1st World Congress on Ga-68 and Peptide Receptor Radionuclide Therapy (PRRNT)

THERANOSTICS - On the Way to Personalized Medicine
Bad Berka, Germany, June 23 - 26, 2011

THERANOSTICS – Where do we go from here?

Richard P. Baum
Dept. of Nuclear Medicine, Center for PET/CT
Zentralklinik Bad Berka, Germany

- **Theranostics:**
  - Concept more than 20 years old: best word selected among “Theragnostics”, “Theranostics” and “Diapeutics”
  - Definition: Theranostics (Tx) is the combination of a Diagnostic (Dx) tool that helps to define the right Therapeutic (Rx) tool for a specific disease.
  - Not specific to radiopharmaceuticals, but developed by pharma industry at the beginning of the 90’s at the same time the concept of Personalized Medicine (PM) appeared.
  - In NM, Tx is easy to apply and to understand, because of an easy switch of radionuclide from Dx to Rx on the same vector, but is restrictive.
- **Personalized Medicine**
  - Tx is now part of the concept of PM: « the right treatment for the right patient at the right time at the right dose – first time », not anymore targeting the “specific disease” but the “specific patient”.
  - The concept of PM has now been extended to Personalized Health Care (PHC) that includes all steps relevant for the cure of the patient at an individual level from the first sign of disease up to full recovery, including the physicians, the technologies, the drugs and of course all economic aspects, but also extended to the environment, relatives, nurses, …
  - NM and Tx within NM are definitely part of Personalized Health Care .

Courtesy Richard Zimmermann

FUTURE OF CANCER TREATMENT

Cancers will be classified by molecular phenotypes

Organ site → secondary classification

Molecular phenotypes will be determined by molecular imaging studies (PET, SPECT, MRI, optical) with specific probes (& biopsy)

Treatment will be targeted against the tumor and its environment

We need to define the

- **targets**
- **ligands**
- **coupling / labeling chemistry**
- **radionuclides**
- **biodistribution modifiers**
- **right patients for personalized treatment**

…this WORLD Congress gave new insights!

Courtesy Helmut Mäcke

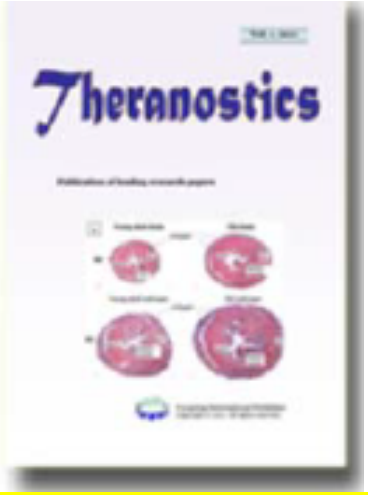
WORLD Theranostics Congress USA 2011

November 15-17, 2011
Sè San Diego Hotel
San Diego, CA

Convergence

reflecting the fields of *in vitro* diagnostics and prognostics, *in vivo* molecular imaging, molecular therapeutics, image-guided therapy, biosensors, system biology and translational medicine, personalized medicine and a broad spectrum of biomedical research that can be applied to future theranostic applications.

Latest articles:



Google Search (June 26, 2011 @4:36 a.m. 317,000 hits

ADAPT

Making Personalized Therapy a Reality

The Personalized Therapy Congress

September 7-9, 2011
Loews Philadelphia Hotel
Philadelphia, PA

Focused Conference Tracks:

PERSONALIZED MEDICINE

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Toward a Personalized Treatment of Hodgkin's Disease

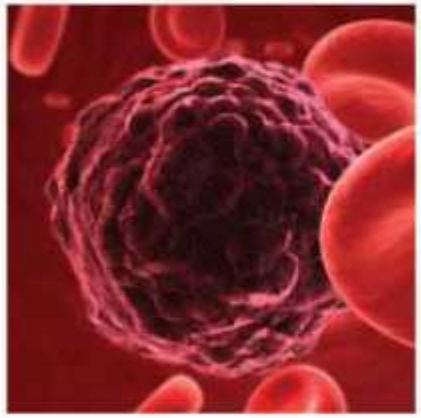
Vincent T. DeVita, Jr., M.D., and José Costa, M.D.

Personalized Medicine: Molecular Imaging Predicts Treatment Success in Many Cancers

Studies show molecular imaging's benefits in the evaluation and successful treatment planning for a wide spectrum of diseases

Reston, Va.— A series of studies published in the *Journal of Nuclear Medicine* (JNM) show that molecular imaging plays a critical role in the evaluation and treatment planning for a broad spectrum of cancers, including thyroid cancer and lymphoma.

RSNA: New era of image-guided personalized cancer care dawns



CHICAGO—The opportunities for imaging have never been greater, offered RSNA President Hedvig Hricak, MD, PhD, chair of radiology at Memorial Sloan-Kettering Cancer Center in New York City, during today's opening session of the annual conference of the Radiological Society of North America (RSNA).

During the president's address—Oncologic Imaging: A Guiding Hand of Personalized Cancer Care--Hricak stated that the ultimate goal of personalized medicine is preemptive medicine. With cancer incidence projected to increase 45 to 50 percent in the next 20 years, the need to expand personalized medicine is significant.

The good news is that the tools that facilitate personalized medicine, genetics and molecular imaging, continue to emerge and develop. "Imaging has continuously advanced cancer care and paved the road to personalized medicine. The pace at which medicine is transformed will be guided not only by the pace of discovery, but also by the pace at which we educate new physicians, ourselves and our co-workers," said Hricak

Personalizing Cancer Therapy with FDG PET: From RECIST to PERCIST

J Nucl Med 2009; 50:122S–150S
DOI: 10.2967/jnumed.108.057307

W.A. Weber, guest editor

FOCUS ON MOLECULAR IMAGING

Somatostatin Receptors as Targets for Nuclear Medicine Imaging and Radionuclide Treatment

J Nucl Med 2011; 52:841–844
DOI: 10.2967/jnumed.110.084236

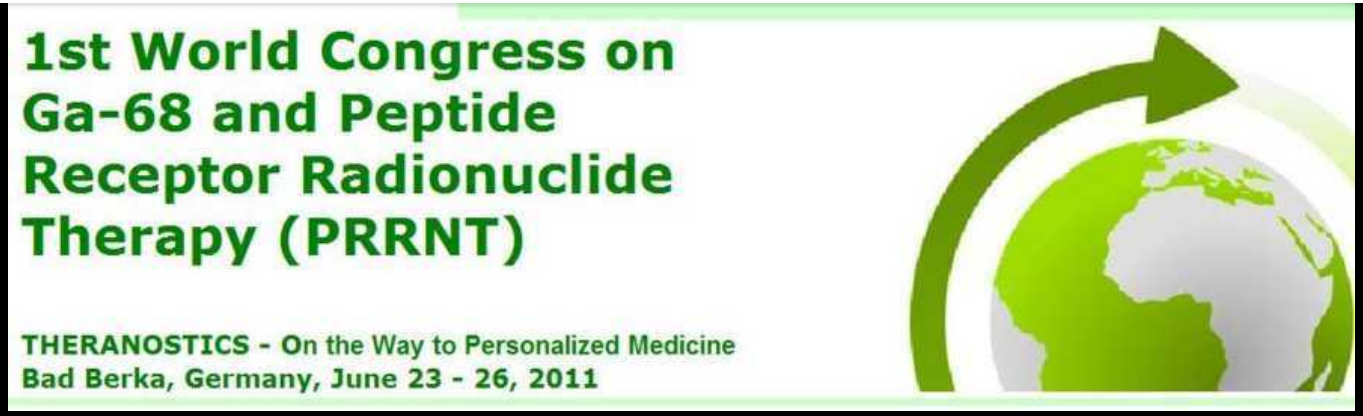
Helmut R. Maecke[1] and Jean Claude Reubi[2]

[1]Department of Nuclear Medicine, University Hospital Freiburg, Freiburg, Germany; and [2]Division of Cell Biology and Experimental Cancer Research, Institute of Pathology, University of Berne, Berne, Switzerland

Seminars in Nuclear Medicine
Table of Contents
Publication Date: May, 2012
Due Date: November 15, 2011
"Theranostics"

THERANOSTIC PAIRS

Personalized medicine is used along with targeted therapy in general. The targeting of somatostatin receptor–positive tumors is an ideal example of this approach. It combines powerful new diagnostics and radiotargeted therapeutics. A diagnostic scan with a γ- or β^+-emitting nuclear probe is used to identify tumors and metastases that overexpress somatostatin receptors and is therefore predictive of the potential for targeted radionuclide therapy in patients. It also allows the study of dosimetry, thereby estimating



Medicine is moving towards personalization.

As we move to personalization or Theranostics - How do we measure data when we are treating at an individual level based on individual response? At ASCO 2011 one of the large plenary session was on that question – how do we move to more personalized medicine while maintaining the gold standard of randomized trials?

From a patient perspective –

We are interested that our clinicians are moving forward - looking to refine treatment and expand our options via new diagnostics and new treatments. It is so encouraging to find so many professionals from around the world working on moving the use of Ga-68 imaging forward on so many avenues and translating these diagnostics tools to therapy.
The patient community is not as aware of all the work all the centers are doing, and will be excited to learn about all that is being worked.

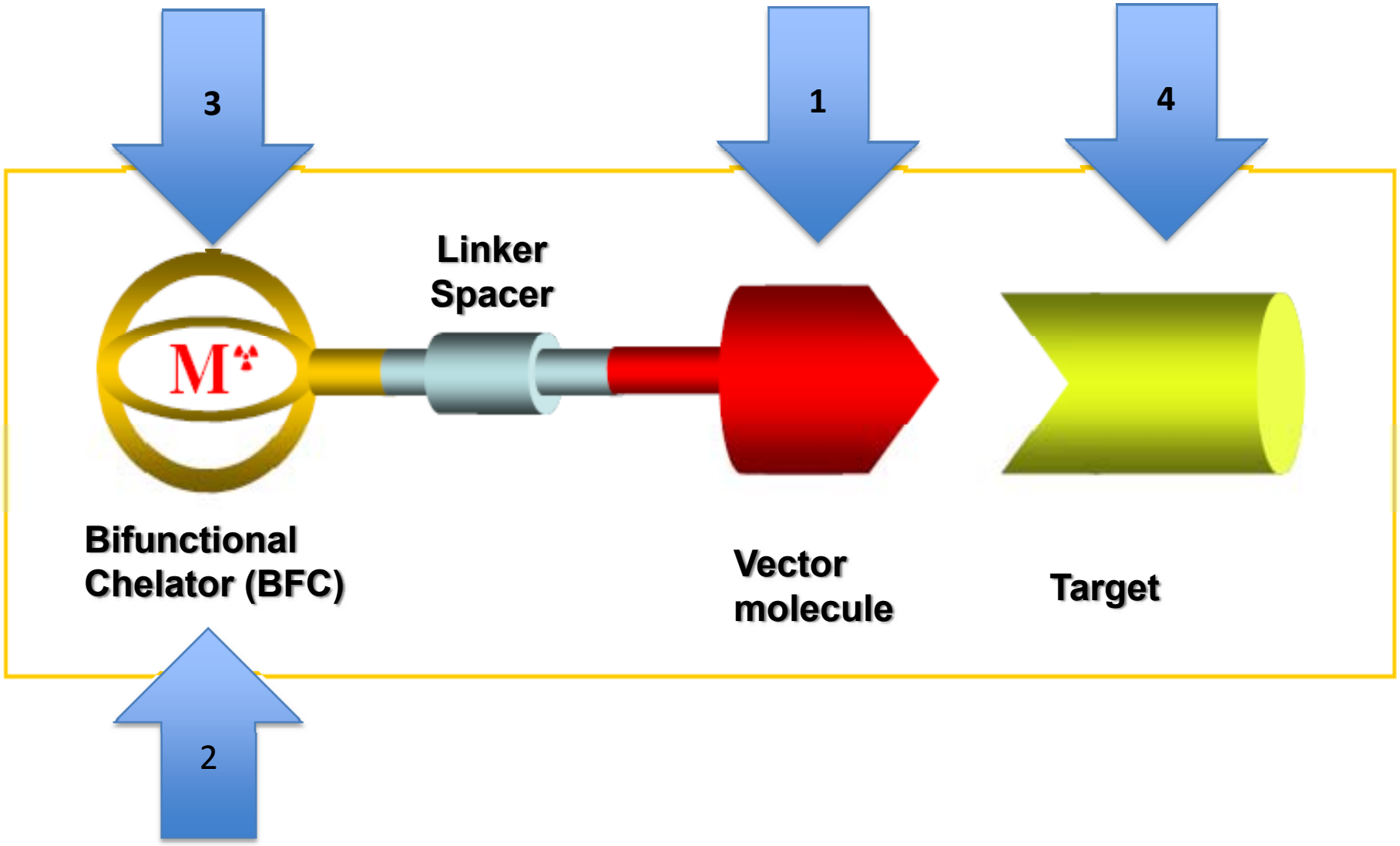
Josh Mailman (a patient treated by PRRNT at Bad Berka), June 25th, 2011

Highlights Chemistry

by

Frank Rösch

Chemistry Highlights: One vision – many challanges



Chemistry Highlights: One vision – many challanges

Optimizing of vector characteristics

Or: *Is ^{68}Ga-DOTA-TOC the golden standard?*

Ga-68 Labeled Peptides targeting
G-protein coupled receptors:
Agonists vs Antagonists

H. R. Maecke

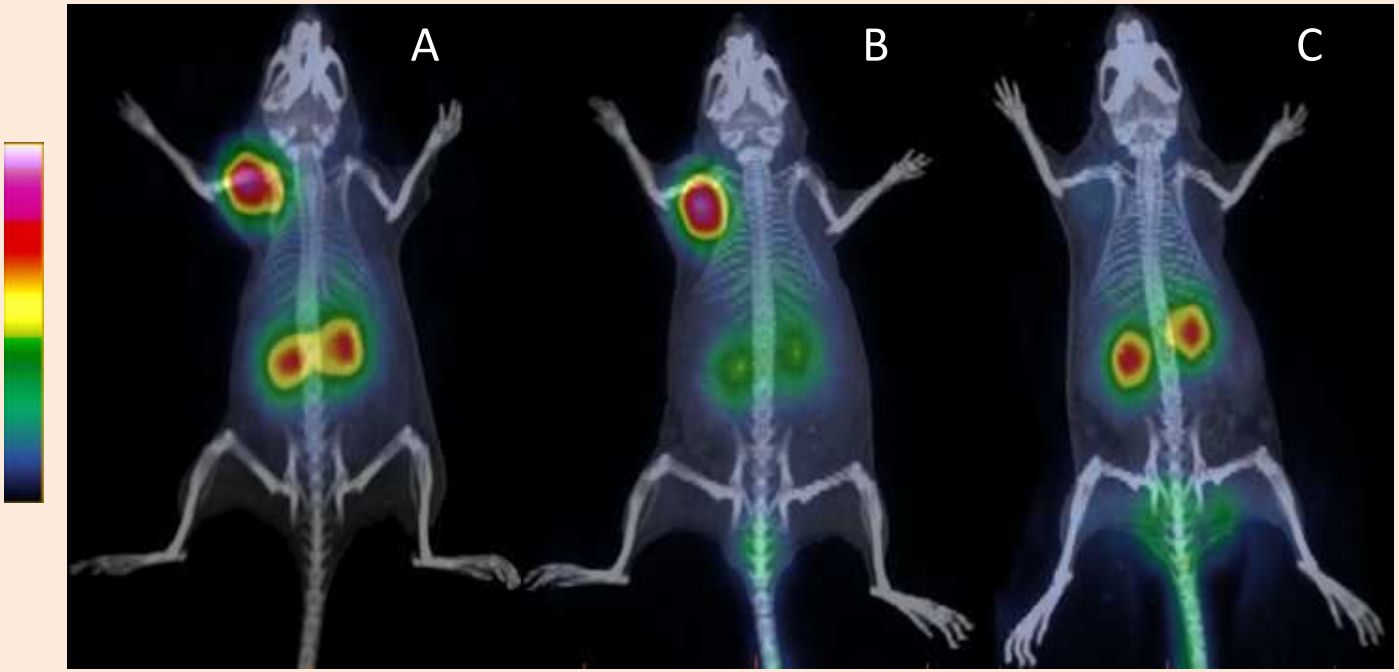
All $^{67/68}$Ga-labeled somatostatin- based **Agonists** are superior to ^{111}In, ^{90}Y, ^{177}Lu-labelled congeners on tumor expressing sst2

Chemistry Highlights: One vision – many challanges

Optimizing of vector characteristics

A novel class of potential radiotracers for PET imaging based on bicyclic somatostatin analogs

AM3: Arg—Cys —Phe —D-Trp —Lys —Thr —Cys —Dab-Tyr-DOTA



^{68}Ga-AM3 | Kidney blocking (Lys + ^{68}Ga-AM3) | Tumor blocking (DOTANOC + ^{68}Ga-AM3)

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THERANOSTICS – on the Way to Personalized Medicine

Chemistry Highlights: One vision – many challenges

Optimizing of vector characteristics

Radiolabeled GRPR-Antagonists: New Promising Tools in the Diagnosis & Therapy of GPR^{+} Tumors

Maina T[1], Nock BA[1], Baum RP[2], Krenning EP[3], de Jong M[3],

[1]*Molecular Radiopharmacy, I/R-RP, NCSR "Demokritos", 15310 Athens, Greece*

[2]*Department of Nuclear Medicine, Center for PET/CT, Zentralklinik Bad Berka, Germany*

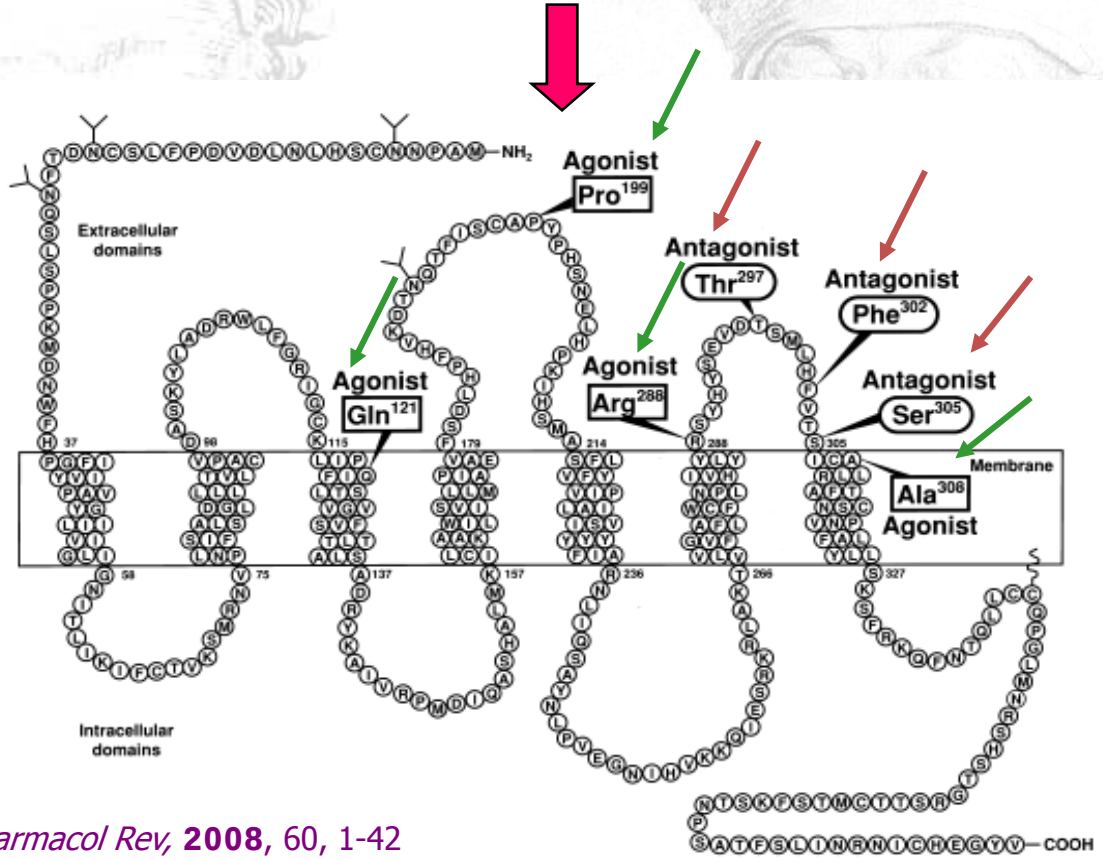
[3]*Department of Nuclear Medicine, Erasmus MC, 3015 CE Rotterdam, The Netherlands*

Chemistry Highlights: One vision – many challenges

Optimizing of vector characteristics

Bombesin Receptor Subtypes in Mammals

NMB-R GRP-R BB_3-R



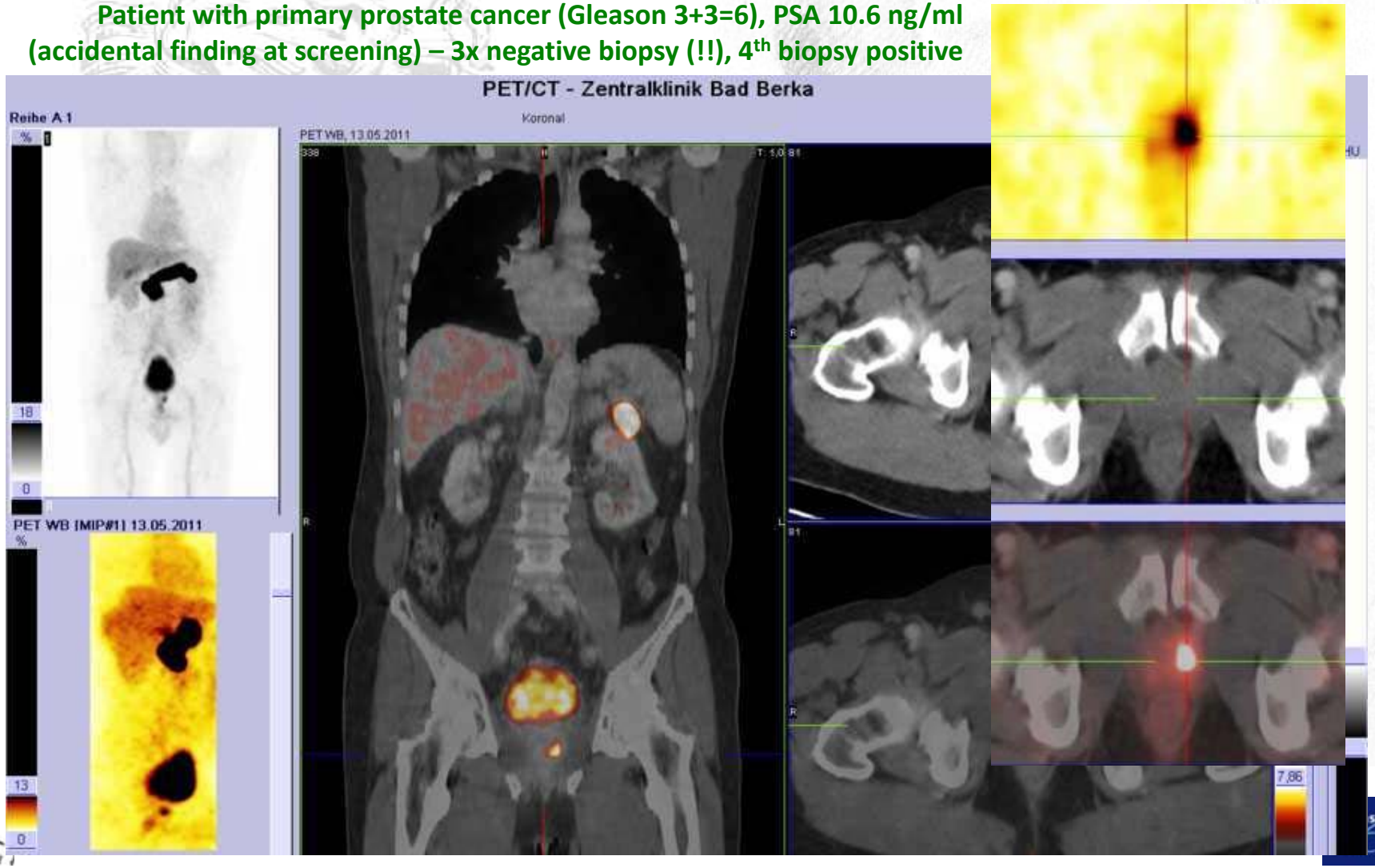
Jensen RT et al, *Pharmacol Rev,* **2008**, 60, 1-42
Tokita K et al. *J Biol Chem,* **2001**, 276, 36652-36663

Chemistry Highlights: One vision – many challenges

Optimizing of vector characteristics

[^{68}Ga]Elafaki in Prostate Cancer

Patient with primary prostate cancer (Gleason 3+3=6), PSA 10.6 ng/ml (accidental finding at screening) – 3x negative biopsy (!!), 4th biopsy positive

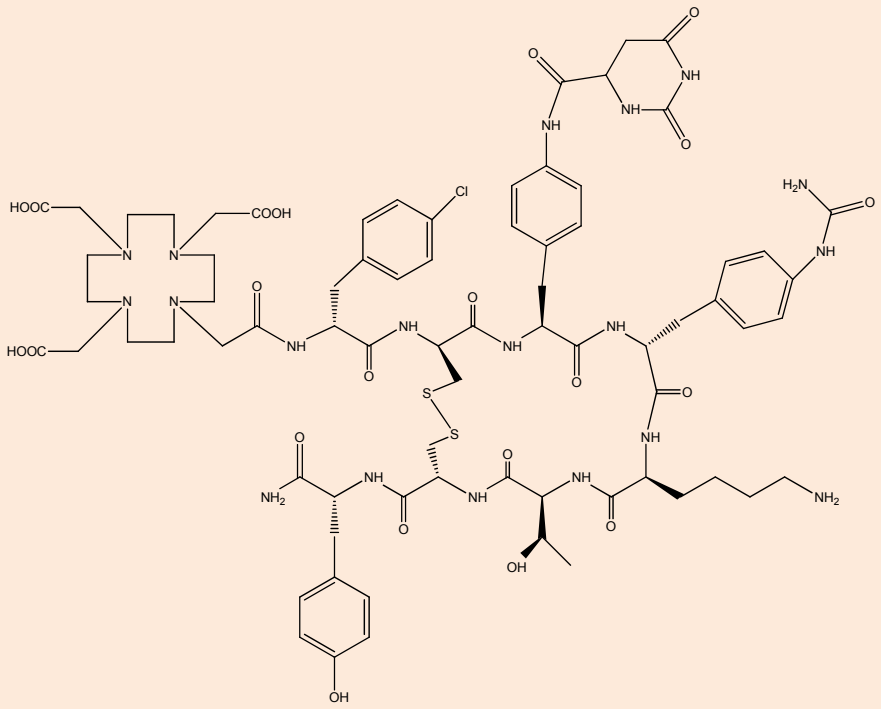


Chemistry Highlights: One vision – many challenges

Understanding impact of Me(III)

The (radio)metal determines receptor affinity !

