THERANOSTICS FOR PERSONALIZED MOLECULAR TARGETED THERAPY OF CANCER

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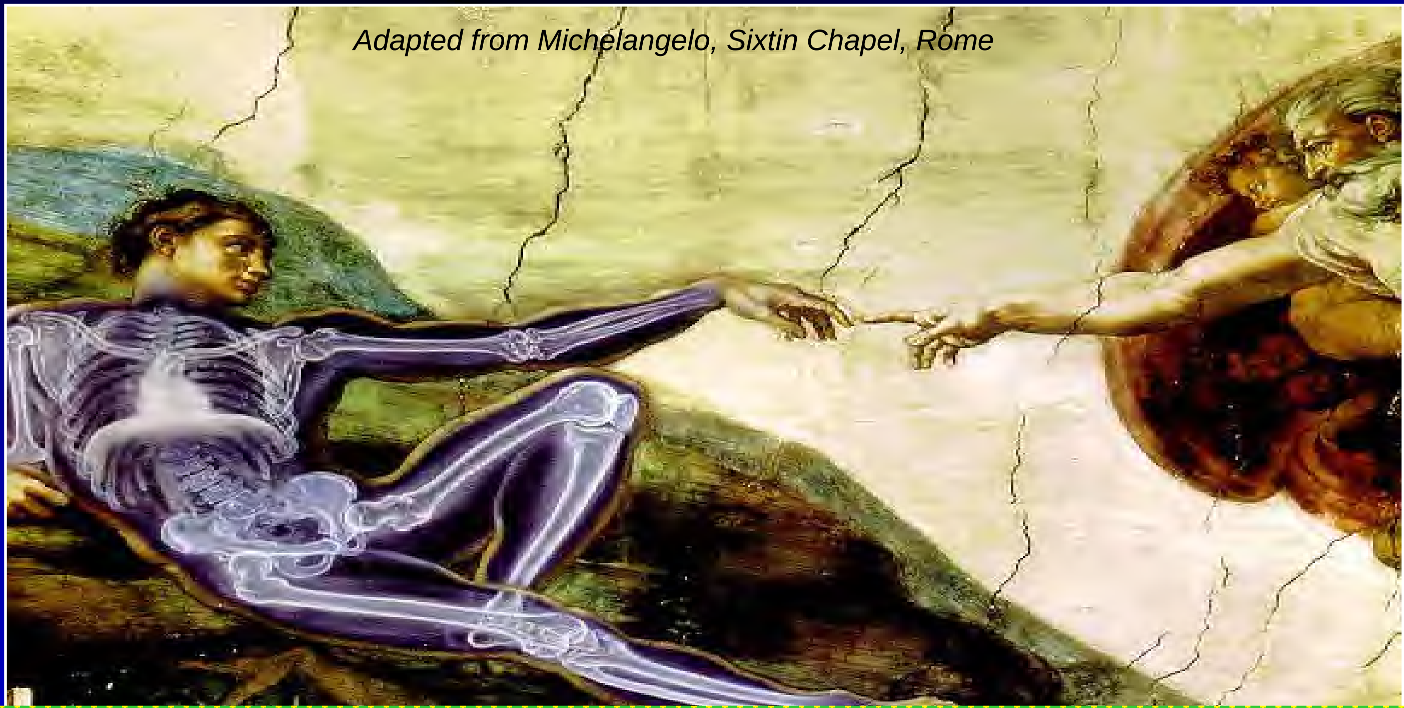


Adapted from Michelangelo, Sixtin Chapel, Rome

20th International Symposium on Radiopharmaceutical Sciences (ISRS2013)
Jeju International Convention Center
Jeju Island, May 12-17, 2013

Lecture Outline

- Definition and principles of THERANOSTICS and Personalized Medicine
- THERANOSTIC radionuclides and Ga-68 generator
- Neuroendocrine tumors (NET) as a paradigm
- Diagnosis of NET by PET/CT (clinical applications)
- Dosimetry (organ & tumor dose calculations)
- Therapy of NET (Peptide Receptor Radiotherapy, PRRT)
- Future perspectives
  - new peptides (antagonists, CXCR4, RGD)
  - PSMA: THERANOSTICS potential for prostate ca.

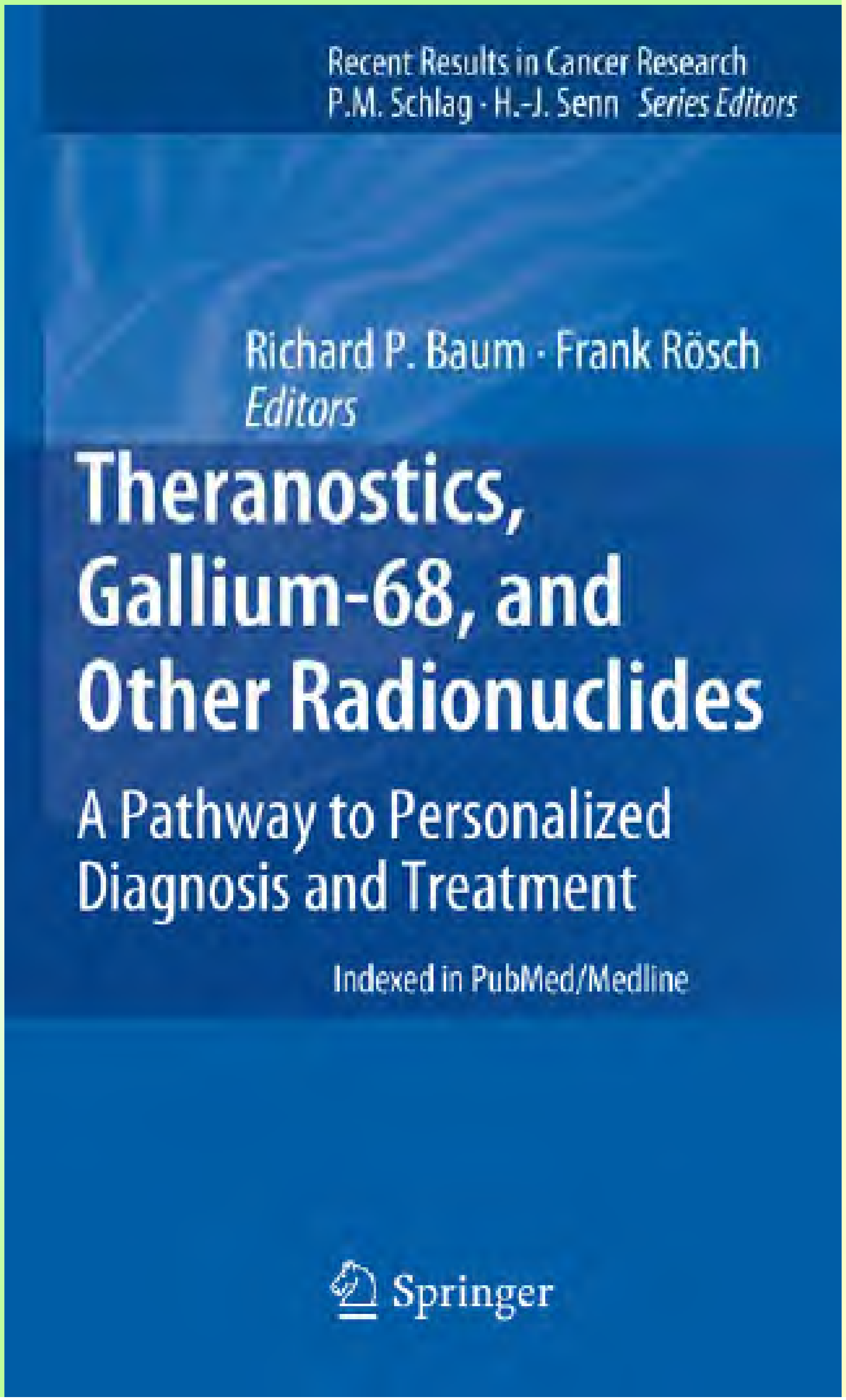
Theranostics

- **Theranostics is the combination of a Diag*nostic* Tool that helps to define the right *Thera*peutic Tool for a specific disease.**
- **The term is not specific to radiopharmaceuticals - but in fact was first used there (e.g. as “THERAGNOSTICS” by Suresh Srivastava).**
- **In NM, THERANOSTICS is easy to apply and to understand, because of an easy switch of the radionuclide from Dx to Rx on the same vector.**
- **The most prominent and oldest application is radioiodine.**
- **Used by pharma industry at the beginning of the 90’s at the same time the concept of Personalized Medicine appeared.**

Personalized Medicine

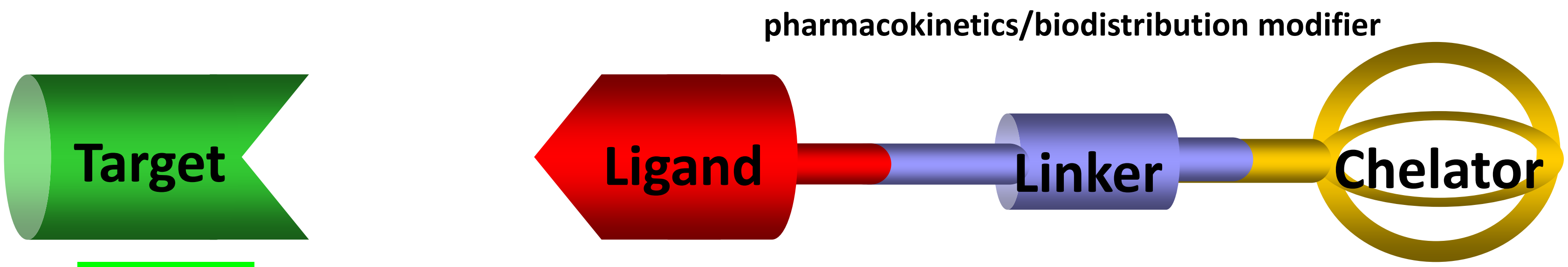
- **The right treatment, for the right patient, at the right time, at the right dose. – first time », not anymore targeting the “specific disease” but the “specific tumor of a patient”.**
- **The concept of PM has now been extended to Personalized Health Care that includes all steps relevant for the 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…**

Molecular Nuclear Medicine and THERANOSTICS within MNM are definitely part of Personalized Health Care.


Recent Results in Cancer Research
P.M. Schlag · H.-J. Senn Series Editors
Richard P. Baum · Frank Rösch
Editors
Theranostics, Gallium-68, and Other Radionuclides
A Pathway to Personalized Diagnosis and Treatment
Indexed in PubMed/Medline
Springer


UNIVERSITY OF IOWA
HOSPITALS & CLINICS
University of Iowa Health Care
2nd World Congress on Ga-68
(Generators and Novel Radiopharmaceuticals)
Molecular Imaging (PET/CT),
Targeted Radionuclide Therapy, and Dosimetry
(SWC-2013): On the Way to Personalized Medicine
28th February - 2nd March, 2013
SWC - 2013
Organized by :
Department of Nuclear Medicine & PET, PGIMER,
Chandigarh, India

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



Lock | **Key** | **^{68}Ga, ^{90}Y, ^{177}Lu**

Target

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

Molecular Address

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

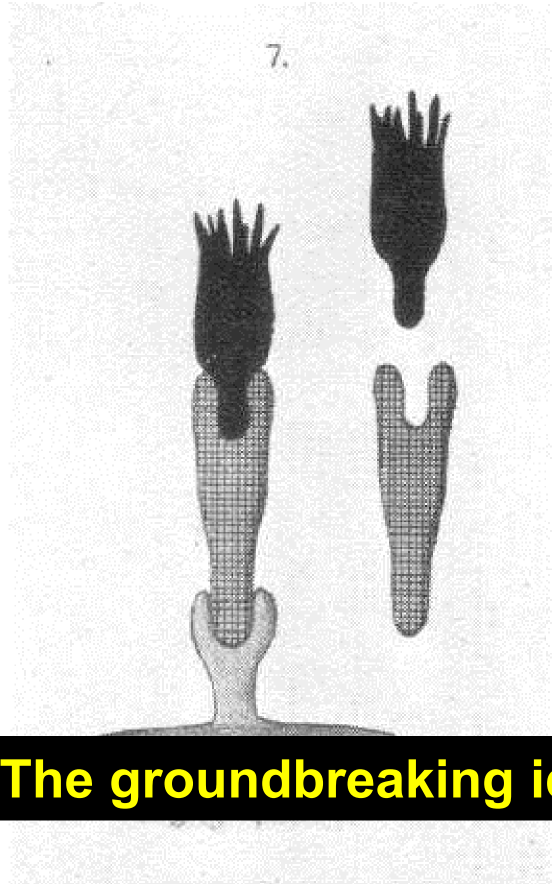
Reporting Unit

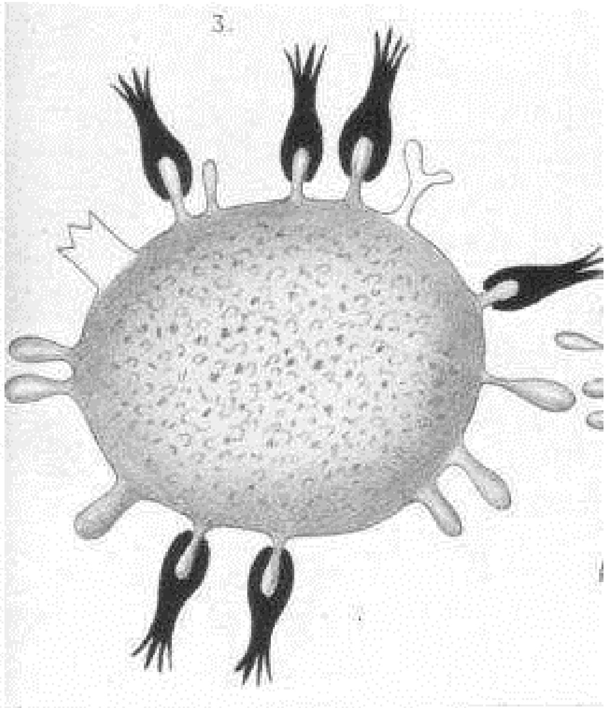
- ^{99m}Tc, ^{111}In, ^{67}Ga
- ^{64}Cu, **^{68}Ga**
- Gd^{3+}

Cytotoxic Unit

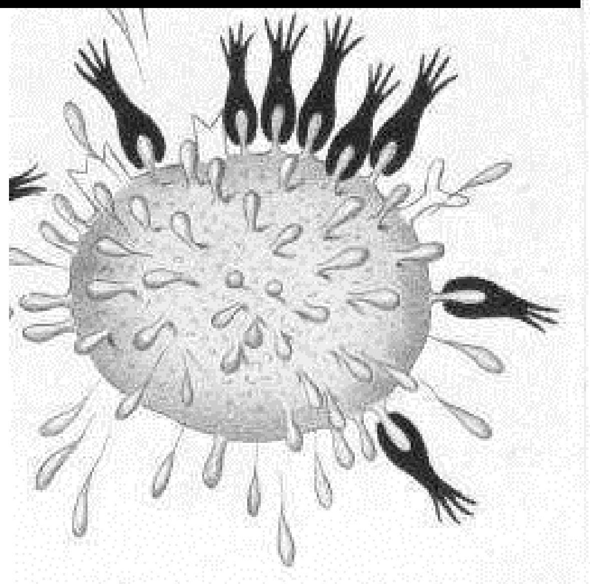
- **^{90}Y, ^{177}Lu**, ^{213}Bi
- ^{105}Rh, ^{67}Cu, ^{186,188}Re

Courtesy Helmut Mäcke (modified)





The groundbreaking idea and basic principle



Paul Ehrlich – Side Chain Theory

Amboceptors and formation of antitoxins

Corpora non agunt nisi fixata –
„Zauberkugeln“ (Magic Bullits)

Frankfurt/Main, Germany (1899)

Nobel Price 1908 – 105 years ago

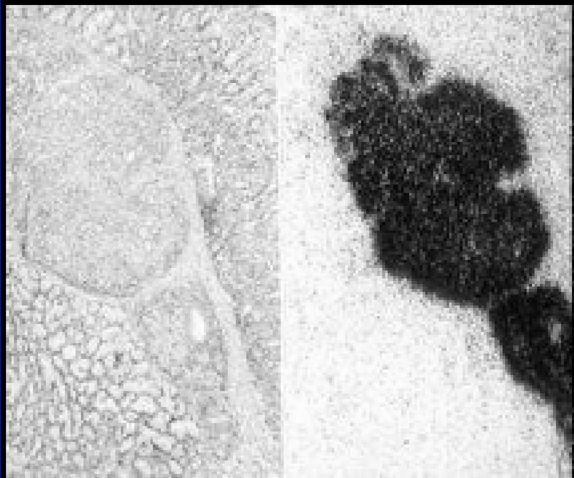
Radiolabeled Octreotide

From bench to bedside: “Proof of principle”

1984

Autoradiography

SMS-R^{125}I-Somatostatin



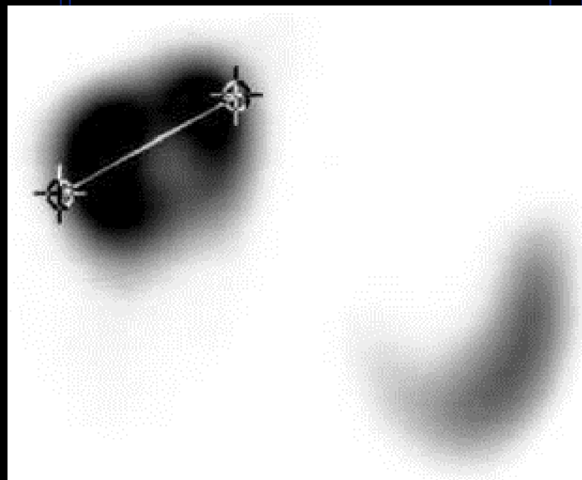
In vitro

Jean-Claude Reubi et al.

1987

Scintigraphy

6 mCi ^{111}In-Octreotide



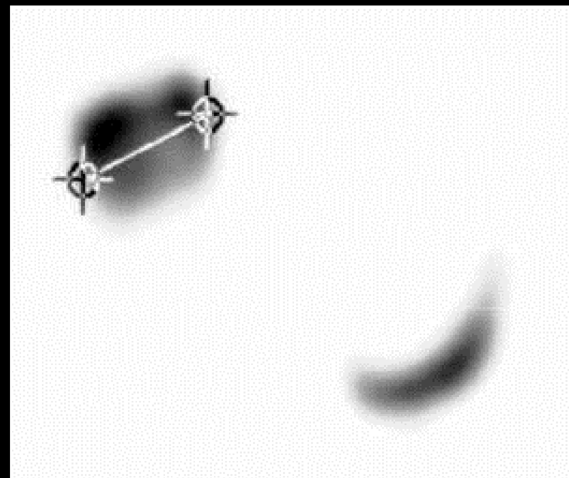
In vivo

Eric Krenning et al.

1992

Radionuclide Therapy

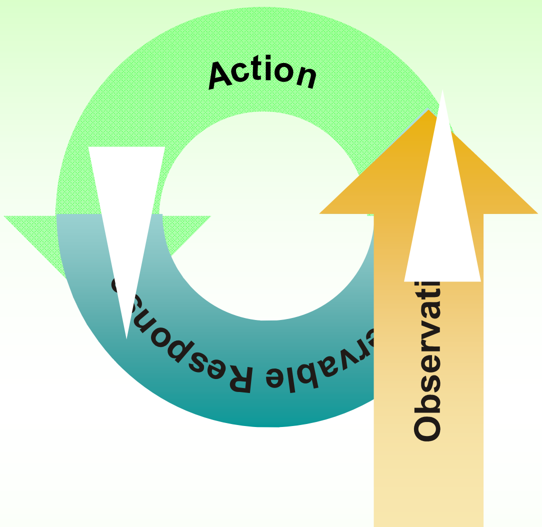
180 mCi ^{111}In-Octreotide



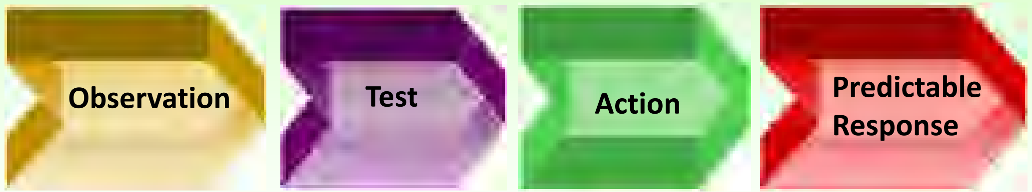
In vivo

Courtesy Marion de Jong, Rotterdam

From Trial and Error Medicine to Personalized Medicine



New paradigm: personalized medicine



Breaking the cycle of trial and error medicine

Targeted radionuclide therapy has unique promise for personalized treatment of cancer, because both the targeting vehicle and the radionuclide can be tailored to the individual patient.

Courtesy Damian Wild

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Peptides and Receptors in Image-Guided Therapy: Theranostics for Neuroendocrine Neoplasms

Richard P. Baum, MD, Harshad R. Kulkarni, MD, and Cecilia Carreras, MD

Selected Theragnostic Radionuclides

Radionuclide	T1/2 (d)	Principal γ energy for imaging, KeV (%)	Therapeutic particle(s) (Avg. Energy, KeV, % abundance)
Scandium-47	3.35	159 (68)	β- (162)
Copper-67	2.58	185 (49)	β- (141)
Gallium-67	3.26	93, 184, 296 (40, 24, 22)	15 Auger, 0.04-9.5 KeV, 572% 10 C.E., 82-291 KeV, 30%
Indium-111	2.80	171, 245 (91, 94)	6 Auger, 0.13-25.6 KeV, 407% 12 C.E., 144-245 KeV, 21%)
Tin-117m	14.0	159 (86)	8 C.E. (141 KeV avg., 114%)
Samarium-153	1.94	103 (30)	β- (280)
Bismuth-213	46 min	441 (26)	β- (425); α (98%, from Tl-209 daughter, 2% from Bi-213)
Actinium-225	10.0	99, 150, 187 (93, 73, 49)	α (7030, 93%)
Iodine-123	13.3h	159 (83)	12 Auger, 23-30.4 KeV,1371% 7 C.E, 0.014-32 keV, 17%
Astatine-211	7.2 h	79 (21)	α (5867, 42%)

Selected Theragnostic PET/Therapy Radiometal Pairs

Radionuclide Pair Imaging/Therapeutic	T1/2 (days)	Imaging positron, KeV (%)	Therapeutic particle(s) (Avg. Energy, KeV)
Scandium-44m/ Sc-47	2.4 / 3.35	γ ± 511 (94%)	β- (162)
Copper-64/Copper-67	0.53 / 2.6	γ ± 511 (38 %)	β- (141)
Gallium-68/Gallium-67	68 min / 3.26	γ ± 511 (176 %)	15 Auger, 0.04-9.5 KeV, 572% 10 C.E., 82-291 KeV, 30%
Yttrium-86/Yttrium-90	0.61 / 2.7	γ ± 511 (35 %)	β- (935)
Iodine-124/Iodine-131	4.2/8.0	± 511 (44%)	β^- (181)

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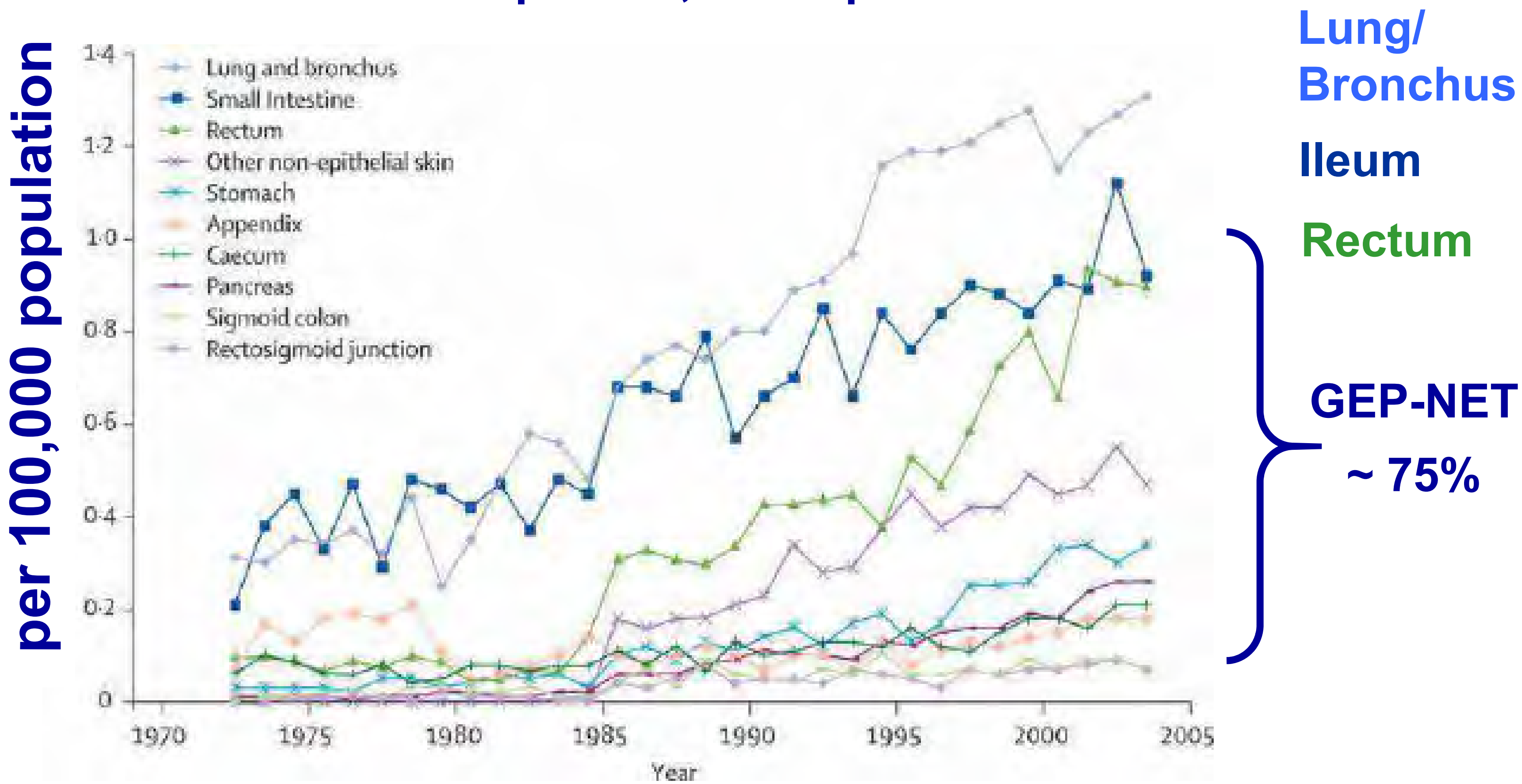
Incidence of Neuroendocrine Tumors

2.5-5.0 per 100,000 Population



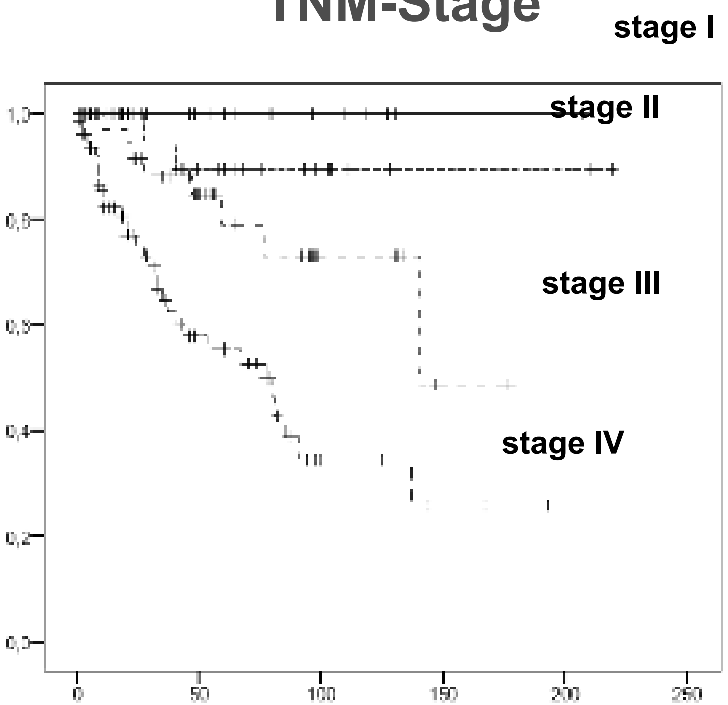
Surveillance, Epidemiology and End Results (SEER), US population 1974-2005

Modlin et al., Lancet Oncol. 2008

Cumulative Survival of Foregut-NET According to TNM Stage and Tumor Grade

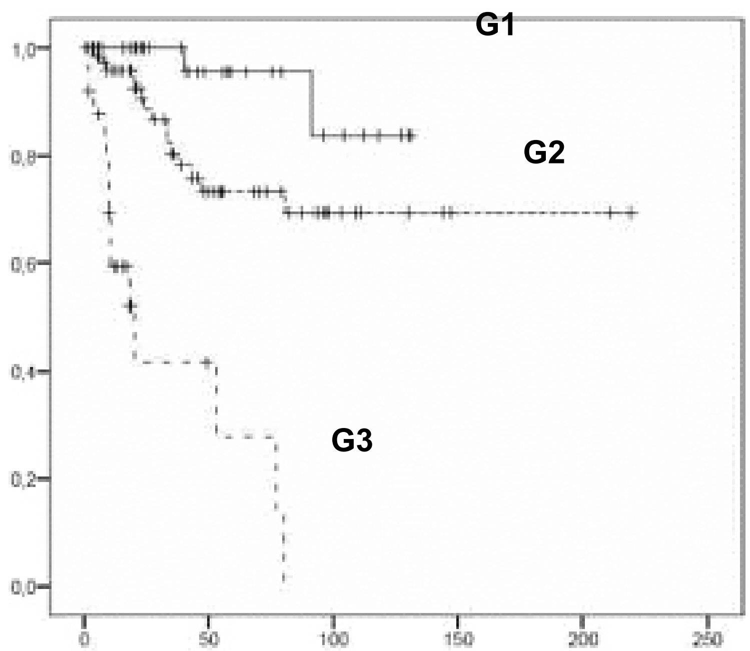
NET - low incidence, but high prevalence!

TNM-Stage



survival time [months]

Grading



survival time [months]

Pape et al., Cancer 2008

Prevalence of neuroendocrine tumors

(cases living with the disease)

= 400 per 1 Million

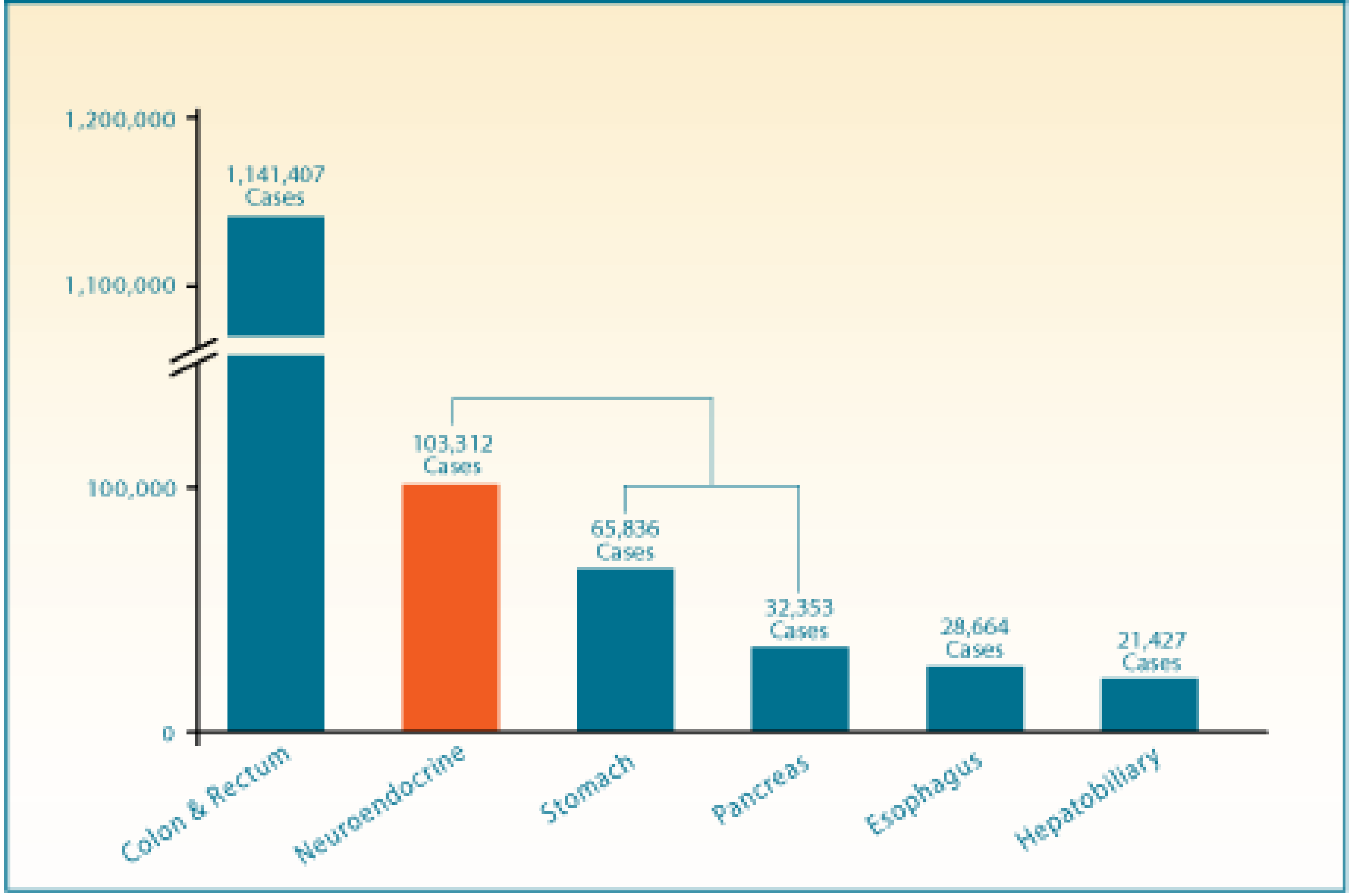
~20,000 in Korea

~120,000 in US

~ 2,400,000 worldwide

NET - low incidence, but high prevalence!

NETs: More Prevalent Than Stomach and Pancreatic Cancer *Combined*[1,2]



1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol.* 2008;26(18):3063-3072.
2. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Stat Fact Sheets. http://seer.cancer.gov/csr/1975_2004/results_merged/topic_prevalence.pdf. Accessed September 30, 2009.

NET are the second most common gastrointestinal cancer!

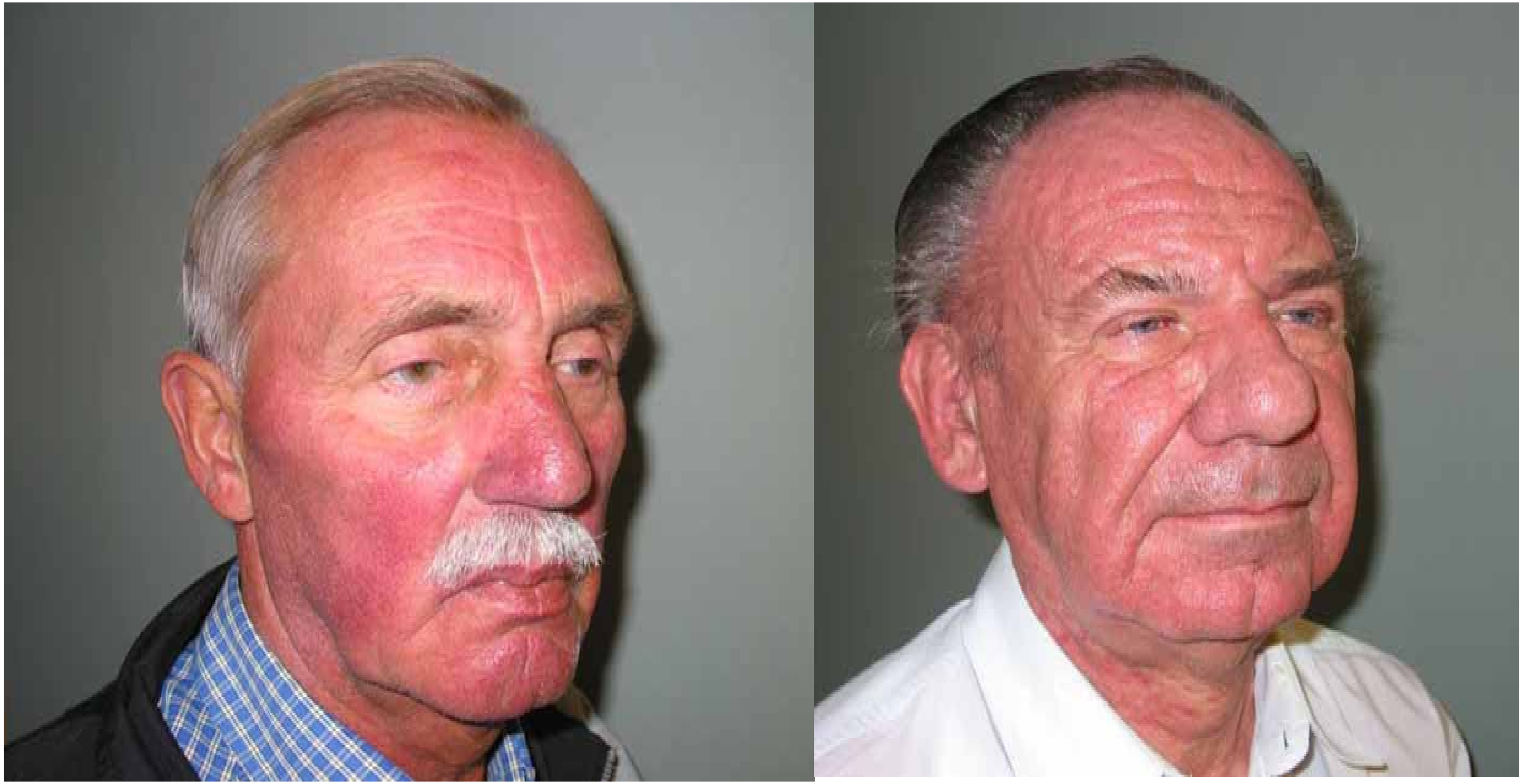
Neuroendocrine Tumors

~ 50%

~ 50%

Tumor/ Syndrome	Symptoms	Secretion Product	Malignancy Rate
Nonfunctioning	unspecific	Chromogranin A, PP, a/ß-HCG, Calcitonin	**60-80%**
Carcinoid Syndrome	**flush, diarrhoea,** bronchial obstruction	Serotonin	**100%**
Insulinoma	hypoglycemia	Insulin, Proinsulin	**5-10%**
Gastrinoma / ZES	ulcera, diarrhoea	Gastrin	**60-80%**
VIPoma / VMS	watery diarrhoea	Vasoactive intestinale peptide	**40-75%**
Glucagonoma	negrolytic migratory erythema, diabetes	Glucagon	**50-80%**
Somatostatinoma	diabetes steatorrhoea, cholelithiasis	Somatostatin	**50%**
GHRHoma **CRH, ACTHoma**	acromegaly Cushing's syndrome	GHRH CRH, ACTH	**100%** **90-100%**

Typical Carcinoid Facies (Flush)



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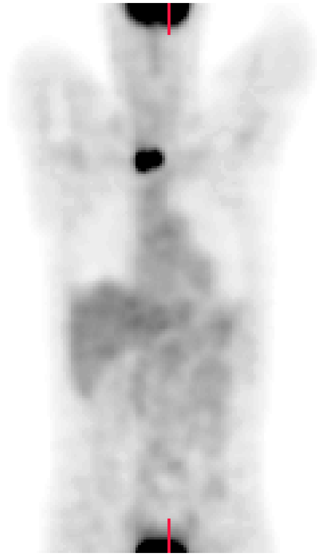
Technical advances in PET/CT scanner design



1998; 75 min scan
ECAT EXACT

Advances in CT:

- increased number of axial slices
- faster gantry rotation times
- incorporation of dual Straton x-ray tubes
- very fast scan times for cardiac applications
- improved use of the radiation dose (TCM, AEC)
- high quality, low mAs clinical CT scans

75 ms/slice
0.26 s total
0.98 mSv

Advances in PET:

- new faster scintillators (LSO, LYSO)
- higher spatial resolution detectors
- increased sensitivity from extended AFOV
- overall improved count rate performance
- iterative recon, accurate system model
- motion corrected PET images with gating
- improved SNR from Time-of-Flight (TOF)

2010; 5 min scan
mCT

Courtesy David Townsend, 2010

Ga-68 Generator System

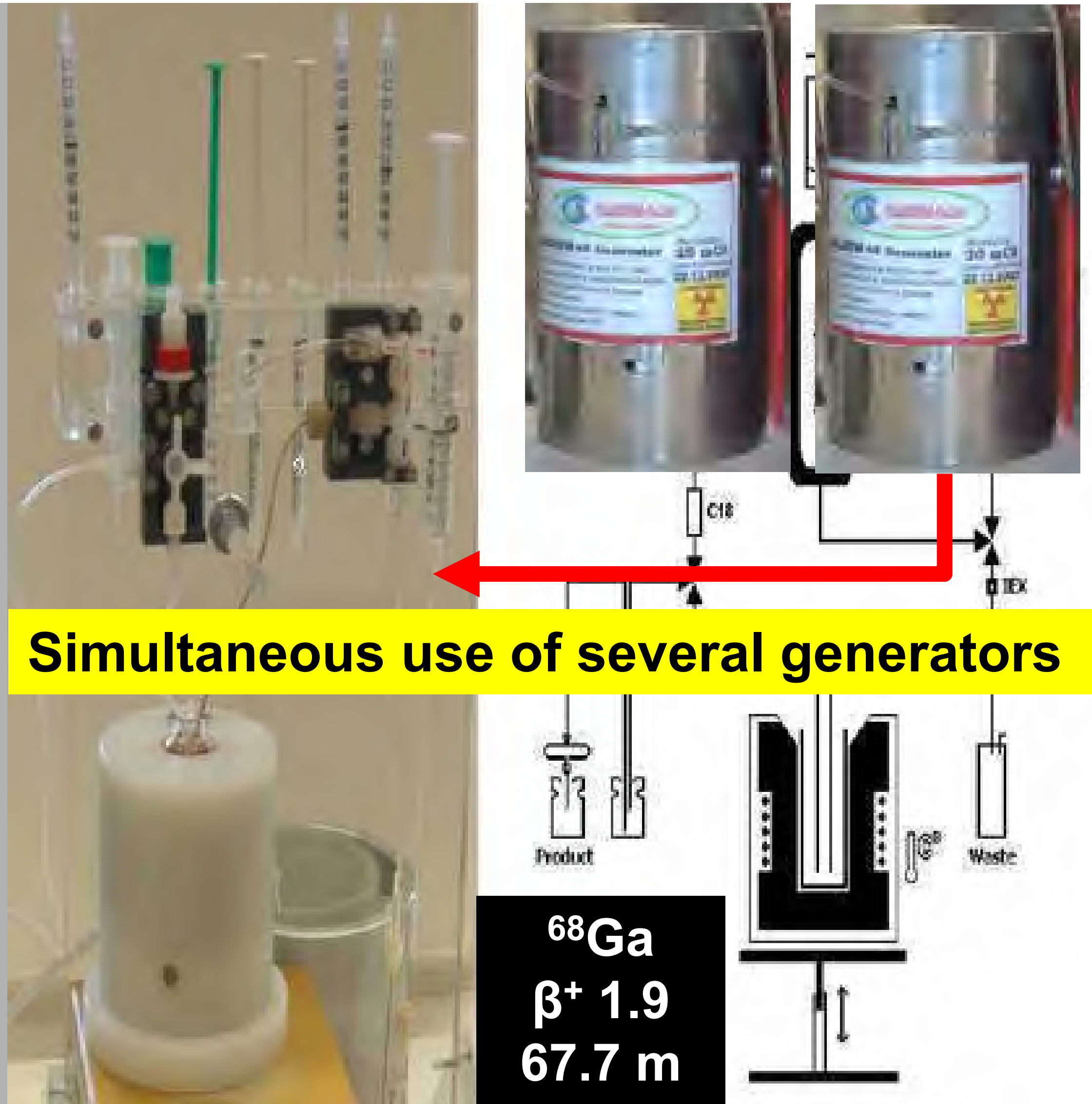
TiO_2 based

Developed in close collaboration between

Radiopharmacy PET/CT Center,
Zentralklinik Bad Berka
and
Institute of Nuclear Chemistry
Johannes Gutenberg-Universität, Mainz, Germany

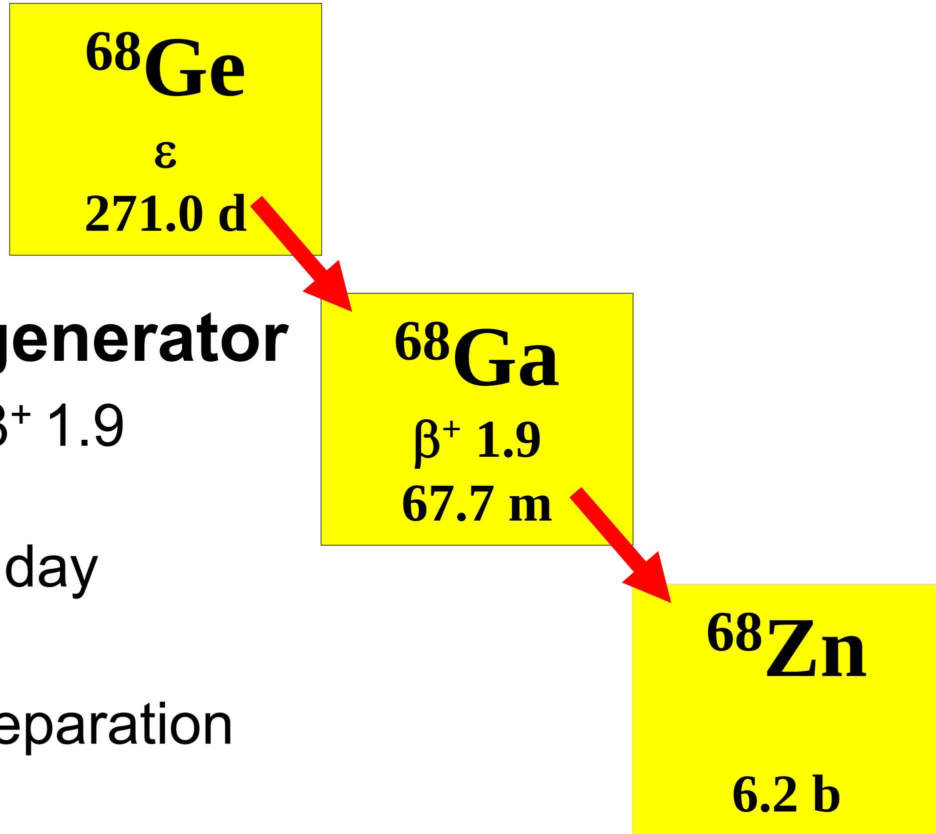
Zhernosekov K, Filosofov DV, Baum RP…. Rösch F

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



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

First clinical studies in 2004, up to now over 7,500 studies done at ZKL Bad Berka.



