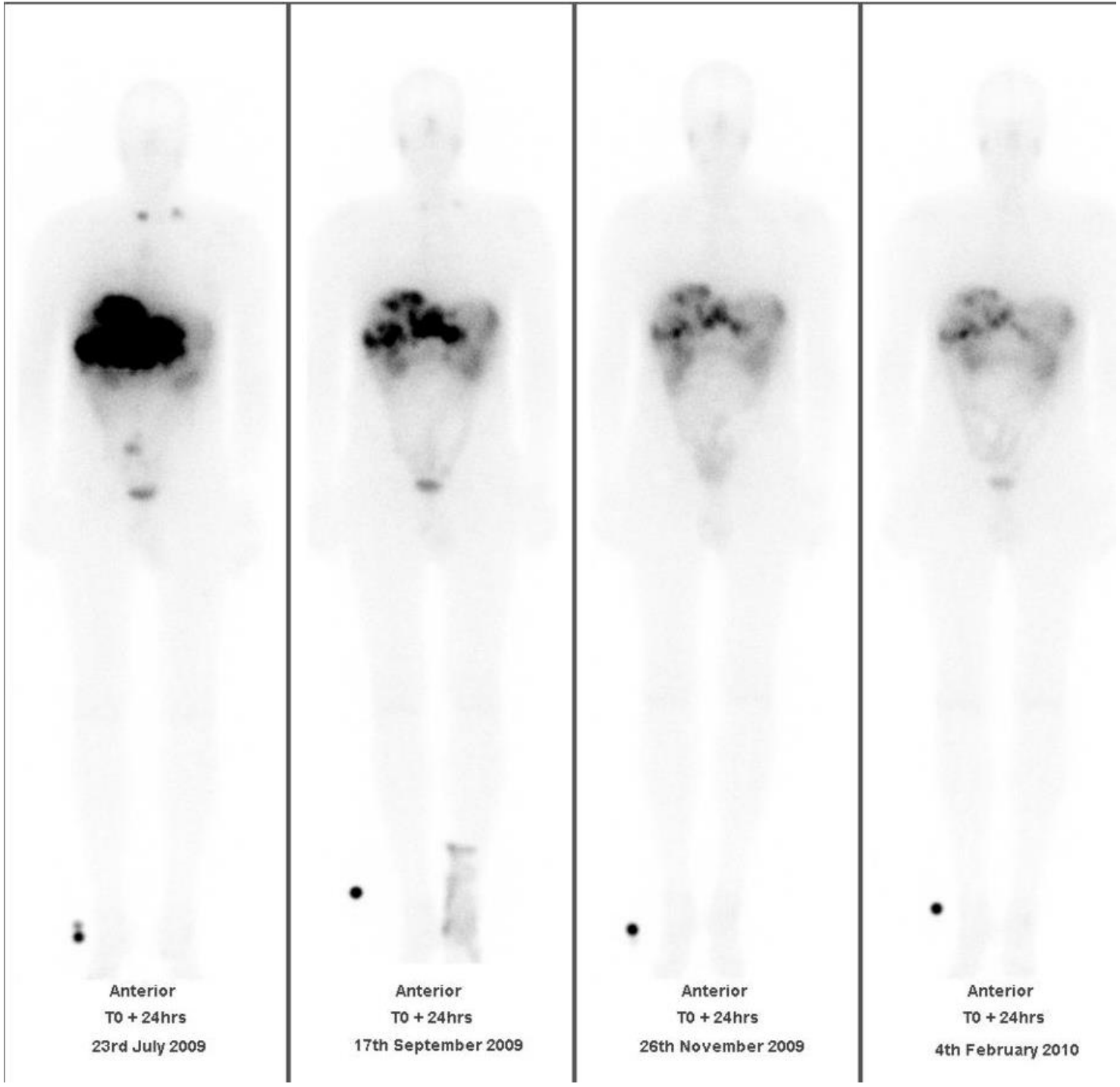
MEDIAN PFS 48 MONTHS

Claringbold PG, Turner JH. Work-in-Progress

The University of Western Australia 2014

P NET ^{177} Lu-octreotate capecitabine/temozolomide




Anterior
T0 + 24hrs
23rd July 2009
Anterior
T0 + 24hrs
17th September 2009
Anterior
T0 + 24hrs
26th November 2009
Anterior
T0 + 24hrs
4th February 2010

SUMMARY AND CONCLUSIONS

- PRRT is effective and well tolerated – even for very advanced NET cases
- Median overall survival from start of treatment: > 46-59 (up to >90) months
- PRRT leads to significant improvement of clinical symptoms
- Cure is rarely possible - but excellent palliation can be achieved
- PRRT: part of the clinical algorithms of major scientific & clinical societies

- Standardized treatments are usually applied - guidelines are available
- Significant kidney damage can be avoided (or reduced)
- PRRT should be performed at specialized centres as NET patients need highly individualized interdisciplinary treatment and long term care.

Future perspectives: individualization of treatment based on

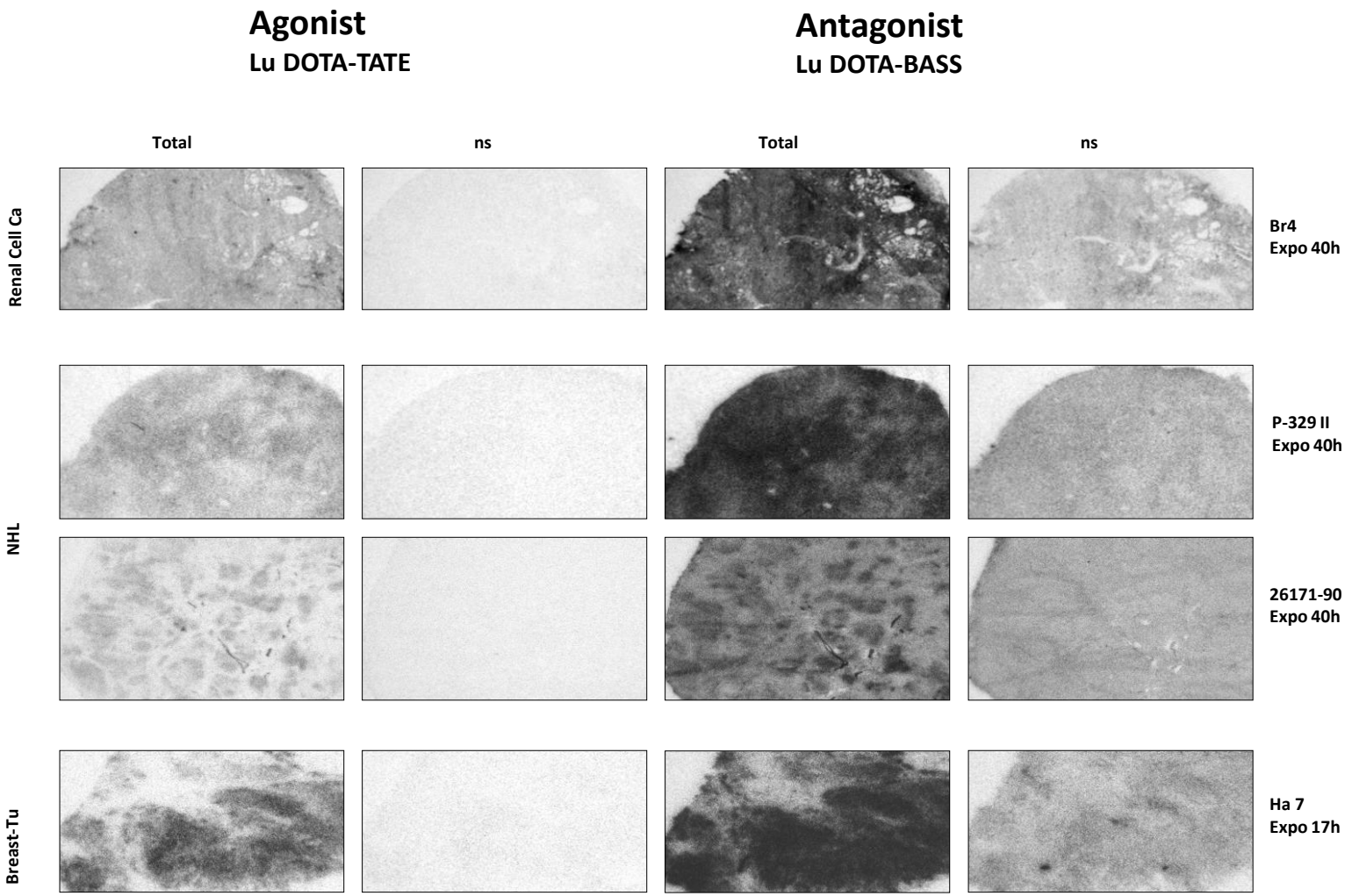
- Clinical features
- Dosimetry
- Biological information regarding the tumor cell and its microenvironment
- Genetic characteristics