Sst2-SOM-antagonist



(Radio)metal	IC_{50} (nM)
$^{68/nat}Ga(III)$	29 ± 2.7
$^{64/nat}Cu(II)$	16 ± 1.2
$^{111/nat}In(III)$	**3.8 ± 0.7**
$^{177/nat}Lu(III)$	0.7 ± 0.15
$^{90/nat}Y(III)$	**0.47 ± 0.05**

- ^{111}In may not be a good surrogate of ^{90}Y
- Ga-complexation lowers the sst2-affinity

Chemistry Highlights: One vision – many challanges

Understanding impact of chelator

PET Imaging Using Ga-68 Labelled Somatostatin Antagonists is Influenced by the Choice of the Chelator

Melpomeni Fani[1], Luigi Del Pozzo[1], Maria Luisa Tamma[2], Guillaume Nicolas[2], Friederike Deininger[2], Wolfgang A. Weber[1], Jean Claude Reubi[3], Helmut R. Maecke[1]

[1]Department of Nuclear Medicine, University Hospital Freiburg, Germany

[2]Department of Nuclear Medicine, University Hospital Basel, Switzerland

[3]Institute of Pathology, University of Bern, Switzerland

Chemistry Highlights: One vision – many challanges

Understanding impact of chelator

Affinity Determination by Receptor Autoradiography

Compound	IC_{50} (nmol/L)
^{nat}Ga-NODAGA-LM3	1.3 ± 0.3
^{nat}Ga-DOTA-LM3	12.5 ± 4.3
^{nat}Ga-NODAGA-BASS	16.7 ± 0.6
^{nat}Ga-DOTA-BASS	40.0 ± 5.0

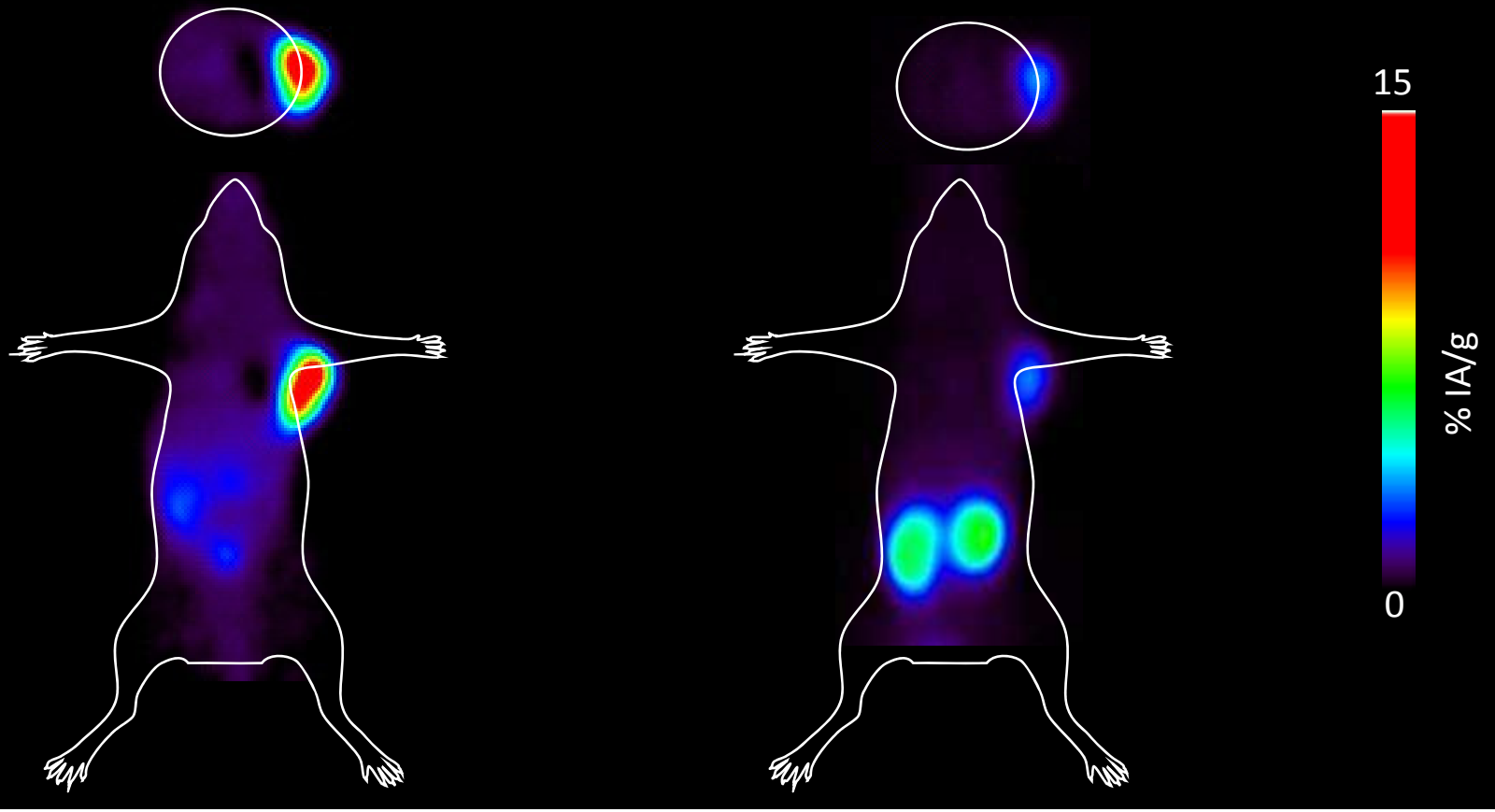
Chemistry Highlights: One vision – many challenges

Understanding impact of chelator

Small-animal PET images: Same mouse used in both experiments

^{68}Ga-NODAGA-BASS

^{68}Ga-DOTA-BASS

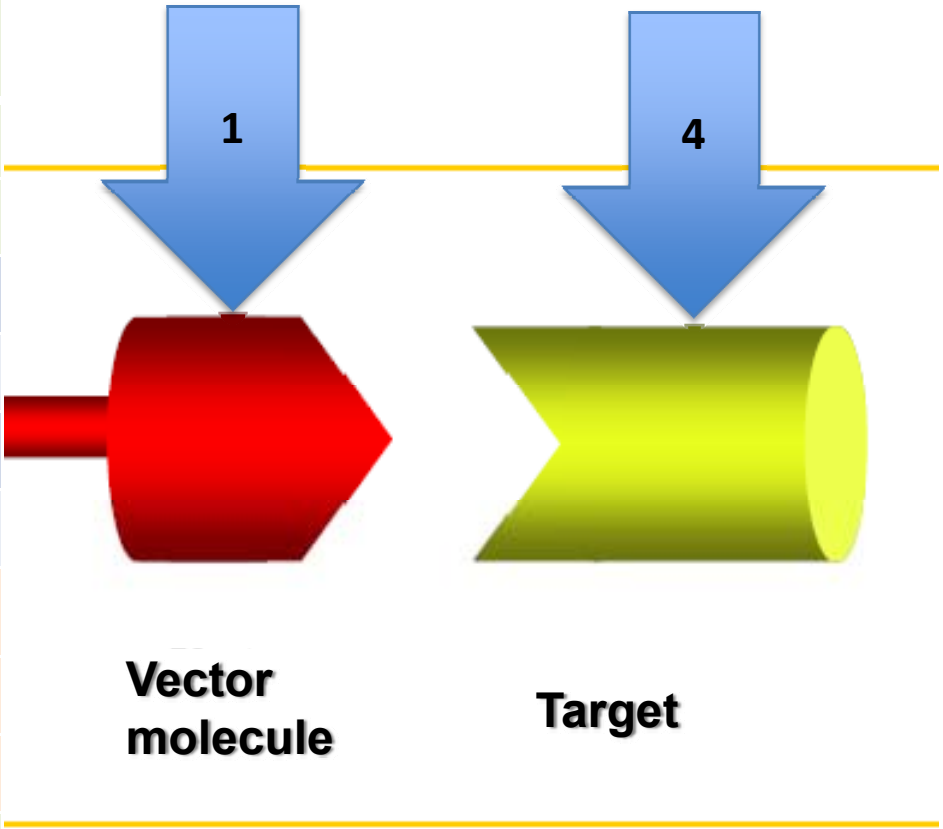


Chemistry Highlights: One vision – many challanges

„Long“ vectors vs. „short“ ^{68}Ga half-life:

Or: *Pre–targeting chemistry* !

Peptides: somatostatin, bombesin	Helmut Mäcke, Melpomeni Fani, Aureli Prignon, Theodosia Maina
α-MSH	Michael Schultz
Neurotensin analogs	Anne Gruaz-Guyon
Annexin	Alfons Verbruggen
transferrin	Vijay Kumar
Amino acids, Nitroimidazoles	Jae Min Jeong
Folic acid	Berit Kühle
Citrate	Vijay Kumar
Bisphosphonates	Marco Fellner
Schiff base ligands	Oliver Thews
Affibodies, Nanobodies	Irina Velikyan, Catarina Xavier
mabs	Otto Boerman, Denis Beckford Vera
nanoparticles	Cathy Cutler

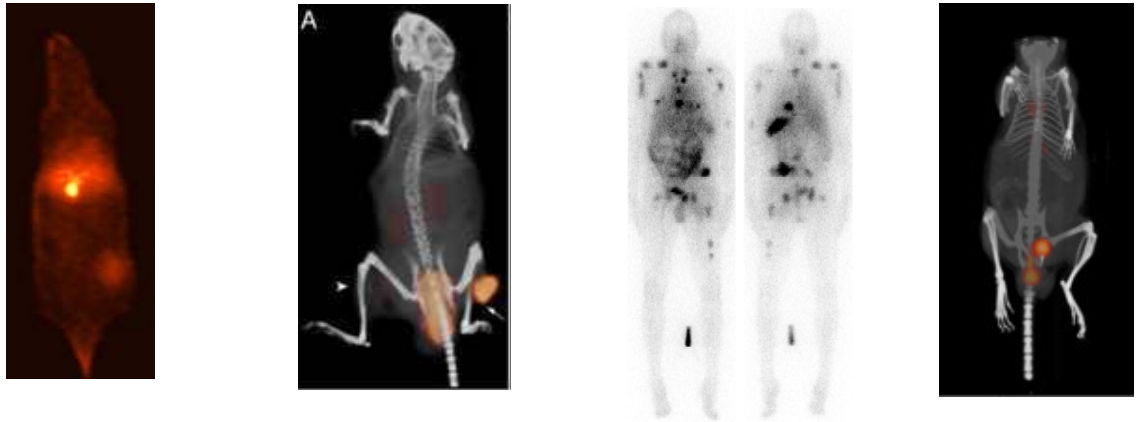


Chemistry Highlights: One vision – many challenges

„Long“ vectors vs. „short“ ^{68}Ga half-life:

Or: *Pre–targeting chemistry*

Pretargeted Immuno-PET of Colorectal Cancer with Bispecific Antibodies

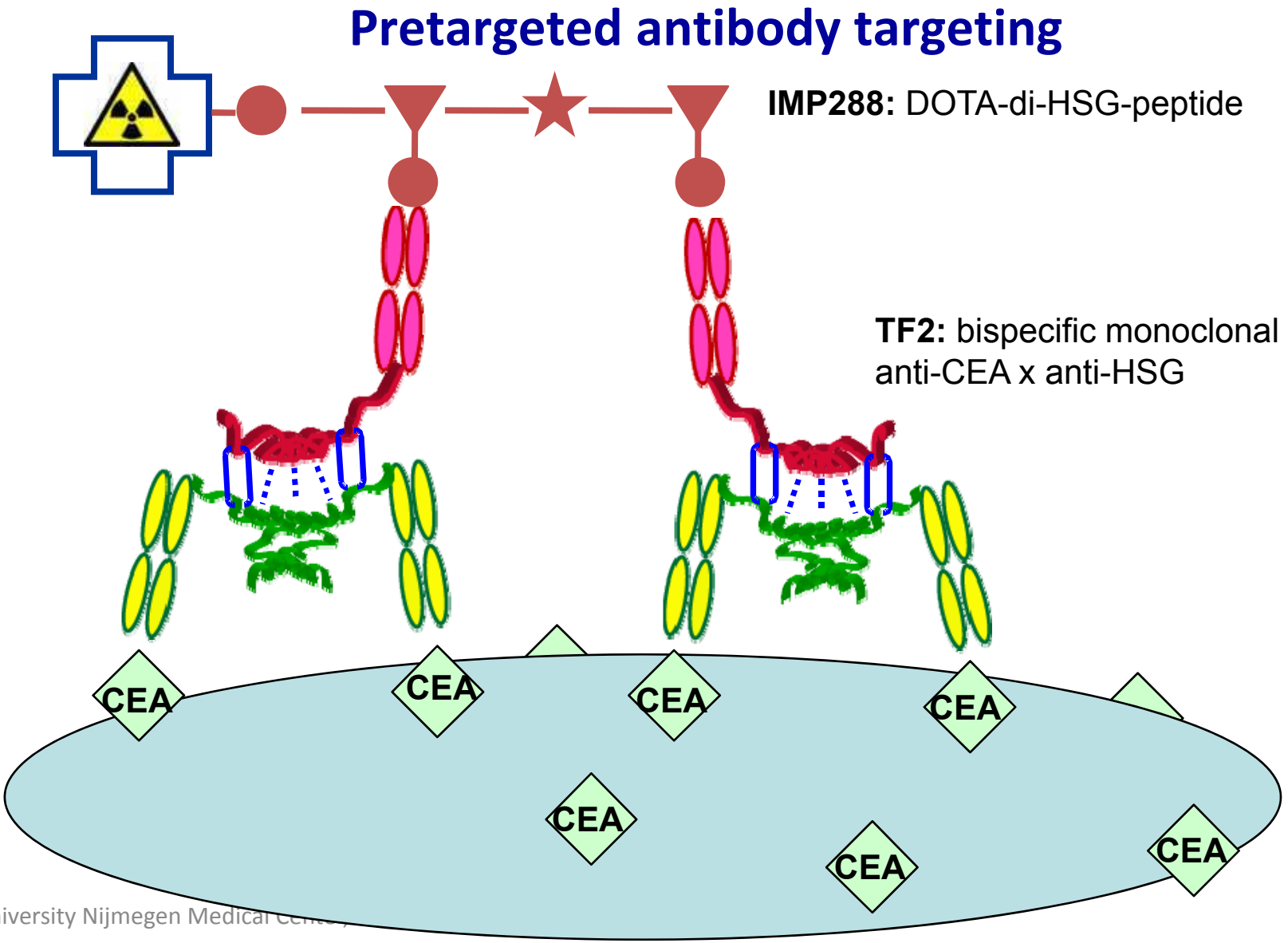


Otto C. Boerman, PhD

Radboud University Nijmegen Medical Centre, The Netherlands

Chemistry Highlights: One vision – many challenges

„Long“ vectors vs. „short“ ^{68}Ga half-life



Chemistry Highlights: One vision – many challanges

„Long“ vectors vs. „short“ ^{68}Ga half-life:

Or: *Pre–targeting chemistry*

Pretargeted imaging of prostate cancer

Nude mice with s.c. PC3 tumor

t = 0 h
anti-EGP-1 x anti-HSG bsAb (2.5 nmol)

t = 16 h
Ga-68-diHSG peptide (0.1 nmol)

t = 17 h
microPET/CT

Chemistry Highlights: One vision – many challanges

„Long“ vectors vs. „short“ ^{68}Ga half-life:

Or: *Pre–targeting chemistry*

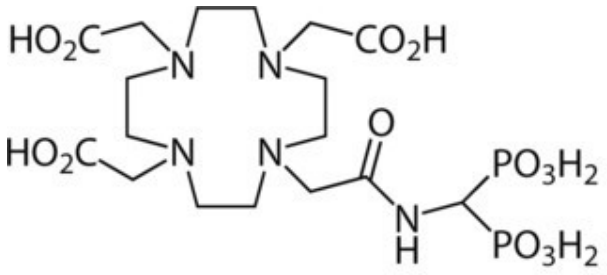
Nanoparticles and Phage Display Selected Peptides for Imaging and Therapy of Cancer

Cathy S. Cutler, Nebiat Sisay, Melchor Cantorias, Ajit Zambre,
Mark McLaughlin, George Smith, Susan Deutscher,
Silvia Jurisson, Raghuraman Kannan and Kattesh Katti

MU Research Reactor, Chemistry Department, Radiology,
Harry S. Truman Memorials Veterans Hospital

Chemistry Highlights: One vision – many challanges

Another example of THERANOSTICS



BPAMD

[^{177}Lu]BPAMD vs. [^{68}Ga]BPAMD: *Theranostics* for bone metastasis

M. Fellner[1], R. P. Baum[2], V. Kubicek[3], P. Hermann[3], V. Prasad[2], F. Rösch[1]

[1] Institute of Nuclear Chemistry, University of Mainz, Germany
[2] Department of Nuclear Medicine, Zentralklinik Bad Berka, Germany
[3] Department of Inorganic Chemistry, University of Prague, Czech Republic

JG|U
JOHANNES GUTENBERG UNIVERSITÄT MAINZ

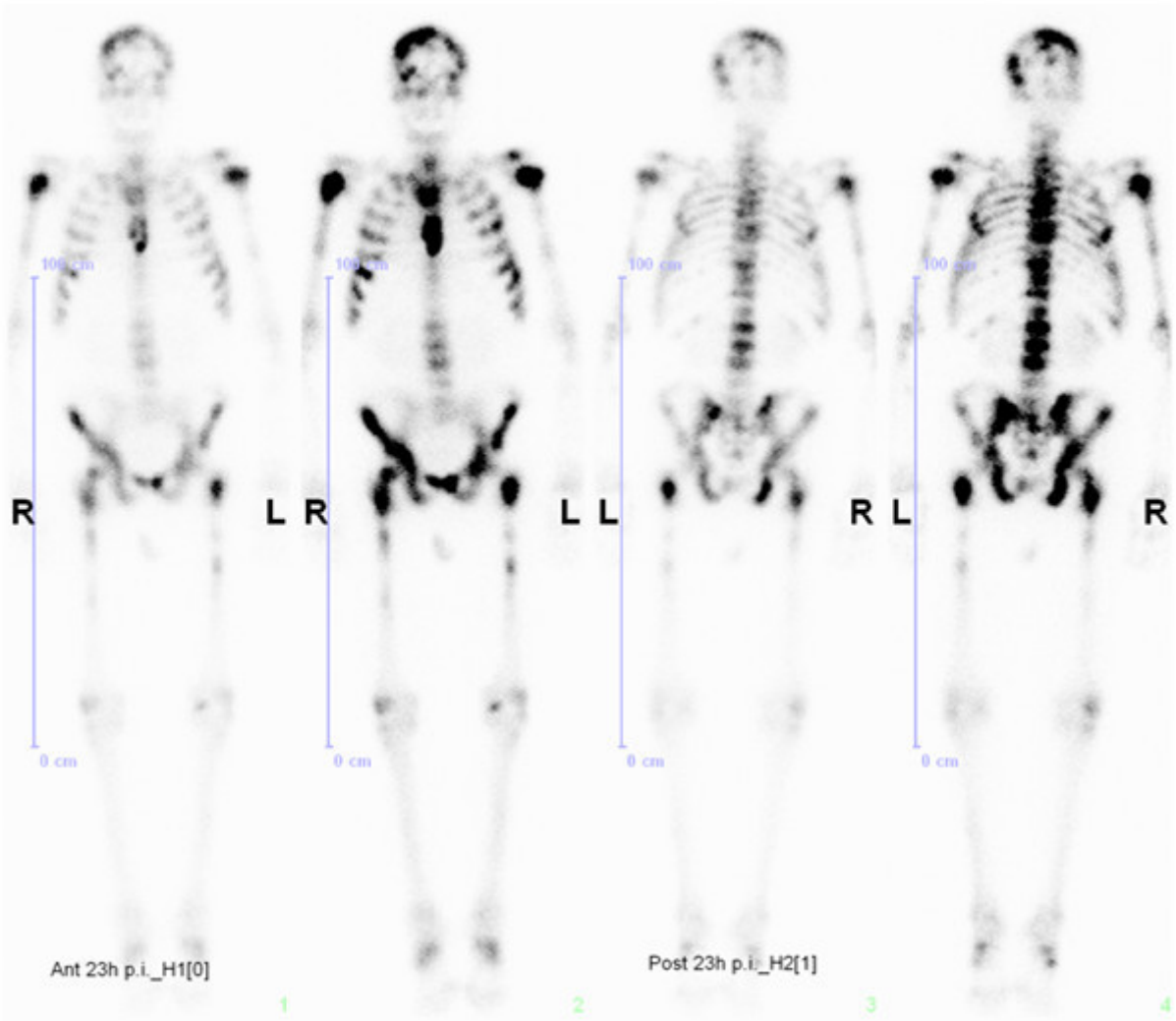
Chemistry Highlights: One vision – many challenges

Another example of THERANOSTICS

- 57 year old male patient with primary prostate cancer
- wide spread bone metastases
- 462 MBq [^{68}Ga]BPAMD (i.v.; PET 50 min p.i.)
- PET (left, coronal) and PET-CT (right, sagital)

Chemistry Highlights: One vision – many challanges

Another example of THERANOSTICS

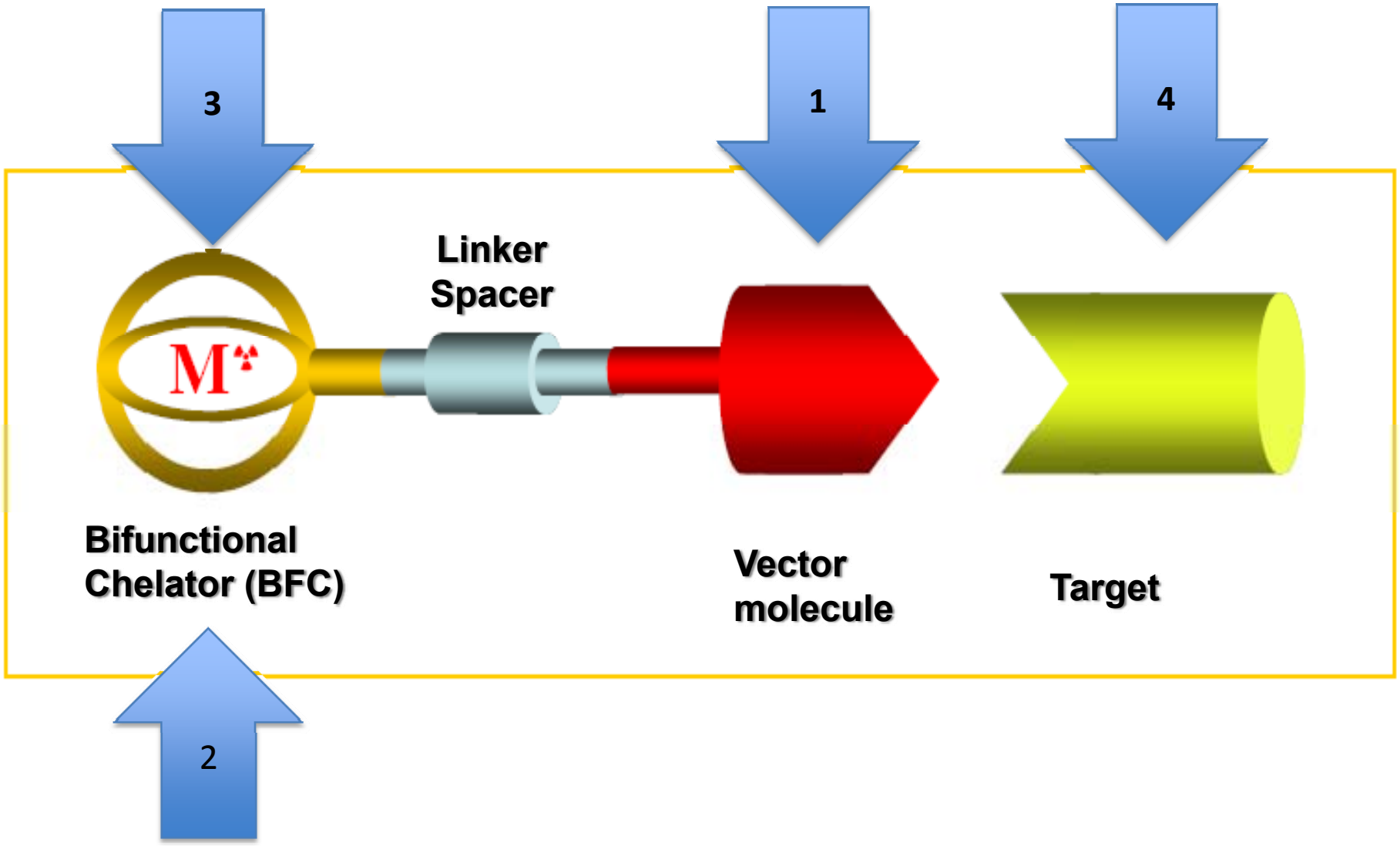


5 GBq [^{177}Lu]BPAMD

monitored with SPECT over 24 h

23 h p.i.

Chemistry Highlights: One vision – many challenges



Highlights Ga-68 & PRRNT

by

Richard P. Baum

1st World Congress on Ga-68 and PRRNT
Golden Jubilee Celebration of Ge-68/Ga-68 Generator System

G.I. Gleason
A positron cow.

Int J Appl Rad Isot 1960;8:90-94

M. W. Greene and W. D. Tucker
An improved gallium-68 cow.

Int J Appl Rad Isot 1961;12:62-63

Hnatowich D.J.

J Nucl Med. 1975;16(8):764-8

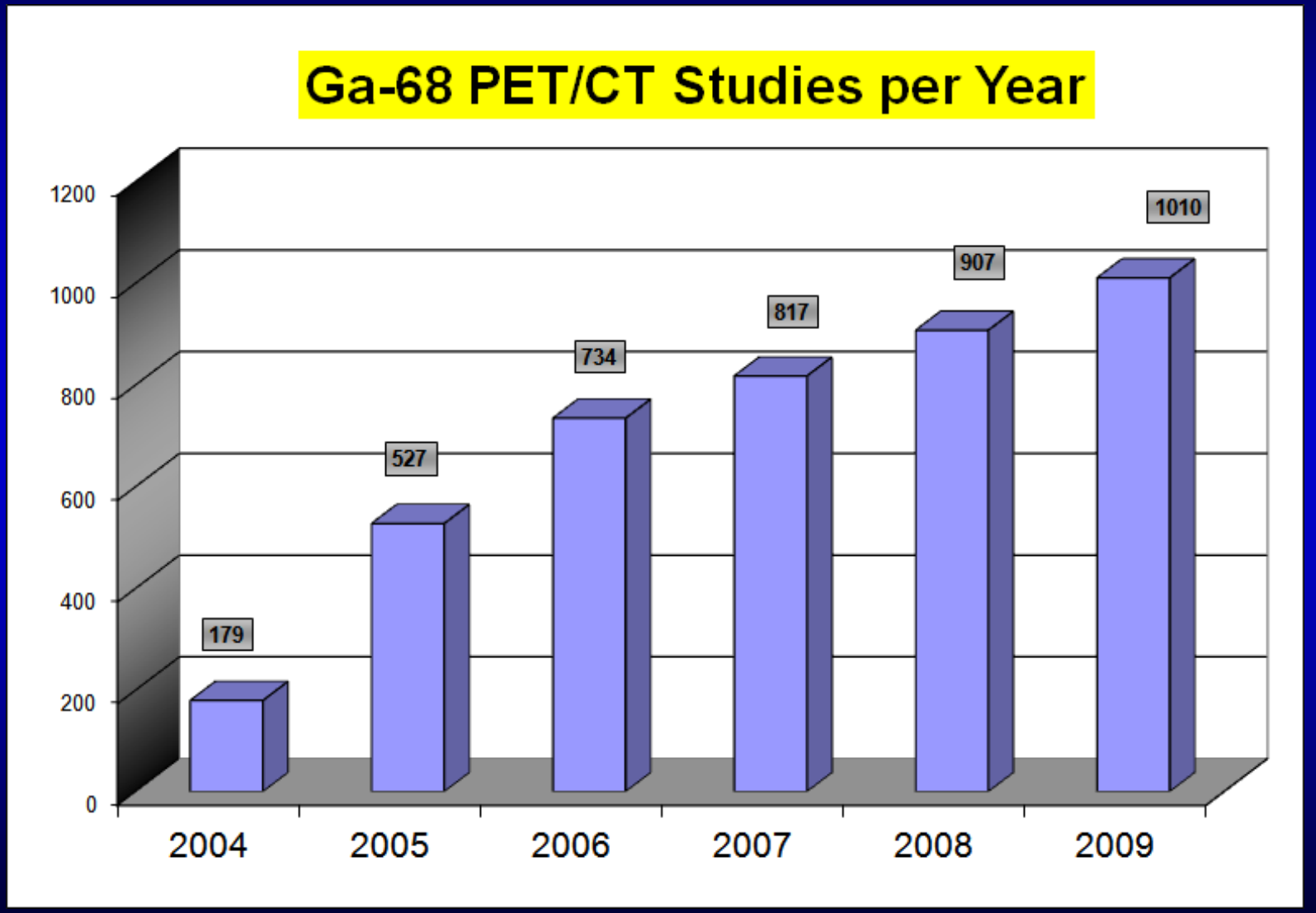
J. Schuhmacher / W. Maier-Borst

Int J Appl Rad Isot 1981;32(1): 31-6

Hofmann M, Maecke H, Börner AR et al. Biokinetics and imaging with the somatostatin receptor PET radioligand Ga-68 DOTATOC: preliminary data.

