Overview of Isotopes/Nuclear Medicine

Where do we need/want go in the coming 10 years

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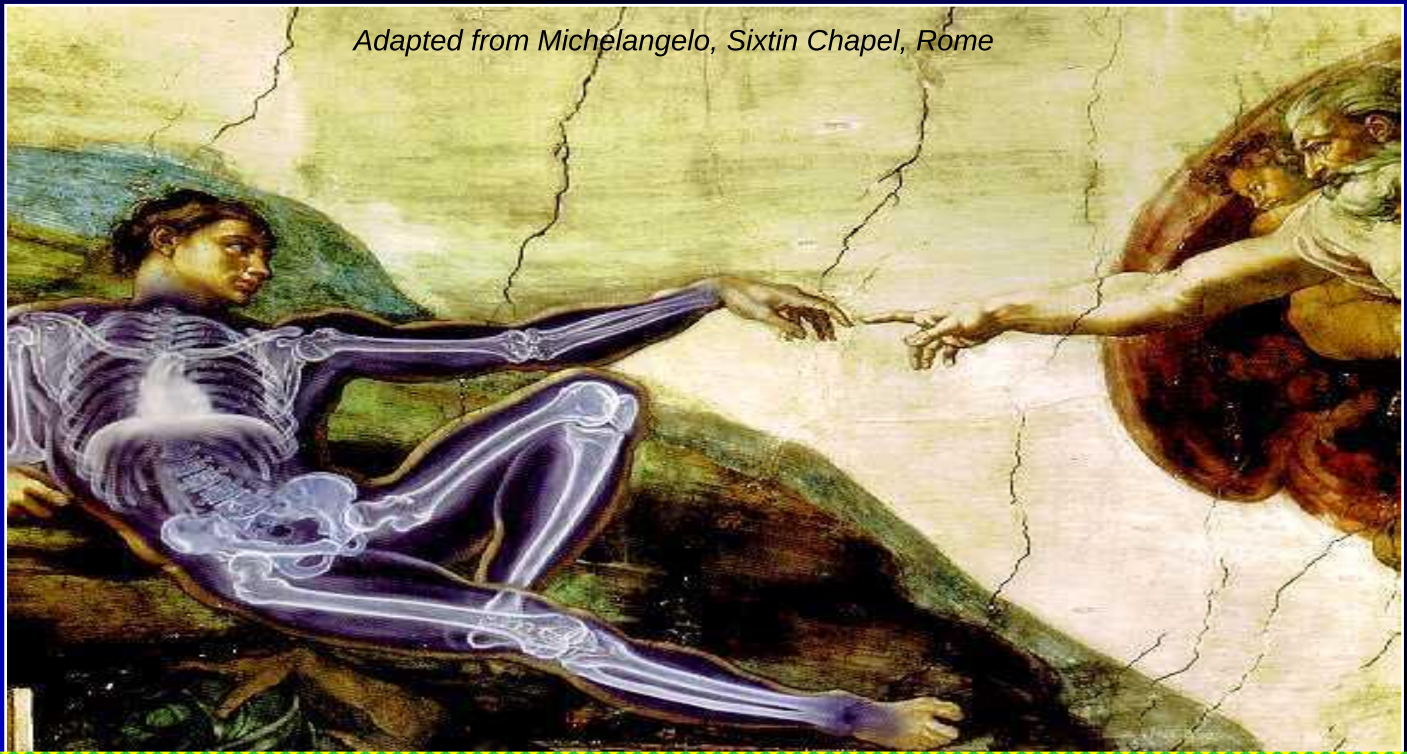


2nd Divonne Brainstorming Meeting on CERN Medical Applications
Domaine de Divonne, February 19-21, 2016

Prediction is very difficult,

especially about the future.

Niels Bohr, Danish physicist (1885 - 1962)

It’s tough to make predictions,

especially about the future.

Yogi Berra

FUTURE OF CANCER TREATMENT

Cancers will be classified by molecular phenotypes

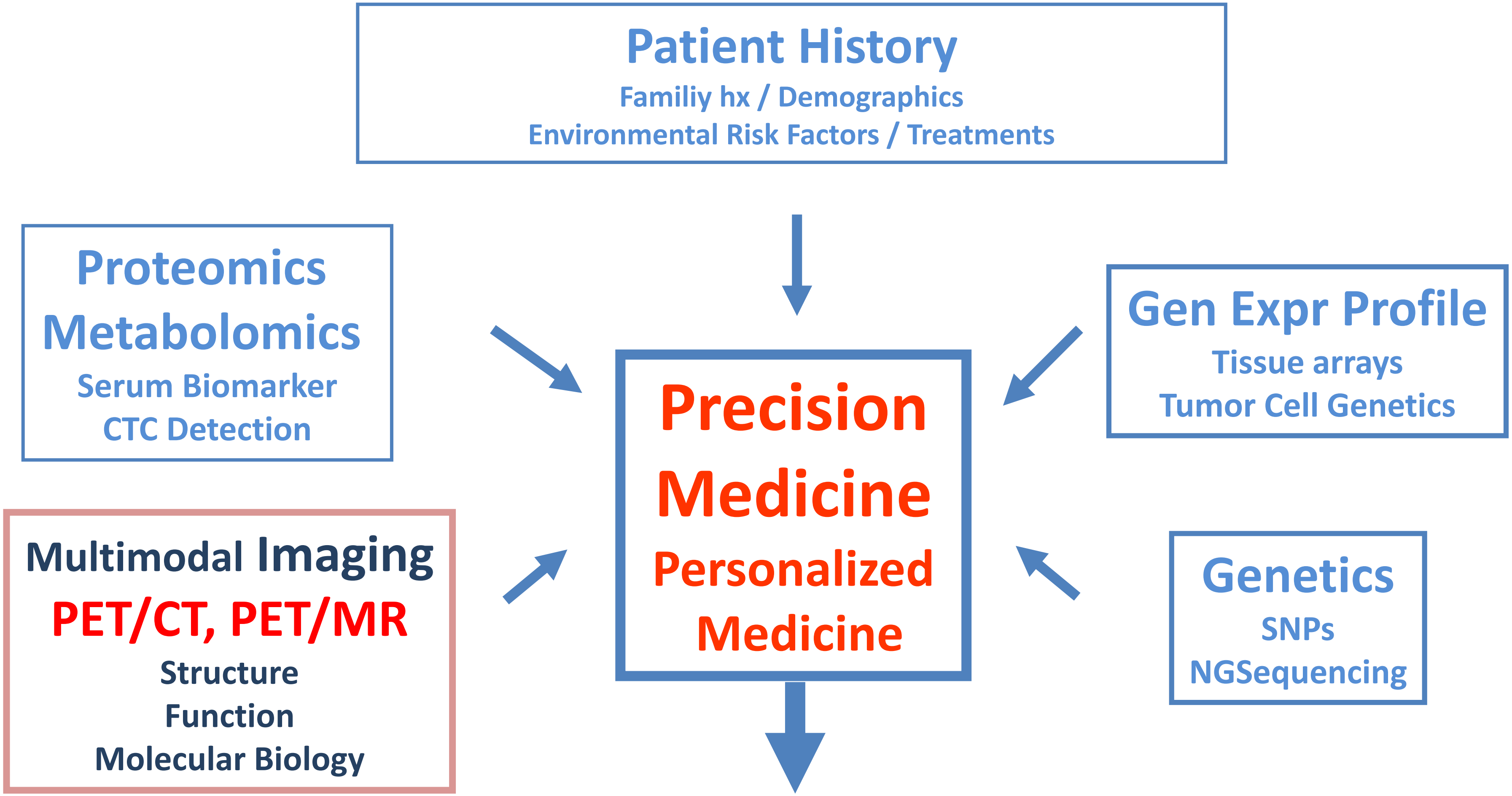
Organ site → secondary classification

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

Treatment will be targeted specifically against the tumor

→ **PRECISION MEDICINE**

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



Epidemiology / Prevention
Early Diagnosis, Risk Assessment
Therapy Selection and Monitoring

Courtesy M. Schwaiger, Munich

Thera(g)nostics

- **Theranostics is the combination of a Diag*nostic* Tool that helps to define the right *Thera*peutic Tool for a specific disease – we see what we treat.**
- **Used first by John Funkhouser/pharma industry at the beginning of the 90's at the same time the concept of Personalized Medicine appeared.**
- **Concerning radioisotopes, the term "THERAGNOSTICS" was created by Suresh Srivastava (Brookhaven National Laboratory).**
- **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.**

Personalized Medicine

- **The right treatment, for the right patient, at the right time, at the right dose.**

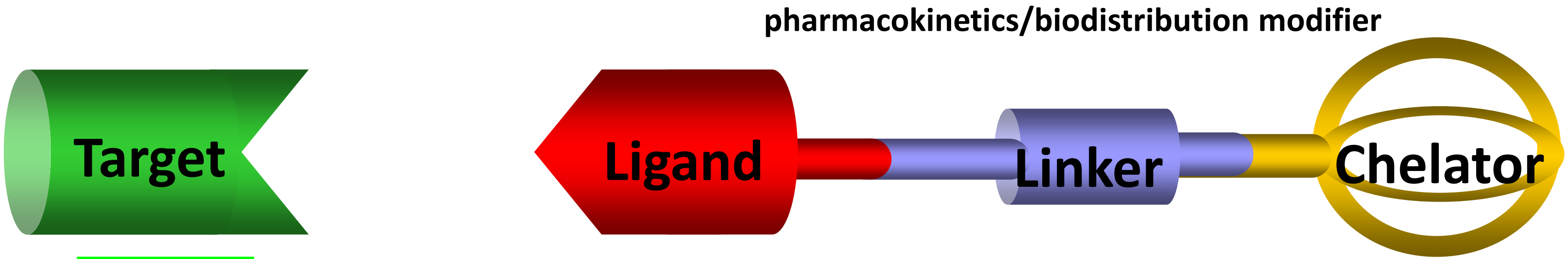
– first time », not anymore targeting the "disease" but the "specific tumor of a patient".

- **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.

THERANOSTIC – we see what we treat
Targeted Molecular Imaging and Therapy
The Key-Lock Principle

Schematic Representation of a Drug for Imaging and Targeted Therapy



Lock

Key

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

Targets

- **Antigens**
  e.g. **CD20**, HER2)
- **GPCR** e.g. **SSTR**
- Enzymes & inhibitors
  e.g. **PSMA**
- Transporters

Molecular Address

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

Reporting Unit

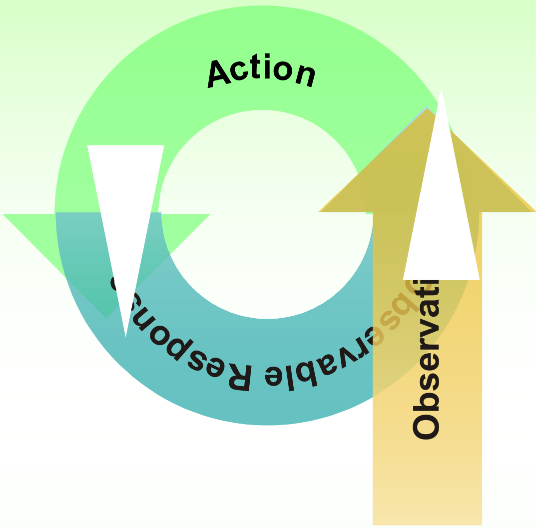
- ^{99m}Tc, ^{111}In, ^{67}Ga
- ^{64}Cu, ^{68}Ga
- Gd^{3+}

Cytotoxic Unit

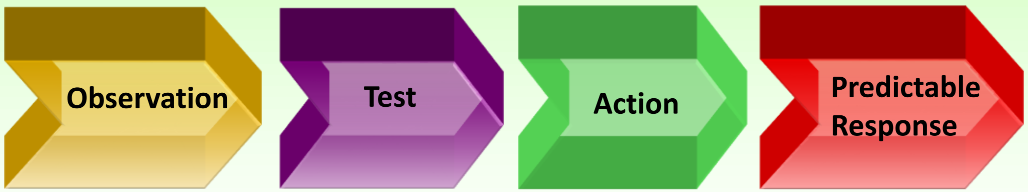
- ^{90}Y, ^{177}Lu, ^{213}Bi
- ^{105}Rh, ^{67}Cu, ^{186,188}Re

Courtesy Helmut Mäcke (modified)

From Trial and Error Medicine to Personalized Medicine



New paradigm: personalized medicine



Breaking the cycle of trial and error medicine

PRECISION 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 of Damian Wild

Ga-68 Generator System

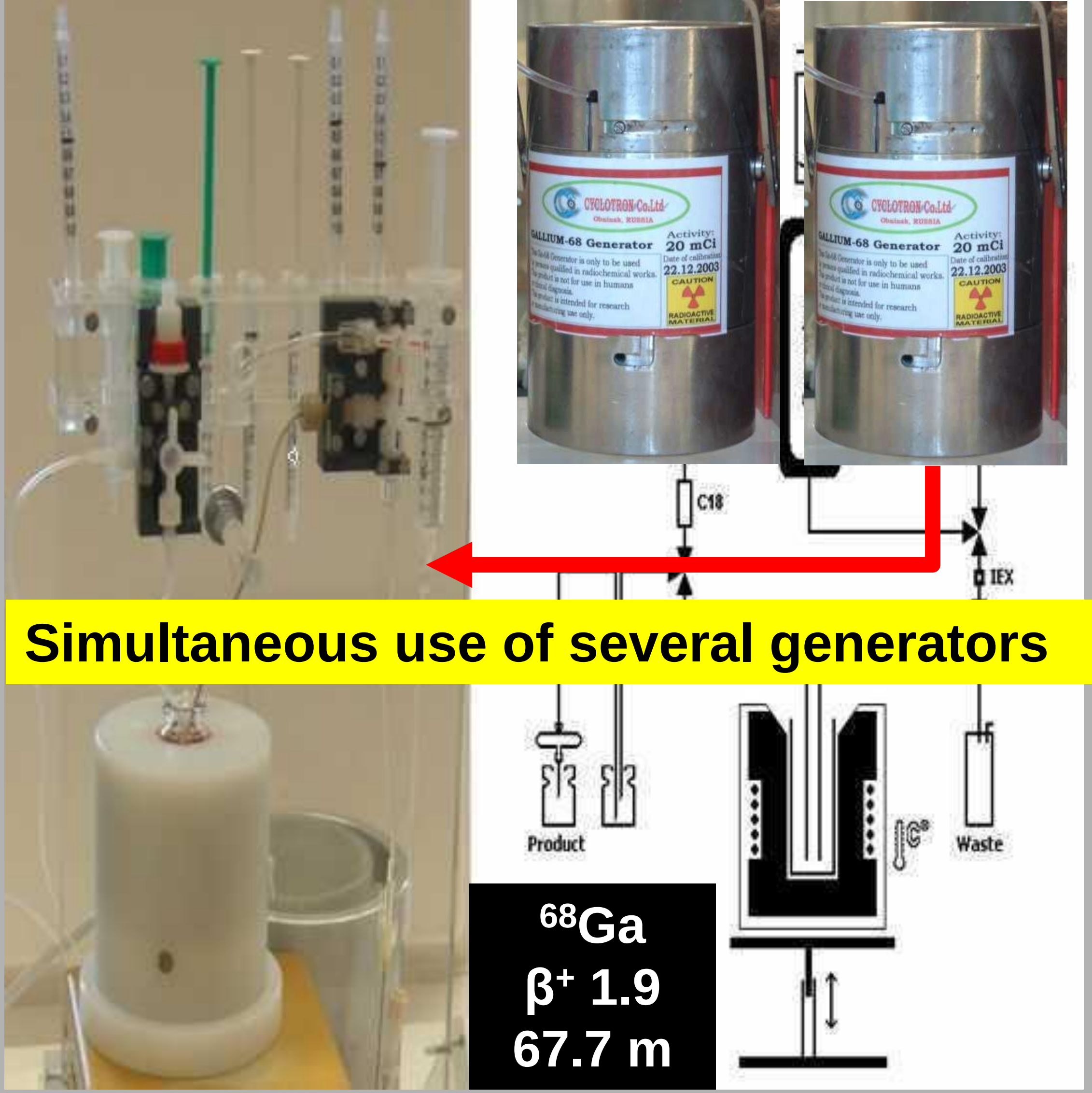
TiO_2 based

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

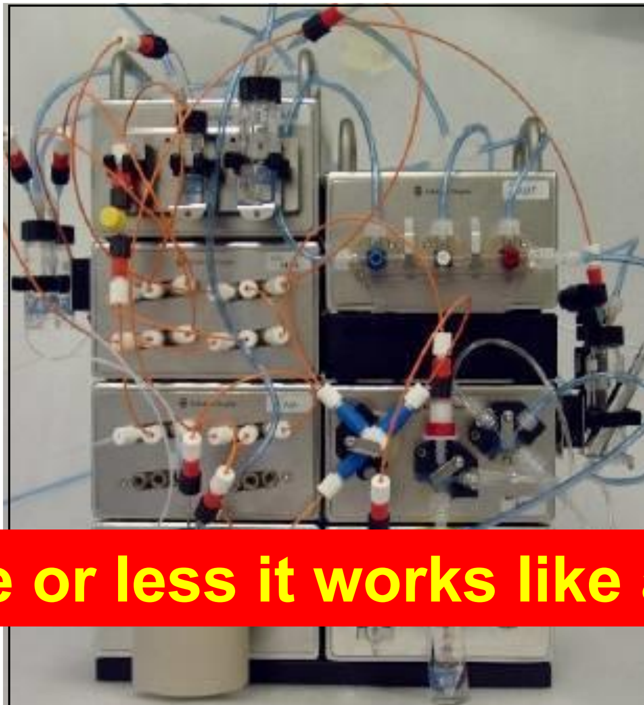
J Nucl Med 2007 (Oct); 48:1741-48



^{68}Ga-elution, <u>purificaton</u> and synthesis module

First clinical studies in 2004, up to now over 10,000 studies done at ZKL Bad Berka

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



Pre-cleaning

More or less it works like a Cappucino machine…

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

Ga-68 Labeled Tracers in Clinical Use in Bad Berka

…and many more to come!