New Avenues to Improve PRRT in Future

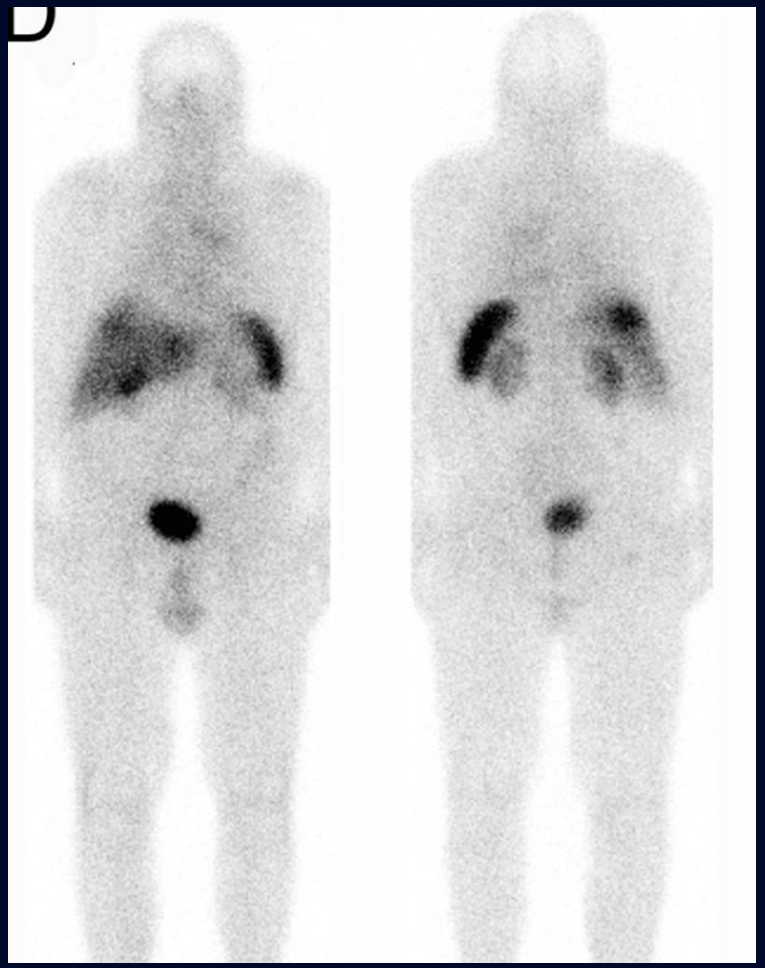
- **DUO-PRRT** (already routine at our center since 8 years)
- **TANDEM-PRRT** (concurrent Lu-177/Y-90 PRRT Kunikowska et al.)
- **Intra-arterial PRRT** (> 100 i.a. treatments up to now)
- **Combined PRRT** (in combination with other treatment modalities)
  - **TACE, SIRT, RFA** (Hörsch et a. ASCO 2010)
  - **chemotherapy** (e.g. Capecitabine, Doxorubicin)
  - **kinase inhibitors** (e.g. Sunitinib, Sorafenib)
- Intra-operative use of probes after PRRT with Lu-177
- Improved dosimetry and radioprotection

Improved peptides (e.g. antagonists)

Antagonist labels more sst_2 sites than agonist in human cancer tissues



Imaging with SSTR antagonists

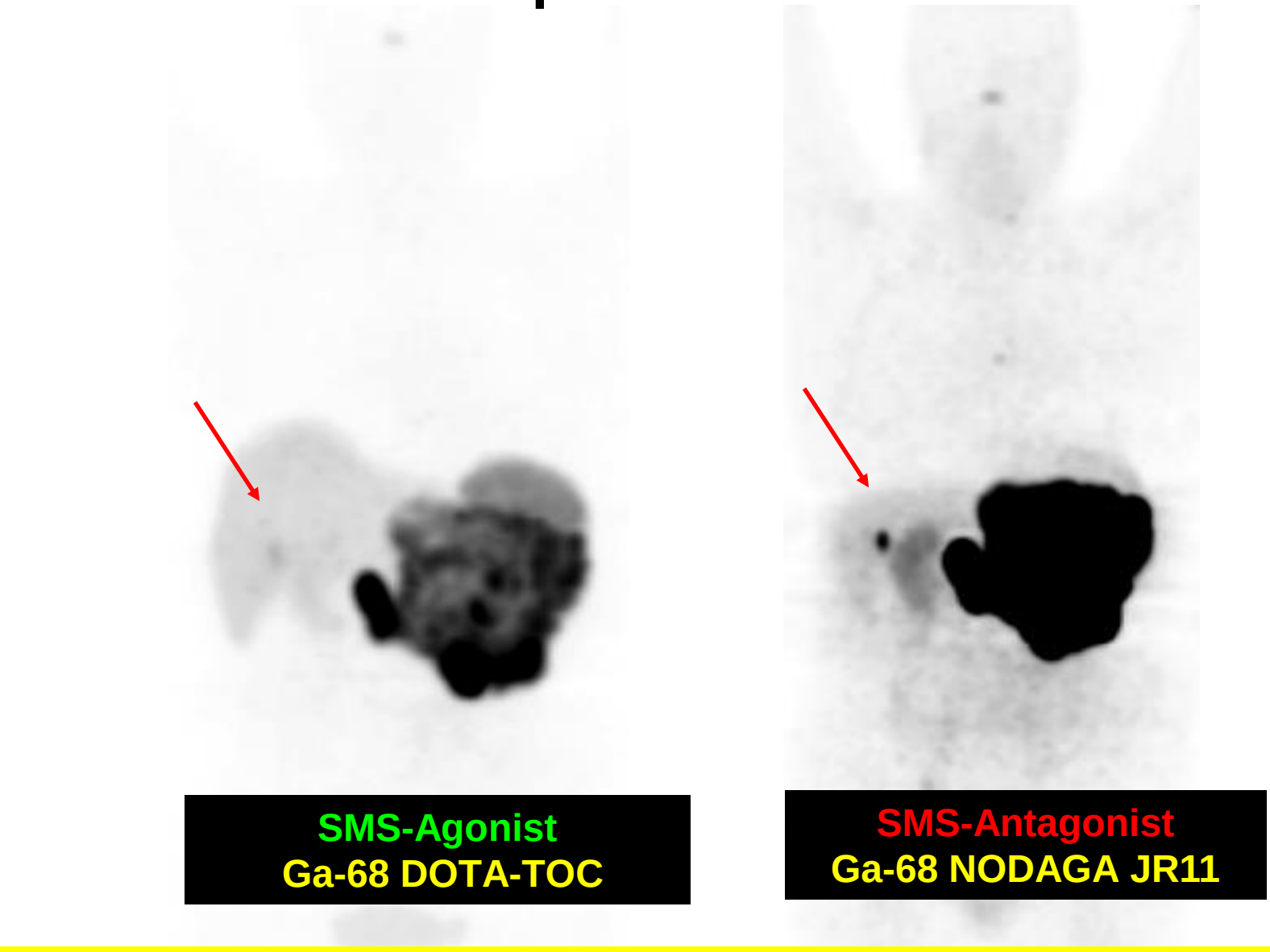


Octreoscan (Agonist)