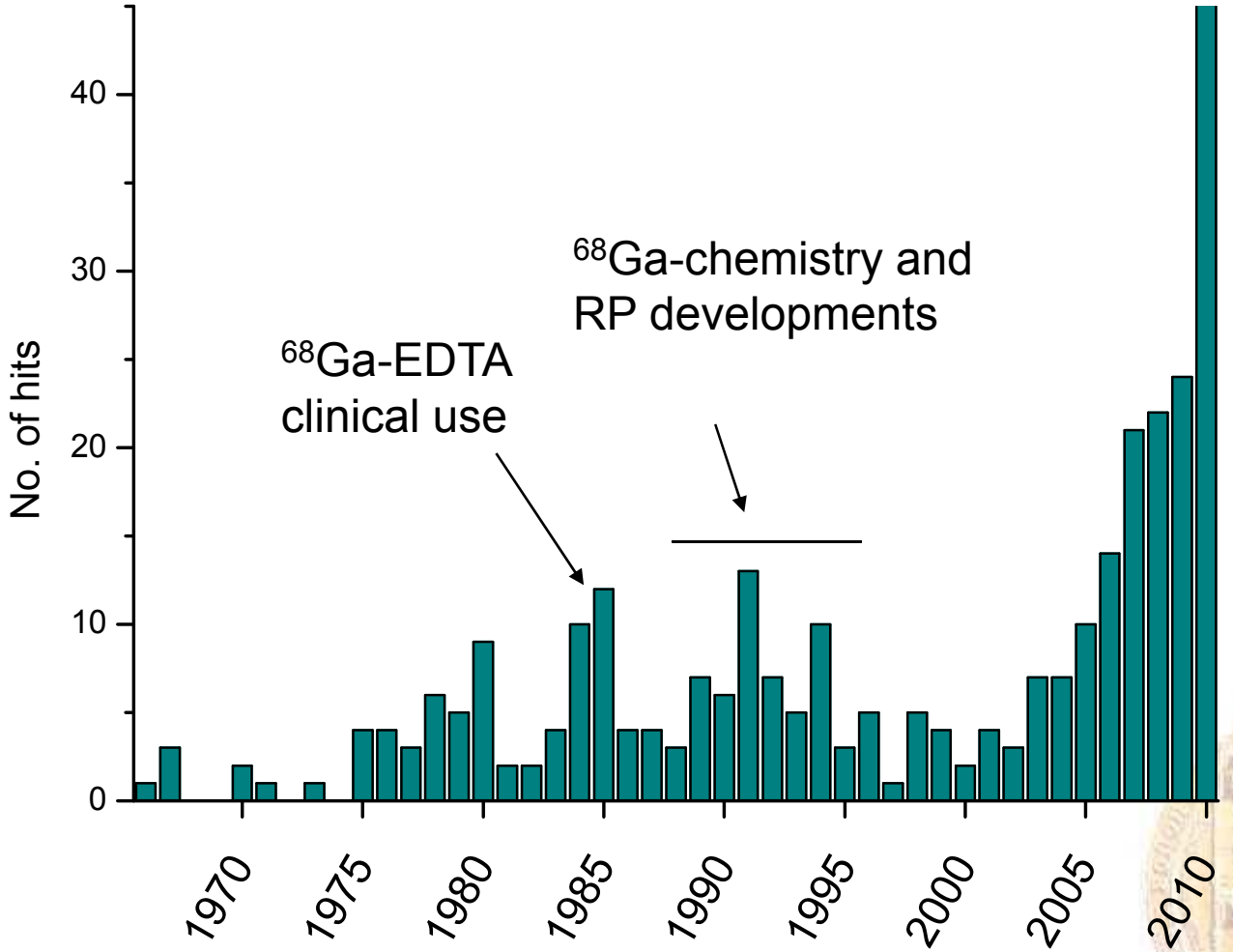
***Eur J Nucl Med* 2001; 28:1751-1757**

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

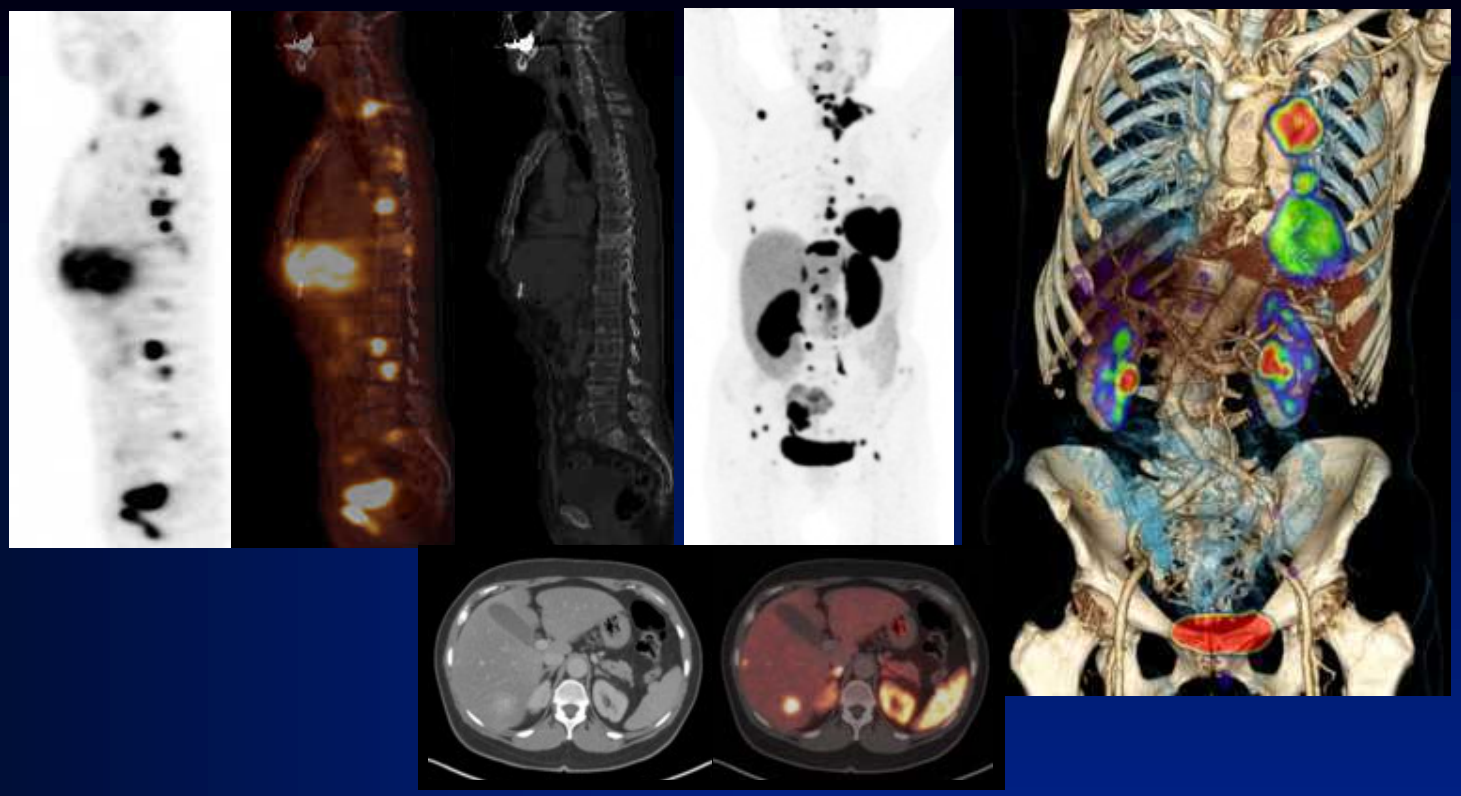


** Prediction by R.P. Baum (2004)*

PUBMED Citation "^{68}Ga, Ga-68"



Courtesy Dr. Clemens Decristoforo



Bad Berka
25th June 2011

Ga-68 Imaging in Clinical Practice: Worldwide Experience

The European Experience

G. Pöpperl
Dept. of Nuclear Medicine – Klinikum Stuttgart

Dept. of Nuclear Medicine
Klinikum Stuttgart

^{68}Ga Imaging – European Experience

^{68}Ga SSR imaging has its roots in Europe and significantly improved diagnostic work-up in European NET centers:

- for primary tumor localization
  in patients with suspicion of NET (clinical and la… patients with known NET metastases (CUP)

- for staging, re-staging and t… of
  higher sensitivity for sma… bone and soft tissue metastases
  (pretherapeutic sta… treatment? Therapy control – earlier change of therapeuti…)
  But: le… mpared to MRI/CT for liver/lung metastases

- …ng and monitoring treatment with cold/hot SSR ligands
  …nvasive identification of SSR positive tumors for treatment
  high prognostic value, sensitive tool for treatment monitoring (limitations for pulmonary and small liver lesions / in dedifferentiation)

Additional information of ^{68}Ga SSR imaging changes therapeutic management in 40 – 60% of NET patients

Frilling A et al. (Ann Surg 2010): The impact of 68Ga-DOTATOC PET/CT on the multimodal management of patients with NET

Ruf J et al. (Neuroendocrinology 2010) Impact of Multiphase 68Ga-DOTATOC-PET/CT on therapy management in patients with NET

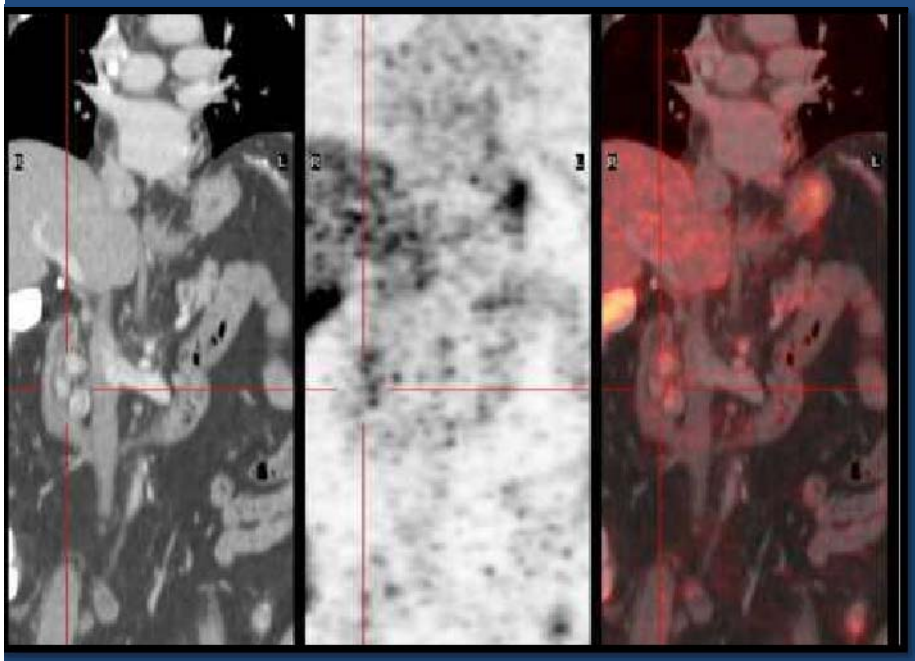
Ga-68 imaging in clinical practice: the Indian experience

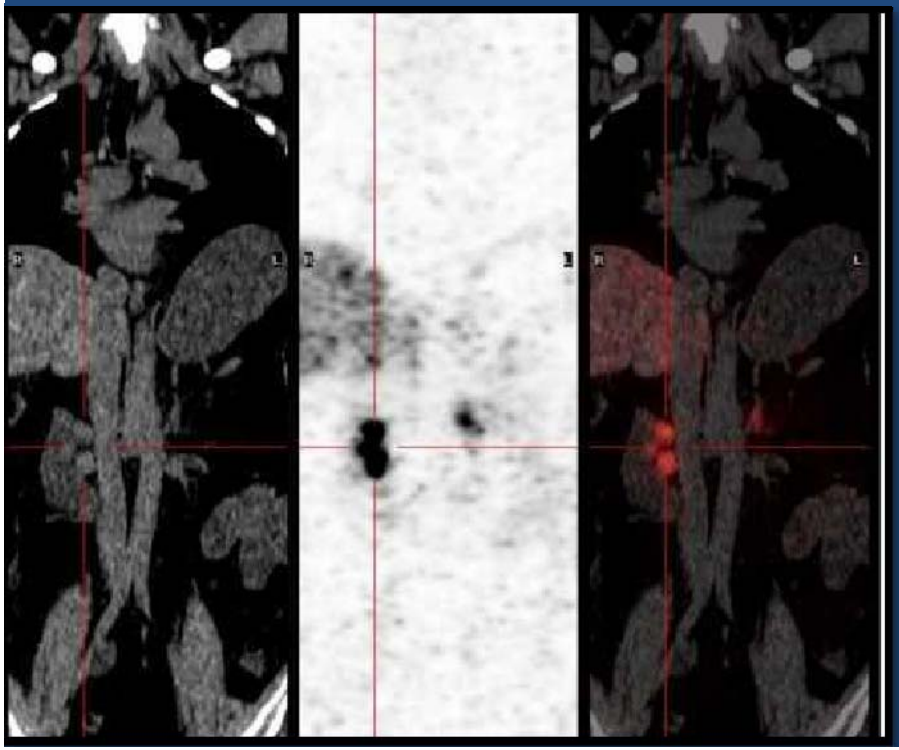
Dr. Vikram Lele MD,DNB, DRM

Jaslok Hospital & Research Centre

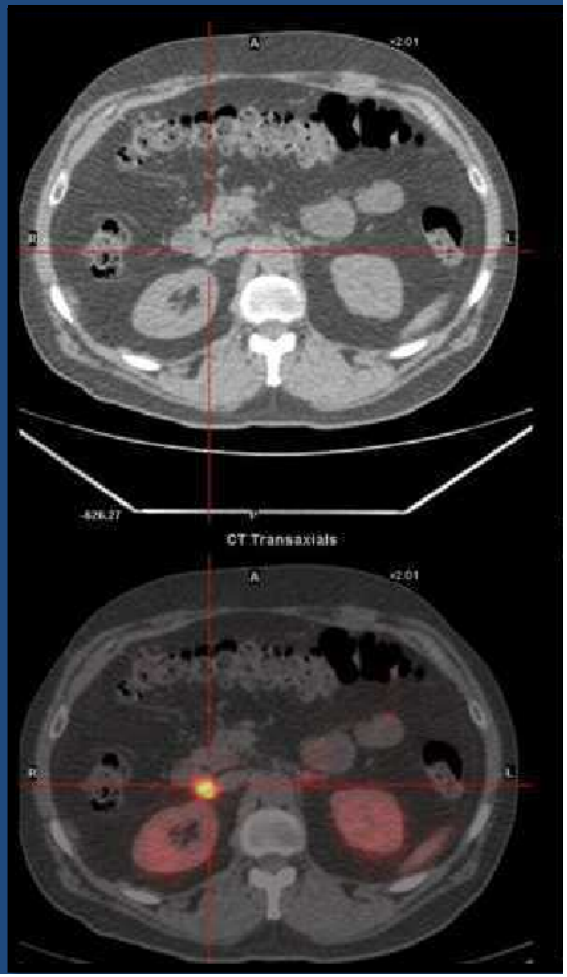
Mumbai, India

- 6 centers actively performing 68Ga-scans since 2007 along with PRRT. 1536 scans performed to date
  - AIIMS, New Delhi
    - 881 scans
  - Jaslok Hospital, Mumbai
    - 190 scans
  - BIO, Bangalore
    - 465 scans
- 3 centers soon to start
  - New Delhi, Chennai





Case of Liposarcoma, post treatment for follow-up evaluation.
FDG PET-CT shows low grade uptake in the enhancing lesion in duodenum with lymph nodes
68Ga-DOTATATE PET-CT shows receptor positive lesions at same site



An Australian Perspective
The Peter Mac Experience

Dr Tim Akhurst FRACP

Bad Berka.

Summer 2011

Case 1: Oncogenic Osteomalacia

43yo ♂ multiple insufficiency fractures,
hypophosphataemia,

↑FGF-23

Multiple investigations over 3 year period:

CT: neck – pelvis

Whole body MRI

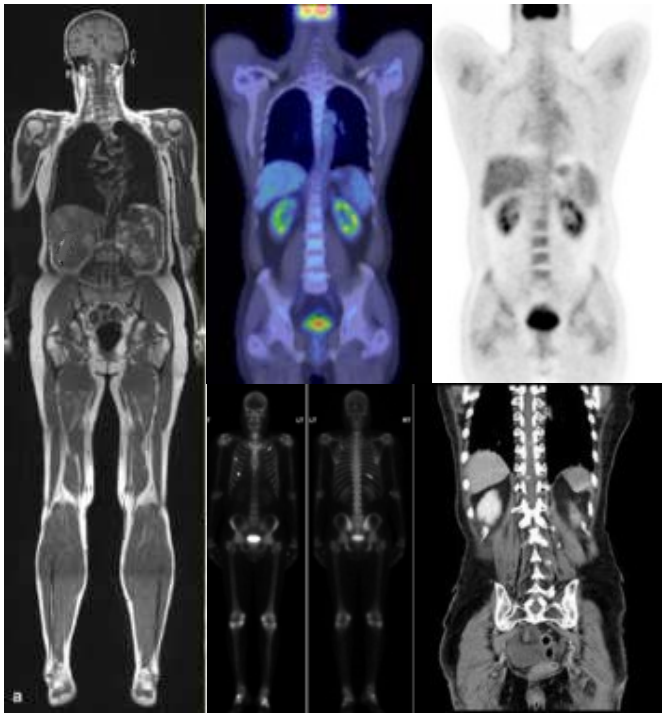
MRI hands & feet

^{18}F-FDG PET/CT x 2

Bone scan x 2

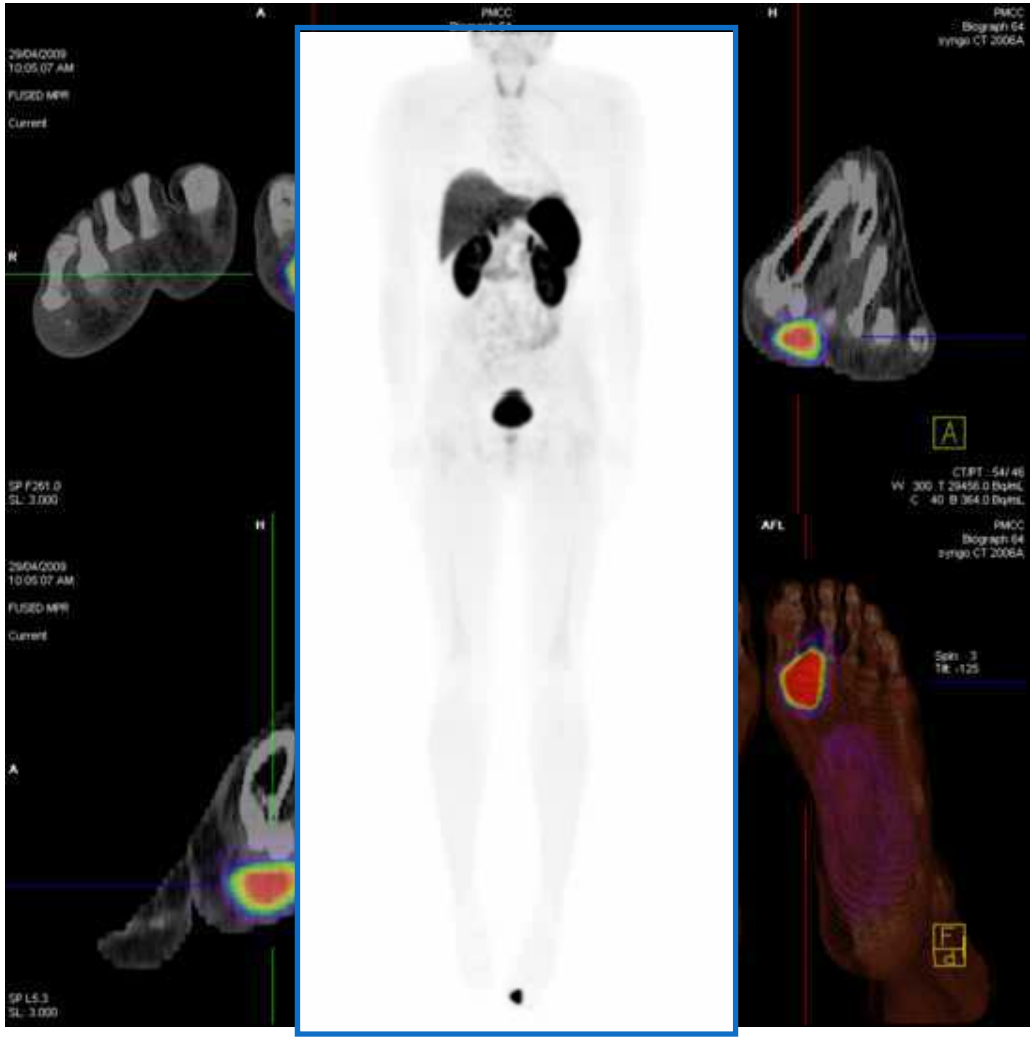
Sestamibi scan

^{111}In-Octreotide SPECT/CT



Case 1:

Surgical Resection→ cure



Receptor Density Indication

- Accurate resolution of disease volume and reporting of receptor density allows tailoring of therapeutic approach.
  - Again strong argument for the use of a PET based tracer over a gamma camera based tracer

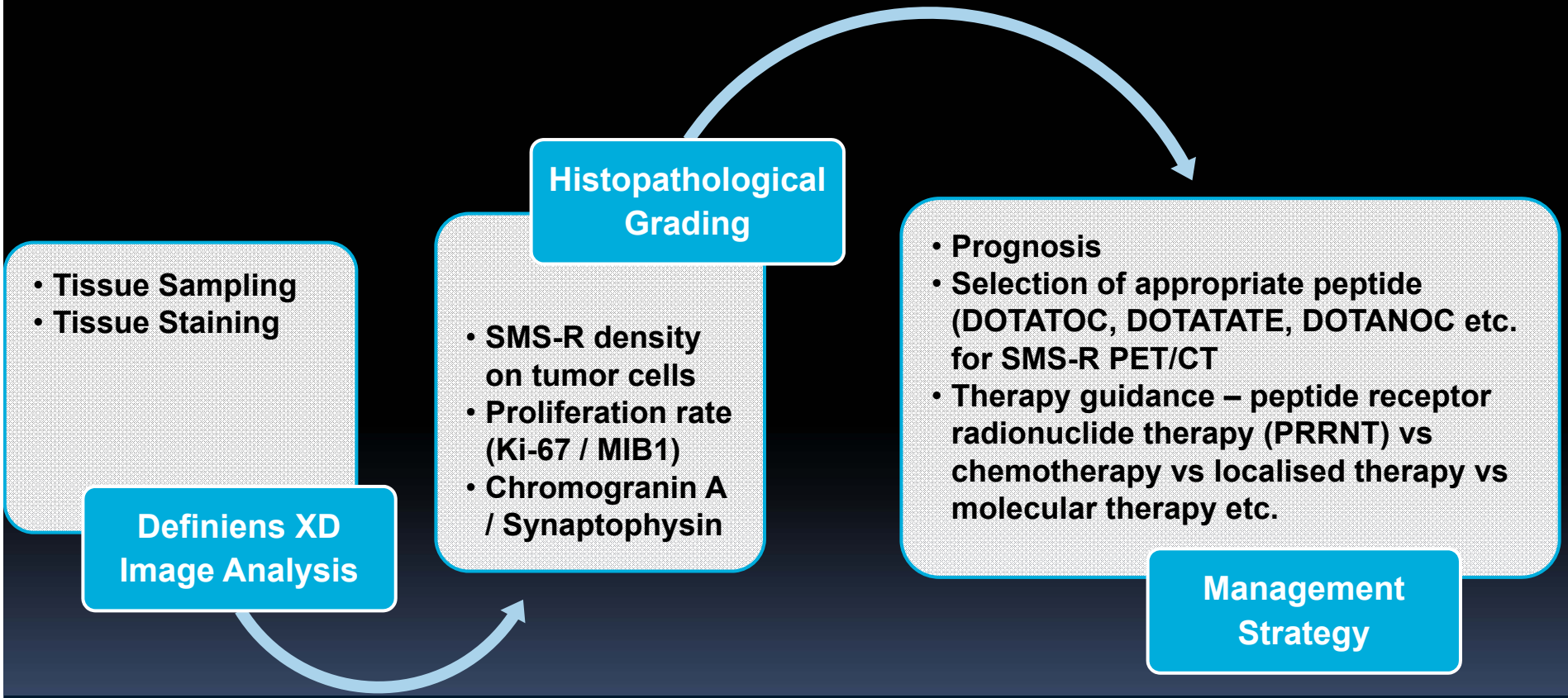
Ga-68 DOTA-NOC receptor PET/CT: SUV of primary tumors and metastases

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 - 105
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

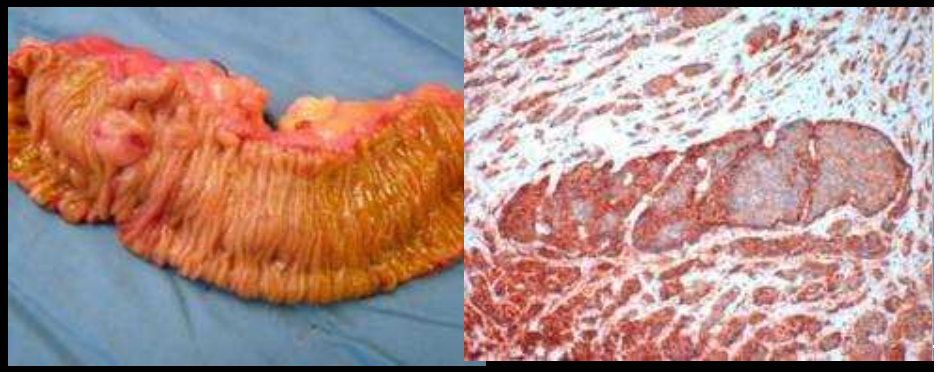
Digitalised Histopathology Combined with Somatostatin Receptor PET/CT –

From Tissue to Molecular Imaging to Therapy



On the Way to Personalized Medicine

Digitialised Histopathological Classification
Definiens XD Image Analysis - Processing



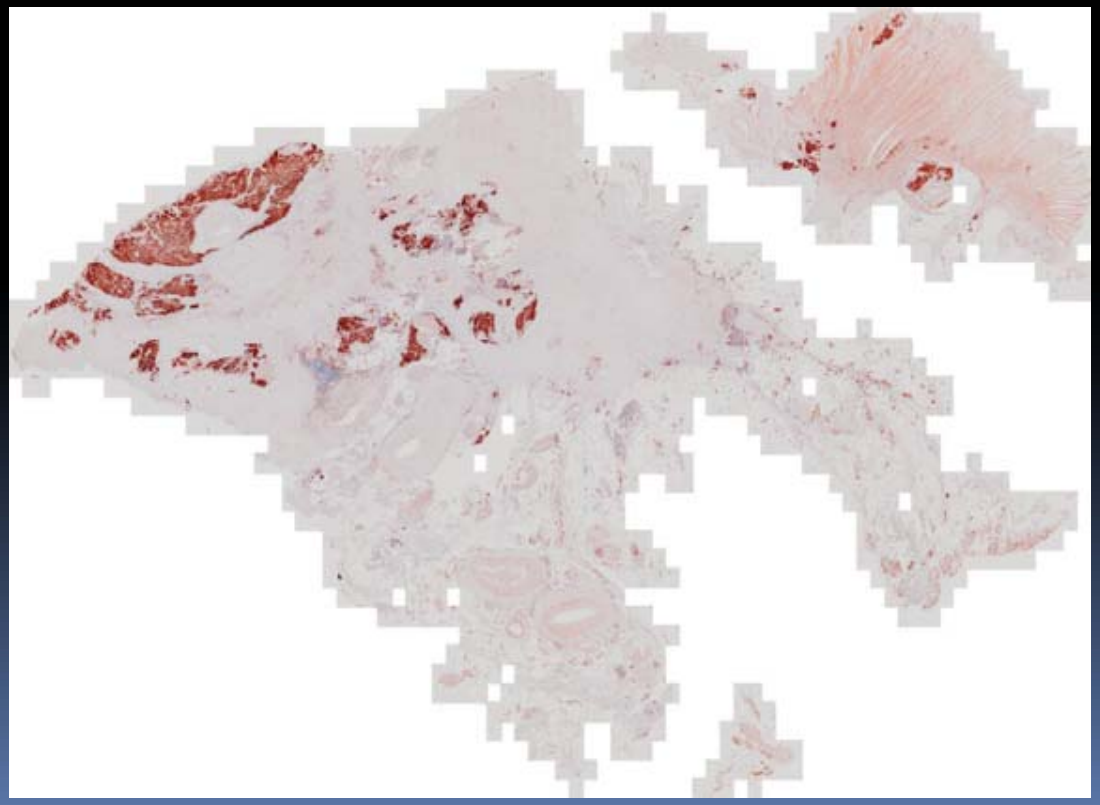
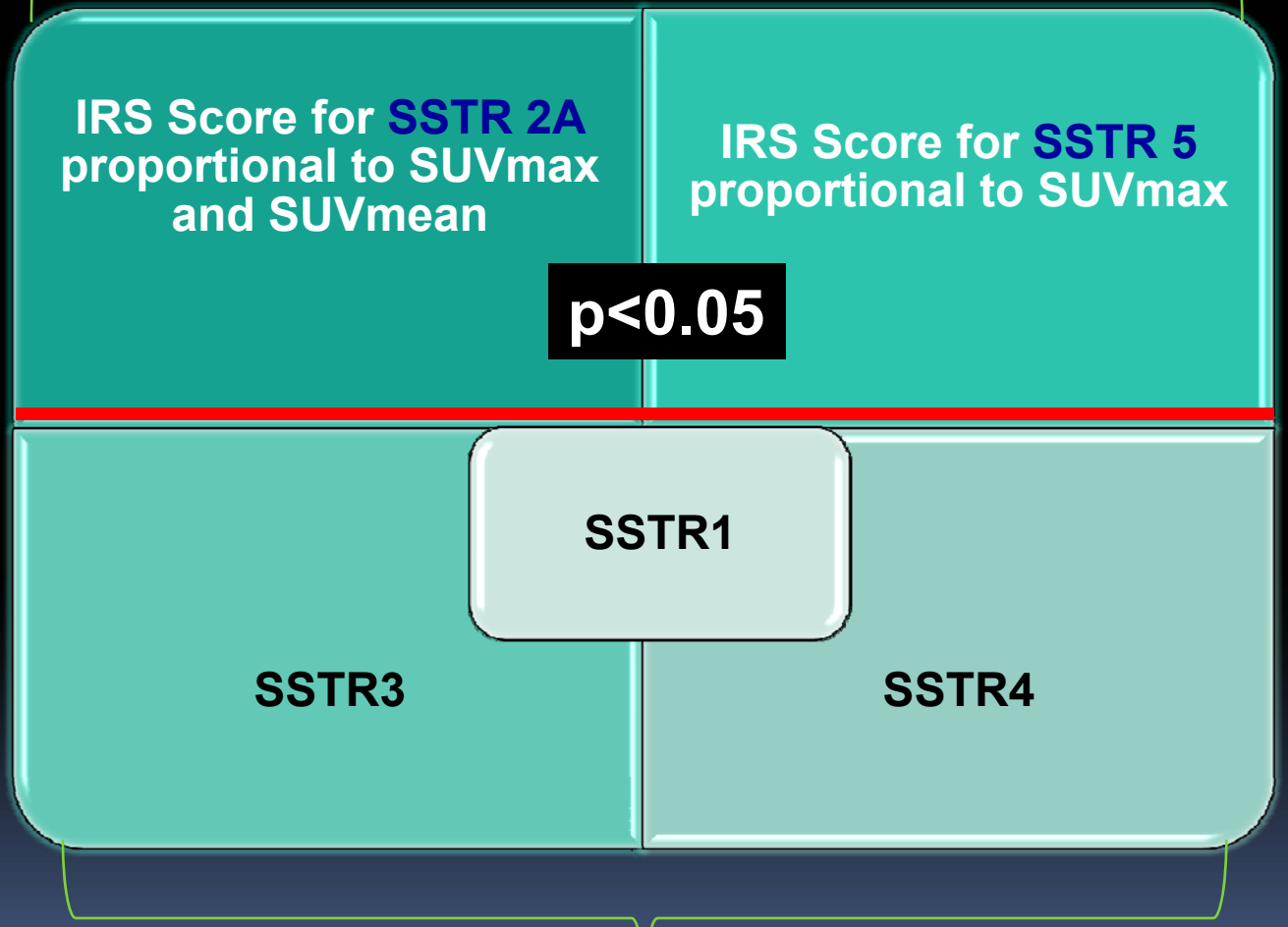