The ^{68}Ge/Ga radionuclide generator

- Positron emitter, $T_{1/2}$=68 min, β^+ 1.9
- ^{68}Ge/^{68}Ga-generator: $T_{1/2}$=271 day
- convenient, fast, “in-house” preparation
- Gallium chemistry well studied
- Rapid increase of PET centers without cyclotron
- The same peptide can be labeled with ^{177}Lu or ^{90}Y for radionuclide therapy

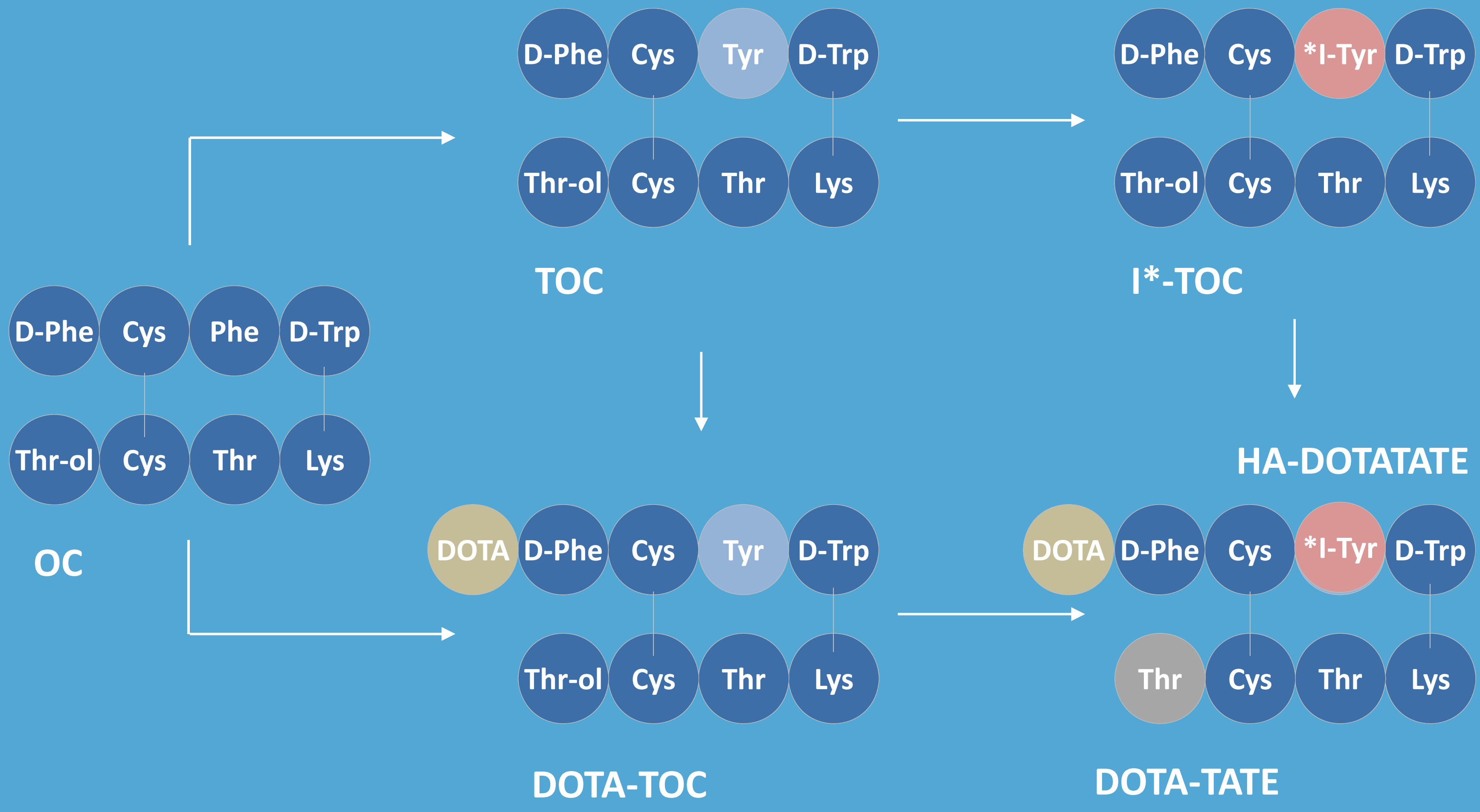
Automated cassette-based synthesis for the daily routine production of radiopharmaceuticals, e.g. Ga-68 HA-DOTA-TATE, PSMA, CPCR4, RGD…..

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)

Improvement of the sst-receptor affinity



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

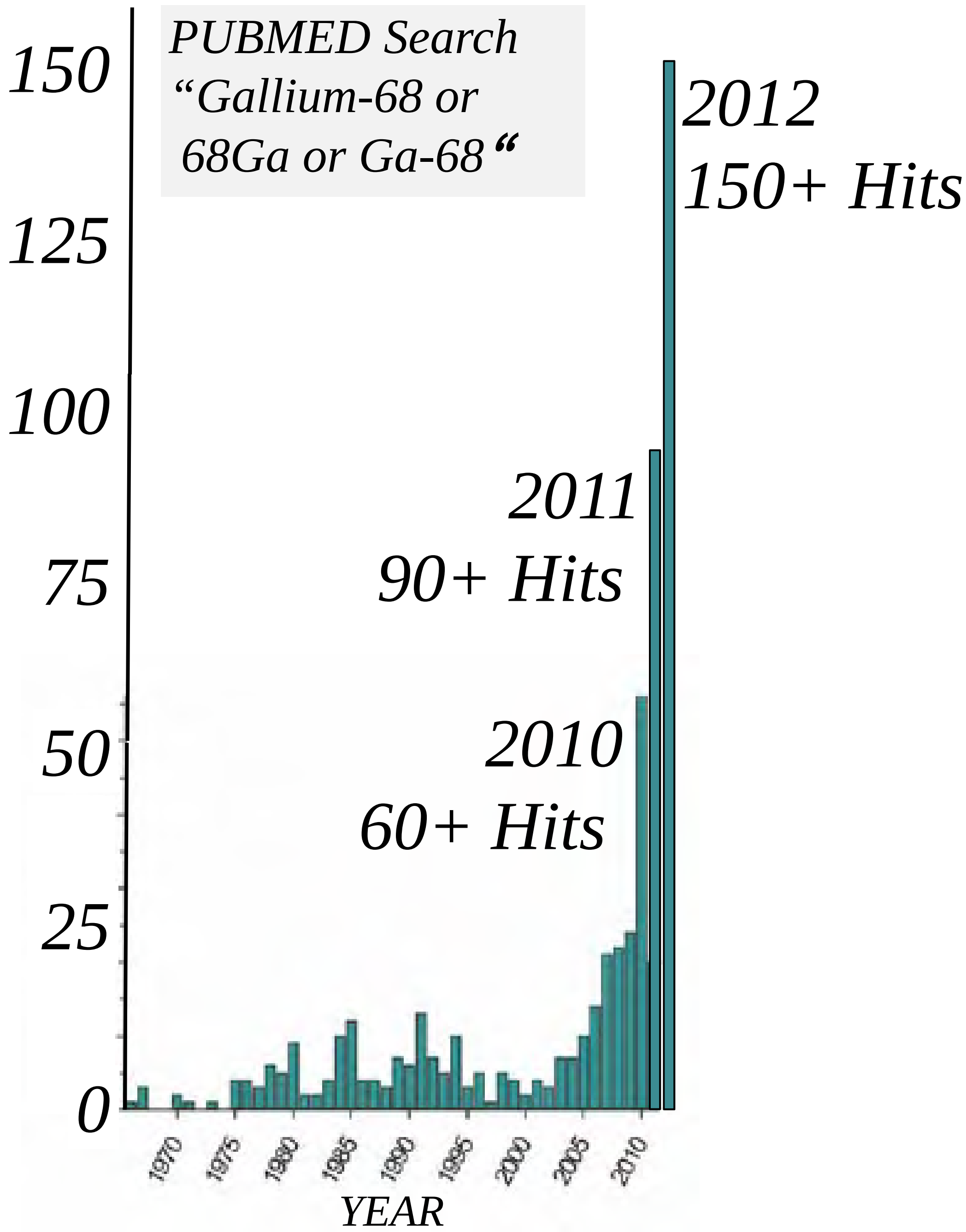
sst-Receptor Affinities
DOTATATE versus HA-DOTATATE

	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 Growth

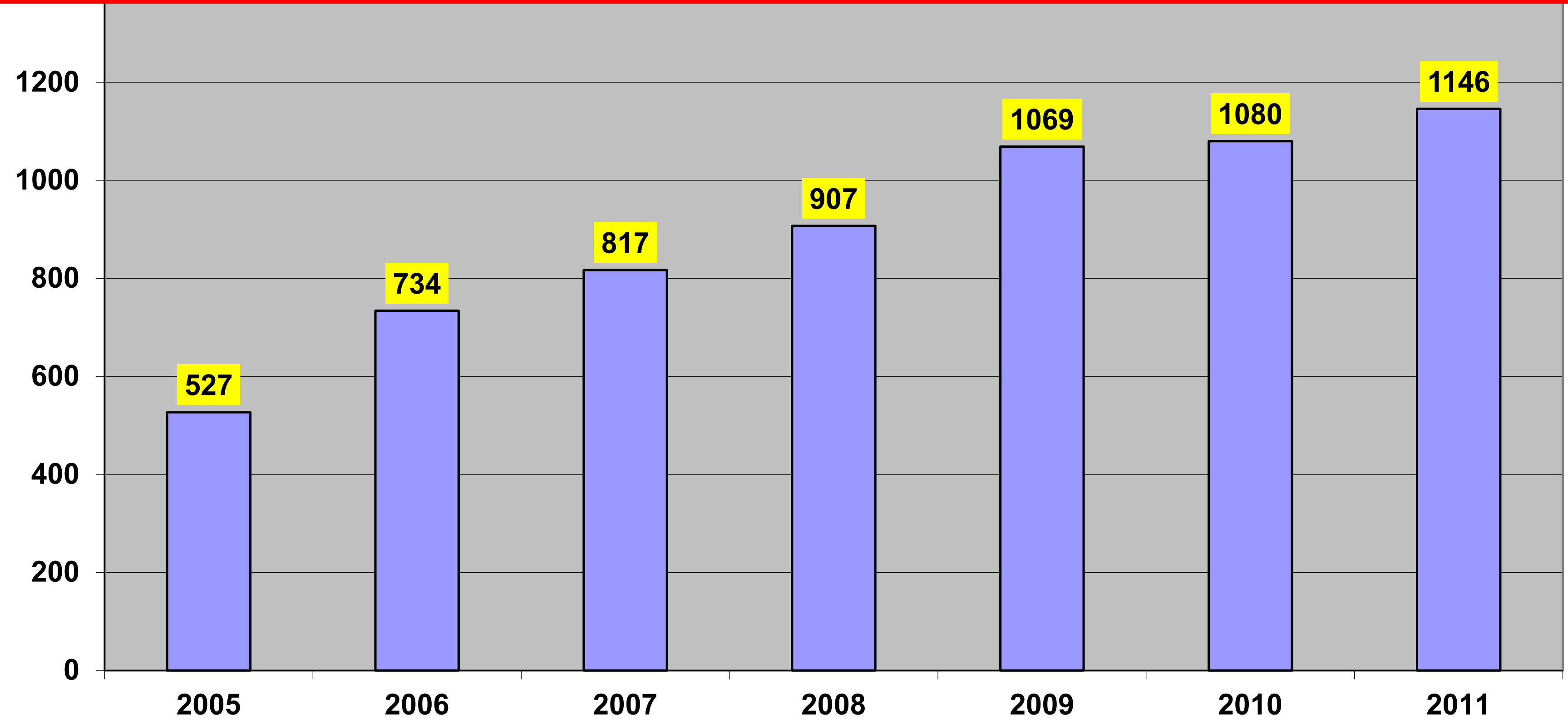
- *Bombesin*
- *RGD*
- *Biotin*
- *Porphyrin-like*
- *Citrate*
- *Octreotides*
- *Affibody*
- *P-glycoprotein targeted*
- *Nanoparticles*
- *Neurotensin*
- *Glycopeptide*
- *Proteins*
- *Nitroimidazoles (hypoxia)*
- *Many more*



Courtesy C. Decristoforo

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

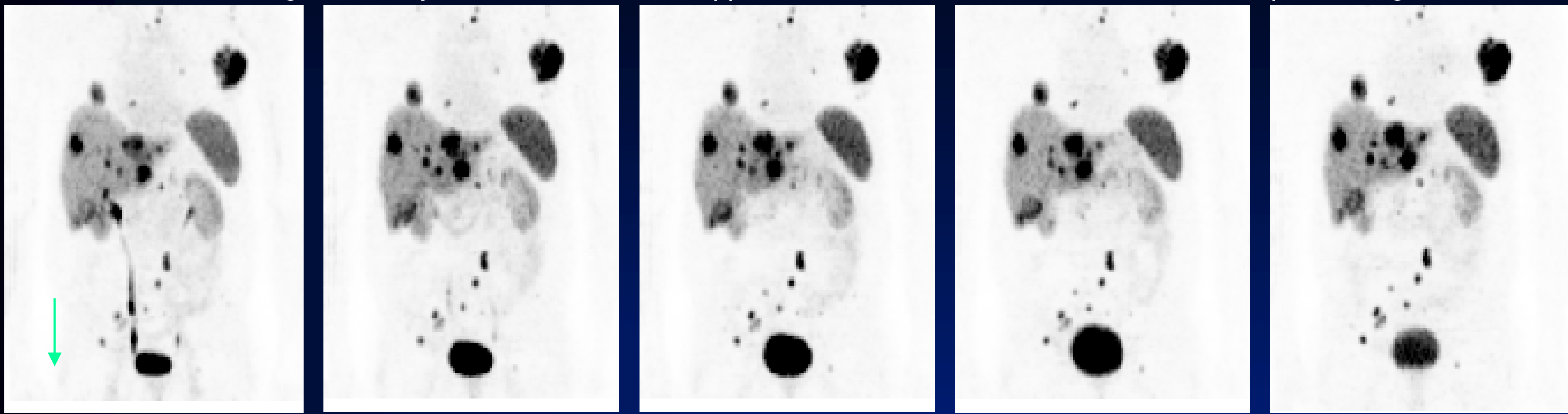
In 2013, we have 8 different Ga-68 labeled radiopharmaceuticals in clinical use!



Ga-68 PET/CT Studies Zentralklinik Bad Berka

Ga-68 SMS Receptor PET – Imaging Technique

Images courtesy Heiner Bihl/Gabriele Pöpperl Klinik für Nuklearmedizin •Katharinen-Hospital, Stuttgart



0:20 p.i. | 0:40 p.i. | 1:00 p.i. | 1:20 p.i. | 1:40 p.i.

Injected activity: 1.5 MBq/kg (100-150 MBq, 3-4 mCi).

Start of acquisition: 60-90 min p.i. (30-180 min)

Acquisition parameters: 2 min. per bed position

Effective radiation dose: 3 mSv for 150 MBq ^{68}Ga-DOTATOC (+CT) (Octreoscan® 12 mSv)

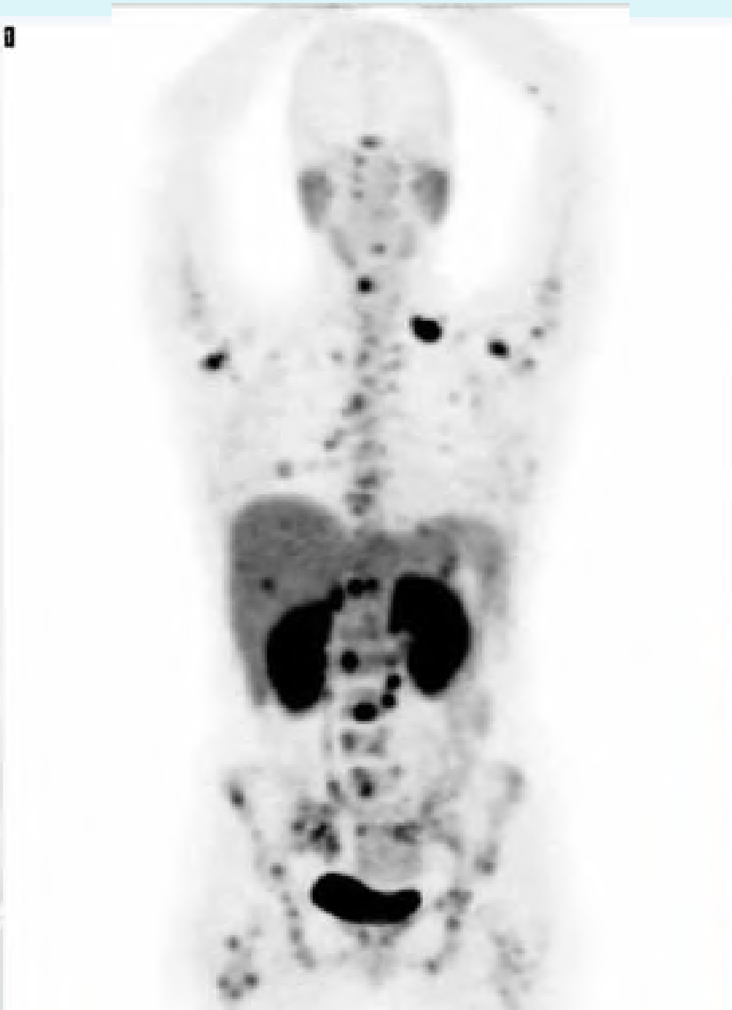
Imaging characteristics: fast kinetics, fast renal clearance, high quality images with very low background → high tumor uptake allows detection of very small lesions (3 to 5 mm) already 30 to 60 min. p.i.

Image analysis: visual and quantitative (SUV) evaluation

Staging

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

^{111}In-octreotide



^{68}Ga-octreotate

4 day time difference

Courtesy Michael Hofman

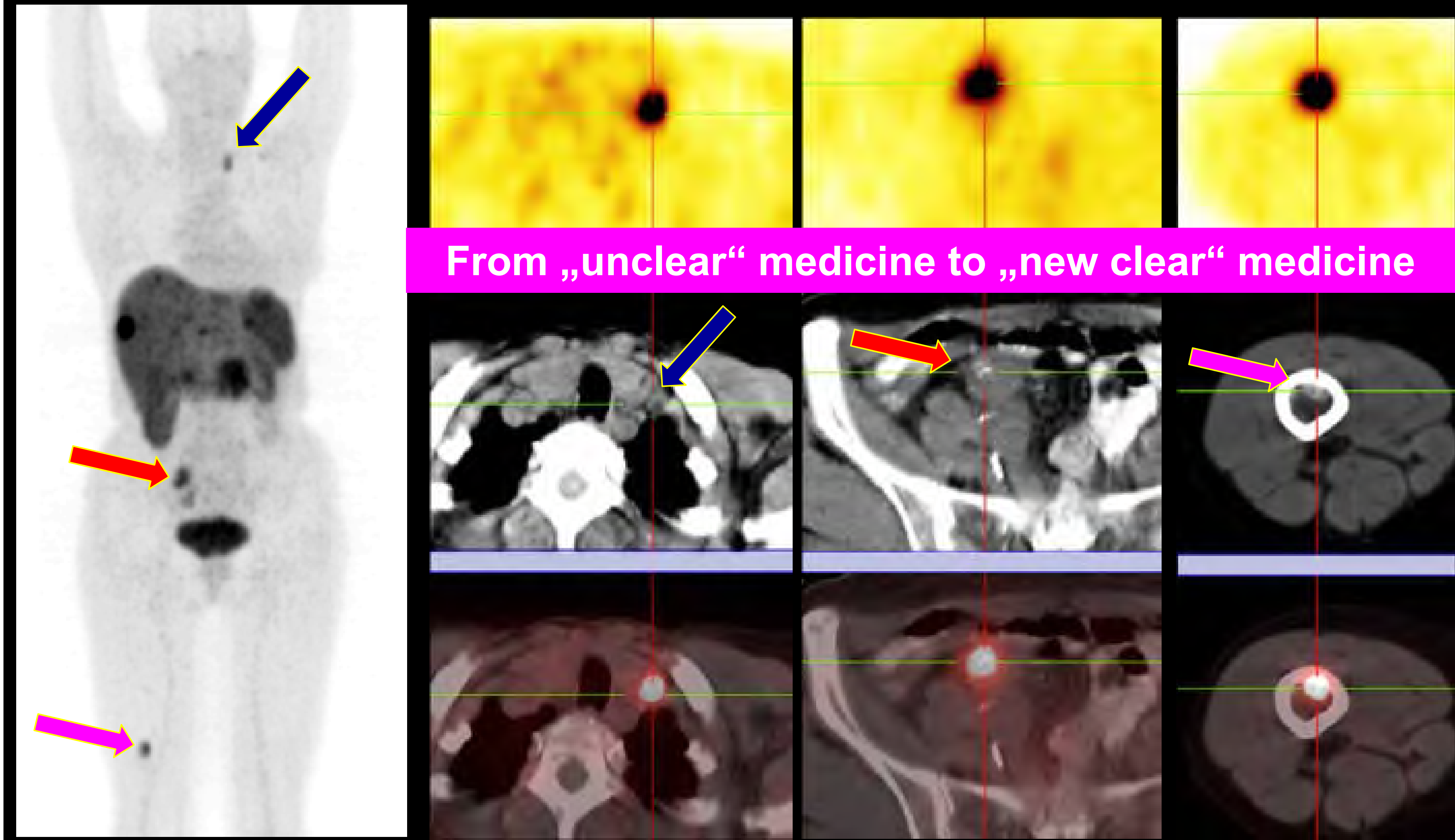
Peter Mac

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

Whole-body diagnosis („one stop shop“)



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

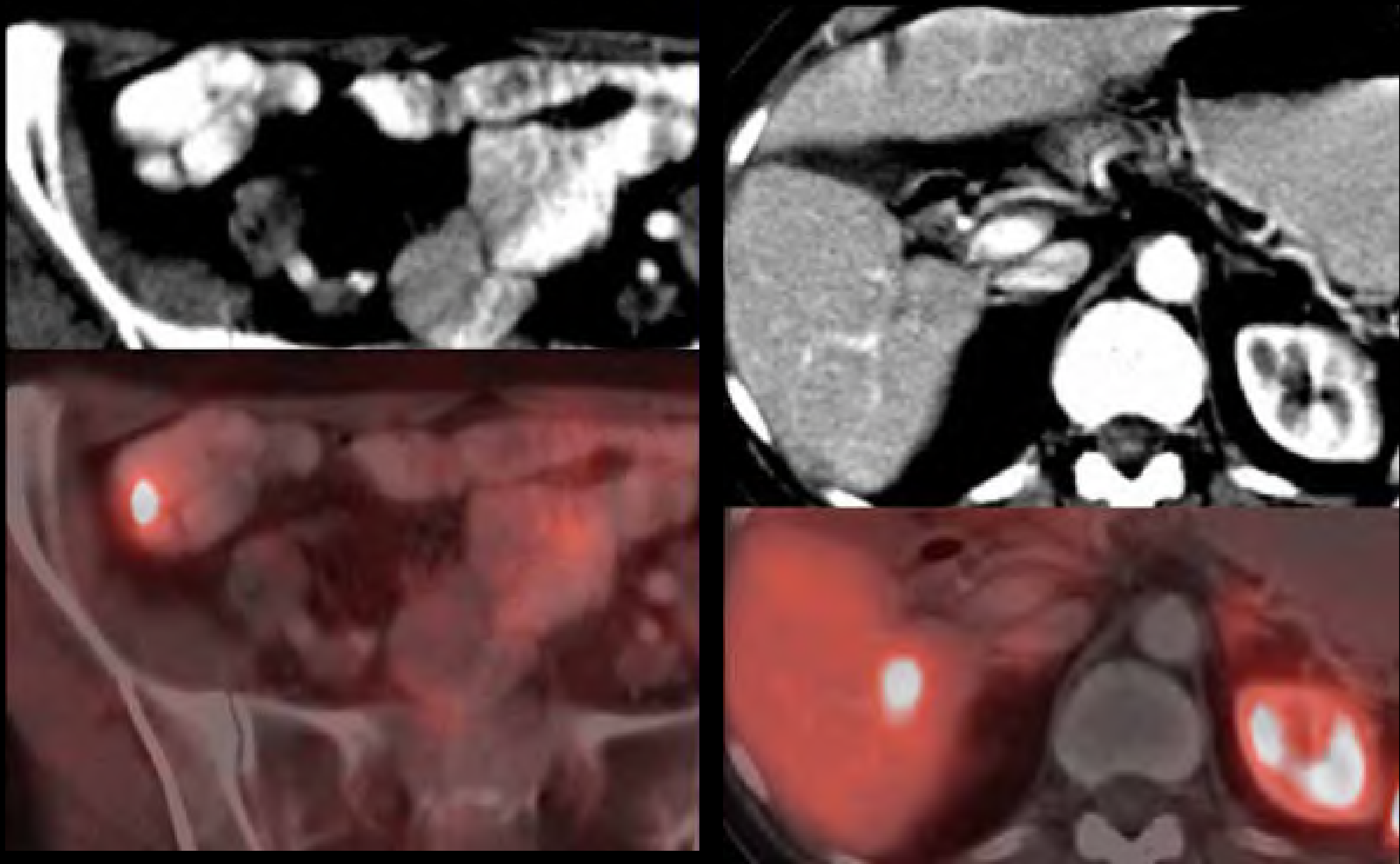
Detection of unknown primary neuroendocrine tumours (CUP-NET) using ^{68}Ga-DOTA-NOC receptor PET/CT

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

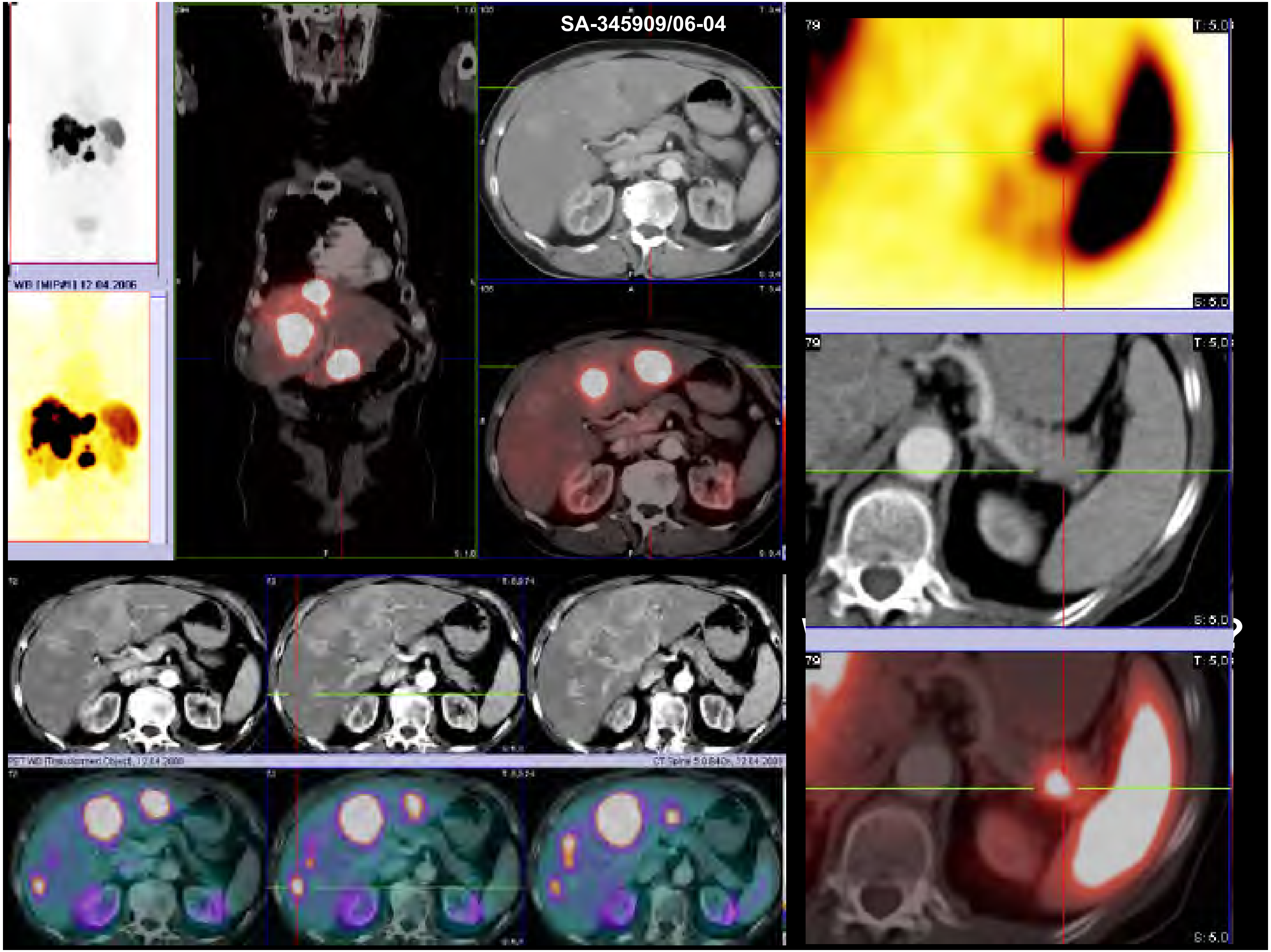
Results In 35 of 59 patients (59%), ^{68}Ga-DOTA-NOC PET/CT localised the site of the primary: ileum/jejunum (14),

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.

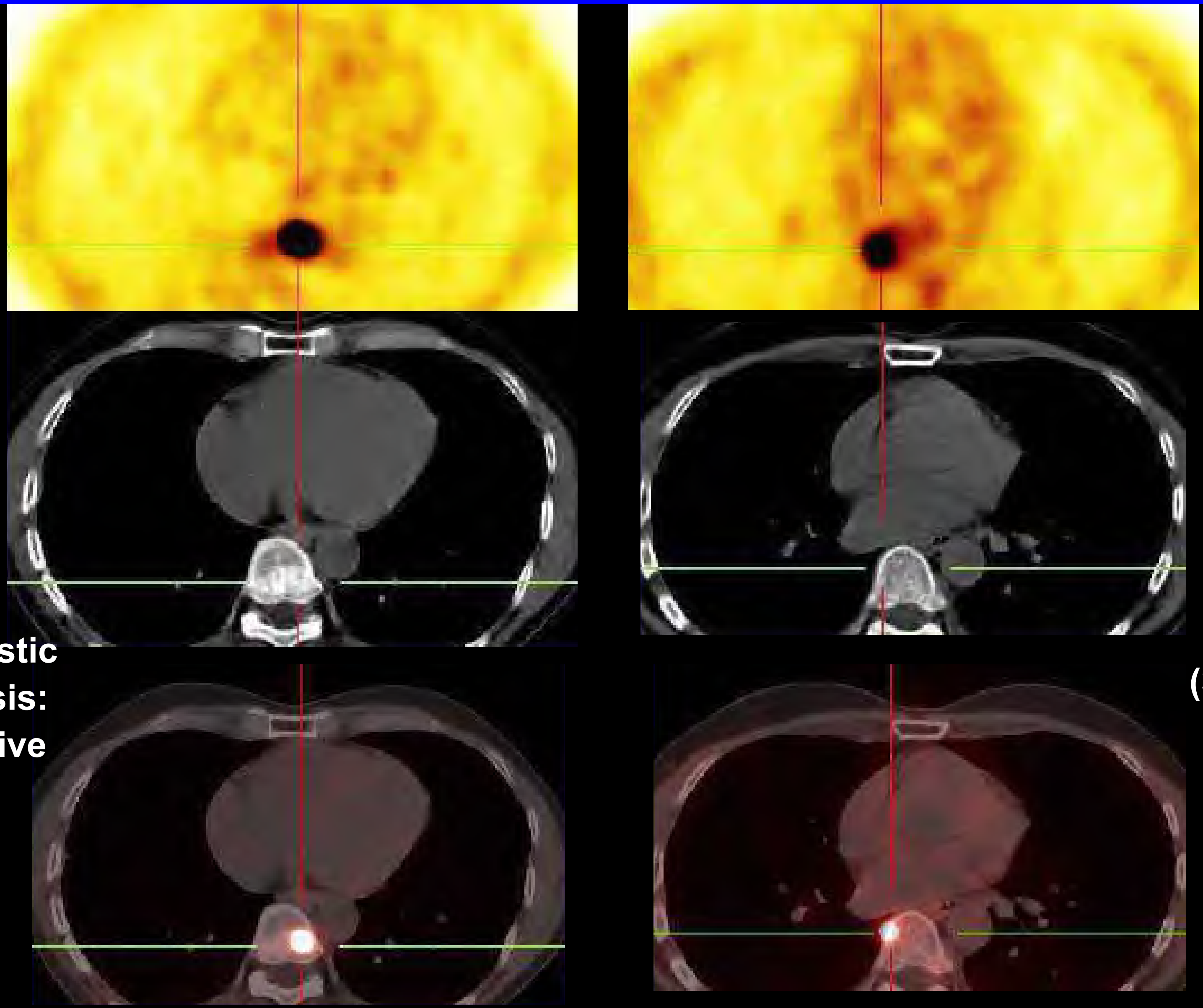


Primary tumor (ileum) and synchronous liver metastasis


SA-345909/06-04

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

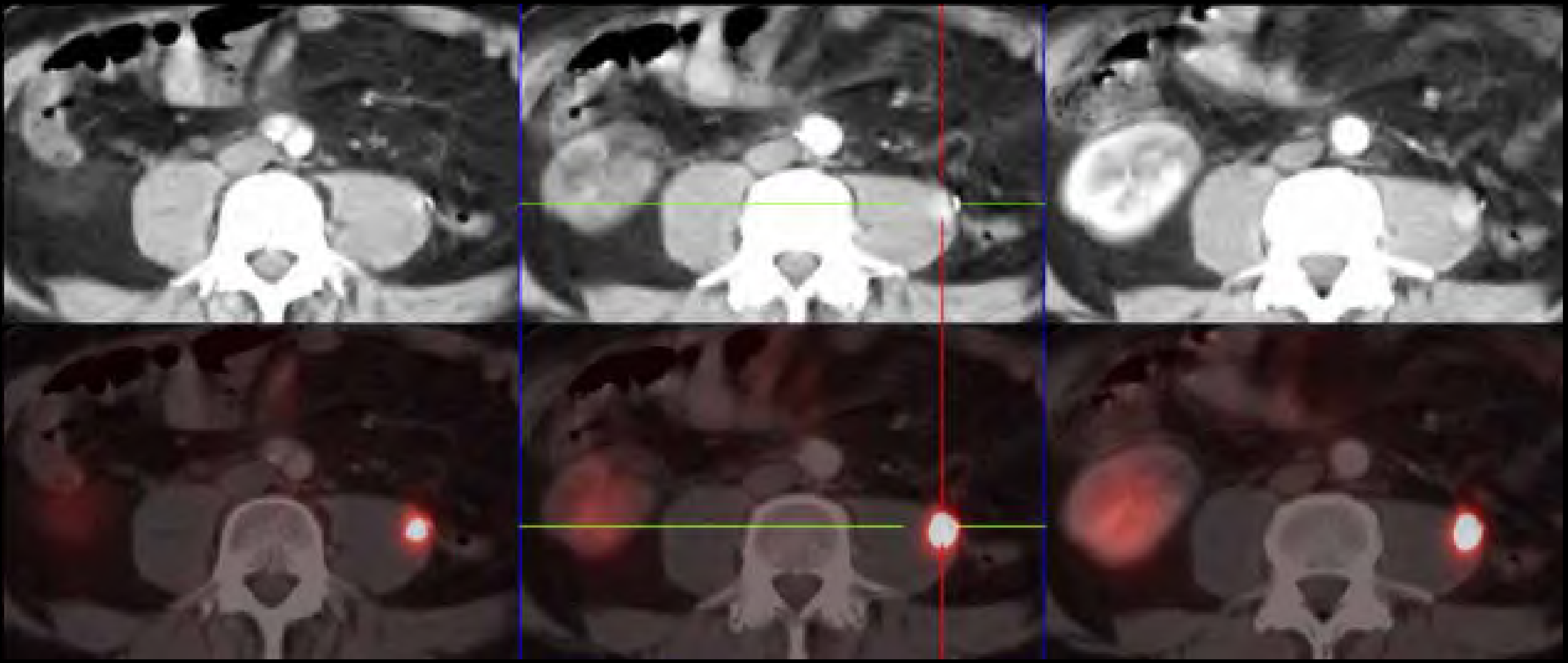
Superiority of Ga-68 DOTANOC PET/CT over conventional imaging



Osteoblastic metastasis: CT positive

CT normal (3 mm lesion on MRI)

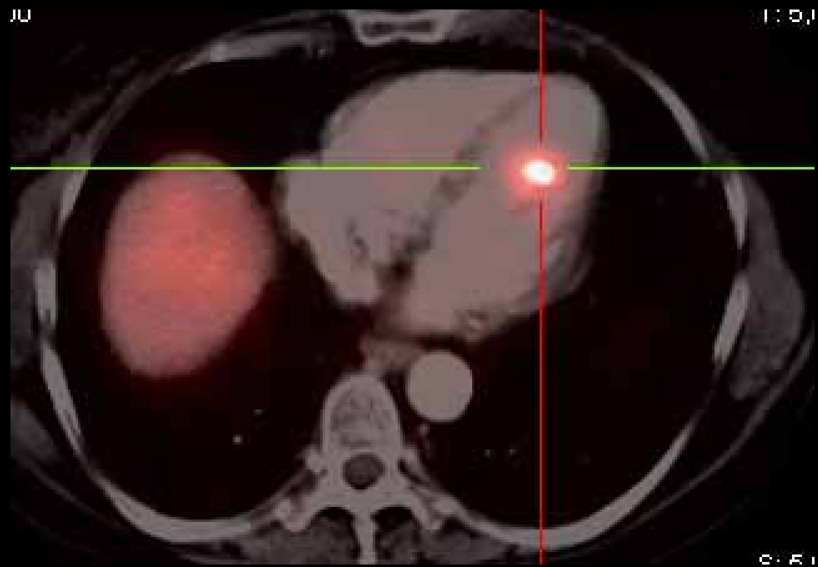
Rare localizations detected by PET/CT



Intramuscular metastasis (psoas muscle)

358.775-P.J.

INTRACARDIAC METASTASIS (SEPTUM)



In Wahl R. (ed.):
Principles and Practice of PET and PET/CT.
Lippincott Williams & Wilkins, Philadelphia 2008 (p. 411-437).

CHAPTER

8.21

PET and PET/CT Imaging of Neuroendocrine Tumors

RICHARD P. BAUM AND VIKAS PRASAD

Principles and Clinical Indications

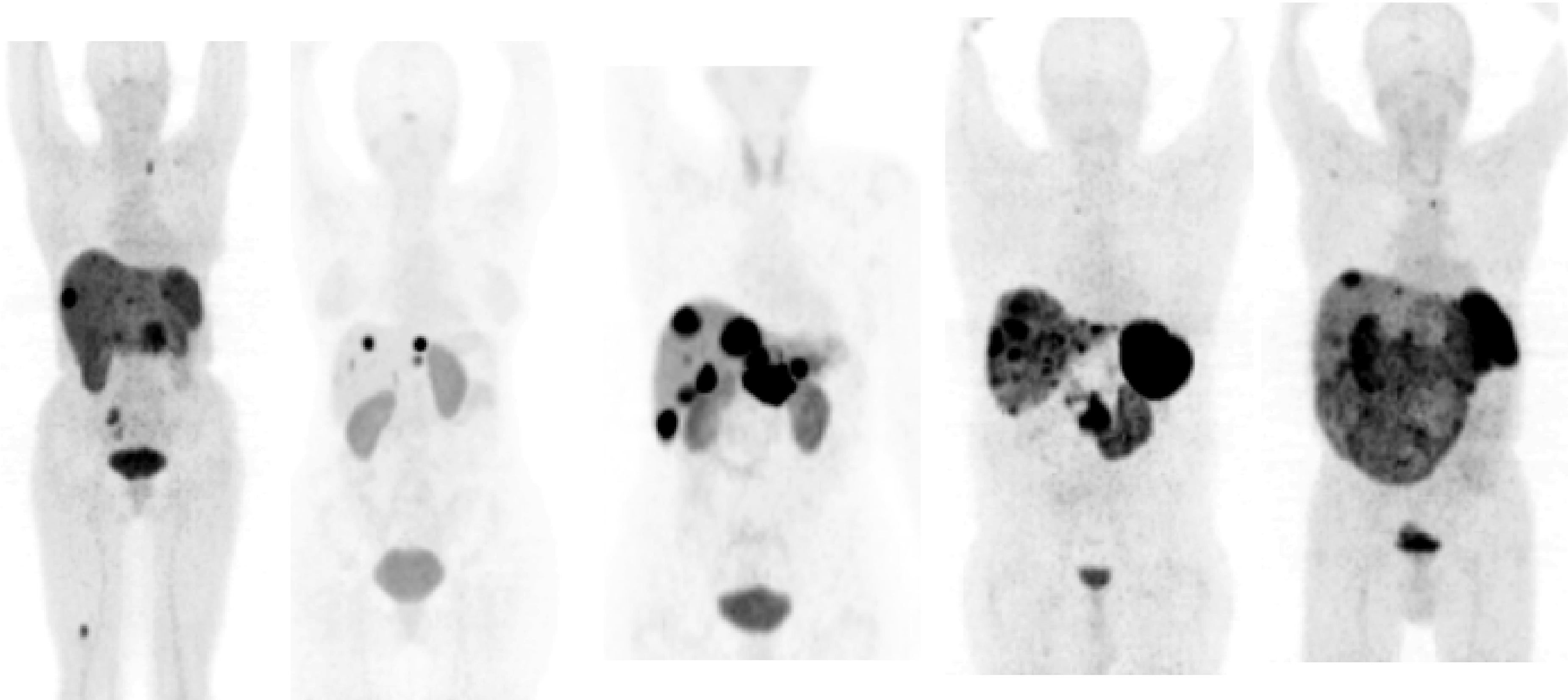
PATIENT EVALUATION BEFORE PRRT

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

semiquantitative measurement by

SUV (Standardized Uptake Values)

More than just looking at images..