^{111}In-DOTA-BASS (Antagonist)

Wild D et al. JNM 2011

Extensive NET of pancreas with liver metastasis



SMS-Agonist
Ga-68 DOTA-TOC

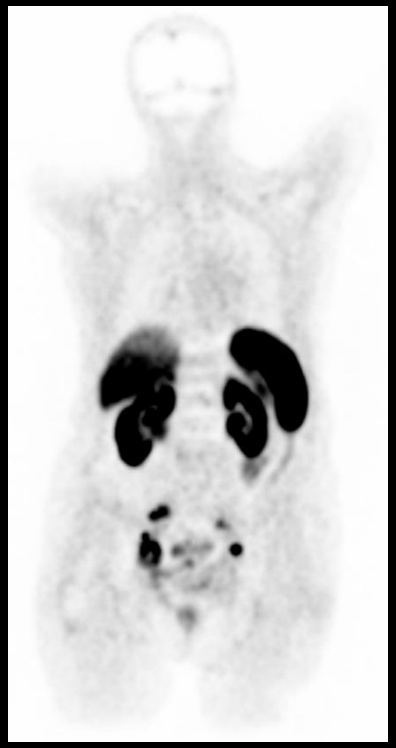
SMS-Antagonist
Ga-68 NODAGA JR11

Antagonist labels more sst_2 sites than agonist in cancer patients leading to higher diagnostic sensitivity (first in human study)

Comparison of ^{177}Lu-DOTATATE and ^{177}Lu-DOTA-JR11 dosimetry

Patient with NEC (G3) of the bladder with lymphnode and uterus metastases, shows progression after surgery and treatment with Somatostatin analogues

^{68}Ga-DOTA-TATE PET



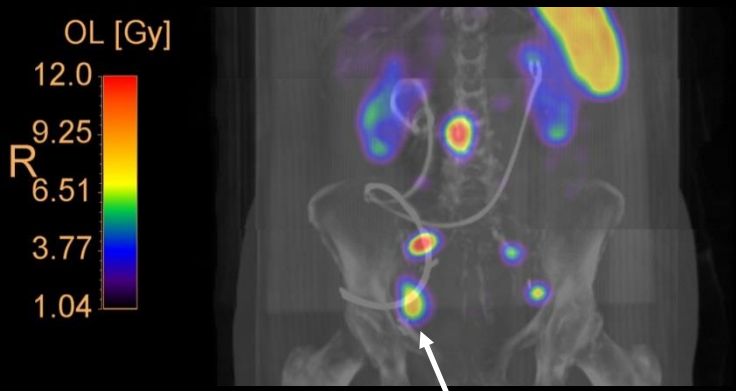
Limited kidney function
Creatinine clearence: 54 ml/min
(norm 90 – 179 ml/min)

^{177}Lu-DOTA-TATE (Agonist)
Isodose curves based on 3D voxel dosimetry analysis

mean dose: 1.4 Gy/GBq
Tumor-to-kidney dose ratio: 1.1

sst$_2$ affinity profile (IC$_{50}$)
0.7 ± 0.15 nM

^{177}Lu-DOTA-JR11 (Antagonist)
Isodose curves based on 3D voxel dosimetry analysis



mean dose: 5.7 Gy/GBq
Tumor-to-kidney dose ratio: 2.5

sst$_2$ affinity profile (IC$_{50}$)
1.5 ± 0.4 nM

UNIVERSITÄTS KLINIKUM FREIBURG

Courtesy Damian Wild

Future of Cancer Treatment

Cancers will be classified by molecular phenotypes

Organ site → secondary classification

Molecular phenotypes will be determined by molecular pathology and by molecular imaging studies (PET, SPECT, MRI, optical) using cancer type specific probes.

Treatment will be targeted specifically against the tumor

PRECISION MEDICINE

Neuroendocrine tumors are a paradigm for this approach as molecular radiotherapy is applied based on molecular features (i.e. somatostatin receptor expression) of tumors and not based on the organ of origin of the tumor.

Molecular Imaging of CXCR4 Expression in Extensive Stage Small Cell Lung Carcinoma using PET/CT

H. R. Kulkarni[1], H.-J. Wester[2,3], S. Dureja[1], S. Kropf [2], P. Fix[4], R. P. Baum[1]

[1]THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging, Zentralklinik Bad Berka, Germany

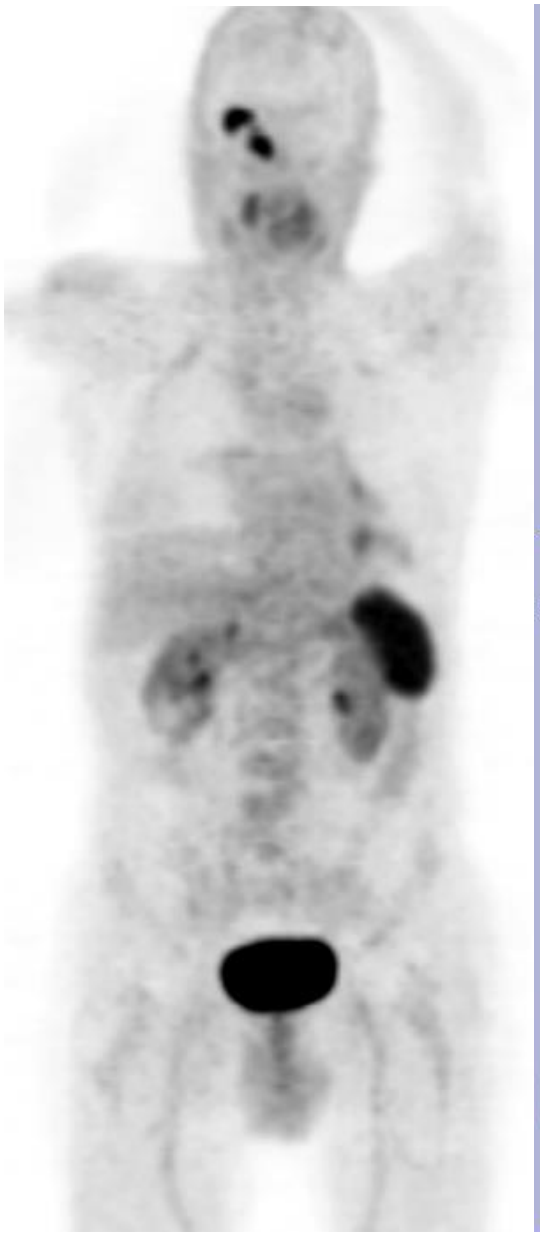
[2]Scintomics GmbH, Fürstenfeldbruck, Germany