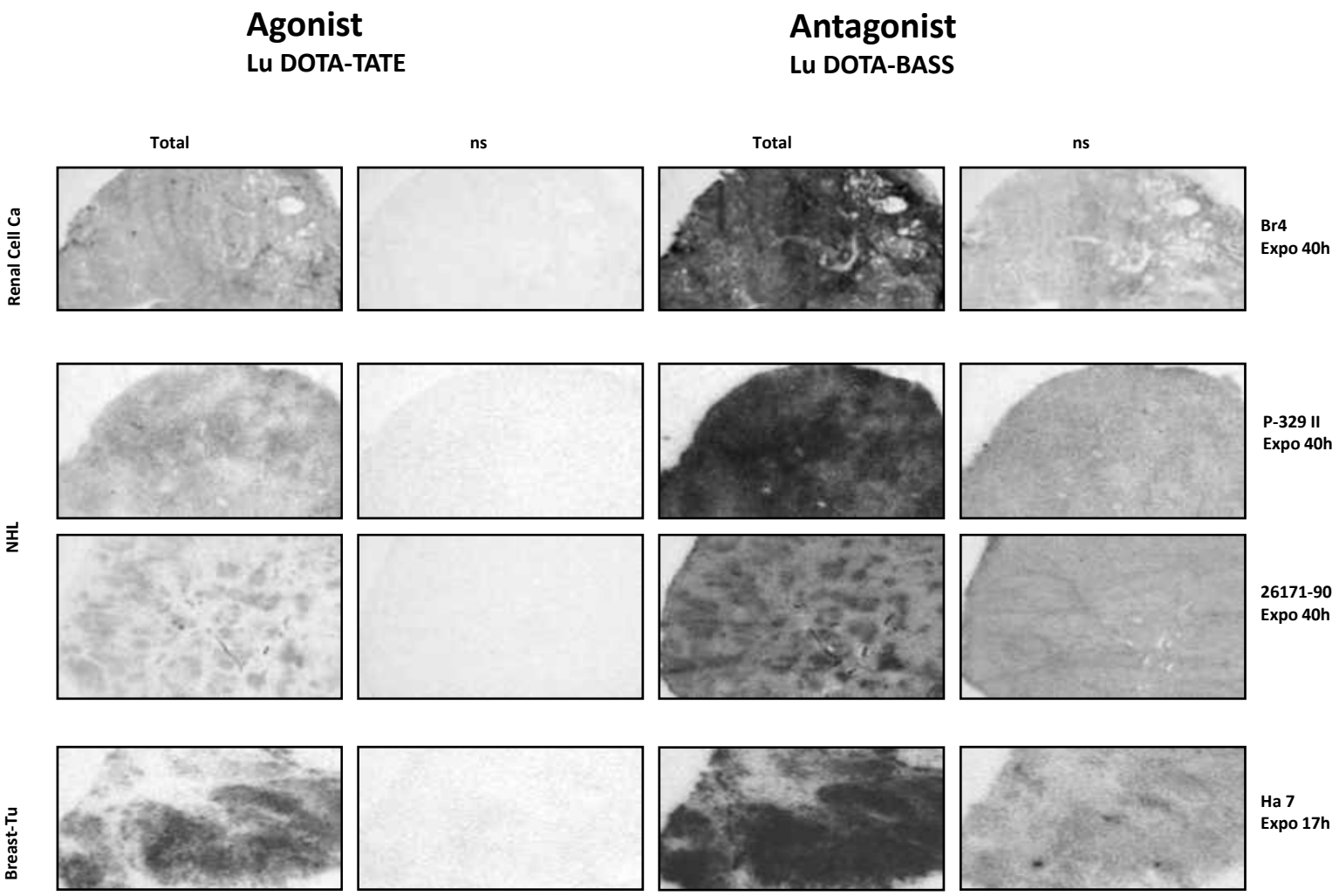
Image Analysis Results SSTR-2	Correlation	Liver Mets SUVmax PET/CT
N1	Correlation Coefficient	-0,733
	P Value	0.02
N2	Correlation Coefficient	-0.750
	P Value	0.0158

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

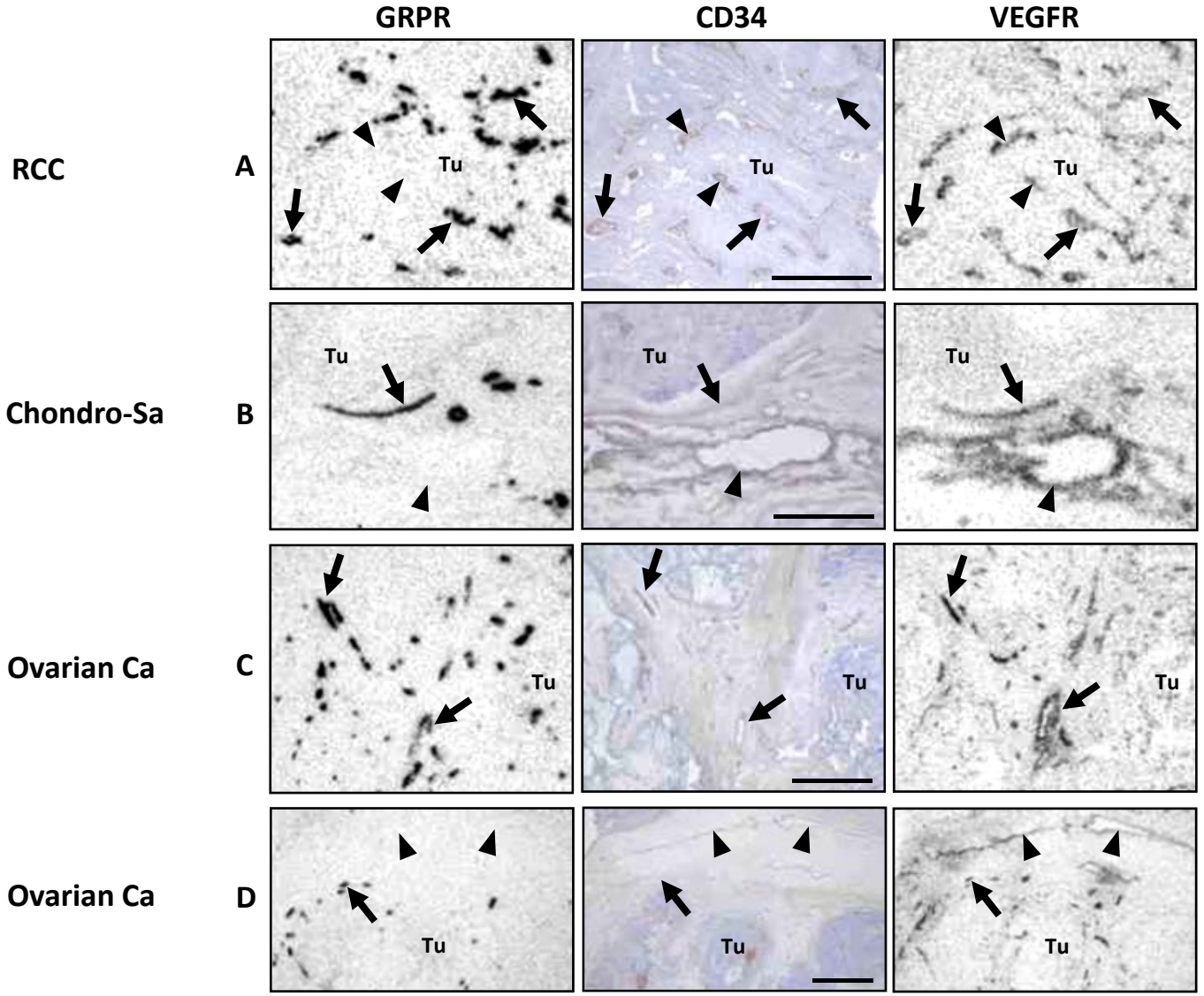


No significant correlation between the IRS score for SSTR1, SSTR3 and SSTR4 with the semiquantitative parameters (p>0.05)

Antagonist labels more sst_2 sites than agonist in human cancer tissues



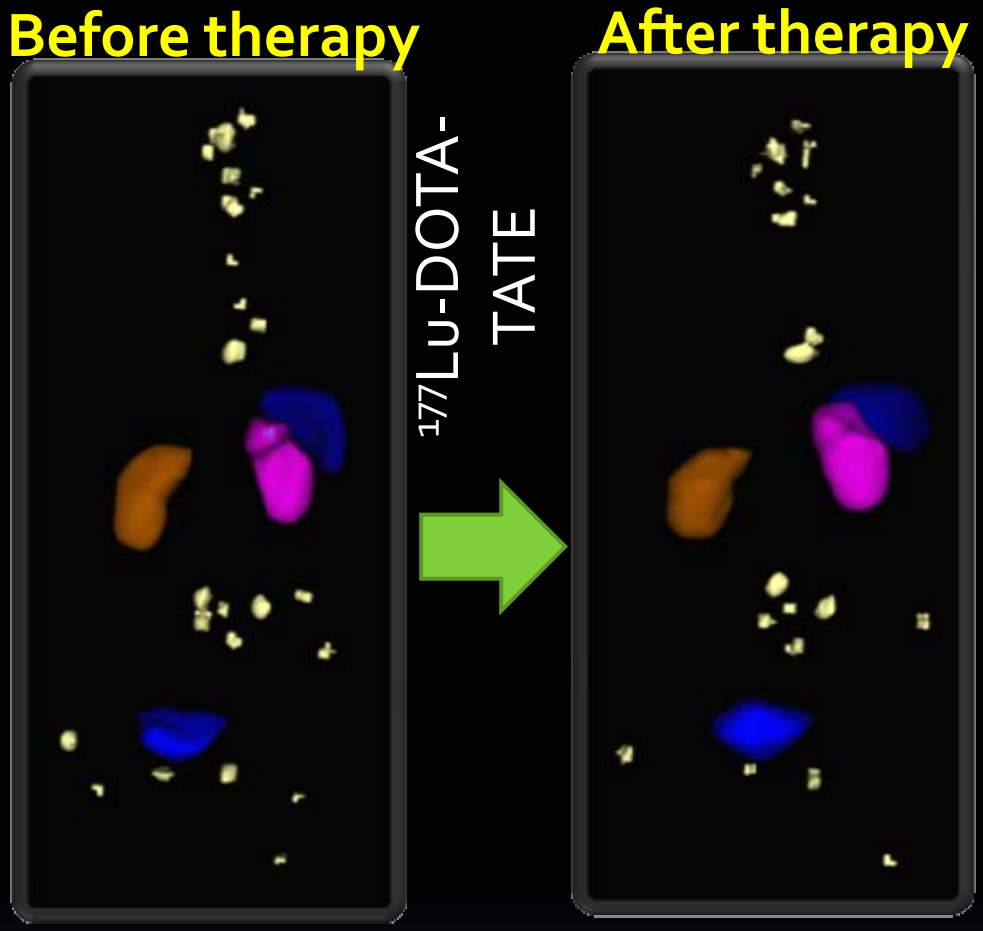
GRP-R vs VEGF-R expression in tumor vessels



Fast Quantification of Tumor Burden

BBQ MIT can measure tumor SUV_{max} SUV_{mean} tumor volume and the whole body molecular or metabolic tumor burden.

BBQ MIT can determine the lesions' borders based on a sudden change in activity values.



Extra-hepatic tumor burden	221	130
Intra-hepatic tumor burden	1723	1052
Whole body tumor burden	1944	1182

VANDERBILT UNIVERSITY
MEDICAL CENTER

68Ga-DOTATATE PET/CT for Neuroendocrine Cancer

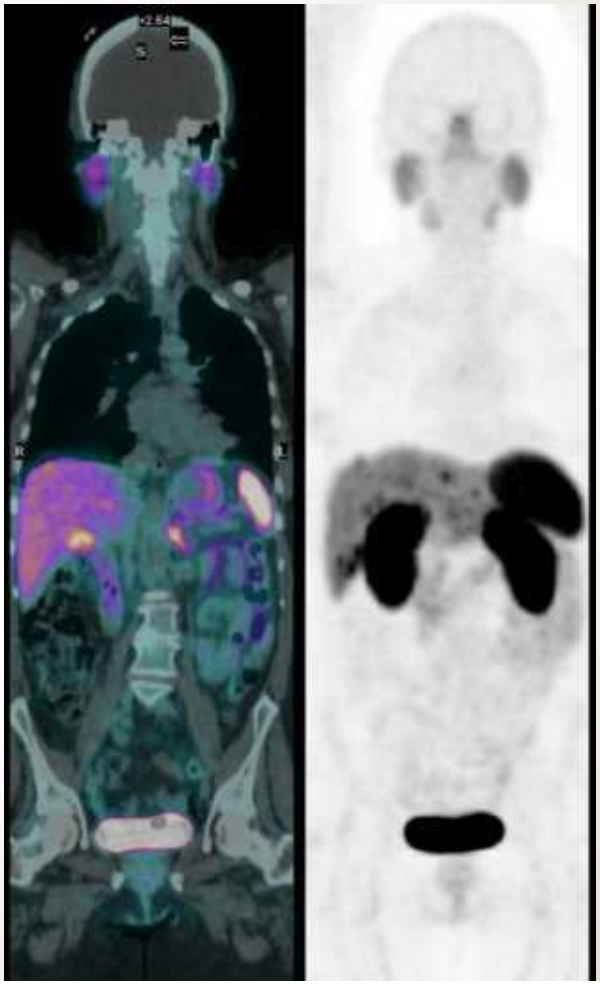
The American Experience

Eric H. Liu, M.D.
Neuroendocrine Center
Department of Surgery
Vanderbilt University Medical Center
Nashville, TN
www.vanderbiltneuroendocrine.com

VANDERBILT UNIVERSITY
MEDICAL CENTER

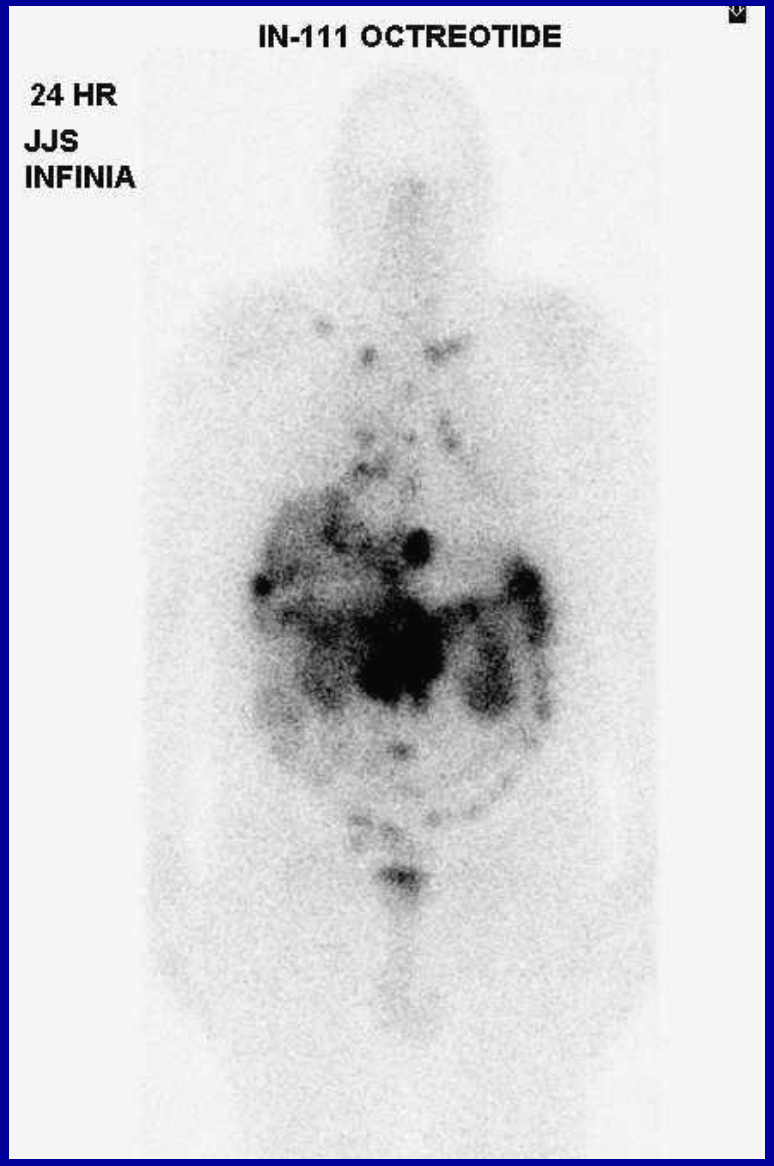
Clinical Experience

- 60 y/o woman, h/o NET, CUP with recurrence



Ga-68 DOTATOC Imaging at the University of Iowa

First Ga-68 DOTATOC Patient in US



In-111 Octreotide

Ga-68 DOTATOC

Techological Advances

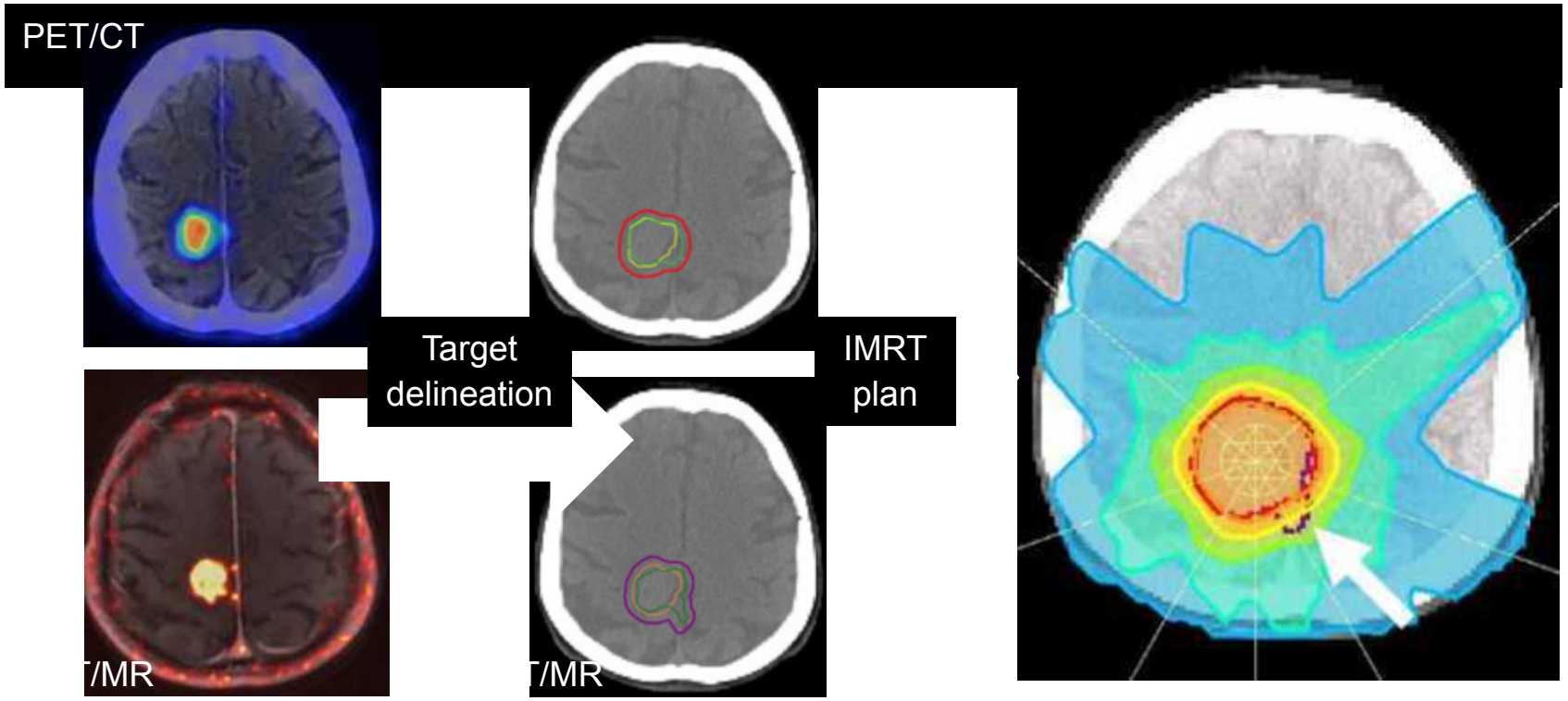
Thomas Beyer,
Tübingen, Germany

Case 1: [^{68}Ga]-DOTATOC-PET/MR

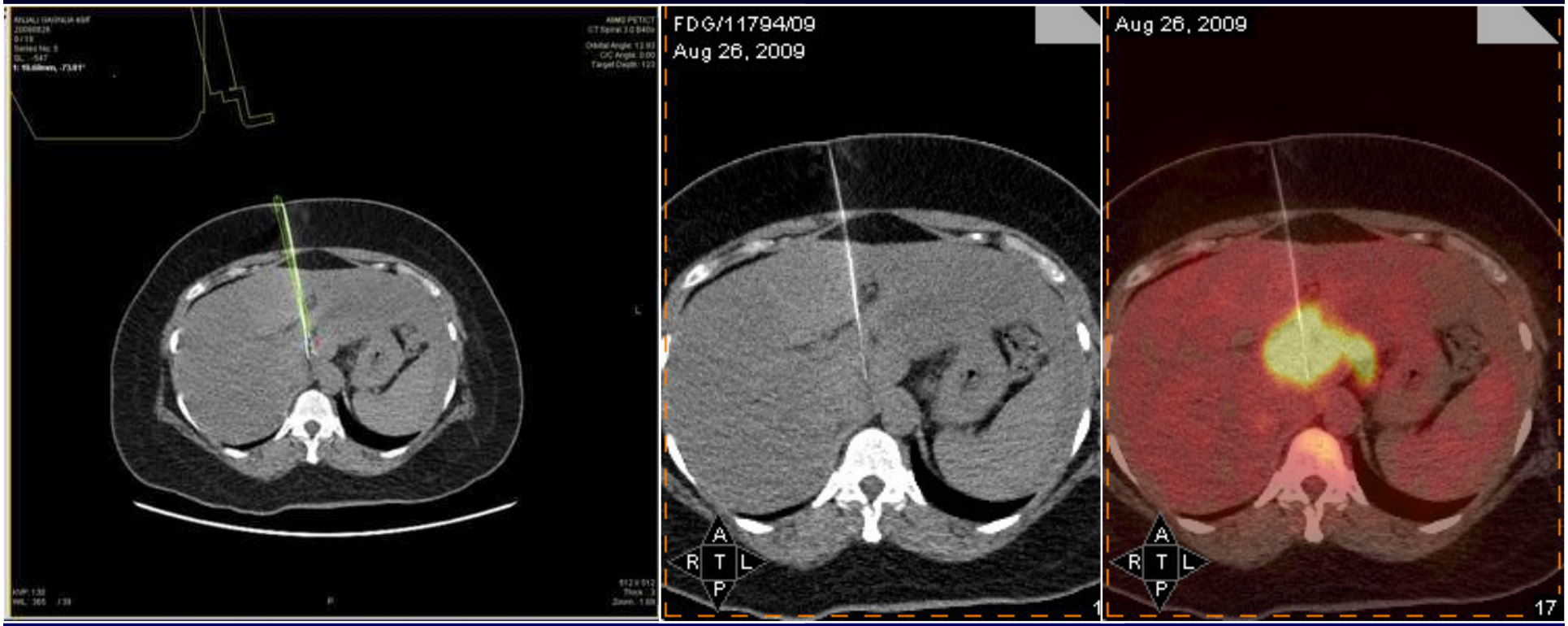
D Thorwarth et al.,
IJROBP (2011)

- 73 y/o female, recurrence of atypical Men. (WHO II)

  [^{68}Ga]DOTATOC-PET/CT (150 MBq, 2x4min @ 40min pi) and -PET/MR (120 min pi, BrainPET)
  Delineation of $PTV_{PET/CT}$ (MRI + PET/CT) and $PTV_{PET/MR}$ (PET/MR)
  IMRT plan (7x6MeV photons, 54 Gy/30 fx) for $PTV_{PET/CT}$, Cross-evaluation of IMRT plan for $PTV_{PET/MR}$



[^{68}Ga]-DOTATOC-PET/MR promising for RTP



PET-CT guided FNAC- Adenocarcinoma

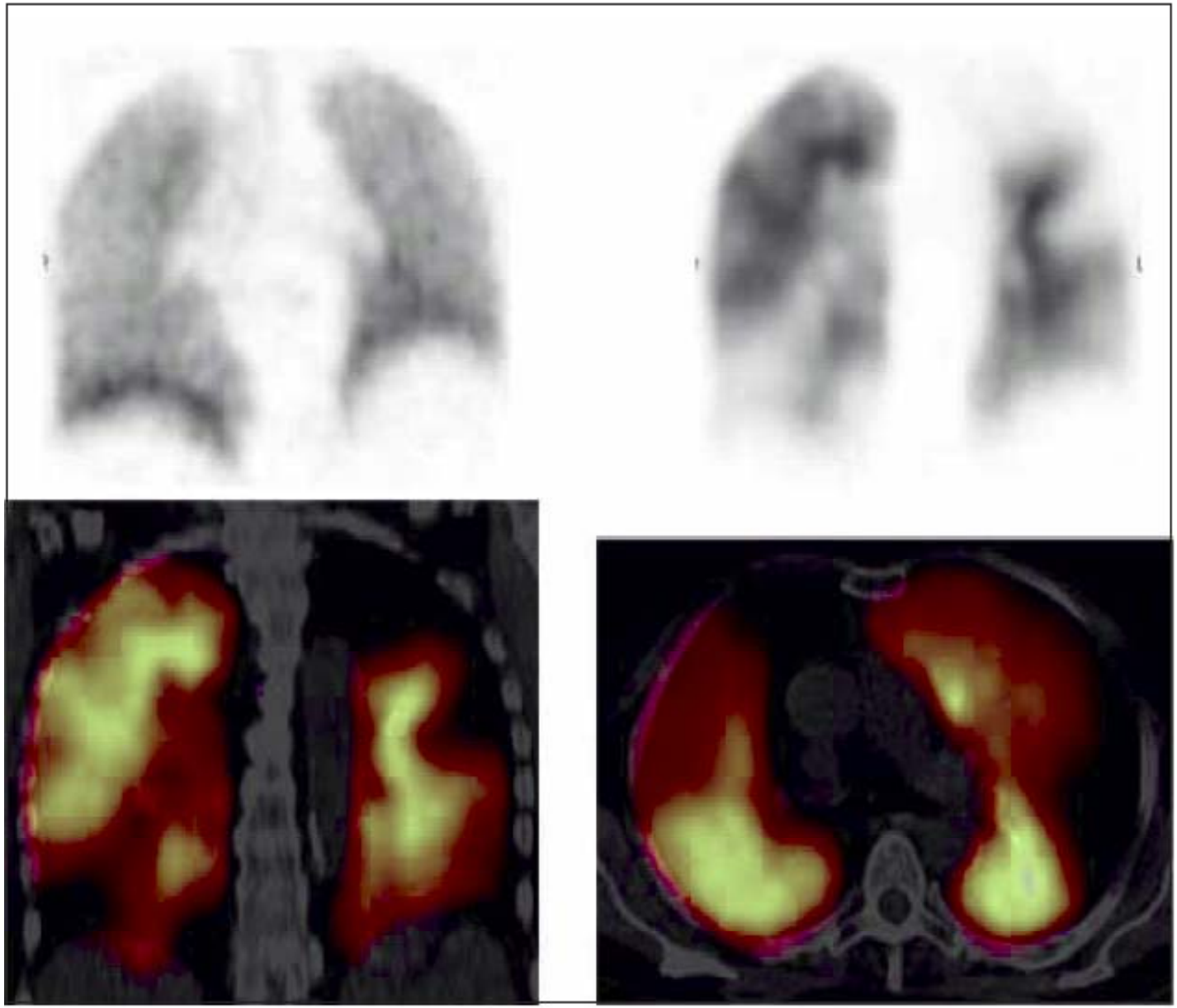
Rakesh Kumar, AIIMS

Jörg Kotzerke, Dresen, Germany

Galligas distribution in a conventional Technegas generator

at different working conditions

Pulmonary embolism



Coronal images of ventilation (top left), perfusion (top right) and PET/CT fused images (coronal, bottom left; transverse, bottom right) in a patient with multiple PE shows multiple wedge-shaped mismatched perfusion defects.