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

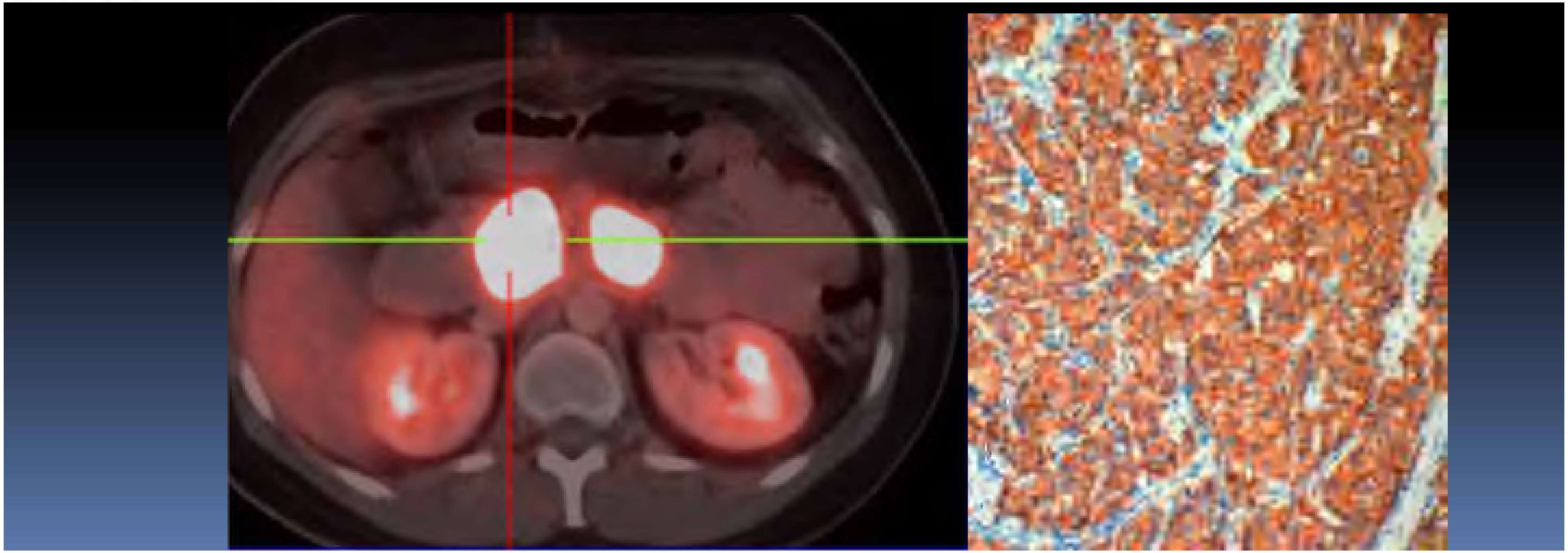
Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-011-1846-5

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

ORIGINAL ARTICLE

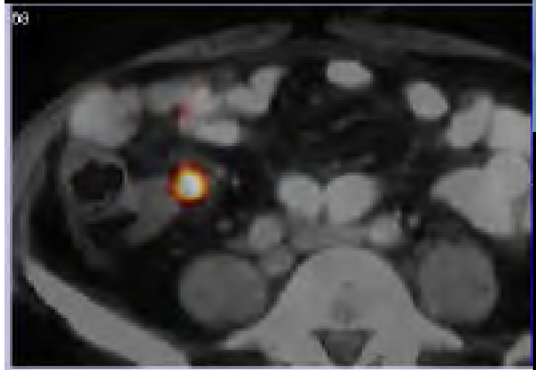
Molecular imaging with ^{68}Ga-SSTR PET/CT and correlation to immunohistochemistry of somatostatin receptors in neuroendocrine tumours

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



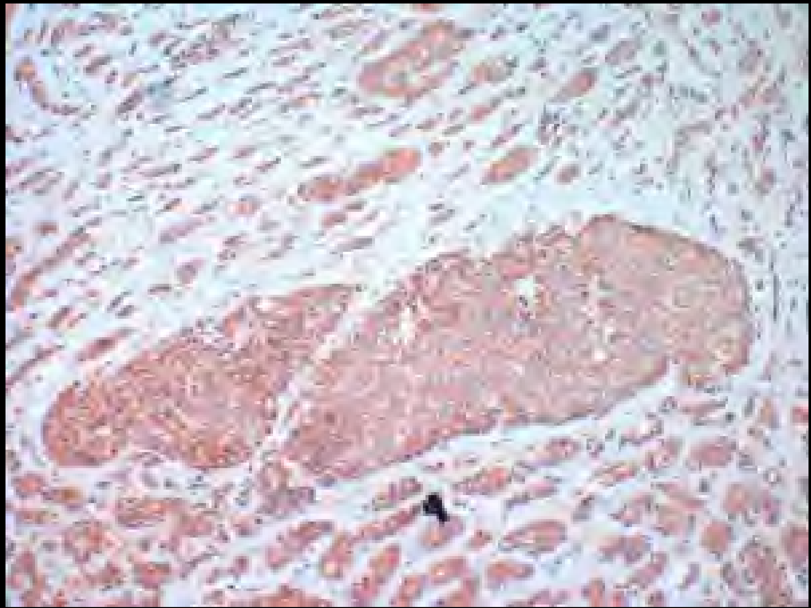
Ileum NET

IHC Scoring for SSTR1-5

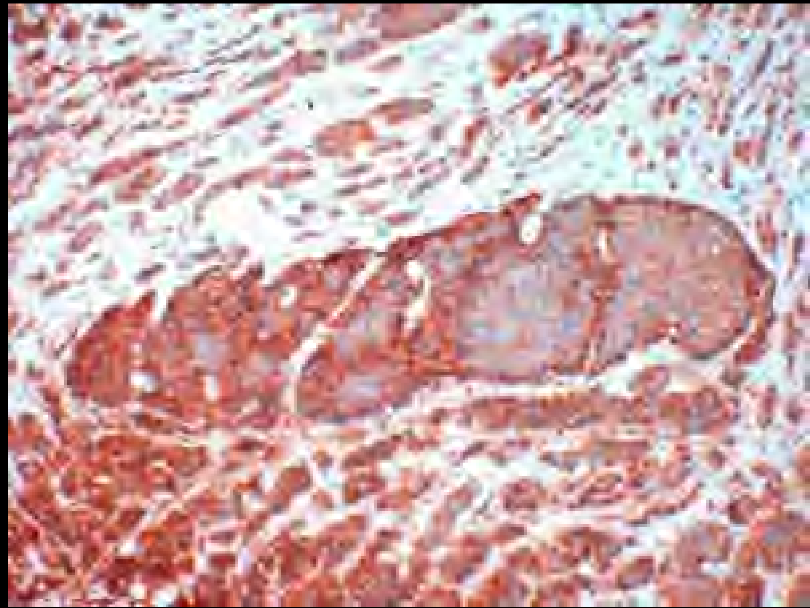
Ga-68 DOTA-SMS PET/CT in 34 histologically documented GEP NET patients

44 surgical specimens generated

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



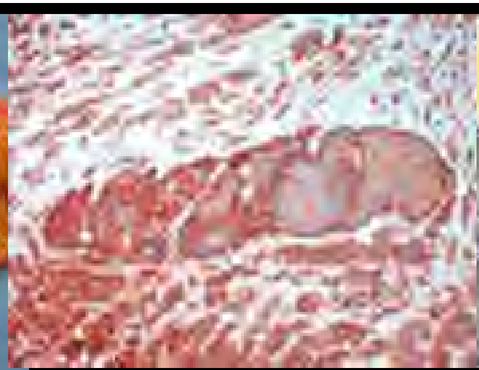
SSTR1: IRS = 2; HER2 = 1+

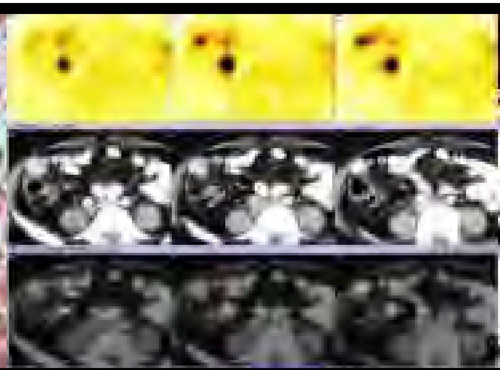


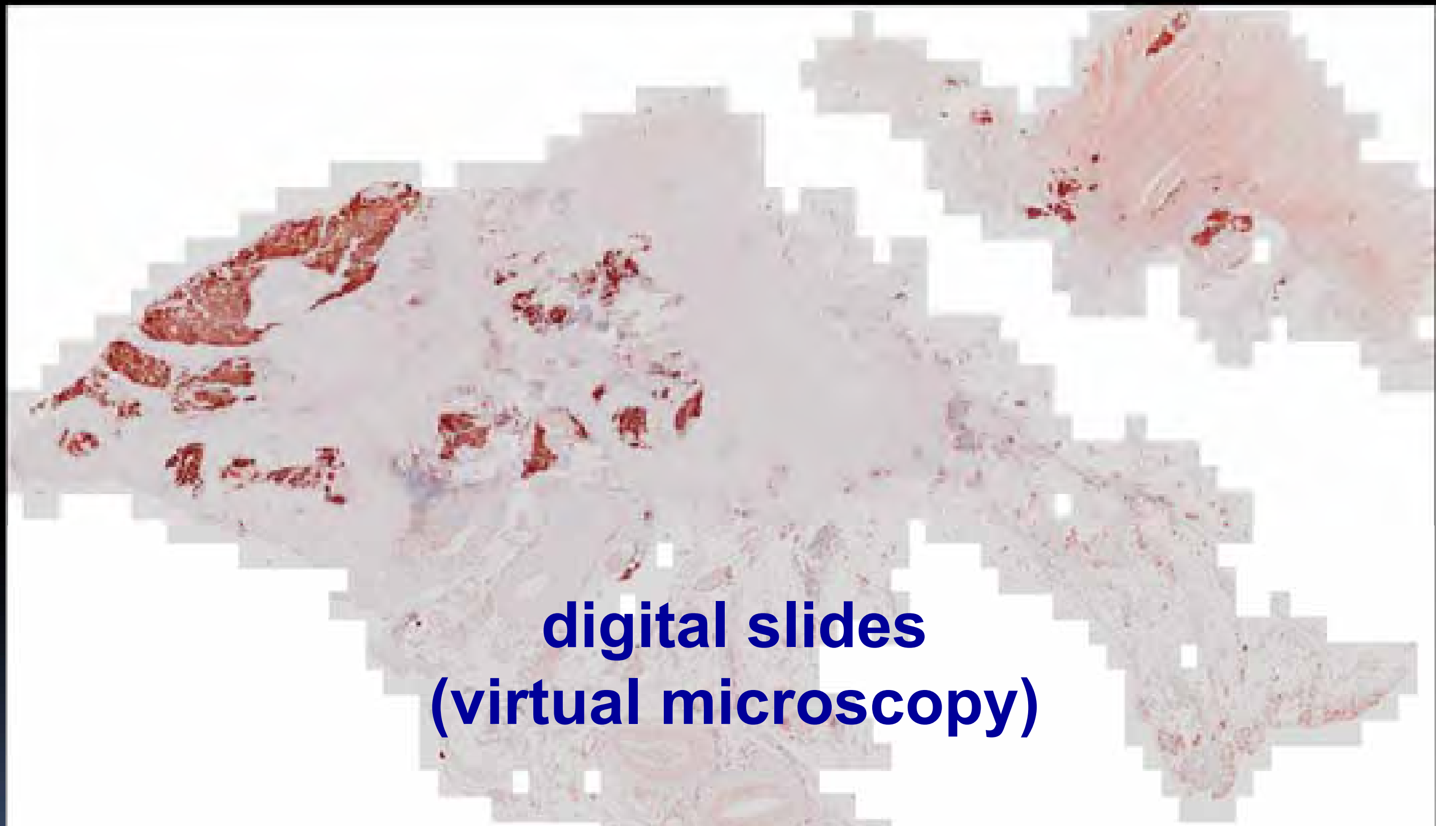
SSTR2A: IRS = 9; HER2 = 3+

Lymph Node

Does receptor density, as predicted by PET/CT (SUV, MTV, MTD) correlate with immunohistochemistry scores (HER2 & IRS)?







Digitialised Histopathological Classification
Definiens XD Image Analysis - Processing

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 correspon-ding pathology grading.

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

Digitalized Histopathology Combined with Somatostatin Receptor PET/CT

From Tissue to Molecular Imaging to Therapy

- 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 (PRRNT) vs chemotherapy vs localised therapy vs molecular therapy etc.

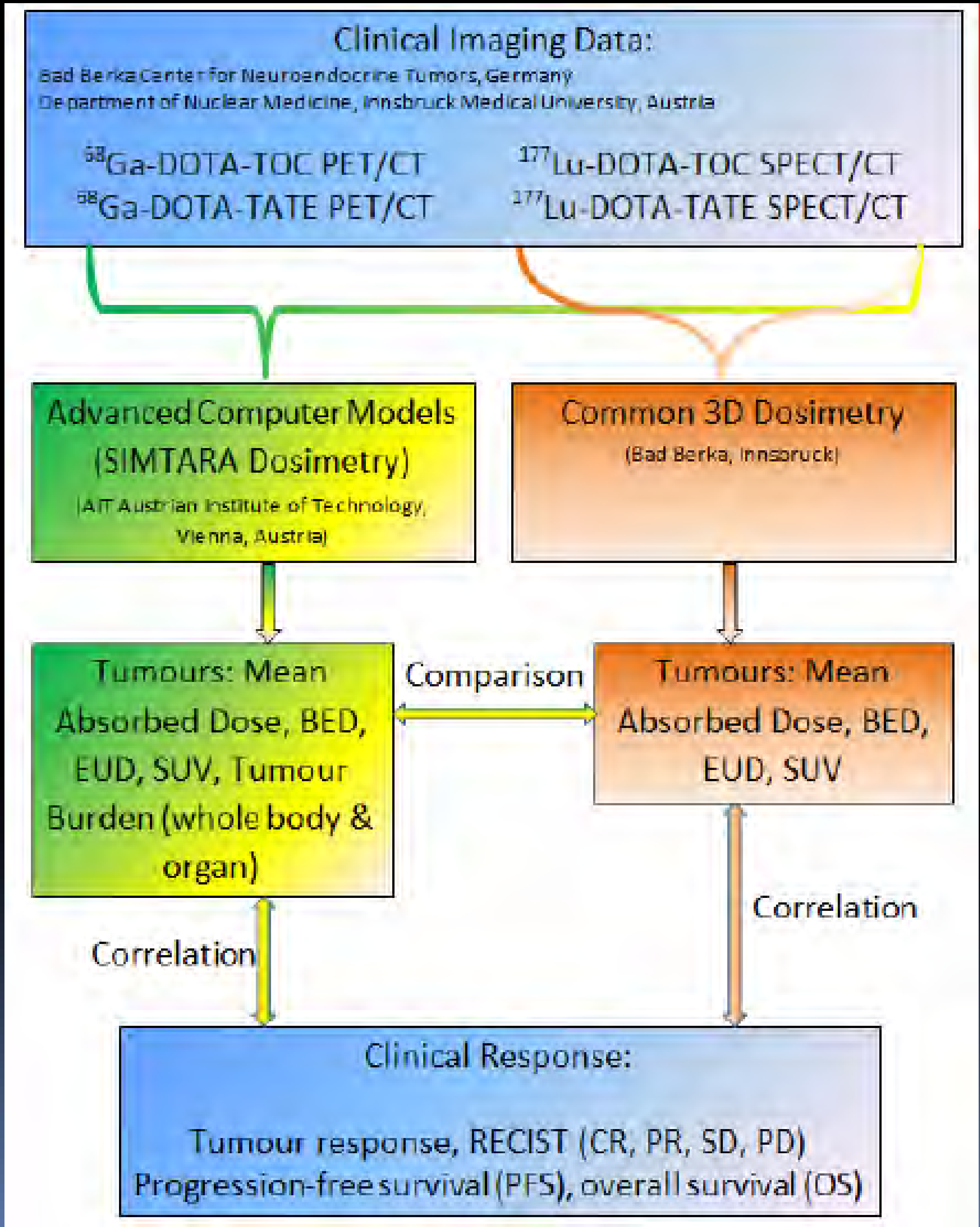
Management Strategy

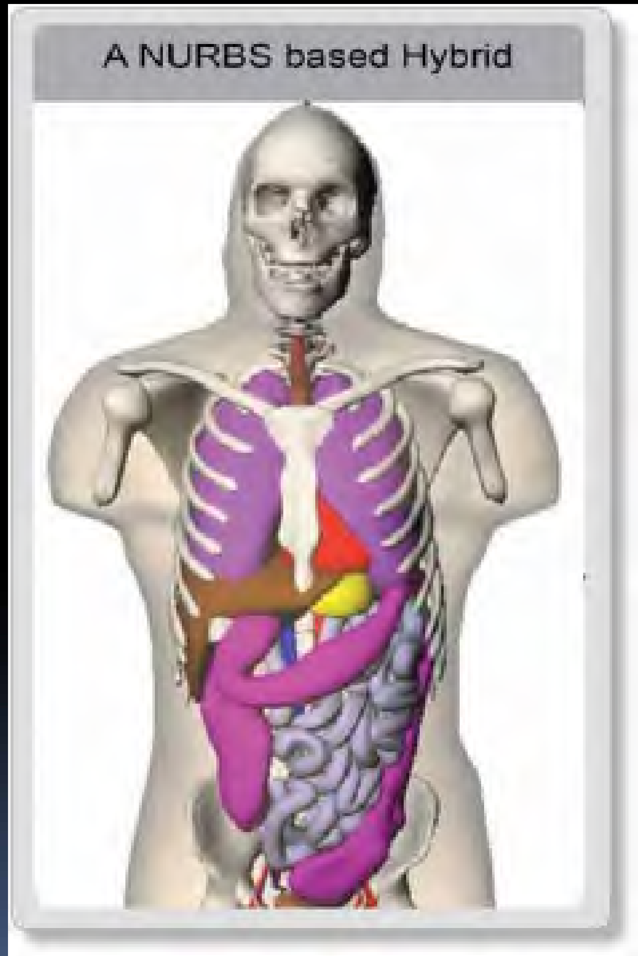
On the Way to Personalized Medicine

Lecture Outline

- Definition and principles of THERANOSTICS and Personalized Medicine
- THERANOSTIC radionuclides and Ga-68 generator
- Neuroendocrine tumors (NET) as a paradigm
- Diagnosis of NET by PET/CT (clinical applications)
- Dosimetry (organ & tumor dose calculations)
- Therapy of NET (Peptide Receptor Radiotherapy, PRRT)
- Future perspectives
    - new peptides (antagonists, CXCR4, RGD)
    - PSMA: THERANOSTICS potential for prostate ca.

Development of new software for more precise dosimetry

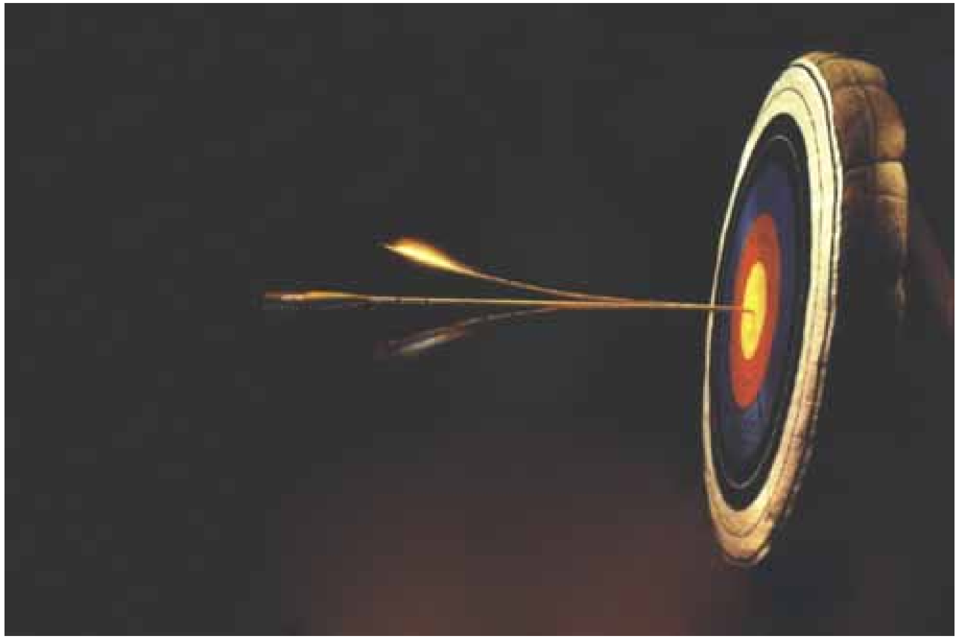




Source: Segars W. Development and application of the new dynamic NURBS-based cardiac-torso (NCAT) phantom. PhD thesis, The University of North Carolina, 2001.

Dosimetry: A comparison

External Beam Therapy



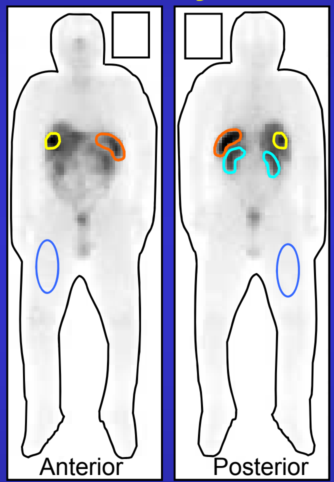
Radionuclide Therapy

Courtesy Matthias Blaickner, AIT

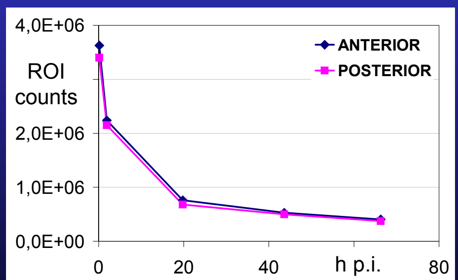
Dosimetry (MIRD-Scheme)

ROI Analysis → Determination of activities → Fit of time-activity graphs

Serial planar whole body scans



ROI statistics



ROI- statistics

↓

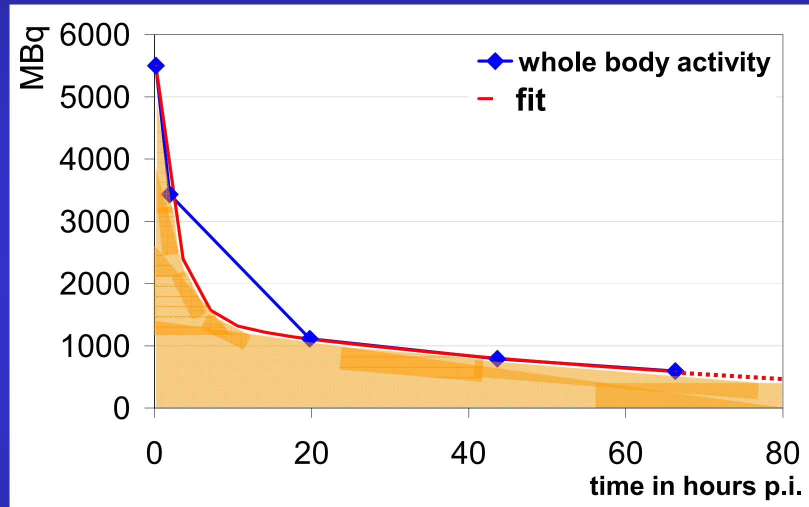
geometric mean + background correction

↓

time-activity graph
- organ and tumor uptake

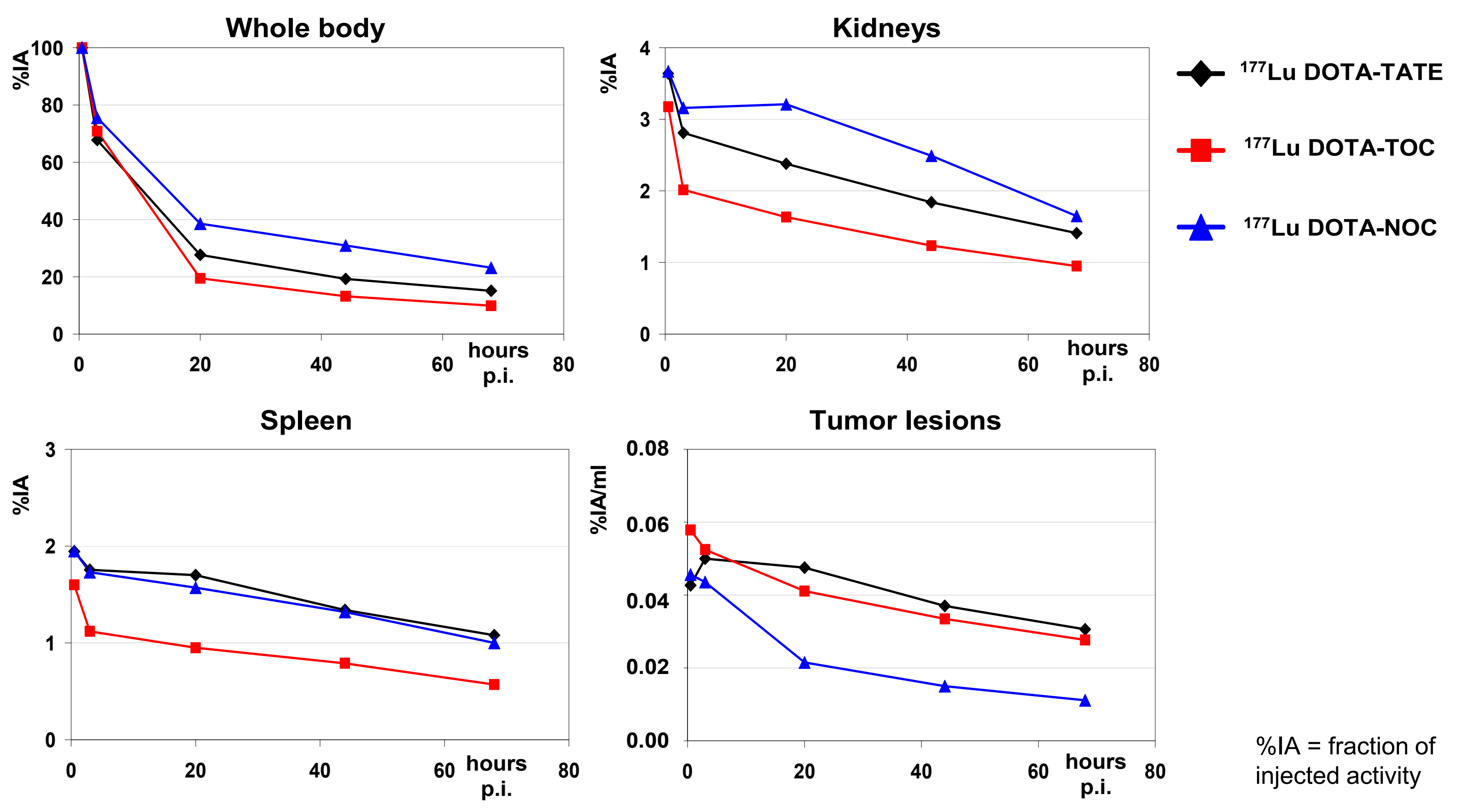
↓

fit to exponential function
- effective half-life
- residence time



Estimation of mean absorbed organ and tumor doses
(using OLINDA/EXM software)

Uptakes



%IA = fraction of injected activity

Results

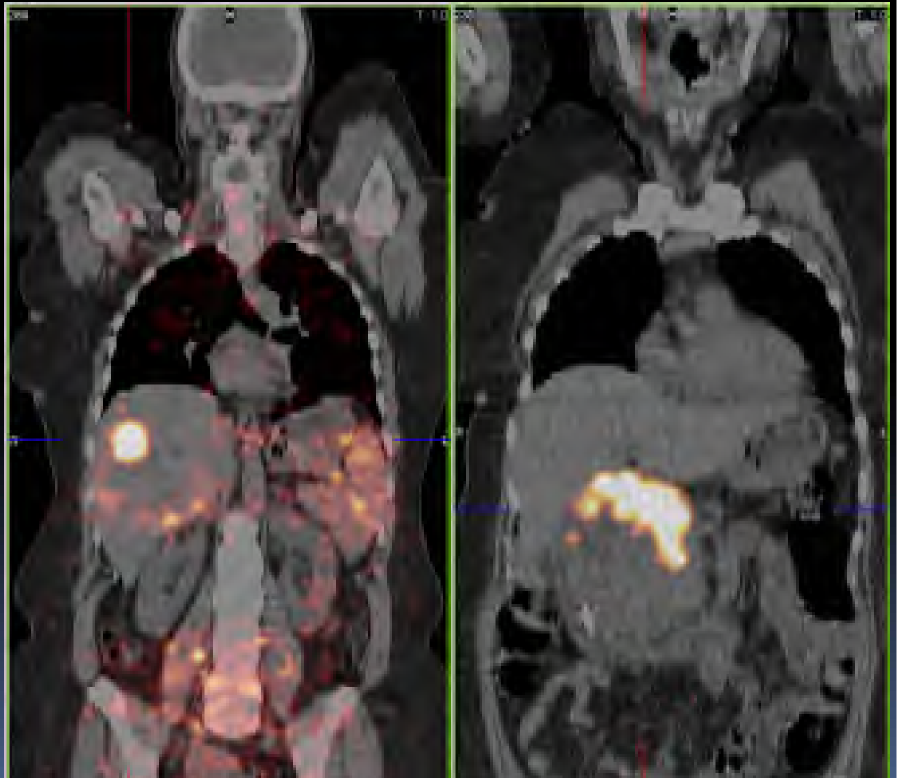
Mean absorbed dose mGy/MBq (Median values and range of variation) *significant		Whole-body	Kidneys	Spleen	Tumor lesions
	DOTA-TATE	0.05 (0.02-0.1)*	0.8 (0.3-2.6)*	1.1 (0.2-9.3)*	5.2 (0.1-89.6)
	DOTA-NOC	0.07 (0.04-0.1)	1.1 (0.6-1.5)	1.3 (0.7-3.4)	2.0 (0.5-31.7)
	DOTA-TOC	0.03 (0.02-0.08)*	0.6 (0.3-1.6)*	0.7 (0.2-2.8)*	4.9 (0.3-39.7)

Dosimetry - Perspectives

Pre-therapeutic organ and tumor dosimetry using receptor PET/CT and longer lived positron emitters, e.g. Sc-44, Y-86 or Cu-64 and comparison with Ga-68 results.

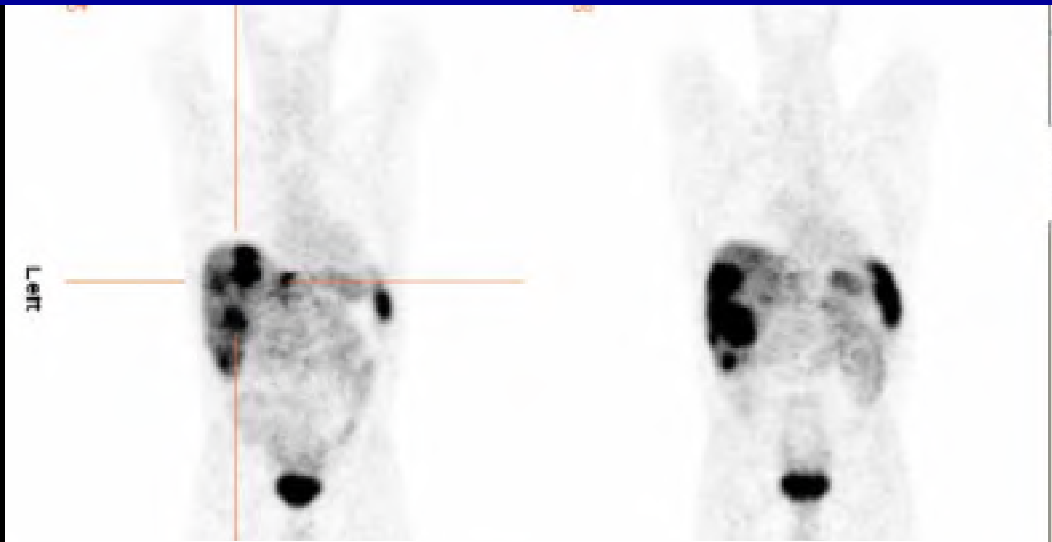
Selection of the optimal peptide and radionuclide for individual therapy of each patient („personalized dosimetry") by pretherapeutic measurement of organ and tumor doses.

Personalized dosimetry



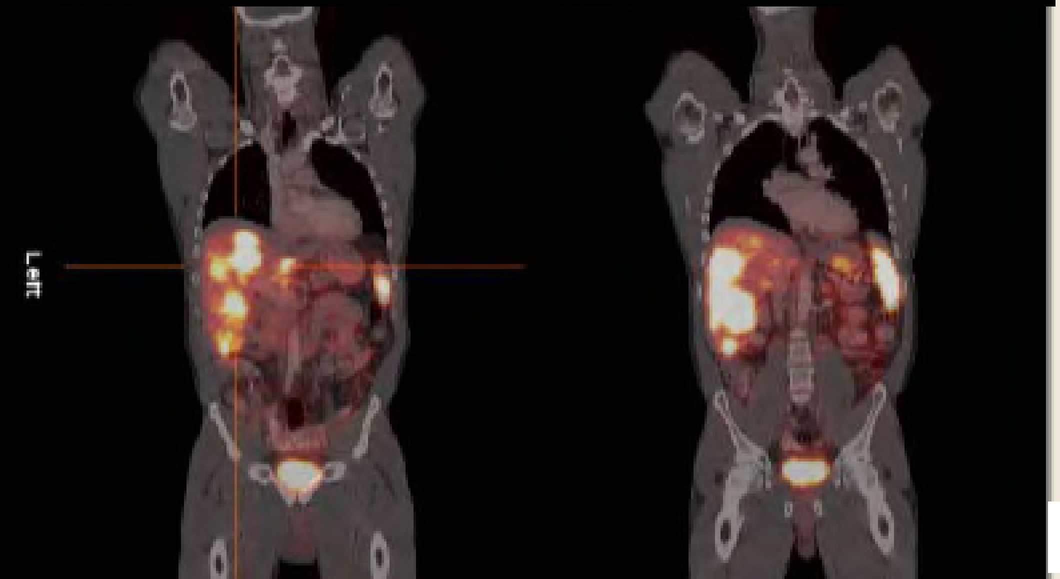
Y-86 DOTA-NOC Receptor PET/CT

Sc-44 ($t_{1/2}$ 3.9 hrs from Titanium-44 generator ($t_{1/2} > 47$ years)



First use of Scandium-44 SR-PET/CT

Scandium-44 DOTA-TOC PET/CT 40 min. p.i.



Injected activity: 32 MBq

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

Lecture Outline

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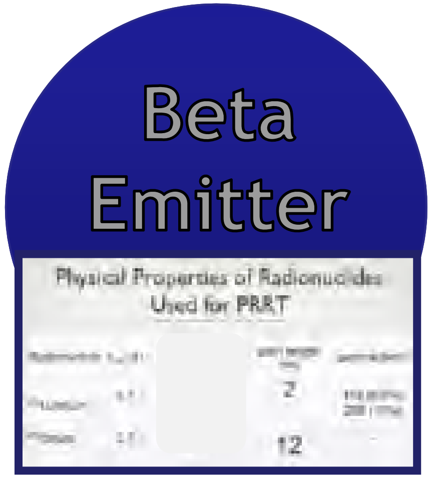
    - PSMA: THERANOSTICS potential for prostate ca.

Courtesy of Dr. Choi SJ

Therapeutic Radionuclides

Nuclide	$T_{1/2}$	Emission	Mean path length
I-125	60.0d	auger	10nm
At-211	7.2h	alpha	65nm
Lu-177	6.7d	beta/gamma	0.7mm
Cu-67	2.58d	beta/gamma	0.7mm
I-131	8.04d	beta/gamma	0.9mm
Sm-153	1.95d	beta/gamma	1.2mm
Re-186	3.8d	beta/gamma	1.8mm
P-32	14.3d	beta	2.9mm
Re-188	17h	beta/gamma	3.5mm
In-114m	50d	beta/gamma	3.6mm
Y-90	2.67d	beta	3.9mm



J Nucl Med 2011; 52:841-844

Somatostatin Receptors as Targets for Nuclear Medicine Imaging and Radionuclide Treatment

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

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

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

GUIDELINES

EJNMMI February 2013 ePub ahead of print

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

The pdf of this guidance is available on our website www.prrtinfo.org

ENETS Center of Excellence since 2011

Zentralklinik Bad Berka*

Int. Medicine, Endocrinology, Gastroenterology, Oncology

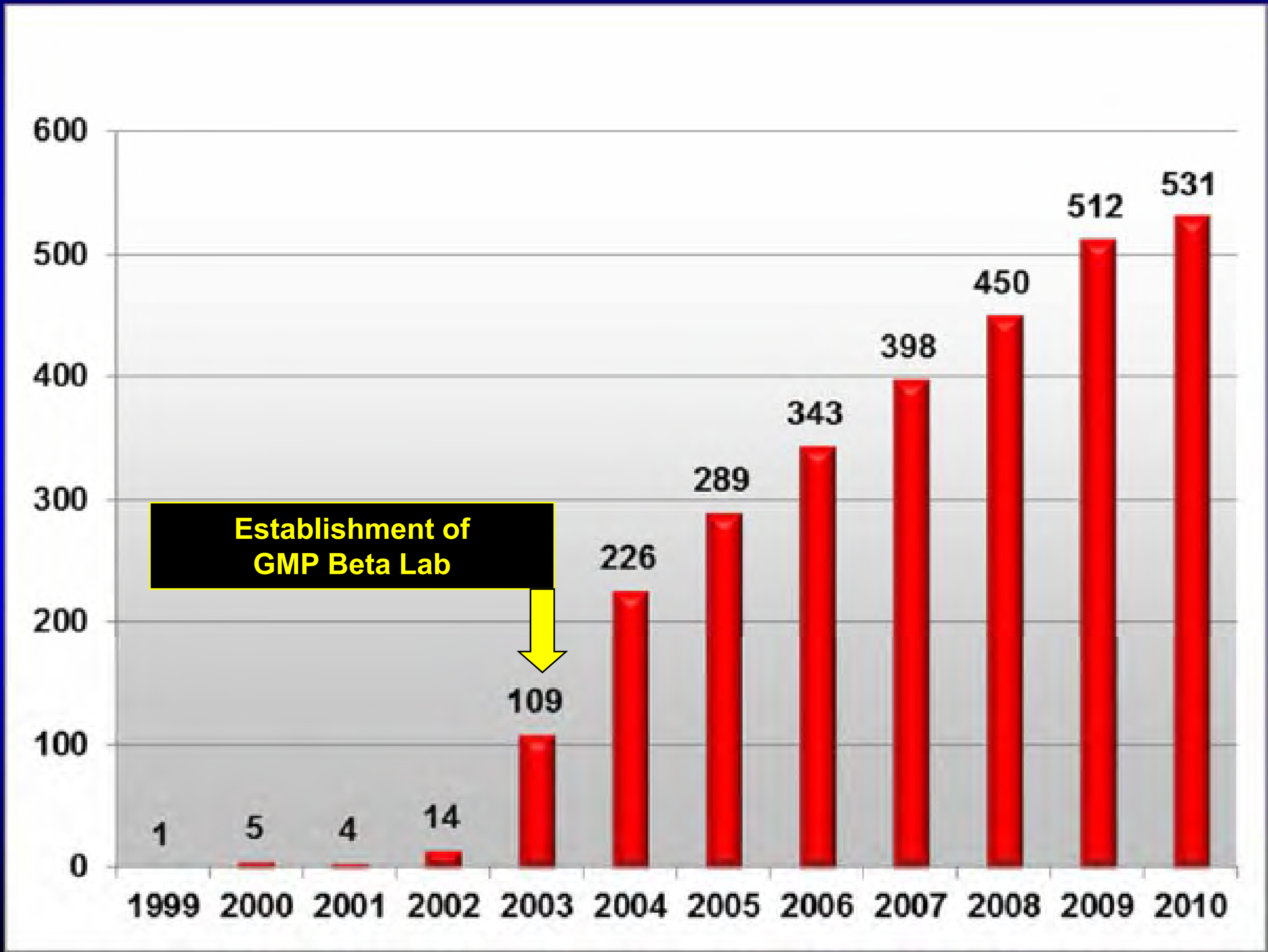
Thoracic, Abdominal/Visceral and Spinal Surgery

Interventional Radiology

Molecular Radiotherapy & Imaging (PET/CT Center)

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

Radiopeptide Therapy Cycles
Zentralklinik Bad Berka 1999 - 2010



FUTURE OF CANCER TREATMENT

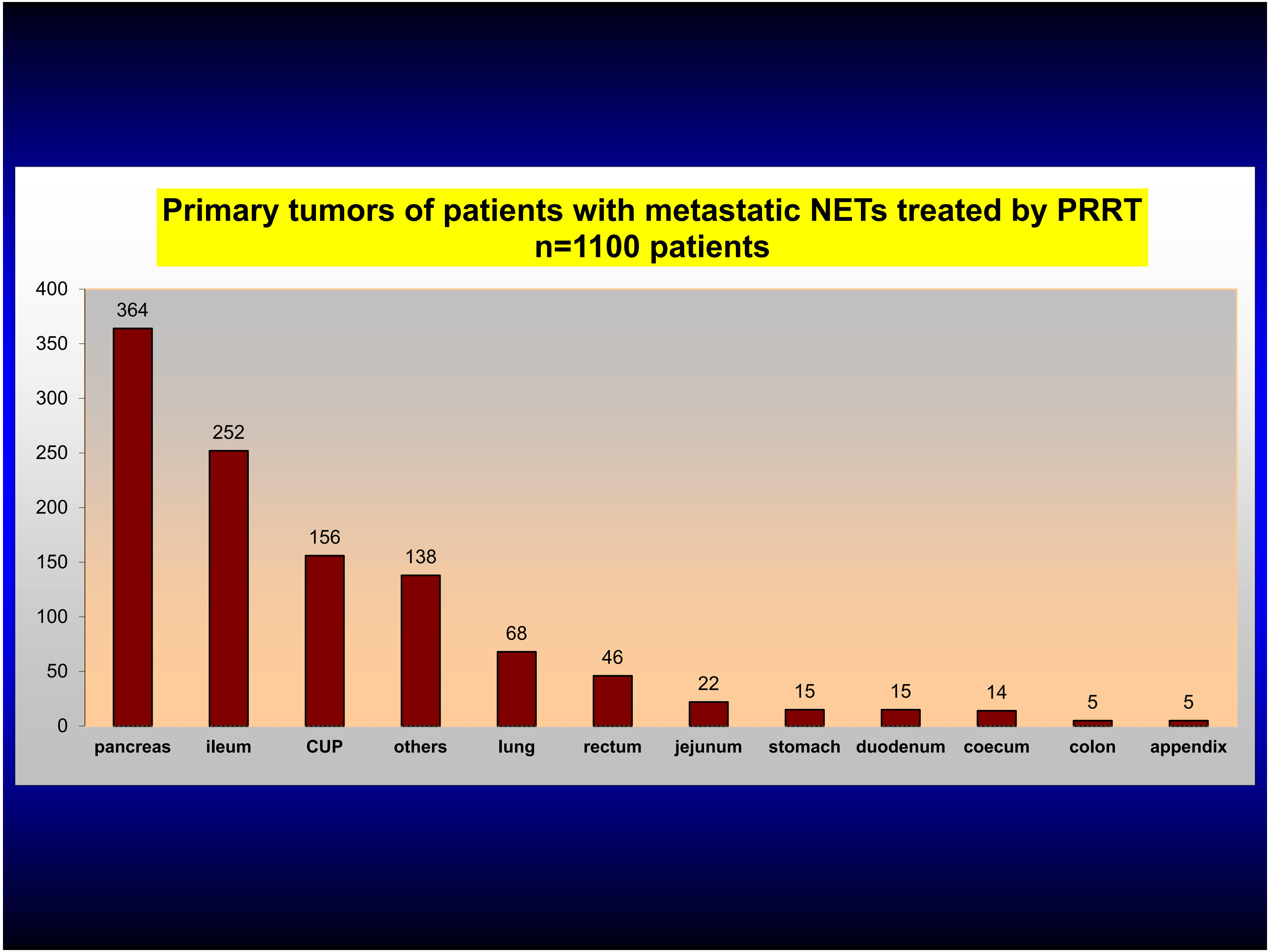
Cancers will be classified by molecular phenotypes

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.