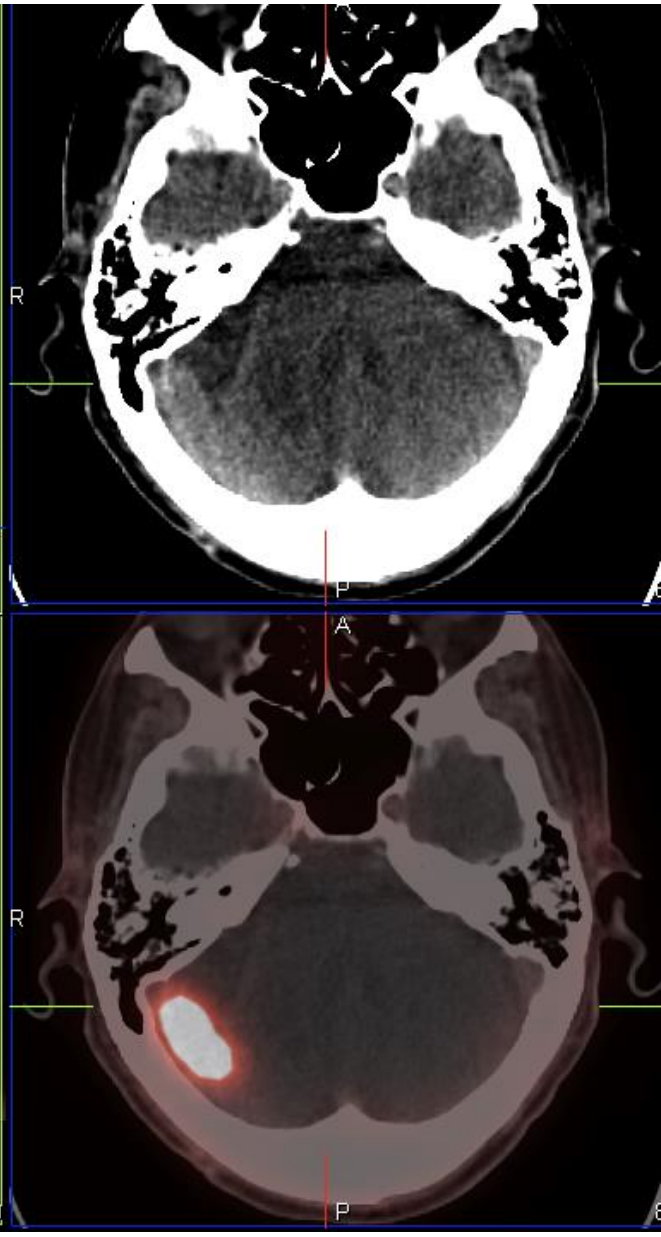
[3]Pharmaceutical Radiochemistry, Technical University, Munich, Germany

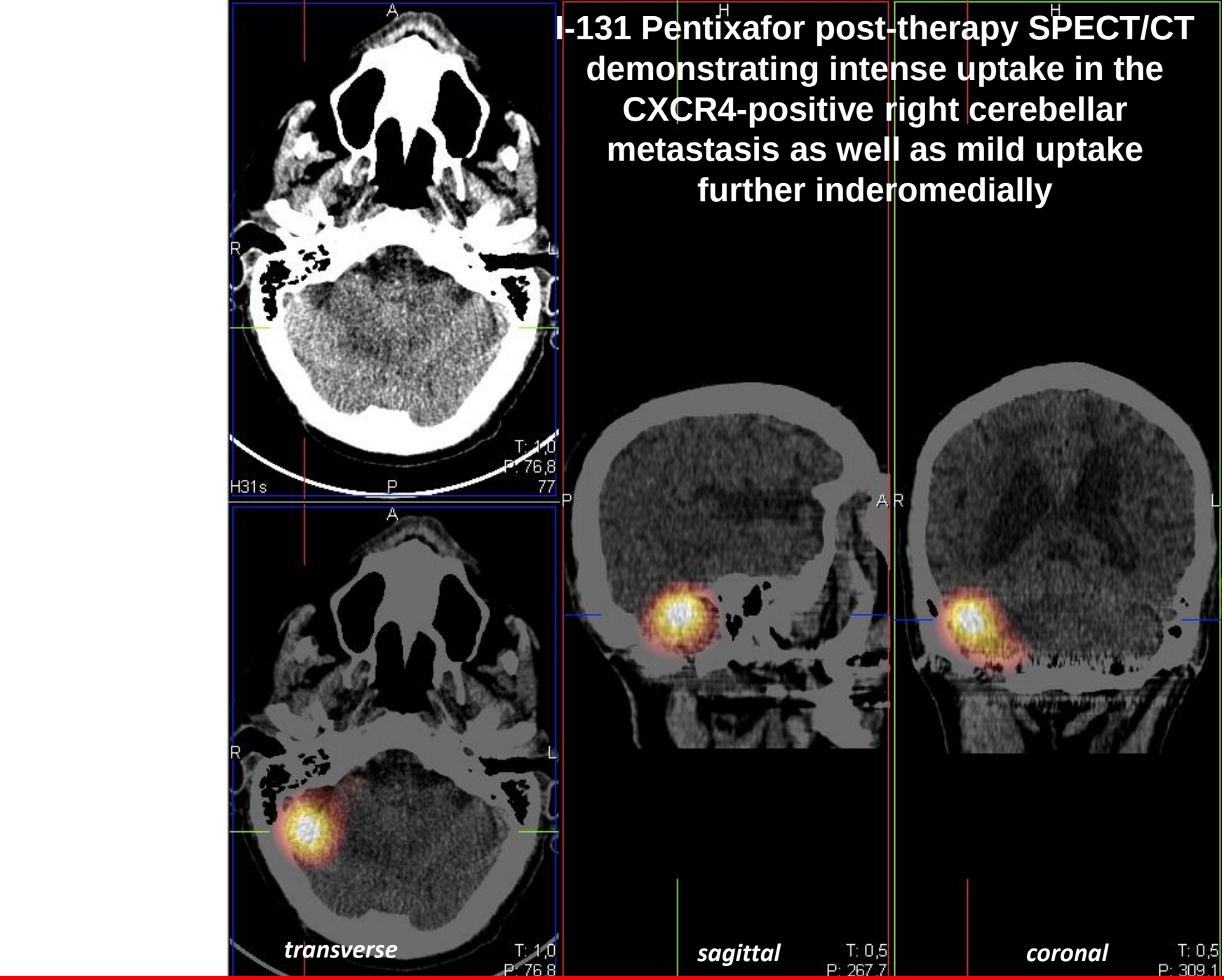
[4]Dept. of Oncology, Zentralklinik Bad Berka, Germany