Zentralklinik Bad Berka

Hand held gamma probe for surgery of neuroendocrine tumors using Ga-68 somatostatin receptor PET/CT: Preliminary results

D. Kämmerer, V. Prasad, S. Senftleben, R.P. Baum, M. Hommann

Presented by Khatib Karl

Department of General and Visceral Surgery

Department of Nuclear Medicine / Center for PET

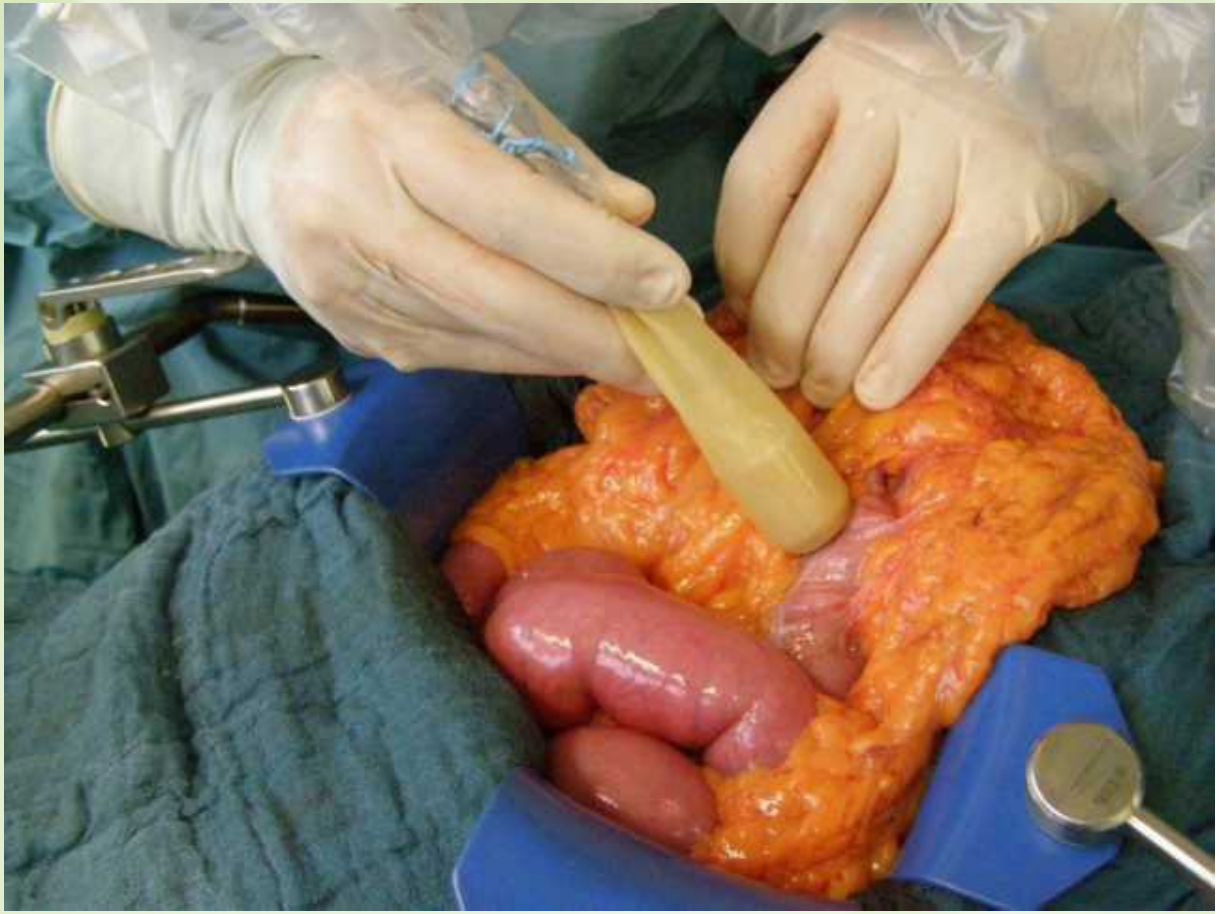
Zentralklinik Bad Berka, Germany





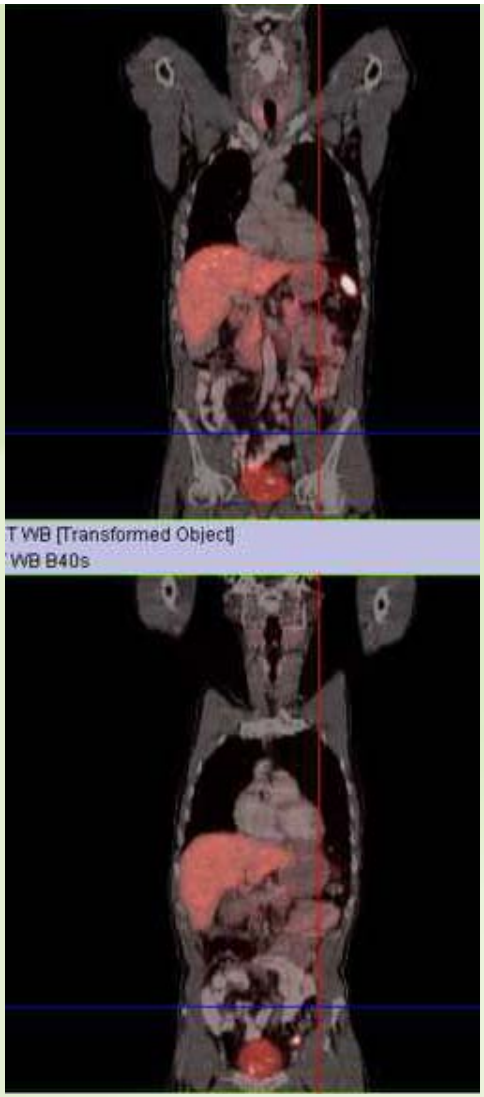

A semiconductor gamma probe Gamma Finder (Silicon Sensor GmbH, Berlin, Germany) was used

The count rate signal was displayed in numerical, graphical and acoustic form. The sensitivity of this gamma probe was found to be 1000 cps/MBq



Example – Iliacal LN metastases

Zentralklinik Bad Berka



Post OP

Pre OP

Zentralklinik Bad Berka

- Radioguided surgery (RGS) eases the detection of metastases smaller than 1 cm, notably lymph node metastases, maybe as well as in the detection of small and multiple primary tumors
- Intraoperative use of RGS helps in the differentiation between the tumorous and scarred tissues
- RGS has the potential to change the operative procedures (extension or limitation of surgery)
- RGS seems to have the potential to reach a higher rate of really R0-resections

New peptides, tracers, new clinical indications

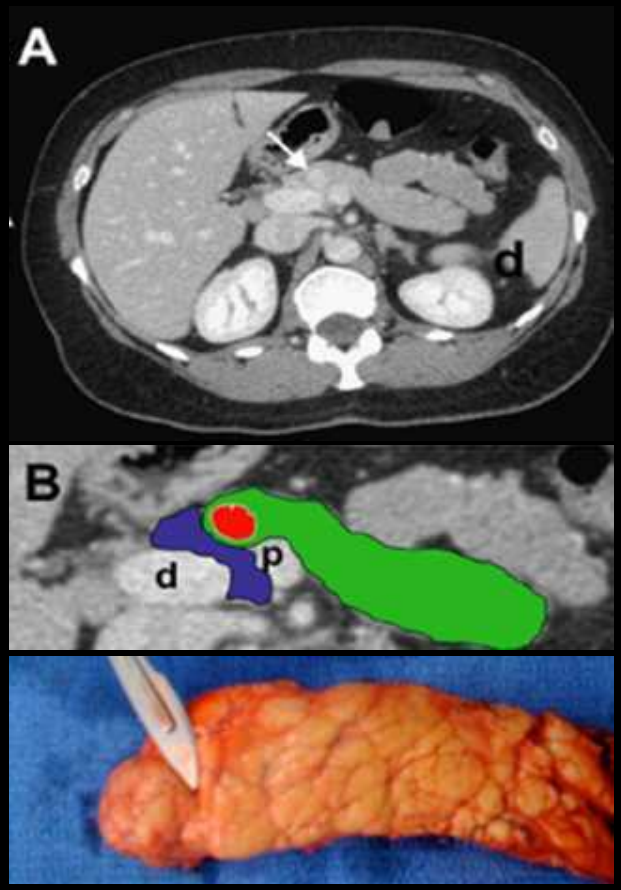
Glucagon-like Peptide-1 (GLP-1) Receptor PET Imaging using ^{68}Ga labelled GLP-1 Analogues

Damian Wild[1], Andreas Wicki[2], Rosalba Mansi[1], Martin Behe[1], Gerhard Christofori[2], Peter J. Ell[3], Helmut R. Mäcke[1]

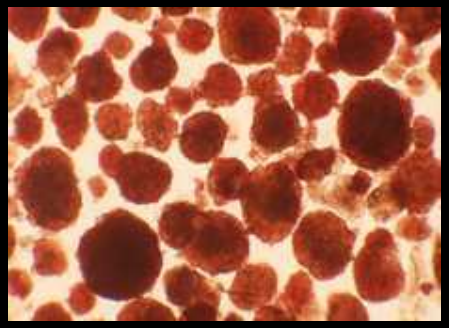
[1]Department of Nuclear Medicine, University Hospital Freiburg, Germany
[2] Institute of Biochemistry and Genetics, University of Basel, Switzerland
[3] Institute of Nuclear Medicine, University College London, United Kingdom

UNIVERSITÄTS KLINIKUM FREIBURG

48-year old female had at least 80% of the pancreas removed due to an insulinoma. Healthy islets were isolated from surgical specimen and were transplanted in the brachoradialis muscle



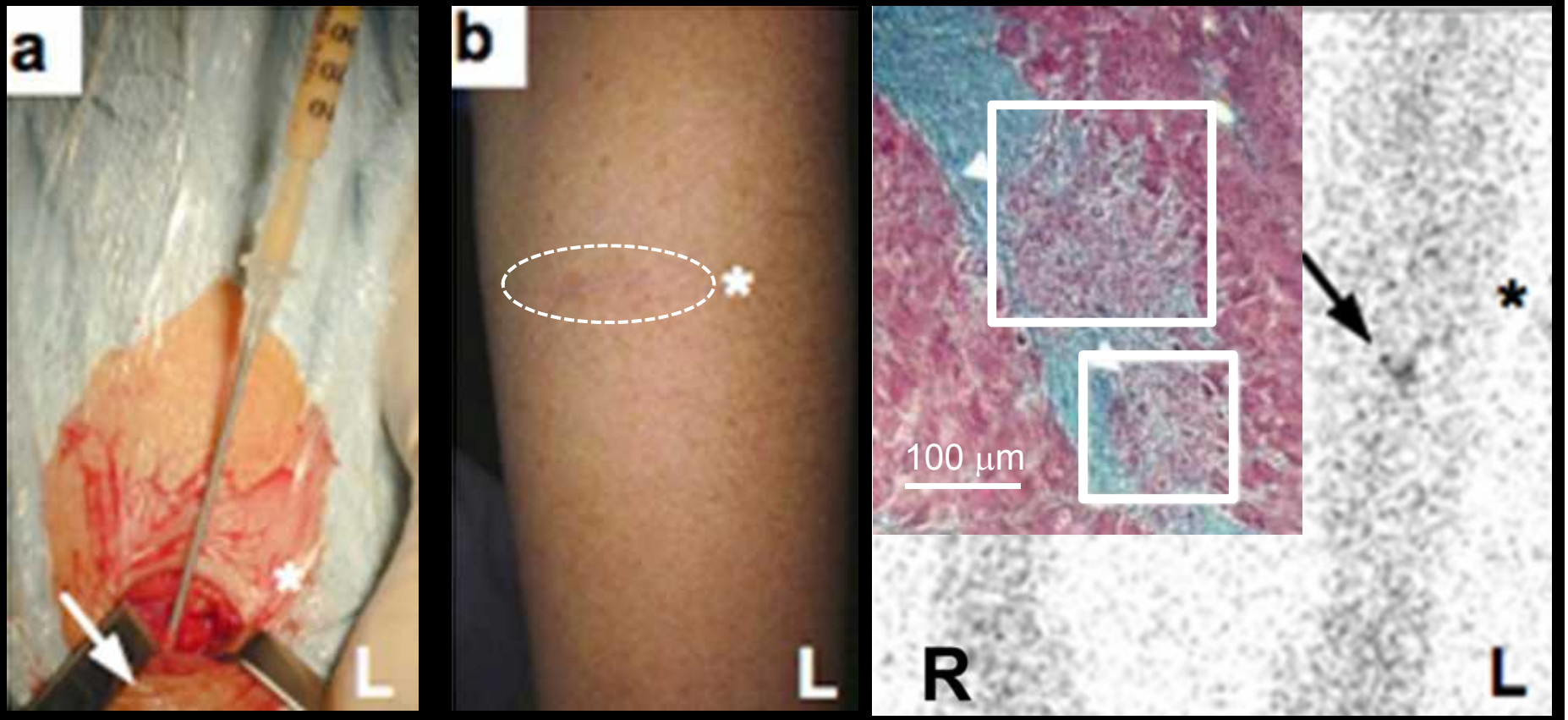
intramuscular
autoTx
of islets



Non invasive in vivo imaging of functional human beta cells with GLP-1 receptor scan

Injection site 12 months after transplantation

^{111}In-DTPA-exendin-4 planar scan 19 h p.i.



Pattou, Kerr-Conte and Wild N Engl J Med 2010

Performance of DOTATOC(68Ga) PET/CT for the detection of insulinomas in adults

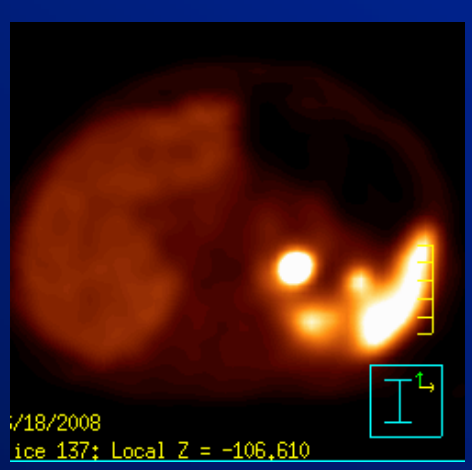
F. Montravers[1], V. Nataf[1], A. Prignon[1], J. Rose[1], S.Balogova[1], M. Calzada[2], G. Maurel[2],

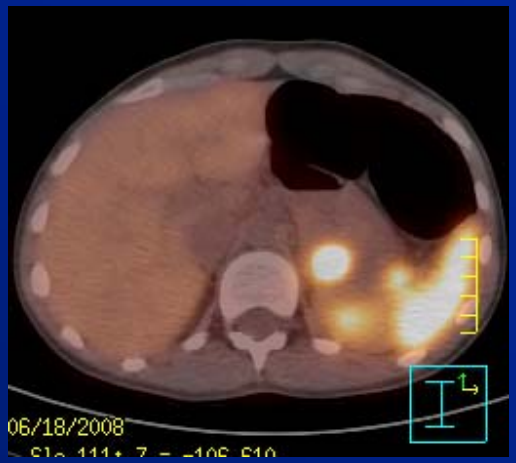
K. Kerrou[1], O. Pascal[1], V. Huchet[1], L. Michaud[1], J.Y. Devaux[2], J.N. Talbot[1]

Hopital Tenon[1], Hôpital Saint-Antoine[2], Paris, FRANCE

Hôpital TENON

DOTATOC PET/CT





Surgery
Insulinoma
+ glucagonoma

FDOPA PET/CT

SRS

CT

Conclusion 2

- DOTATOC PET/CT seems also superior to FDOPA PET/CT in adult insulinomas.

- In our experience, the performance of FDOPA PET/CT is poor to detect insulinomas in adults, in contrast with its very good results in congenital hyperinsulinism in newborns.

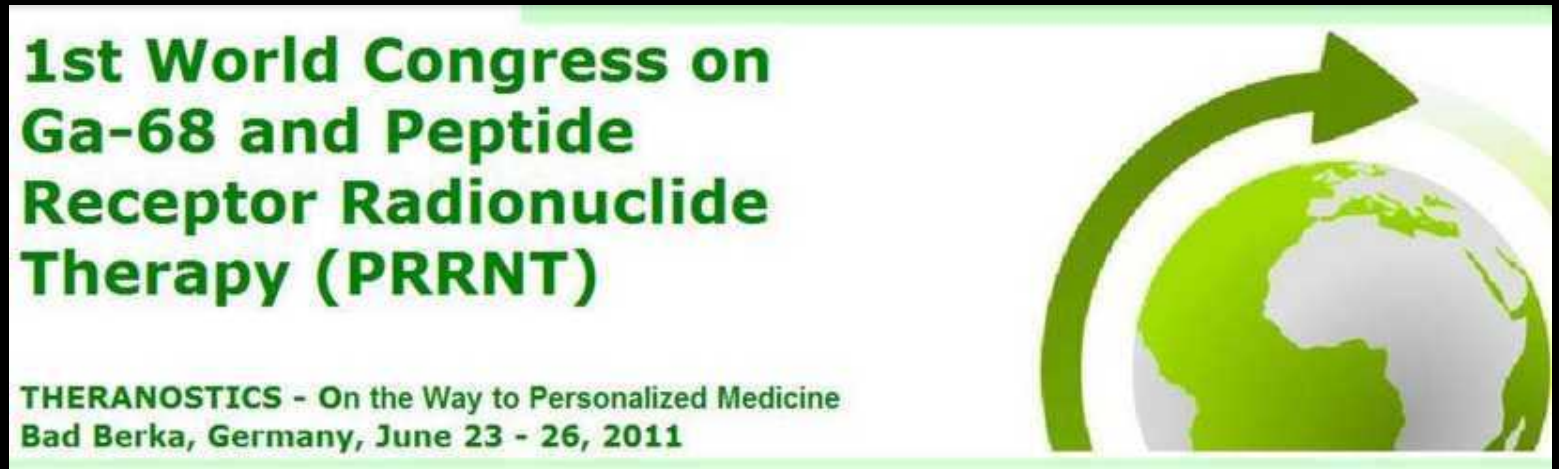
- These encouraging results of our pilot study with DOTATOC-(68Ga) need to be confirmed in a multicentre trial.

vp2

Role of Ga-68 DOTA-SMS-R PET/CT In The Detection Of Cardiac Metastases In Patients With Neuroendocrine Tumors

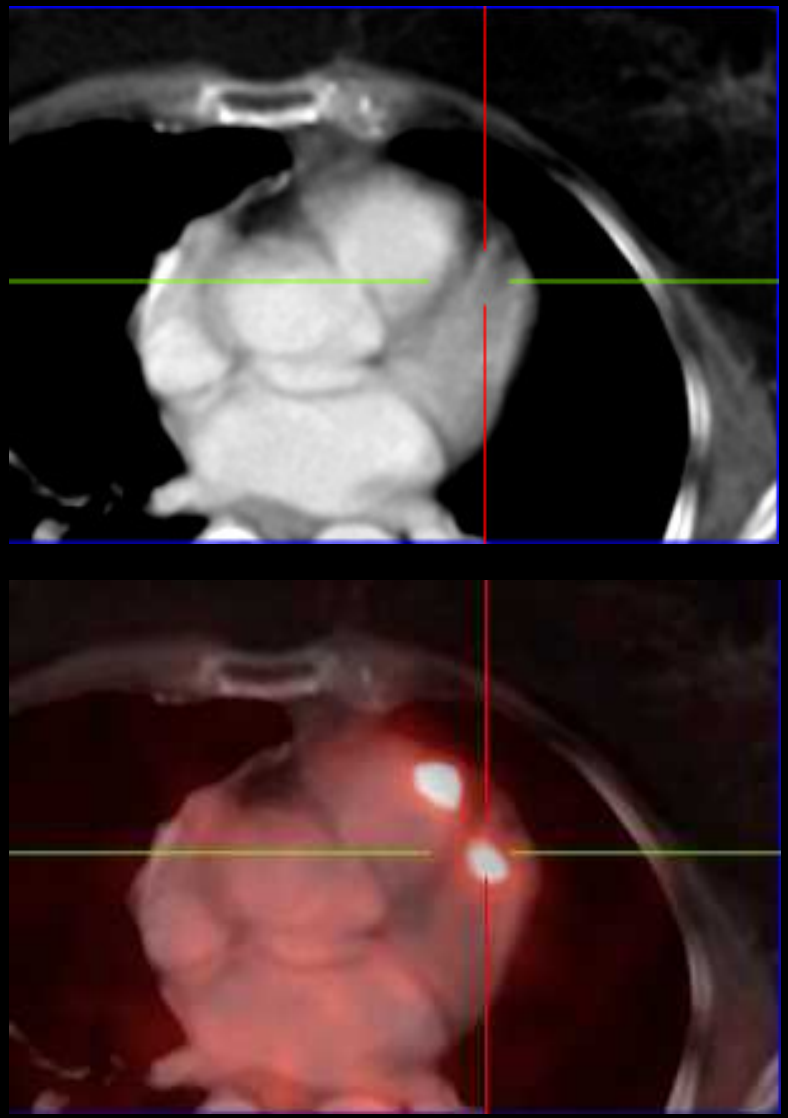
V. Prasad[1], A. Salavati[1], H. Kulkarni[1],M.A. Secknus[2] , B. Lauer [2], R.P. Baum[1]

[1]Department of Nuclear Medicine / PET Center, Zentralklinik Bad Berka, Germany
ENETS Centre of Excellence
[2]Department of Cardiology , Zentralklinik Bad Berka, Germany

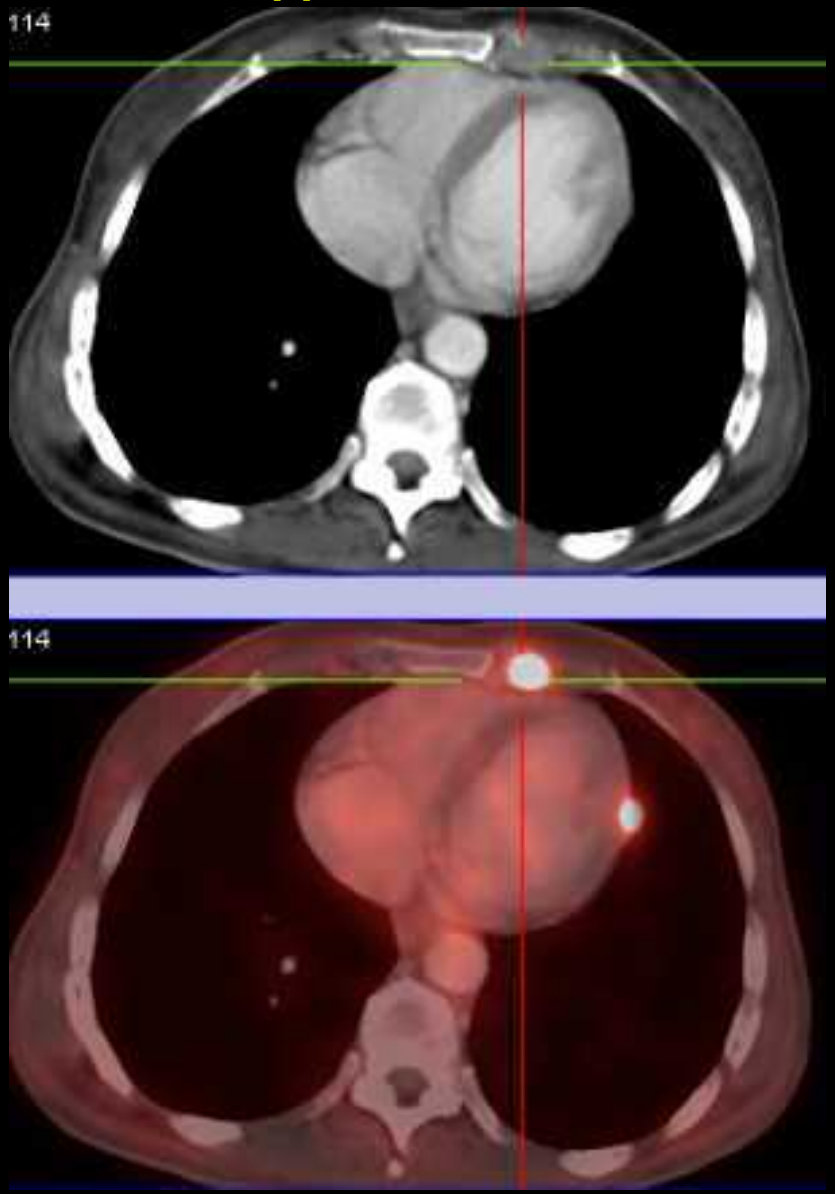


vp2 vikas; 10.10.2007

Pericardiac and myocardial mets



Pericardial mets well appreciated on CT



Results - continued

	SMS-R PET/CT	MRI	Echocardiography	CT
Sensitivity	92%	81%	57%	32%

MRI and SMS-R PET/CT were concordant in 91% of the cases, whereas echo-MRI and CT-MRI were concordant in only 63% of the cases.

In two cases, MRI was nonconclusive because of the presence of intractable cardiac arrhythmias. The size ranged from 17-45 mm for myocardial metatsases and 16-40 for pericardial metastases

Bulky abdominal lymph node metastases were present in 15 patients
4 cases had also mediastinal metastases.