Neuroendocrine tumors are a <u>paradigm</u> 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.


Primary tumors of patients with metastatic NETs treated by PRRT
n=1100 patients
400
350
300
250
200
150
100
50
0
364
252
156
138
68
46
22
15
15
14
5
5
pancreas
ileum
CUP
others
lung
rectum
jejunum
stomach
duodenum
coecum
colon
appendix

RADIOPEPTIDE THERAPY (ZKL BAD BERKA)

As of 31 December 2012

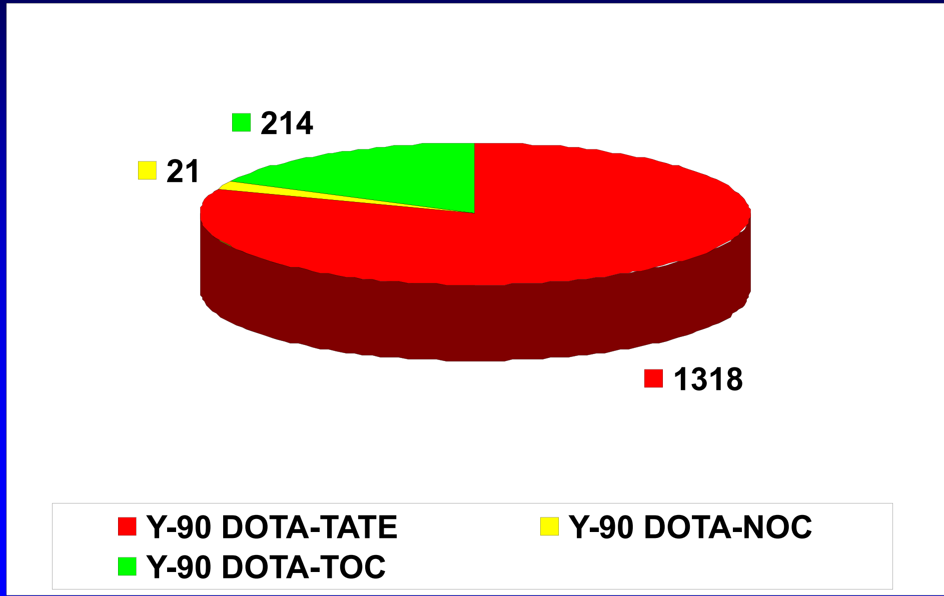
Patients treated	n = 1100
Therapy cycles	n = 3698

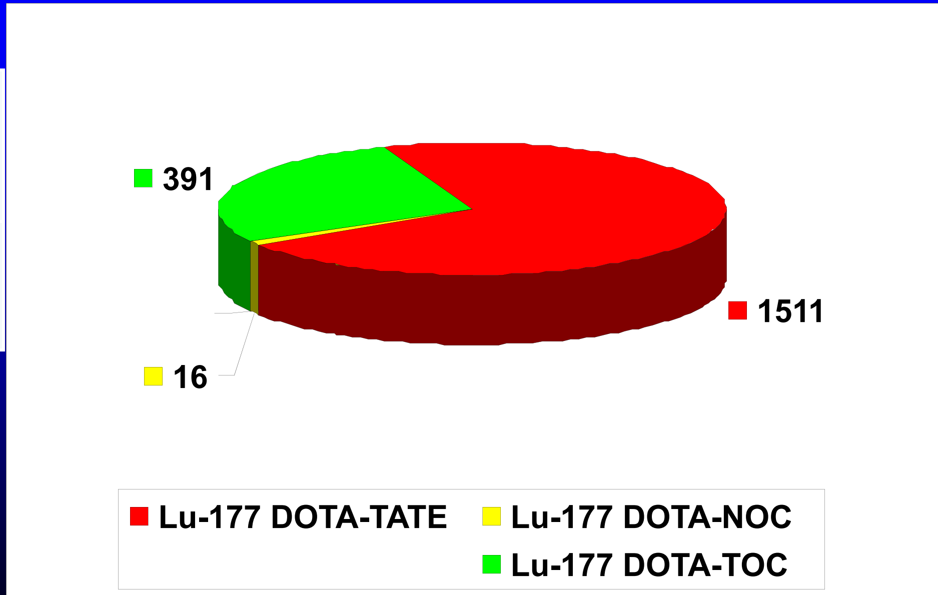
Lu-177	n = 2198
Y-90	n = 1500

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

Age: 4 – 85 years

Median: 59.6 years





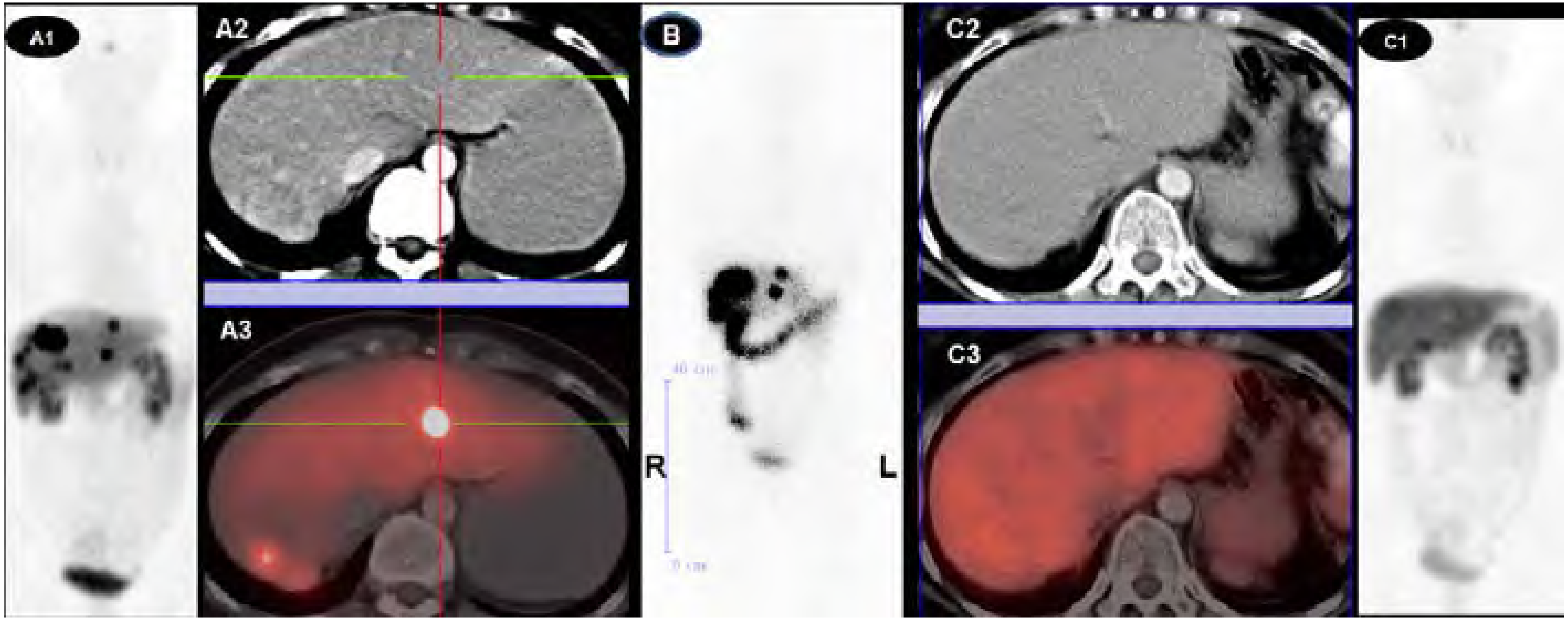
Dept. of Nuclear Medicine/P.E.T. Center, Zentralklinik Bad Berka

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

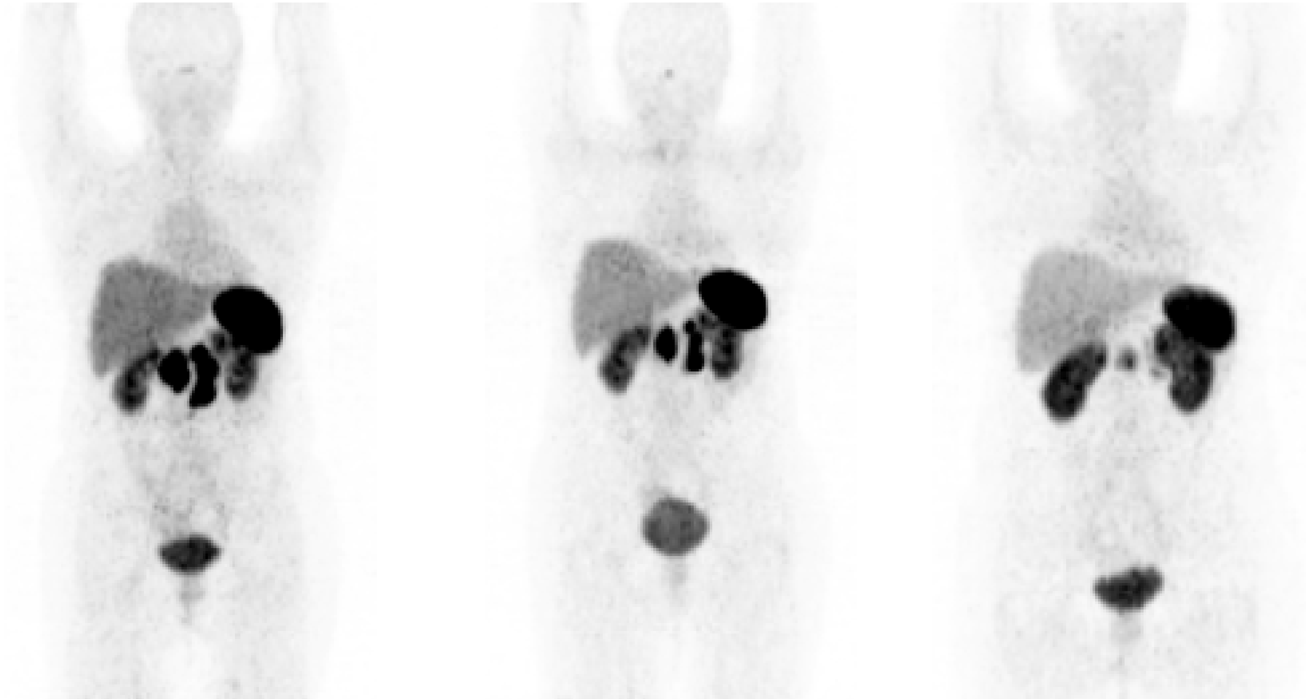
May 2009 – before PRRT	Sept. 2009 - after 1st PRRT	Jan. 2010 - 4mo after 2nd PRRT
TER 97 ml/min (35 %)	*TER 147 ml/min (54 %)*	*TER 202 ml/min (74 %)*

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



MOLECULAR RESPONSE DEMONSTRATED BY ^{68}GA DOTATOC PET/CT
COMPLETE REMISSION OF LIVER METASTASES

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

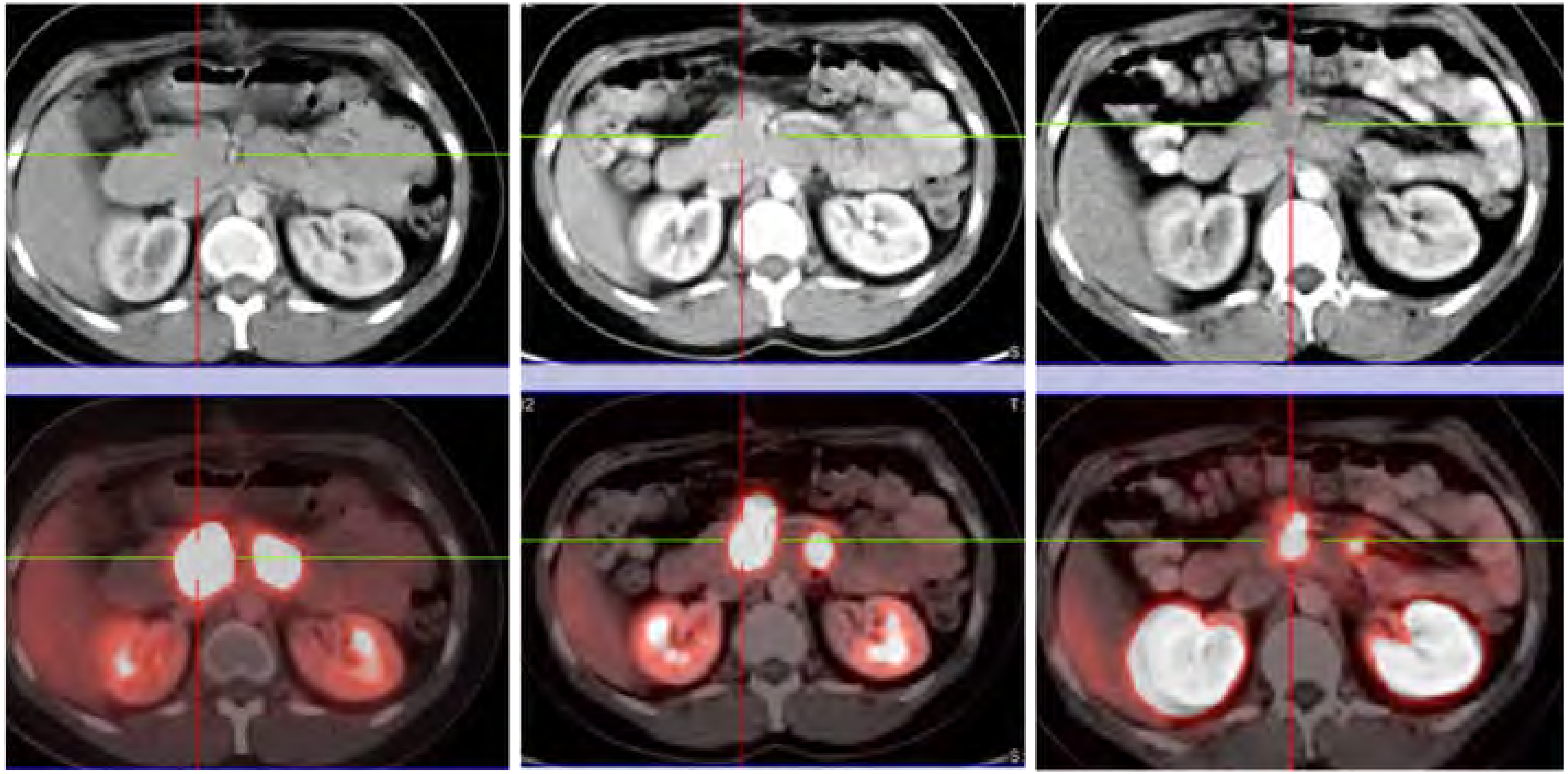


Before PRRT-1	Before PRRT-2	5-mo after PRRT-2
6 GBq Y-90	4.5 GBq Y-90	pre Op.
SUV 29.4	SUV 25.4	SUV 12.5

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

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

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



Before PRRT-1	Before PRRT-2	5-mo after PRRT-2
6 GBq Y-90	4.5 GBq Y-90	pre Op.
SUV 29.4	SUV 25.4	SUV 12.5
Jan. 2007	**May 2007**	**Oct. 2007**

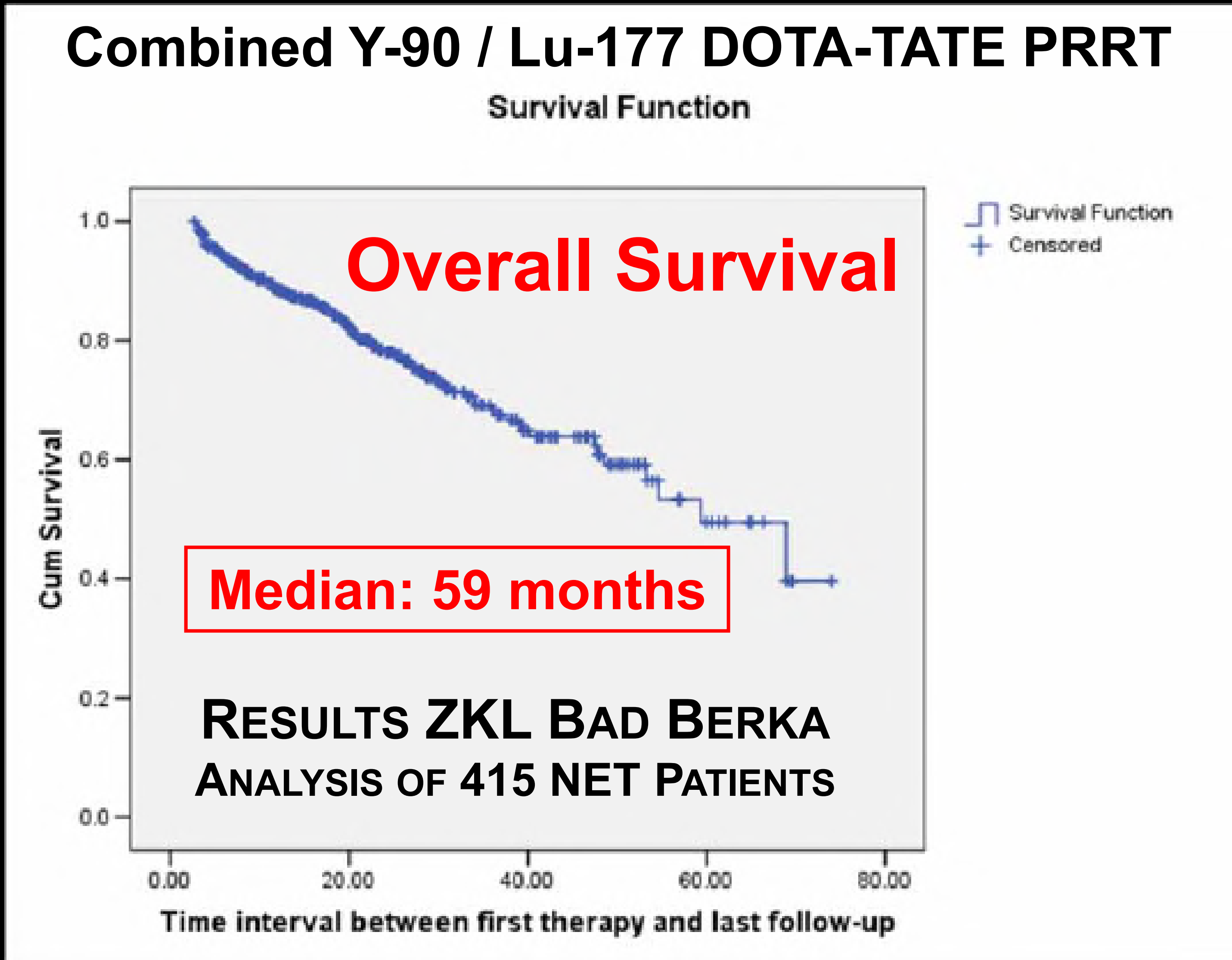
Dept. of Nuclear Medicine/P.E.T. Center, Zentralklinik Bad Berka

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

Histology revealed nearly total tumor necrosis typical for radiation necrosis

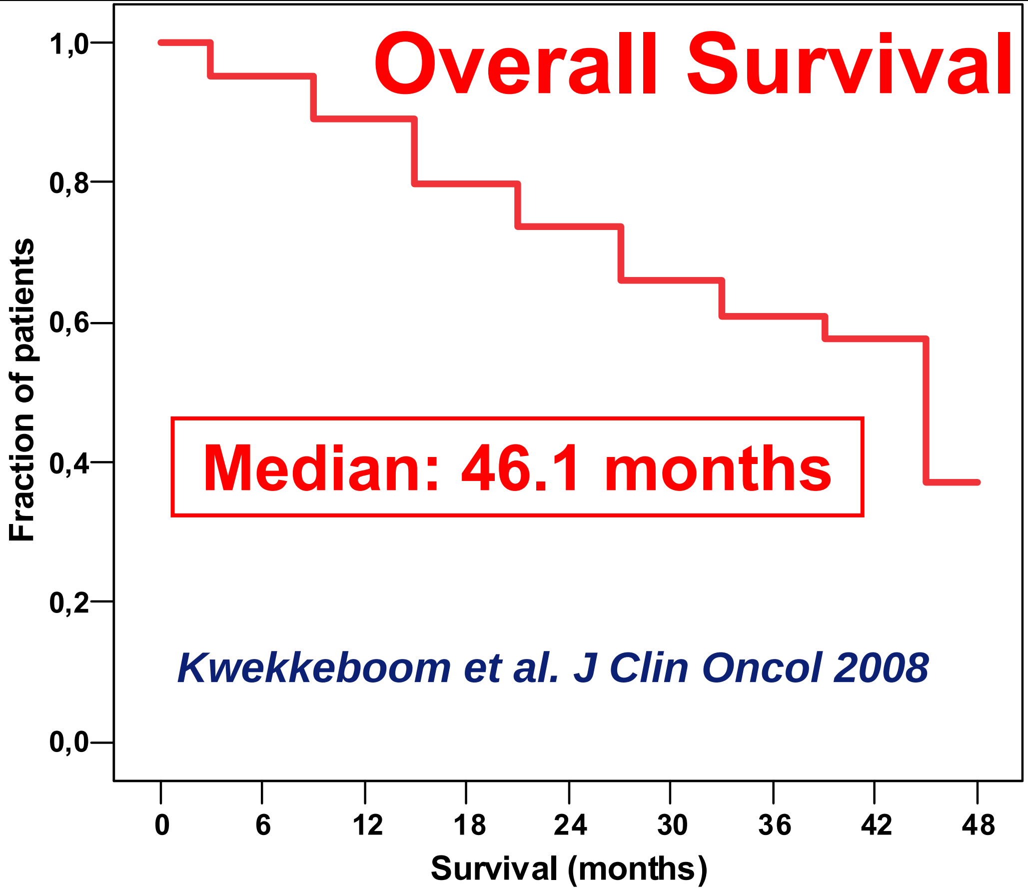
Follow-up at 54 months: Complete Remission

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



[^{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

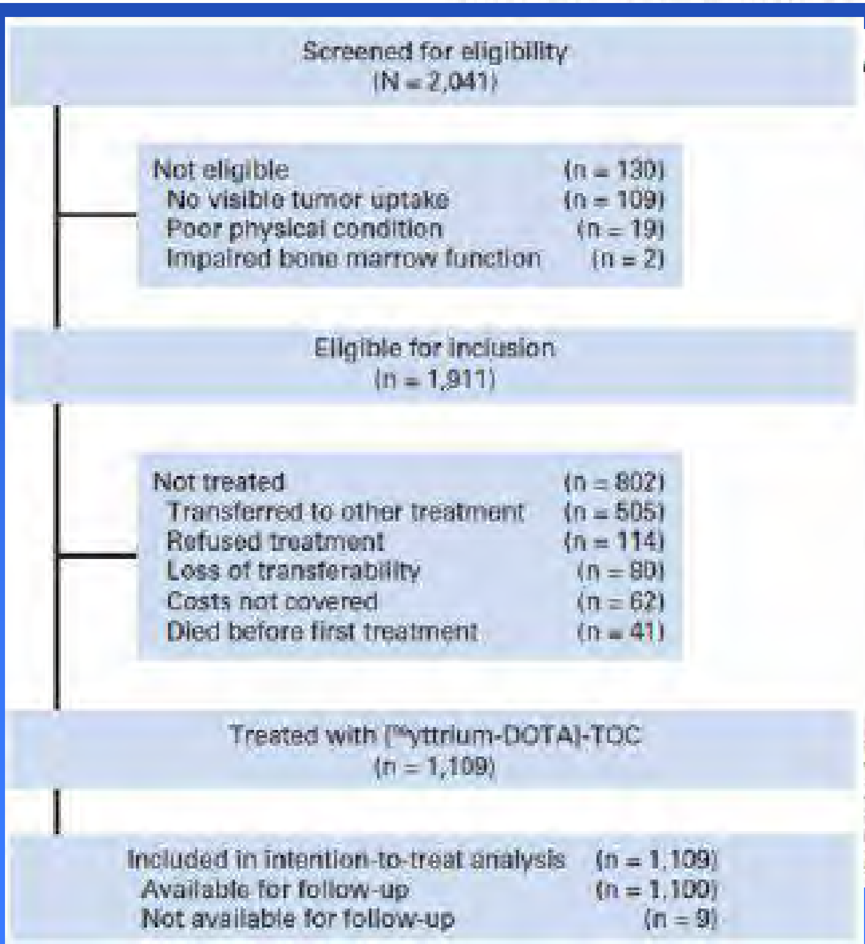
JOURNAL OF CLINICAL ONCOLOGY

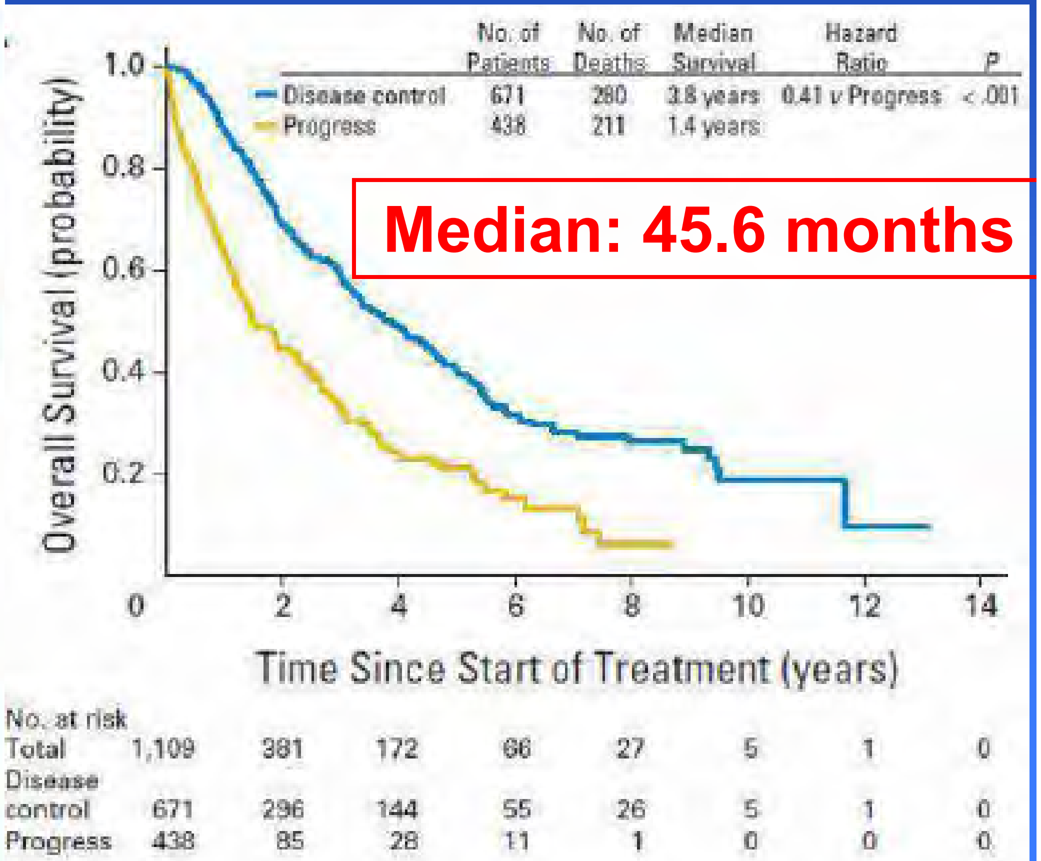
ORIGINAL REPORT

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 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

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- Future perspectives
    - new peptides (antagonists, CXCR4, RGD)
    - PSMA: THERANOSTICS potential for prostate ca.

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) and novel molecules

Ga-68 Labeled Tracers in Clinical Use

- [^{68}Ga-DOTA,Tyr^{3}]octreotide (DOTA-TOC)
- [^{68}Ga-DOTA,1-Nal]octreotide (DOTA-NOC)*
- [^{68}Ga-DOTA]-TATE*
- [^{68}Ga-DOTA]-Lanreotide
- [^{68}Ga-DOTA]-Bombesin / AMBA* and DEMOBESIN*
- [^{68}Ga-DOTA]-D-Glu-Gastrin (MTC, NET)*
- [^{68}Ga-DOTA]-F(ab')$_2$-herceptin (breast cancer)
- ^{68}Ga-Citrate (infection, inflammation)
- ^{68}Ga-DOTA-Tyrosin (brain tumors)*
- ^{68}Ga-DOTA-HSA Microspheres (lung perfusion)*
- ^{68}Ga-NODAGA-RGD (angiogenesis)*
- ^{68}Ga-BPAMP (osteoblastic metastases)*
- ^{68}Ga-DOTA-α-MSH (melanoma)*
- ^{68}Ga-DOTA-SHAL (lymphoma)*
- ^{68}Ga-PSMA (prostate cancer
- ^{68}Ga-CXCR4 (acdenocarcinomas)

…and many more to come!

**first use in Bad Berka*

IVYSPRING
INTERNATIONAL PUBLISHER

Theranostics

2012; 2(5):437-447. doi: 10.7150/thno.3645

Review

THERANOSTICS: From Molecular Imaging Using Ga-68 Labeled Tracers and PET/CT to Personalized Radionuclide Therapy – The Bad Berka Experience

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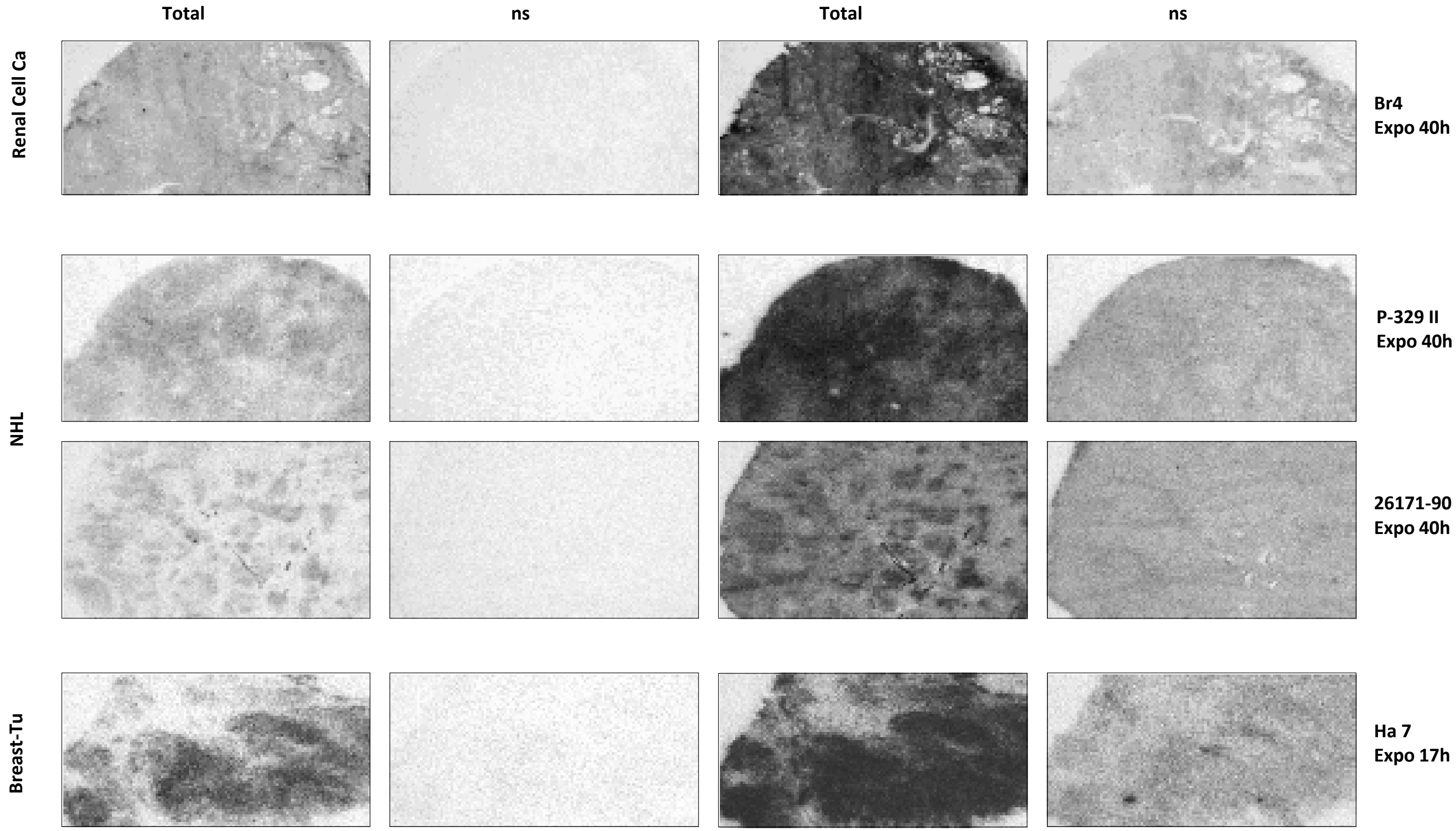
Received: 2011.10.16; Accepted: 2011.12.02; Published: 2012.05.07

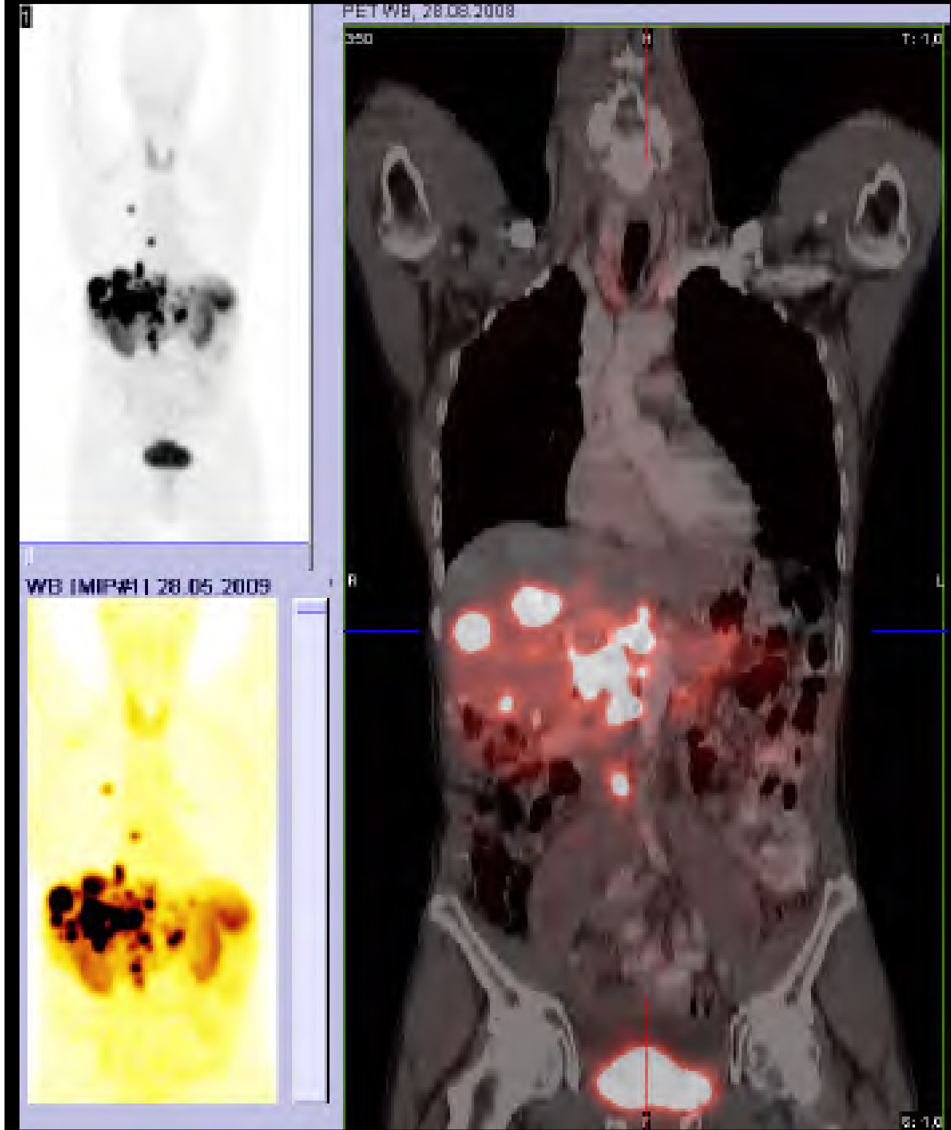
Antagonist labels more sst_2 sites than agonist in human cancer tissues

Agonist
Lu DOTA-TATE

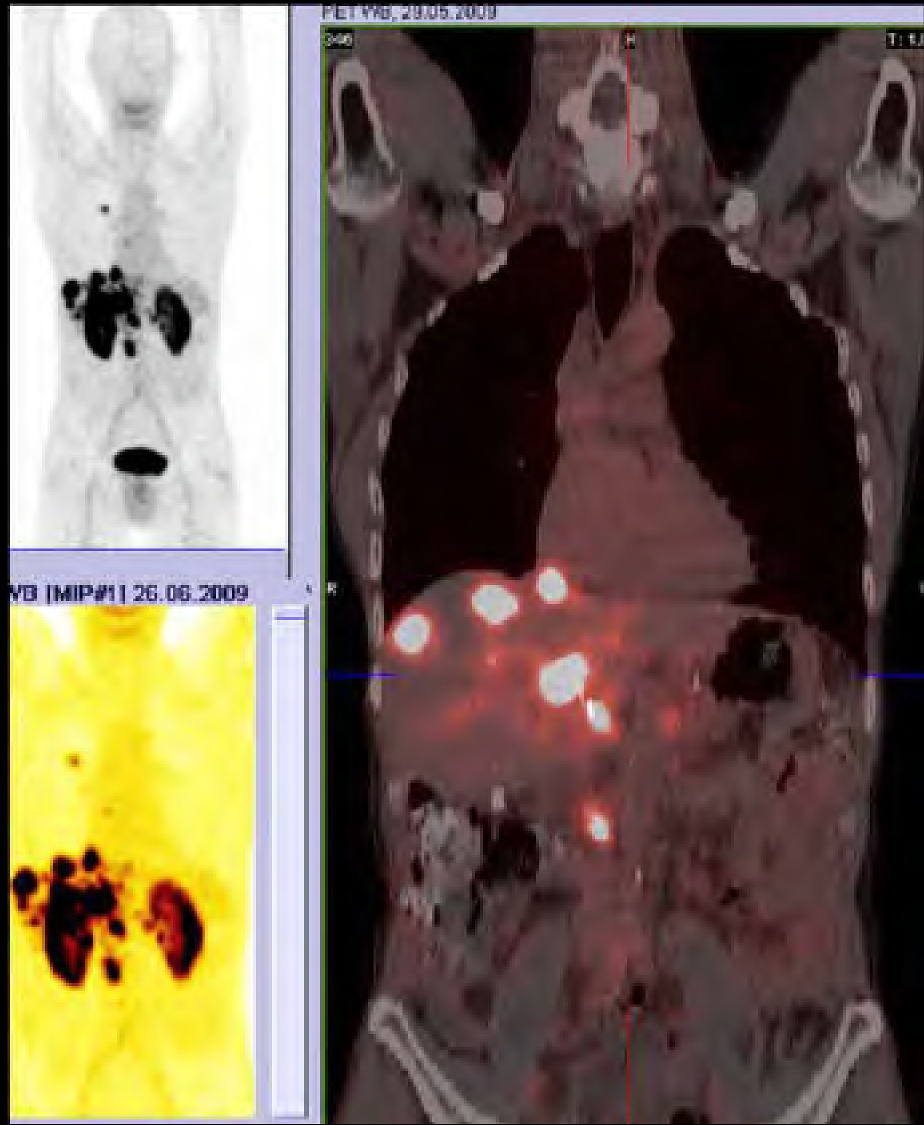
Antagonist
Lu DOTA-BASS



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



SMS-Agonist
Ga-68 DOTA-TOC PET/CT



SMS-Antagonist:
Ga-68 DOTA-JR10 PET/CT

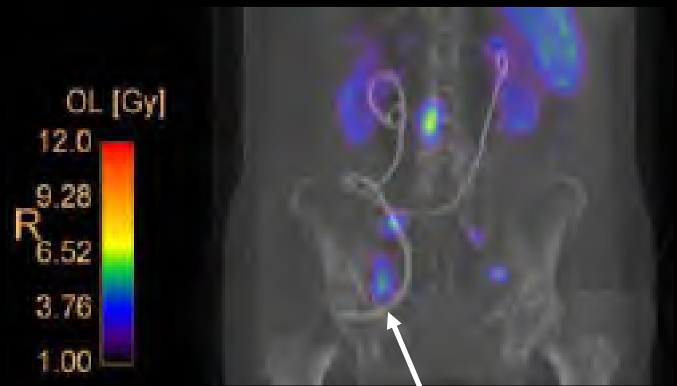
Comparison of ^{177}Lu-DOTATATE and ^{177}Lu-DOTA-JR11 dosimetry

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)

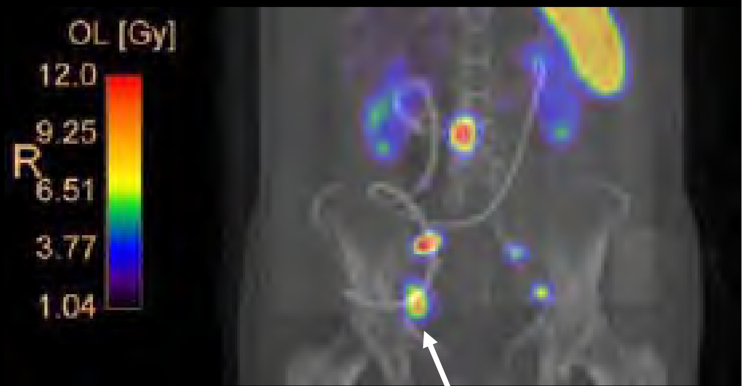
^{177}Lu-DOTA-TATE (Agonist)
Isodose curves based on 3D voxel dosimetry analysis



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

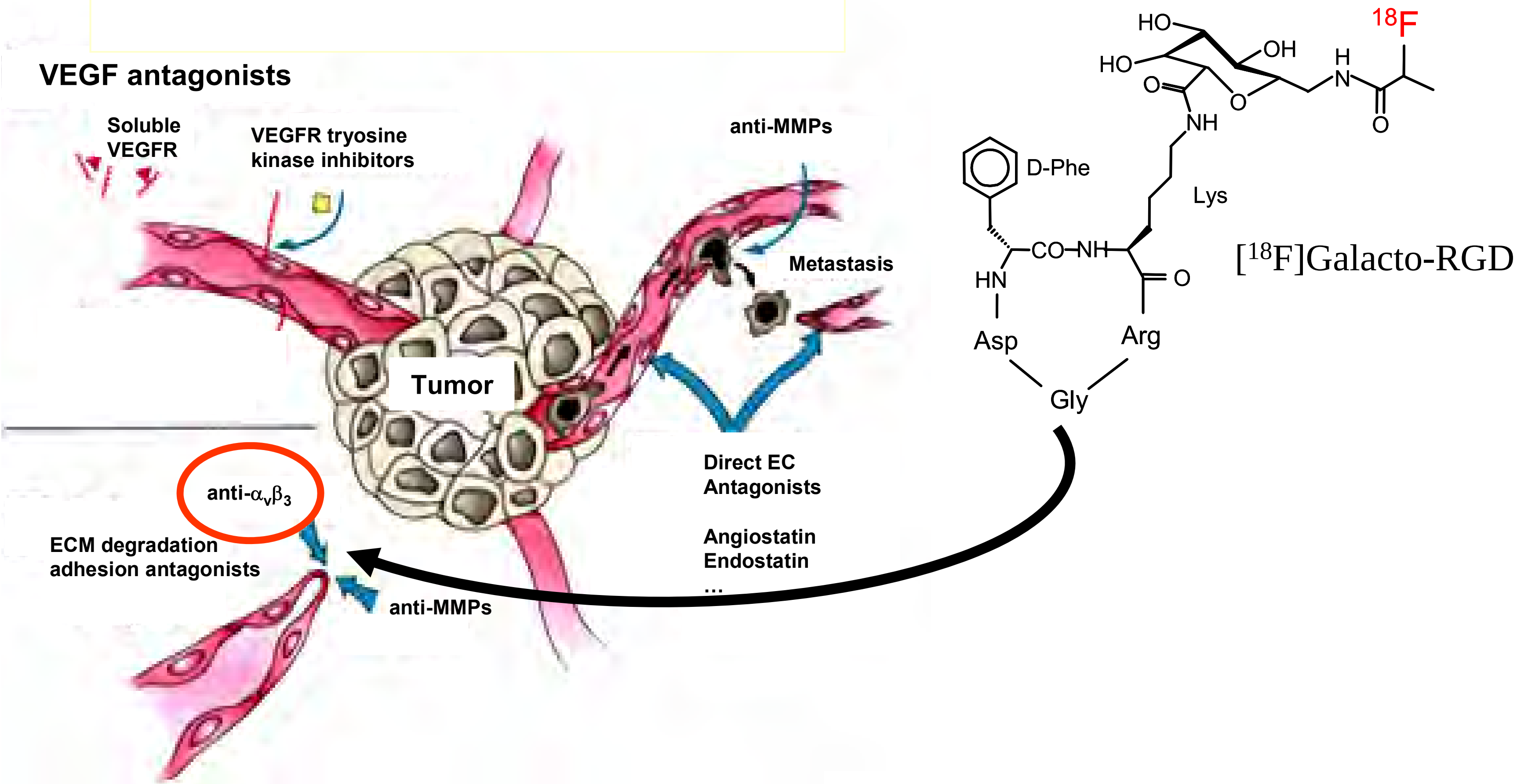
sst_2 affinity profile (IC_{50})
1.5 ± 0.4 nM