2014 SNMMI Annual Meeting, St. Louis

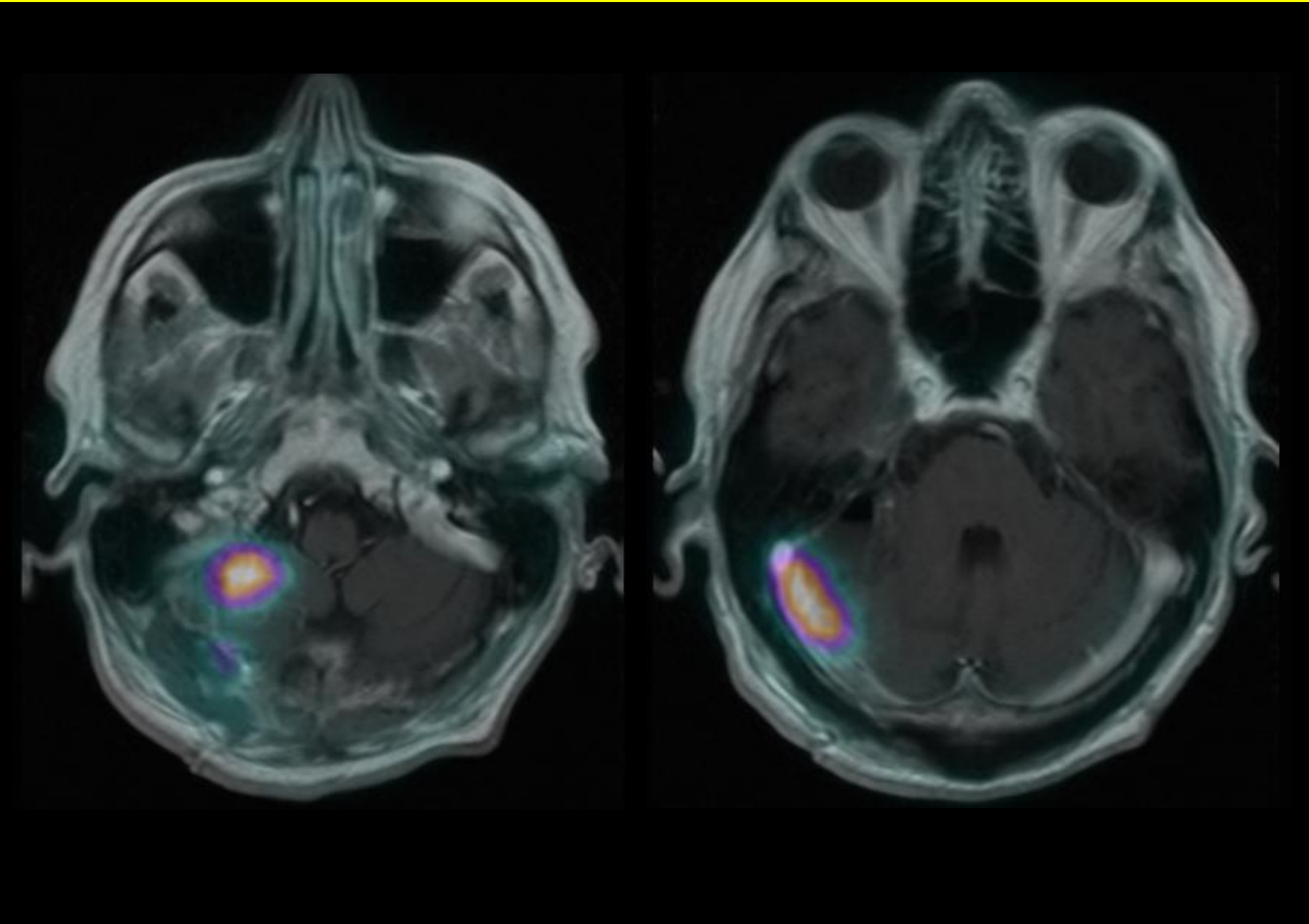
Ga-68 CPCR4 PET/CT showing at least 2 intensely chemokine-receptor-positive right cerebellar metastases (SUVmax 11.9 and 12.5 respectively)





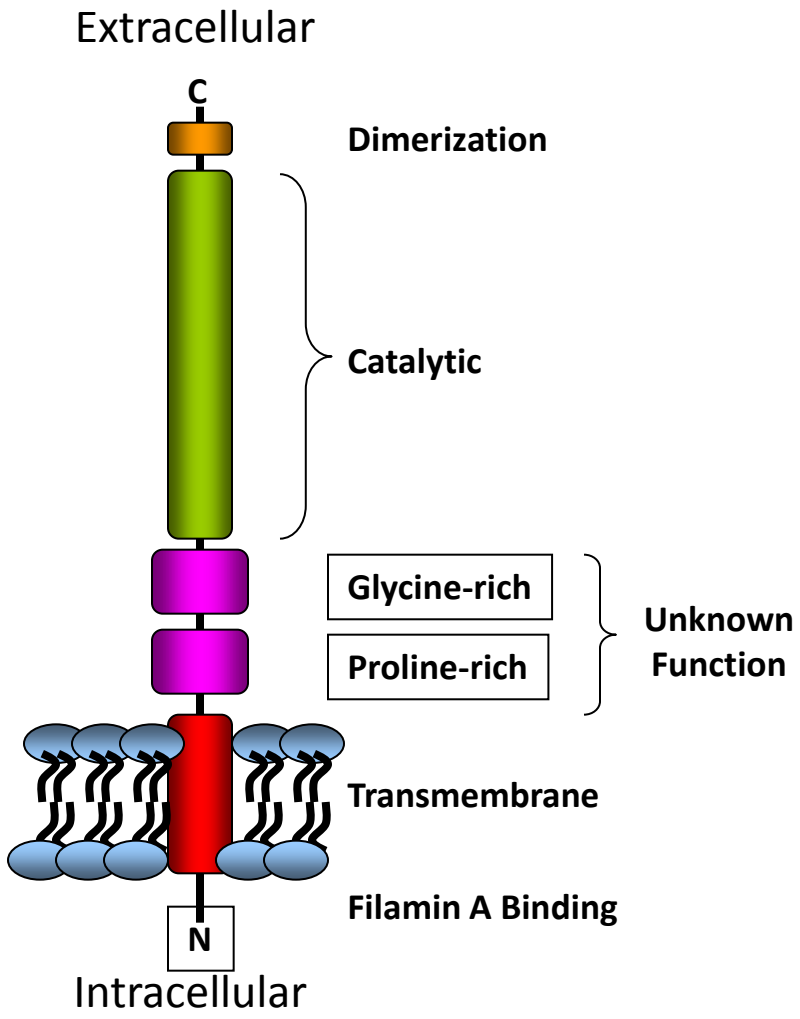

I-131 Pentixafor post-therapy SPECT/CT demonstrating intense uptake in the CXCR4-positive right cerebellar metastasis as well as mild uptake further inderomedially
transverse
sagittal
coronal

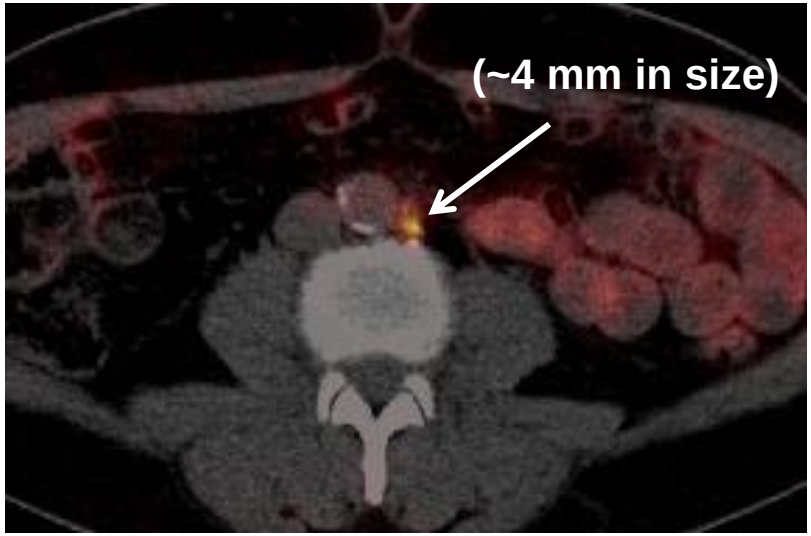
Ga-68 Pentixafor PET/MRI demonstrating the right cerebellar metastases