PRRNT – novel insights and approaches

Erasmus MC
University Medical Center Rotterdam

Lessons from/highlights of preclinical studies and future directions for PRRT

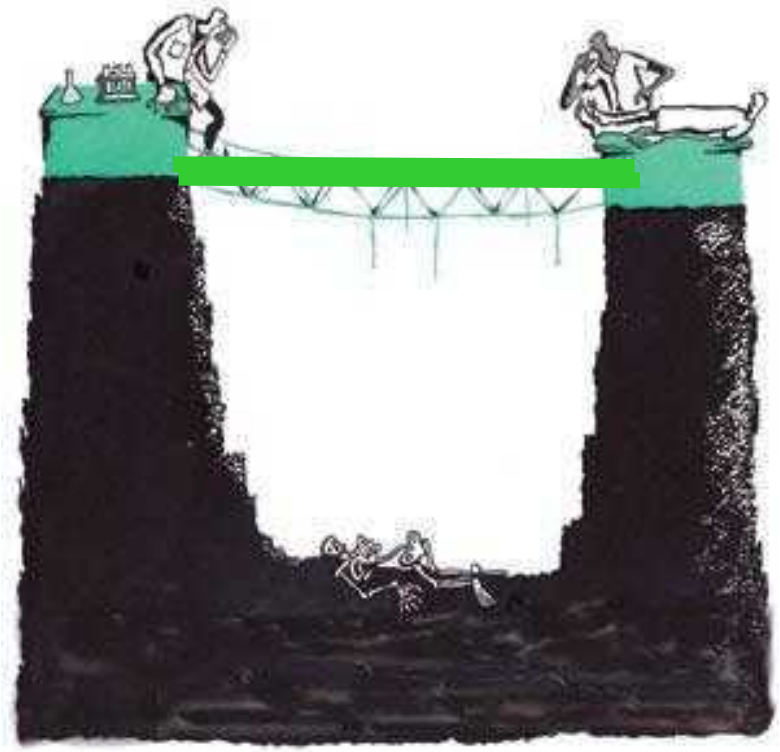
Marion de Jong
Erasmus MC Rotterdam
The Netherlands

Another point about Translational Research: crossing the valley of death

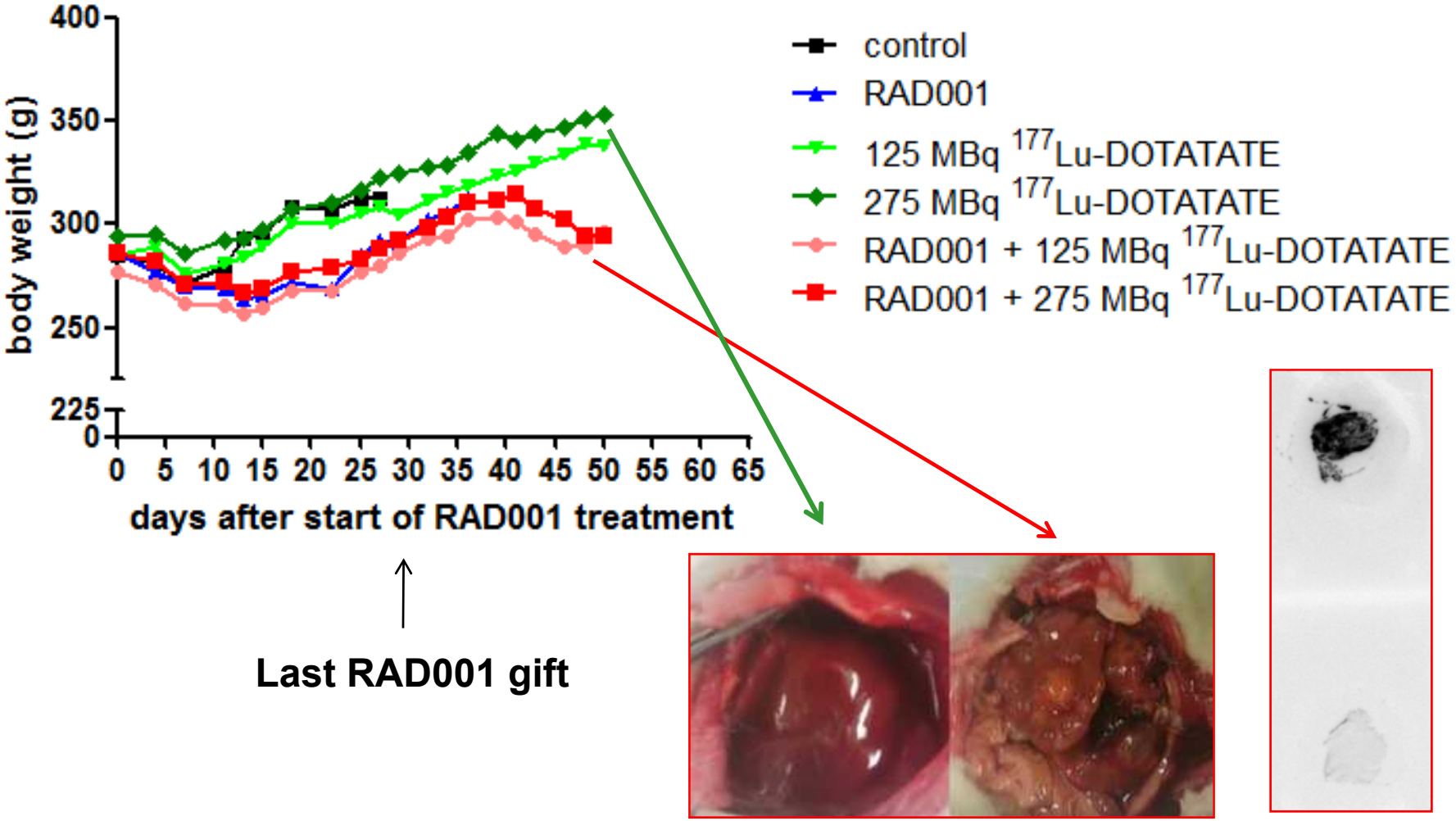
- *Nature* **453**, 840-842, 2008

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

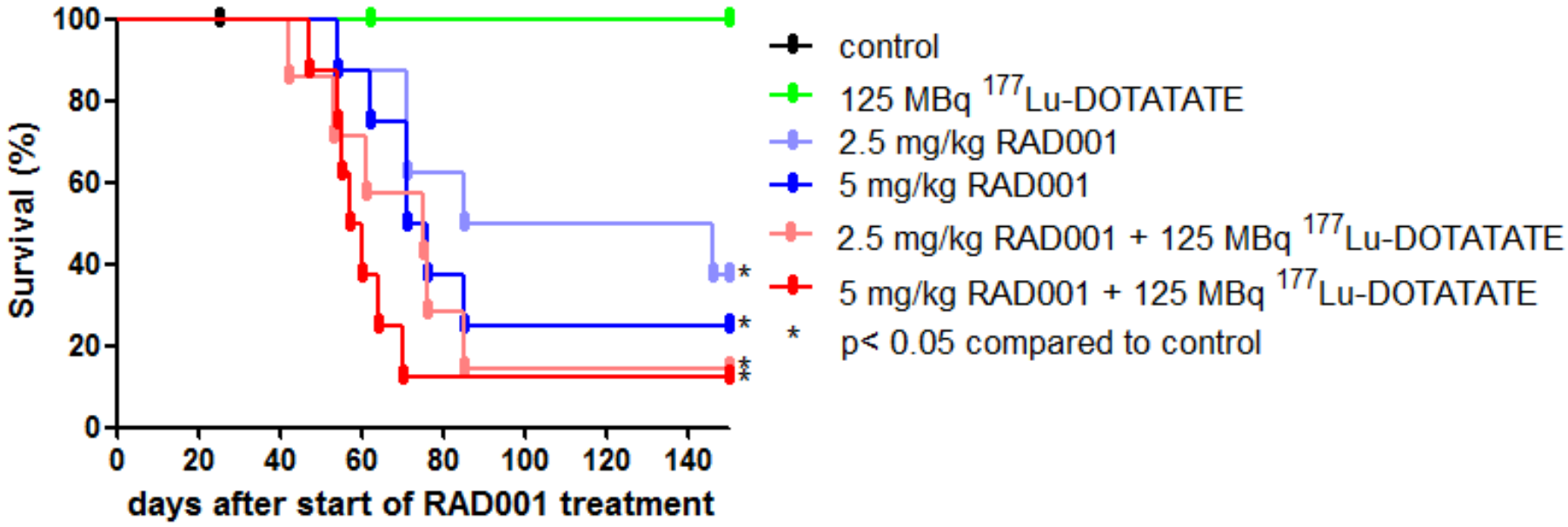
- Meetings like this most important! Chemist, translational scientists and clinicians in the same room to provide a solid bridge between the disciplines.



Body weight


400
350
300
250
225
0
body weight (g)
0 5 10 15 20 25 30 35 40 45 50 55 60 65
days after start of RAD001 treatment
control
RAD001
125 MBq 177Lu-DOTATATE
275 MBq 177Lu-DOTATATE
RAD001 + 125 MBq 177Lu-DOTATATE
RAD001 + 275 MBq 177Lu-DOTATATE
Last RAD001 gift

Results, survival (surgery)!
Death due to metastasis



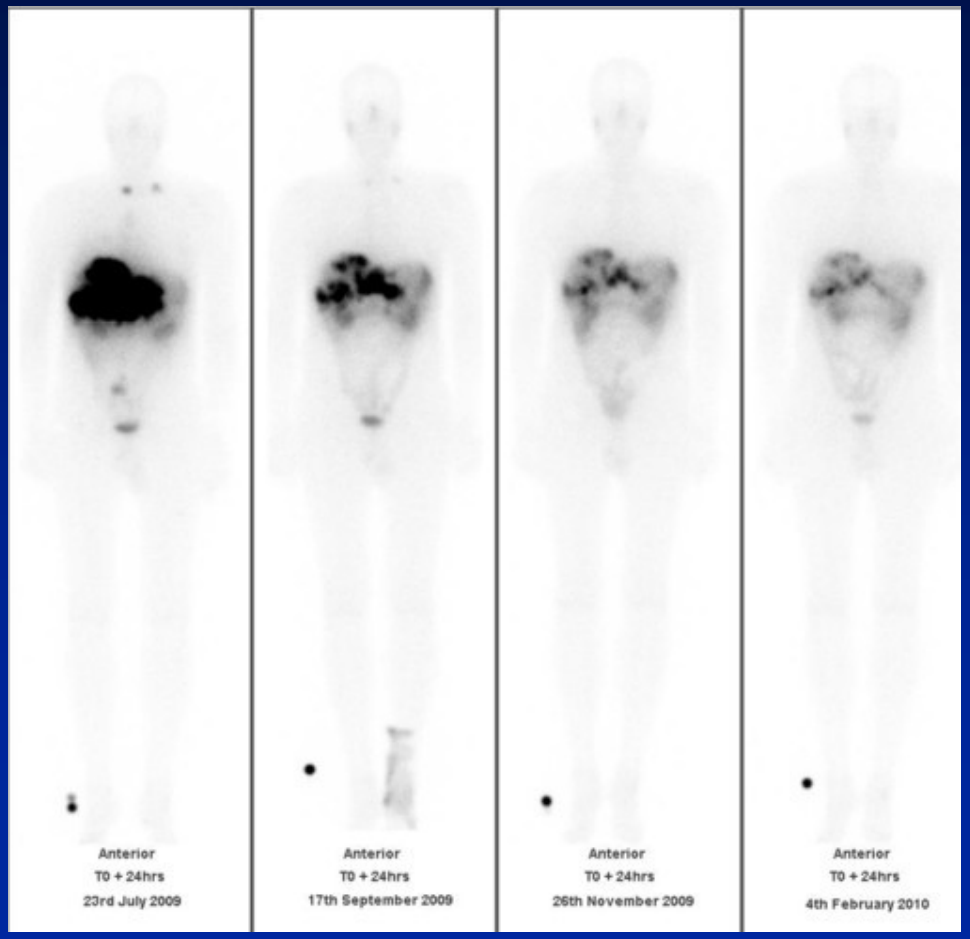
After RAD001 treatment:
more invasive and metastatic behaviour of this tumour:
immunosuppression?, VEGF rebound?, vessel damage?

NET RADIOPEPTIDE THERAPY
COMBINATION ^{177}Lu-OCTREOTATE
CHEMO / BIOLOGICAL THERAPY
PHASE I/II CLINICAL STUDIES

	mg/m^2	
1. CAPECITABINE	1650	14 days
2. CAPECITABINE	1500	14 days
TEMOZOLOMIDE	100, 150, 200	5 days
3. EVEROLIMUS	5, 7.5, 10 mg/d	6 mths

J. Harvey Turner, Fremantle, Australia

NET RADIOPEPTIDE THERAPY
^{177}Lu-OCTREOTATE - CAPECITABINE TEMOZOLOMIDE



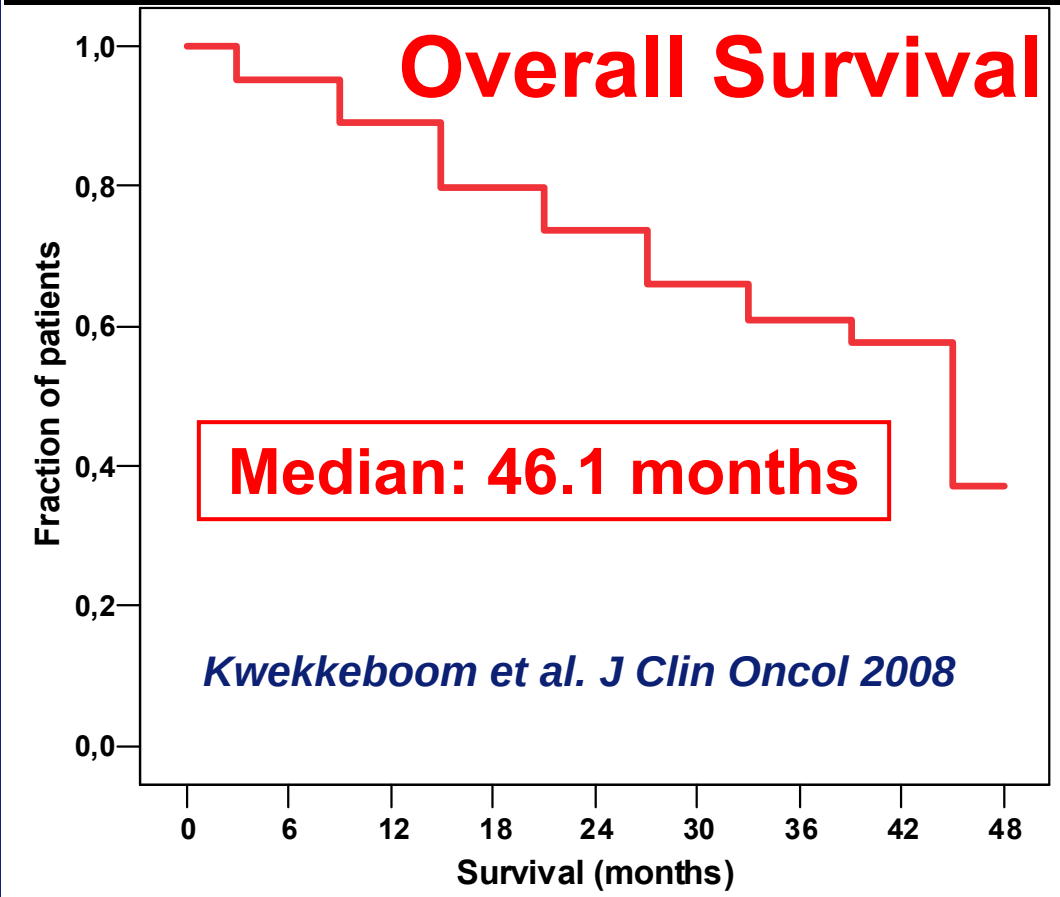
NET RADIOPEPTIDE THERAPY
PANCREATIC v CARCINOID
PARTIAL RESPONSE RATE

^{177}Lu-OCT + CAP	+ CAP & TEM
44 v 20%	60 v 7%	87 v 25%

Kwekkeboom DK, J Clin Oncol 2008
Claringbold PG, Eur J Nucl Med Mol Imaging 2011
Claringbold PG, ESMO 2011

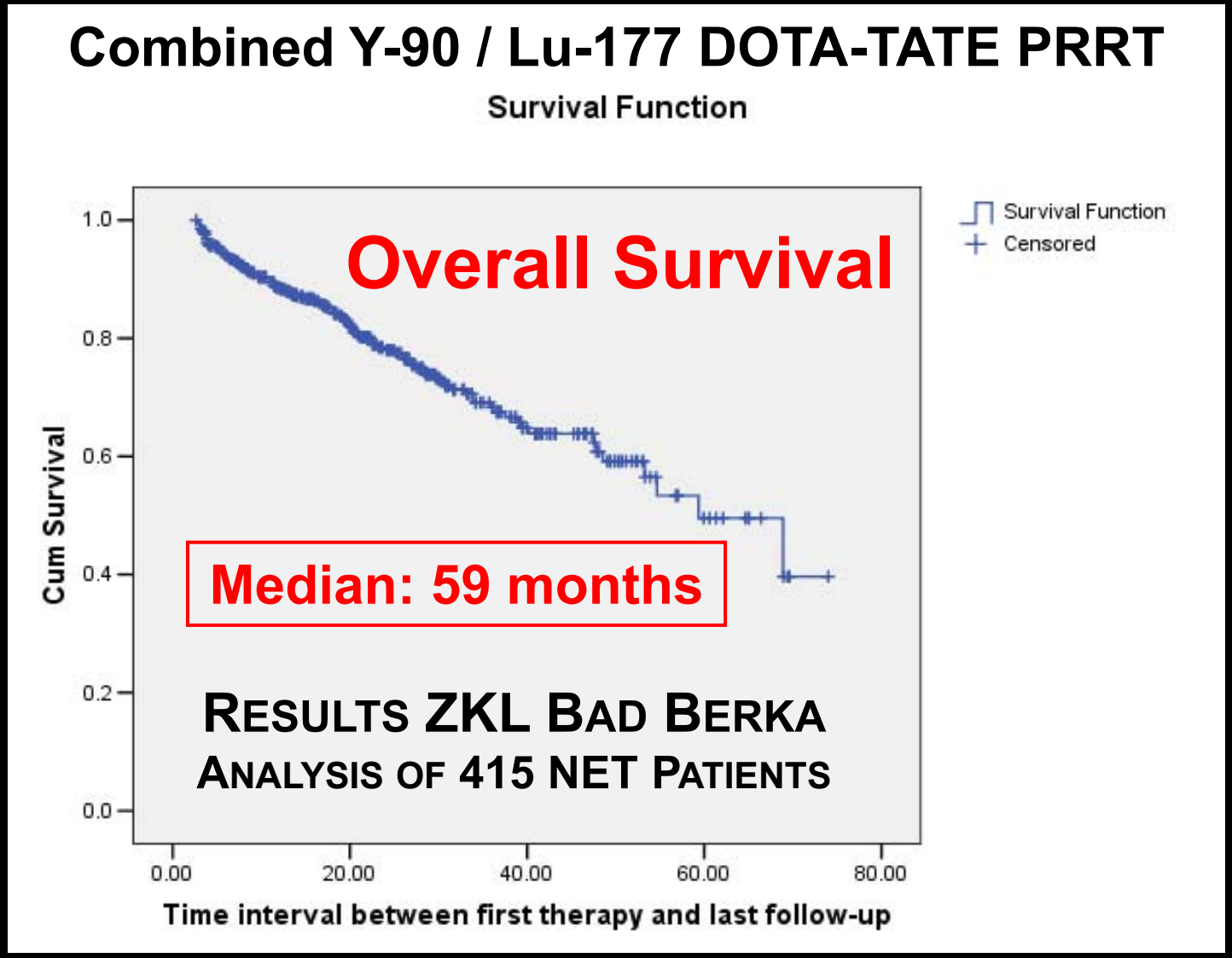
[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy
310 GEP Tumor Patients / Survival

Median OS from diagnosis was 128 months. Compared with historical controls, there was a survival benefit of 40 to 72 months.



Erasmus MC

Median overall survivial from start of DUO-PRRT: 59 months (415 NET patients)



[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy Conclusions

- PRRT is a fascinating new tool
- High tumor response rate
- Limited side-effects
- Good quality of life
- Long progression free period
- Compared to historical controls:

  survival benefit 3.5-4 years
- Registration trial expected 2011

Erasmus MC

Dik Kwekkeboom, Rotterdam, Holland

Radiolabelled [DOTA^0,Tyr^3]Octreotate Therapy: Registration

- FIRST step: approval by FDA and EMEA !!
- Prospective randomised trial planned (AAA / Biosynthema)

^{177}Lu-Octreotate 4*200 mCi Sandostatin LAR 30 mg	High Dose Sandostatin LAR (40 mg/4 wks)

- Midgut carcinoid patients, progressive under Sandostatin LAR
- Primary endpoint: PFS

Erasmus MC

Dik Kwekkeboom, Rotterdam, Holland

1st World Cogress on ^{68} Ga and PRRNT

^{90}Y-DOTATOC-therapy
The Swiss Experience

Jan Müller-Brand

jmuellerbrand@gmail.com

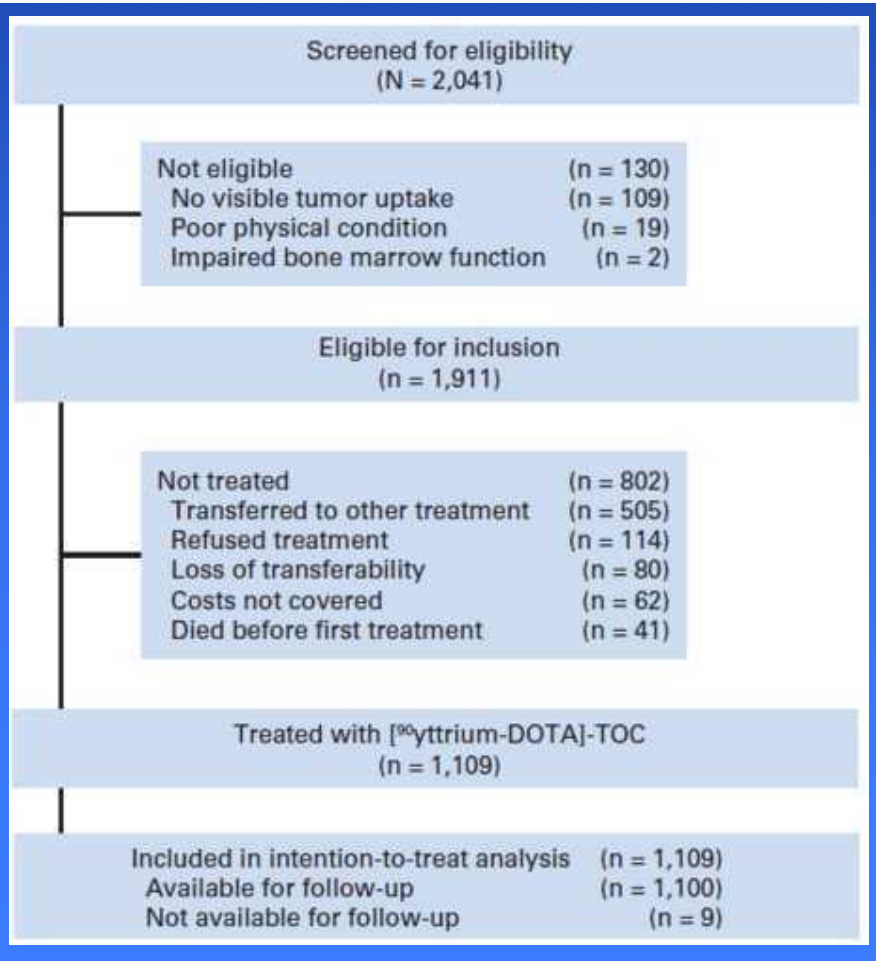
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

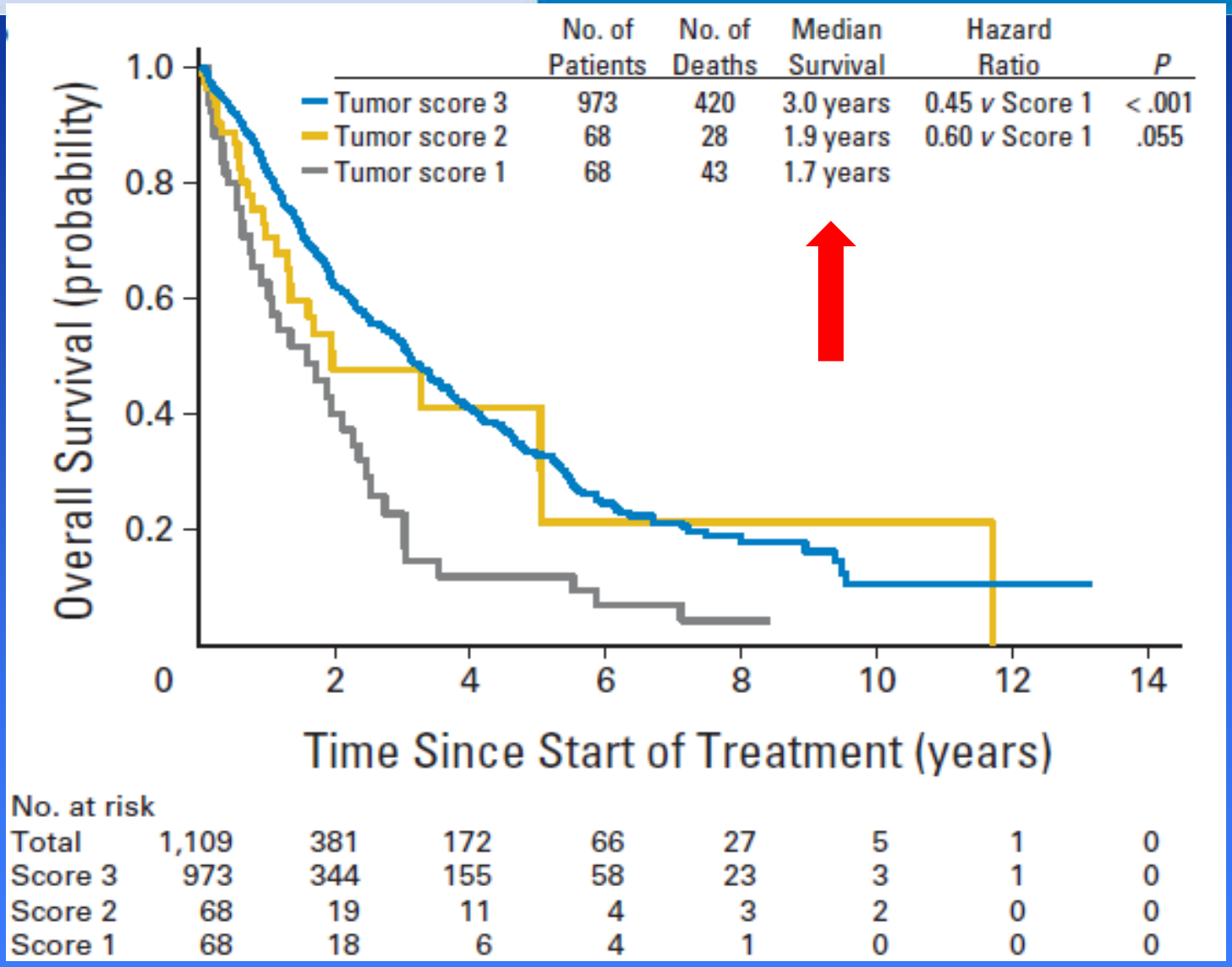
Submitted November 15, 2010; accepted March 14, 2011; published online ahead of print at www.jco.org on May 9, 2011.

Response, Survival, and Long-Term Toxicity After Therapy With the Radiolabeled Somatostatin Analogue [^{90}Y-DOTA]-TOC in Metastasized Neuroendocrine Cancers

Anna Imhof, Philippe Brunner, Nicolas Marincek, Matthias Briel, Christian Schindler, Helmut Rasch, Helmut R. Mäcke, Christoph Rochlitz, Jan Müller-Brand, and Martin A. Walter



JOURNAL OF CLINICAL ONCOLOGY



→ **Tracer uptake predicts survival after [^{90}Y-DOTA]-TOC**

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adverse events

Hematological toxicity 3 or 4: **12,8 %**
(transient)

Renal toxicity

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

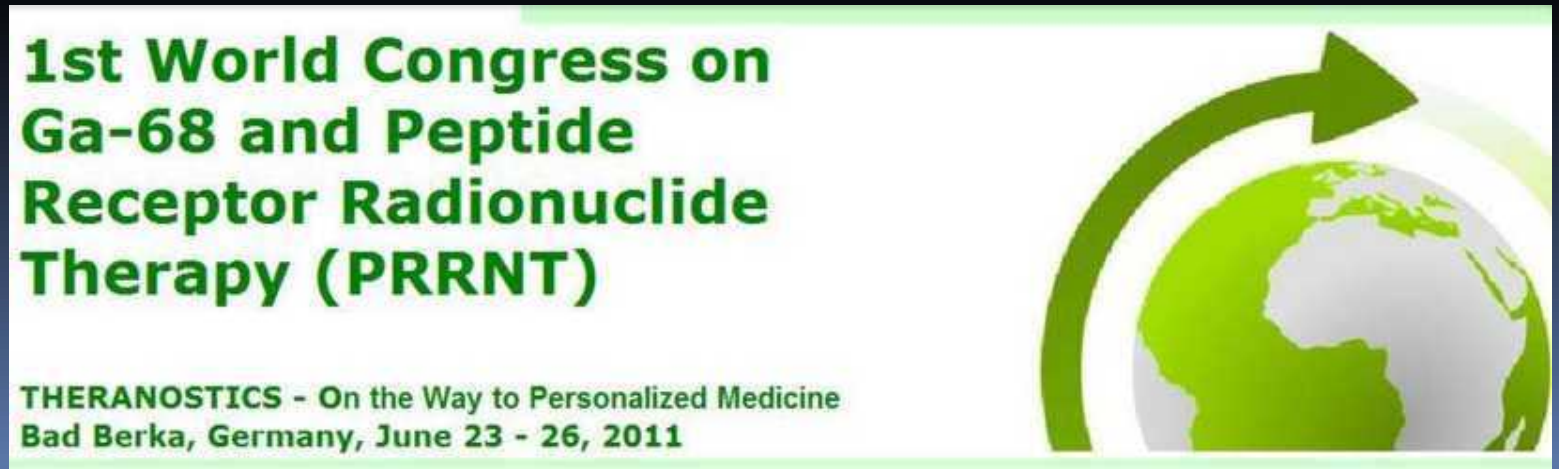
Renal Protection And Toxicity Related To Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumor

V. Prasad, R. P. Baum

Dept. of Nuclear Medicine / Center for PET–CT

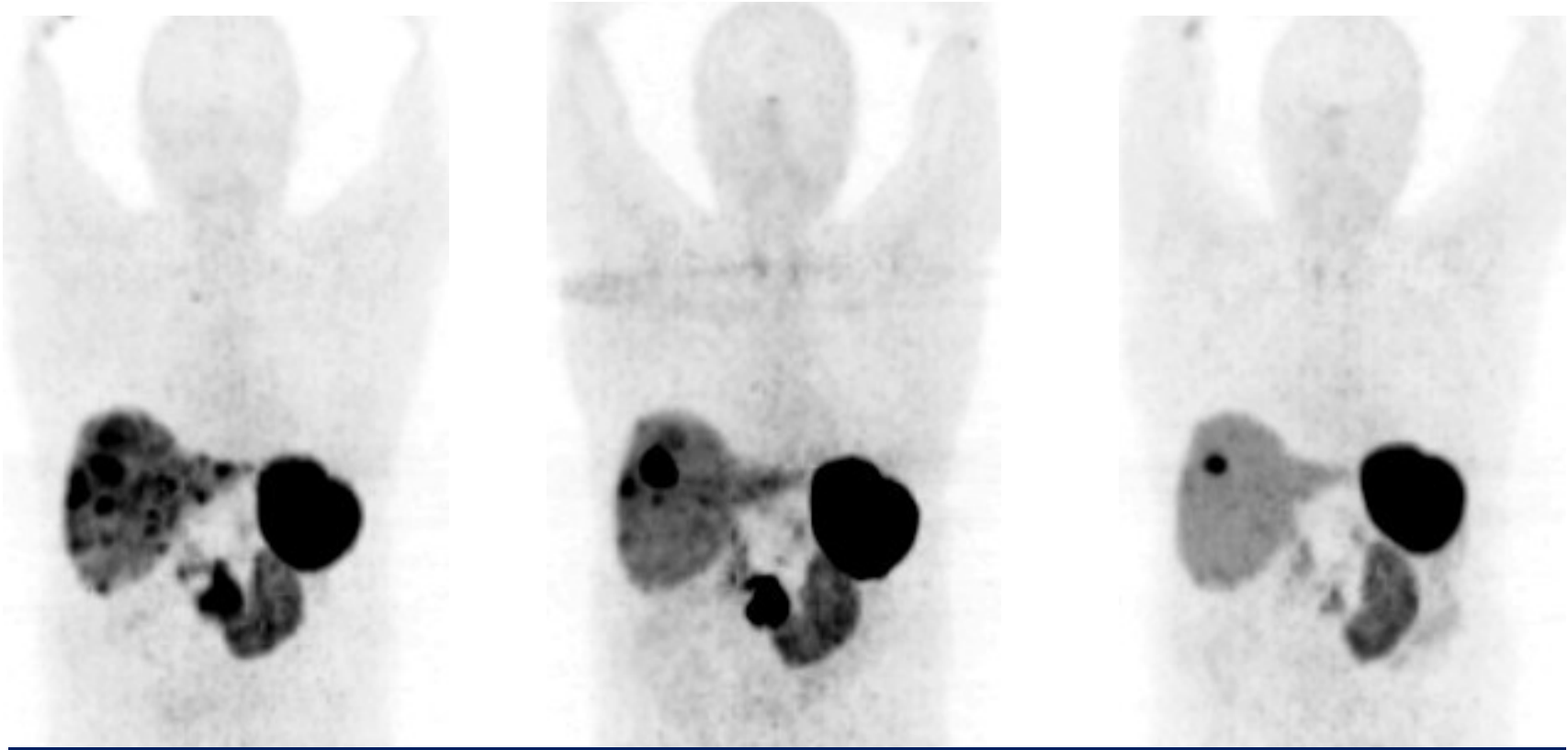
ENETS Centre of Excellence

Zentralklinik Bad Berka, Germany



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

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 %)*

Results- Long Term Follow-up Of More Than 5 Years

- None of the patients had grade 3 or higher toxicity.
- 9/32 patients (28%) showed grade 1 toxicity.
- 5/32 (16%) patients showed grade 2 toxicity.
- Seven patients showed a fall in renal function of more than 20%.
- One patient with a TER decrease of 51% had recurrent urinary tract infection.
- Arterial hypertension, long standing diabetes mellitus, carcinoid heart disease, tumor-induced hypercalcemia, cachexia and hepatomegaly were found to be co-existing risk factors.