UNIVERSITÄTS KLINIKUM FREIBURG

Courtesy Damian Wild

Imaging of Neoangiogenesis

Imaging neovascularization by addressing $\alpha_v ß_3$-integrins
(cell adhesion proteins)



A new approach: [^{68}Ga]-RGD

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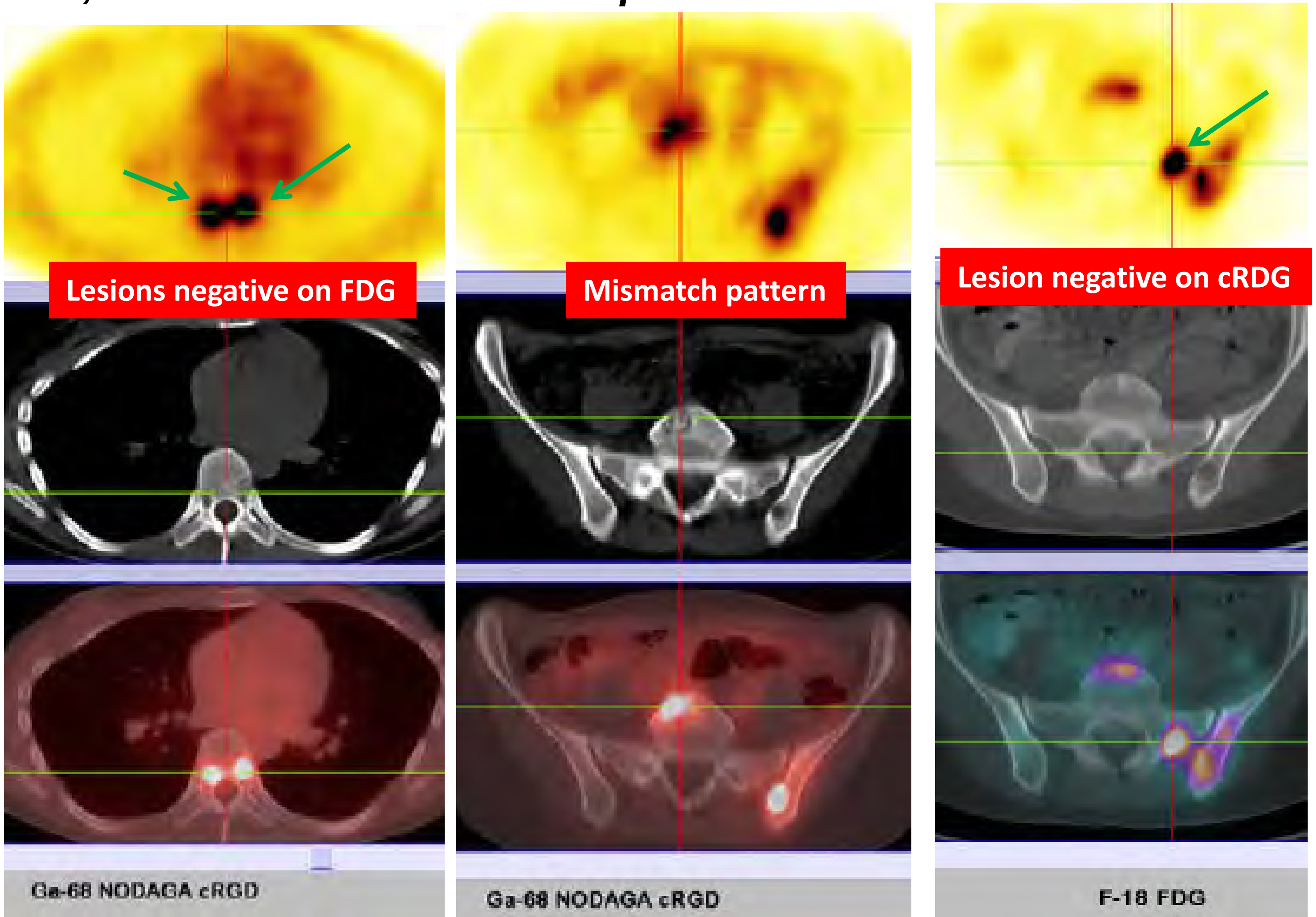
Ga-68 RGD PET/CT in adenocarcinoma of lung

Molecular imaging of angiogenesis

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

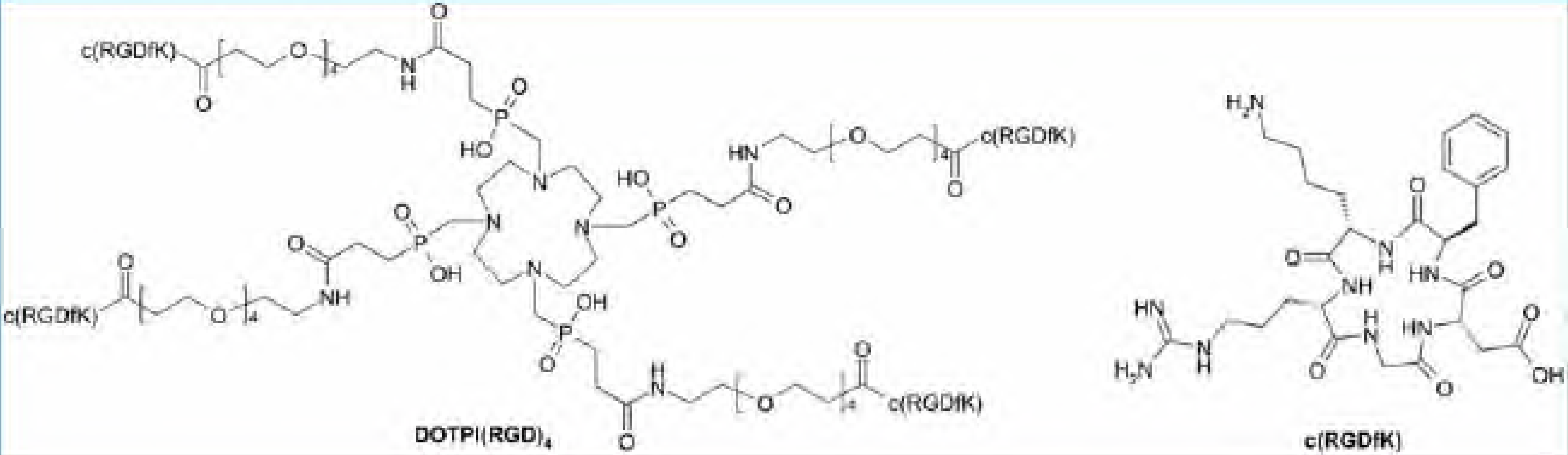
Breast cancer with extensive bone metastases (first in human study).
In total, 25 metastases were RGD positive and 12 lesions were FDG-avid.

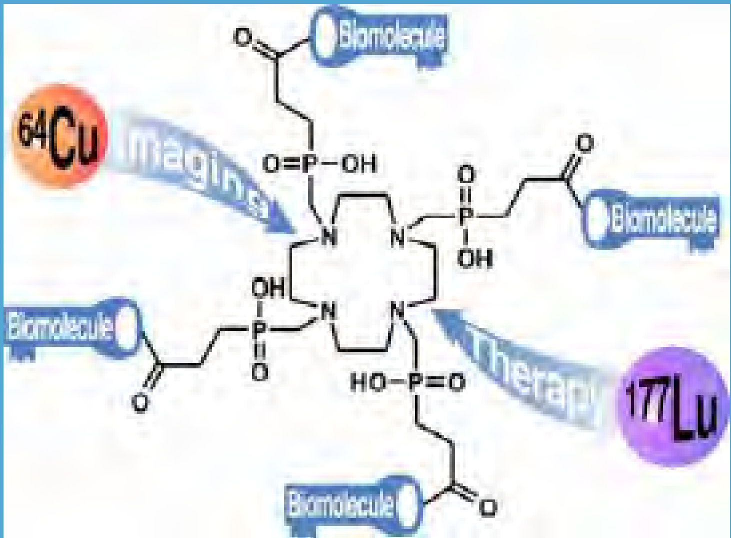


MOLECULAR IMAGING OF TUMOR NEOANGIONESIS BY THERANOST ^{68}GA NODAGA RGD VS. METABOLIC FDG IMAGING

Cyclen-based tetraphosphinate chelator

for preparation of radiolabeled **tetrameric bioconjugates with ultrahigh affinity**





Compound	IC_{50} [pM]	relative activity
DOTPI(RGD)$_4$	109 ± 7	12.2
Cu-DOTPI(RGD)$_4$	73 ± 5	18.2
Lu-DOTPI(RGD)$_4$	72 ± 4	18.5
TRAP(RGD)$_3$	249 ± 7	5.3
Ga-TRAP(RGD)$_3$	193 ± 5	6.9
c(RGDfK)	1330 ± 90	1

^{177}Lu- and ^{64}Cu-DOTPI(RGD)4 are fully stable in DTPA / EDTA and plasma over 7 d / 12 h.

Notni J, Simecek et al. 2013

Cu-64 labelled triazacyclononane-triphosphinate chelators

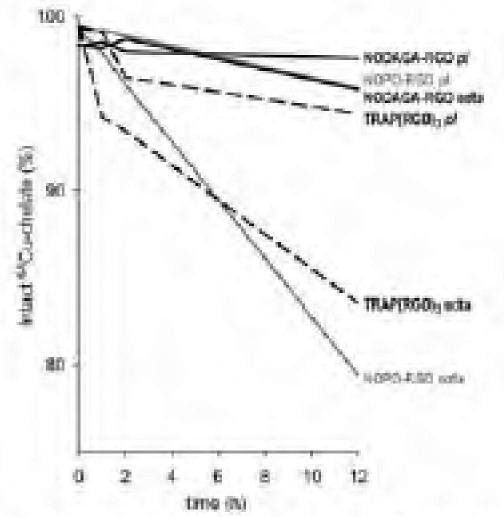


Fig. 3 Stability of ^{64}Cu-labelled conjugates in 0.1 M EDTA (edta) and human plasma (pl). Error bars are omitted for clarity. Percentages of intact ^{64}Cu chelates were determined after 1, 2 and 12 h.

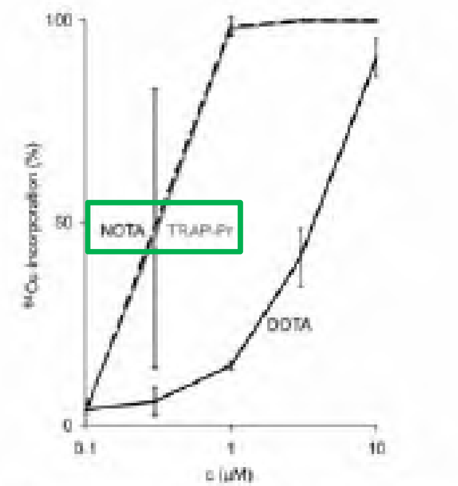
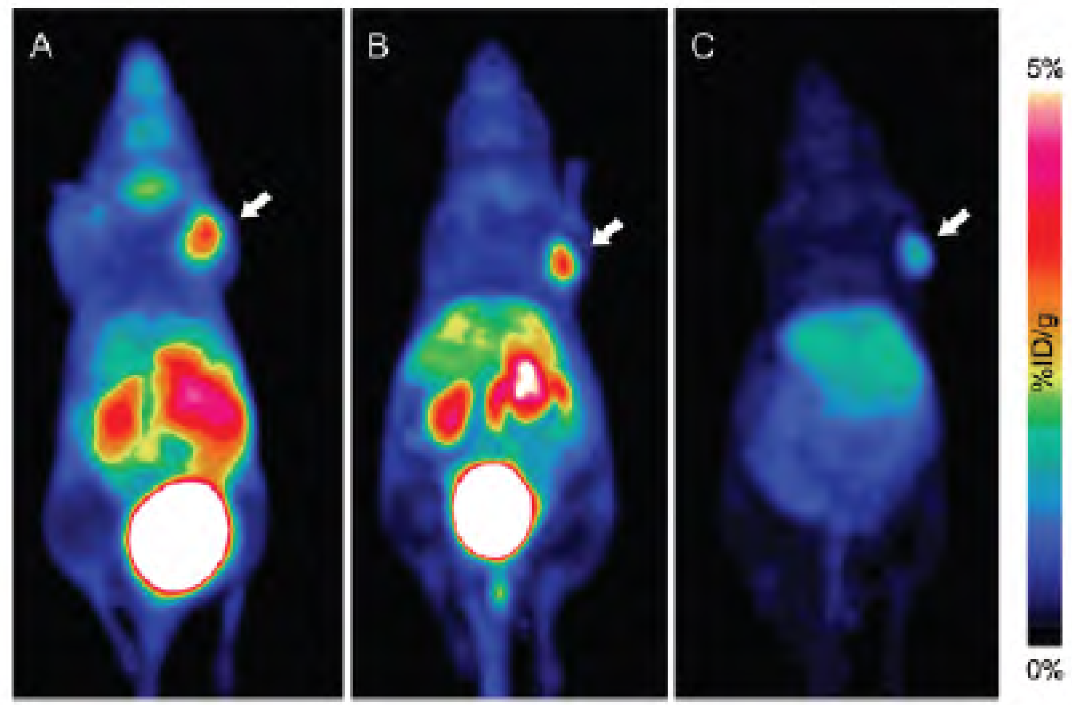


Fig. 1 ^{64}Cu incorporation as a function of chelator concentration. 1.9–2.5 MBq of ^{64}Cu in 1 mM HCl (0.1 mL, pH 3), 25 °C, 5 min, n = 3.

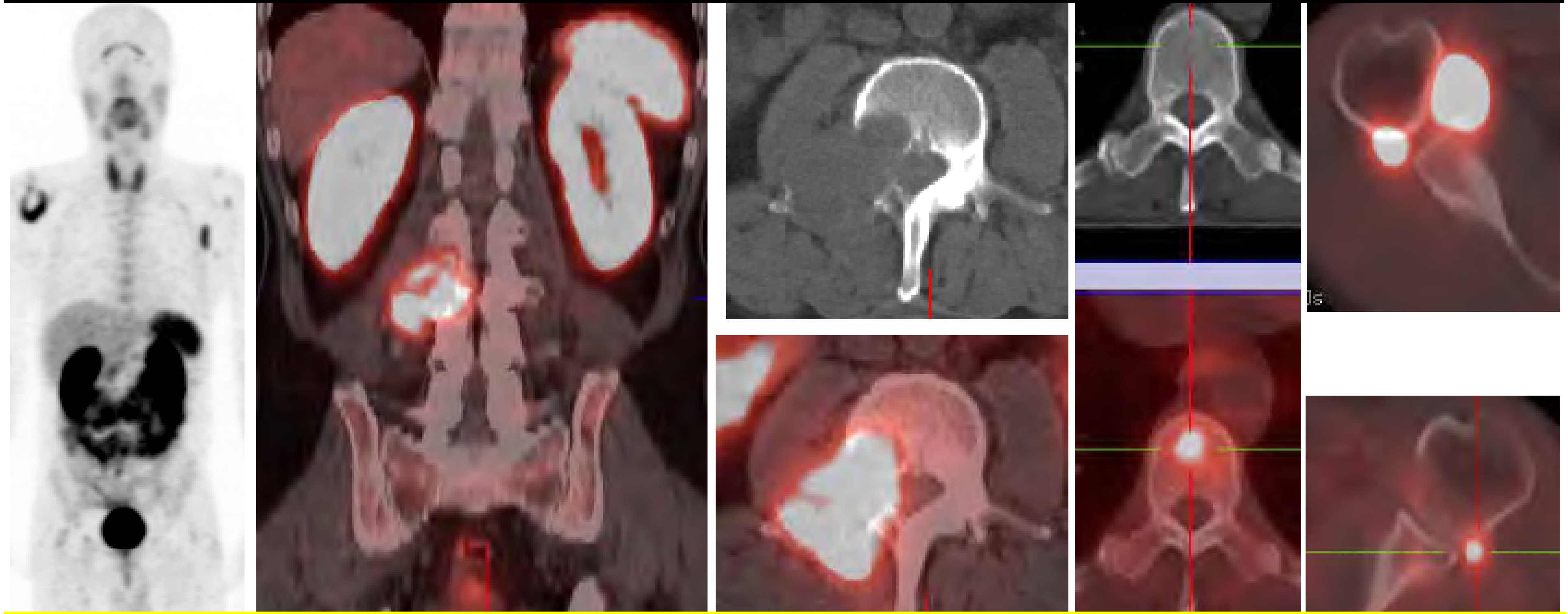


^{68}Ga-TRAP(RGD)$_3$, 75 min | ^{64}Cu-TRAP(RGD)$_3$ 75 min | ^{64}Cu-TRAP(RGD)$_3$ 18h p.i.

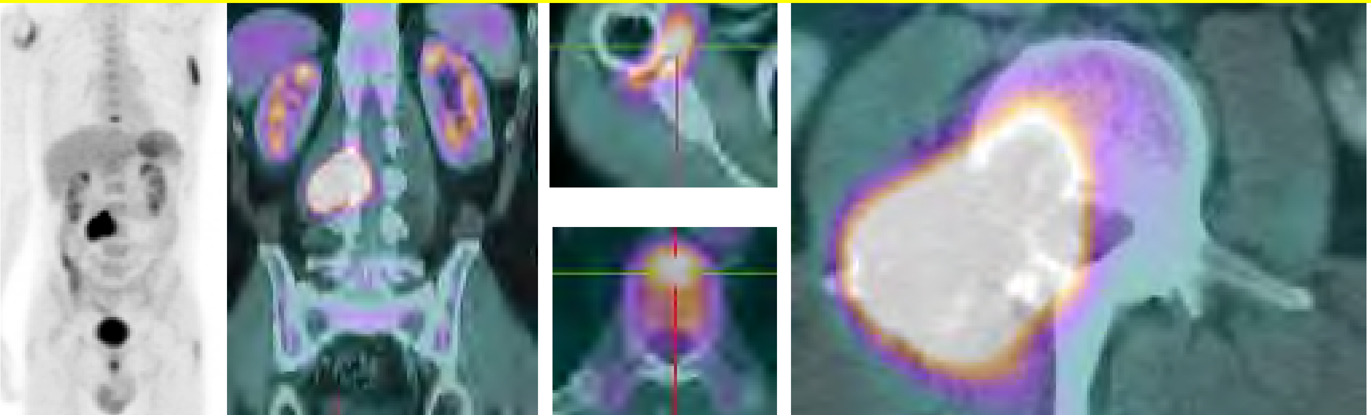
Possible theranostic pair: ^{64}Cu and ^{67}Cu !

Simecek et al. Dalton Transactions 2012

Ga-68 TRAP(RGD)$_3$ PET/CT



Center for Molecular Imaging and Molecular Radiotherapy, Zentralklinik Bad Berka, Germany in collaboration with H.J. Wester (labeling performed using SCINTOMICS module)



FDG PET/CT

Bone infiltration (L3) of plasmacytoma with invasion of the spinal cord and of the psoas muscle. There is also involvement of T-9 vertebra (marrow) and left scapula. Periarthritis right shoulder.

CXCR4 is highly expressed in various tumors and metastases

CXCR4

- Chemokine-Receptor (GPCR)
- Coreceptor for HIV-infection
- CXCL12 is the only endogenous ligand

SDF-1α (CXCL12)

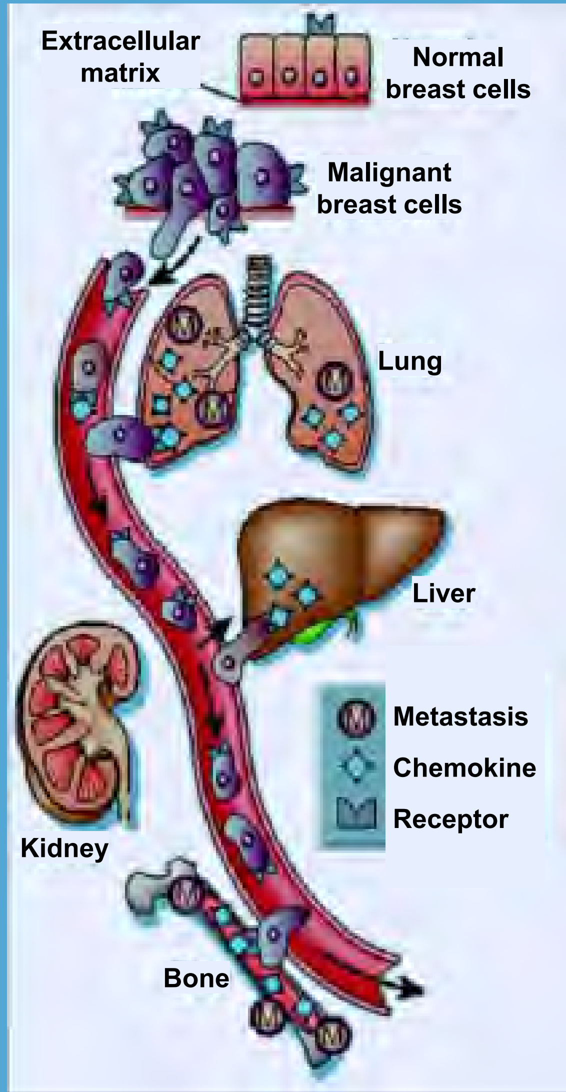
Stromal Cell derived Factor

- chemotactic cytokine
- 68 amino acids

CXCR4 and SDF-1a mediate

- **Physiological conditions:**
  Homing of lymphocytes and hematopoietic stem and progenitor cells (HSPC)

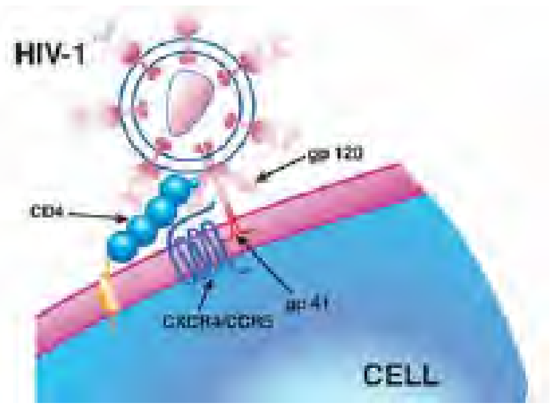
- **Pathological conditions:**
  tumorigenesis
  tumor progression
  metastasis



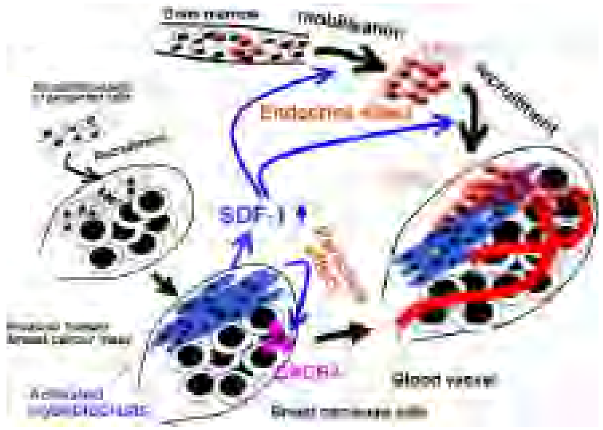
Liotta LA *Nature* (2001)410:24

Functional roles of the chemokine receptor CXCR4

Co-receptor for HIV-entry

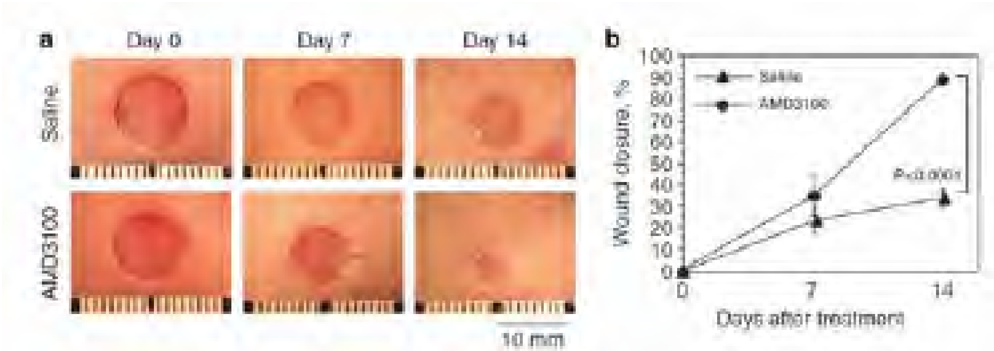


Tumor progression and metastasis



Angiogenesis

Healing and tissue remodelling



skin wounds, genetically diabetic mice, treated with 6mg/kg AMD3100 in saline or saline alone, and then examined 0, 7, and 14 days later

IVYSPRING INTERNATIONAL PUBLISHER

Theranostics

2013; 3(1):1-2. doi: 10.7150/thno.5760

Editorial

CXCR4 Chemokine Receptor Overview: Biology, Pathology and Applications in Imaging and Therapy

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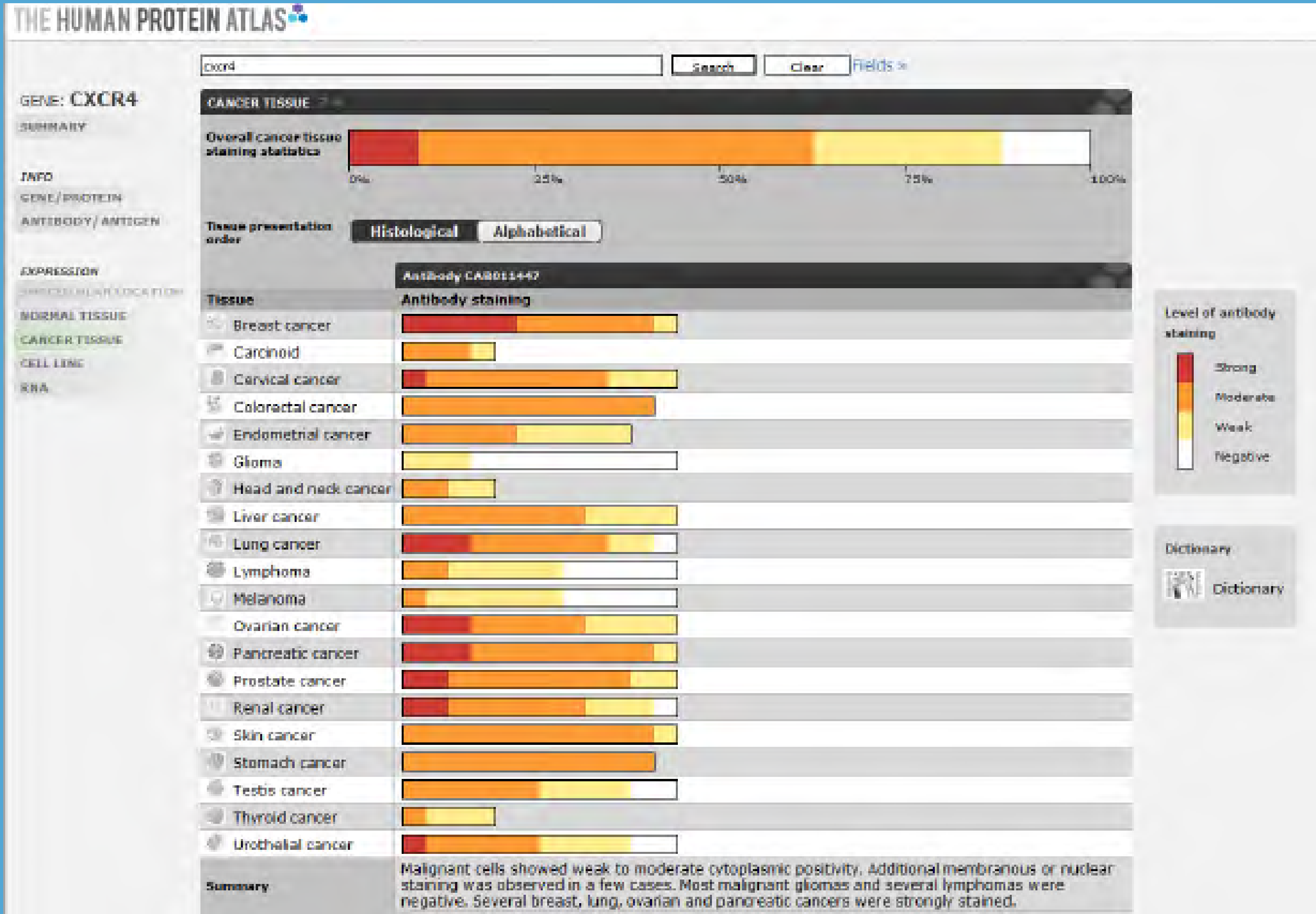
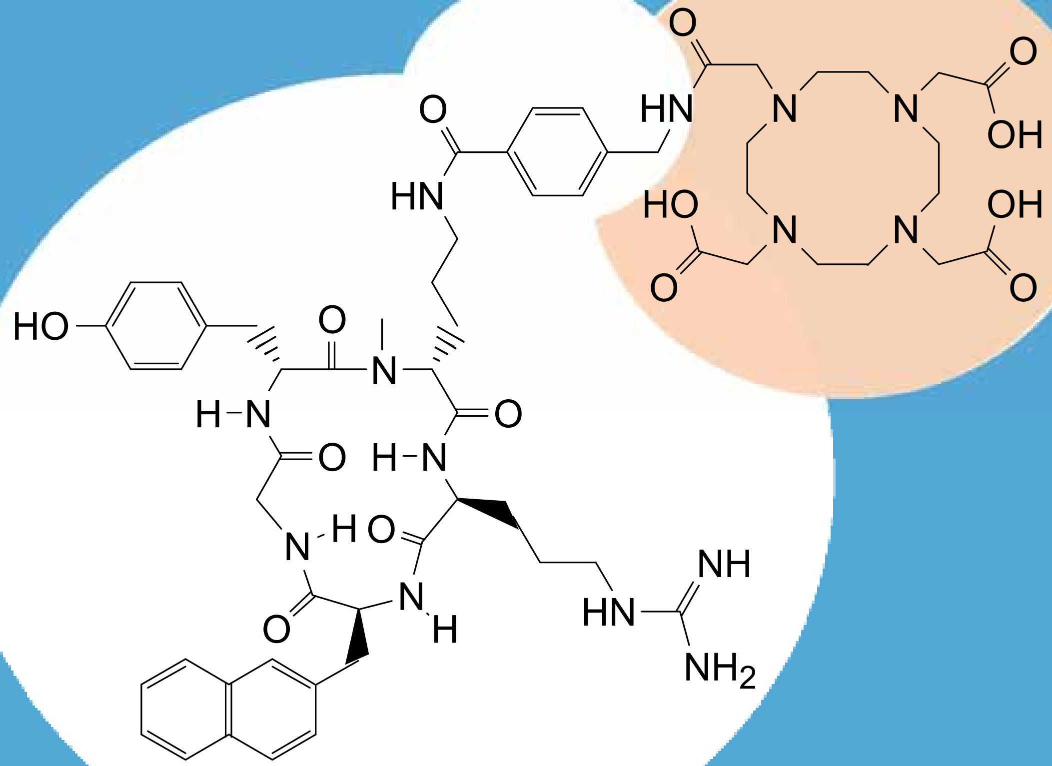
1. Hadassah Hebrew University Hospital, Cyclotron radiochemistry unit, Jerusalem, Israel.
2. Hadassah Hebrew University Hospital, the Goldyne Savad Gene Therapy Institute, Jerusalem, Israel.



THE HUMAN PROTEIN ATLAS
cxcr4
Search
Clear
Fields »
GENE: CXCR4
SUMMARY
INFO
GENE/PROTEIN
ANTIBODY/ANTIGEN
EXPRESSION
NORMAL TISSUE
CANCER TISSUE
CELL LINE
RNA
CANCER TISSUE
Overall cancer tissue staining statistics
0%
25%
50%
75%
100%
Tissue presentation order
Histological
Alphabetical
Antibody CAB011447
Tissue
Antibody staining
Breast cancer
Carcinoid
Cervical cancer
Colorectal cancer
Endometrial cancer
Glioma
Head and neck cancer
Liver cancer
Lung cancer
Lymphoma
Melanoma
Ovarian cancer
Pancreatic cancer
Prostate cancer
Renal cancer
Skin cancer
Stomach cancer
Testis cancer
Thyroid cancer
Urothelial cancer
Summary
Malignant cells showed weak to moderate cytoplasmic positivity. Additional membranous or nuclear staining was observed in a few cases. Most malignant gliomas and several lymphomas were negative. Several breast, lung, ovarian and pancreatic cancers were strongly stained.
Level of antibody staining
Strong
Moderate
Weak
Negative
Dictionary
Dictionary

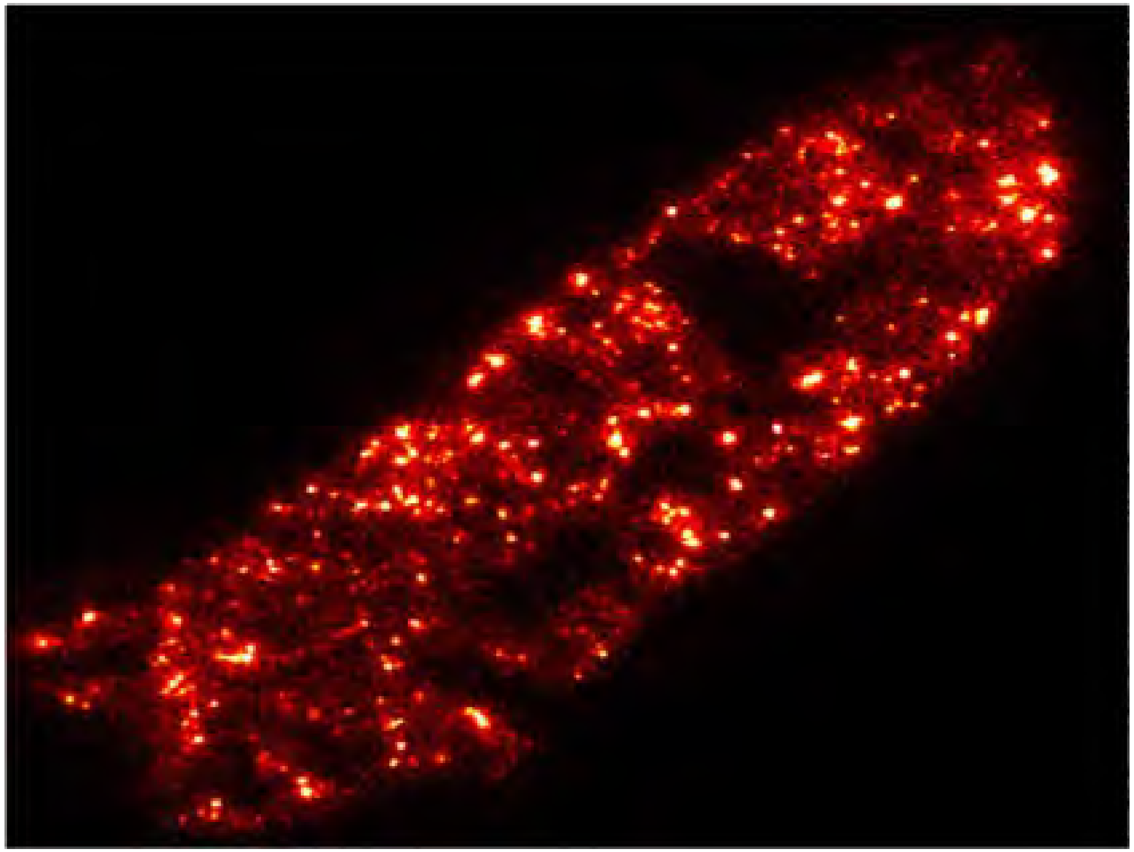
Structure of ^{68}Ga-CPCR4-2



compound	IC_{50} [nM]
FC131	4.43 ± 0.82
DOTA-CPCR4-2	177
^{nat}Ga-DOTA-CPCR4-2	**4.99±0.72**

Gourni E. et al. J Nucl Med. **2012**; O.Demmer et al. *Chem. Med. Chem.* **2011**

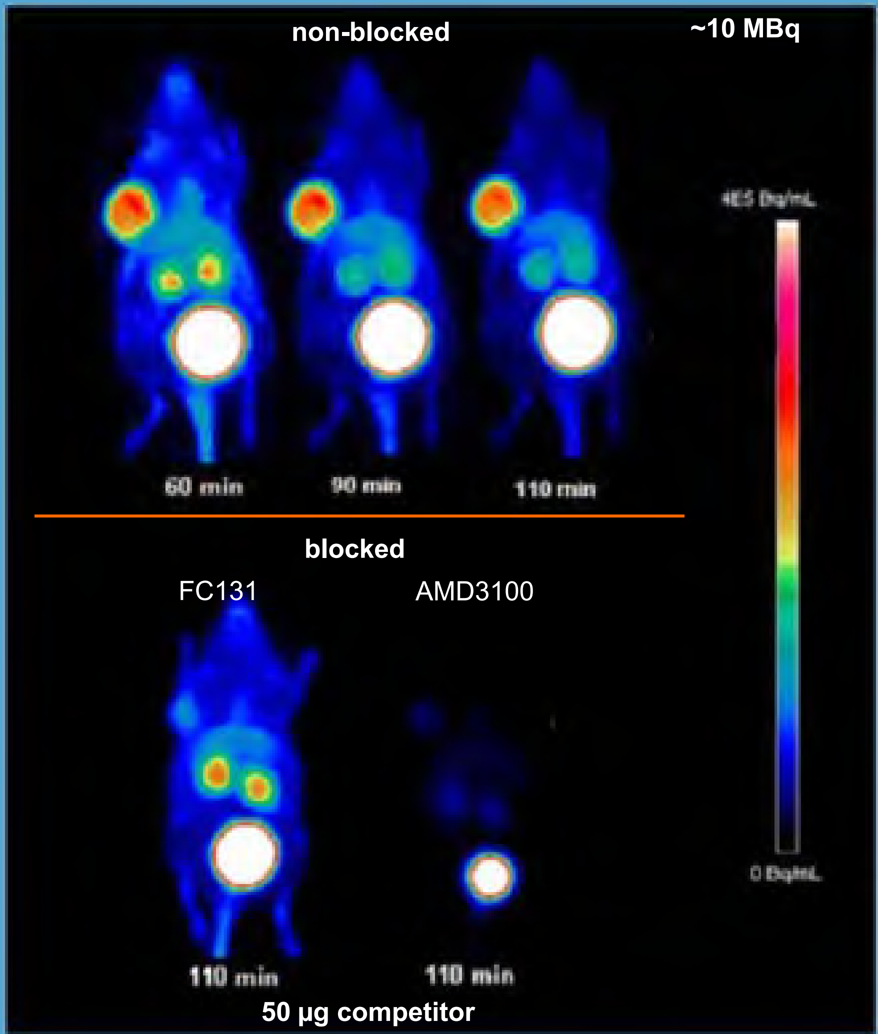
Imaging CXCR4 Receptor Expression of Lung Metastases

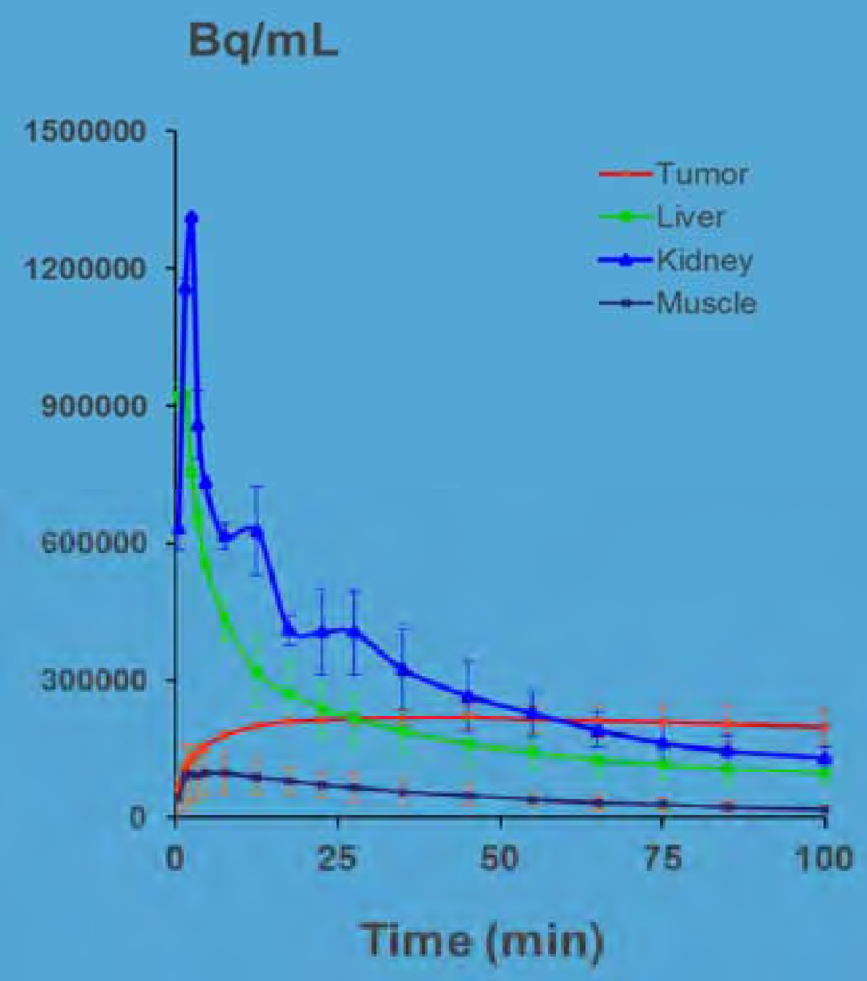


ex-vivo μ-Autoradiography: lung of a mouse 1h p.i. of n.c.a. ^{124}I-CPCR4 with OH-1 tumor on the shoulder

Quantitative PET Imaging Study

in OH-1 SCLC Tumor Bearing Mice



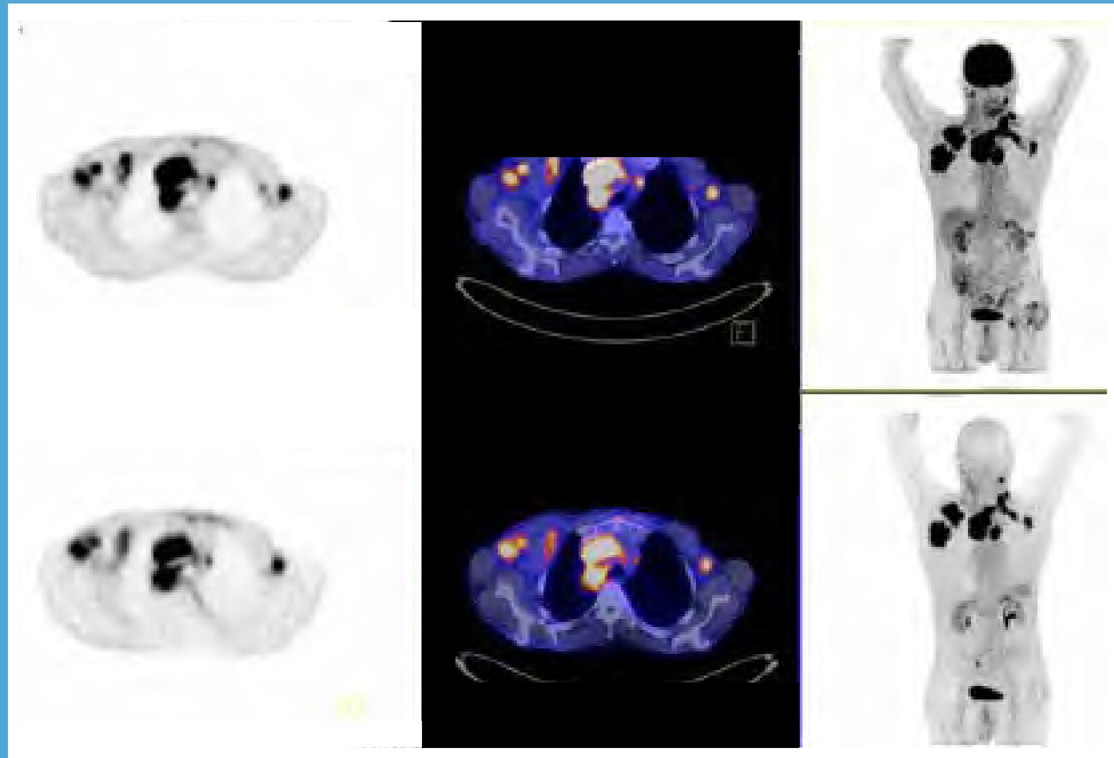


Gourni E. et al. J Nucl Med. **2012**

$[^{68}Ga]$CPCR4-2 PET

$[^{68}Ga]$CPCR4-2 PET

$[^{18}F]$FDG PET/CT

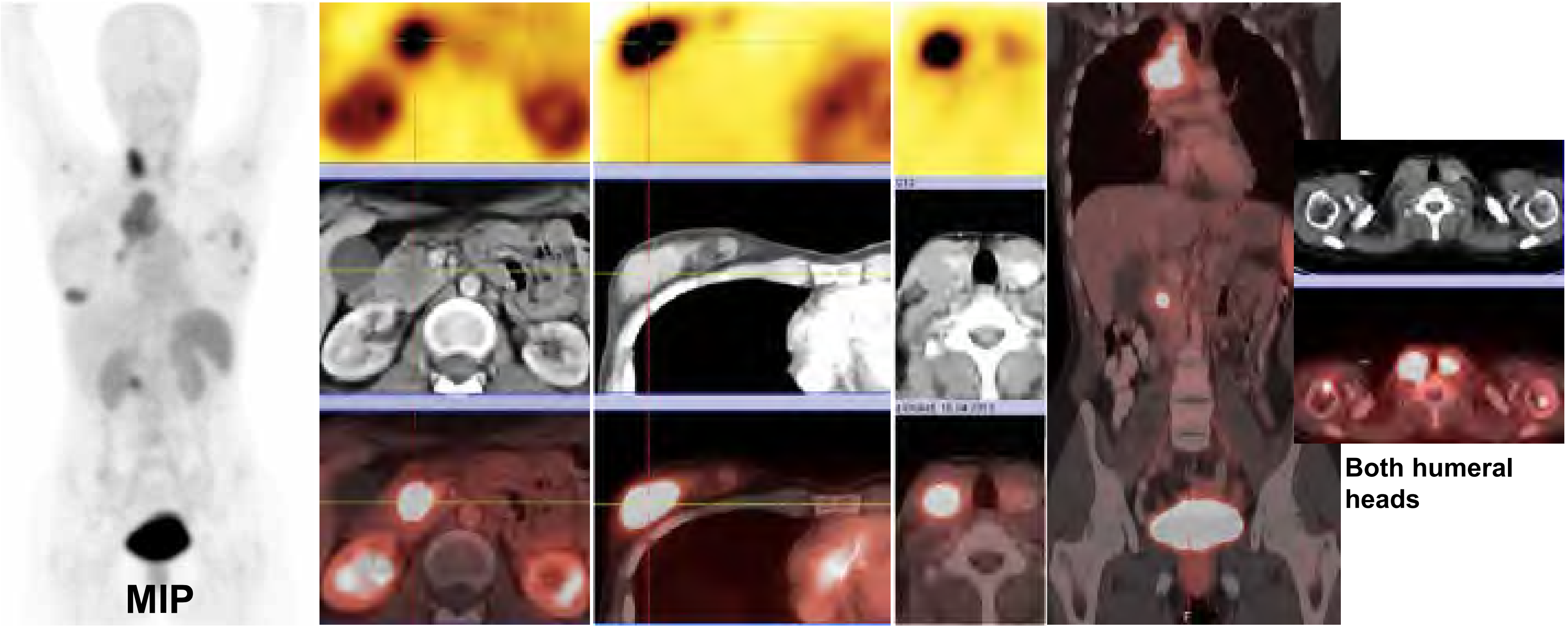


$[^{68}Ga]$CPCR4-2 PET/CT

Patent: SCINTOMICS

Wester HJ, Schwaiger M, Beer A, Keller U et al. (unpublished)

^{68}Ga CPCR4-2 PET/CT



Both humeral heads

Pancreatic head Right breast tumor LN

29 year-old female patient with poorly differentiated neuroendocrine carcinoma of unknown primary (CUP-NEC, first appearance in the left breast) with extensive lymph node metastases.
Ga-68 CXCR-4 PET/CT shows intense CXCR-4 expression in the previously SMS-R positive metastases, most pronounced in the cervical and mediastinal lymph nodes as well as in the right breast (relatively mild to moderate in the other breast lesions). In the pancreatic head, a CXCR-4 positive, SMS-R negative lesion is detected (most probably corresponding to the primary tumor).
Uptake is also noted in metastases in both humeral heads.