- [^{68}Ga-DOTA,Tyr^{3}]octreotide (DOTA-TOC)
- ^{44}Sc-DOTA,Tyr^{3}]octreotide (DOTA-TOC)* - potential for dosimetry
- [^{68}Ga-DATA,Tyr^{3}]octreotide (DATA-TOC)* - possible kit preparation
- [^{68}Ga-DOTA,1-Nal]octreotide (DOTA-NOC)
- [^{68}Ga-DOTA]-TATE
- [^{68}Ga-DOTA]-Lanreotide
- [^{68}Ga-DOTA]-Bombesin / AMBA, DEMOBESIN and Sarabesin
- [^{68}Ga-DOTA]-D-Glu-Gastrin (MTC, NET)
- [^{68}Ga-DOTA]-F(ab')$_2$-herceptin (breast cancer)
- ^{68}Ga-DOTA-Tyrosin (brain tumors)* - potential for brain tumor THERANOSTICS
- ^{68}Ga-DOTA-HSA Microspheres (lung perfusion)
- ^{68}Ga-NODAGA-RGD (angiogenesis)
- ^{68}Ga-BPAMP & NO2A-BP (bone metastases)* - potential for bone THERANOSTICS
- ^{68}Ga-DOTA-α-MSH (melanoma)
- ^{68}Ga-DOTA-SHAL (lymphoma)
- ^{68}Ga-PSMA (prostate cancer
- ^{68}Ga-CXCR4 (lymphoma and many different cancers)

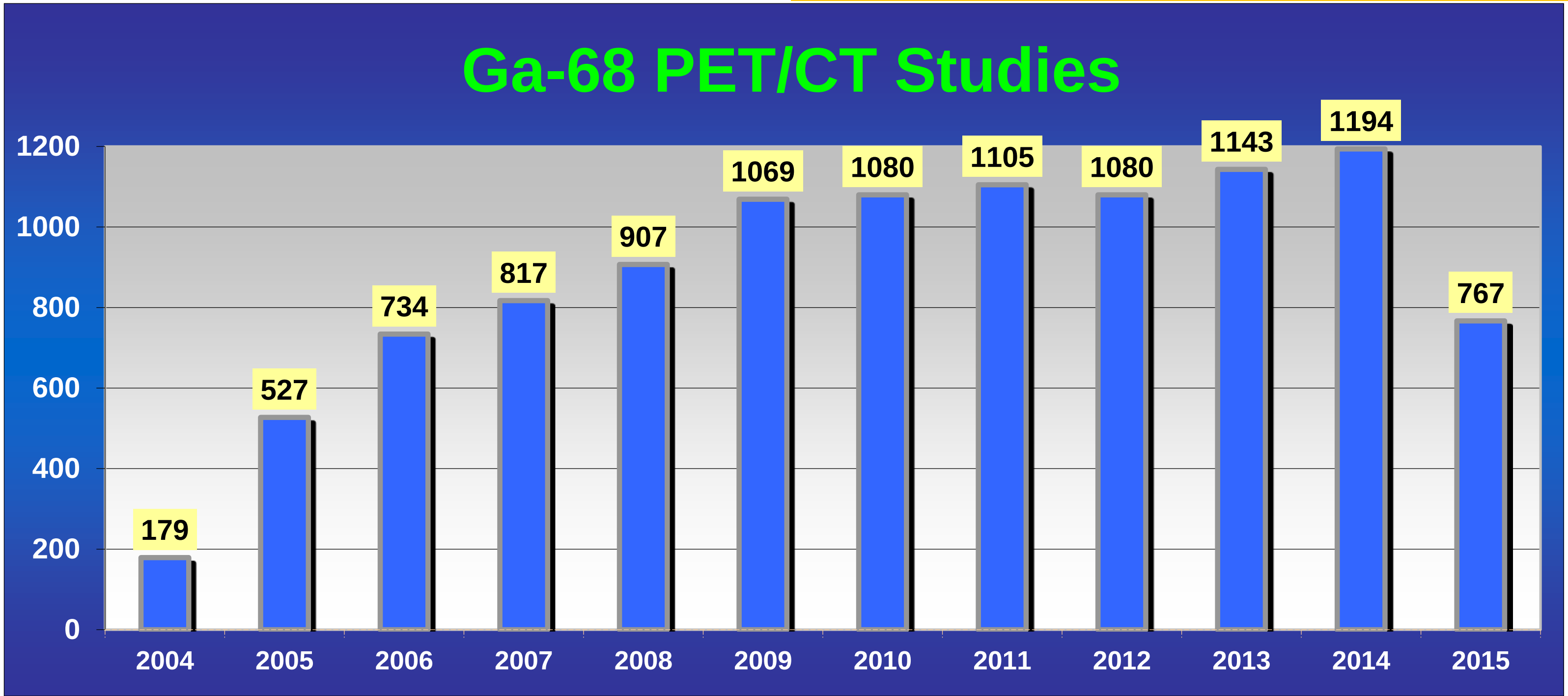
****made in Mainz first clinical use in Bad Berka***

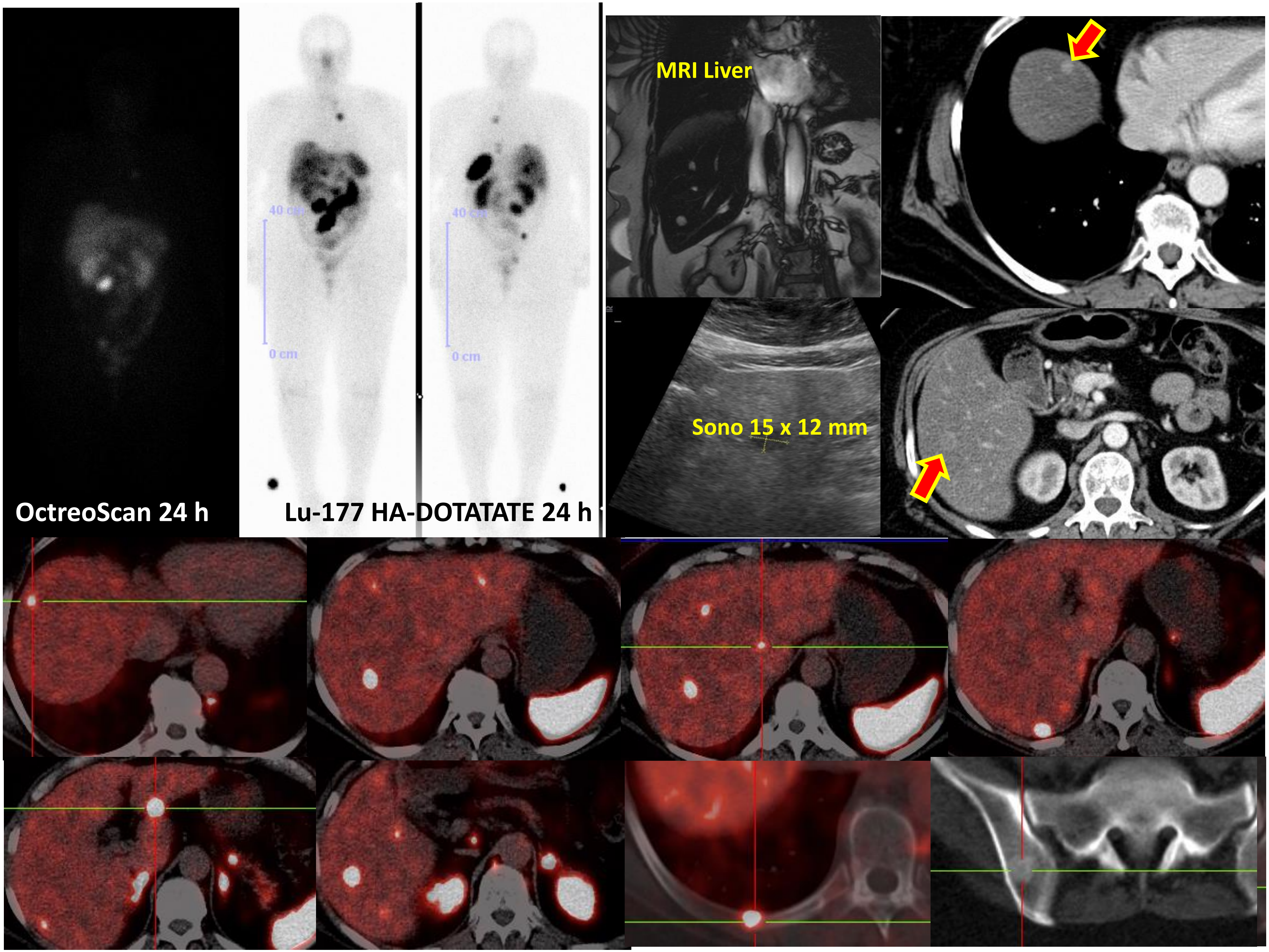
Center for Molecular Radiotherapy / Department of Molecular Imaging (PET/CT) Zentralklinik Bad Berka

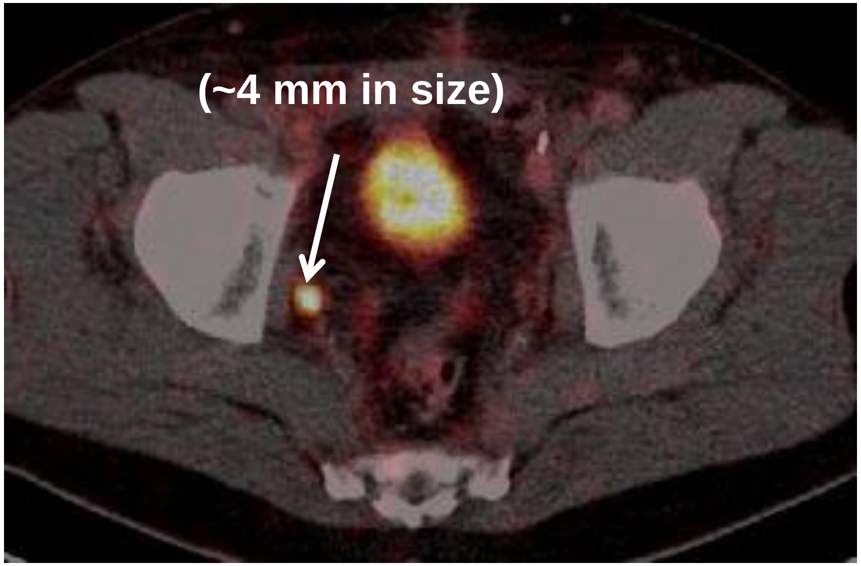
Dept. of Molecular Imaging, Zentralklinik Bad Berka

Installation Biograph mCT Flow on February 24, 2014

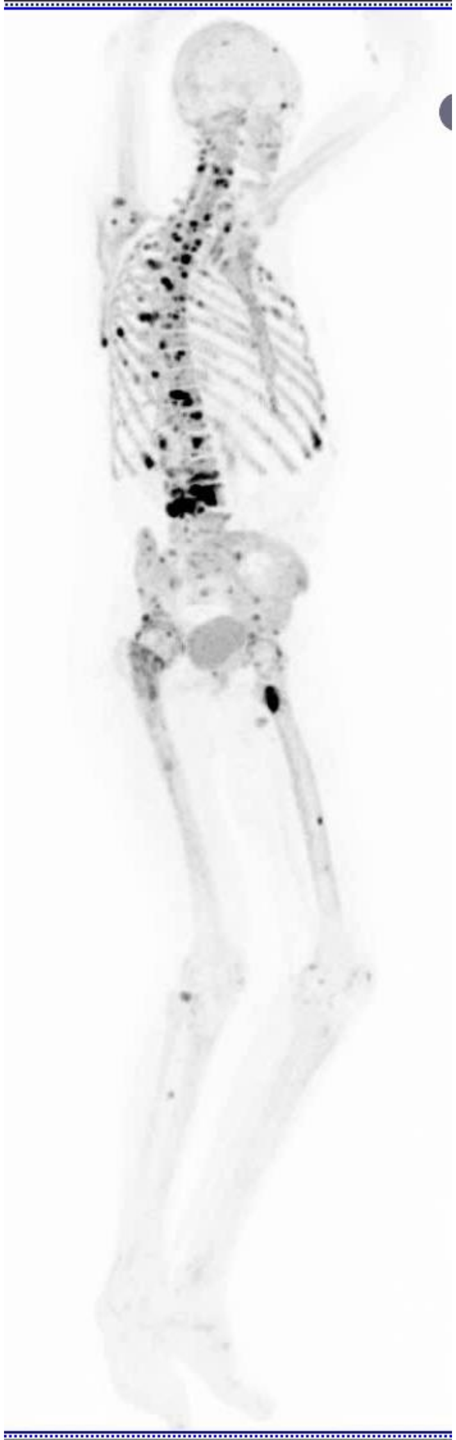
>95% oncological studies (fast WB)

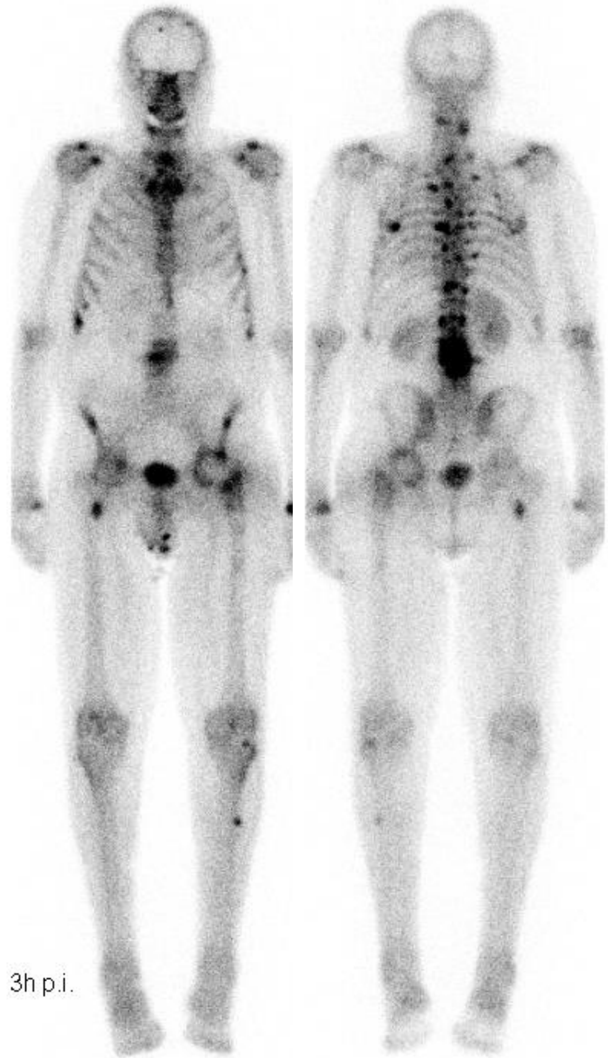



MRI Liver
Sono 15 x 12 mm
OctreoScan 24 h
Lu-177 HA-DOTATATE 24 h
40 cm
0 cm
Ga-68 DOTATOC mCT Flow PET/CT