PROGRAMME

1st World Congress on Gallium-68 and
Peptide Receptor Radio Nuclide Therapy (PRRNT)

THERANOSTICS – on the Way to Personalized Medicine

June 23 – 26, 2011

PRRNT: the Italian experience

Lisa Bodei, MD, PhD
Division of Nuclear Medicine
European Institute of Oncology, Milano
Italy

IEO
Istituto Europeo di Oncologia

PRRNT in Italy

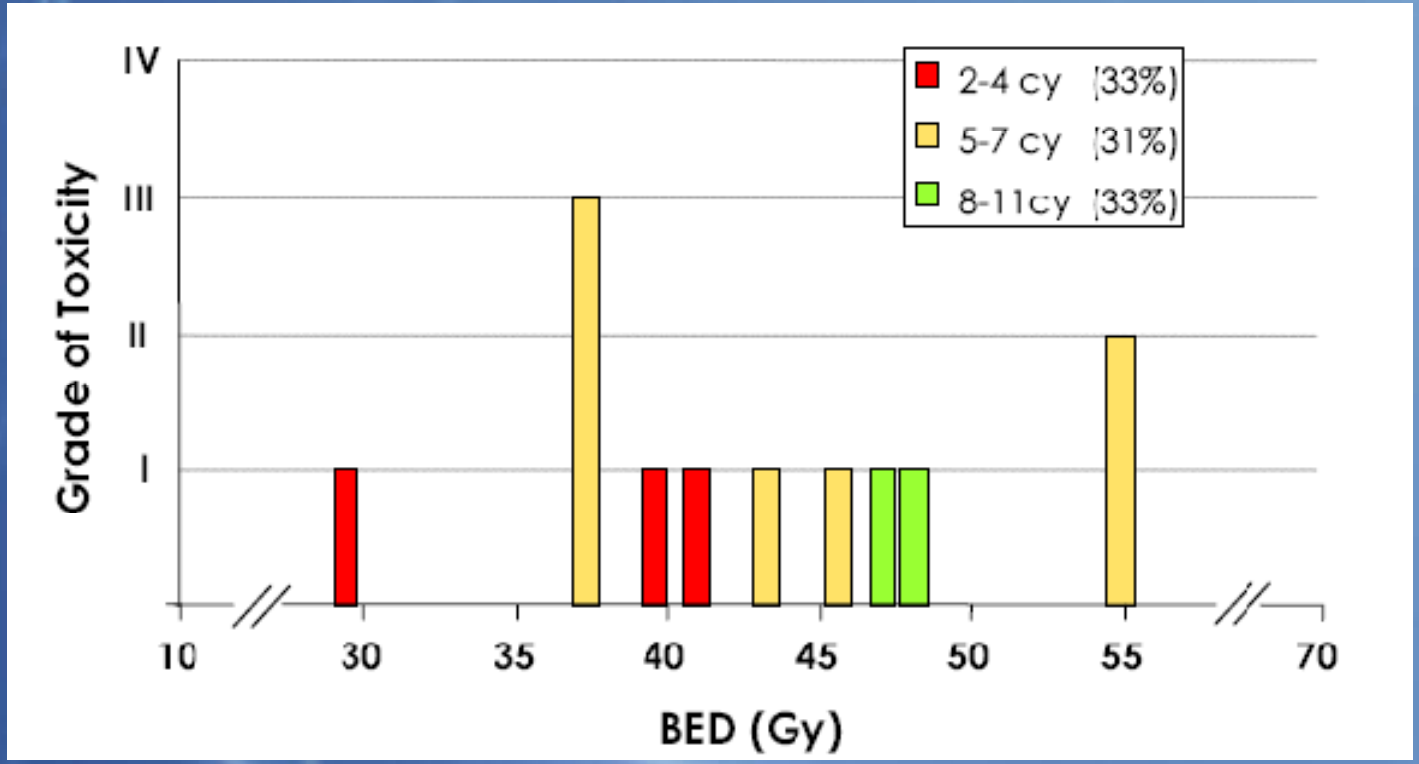
IEO Milano: since 1997

Others: since 2002-2008

PRRNT at IEO -Milano

- Presently we perform about 10 treatments/week
- We perform about 500 treatments/year

Renal toxicity: the role of fractionation

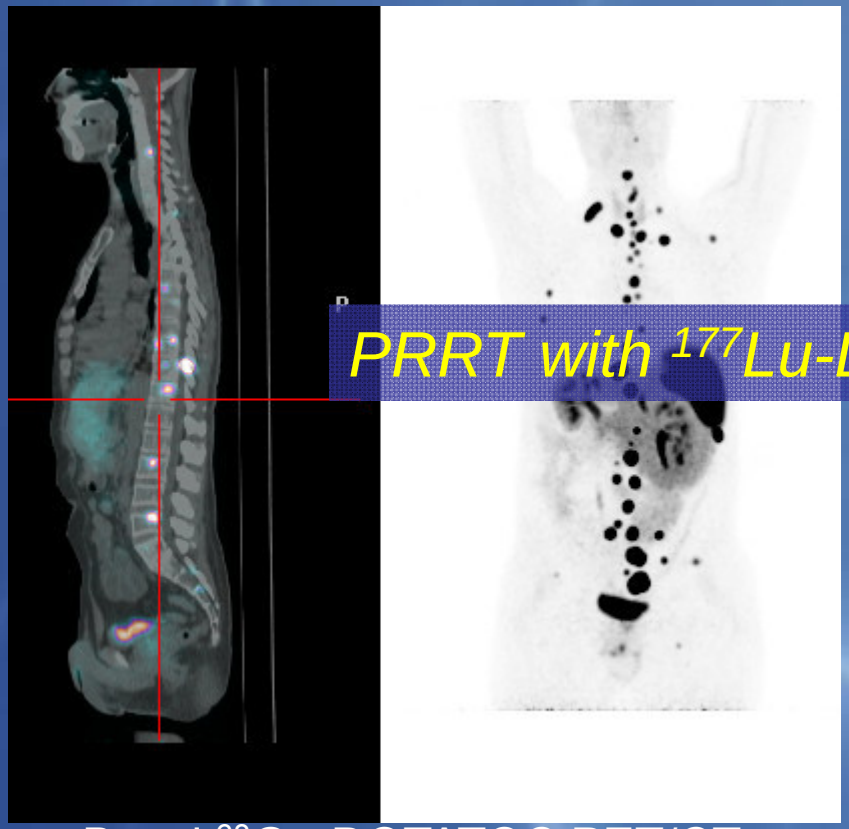


Bodei L. et al. Eur J Nucl Med Mol Imaging 2008
Cremonesi M. et al Q J Nucl Med Mol Imaging 2011

Bone marrow mets from a pancreatic NET G2

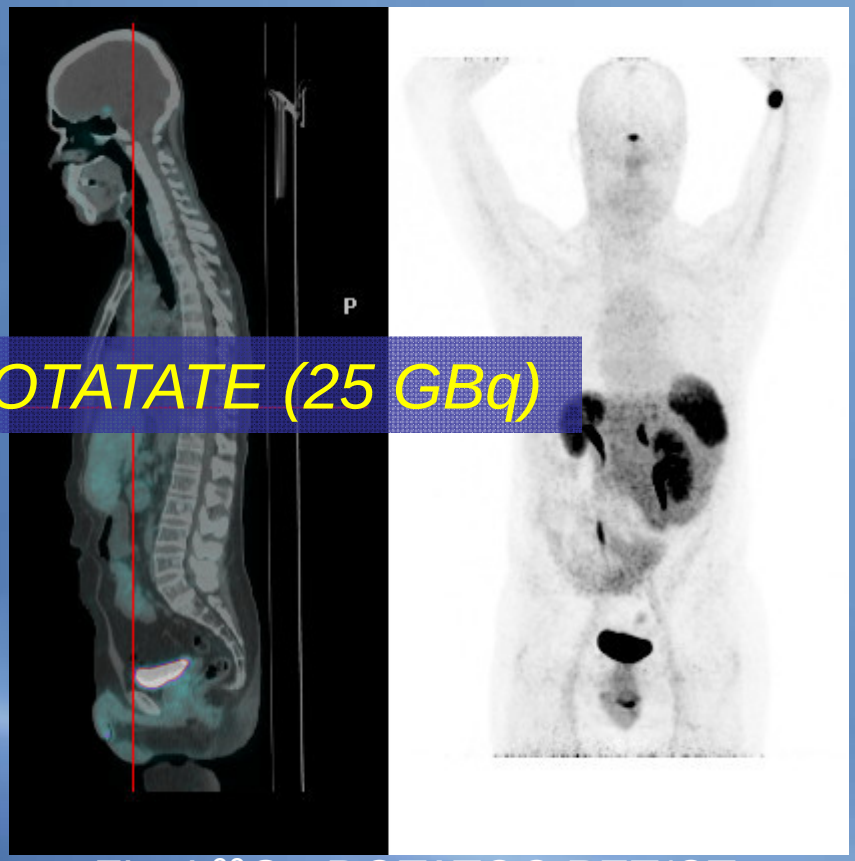
Ki-67 10%

Resection of a 16-cm liver met involving right lobe

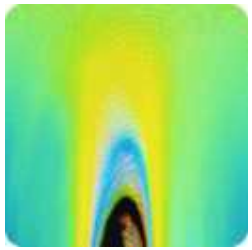


Basal ^{68}Ga-DOTATOC PET/CT

PRRT with ^{177}Lu-DOTATATE (25 GBq)



Final ^{68}Ga-DOTATOC PET/CT



TILAK — Tiroler Landeskrankenanstalten GmbH
Landeskrankenhaus Innsbruck – Universitätskliniken
Medizinische Universität Innsbruck
Universitätsklinik für Nuklearmedizin
Direktor: Univ.-Prof. Dr. Irene J. Virgolini

Peptide Receptor Radionuclide Therapy at Innsbruck (Results 4/2005 - 12/2010)

1st World Congress on Ga-68 and PRRNT
Zentraklinik Bad Berka
Germany

tilak
Unternehmen Gesundheit

MEDIZINISCHE UNIVERSITÄT
INNSBRUCK

What can we learn from Innsbruck PRRT?

- Effective treatment option for 75% of patients (CR, PR, SD)
- Long progression-free survival
- Low rate of side effects (renal, bone marrow)
- RESPONSE PREDICTORS:
  - Extend of tumour disease (liver, bone involvement)
  - Functional Imaging: ^{68}Ga-SSTR +/- ^{18}F-FDG-PET
  - KARNOFSKY SCORE
- Improved Quality-of-Life in 2/3 of patients

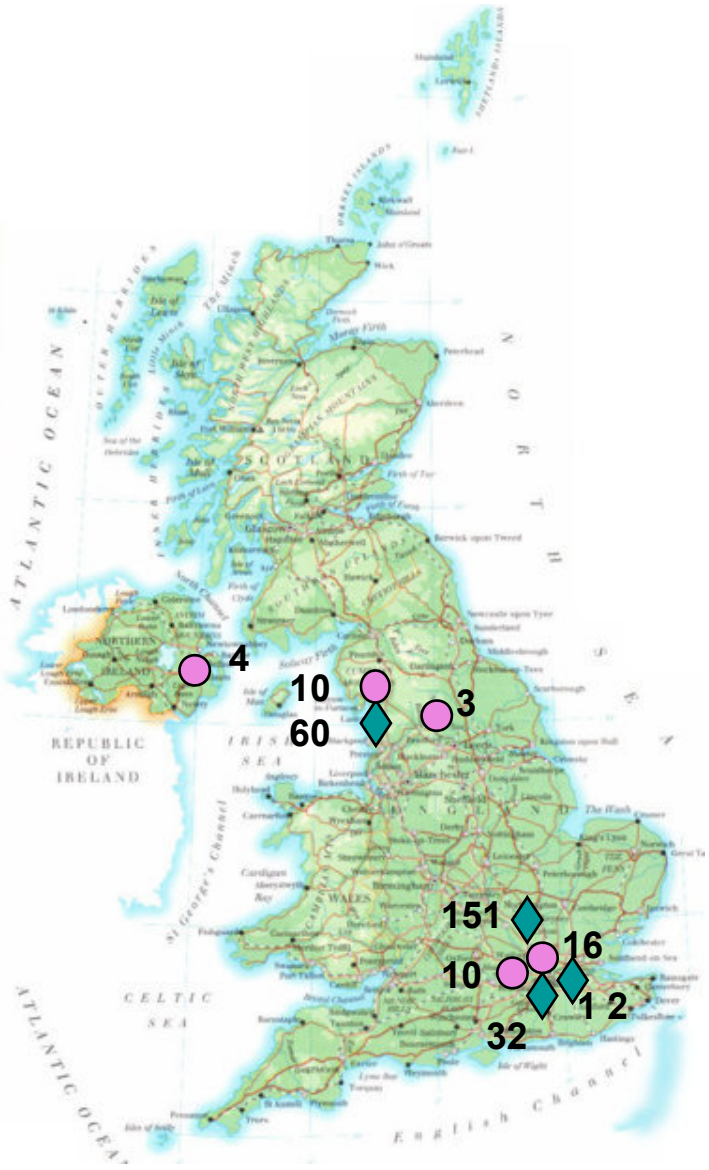
Treating NETs with PPRT
The UK experience

Prof John Buscombe

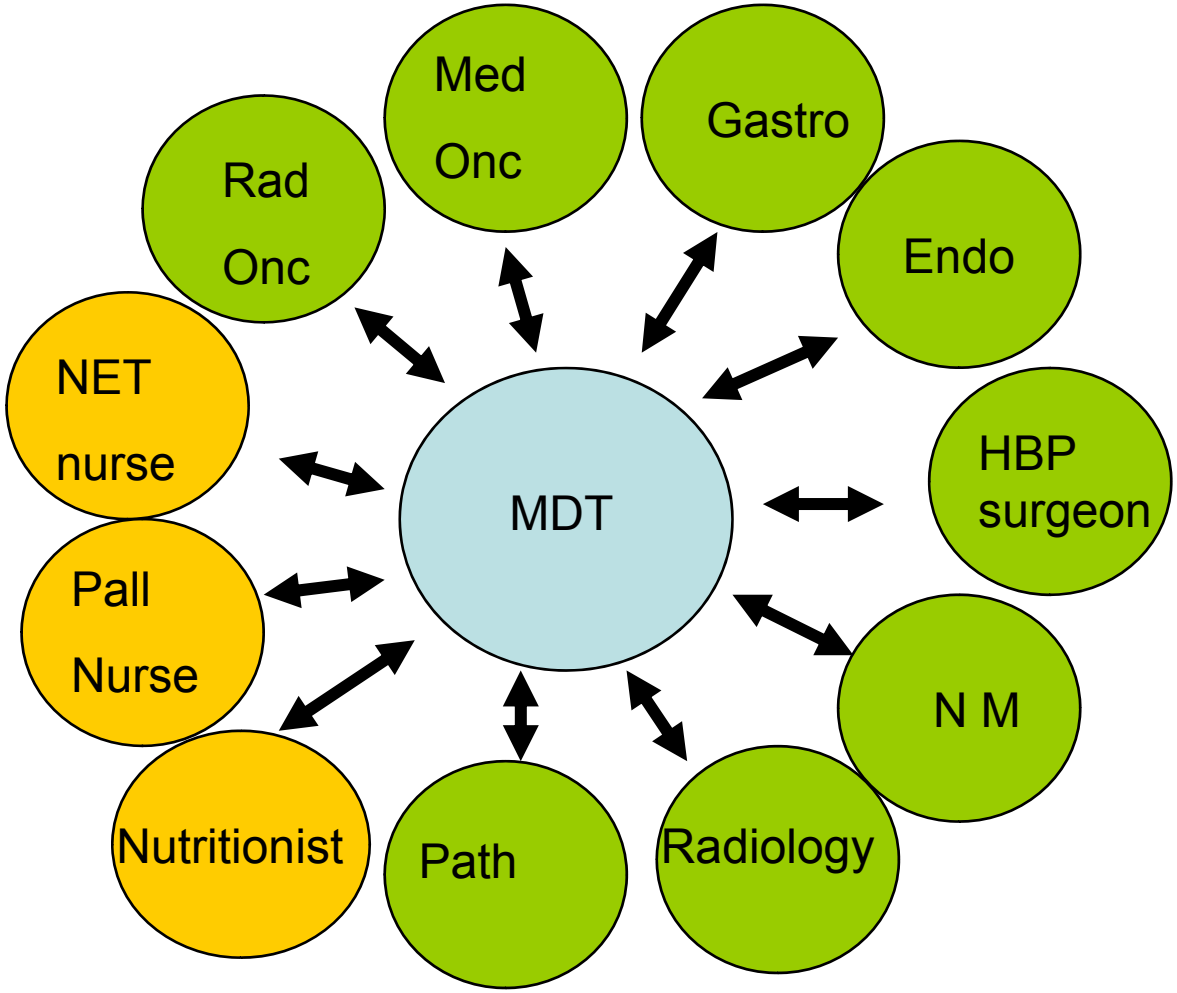
UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

NET therapy in the UK 2005-2011

- UKNETs have attempted to build a network of management centres
- Largest RFH with over 1400 patients
- Treatments available depends on local factors



NET MDT


Med Onc
Gastro
Rad Onc
Endo
NET nurse
MDT
HBP surgeon
Pall Nurse
N M
Nutritionist
Path
Radiology

ENETS Center of Excellence since 2011

Zentralklinik Bad Berka*

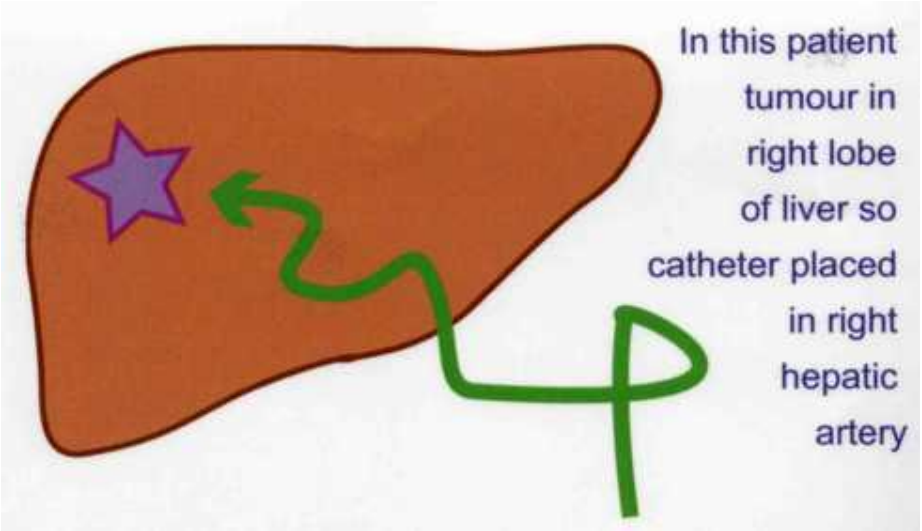
Int. Medicine, Endocrinology, Gastroenterology, Oncology
Thoracic, Abdomino/Visceral and Spinal Surgery
Interventional Radiology
Nuclear Medicine & Molecular Imaging (PET/CT Center)

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

>1200 NET patients‘ visits/year*

Nuclear Medicine Ward (22 beds for RN treatment)

Intra-arterial treatments

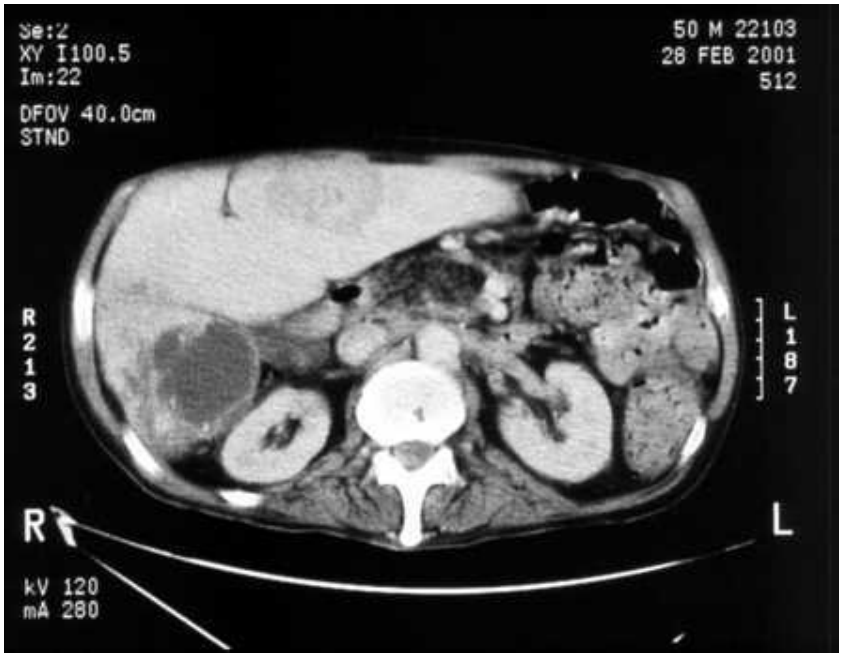


Catheters placed by interventional radiologist. Normally 5 French used but in liver “tracker” may be needed

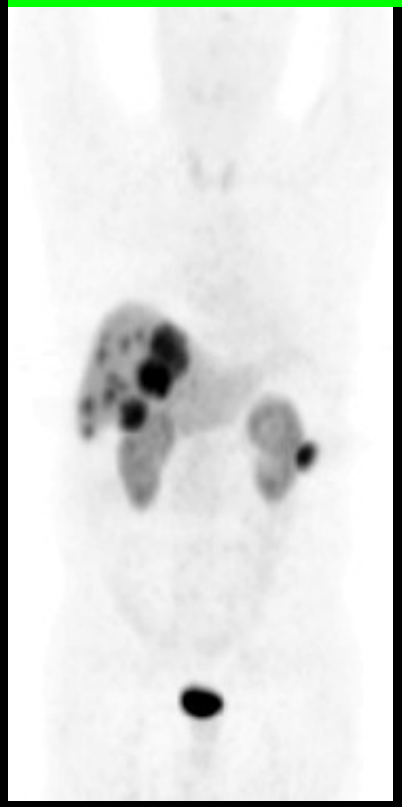
CT before and after therapy

Before Y-90 Lanreotide

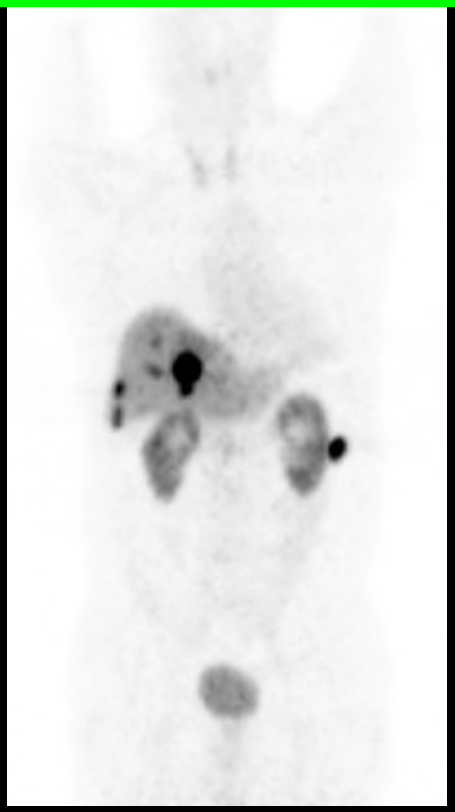
After Y-90 Lanreotide



Future Improvement: Intra-arterial PRRT



pre 1. PRRT



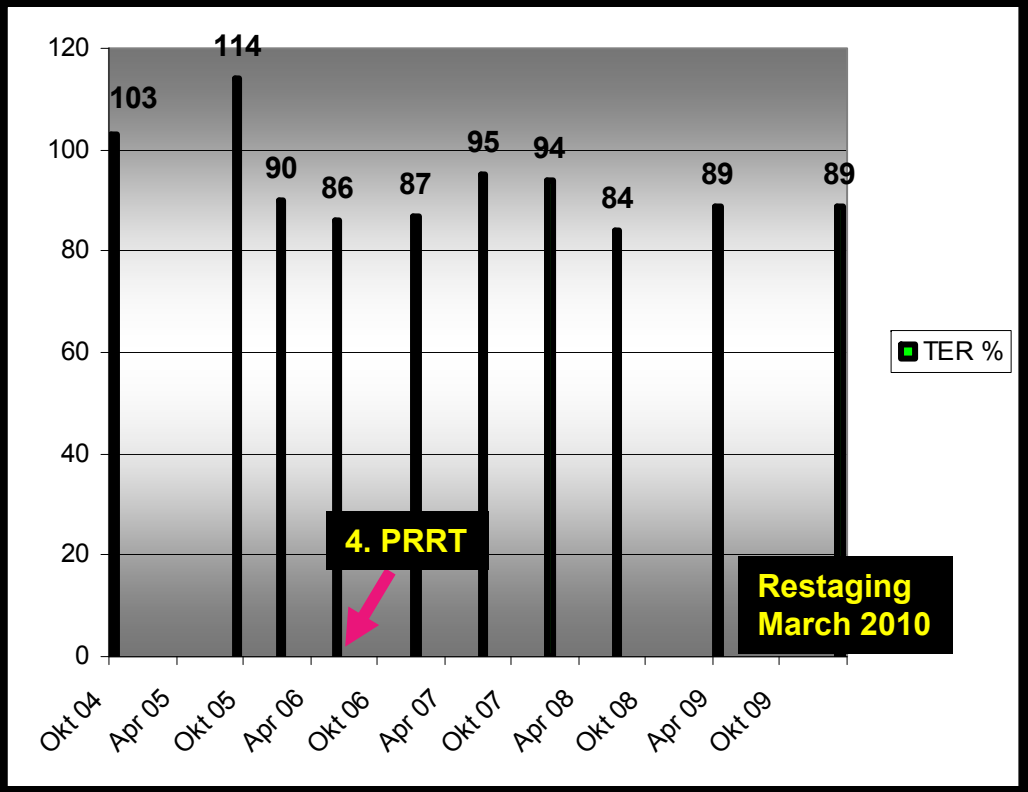
post 2. PRRT

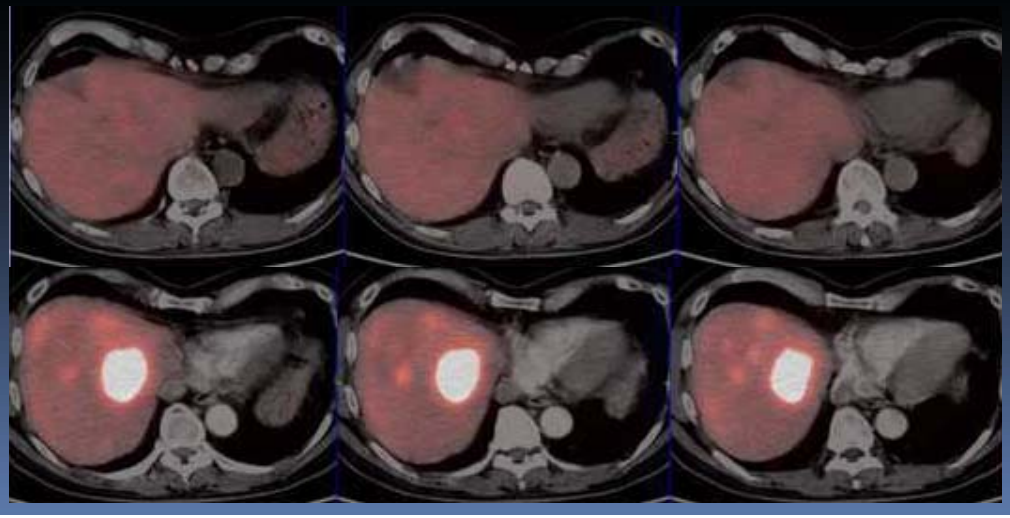
post 3. PRRT

Regression of liver and paracolic metastases after 3 PRRT cycles

BW 32 84 24

Restaging
42 months
after 4. PRRT





42 months
after 4. PRRT

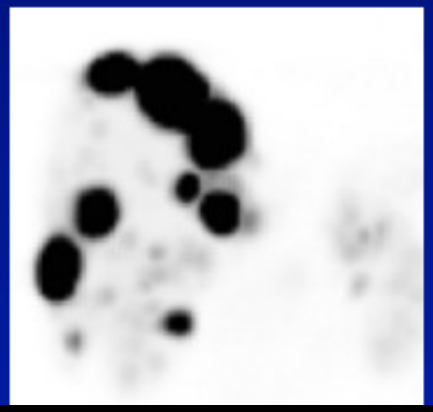
Patient cured!