Center for Molecular Imaging and Molecular Radiotherapy, Zentralklinik Bad Berka, Germany in collaboration with H.J. Wester (labeling performed using SCINTOMICS module)

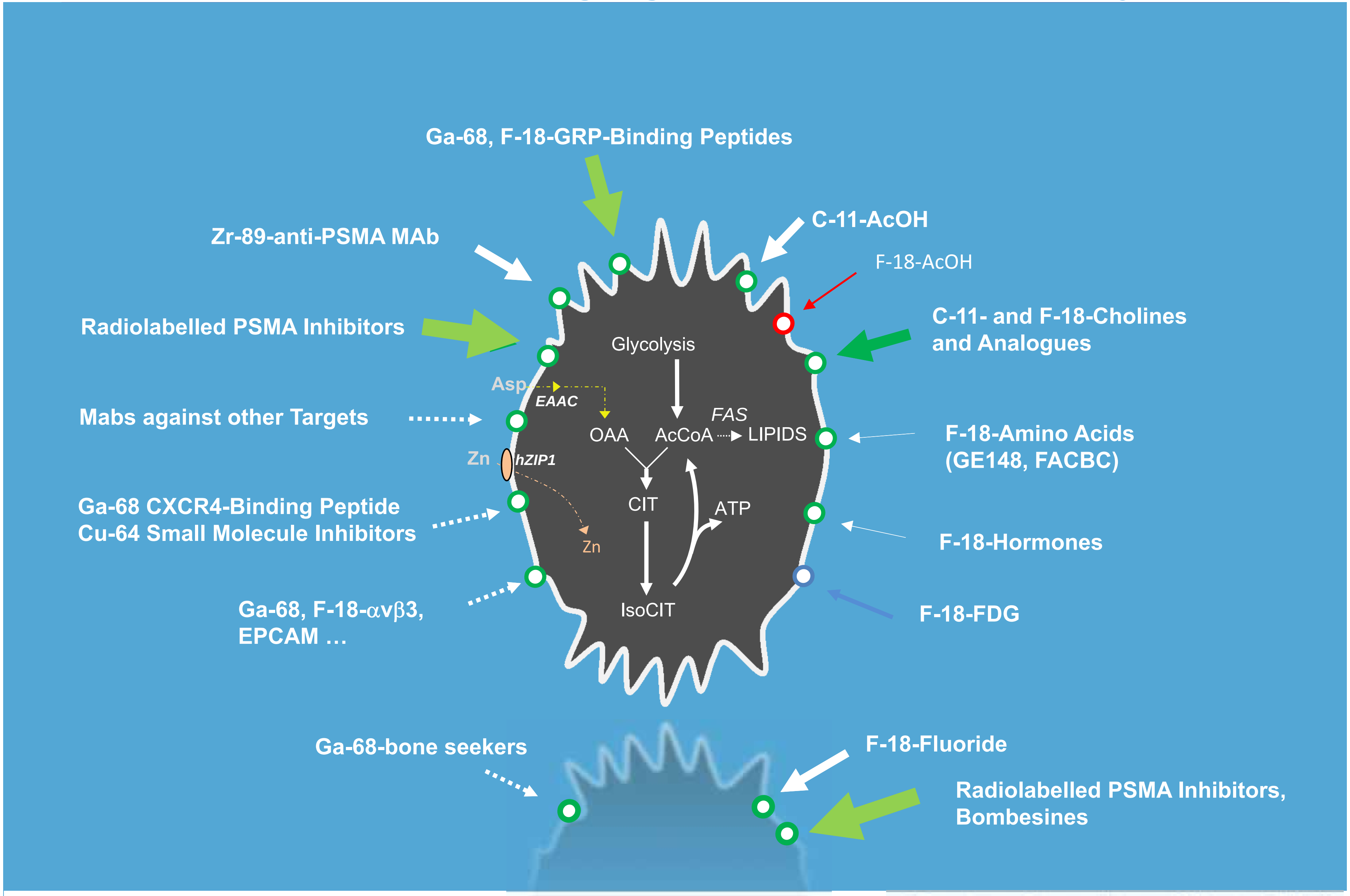
Lecture Outline

- Definition and principles of THERANOSTICS and Personalized Medicine
- THERANOSTIC radionuclides and Ga-68 generator
- Neuroendocrine tumors (NET) as a paradigm
- Diagnosis of NET by PET/CT (clinical applications)
- Dosimetry (organ & tumor dose calculations)
- Therapy of NET (Peptide Receptor Radiotherapy, PRRT)
- Future perspectives
    - new peptides (antagonists, CXCR4, RGD)
    - PSMA: THERANOSTICS potential for prostate ca.

Prostate Cancer 2013

- Prostate cancer is the most common cancer diagnosis in Western countries
  - > 220,000 new cases annually in the U.S
  - > 400,000 new cases in Europe
  - > 900,000 worldwide incidence
- Second most common cause of cancer-related death in Western men
  - Estimated 32,000 deaths in 2011 in U.S
  - Estimated 89,000 deaths in Europe
  - Estimated 258,000 deaths worldwide
- >20% reduction in deaths since 1990 in U.S
    - Screening
    - Improved treatment
    - Statin use
    - But increasing population of at-risk men

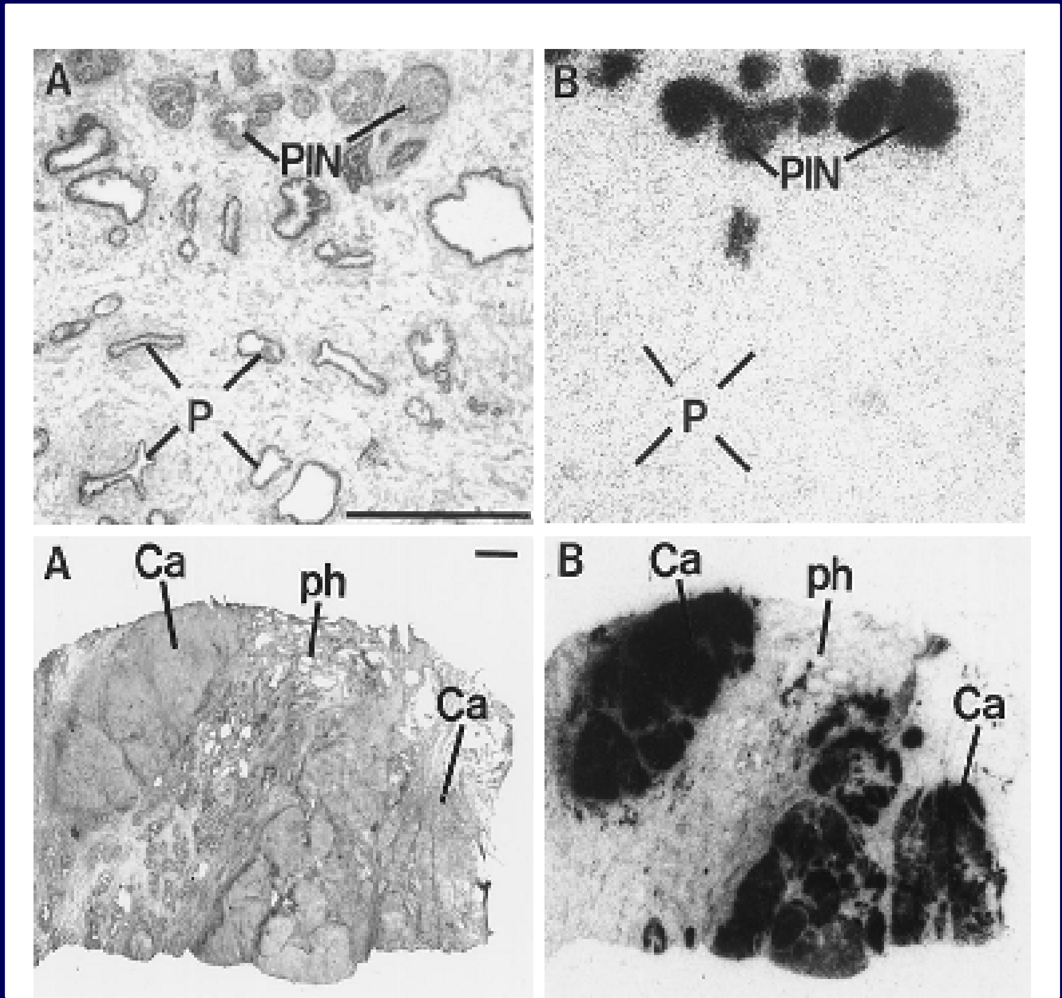
Molecular Imaging of Prostate Cancer by PET



Courtesy Hans-Jürgen Wester, TUM

Bombesin Receptors in Human Prostate Cancer

Histology **Autoradiography**

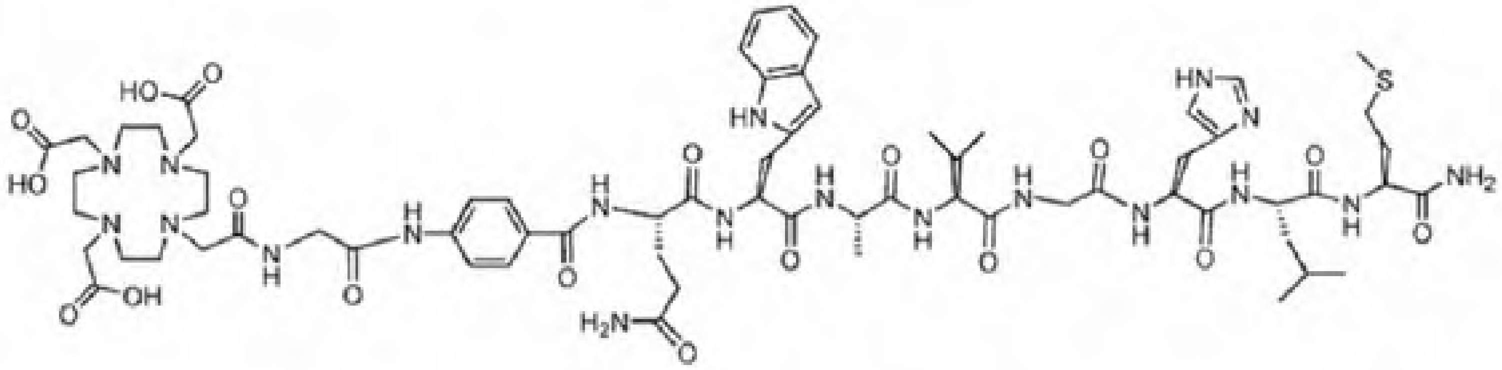


Bombesin receptors are expressed in PIN (prostate intraepithelial neoplasia) and prostate cancer, but not in normal prostate or hyperplasia (N=36)

Markwalder & Reubi.
Cancer Res (1999) 59:1152-1159

Clinical Work with Bombesin-based Agonists

- ^{177}Lu-AMBA — L. Bodei et al, R.P. Baum et al
- ^{68}Ga-AMBA — R.P. Baum et al
- ^{68}Ga-BZH3 — L. Strauss et al
- ^{99m}Tc-BOM — C. Van de Wiele et al
- F. Scopinaro et al



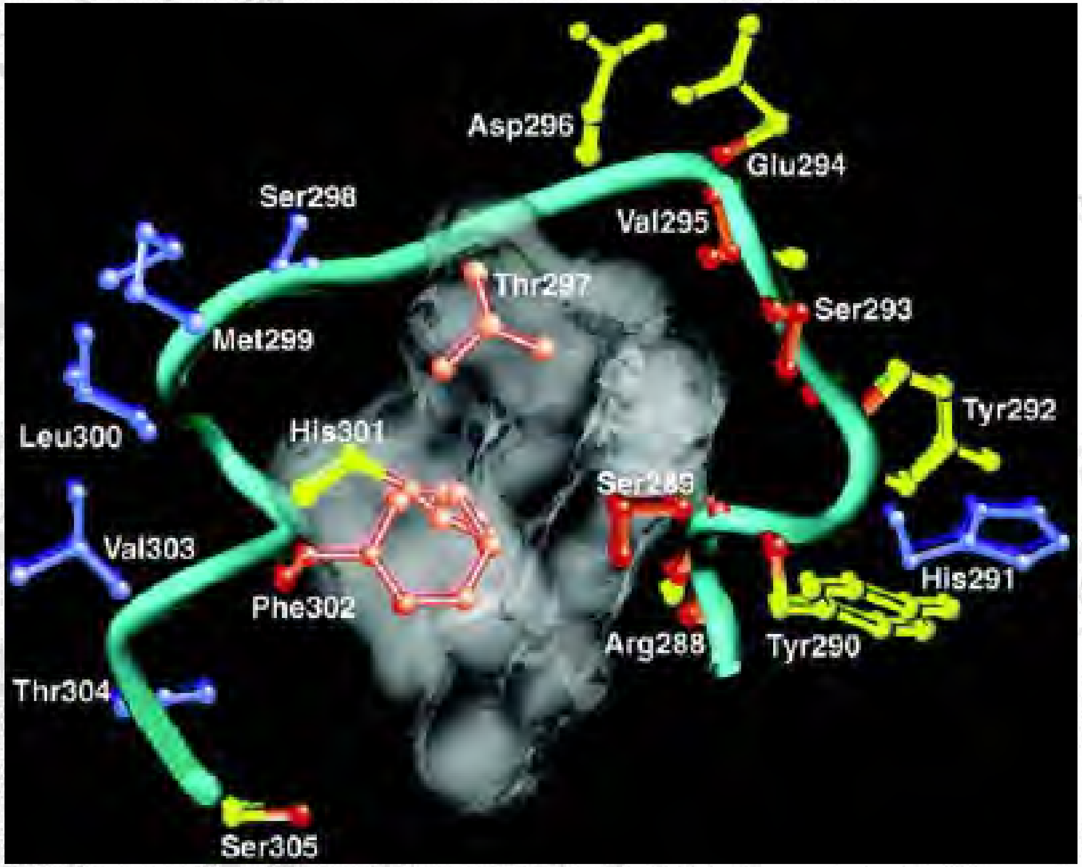
AMBA, a powerful bombesin-based agonist

Lantry et al. J Nucl Med 2007

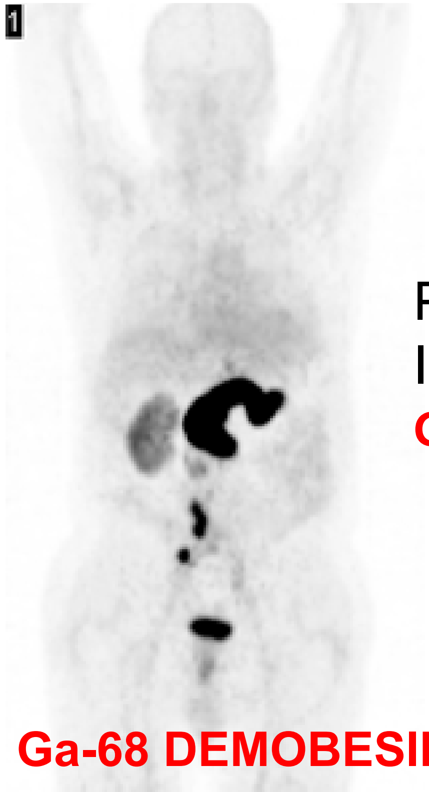
R.P. Baum et al.J Nucl Med 2007 (abstr.)

L. Bodei et al. EJNMMI 2007 (abstr.)

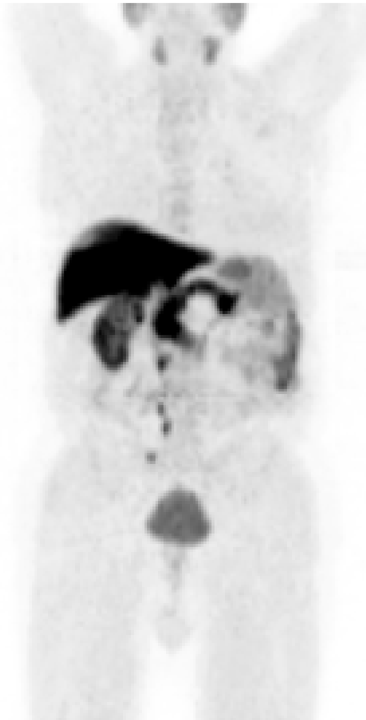
Antagonist Binding Domain of GRPRs



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



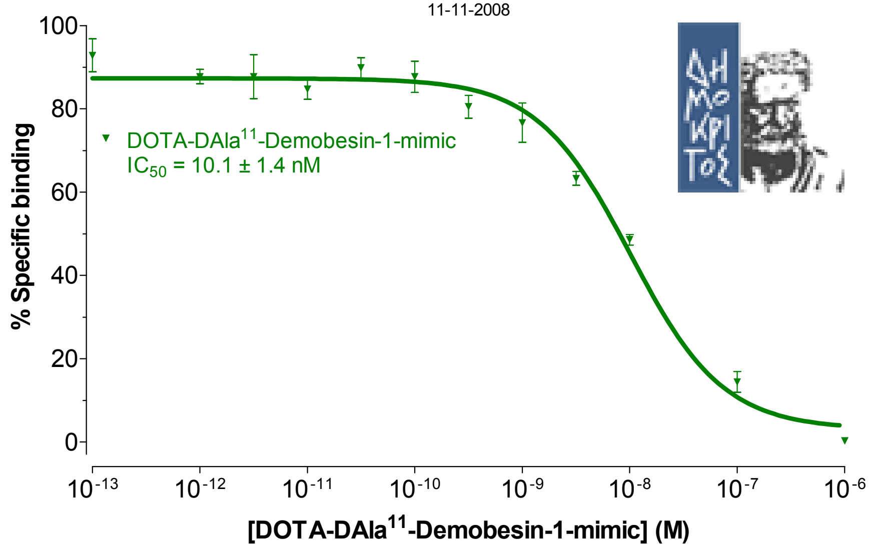
Patient with prostate cancer recurrence
Increasing PSA, CI normal.
Ga-68 GRPR antagonist PET/CT 60 Min p.i.



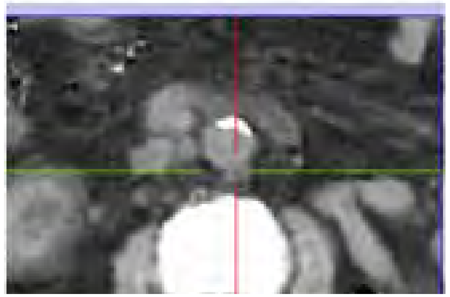
F-18 Cholin

Ga-68 DEMOBESIN

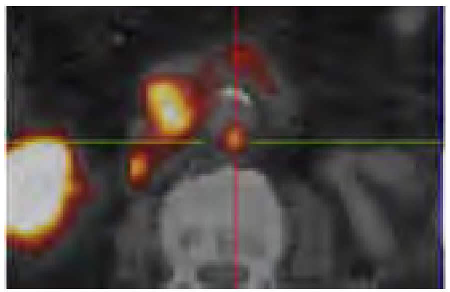
Displacement of [^{125}I-Tyr^4]bombesin (31,200 cpm; 39,000 dpm) from PC-3 membranes (50 μg/batch 19/07/2005) by increasing amounts of DOTA-DAla^{11}-Demobesin-1-mimic
11-11-2008

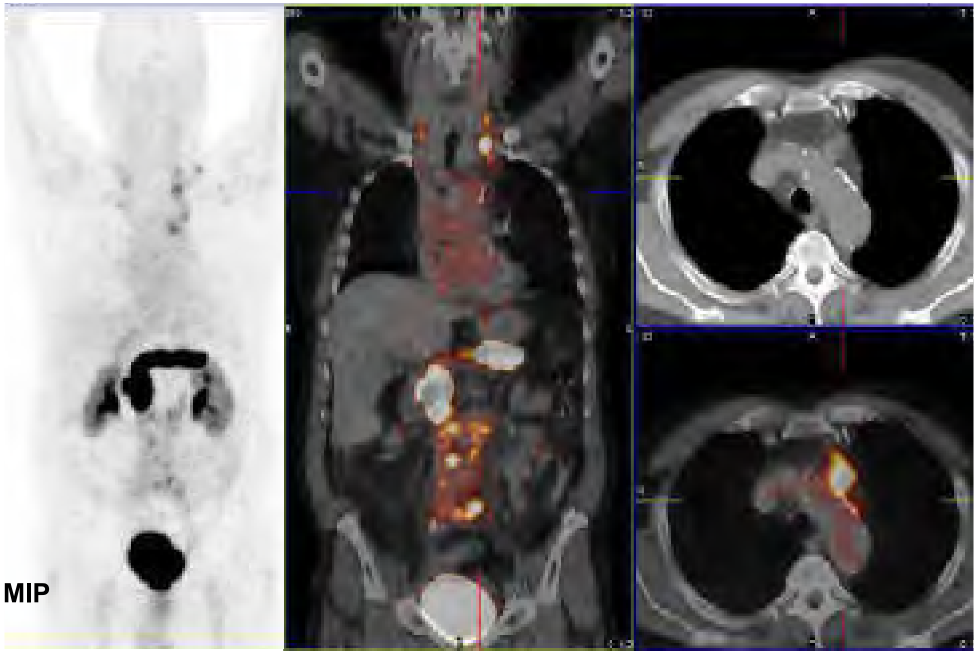


Lymph node mets



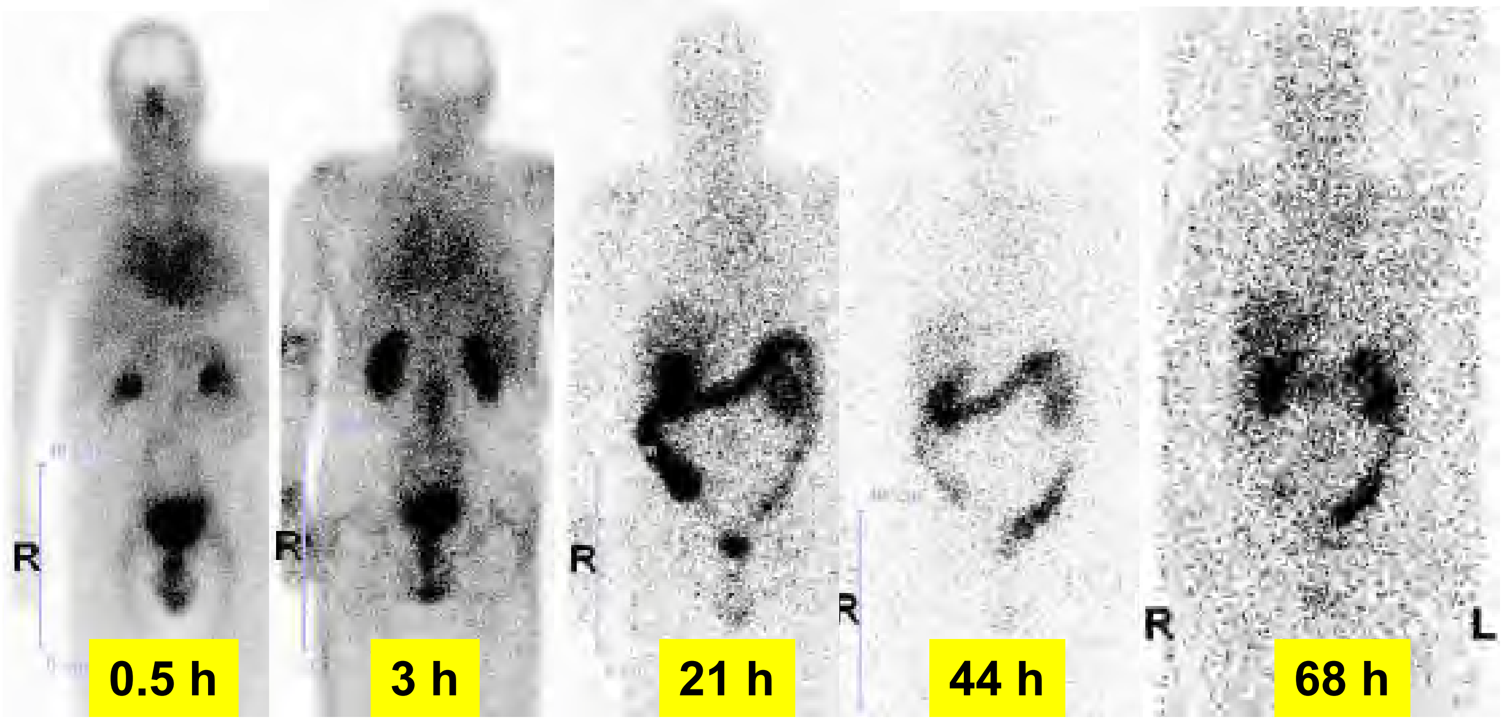
Ga-68 DOTA-Demobesin





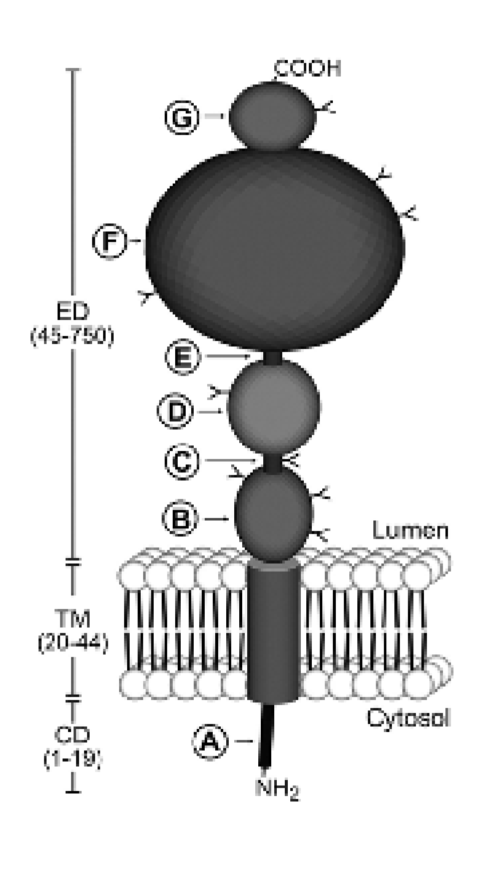
Ga-68 DOTA-Demobesin PET/CT in a 71 year-old patient with poorly differentiated carcinoma of the prostate demonstrates bombesin receptor positive mediastinal, axillary and abdominal lymph node metastases.

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

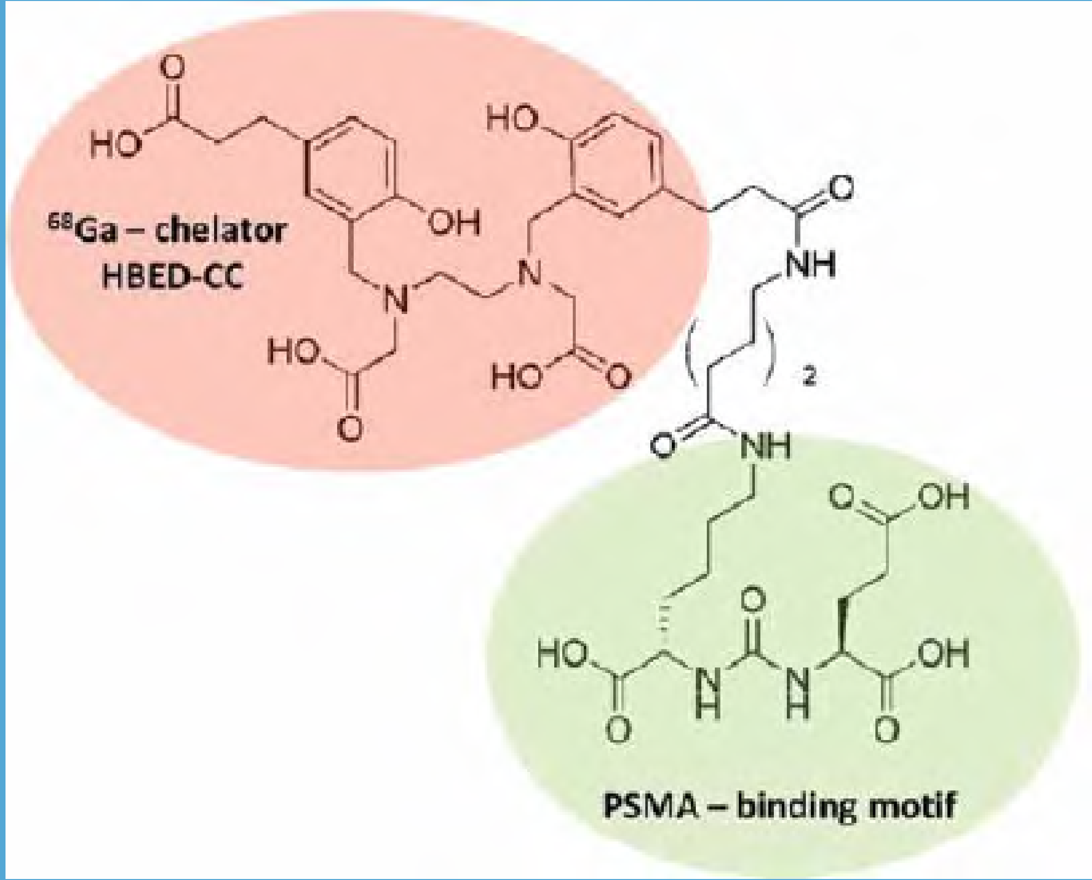


Post-therapy scans (anterior view) with Lu-177 DOTA-Demobesin in the same patient exhibit rapid wash-out of the tracer from the metastases with time.

Urea-based ^{68}Ga-PSMA Inhibitor (GCP-II) for PET Imaging



Glutamate Carboxypeptidase II
(GCP II)

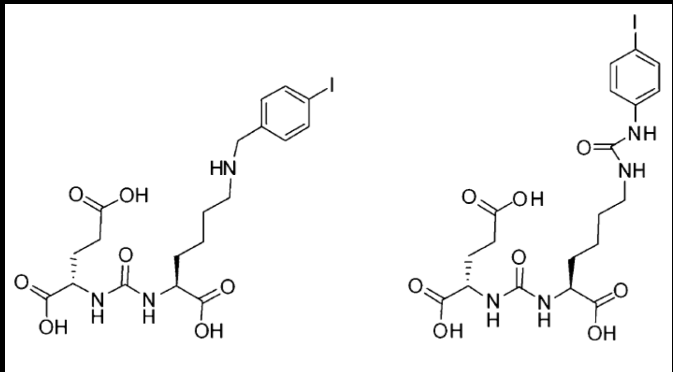


N,N′-bis [2-hydroxy-5-(carboxyethyl)benzyl] ethylenediamine-N,N′- diacetic acid (**HBED-CC**) was introduced as a lipophilic side chain into the hydrophilic pharmacophore **Glu-NH-CO-NHLys**

Rajasekaran A et al. Am J Physiol Cell Physiol. 2005

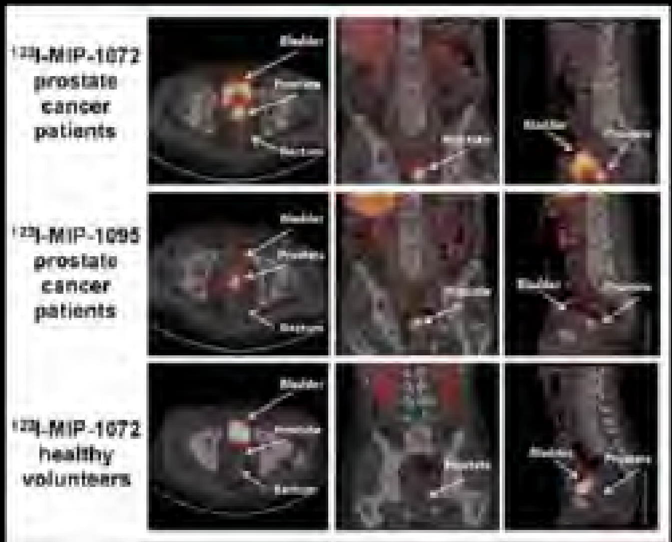
Eder et al. Bioconjugate Chem. 2012

Evaluation of PSMA-avid small molecules

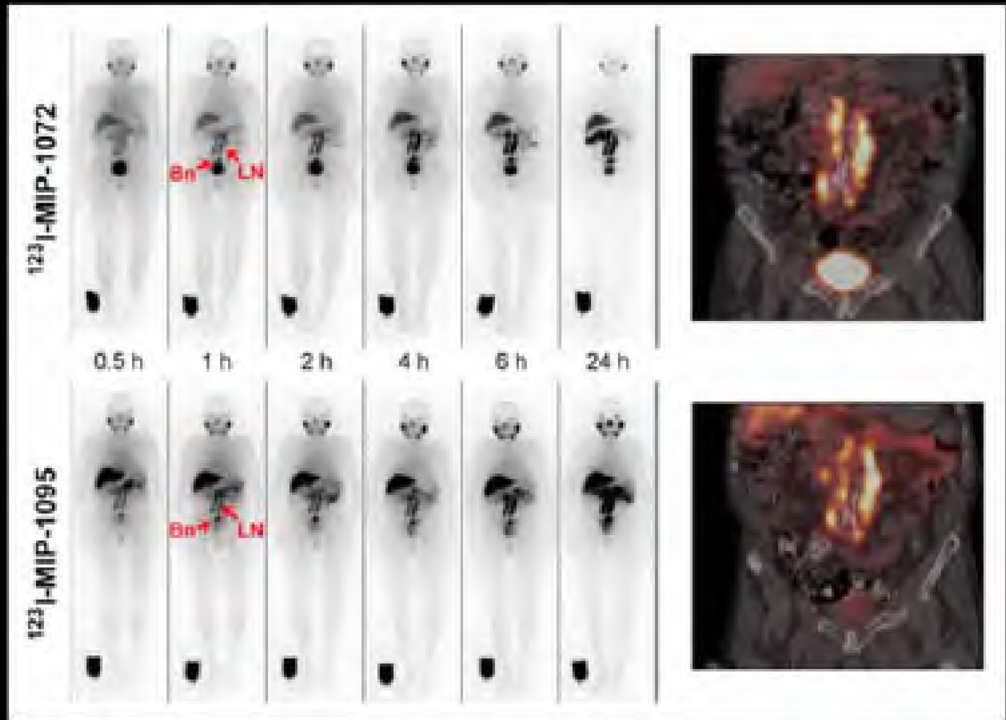


MIP-1072
cLogP = 0.20

MIP-1095
cLogP = 1.97



SPECT/CT scans at 4 h p.i.



370 MBq, planar WB scans (left) and SPECT/CT, 4h p.i.

Barret JA et al. J Nucl Med 2013; 54:380–387

PSMA as a target for radiolabeled small molecules.

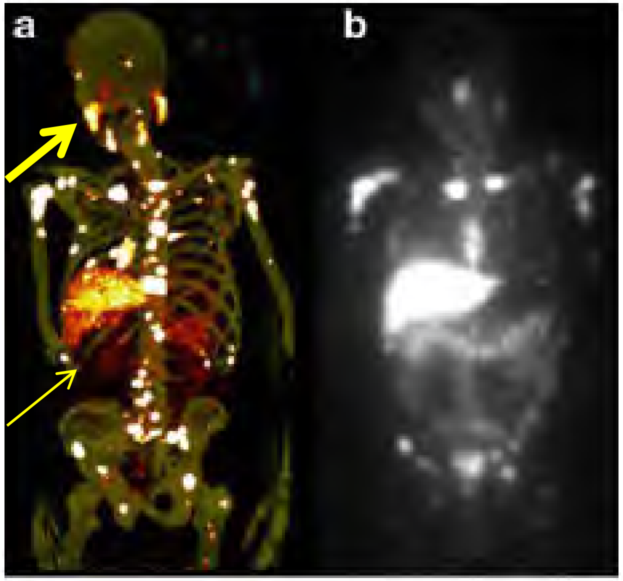


Fig. 1 a Maximum intensity projection image of a PET scan performed on day 5 after administration of ^{124}I-MIP-1095 shows multiple lesions in bones and lymph nodes, and also accumulation in the salivary and lacrimal glands. b Whole-body scan 7 days after administration of 5 GBq ^{131}I-MIP-1466 in the same patient

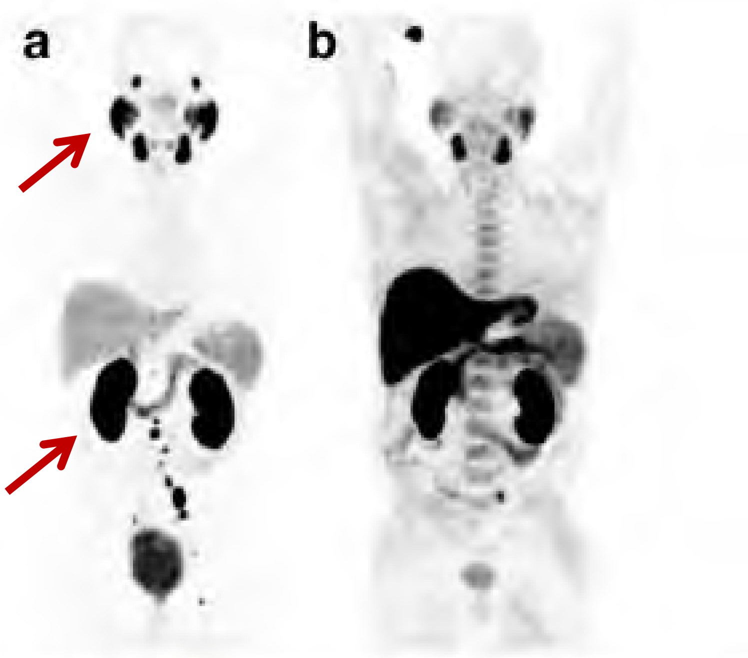
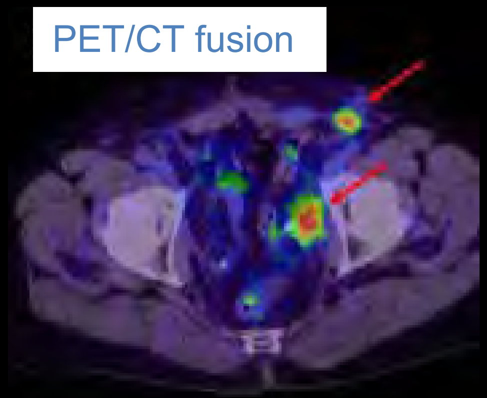


Fig. 2 PET images in the same patient using the ^{68}Ga-labelled PSMA inhibitor Glu-NH-CO-NH-Lys(Ahx)-HBED-CC (a) and ^{18}F-fluoroethylcholine (b). The scan with the PSMA ligand shows significantly more lesions than the fluoroethylcholine scan in which only one metastasis is seen

^{68}Ga-PSMA PET/CT

^{68}Ga-PSMA PET/CT

Patient representative for disseminated lymph node and bone metastases of prostate cancer.