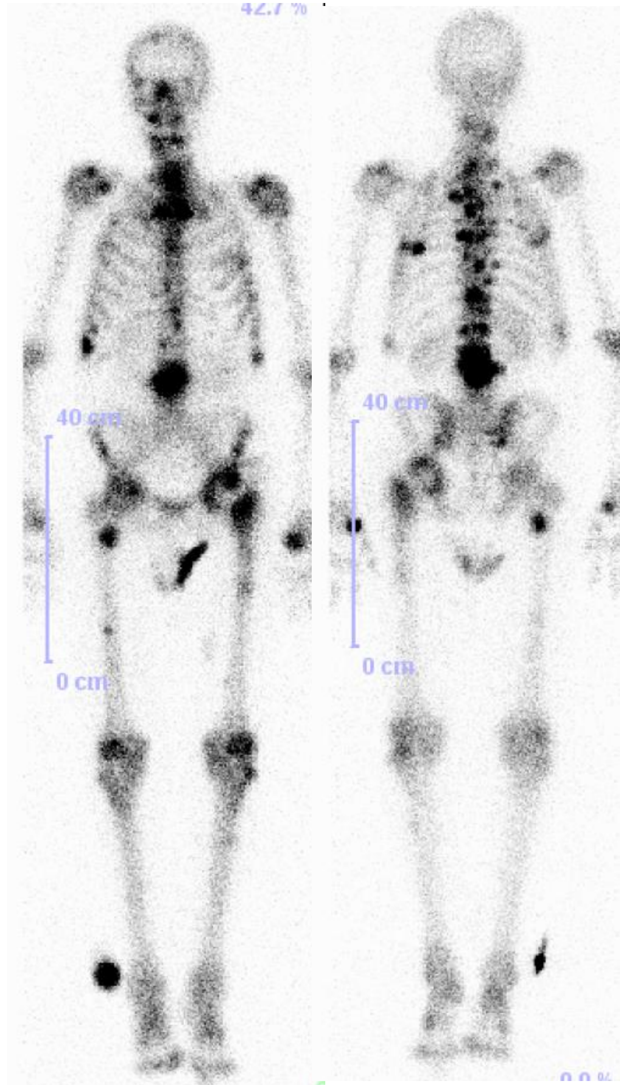


Ga-68 PSMA PET/CT: METASTATIC ILIAC AND PERIRECTAL NODES





Tc-99m MDP
Scintigraphy



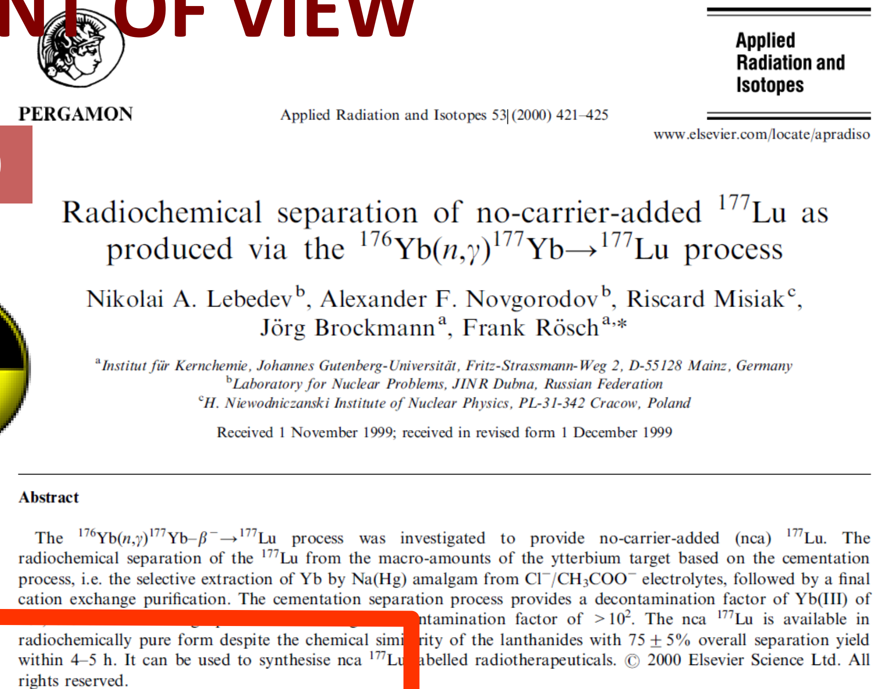
Lu-177 BPAMD
Therapy Scan

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

^{177}Lu production CARRIER FREE:

A NUCLEAR CHEMISTS POINT OF VIEW

DEVELOPED AT THE TRIGA MAINZ REACTOR IN 2000



PERGAMON

Applied Radiation and Isotopes 53 (2000) 421–425

Applied Radiation and Isotopes

www.elsevier.com/locate/apradiso

Radiochemical separation of no-carrier-added ^{177}Lu as produced via the $^{176}Yb(n,\gamma)^{177}Yb \rightarrow ^{177}Lu$ process

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[a] Institut für Kernchemie, Johannes Gutenberg-Universität, Fritz-Strassmann-Weg 2, D-55128 Mainz, Germany
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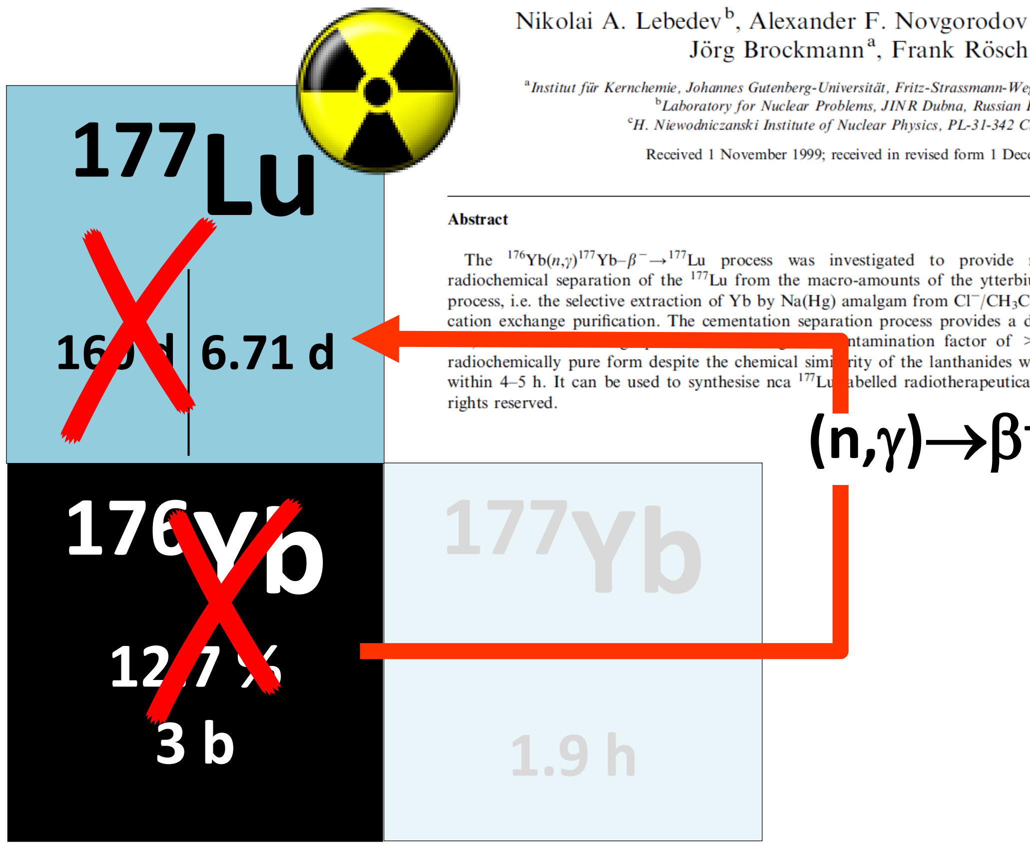
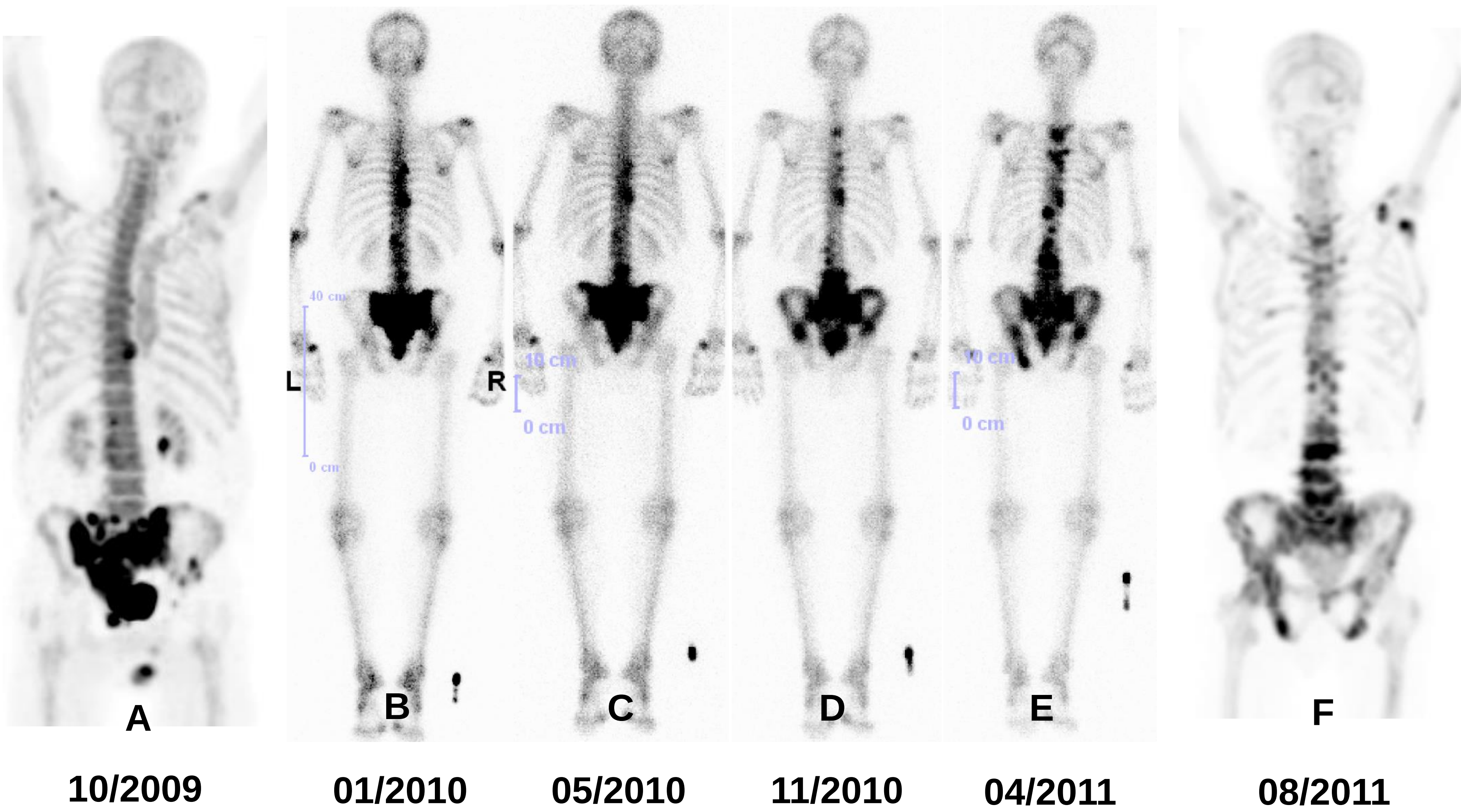
Received 1 November 1999; received in revised form 1 December 1999

Abstract

The $^{176}Yb(n,\gamma)^{177}Yb\text{–}\beta^- \rightarrow ^{177}Lu$ process was investigated to provide no-carrier-added (nca) ^{177}Lu. The radiochemical separation of the ^{177}Lu from the macro-amounts of the ytterbium target based on the cementation process, i.e. the selective extraction of Yb by Na(Hg) amalgam from Cl^-/CH_3COO^- electrolytes, followed by a final cation exchange purification. The cementation separation process provides a decontamination factor of Yb(III) of ... ntamination factor of $>10^2$. The nca ^{177}Lu is available in radiochemically pure form despite the chemical simi rity of the lanthanides with 75 ± 5% overall separation yield within 4–5 h. It can be used to synthesise nca ^{177}Lu abelled radiotherapeuticals.





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).

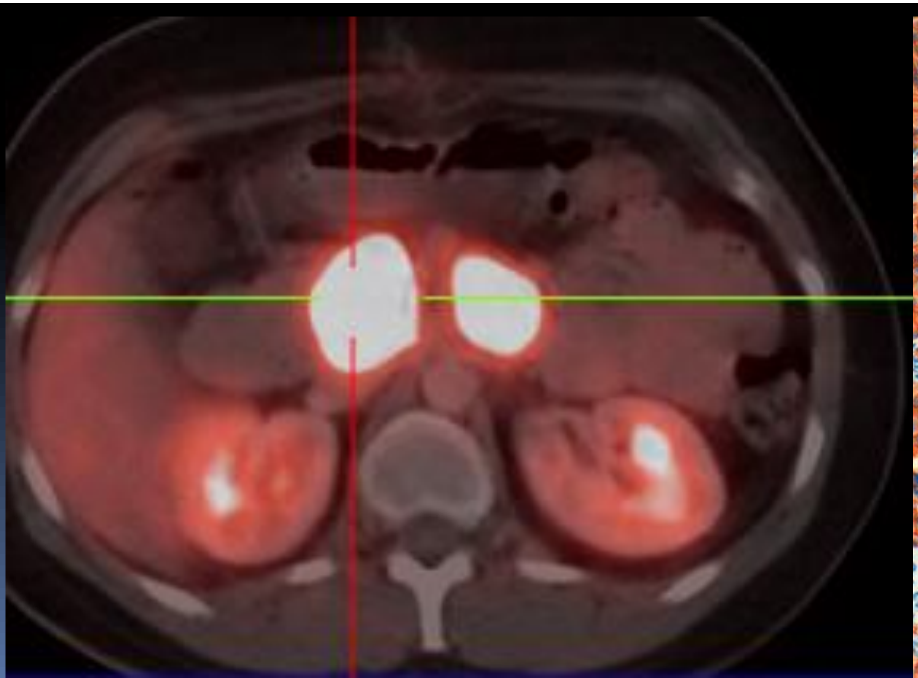
Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-011-1846-5

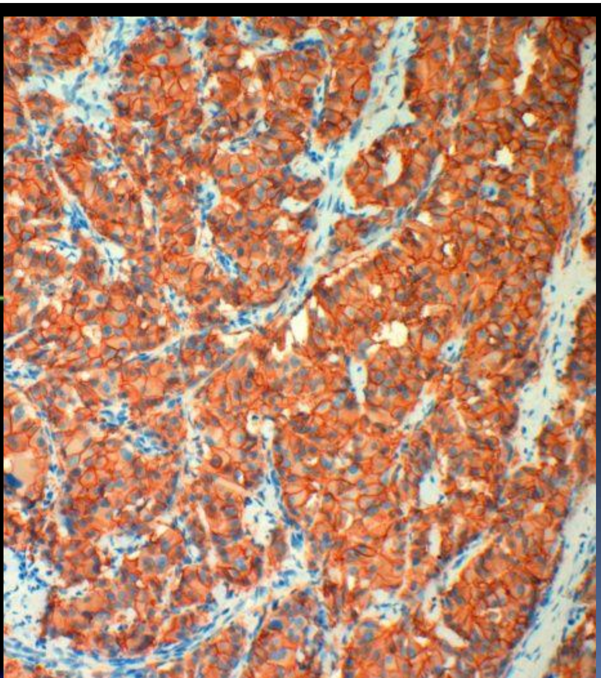
Eur J Nucl Med Mol Imaginge 2011 Sep;38(9):1659-68

ORIGINAL ARTICLE

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

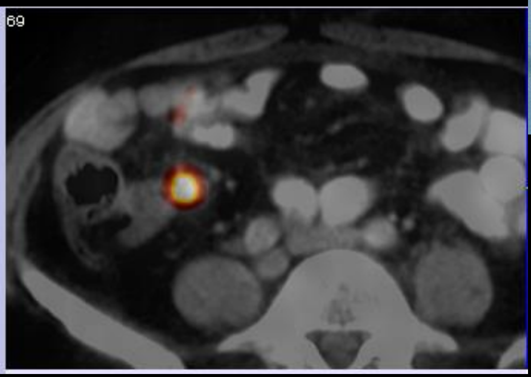
Daniel Kaemmerer · Luisa Peter · Amelie Lupp · Stefan Schulz · Jörg Sänger · Vikas Prasad · Harshad Kulkarni · Sven-Petter Haugvik · Merten Hommann · Richard Paul Baum

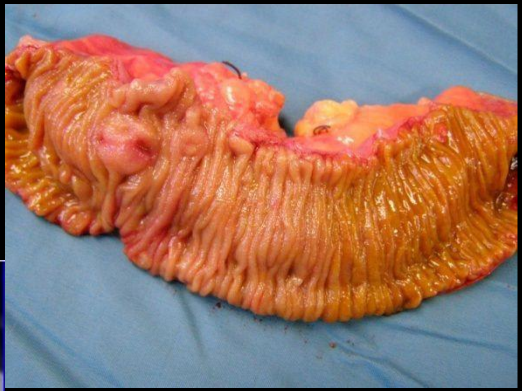




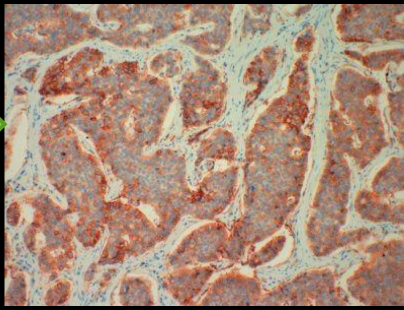
From Molecular Imaging to Therapy

Ileum NET, size 4 mm





Ileum NET



IHC Scoring for SSTR1-5

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

44 surgical specimens generated

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

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

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

Number of Patients : 9

Results

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

The tumor SUVmax showed a significant correlation with immunohistopathology scores.

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

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

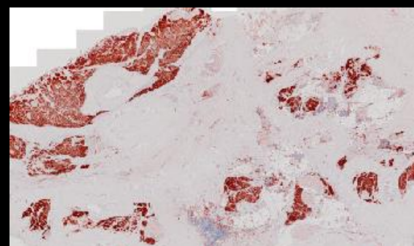
Digitalized Histopathology Combined with Receptor PET/CT

From Tissue to Molecular Imaging to Therapy

Surgical specimen

- Tissue Sampling
- Tissue Staining

Definiens XD Image Analysis



Digital pathology - virtual microscopy

Histopathological Grading

- Receptor density on tumor cells
- Proliferation rate (Ki-67 / MIB1)
- Tumor-specific features, e.g. CgA, Synaptophysin
- Genetic profiling

PET/CT - ileum NET, Ø 4 mm

- Prognosis
- Selection of most appropriate peptide for Receptor PET/CT
- Therapy guidance – peptide receptor radionuclide therapy (PRRT) versus chemotherapy vs localised therapy vs molecular targeted therapies etc.