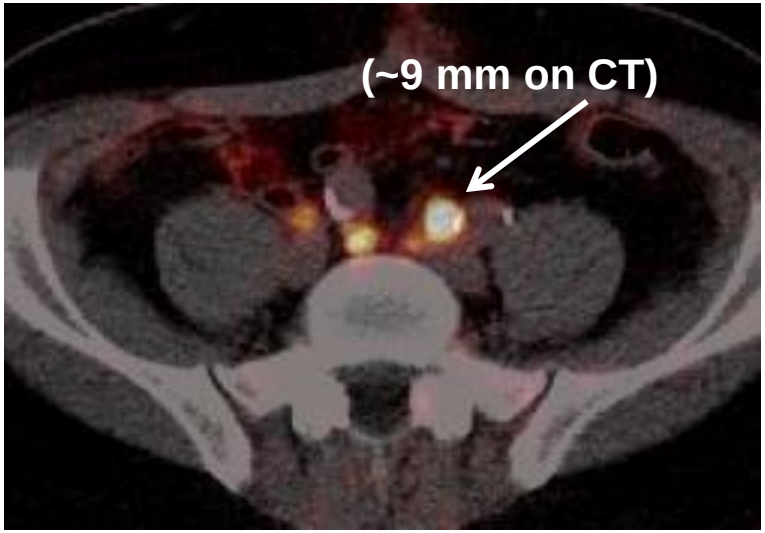


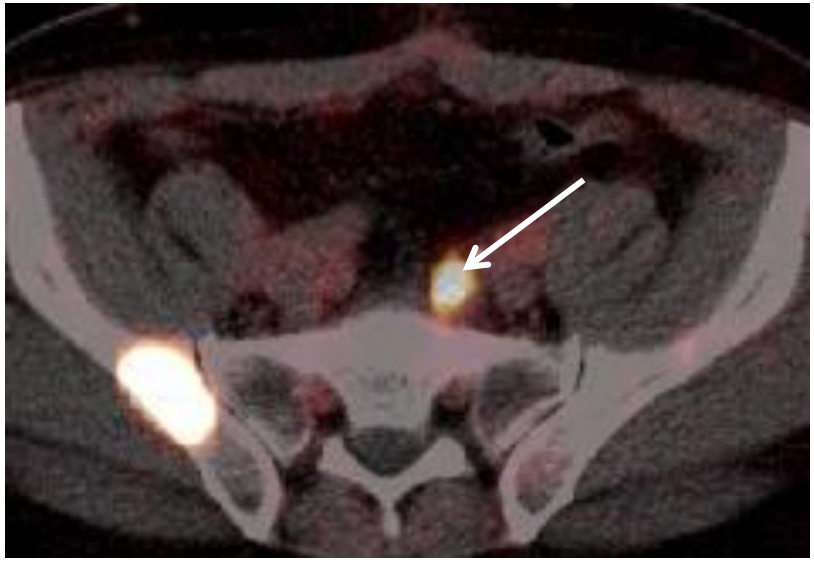
PSMA for Targeting Prostate Cancer

- Glutamate carboxypeptidase II (GCP-II) activity
- Folate hydrolase (FOLH1) activity
- Hydrolyses y-peptide bonds between N-acetylaspartate and glutamate
- PSMA expression increases progressively in:
  - Higher grade tumors
  - Metastastic disease
  - Hormone-refractory prostate cancer
  - also in tumor neovasculature
- PSMA thought to play a role in tumor invasiveness
- Target validated with anti-PSMA antibodies (J591)