^{68}Ga-PSMA PET/CT

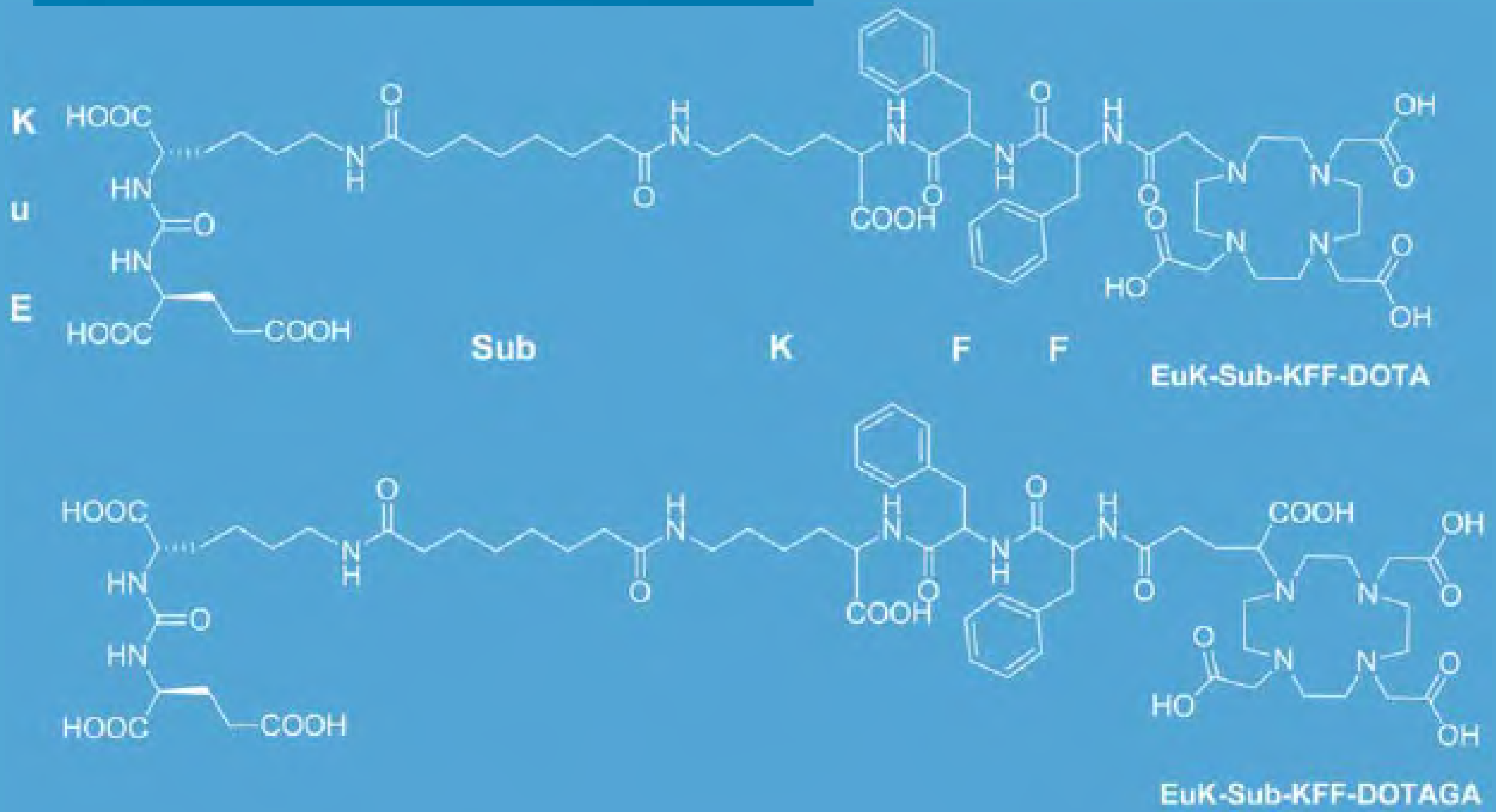
Patient with low PSA level (0.01 ng/ml) and lymph node metastases.
Minimal PSA elevation despite visible tumor lesions suggests dedifferentiation of prostate cancer metastases.

At PSA levels < 2.2 ng/ml, lesions suspicious for cancer were observed in 60 % of the patients.
At PSA levels > 2.2 ng/ml, lesions were detected in all patients.

A. Afshar-Oromieh et al. EJNM MI 2012

A KFF DOTA Analogue

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



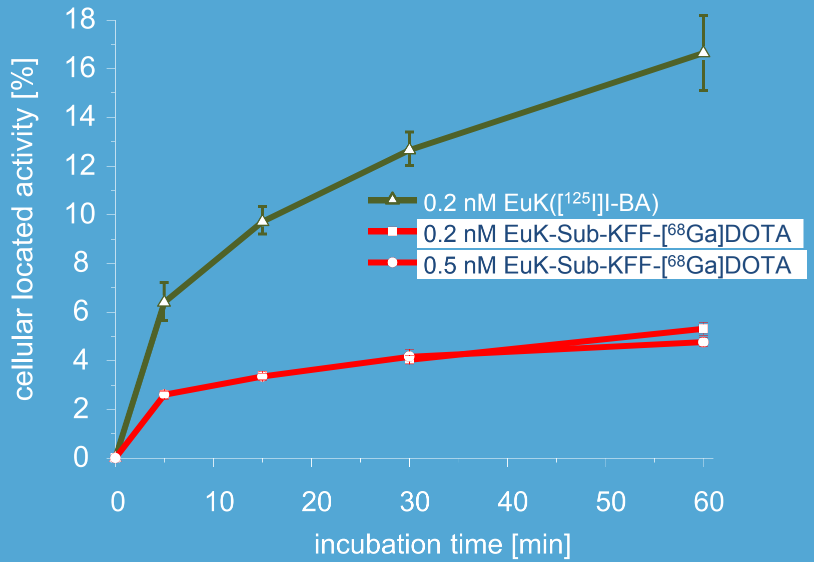
A KFF DOTAGA Analogue

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

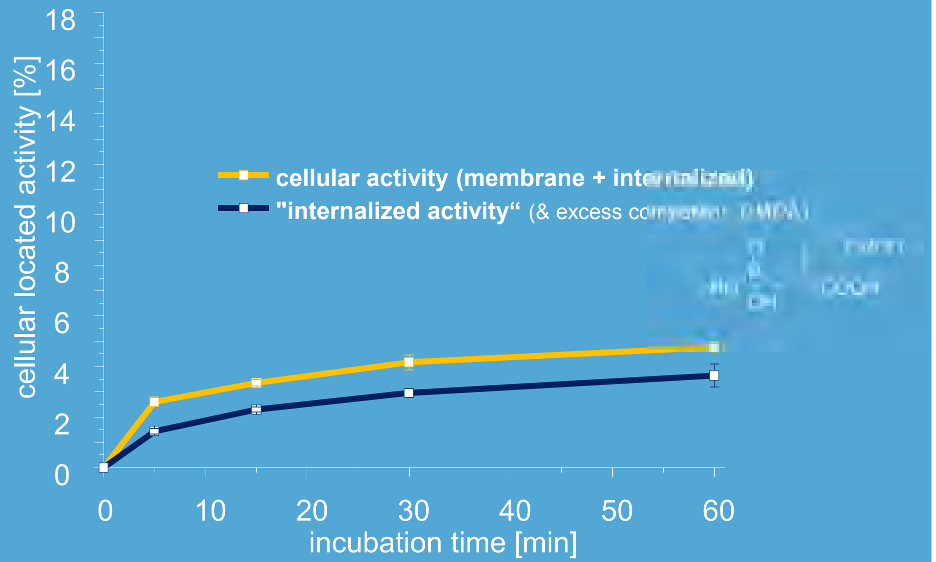
Weineisen M, Schottelius M, Simecek J et al. (unpublished)

Internalization, LNCaP cells (37°C, DMEM + 5% BSA)

Activity accumulation of EuK-Sub-KFF-[^{68}Ga]DOTA



Activity accumulation of 0.5 nM EuK-Sub-KFF[^{68}Ga]DOTA

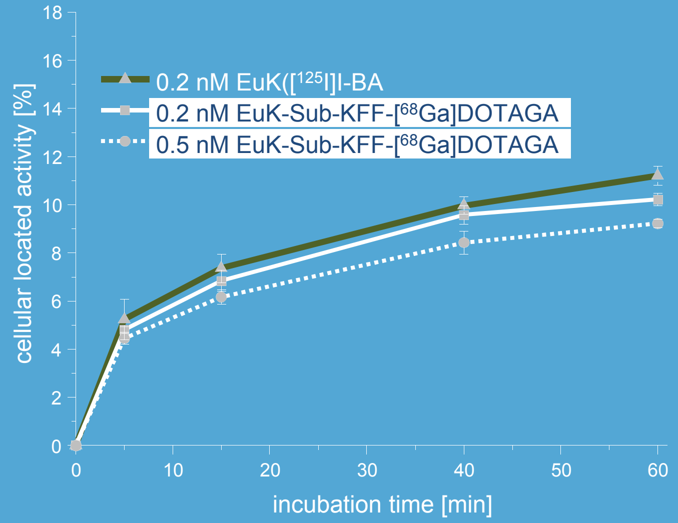


Internalization, 125.000 LNCaP cells/well; 37°C, DMEM + 5% BSA

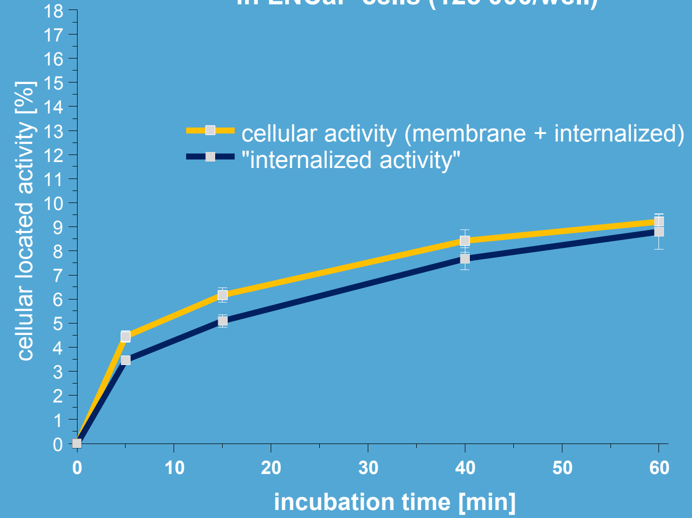
Weineisen M, Schottelius M, Simecek J et al. (unpublished)

New GCP-II Ligands for Imaging and Therapy

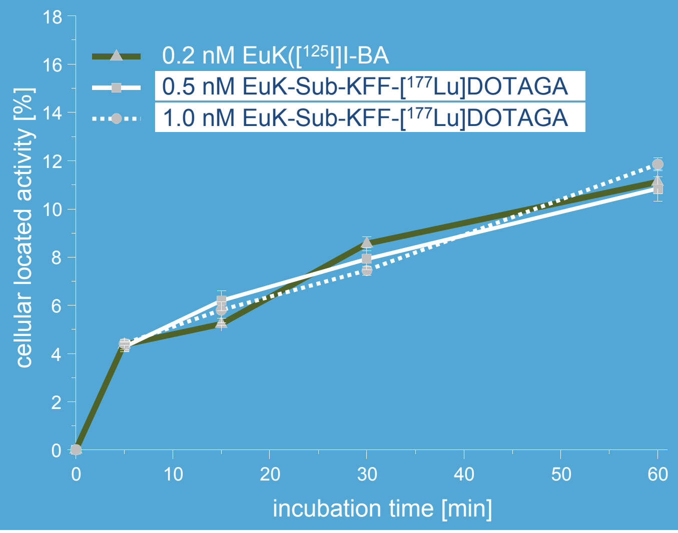
Activity accumulation of EuK-Sub-KFF-[^{68}Ga]DOTAGA



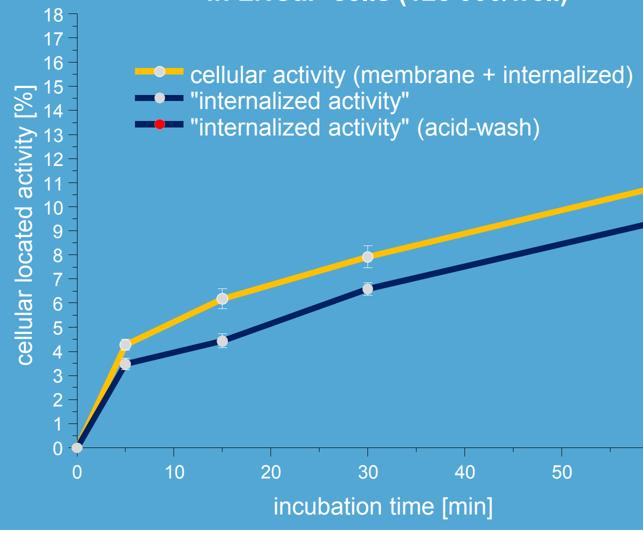
Activity accumulation of 0.5 nM EuK-Sub-KFF-[^{68}Ga]DOTAGA in LNCaP cells (125 000/well)



Activity accumulation of EuK-Sub-KFF-[^{177}Lu]DOTAGA

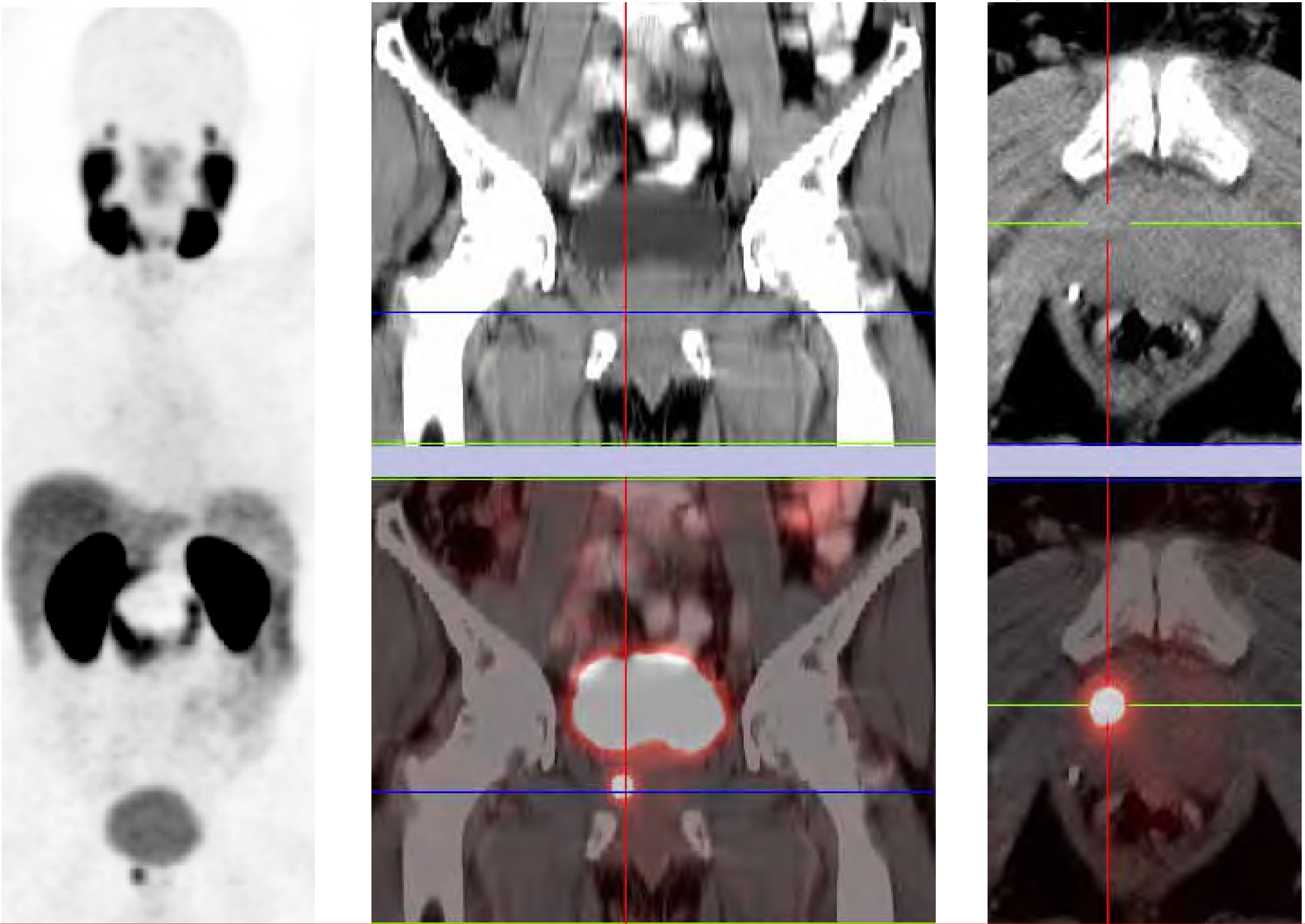


Activity accumulation of 0.5 nM EuK-Sub-KFF-[^{177}Lu]DOTAGA in LNCaP cells (125 000/well)



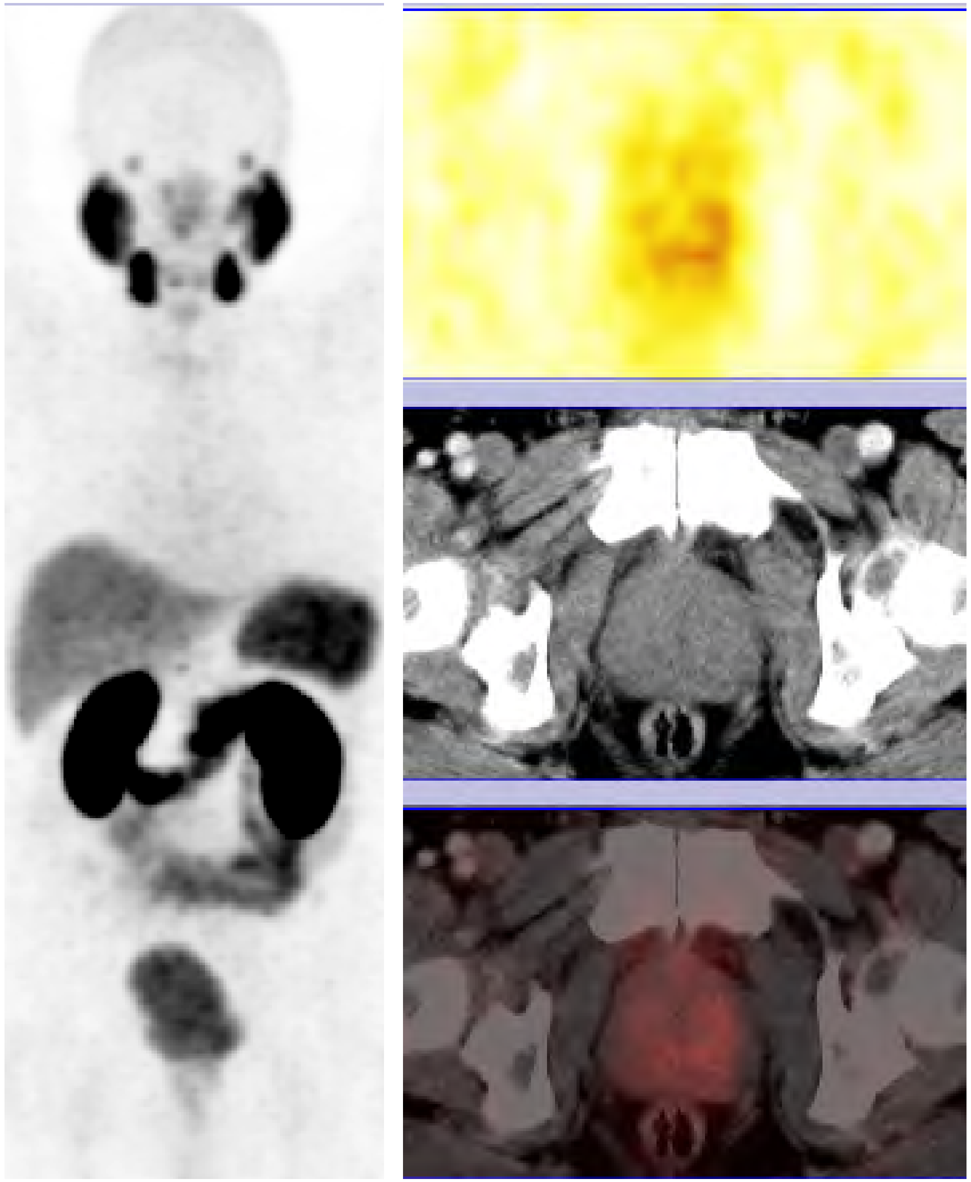
Weineisen M, Schottelius M, Simecek J et al. (unpublished)

Indication: rising PSA (8 ng/ml); intense PSMA-avid tumor in right lower quadrant of the prostate with an SUV of 9.3, high probability of malignancy



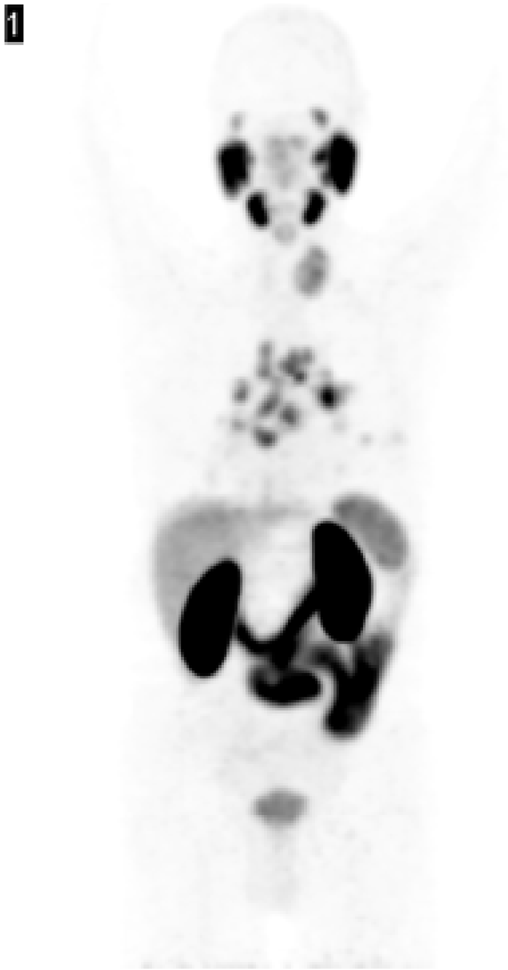
Ga-68 PSMA PET/CT – Detection of Primary Tumor

Benign prostatic hyperplasia: Enlarged prostate (6.2 x 5.6 cm), PSA 50 ng/ml.
No evidence of a PSMA-avid primary tumor or metastases



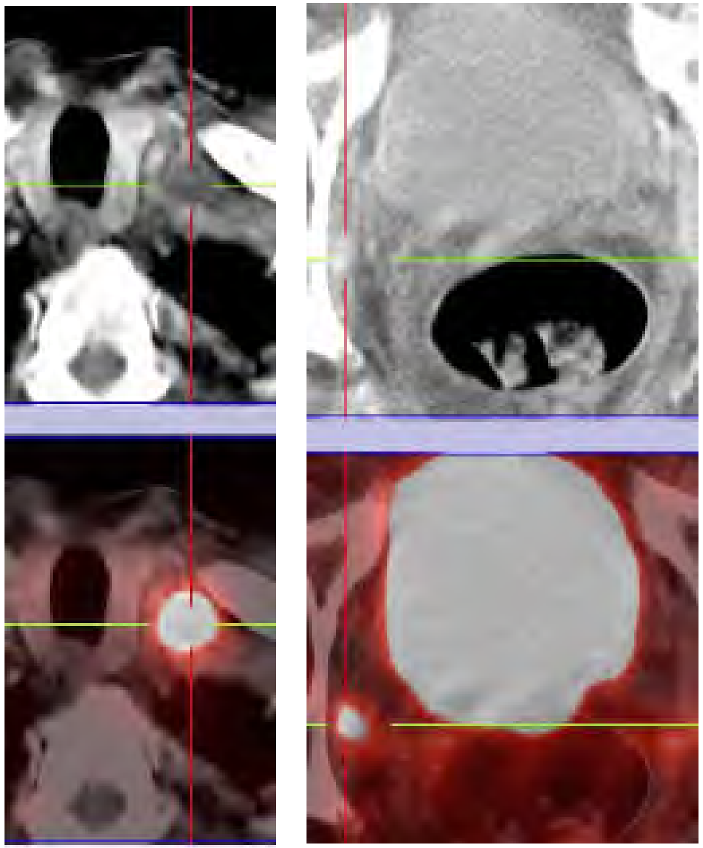
Ga-68 PSMA PET/CT seems to be highly specific!

Recurrent prostate cancer with multiple metastases (pulmonary, bone and lymph nodes)

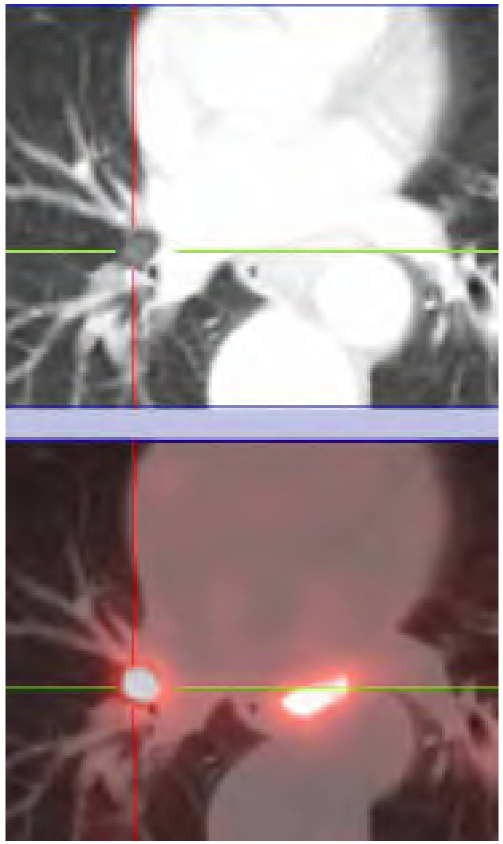


Center for Molecular Imaging and Molecular Radiotherapy, Zentralklinik Bad Berka, Germany in collaboration with H.J. Wester (labeling performed using SCINTOMICS module)

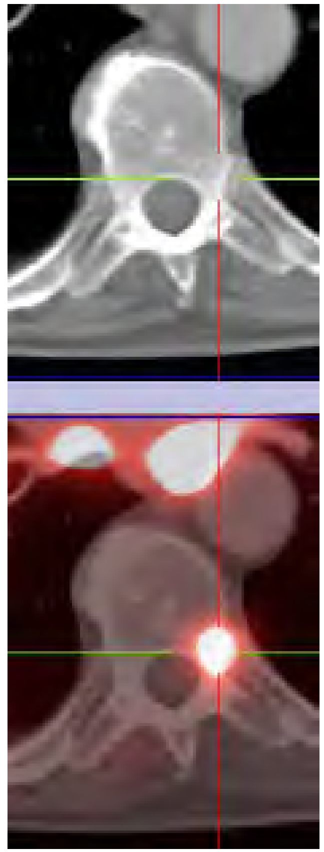
MULTIPLE METASTASES OF PROSTATE CANCER



Lymph nodes



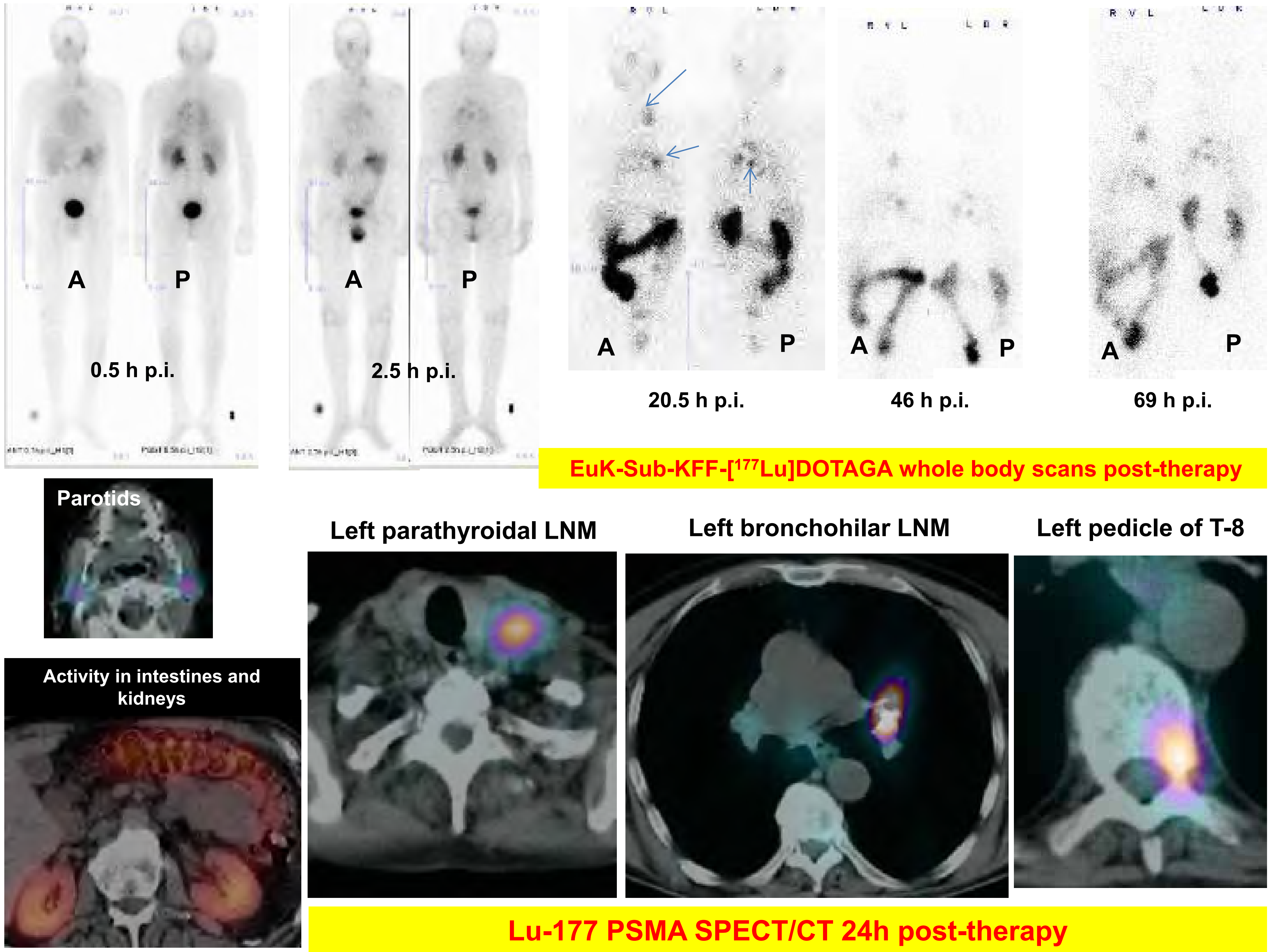
Pulmonary



Skeletal

Ga-68 PSMA PET/CT

Center for Molecular Imaging and Molecular Radiotherapy, Zentralklinik Bad Berka, Germany in collaboration with H.J. Wester (labeling performed using SCINTOMICS module)

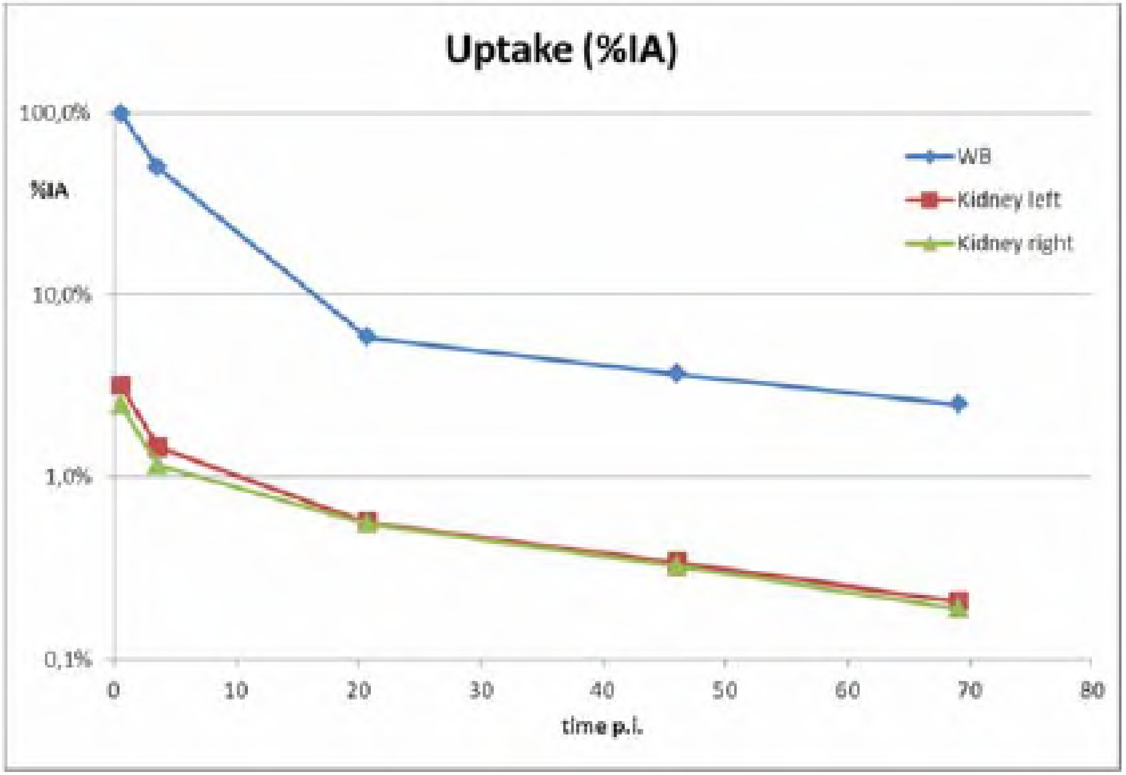


A
P
0.5 h p.i.
A
P
2.5 h p.i.
A
P
20.5 h p.i.
A
P
46 h p.i.
A
P
69 h p.i.
EuK-Sub-KFF-[177Lu]DOTAGA whole body scans post-therapy
Parotids
Left parathyroidal LNM
Left bronchohilar LNM
Left pedicle of T-8
Activity in intestines and kidneys
Lu-177 PSMA SPECT/CT 24h post-therapy

First Results

4200 MBq EuK-Sub-KFF-[^{177}Lu]DOTAGA

	MBq		
Time	GK	Kidney left	Kidney right
0,6	4200,00	133,69	104,40
3,6	2104,04	60,66	48,50
20,7	246,66	23,38	23,17
46,0	154,57	14,13	13,42
69,1	104,26	8,72	8,04
	%IA		
Time	GK	Kidney left	Kidney right
0,6	100,0%	3,2%	2,5%
3,6	50,1%	1,4%	1,2%
20,7	5,9%	0,6%	0,6%
46,0	3,7%	0,3%	0,3%
69,1	2,5%	0,2%	0,2%

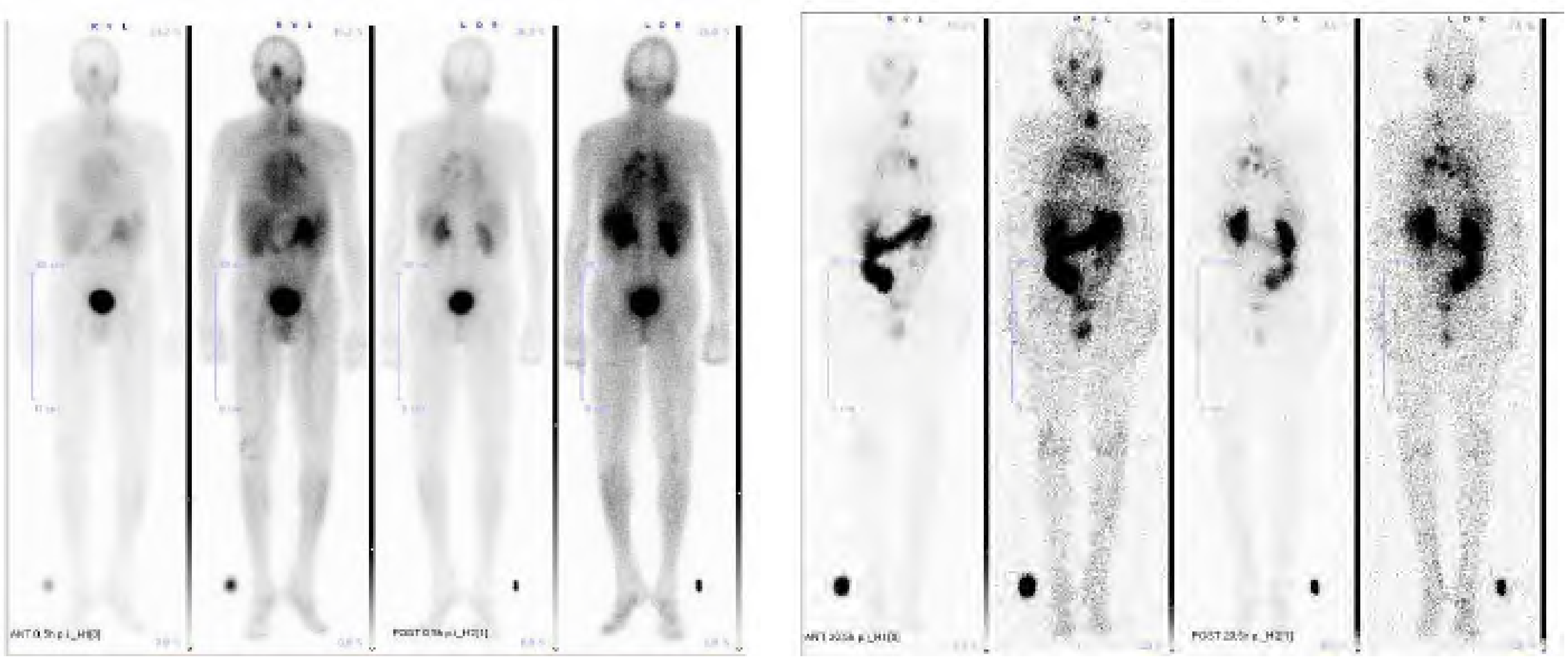


Half-life:

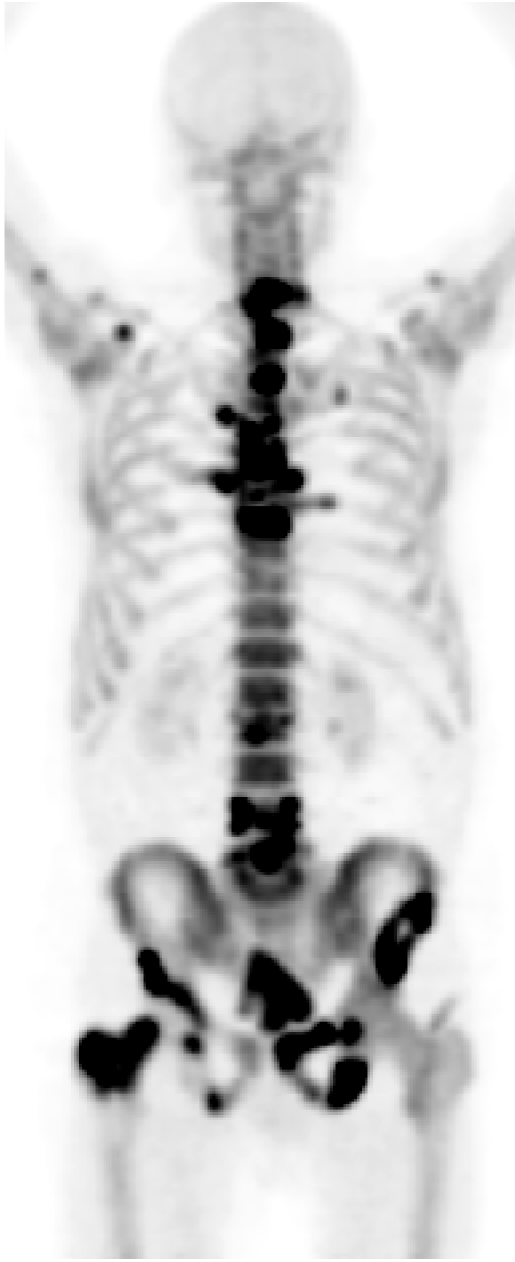
Whole Body = 45h

Kidneys = 34h

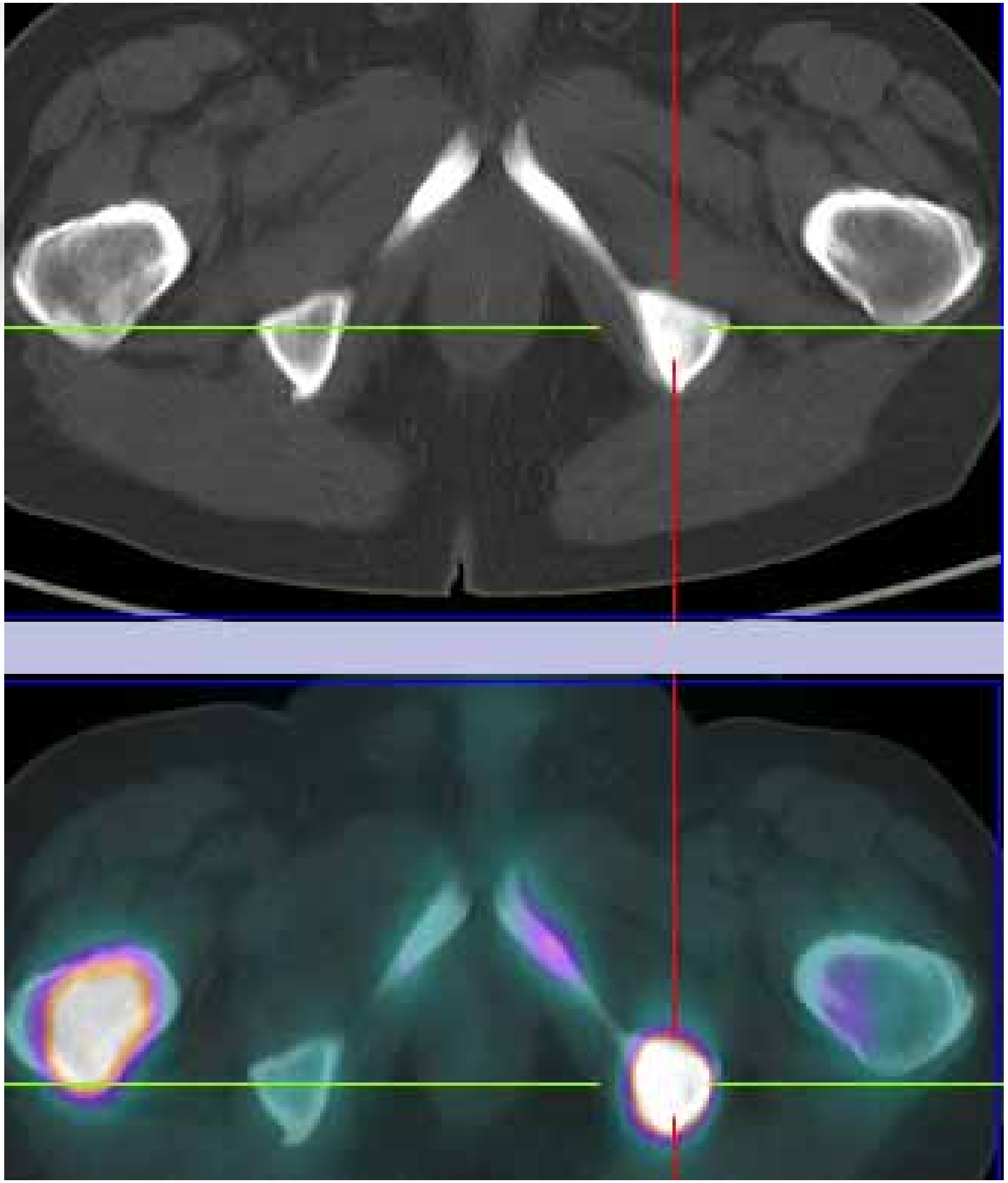
First in human treatment with a PSMA targeting probe - **EuK-Sub-KFF-$[^{177}Lu]$DOTAGA** for Lu-177 labeling