Management Strategy

On the Way to Precision Medicine

STRATIFYER

Zentralklinik Bad Berka

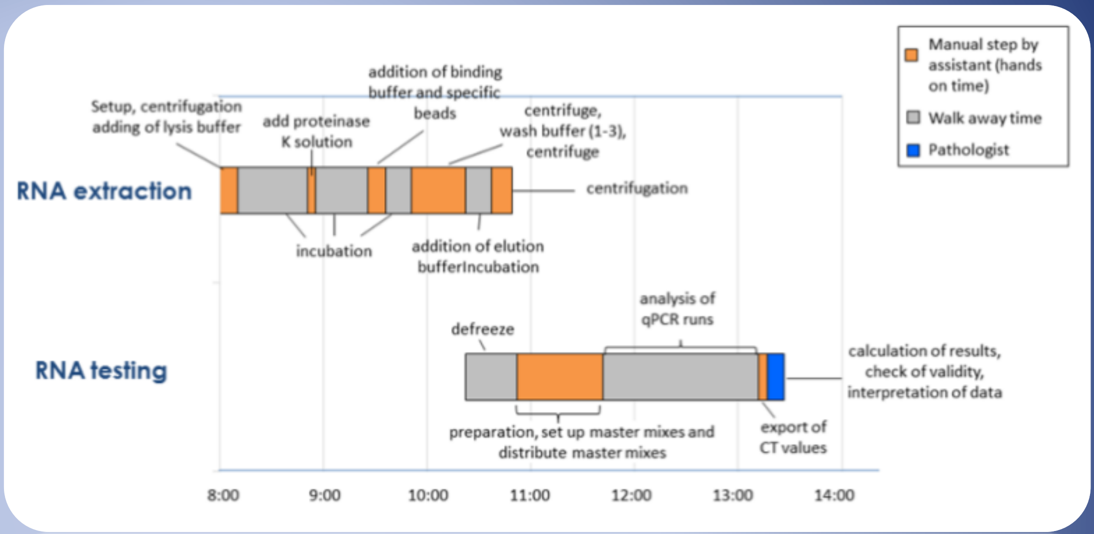
Universitätsklinikum Jena

Institut für PATHOLOGIE am St. Elisabeth - Krankenhaus

NET TYPER

Molecular analysis of neuroendocrine tumors by quantitative mRNA analysis of formalin fixed tissue samples

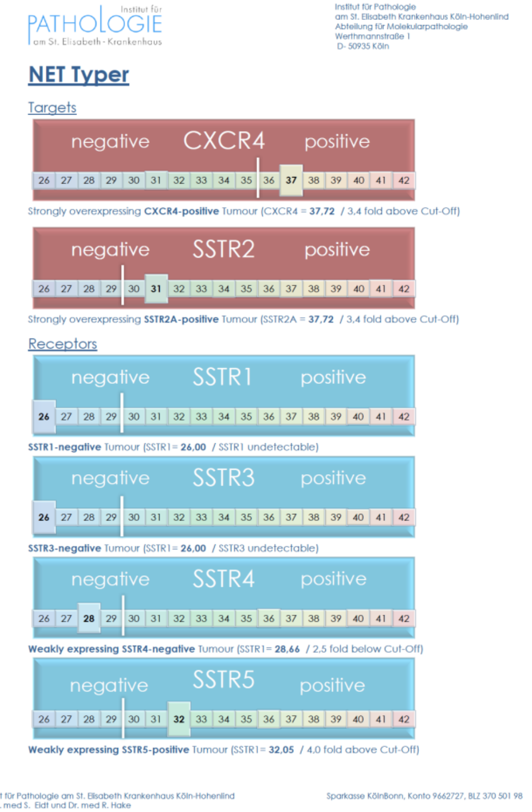
Molecular analysis of DNA and mRNA from formalin fixed, paraffin embedded tissue samples



Advantages of molecular assessment of Target Genes:

1) **High Specificity** - no cross-reactivity as for IHC; Isoforms and mutations detectable
2) **High Sensitivity** - low tissue input required (1,5mm x 5µm); few molecules detectable
3) **Objective Testing** - no subjective interpretation; high reproducibility & reliability
4) **Fully quantitative** - large dynamic range (2 logs); no „upper limit“ in positive cases
5) **Fast & automated** - result until lunch (2.5h RNA for extraction & 2h for measurement)

The NET Typer
- Validation of CXCR4 as target for radioimaging



Institut für PATHOLOGIE am St. Elisabeth-Krankenhaus

Institut für Pathologie
am St. Elisabeth Krankenhaus Köln-Hohenlind
Abteilung für Molekularpathologie
Werthmannstraße 1
D- 50935 Köln

NET Typer

Targets

Strongly overexpressing **CXCR4-positive** Tumour (CXCR4 = **37,72** / 3,4 fold above Cut-Off)

Strongly overexpressing **SSTR2A-positive** Tumour (SSTR2A = **37,72** / 3,4 fold above Cut-Off)

Receptors

SSTR1-negative Tumour (SSTR1= **26,00** / SSTR1 undetectable)

SSTR3-negative Tumour (SSTR1= **26,00** / SSTR3 undetectable)

Weakly expressing SSTR4-negative Tumour (SSTR1= **28,66** / 2,5 fold below Cut-Off)

Weakly expressing SSTR5-positive Tumour (SSTR1= **32,05** / 4,0 fold above Cut-Off)

Institut für Pathologie am St. Elisabeth Krankenhaus Köln-Hohenlind
PD Dr. med S. Eidt und Dr. med R. Hake

Sparkasse KölnBonn, Konto 9662727, BLZ 370 501 98

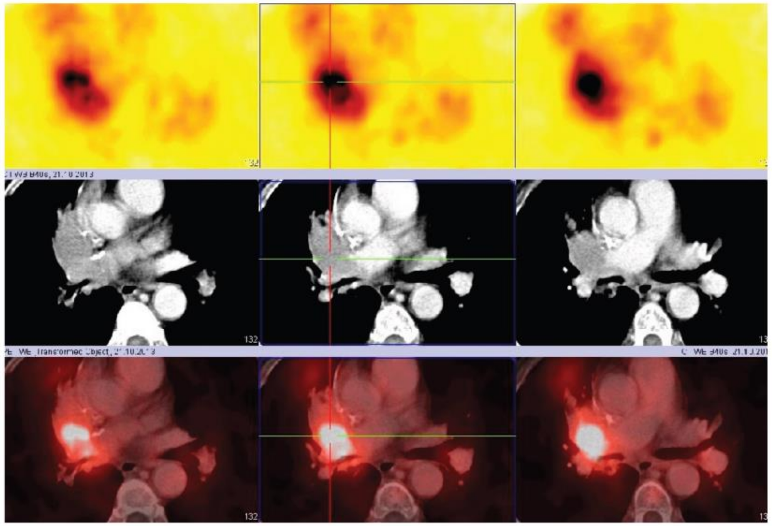
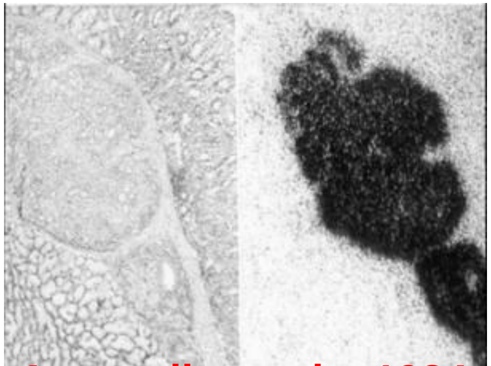


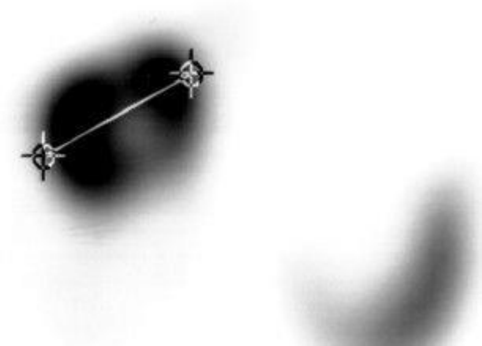
Figure 6: ^{68}Ga-CPCR4-2 PET/CT (transversal images): local recurrence of an centrally localized SCLC (upper panel: PET scan, middle panel: CT scan, lower panel: PET + CT fusion image)

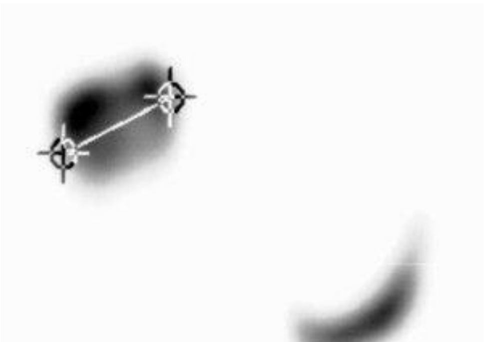
Kaemmerer et al., Oncotarget 2015

RT-qPCR of CXCR4 to predict SUV of ^{68}Ga CPCR4-2 PET/CT …

From bench to bedside: a long story…


Autoradiography 1984


Scintigraphy 1987


PRRT 1994

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

NETTER-1 trial: First results reported at AOCNMB 2015

Radiopeptide therapy (ZKL Bad Berka)

As of December 9, 2015

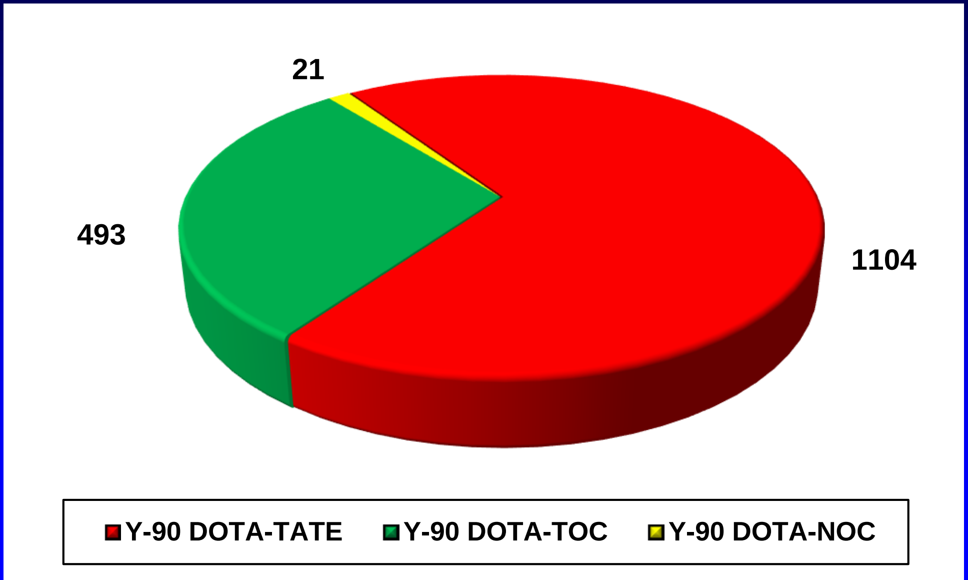
Patients treated	**n = 1358**
Therapy cycles	**n = 4791**