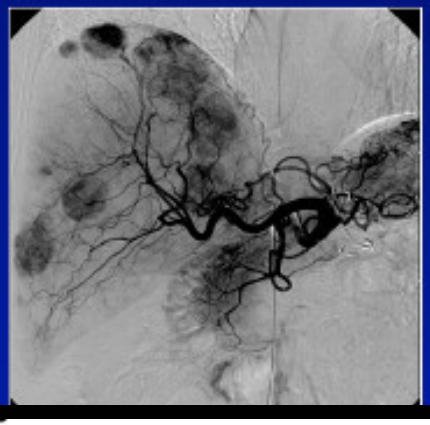
before 1. PRRT

Intraindividual Comparison of Selective Arterial versus Venous ^{68}Ga-DOTATOC PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors

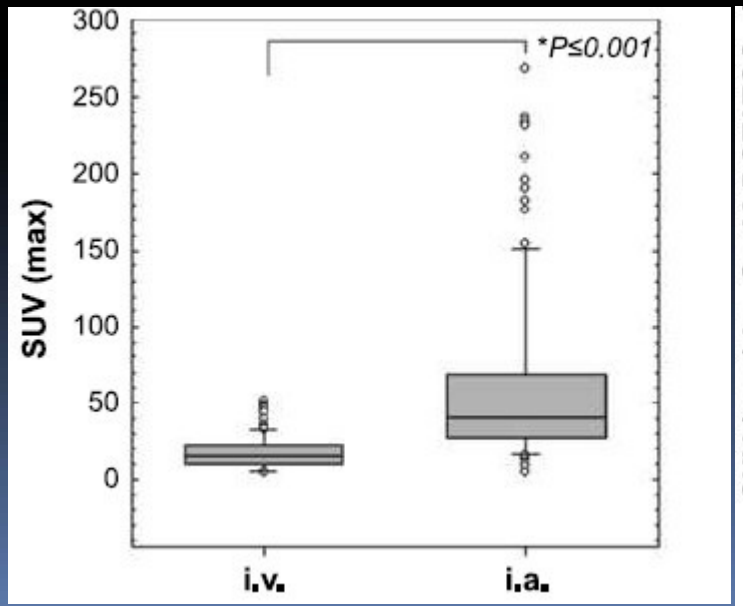
Clin Cancer Res; 16(10) May 15, 2010

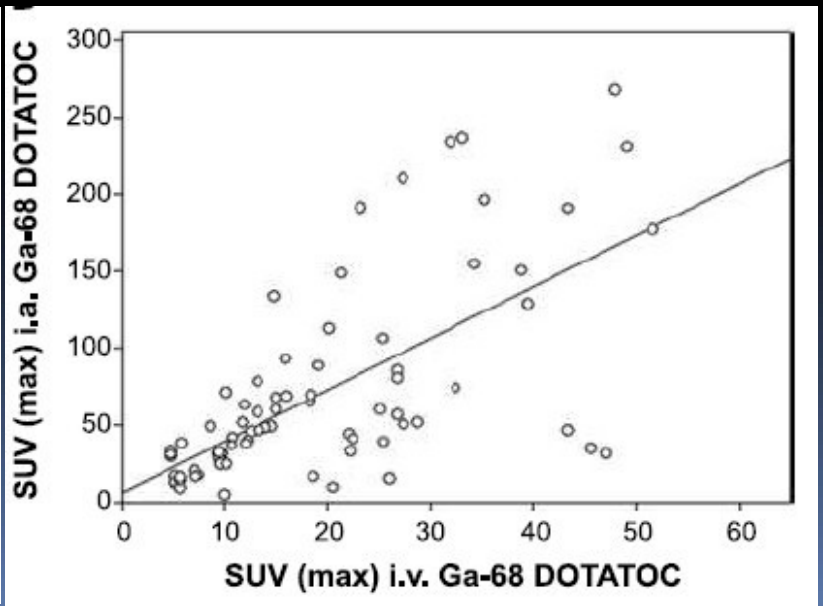
Clemens Kratochwil[1], Frederik L. Giesel[1,2], Ruben López-Benítez[2], Nadine Schimpfky[1], Kirsten Kunze[1], Michael Eisenhut[3], Hans-Ulrich Kauczor[2], and Uwe Haberkorn[1]





Intraindividual comparison using ^{68}Ga-DOTATOC PET: Tumor uptake 3.75 fold higher after selective arterial infusion





UniversityHospital Heidelberg

Regional ^{213}Bi-DOTATOC peptide receptor alpha-therapy in patients with NETs refractory to beta-radiation

C. Kratochwil[1], F. Giesel[1], A. Morgenstern[2], F. Bruchertseifer[2], W. Mier[1], C. Zechmann[1], C. Apostolidis[2], U. Haberkorn[1]

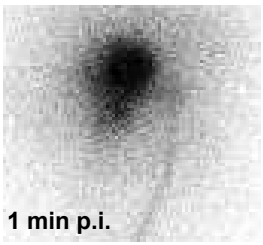
(1) Nuclear Medicine, University Hospital, Heidelberg, Germany
(2) Institute for Transuranium Elements, European Commission JRC, Karlsruhe, Germany

Results:

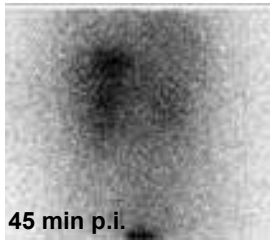
Diagnostic

^{68}Ga-DOTATOC
(PET Scan; MIP)

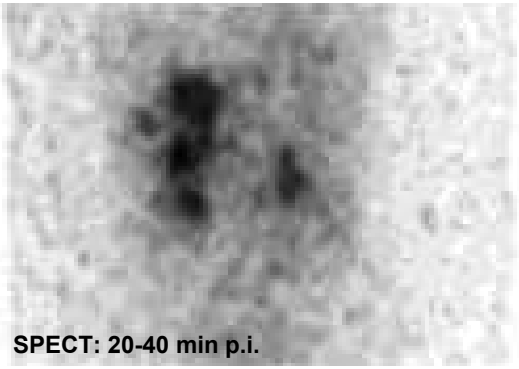
Therapy



1 min p.i.



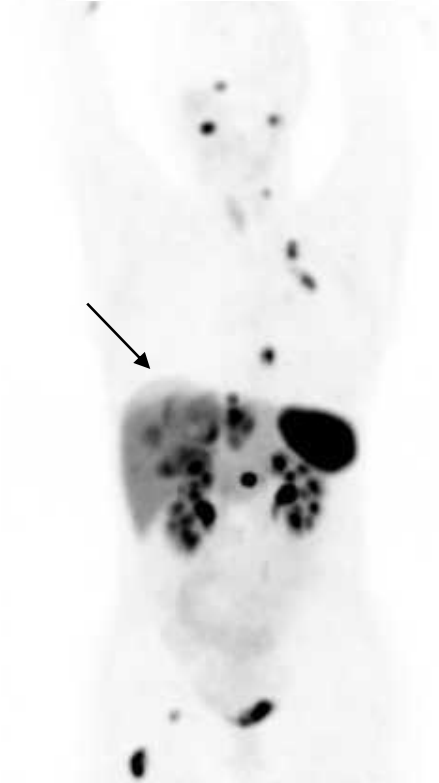
45 min p.i.



SPECT: 20-40 min p.i.

440keV-Scan:
4 GBq Bi-213 (Σ8GBq)

Post Therapy



^{68}Ga-DOTATOC
(PET Scan; MIP)

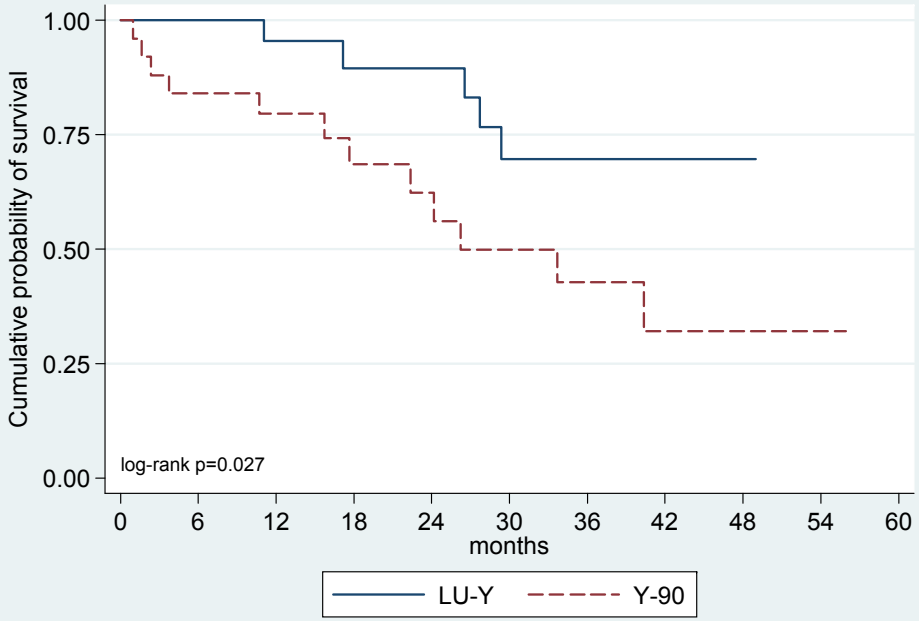
Polish experience in Peptide Receptor Radionuclide Therapy

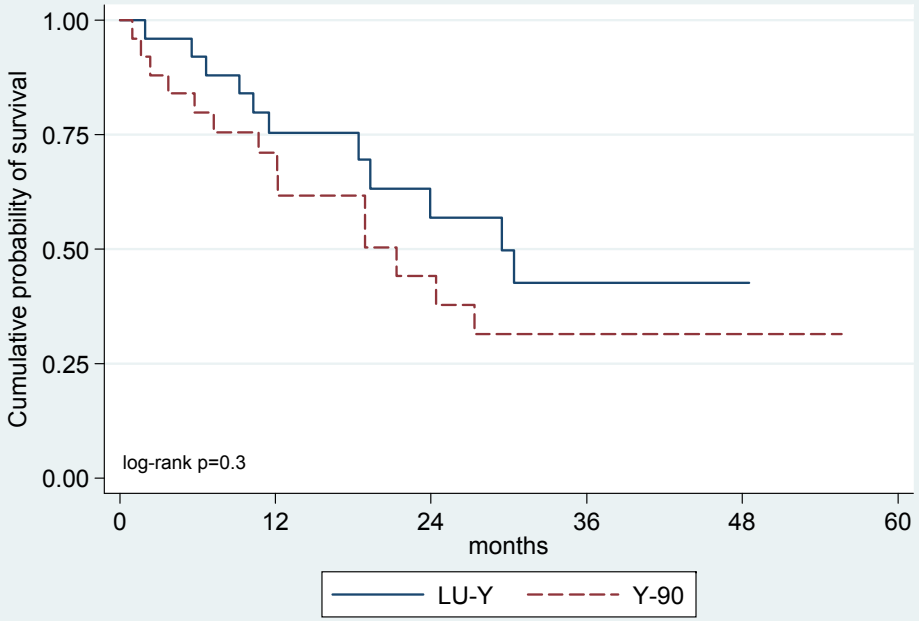
Jolanta Kunikowska, Leszek Królicki, Anna Sowa-Staszczak, Alicja Hubalewska-Dydejczyk, Dariusz Pawlak, Renata Mikołajczak, Daria Handkiewicz-Junak, Norbert Szaluś, Grzegorz Kamiński, Jarosław Ćwikła, Maciej Jakuciński , Anna Łukiewicz, Aldona Kowalska, Paweł Gut

Nuclear Medicine Department, Medical University of Warsaw

Jolanta Kunikowska, Leszek Królicki

- First treatment 26.04.2004





	TTP	EFS	OS
^{90}Y DOTATATE	27.8 months	21 months,	34.2 months
^{90}Y/^{177} Lu DOATATE	24.2 months	24.2 months	49.8 months

Conclusions

- Nevertheless used procedures and isotope PRRT is effective and safe therapy option for patients with NET.
- Tandem therapy with $^{90}Y/^{177}Lu$-DOTATATE leads to longer overall survival time than single isotope treatment.
- More extensive studies with a larger number of patients in the same protocol are required.

Zentralklinik Bad Berka

Bad Berka Dose Protocol (BBDP)

Results in 350 patients with a Routinely Applicable Protocol for Dosimetry in Peptide Receptor Radio Nuclide Therapy (PRRNT)

Christiane Schuchardt

Dept. of Nuclear Medicine / Center for PET
Zentralklinik Bad Berka
Germany

Dosimetry in PRRNT using ^{177}Lu DOTATATE/-TOC/-NOC

Zentralklinik Bad Berka

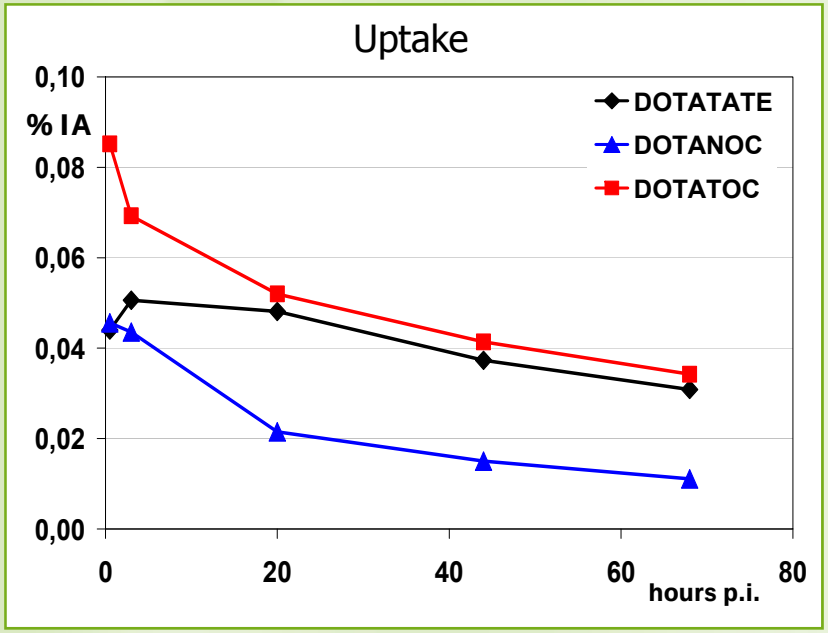
Tumor lesions

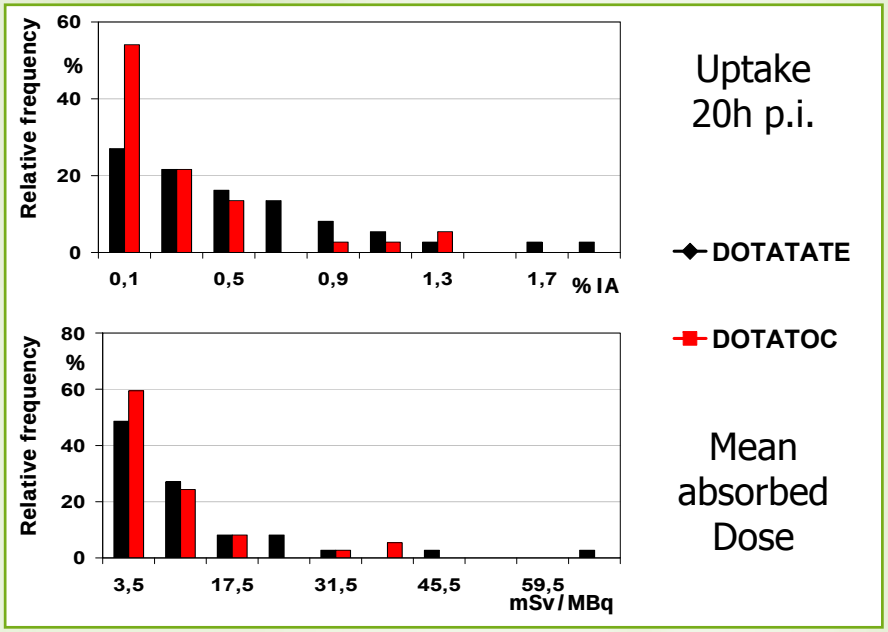
Group 1

	TATE	TOC	NOC
Patients	457	309	18
Half-life (hours)	**73**	**77**	**64**
Mean ab. dose (mGy/MBq)	**5.3**	**6.2**	**2.0**

Group 2

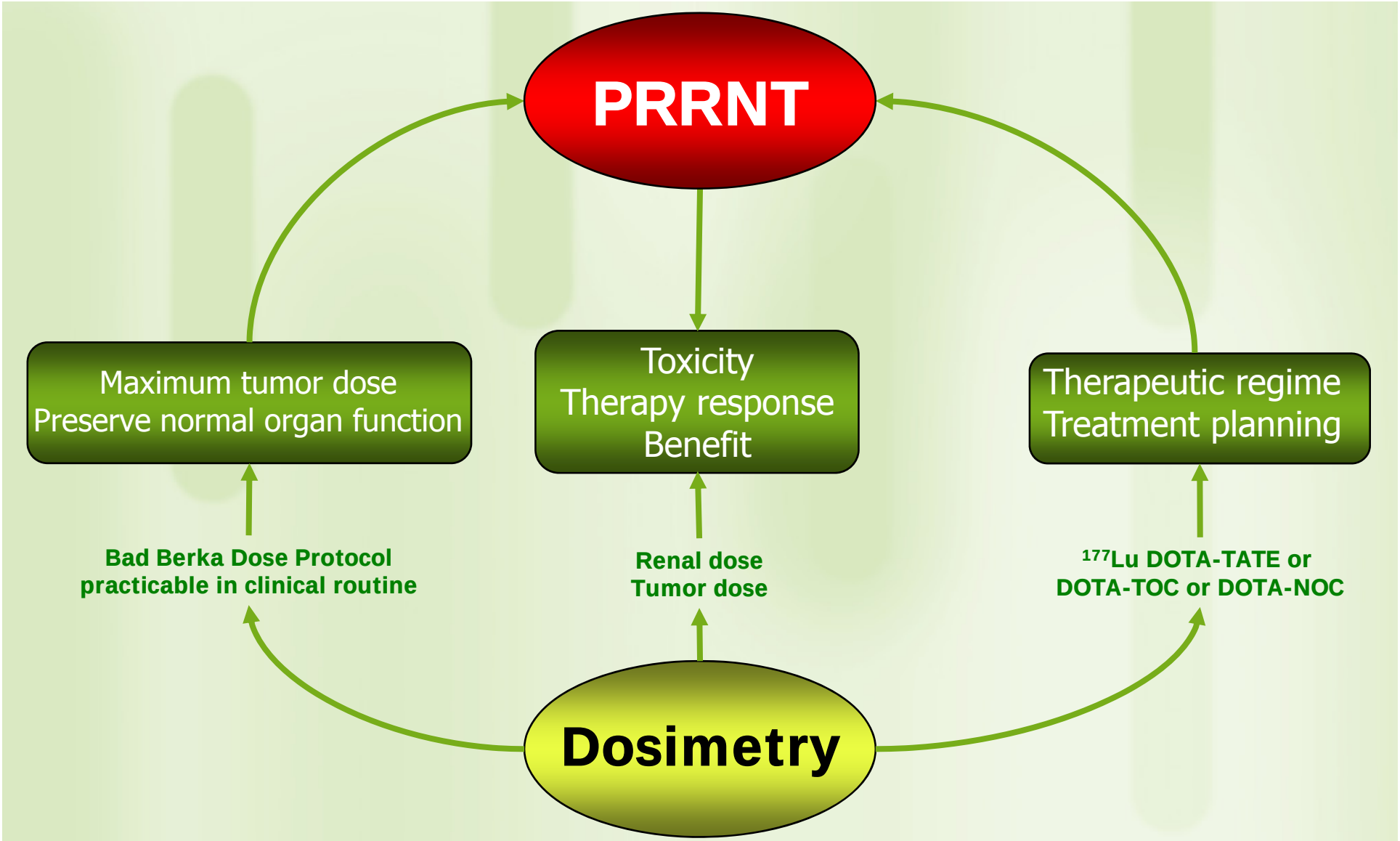
	Uptake 20h p.i.	Half-life (hours)	Dose (mGy/MBq)
TATE > TOC	**85 %**	**50 %**	**65 %**
Significance (p≤0.05)	✓		✓





Conclusion

Zentralklinik Bad Berka



4-D SPECT/CT for 3-D dose calculation and planning in clinical PRRT practice

Kalevi Kairemo, MD, PhD, MSc(Eng), prof
Chief Physician, Molecular Radiotherapy & Nuclear Medicine
Specialist in Nuclear Medicine, Clinical Chemistry
and Clinical Pharmacology (FMA)
International Comprehensive Cancer Center Docrates
Saukonpaadenranta 2, FI-00180 Helsinki, Finland
kalevi.kairemo@docrates.com
www.docrates.com

Summary & future prospects

- A new method for clinical routine; 15 min/ patient
- Reliable individualized tumor dosimetry in an arbitraty geometry (as compared to existing tools, when possible)
- Information about intraorgan dose distribution, e.g. intratumoral, bone marrow

- Dose planning seems to be relevant; existing data gave correct tumor and liver dose, overestimated spleen and kidney dose
- Multicenter trials (independent data for evaluation, “better extrapolation factors” for dose planning)

IAEA
International Atomic Energy Agency

Practical Guidance for Peptide Receptor Radionuclide Therapy (PRRNT) in Neuroendocrine Tumors

IAEA 2011 (John Zaknun) – to be published soon

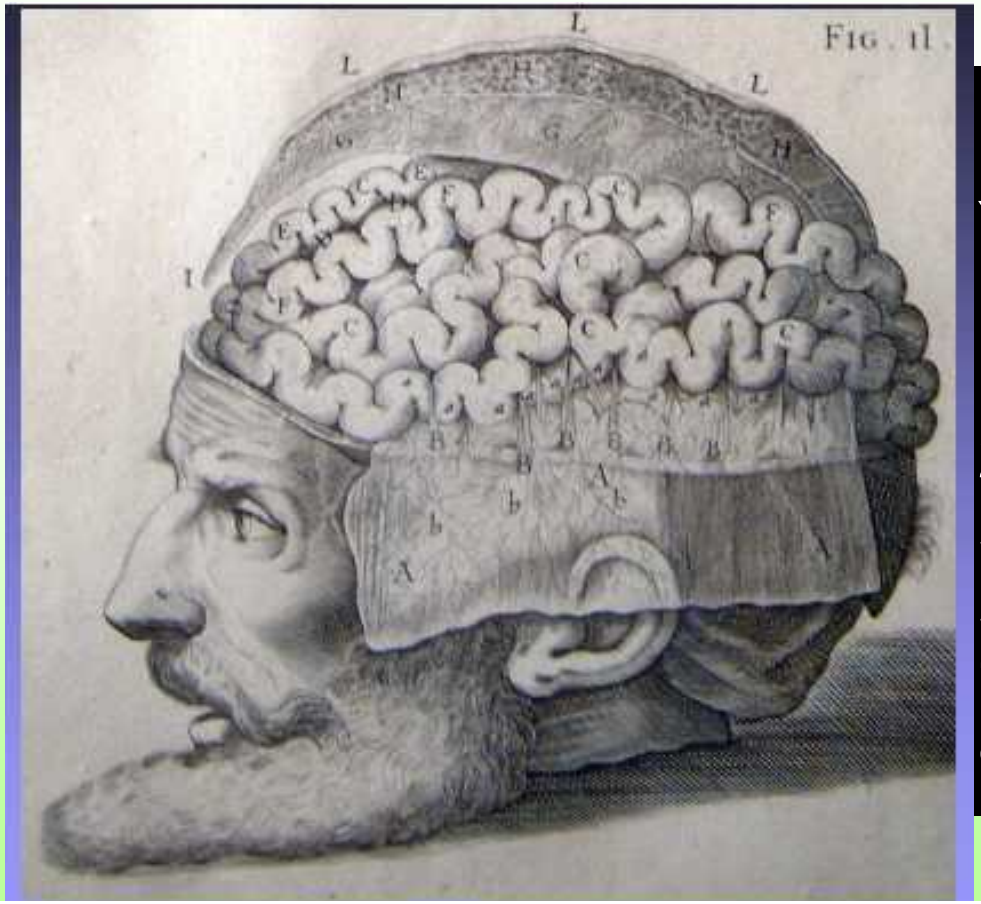
C.S. Bal, Aron J. Belfer, Lisa Bodei, Richard P. Baum, Dieter Hörsch, Jan Müller-Brand, Sue O'Doriso, Tom O'Doriso, Marianne Pavel, …….

New Avenues to Improve PRRT in Future

- DUO-PRRT (already routine at our center since 7 years)
- TANDEM-PRRT (concurrent Lu-177/Y-90 PRRT Kunikowska et al.)
- Intra-arterial PRRT (> 50 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)
  - antibodies (e.g. Bevacizumab)
- Improved peptides (e.g. antagonists)
- Intra-operative use of probes after PRRT with Lu-177
- Improved dosimetry and radioprotection

1st World Congress on Ga-68 and Peptide Receptor Radionuclide Therapy (PRRNT)

THERANOSTICS - On the Way to Personalized Medicine
Bad Berka, Germany, June 23 - 26, 2011



Memorizing..

You remember

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

1st World Congress on Ga-68 and Peptide Receptor Radionuclide Therapy (PRRNT)

THERANOSTICS - On the Way to Personalized Medicine
Bad Berka, Germany, June 23 - 26, 2011

Total number of participants: >400

Europe:	**307**
Amerika:	**35**
Asia :	**51**
Australia:	**9**
Africa:	**6**

The congress took place under the auspices of

CME Accreditation

The Landesärztekammer Thüringen designates this international congress for a maximum of 23 CME credits (category A).

Telemann & Bach

Speaker´s Dinner

Goethe and his „secret love“ chemistry..

… the congress runs

.. the youngest participant

Welcome Reception

Schloss Ettersburg

Midsummer Night

Rittergut München

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LEAD SPONSORS

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- Forschungsgesellschaft m.b.H.

- GE Healthcare
- IBA Molecular Equipment
- Sanofi-Aventis Deutschland GmbH
- Scintomics GmbH
- Veenstra Instrumenten BV

Acknowledgements……

and Post-congress

Post-Congress

Post-congress hands-on training course on the PET generators $^{68}Ge/^{68}Ga$ and $^{44}Ti/^{44}Sc$

radionuclide generators, post-processing, labelling, quality controll, automatization

JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Institute of Nuclear Chemistry
June 27-28, 2011, Mainz

Radiopharmcy:
Prof. Tobias Ross
Prof. Frank Rösch

1st World Congress on Gallium-68 and Peptide Receptor Radionuclide Therapy (PRRNT) -
THERANOSTICS – on the way to personalized medicine
June 23-26, 2011, Bad Berka / June 27-28, 2011, Mainz

Post-Congress

Post-congress hands-on training course on the PET generators $^{68}Ge/^{68}Ga$ and $^{44}Ti/^{44}Sc$

radionuclide generators, post-processing, labelling, quality controll, automatization

10 generators from all companies

	Marco FELLNER	
Elisabeth EPPARD	Marian MECKEL	Benedikt SANDHÖFER
Berit KÜHLE	Verena NAGEL	Johanna SEEMANN
Natasha LOKTIONOVA	Achim REIBEL	Melanie ZIMNY

Institute of Nuclear Chemistry
June 27-28, 2011, Mainz

Radiopharmcy:
Prof. Tobias Ross
Prof. Frank Rösch

1st World Congress on Gallium-68 and Peptide Receptor Radionuclide Therapy (PRRNT) - THERANOSTICS – on the way to personalized medicine
June 23-26, 2011, Bad Berka / June 27-28, 2011, Mainz

Awards

Best Oral Presentations

Best Posters

Award Committee:

Henry VanBrocklin

Vikram Lele

Baljinder Singh

1st World Congress on Ga-68 and Peptide Receptor Radionuclide Therapy (PRRNT)

THERANOSTICS - On the Way to Personalized Medicine
Bad Berka, Germany, June 23 - 26, 2011

Zentralklinik Bad Berka

JG|U JOHANNES GUTENBERG UNIVERSITÄT MAINZ

Institut für Kernchemie

…and the 2nd World Congress will take place in 2013 in Chandigarh, India (Congress President: Baljinder Singh)