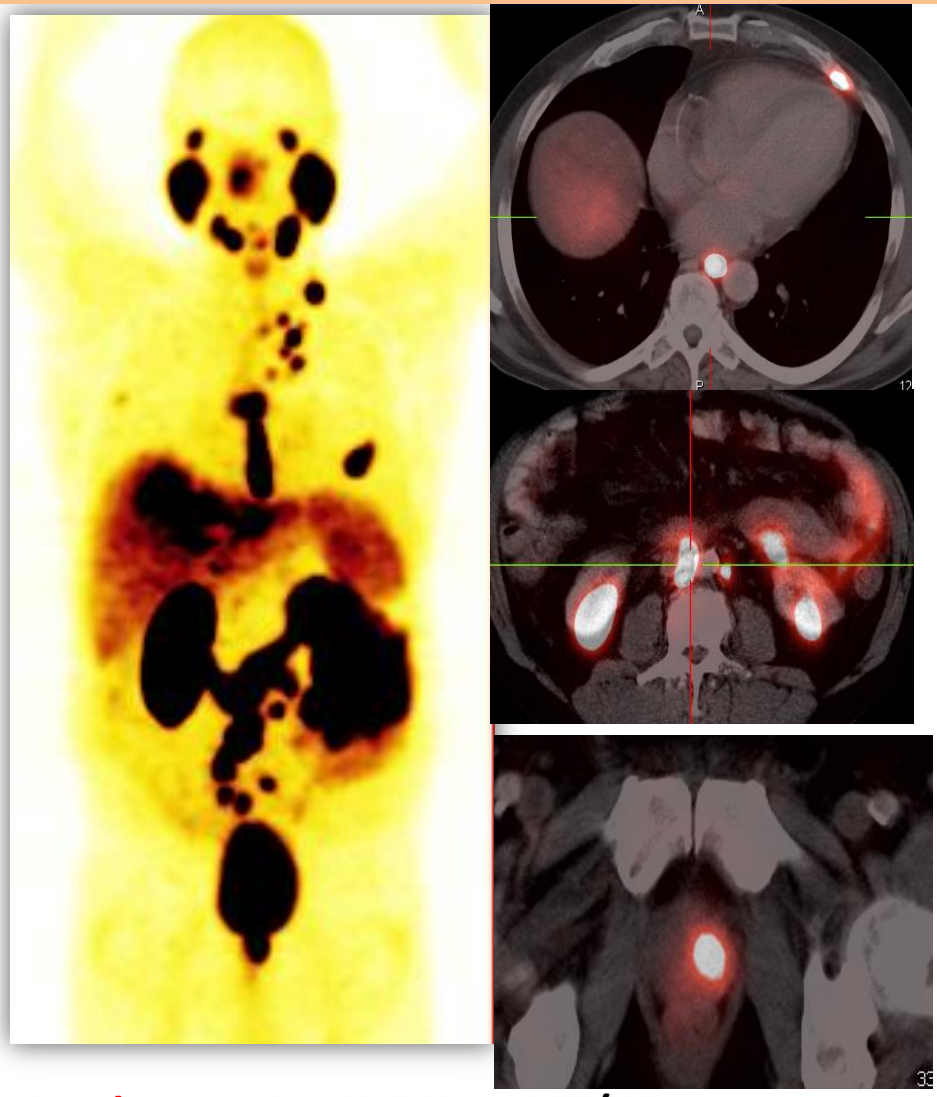




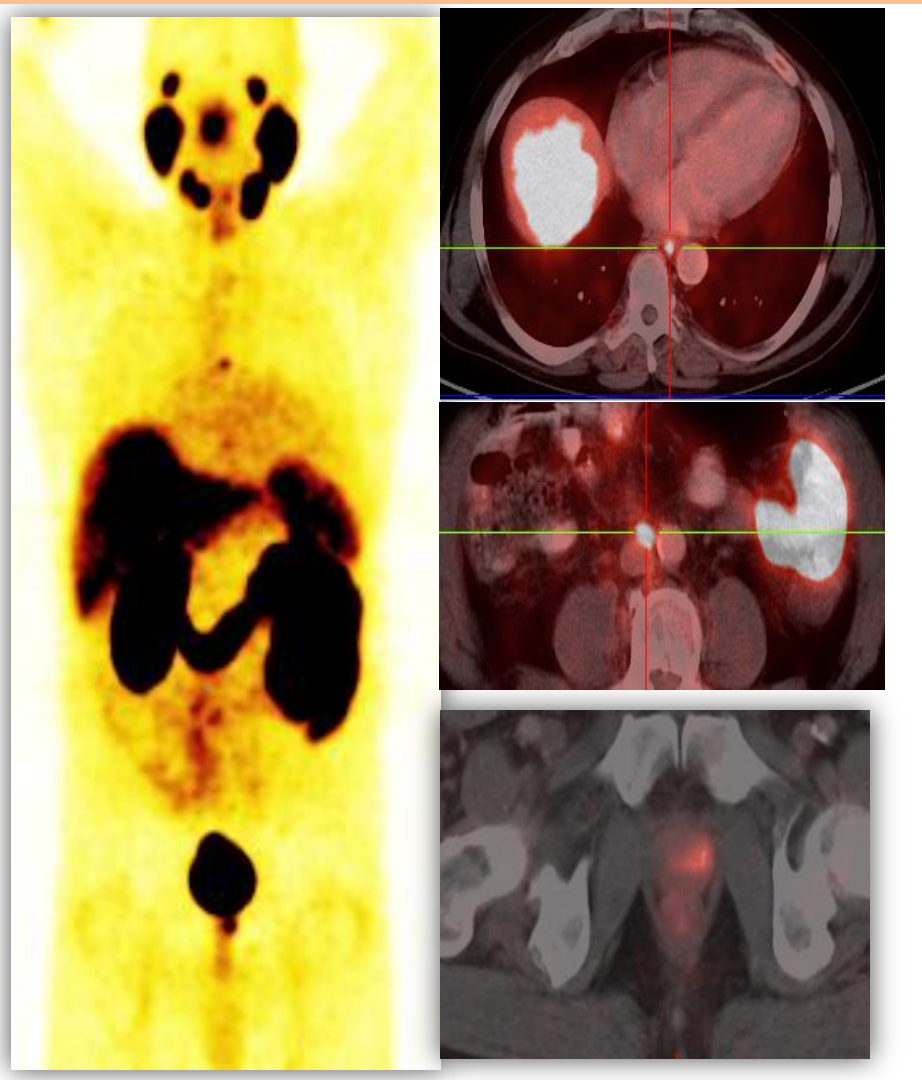




METASTATIC RETROPERITONEAL NODES



Pretherapy Ga-68 PSMA PET/CT
Local prostate cancer involving the seminal vesicles with lymph node and extensive bone metastases.



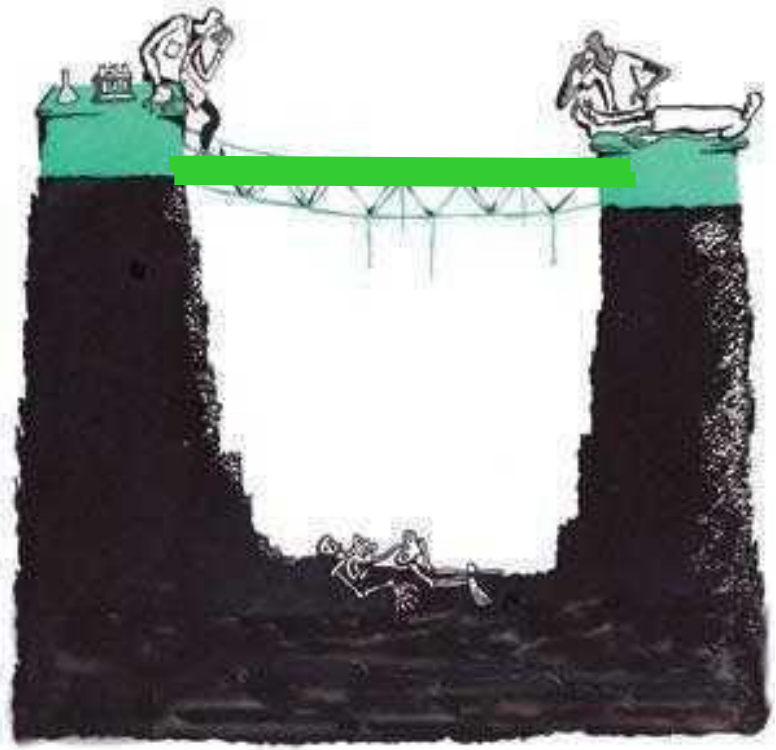
3 months post Lu-177 PSMA Therapy
Excellent response to radioligand therapy.
Most of the intense PSMA positive metastases are not discernible anymore.

Translational Research: Crossing the Valley of Death

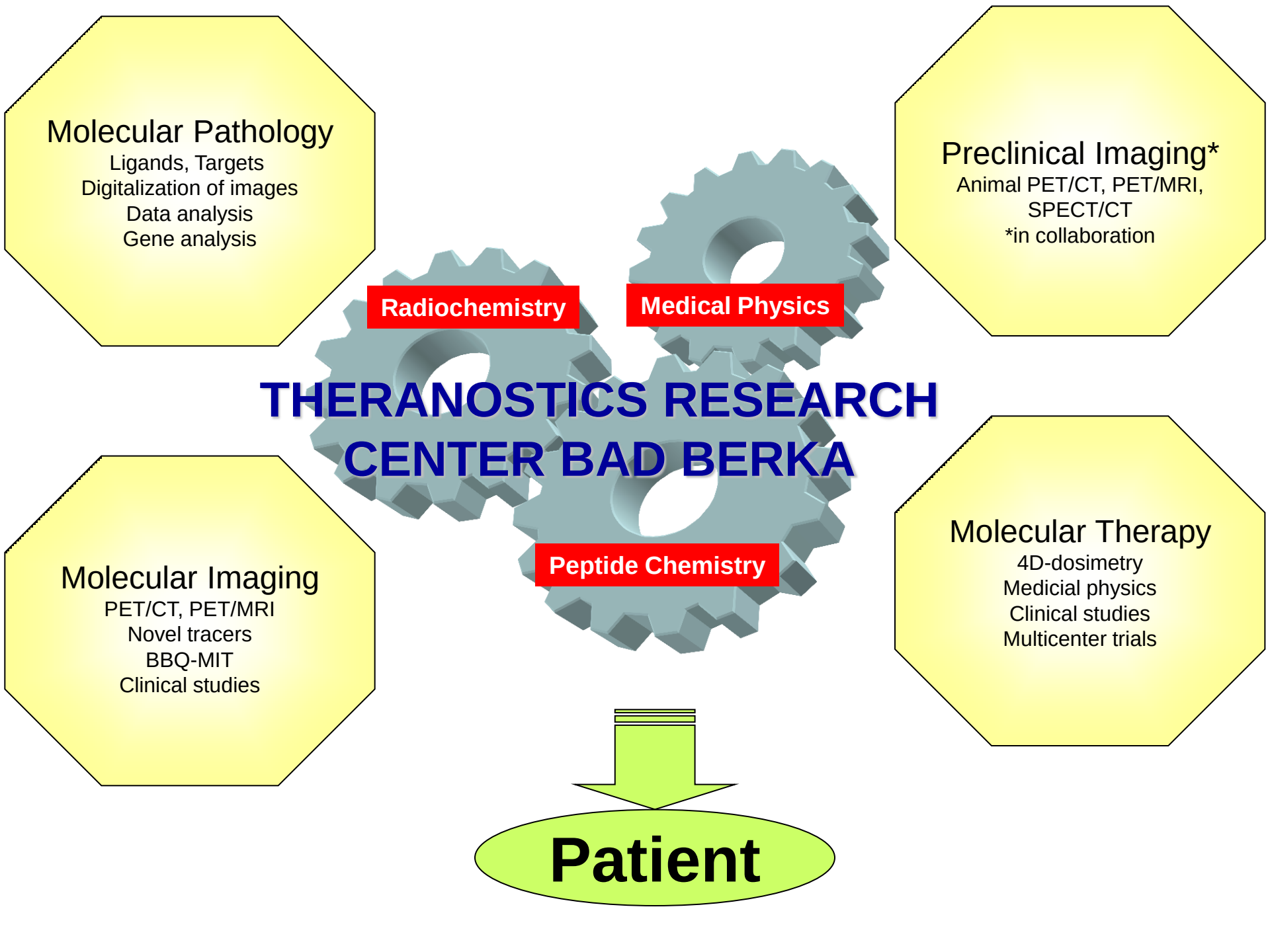
National Institutes of Health (NIH):

- “Clinical and basic scientists don't really communicate”
- Excellent basic research, but lack of translation

- Where do we go from here?