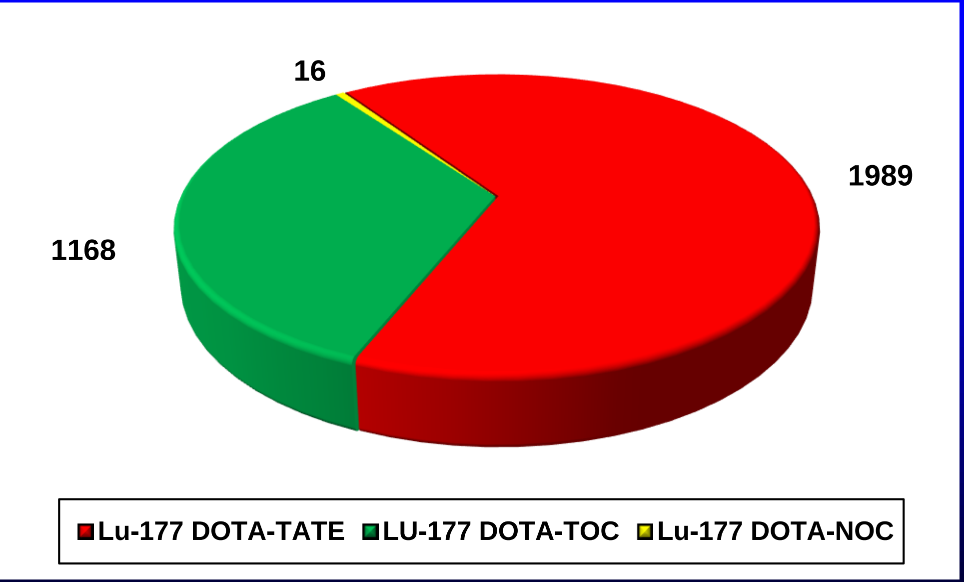
Lu-177	**n = 3173**
Y-90	**n = 1618**

	Y-90	Lu-177
Mean	3.35 GBq	6.46 GBq
Max.	9,50 GBq	12.0 GBq

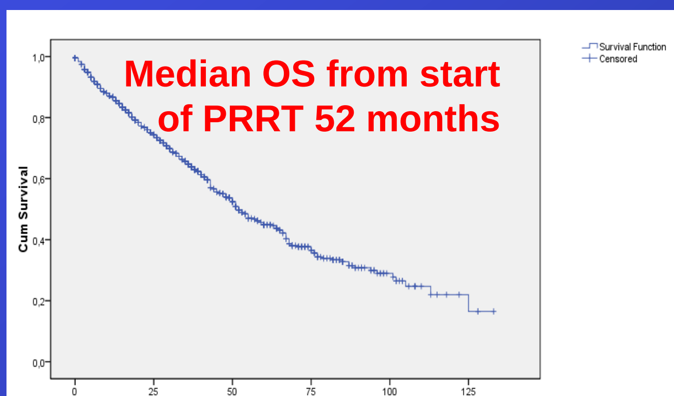
Age: 4 – 85 years

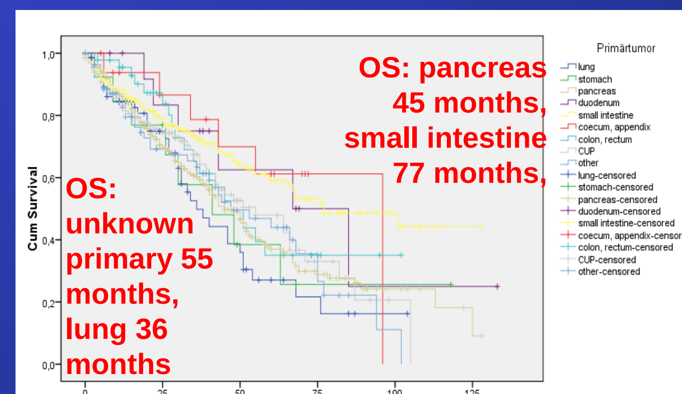
Median: 59.7 years

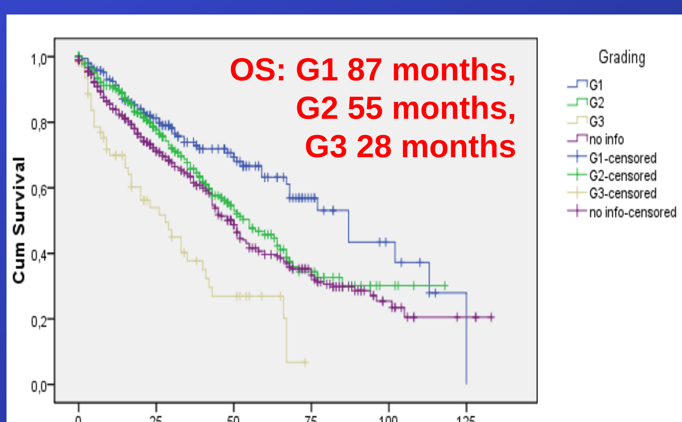


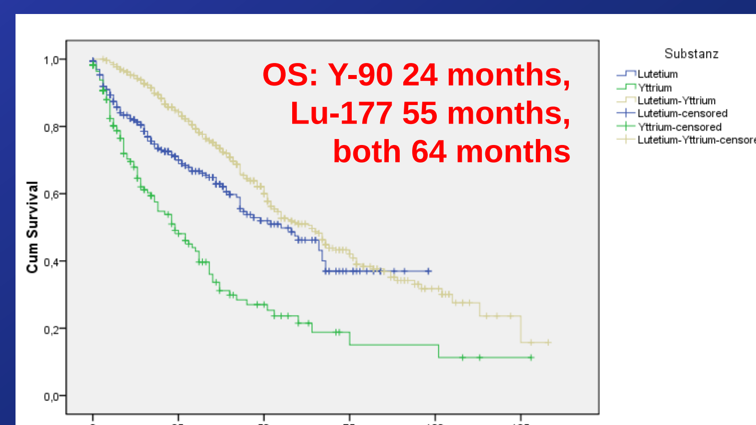


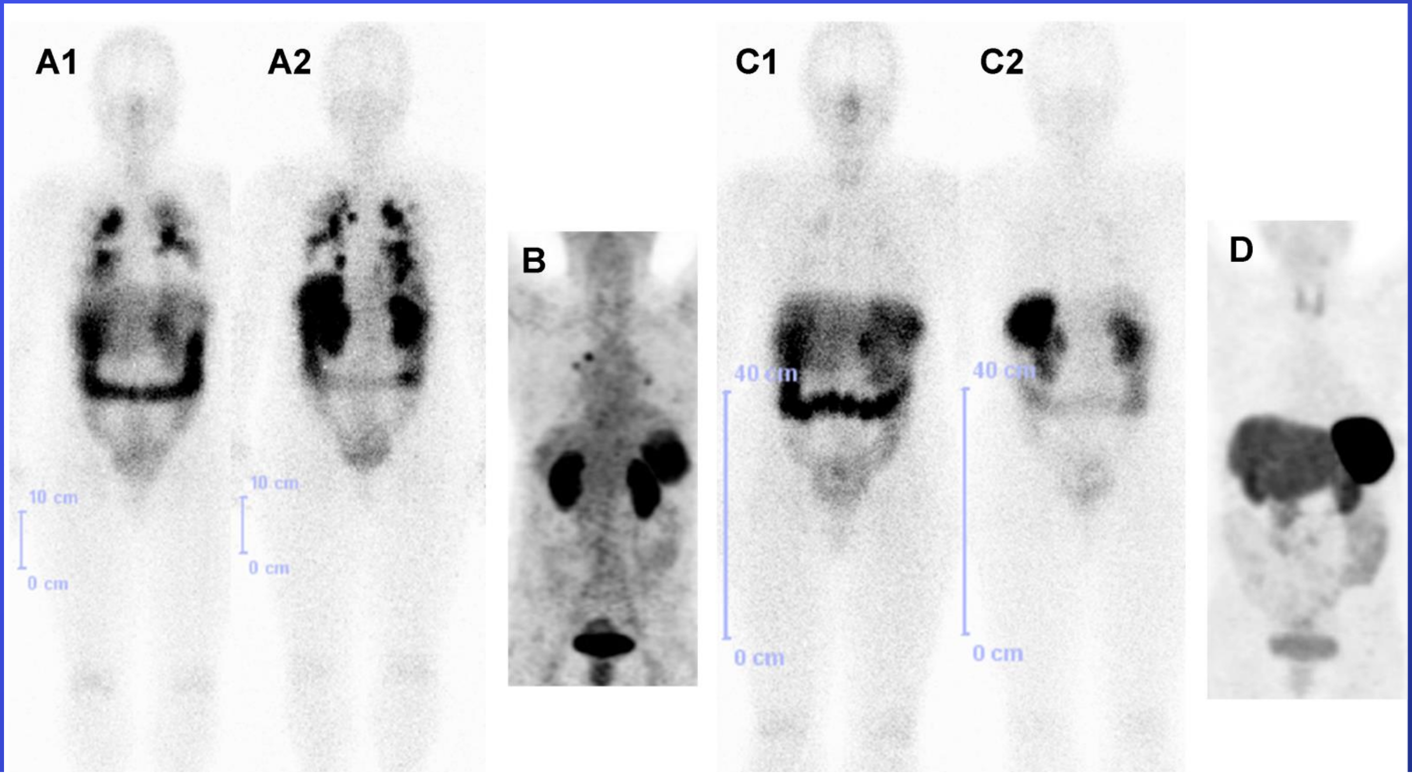
- Retrospective analysis using a prospective database in 1000 patients with metastatic, progressive NENs, undergoing 1–9 cycles of PRRT using Lu-177 (n=331), Y-90 (n=170) or both (n=499)
- Median total administered activity was 17.5 GBq
- Patients were followed up for up to 132 months after the 1st cycle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











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

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

First Presentation at ESMO, Sep. 27, 2015 (Vienna)

^{177}Lu-Dotatate Significantly Improves Progression-Free Survival in Patients with Midgut Neuroendocrine Tumours: Results of the Phase III NETTER-1 Trial

Jonathan Strosberg[1], Edward Wolin[2], Beth Chasen[3], Matthew Kulke[4], David Bushnell[5], Martyn Caplin[6], Richard P. Baum[7], Erik Mittra[8], Timothy Hobday[9], Andrew Hendifar[10], Kjell Oberg[11], Maribel Lopera Sierra[12], Philippe Ruszniewski[13], Dik Kwekkeboom[14]
on behalf of the NETTER-1 study group

[1] Moffitt Cancer Center, Tampa, FL 33612, USA;[2] Markey Cancer Center, University of Kentucky, Lexington, KY 40536-0093, USA;[3] University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA;[4] Dana-Farber Cancer Institute, Boston, MA 02215, USA;[5] University of Iowa, Iowa City, IA 52242, USA;[6] Royal Free Hospital, London, United Kingdom;[7] Zentralklinik, Bad Berka, Germany;[8] Stanford University Medical Center, Stanford, CA 94305, USA;[9] Mayo Clinic College of Medicine, Rochester, MN 55905, USA;[10] Cedars Sinai Medical Center, Los Angeles, CA 90048, USA;[11] University Hospital, Uppsala University, Uppsala, Sweden;[12] Advanced Accelerator Applications, New York, NY 10118, USA;[13] Hopital Beaujon, Clichy, France;[14] Erasmus Medical Center, Rotterdam, Netherlands

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Progression-Free Survival

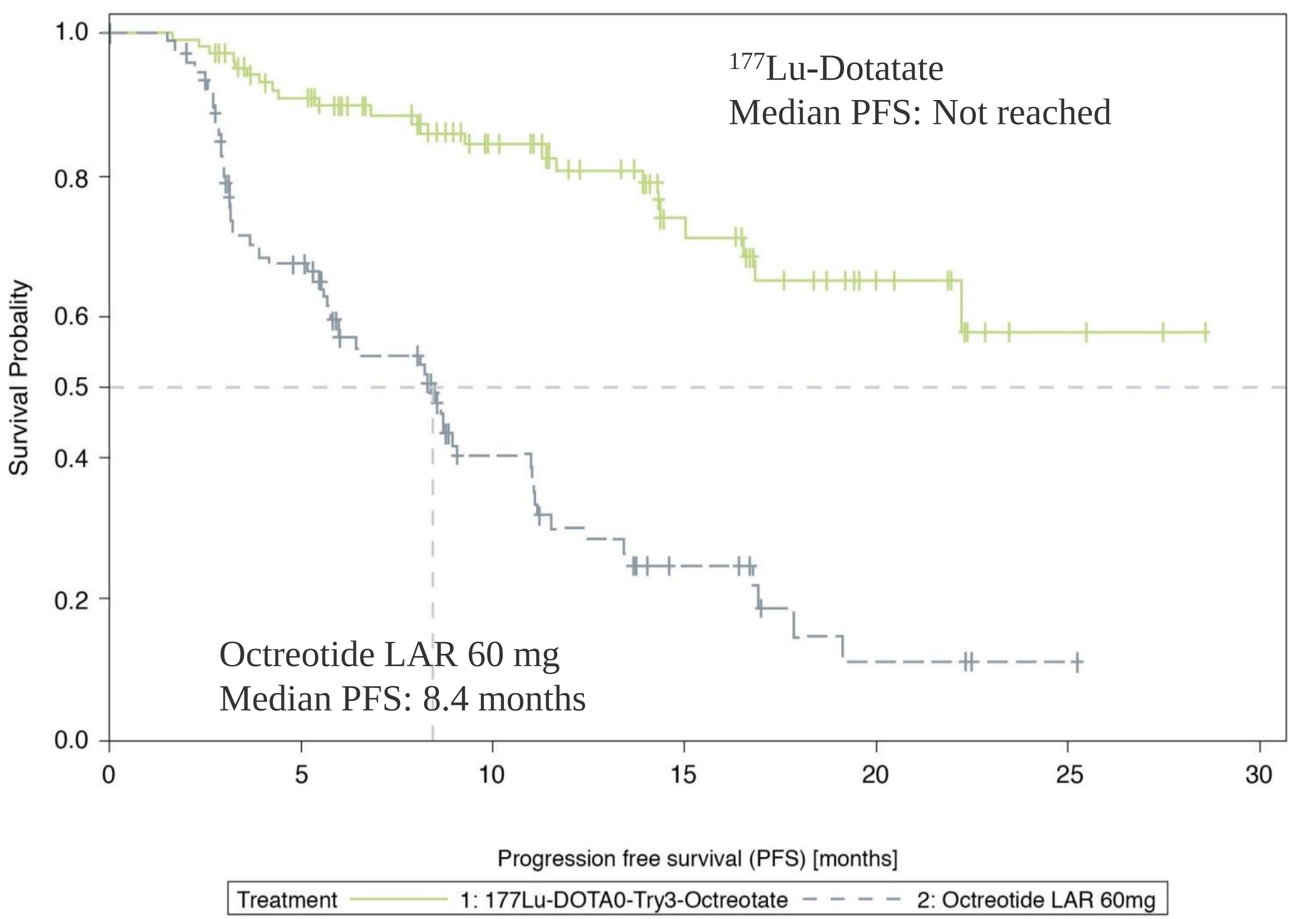
N = 229 (ITT)
Number of events: 90

- [177]Lu-Dotatate: 23
- Oct 60 mg LAR: 67

Hazard ratio : **0.21** [0.129 – 0.338] p < 0.0001

79% reduction in the risk of disease progression/death

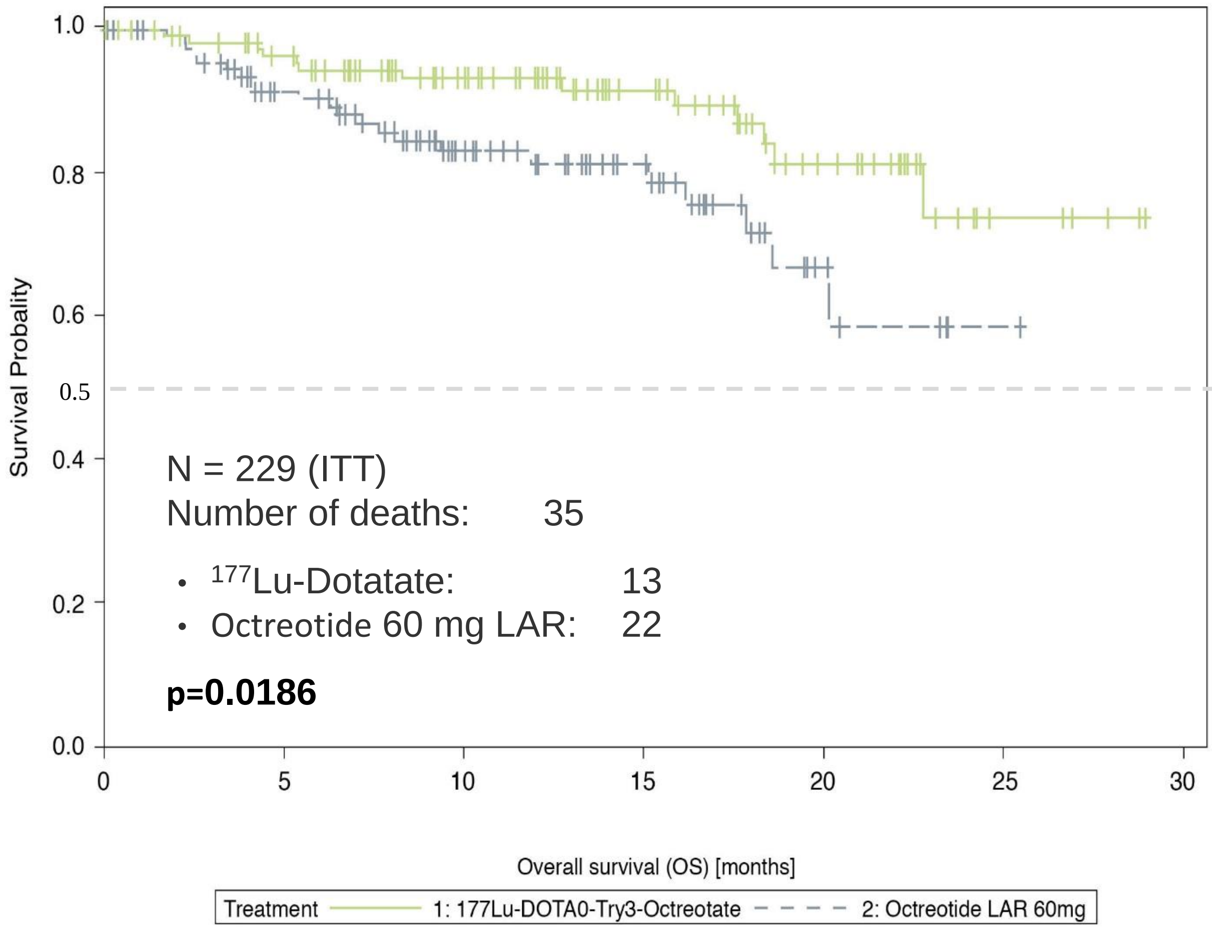
Estimated Median PFS in the [177]Lu-Dotatate arm **≈ 40 months**



All progressions centrally confirmed and independently reviewed for eligibility (SAP)

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Overall Survival (interim analysis)



Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Summary and Conclusions

- Final analysis: In this first prospective randomized study in patients with progressive metastatic midgut NETs, ^{177}Lu-Dotatate was superior to Octreotide 60 mg in terms of:
  - PFS (Not Reached vs 8.4 months, $p<0.0001$)
  - ORR (19% vs 3%, $p<0.0004$)
- Treatment with ^{177}Lu-Dotatate induce a 79% reduction in the risk of disease progression/death (Hazard ratio : 0.21)
- Interim analysis suggests increased OS (13 vs 22 deaths), to be confirmed by final analysis
- Currently available safety data confirm the results of Phase I-II study, with favorable safety profile
- **While few treatment options are available for patients progressing under SSAs, ^{177}Lu-Dotatate appears as a major advance for this patient population**

Presentation Presidential Session II of the 18th ECCO – 40th ESMO – European Cancer Congress 2015, 27 September 2015, abstract 6LBA, Vienna

Zentralklinik Bad Berka

Dosimetry in Targeted Radionuclide Therapy:

The Bad Berka Dose Protocol

Experience after more than 1,000 Evaluations

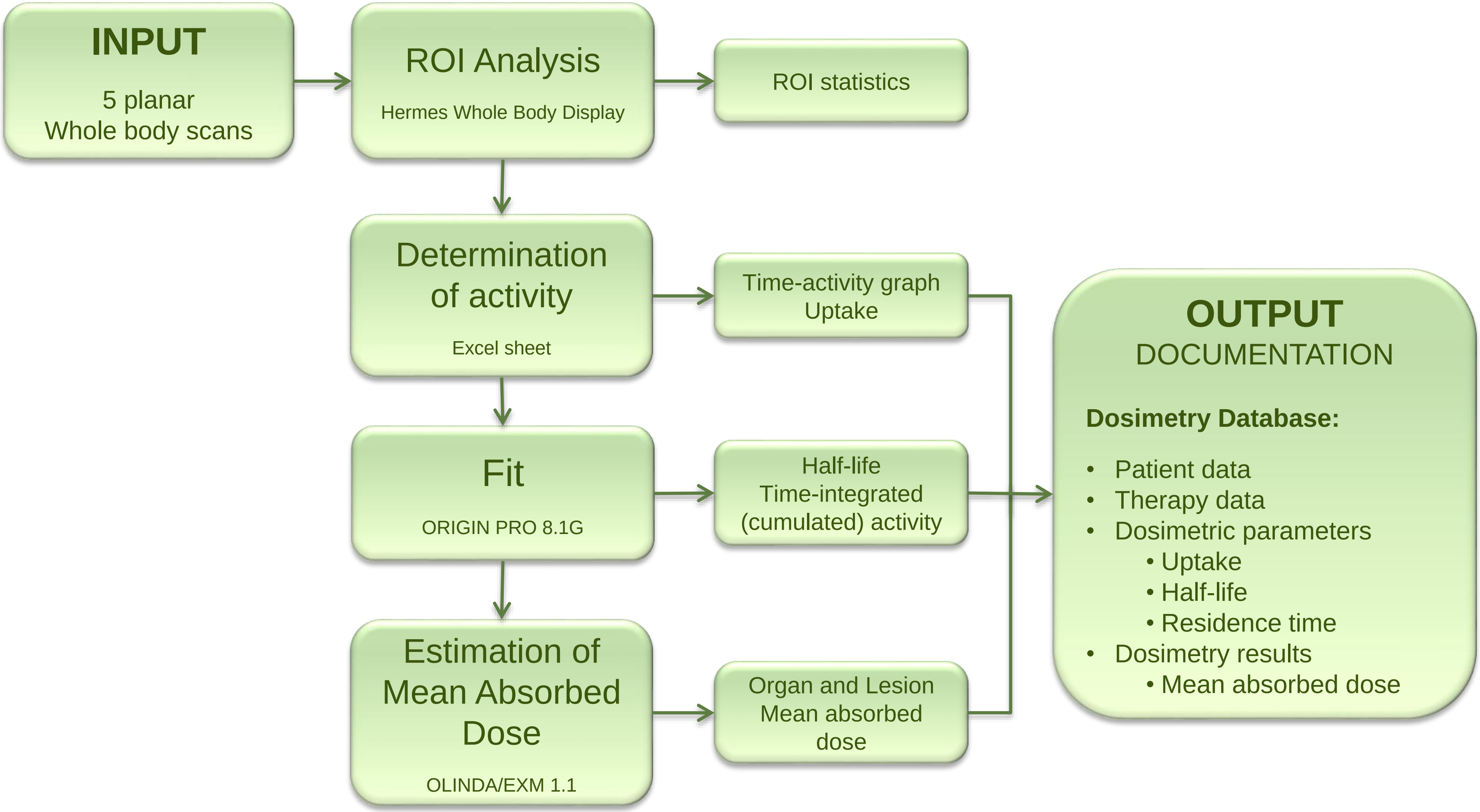
Christiane Schuchardt

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

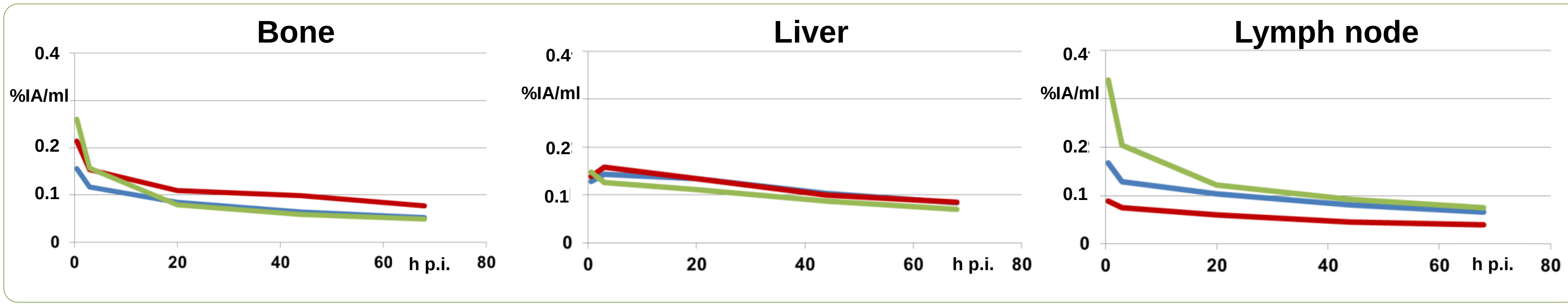
Dosimetry

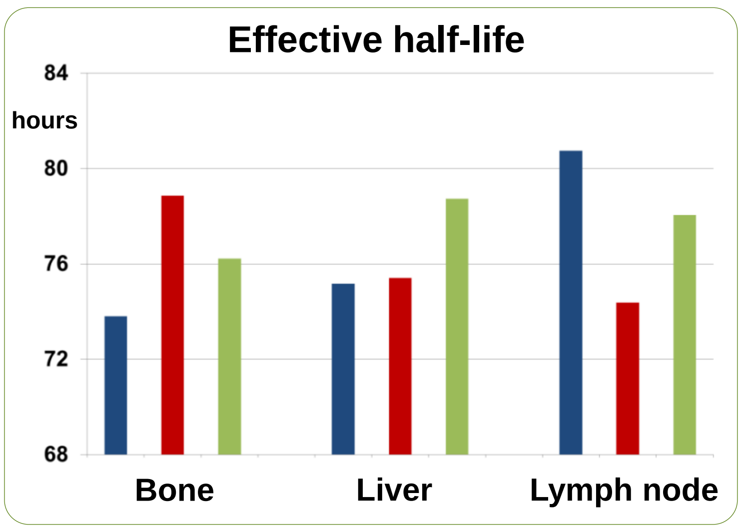
Zentralklinik Bad Berka

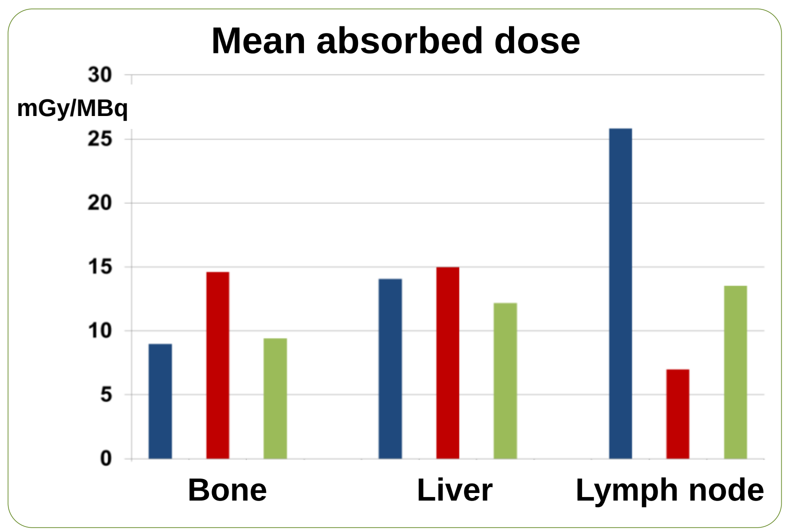
Bad Berka Dose Protocol



Tumor lesions







DOTATATE
183 bone lesions
333 liver lesions
152 lymph node lesions

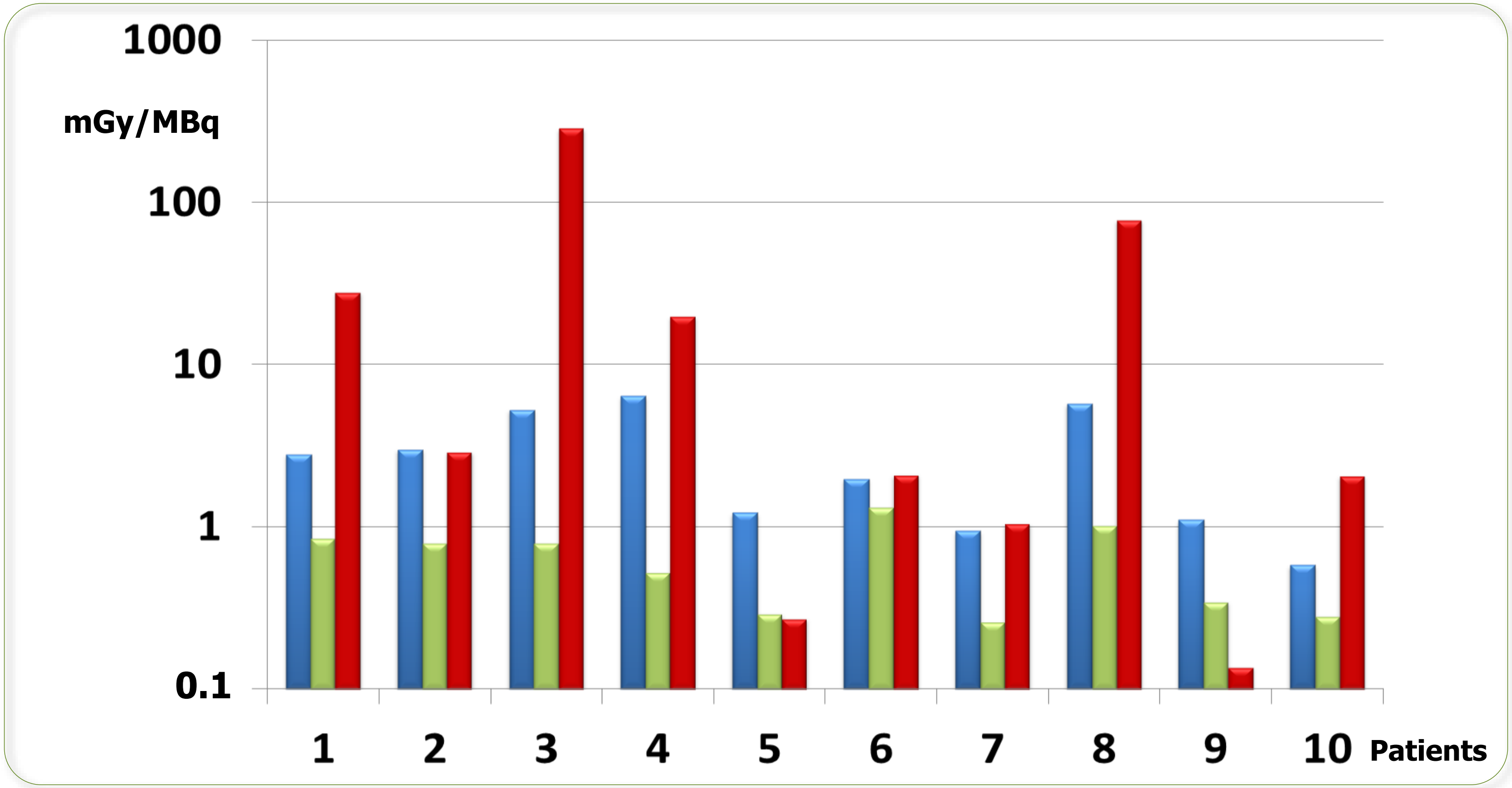
HA-DOTATATE
8 bone lesions
19 liver lesions
15 lymph node lesions

DOTATOC
151 bone lesions
198 liver lesions
94 lymph node lesions

Dosimetry

^{177}Lu PSMA: Prostate cancer

→ 39 Dosimetric Evaluations



Parotid glands
4-37 Gy per treatment

Kidneys
1-8 Gy per treatment

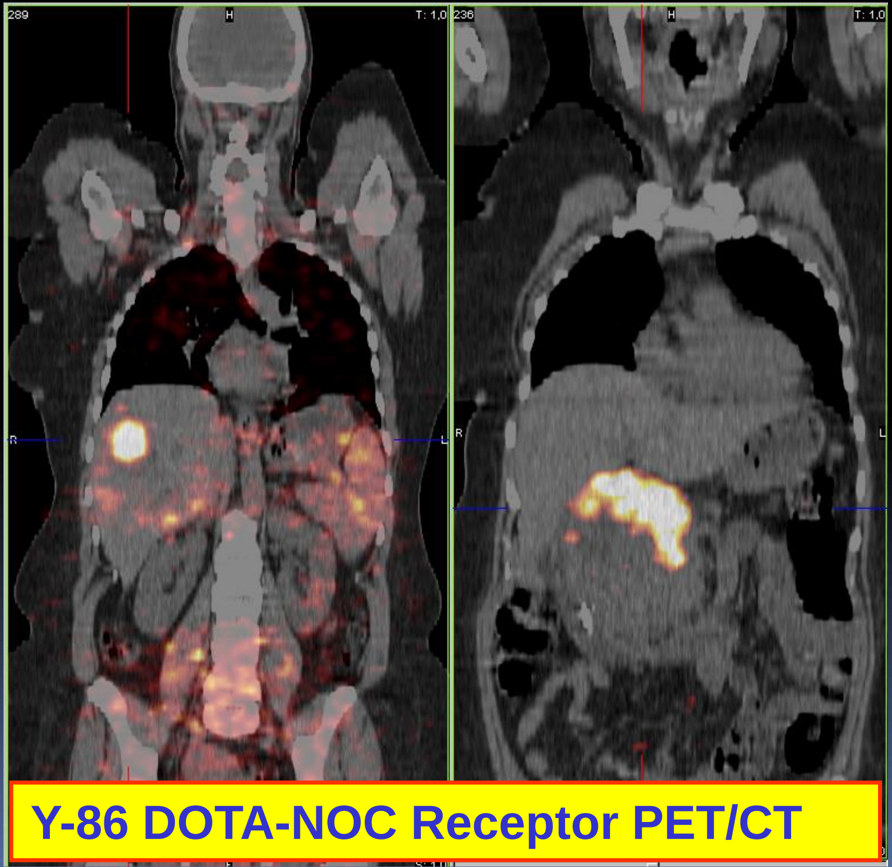
Lesions (bone and lymph nodes)
up to 300 Gy per treatment

Mean absorbed dose to parotid glands higher than renal absorbed dose

New Isotopes

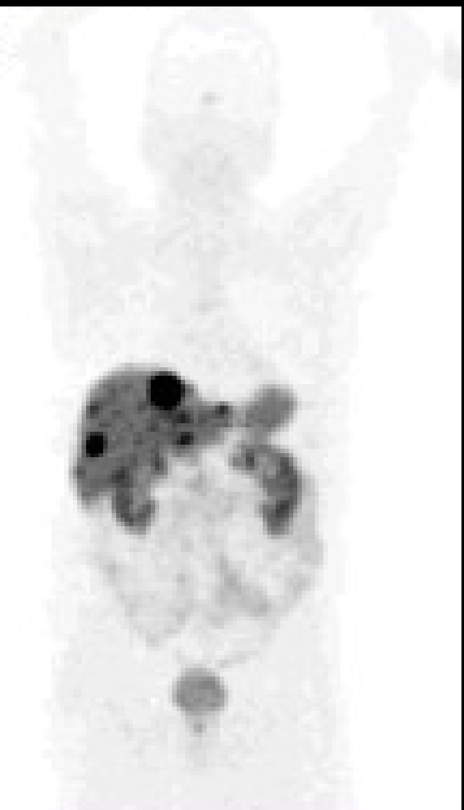
Pre-therapeutic organ and tumor dosimetry using receptor PET/CT and longer lived positron emitters, e.g. Sc-44, Zr-89, Y-86 or Cu-64 and comparison with Ga-68 results.

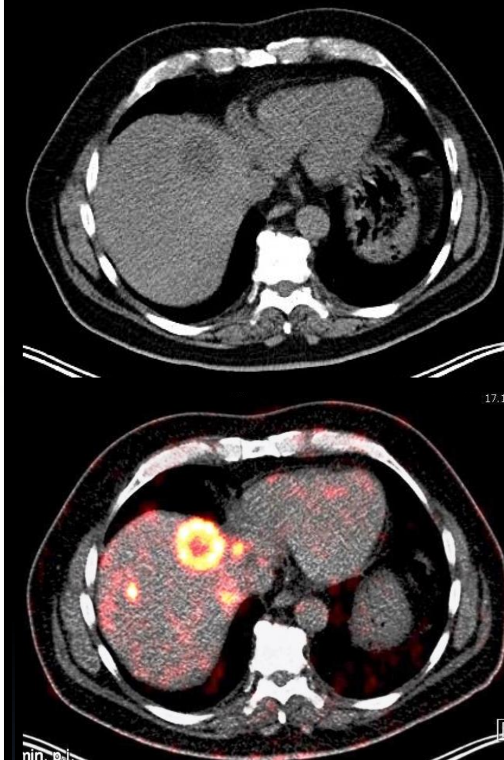
Selection of the optimal peptide and radionuclide for individual therapy of each patient („personalized dosimetry“) by pretherapeutic measurement of organ and tumor doses.



Y-86 DOTA-NOC Receptor PET/CT

Ga-68 DOTATOC --- PET/CT --- Sc-44 DOTATOC

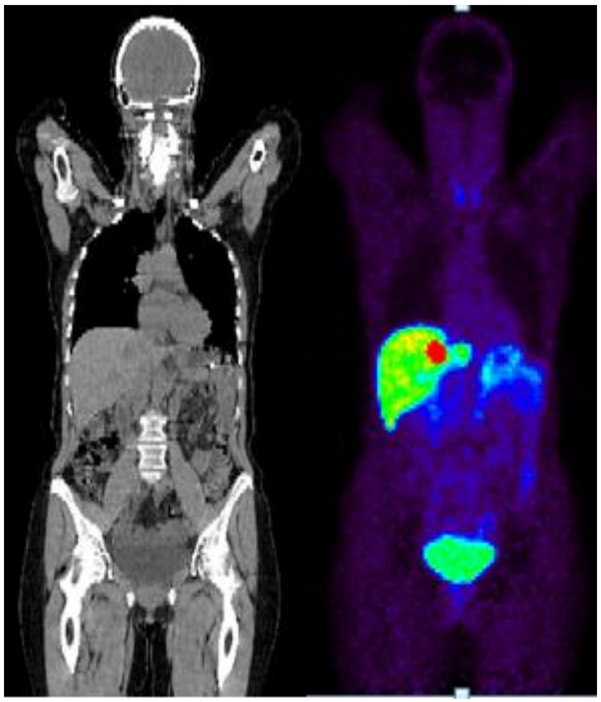




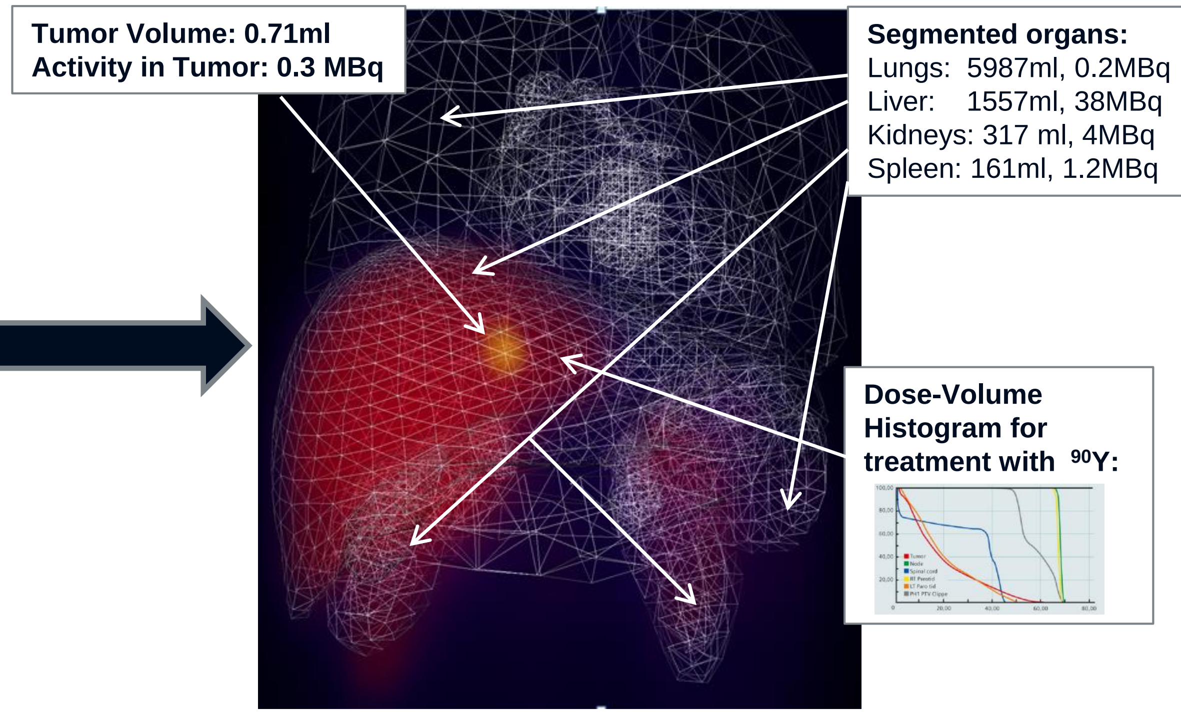
Personalized dosimetry

Visions on Dosimetry

- Fast, reproducible dosimetry for a **fully segmented** data set!
- Segmentation by deformation of deformable phantoms (SubD)