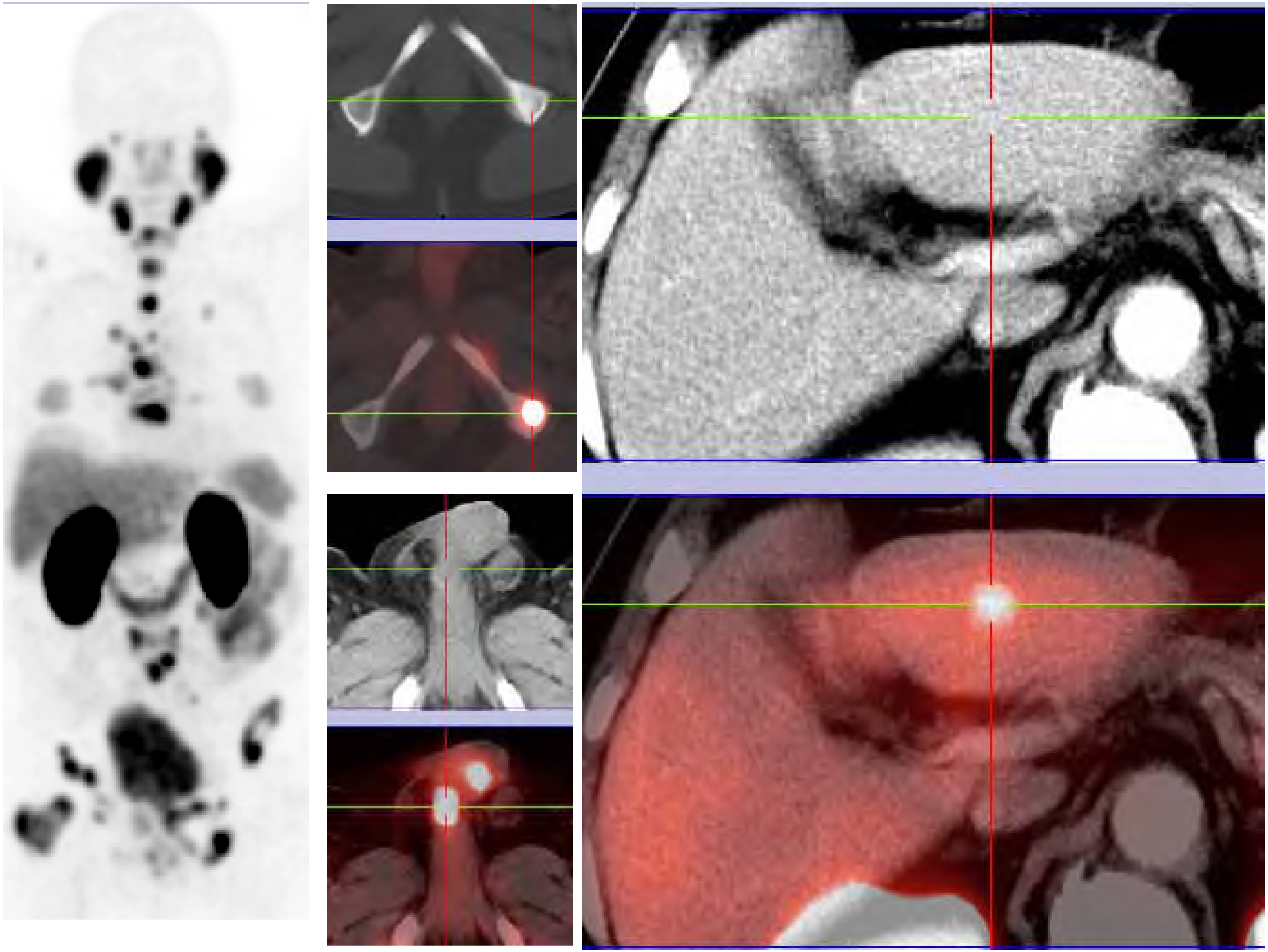
Center for Molecular Imaging and Molecular Radiotherapy, Zentralklinik Bad Berka, Germany in collaboration with H.J. Wester (labeling performed using SCINTOMICS module)



F-18 Fluoride PET/CT

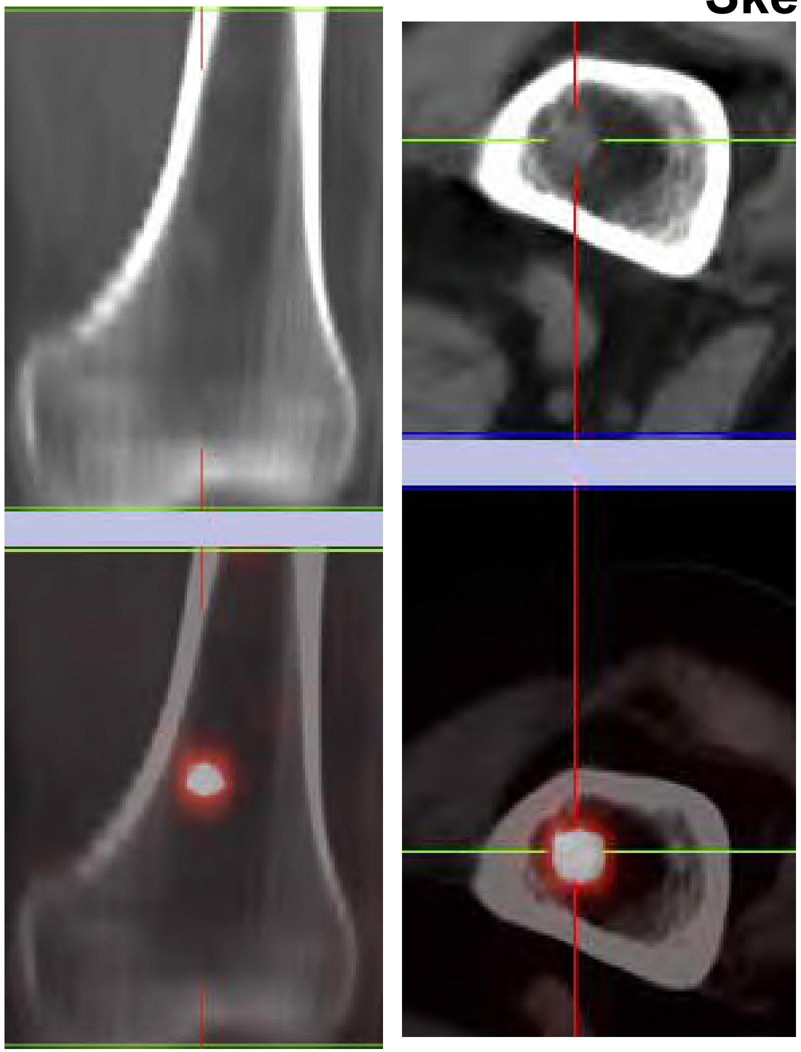


Target lesion in left ischium

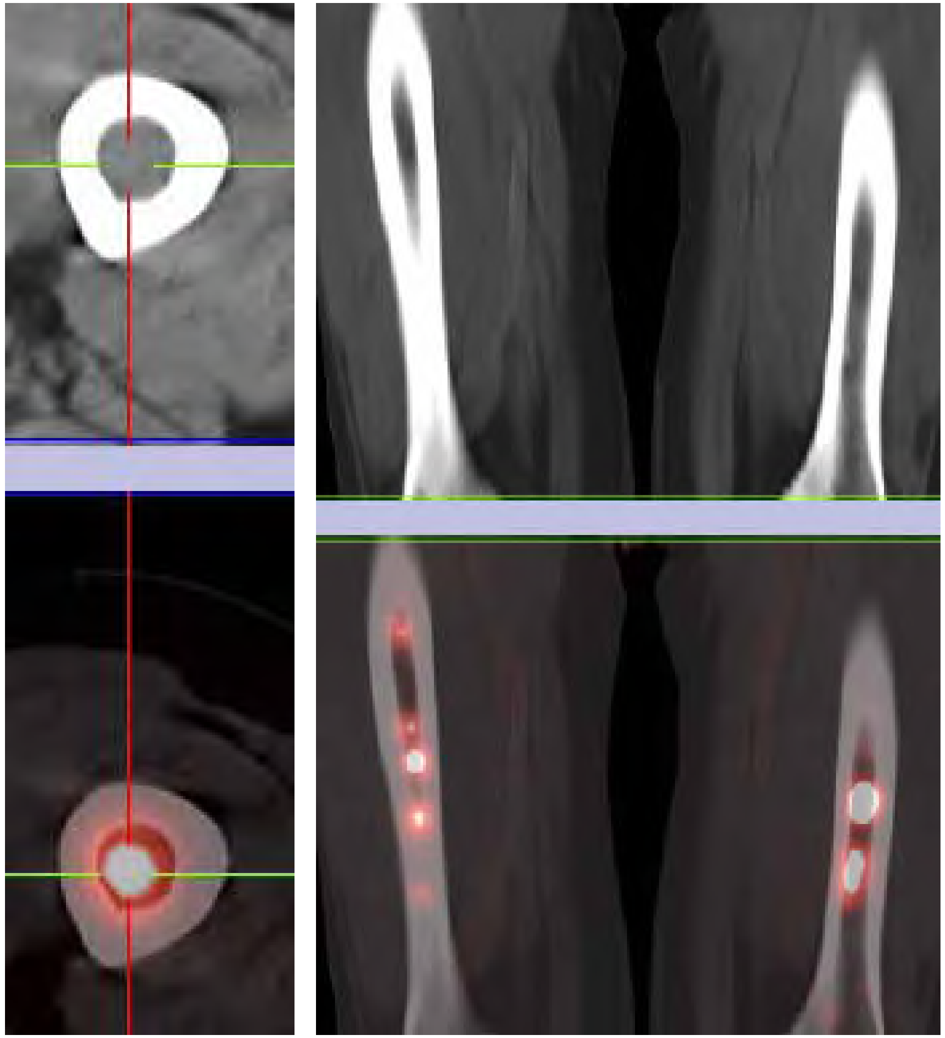


Ga-68 PSMA PET/CT shows additionally liver metastasis and infiltration of the glans penis (histologically proven)

Skeletal metastases



CT positive



CT negative (marrow metastases)

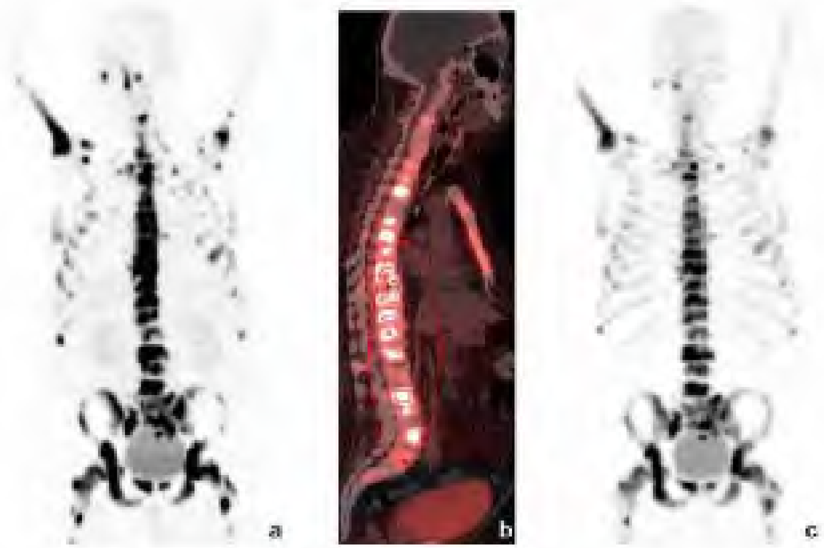
Ga-68 PSMA PET/CT

Eur J Nucl Med Mol Imaging (2010) 37:834
DOI 10.1007/s00259-009-1355-y

IMAGE OF THE MONTH

PET/CT imaging of osteoblastic bone metastases with ^{68}Ga-bisphosphonates: first human study

Marco Fellner · Richard P. Baum · Vojtěch Kubíček · Petr Hermann · Ivan Lukeš · Vikas Prasad · Frank Rösch



Acknowledgments Support by the EC through COST actions D38 and BM0607 is gratefully acknowledged.

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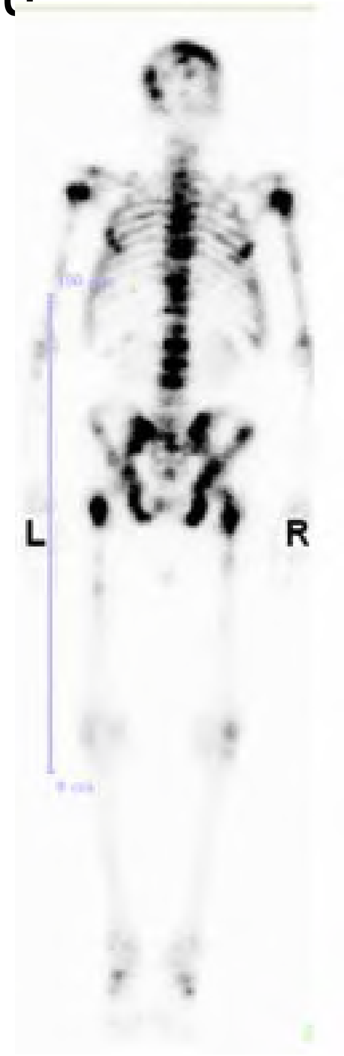
Bad Berka, Germany

V. Kubíček · P. Hermann · I. Lukeš
Department of Inorganic Chemistry, Faculty of Science,
Charles University in Prague,
Prague, Czech Republic

BPAMD

- labeling in almost quantitative yield with ^{177}Lu
- perfect for routine: dilute 15 GBq batch to 20 mL in syringe with stabilizing gentisic acid (1-2 mg total)
- stability of >95 % in 24 h



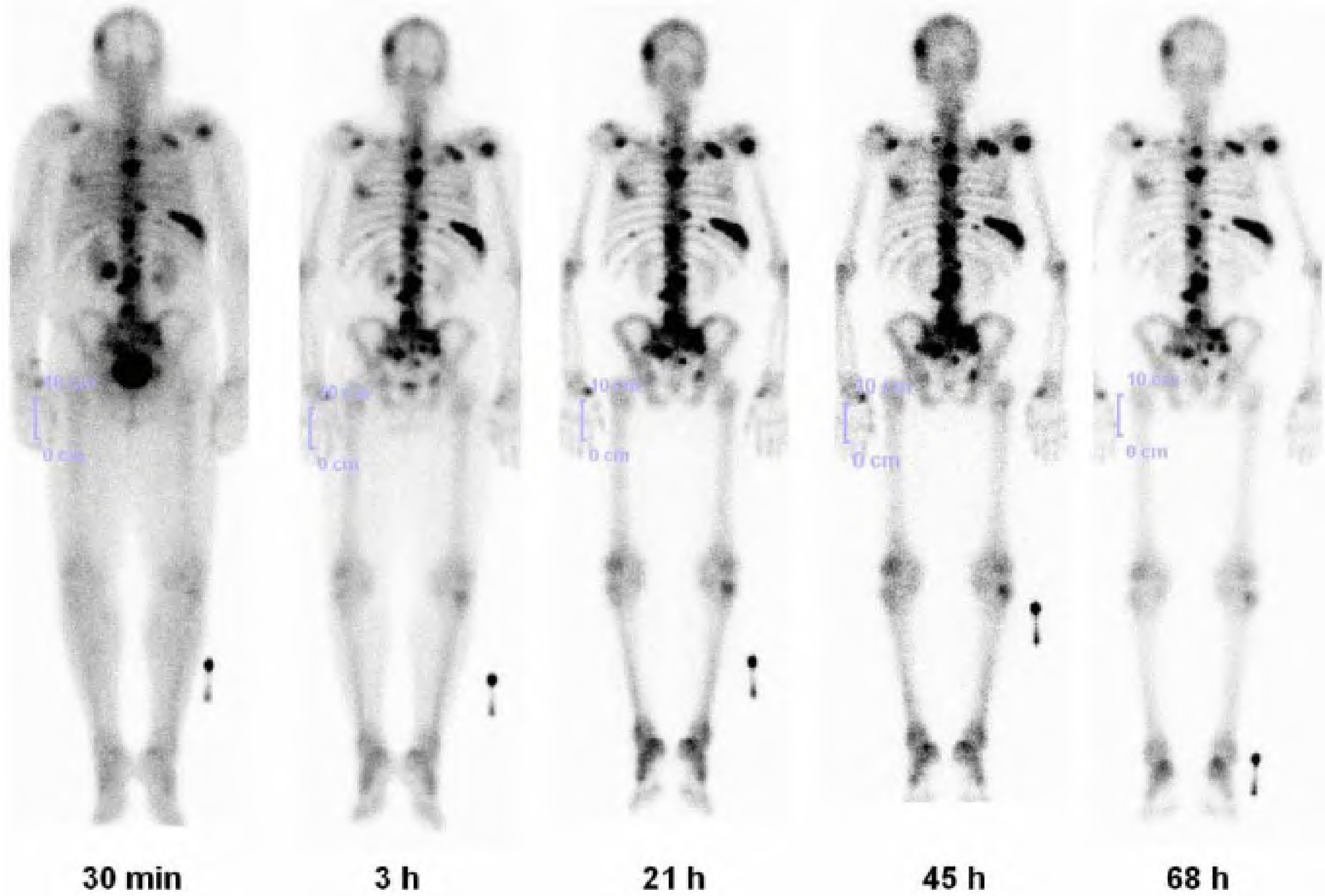
Combine diagnosis

AND

therapy with the same ligand!

=THERANOSTICS

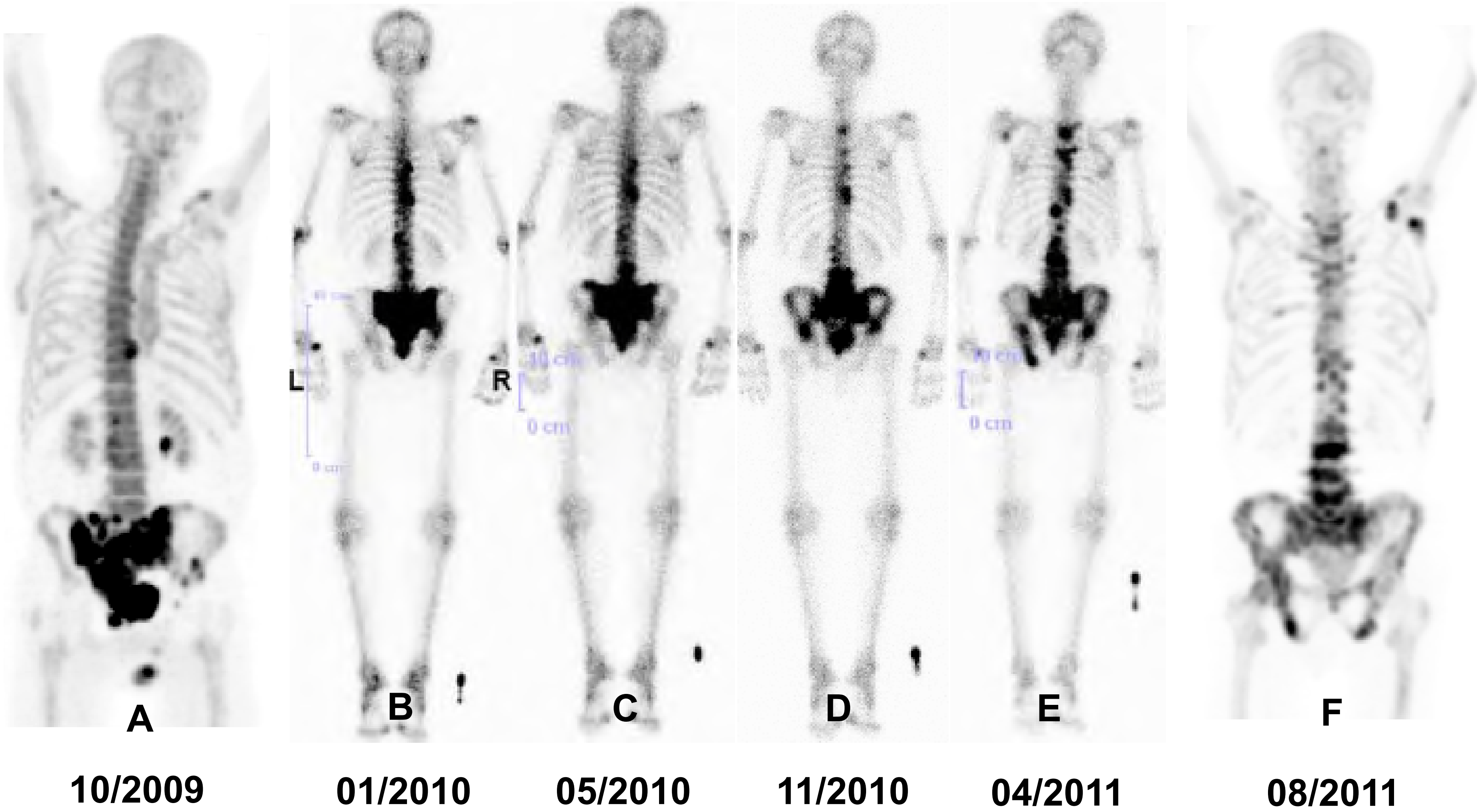
Lu-177 BPAMD post-therapy planar images (posterior views) in a patient with metastatic prostate cancer, showing rapid renal clearance, high uptake in skeletal metastases and long effective half life.



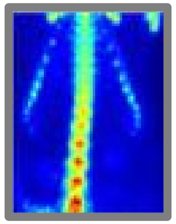
Baum and Kulkarni. *Theranostics* 2012, 2(5)

72 year-old male patient with poorly differentiated adenocarcinoma of the prostate, Gleason score 7 (4 +3), first diagnosed 6 years before, s.p. radical prostatectomy, pelvic lymphadenectomy, EBRT (66.6 Gy) of the prostate, seminal vesicles and iliac lymph nodes developed painful bone metastases treated by androgen blockade and biphosphonates, followed by palliative treatment with Sm-153 EDTMP.

For progressive metastases with intense skeletal pain, he underwent 4 cycles of Lu-177 BPAMD treatment with a cumulative administered activity of 19.9 GBq Lu-177. F-18 (fluoride) PET/CT was performed pre- and post-therapy. Compared to the previous examination, there was a mixed pattern, i.e., on the one hand, clear regression with significant reduction in the intensive osteometabolic activity (uptake on F-18 PET/CT) of the metastases in pelvis and sacrum, but also evidence of new osseous metastases in the axial skeleton.

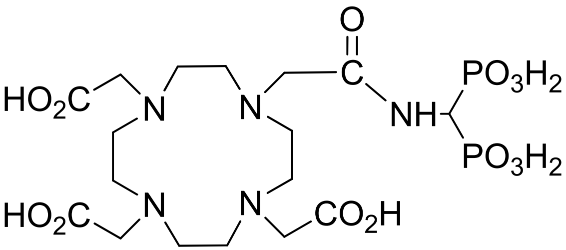


A: F-18 PET/CT MIP image pre-therapy;
F: F-18 PET/CT MIP image after 4 cycles of Lu-177 BPAMD treatment;
B, C, D, E: Lu-177 BPAMD whole-body planar images 45 hours after injection (first, second, third and fourth cycles respectively).

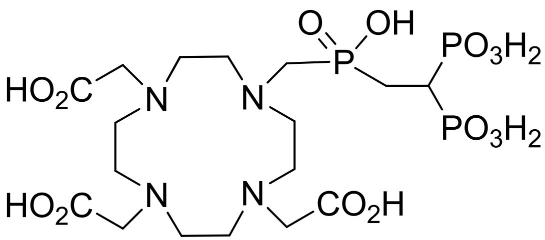


Macrocyclic Bisphosphonates

DOTA derivatives

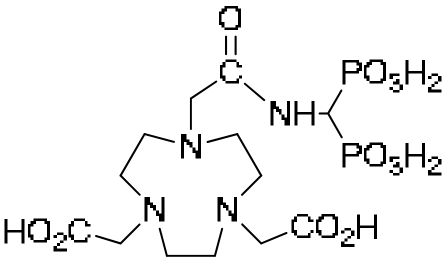


$DOTAM^{BP}$

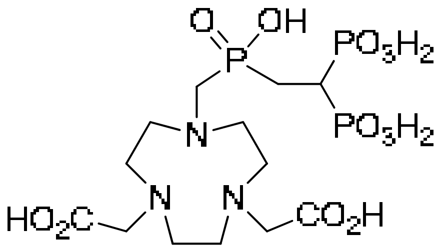


$DO3AP^{BP}$

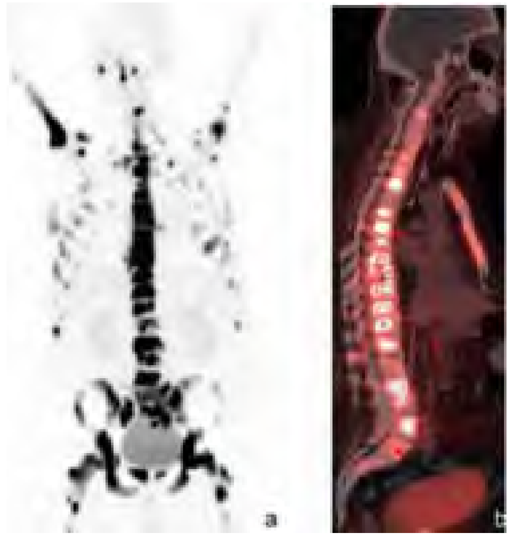
NOTA derivatives



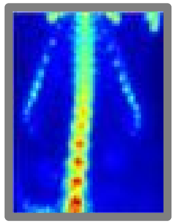
$NOTAM^{BP}$



$NO2AP^{BP}$

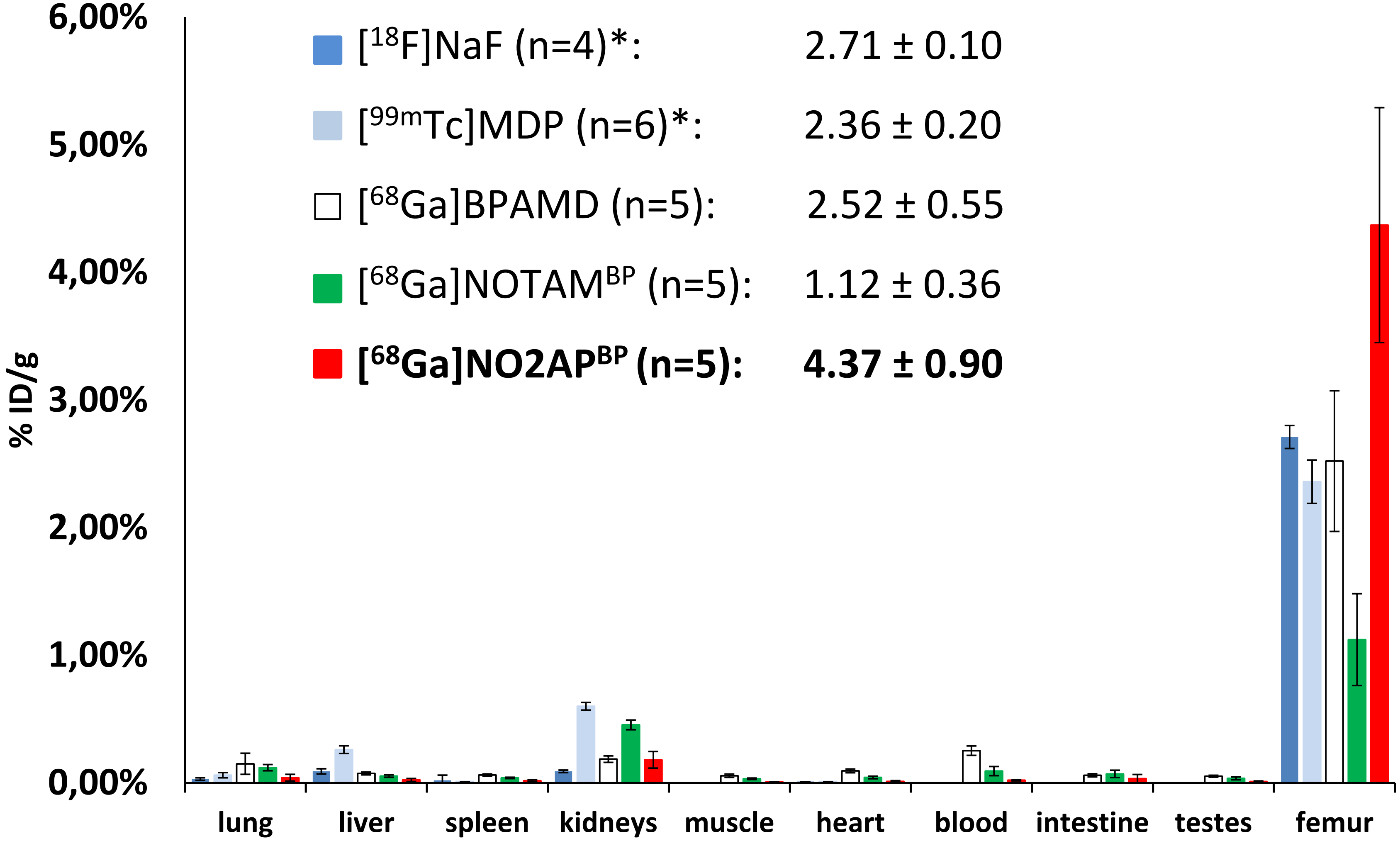


M. Fellner, R. P. Baum, V. Kubíček, P. Hermann, I. Lukeš, V. Prasat, F. Rösch *Eur. J. Nucl. Med. Mol. Imaging* 2010, *37*, 834.



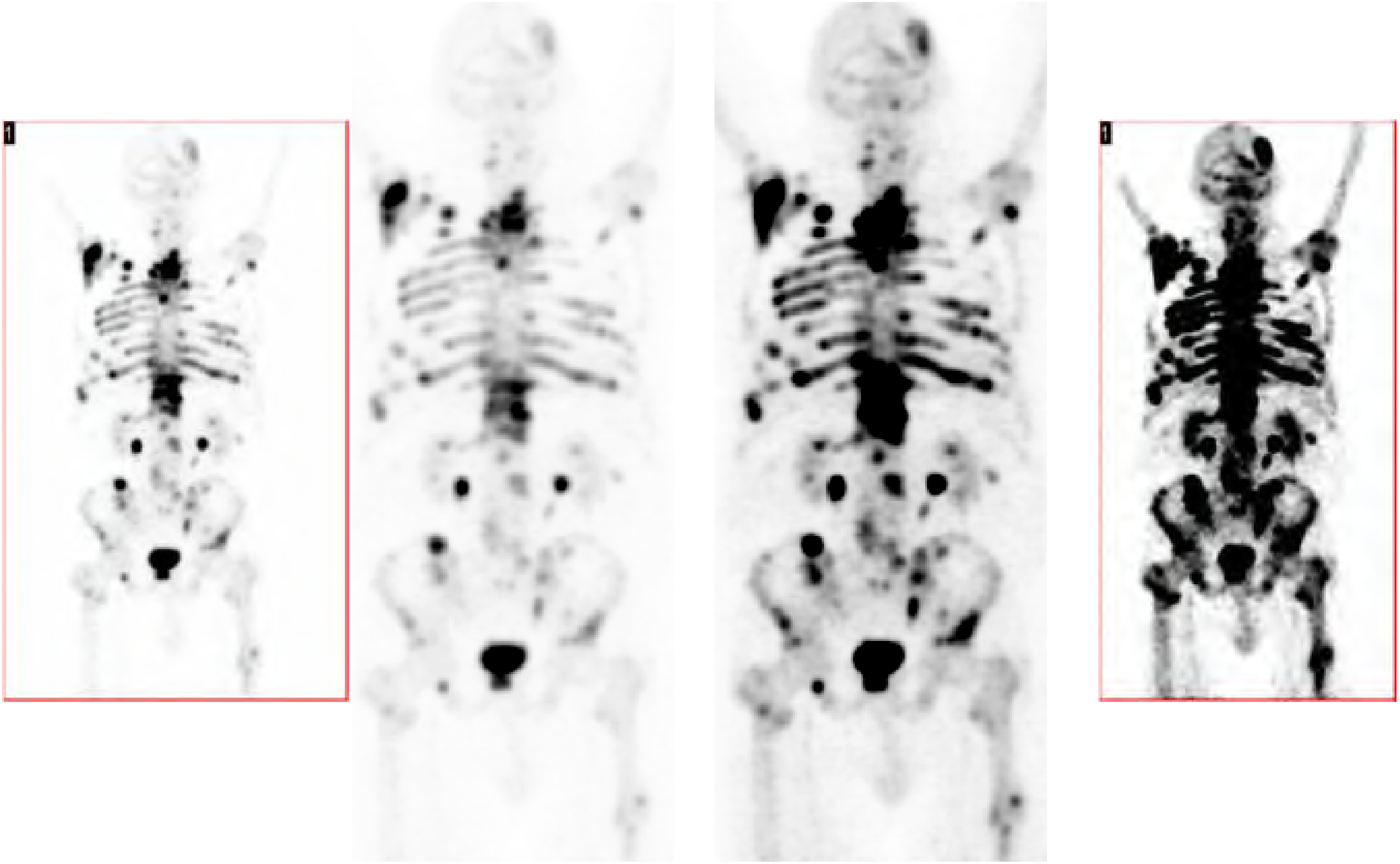
ex vivo Biodistribution

male Wistar rats, 60 min p.i.



* Data: Fellner M, Bergmann R, *In Vivo* Comparison of DOTA Based Ga-68 Bisphosphonates for Bone Imaging 2013

Ga-68 NO2A-BP - a new and improved biphosphonate



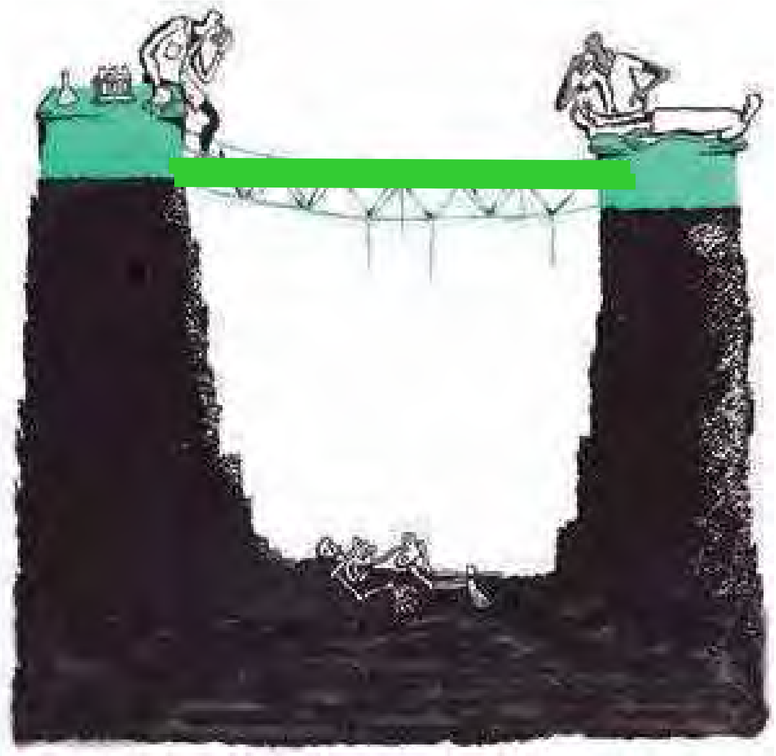
77-year-old male with Ca prostate with multiple skeletal metastases, s.p. palliative TUR-P, lymphadenectomy, radiotherapy to prostate and multiple vertebrae, palliative chemotherapy and Strontium-89 therapy

Translational Research: Crossing the Valley of Death

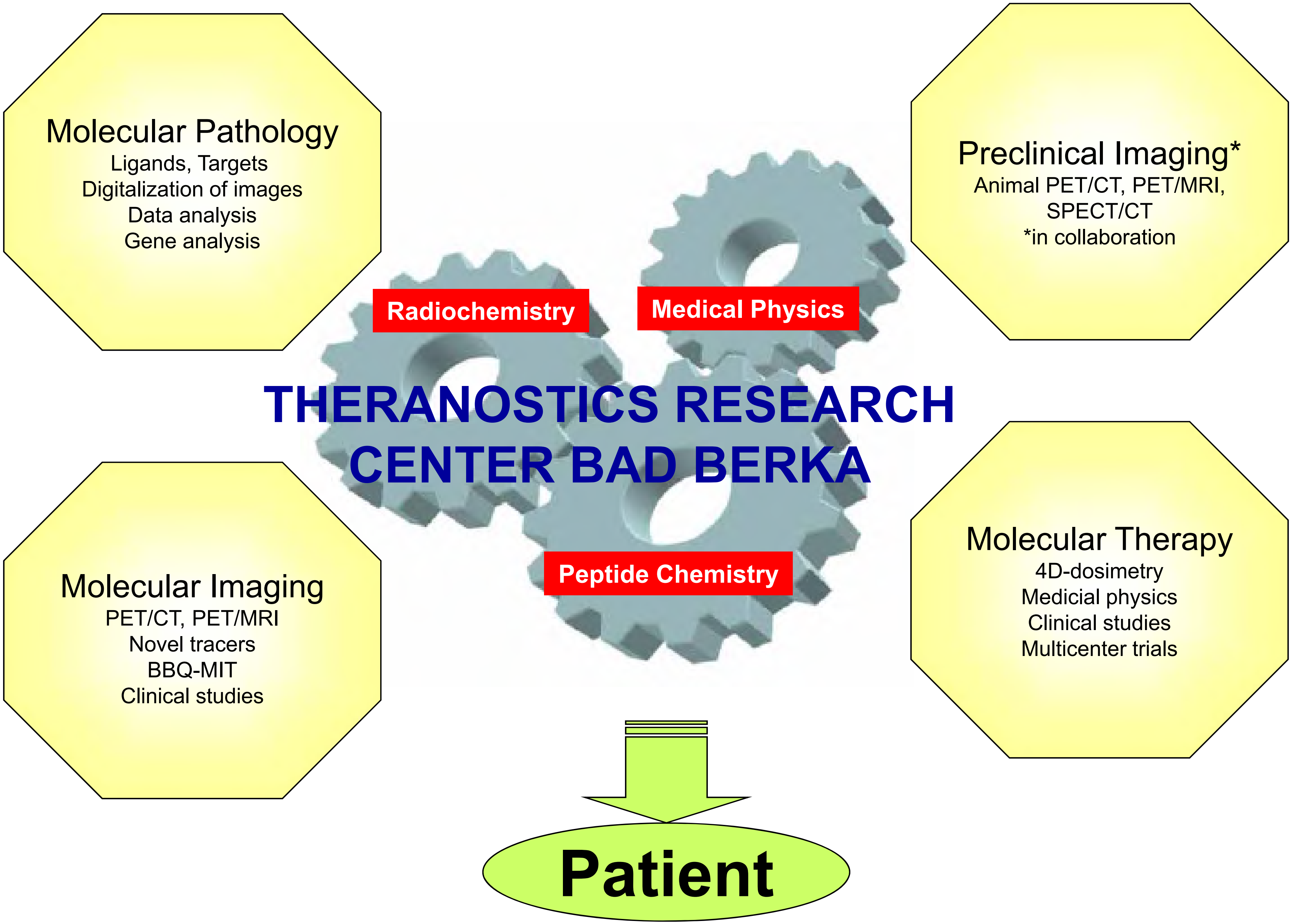
National Institutes of Health (NIH):

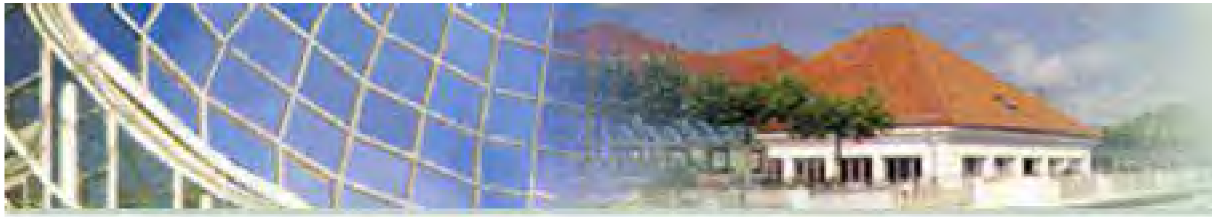
- "Clinical and basic scientists don't really communicate"
- Excellent basic research, but lack of translation

- 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!

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- Eric Krenning, Rotterdam

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- Maria Athelogou, Munich

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- Stanley Satz, Miami

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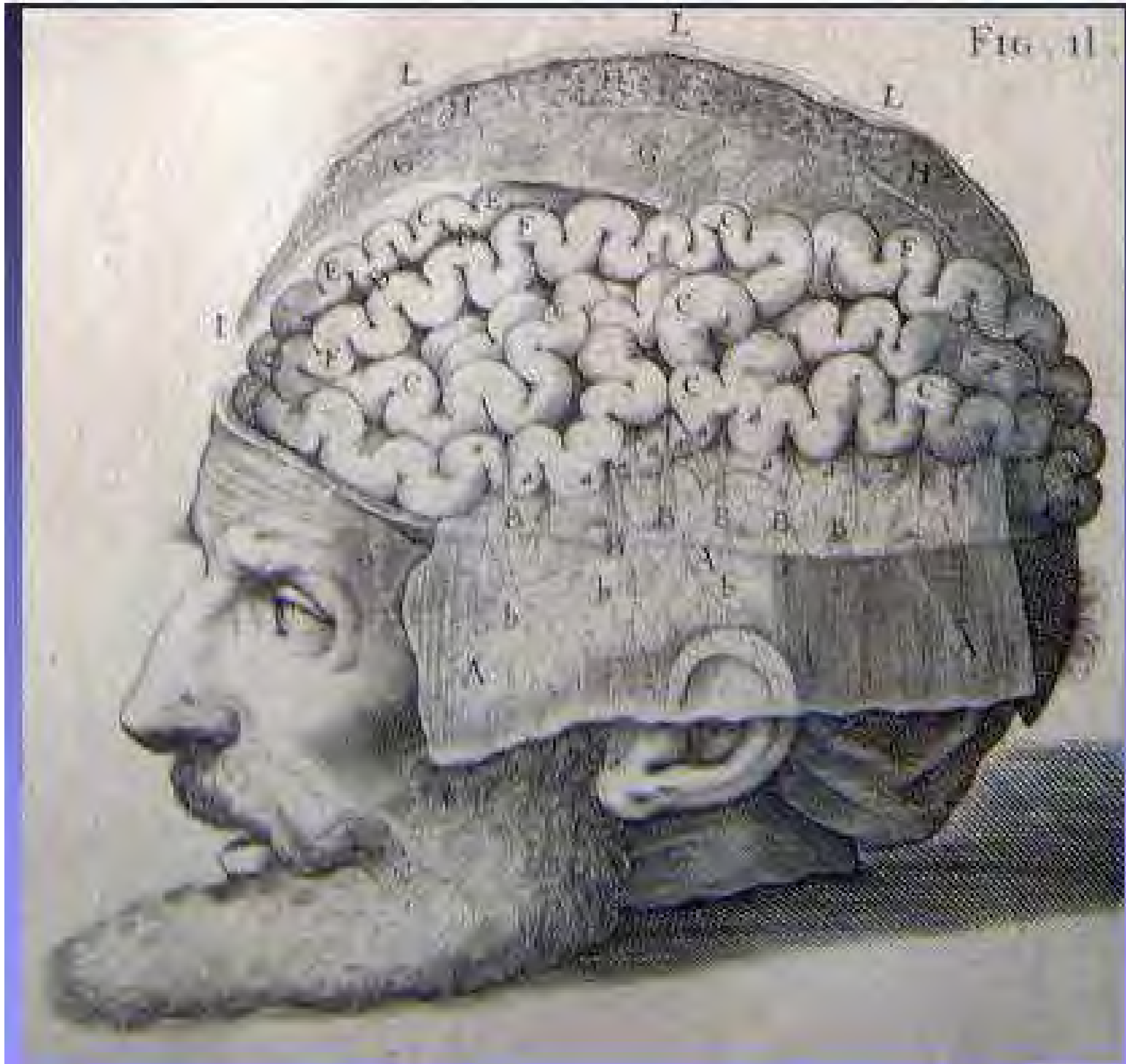
  - Dinse-Stiftung, Hamburg



Memorizing..

You remember

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