Nature **453**, 840-842, 2008


Molecular Pathology
Ligands, Targets
Digitalization of images
Data analysis
Gene analysis
Preclinical Imaging*
Animal PET/CT, PET/MRI, SPECT/CT
*in collaboration
Radiochemistry
Medical Physics
THERANOSTICS RESEARCH CENTER BAD BERKA
Peptide Chemistry
Molecular Imaging
PET/CT, PET/MRI
Novel tracers
BBQ-MIT
Clinical studies
Molecular Therapy
4D-dosimetry
Medicial physics
Clinical studies
Multicenter trials
Patient

Thanks to the team…

and to our patients!

Acknowledgements
National and International Collaborators

- Hans-Jürgen Wester, Munich
- Frank Rösch, Mainz
- Helmut Mäcke, (Freiburg/Basel)
- Thea Maina-Nock, Athens
- Jae Min Jeong, Seoul
- Michael Schultz, Iowa

- Marion de Jong, Rotterdam
- Eric Krenning, Rotterdam

- Jean-Claude Reubi, Bern
- Stefan Schulz, Jena
- Amelie Lupp, Jena

- Gerd Binnig, Munich
- Maria Athelogou, Munich

- Matthias Blaickner, Seibersdorf
- Dale Bailey, Sydney
- Anna Celler, Vancouver

- Andrew Schally, Miami

- Rodney Balhorn, San Francisco

- THERANOSTICS Network, Germany

- THERANOSTICS Research Center

- Funds
  - Dinse-Stiftung, Hamburg
  - Keymar Foundation, Canada

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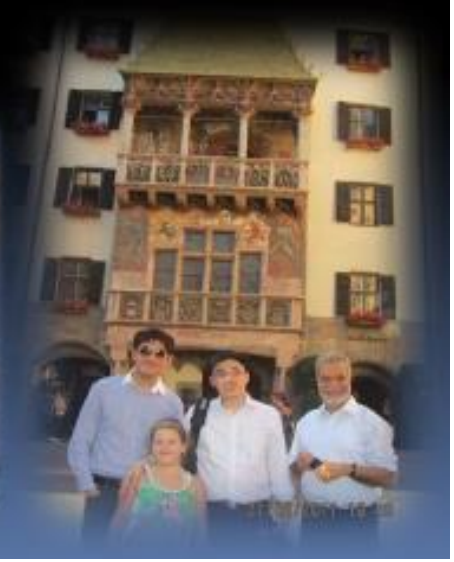
WARMTH

WORLD ASSOCIATION OF RADIOPHARMACEUTICAL & MOLECULAR THERAPY

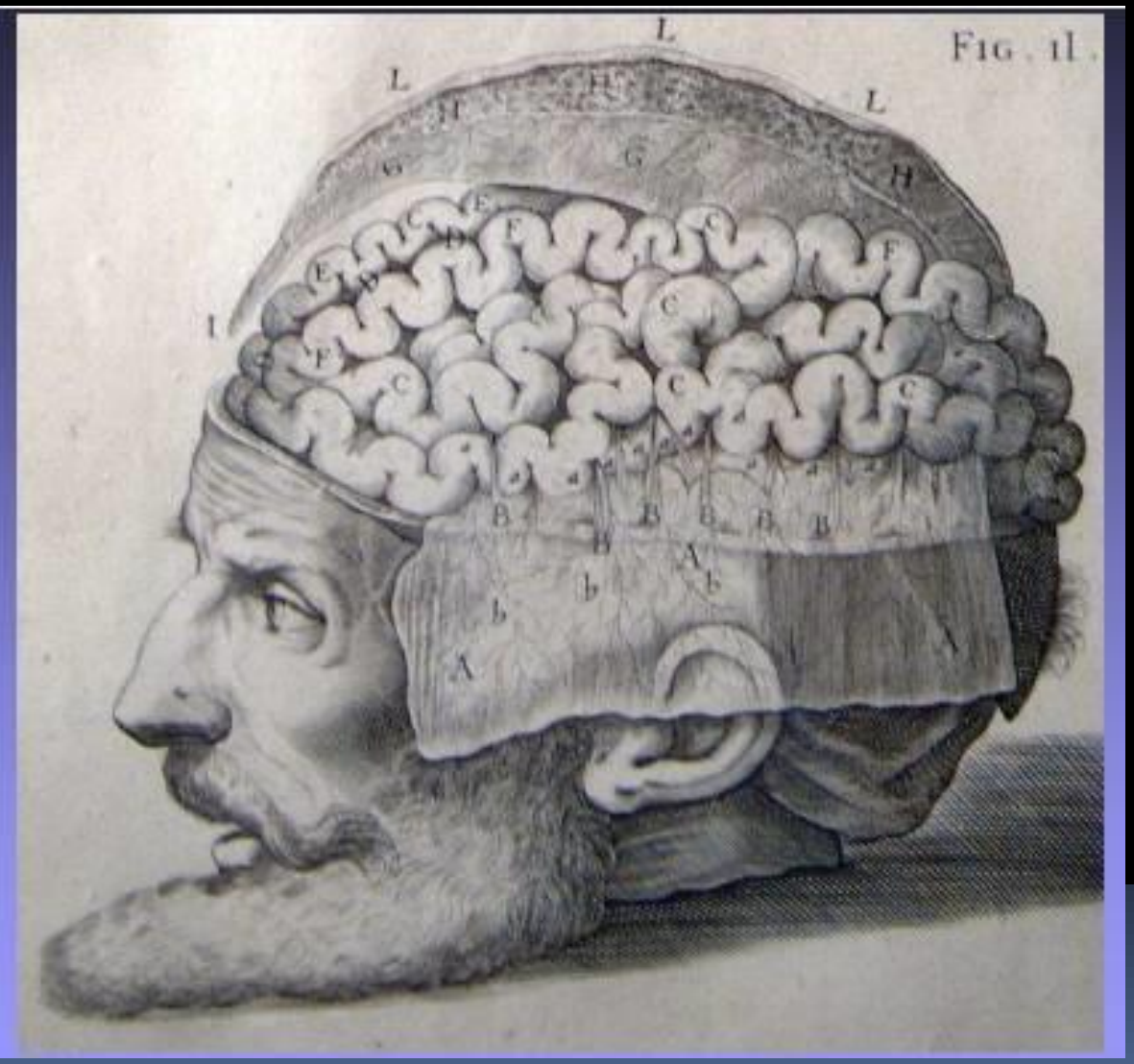
ICRT-2015, May 4-8th

10th INTERNATIONAL CONFERENCE ON RADIOPHARMACEUTICAL THERAPY

HOST: Medical University of Innsbruck, Austria



Thank you for your attention!



Memorizing..

You remember

10 % - reading
20% - listening
30 % - seeing
50 % - seeing & hearing
70 % - talking about
90 % - what you‘re doing

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