PET/SPECT/CT Image



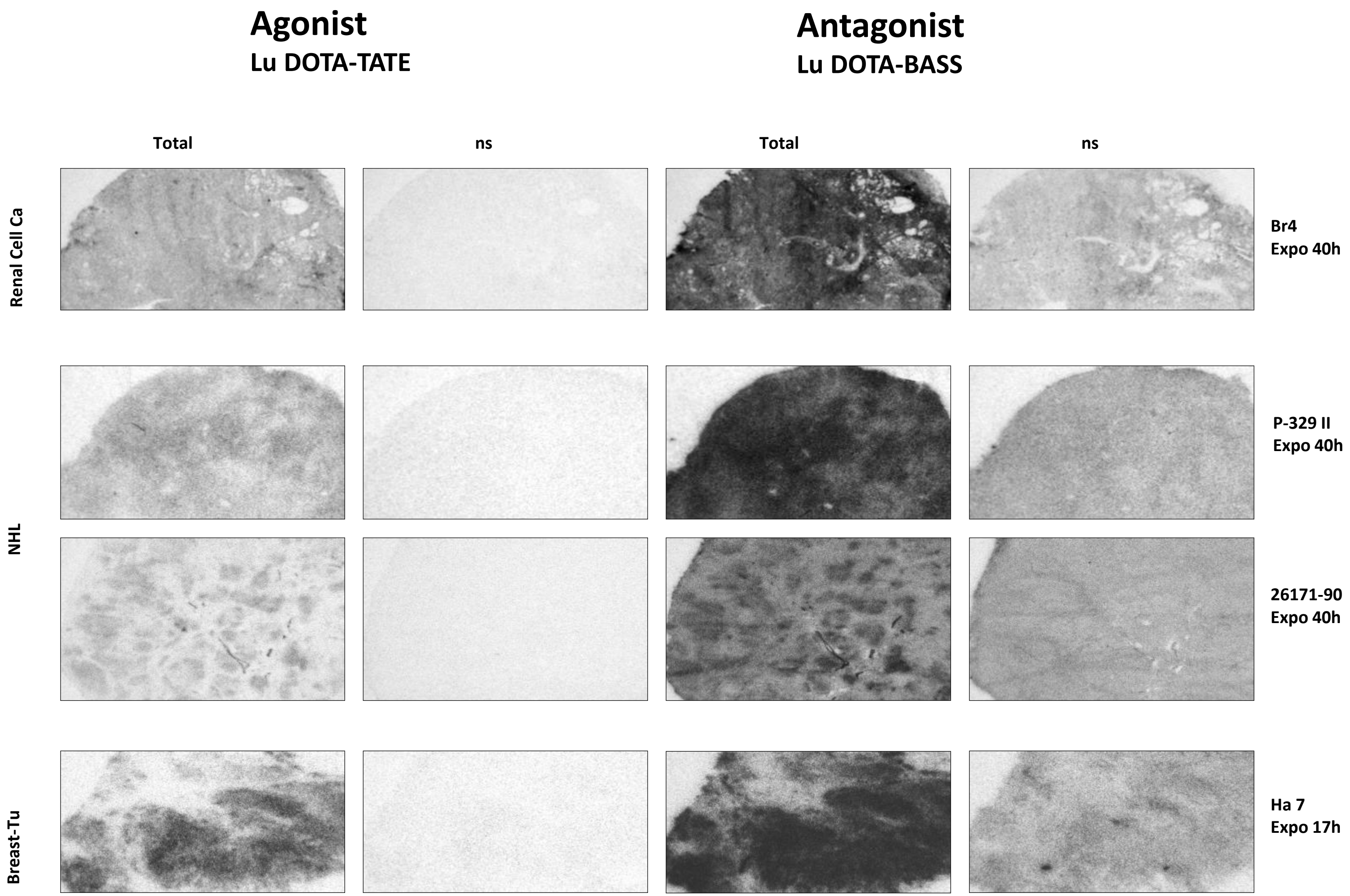
Deformed SubD phantom, matching the patient

New Avenues to Improve PRRT in Future

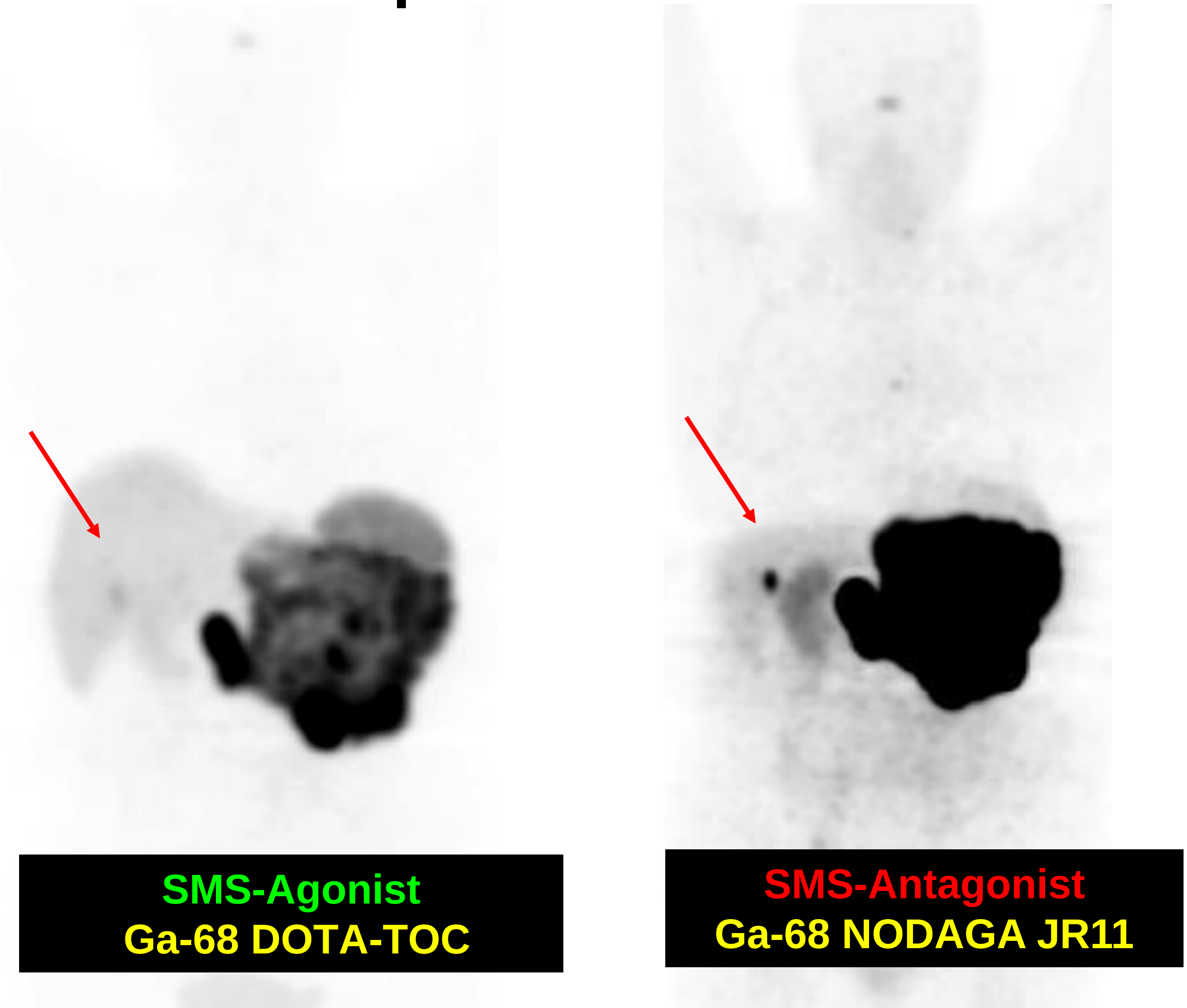
- **DUO-PRRT** (already routine at our center since 8 years)
- **TANDEM-PRRT** (concurrent Lu-177/Y-90 PRRT Kunikowska et al.)
- **Intra-arterial PRRT** (> 100 i.a. treatments up to now)
- **Combined PRRT** (in combination with other treatment modalities)
  - **TACE, SIRT, RFA** (Hörsch et a. ASCO 2010)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

Improved peptides (e.g. antagonists)

Antagonist labels more sst_2 sites than agonist in human cancer tissues



Extensive NET of pancreas with liver metastasis

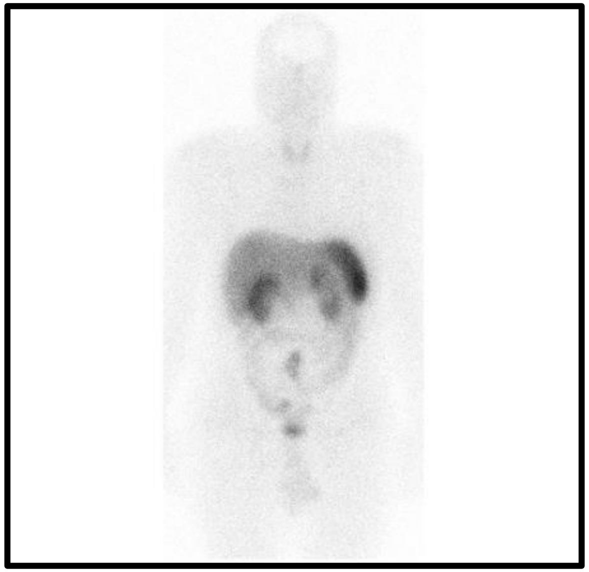


Antagonist labels more sst_2 sites than agonist in cancer patients leading to higher diagnostic sensitivity (first in human study)

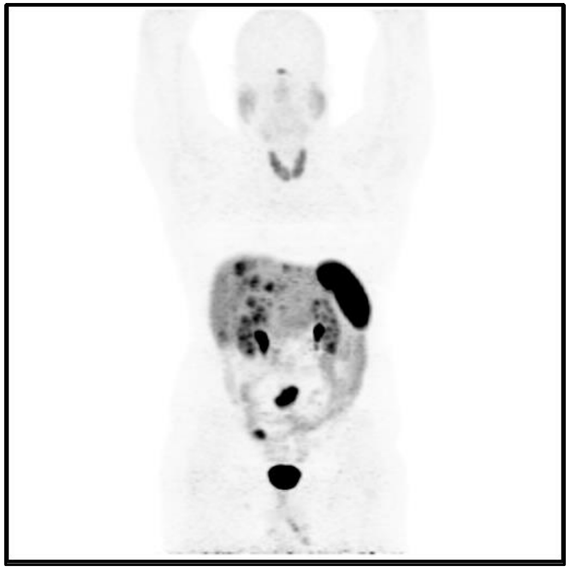
20 years after ^{111}In-Octreotide Prospects in Molecular Imaging of gastro-entero-pancreatic NET: ^{68}Ga-OPS202

24 h post injection

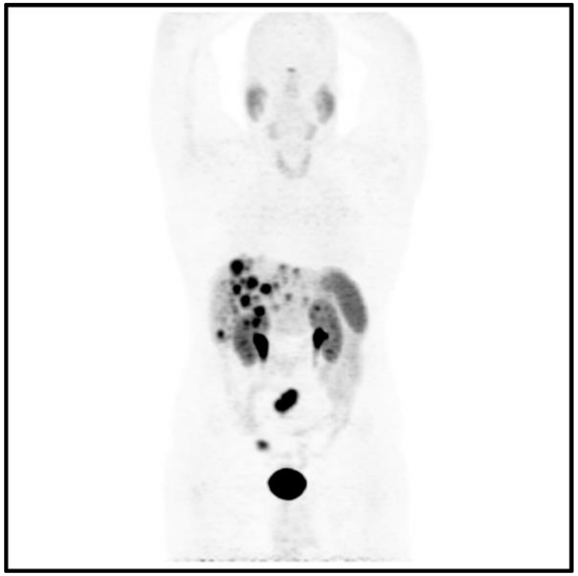
1 h post injection



^{111}In-Octreotide



^{68}Ga-DOTA-TOC

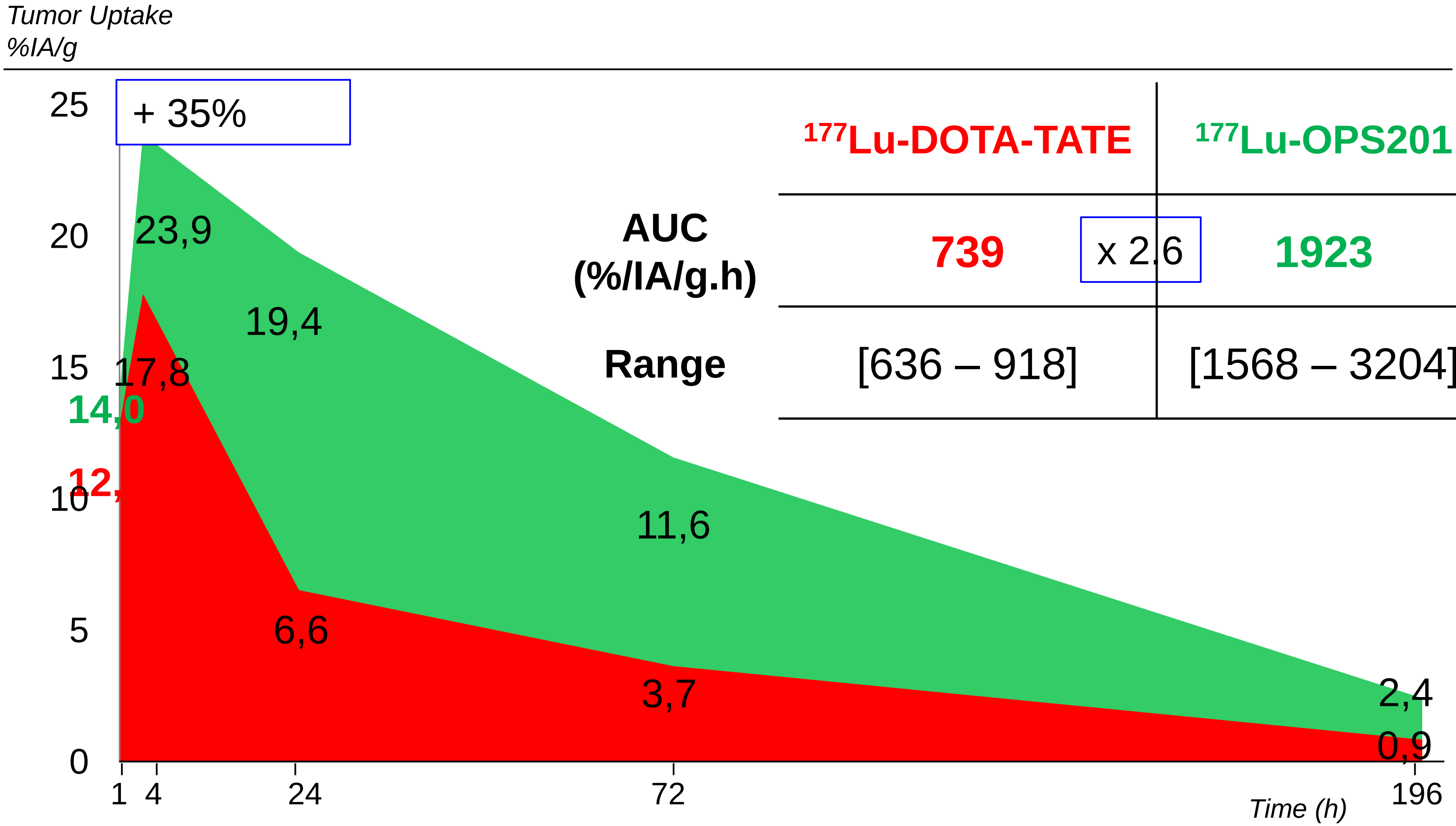


^{68}Ga-OPS202

G. P. Nicolas

University Hospital Basel

Tumor Dose *(Tumor Time Activity Curve)*



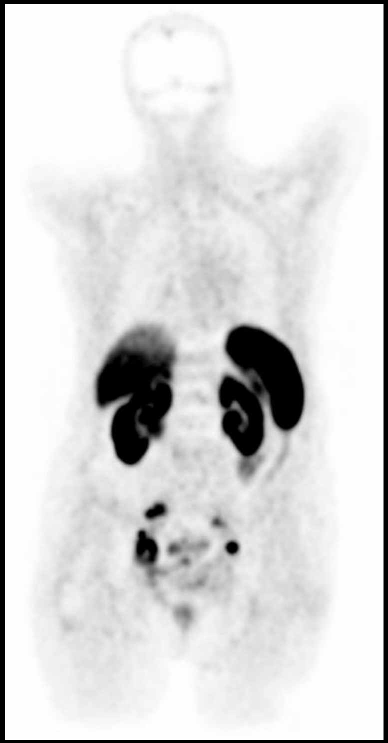
	^{177}Lu-DOTA-TATE	^{177}Lu-OPS201
AUC (%/IA/g.h)	**739**	**1923**
Range	[636 – 918]	[1568 – 3204]

x 2,6

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



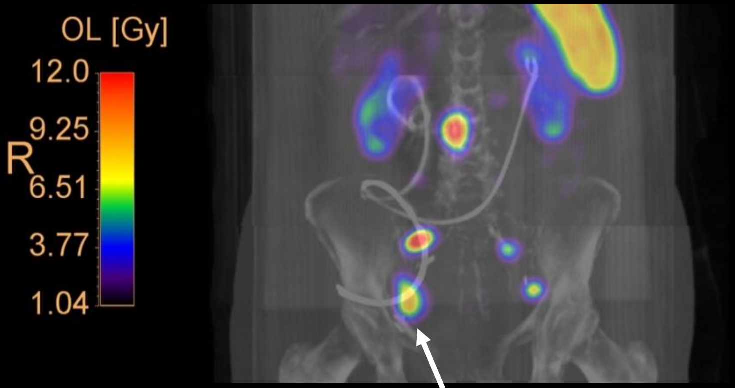
Limited kidney function
Creatinine clearence: 54 ml/min
(norm 90 – 179 ml/min)

^{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



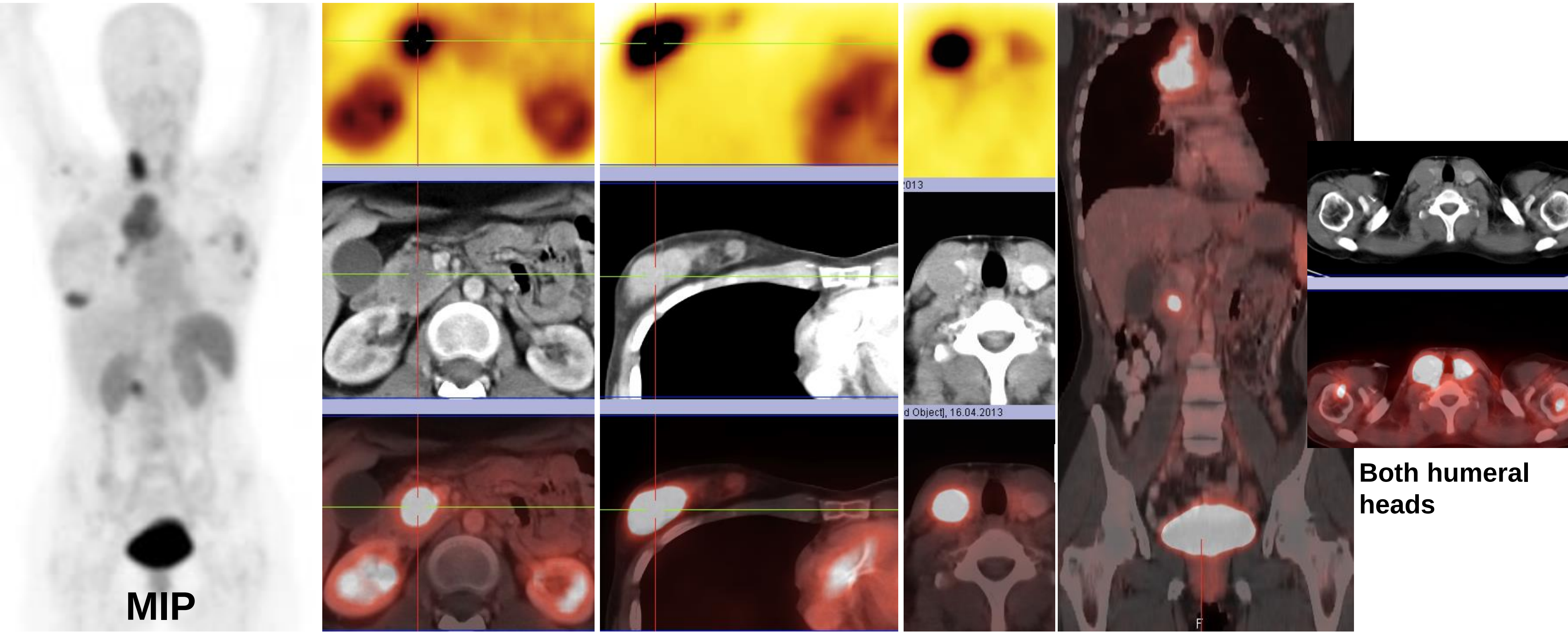
mean dose: 5.7 Gy/GBq
Tumor-to-kidney dose ratio: 2.5

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

UNIVERSITÄTS KLINIKUM FREIBURG

Courtesy of Damian Wild

^{68}Ga CPCR4-2 PET/CT for Imaging of NEC (G3)



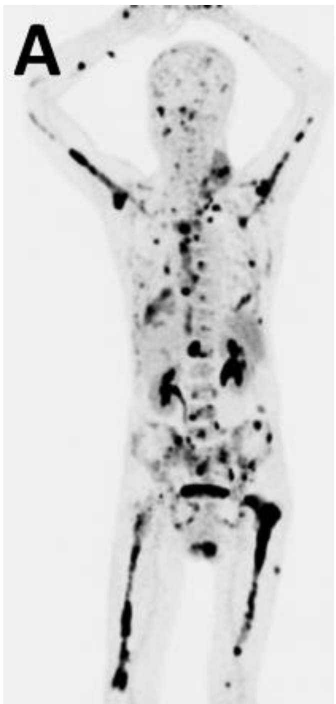
Pancreatic head Right breast tumor LN

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.

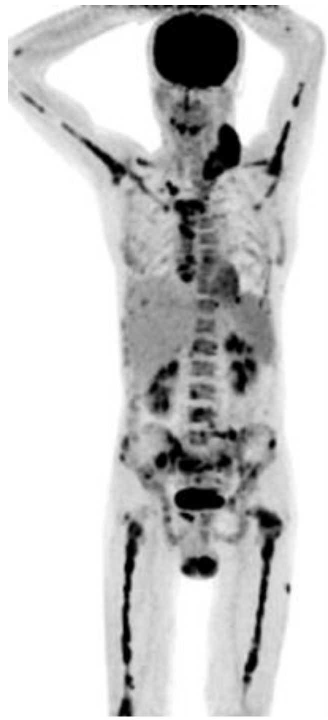
Center for Molecular Imaging and Molecular Radiotherapy, Zentralklinik Bad Berka, Germany in collaboration with H.J. Wester (labeling performed using SCINTOMICS module)

Myeoma treatment with ^{177}Lu-CPCR4-2 (Pentixather)

^{68}Ga-Pentixafor

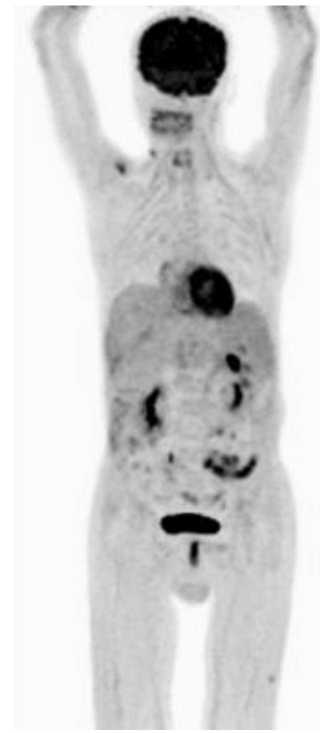


^{18}F-FDG



Prior to Pentixather

^{18}F-FDG



14 d after Pentixather

World Association of Radionuclide & Molecular Therapy (WARMTH)

^{188}ReNAISSANCE

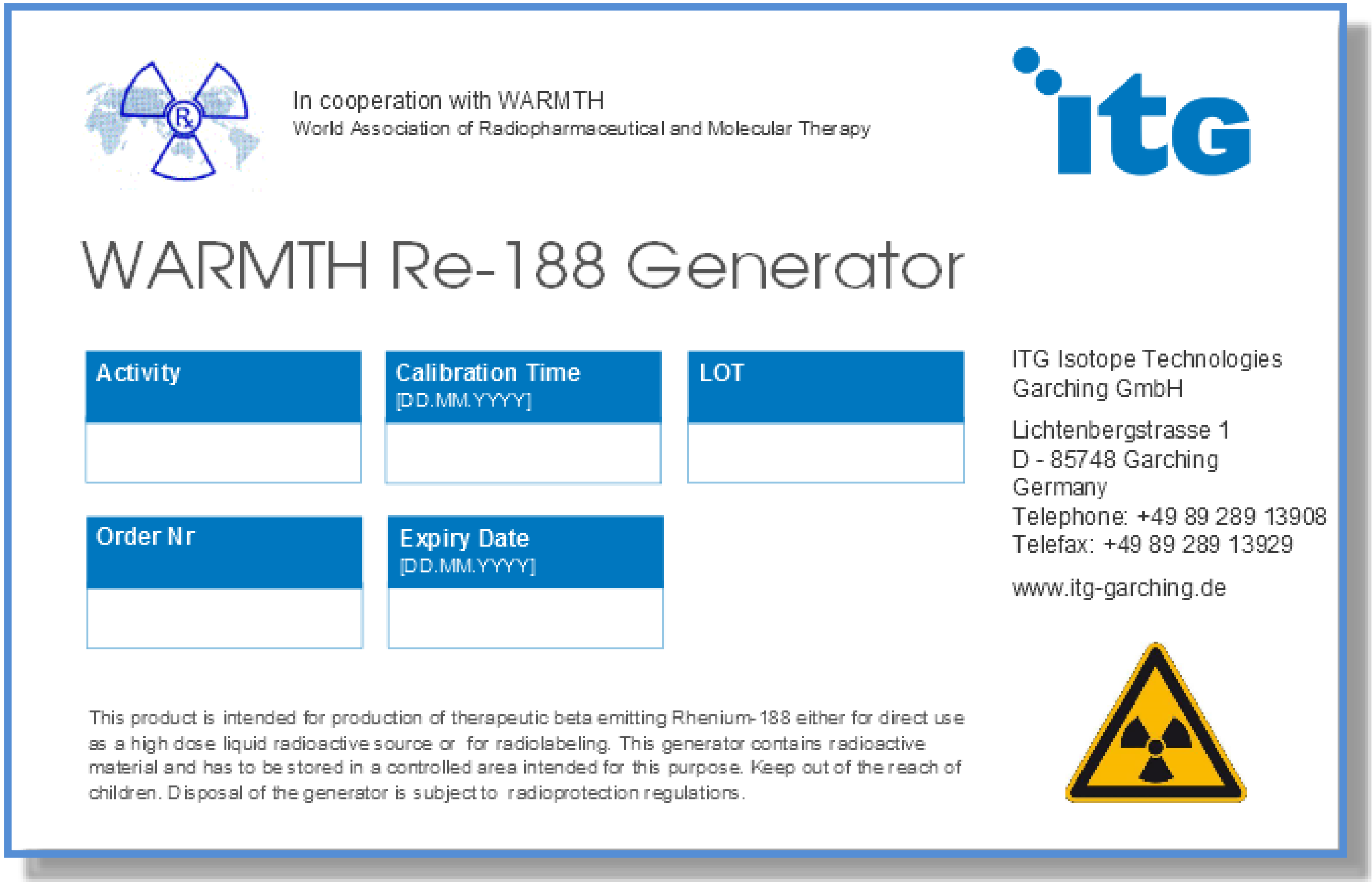
TReAT HCC

Targeted Rhenium–188 Arterial Therapy

EANM Goetheborg Oct. 2014 – Prof. Baum obtained agreement of ITM for offering the

WARMTH W-188/Re-188 Generator

In cooperation with ITG



WARMTH Rhenium project

The project was re-initiated after the last ICRT in Cancun (2014)

Dr Ajit Shinto was nominated to prepare a vision of the propogation of Re-188 use, mainly for liver cancer therapy.

NM dept at KMCH Coimbatore would be the lead center for this project and provide training.

Issues that have been addressed:

Generator: availability and cost

WARMTH Rhenium generator (initiated by R.P. Baum)

Kits for conjugation: SNU

Other issues to be addressed:

Dosimetry

Clinical trials

Other generators

Other kits

Future directions

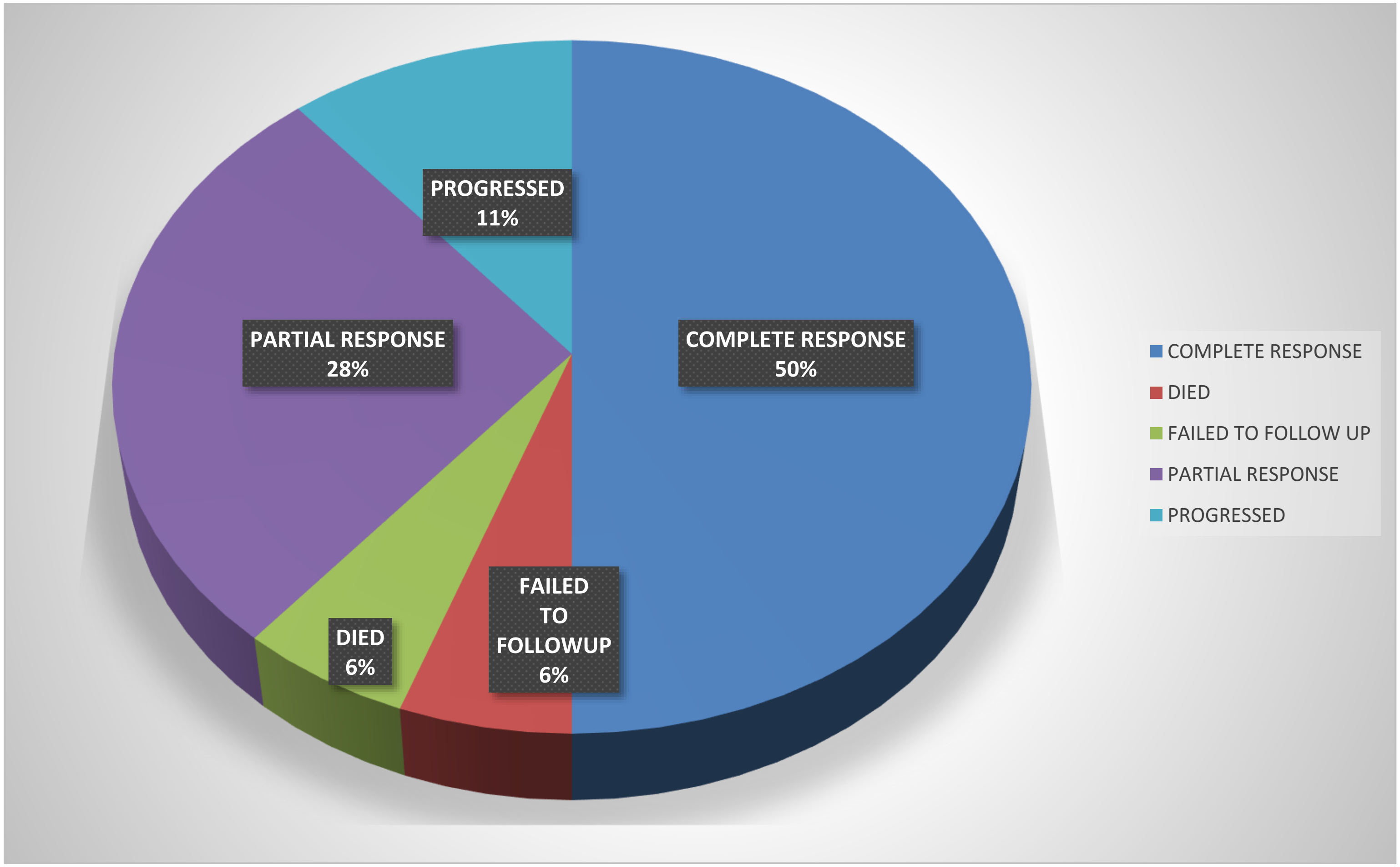
WARMTH support in training and setting up a new facility.

WARMTH Research Fund (initiated by R.P. Baum)

NM dept at KMCH Coimbatore

Follow up CT

till now 46 patients in 24 months, all HCC
except 5 patients: 3 cholangio Ca and 2 mets

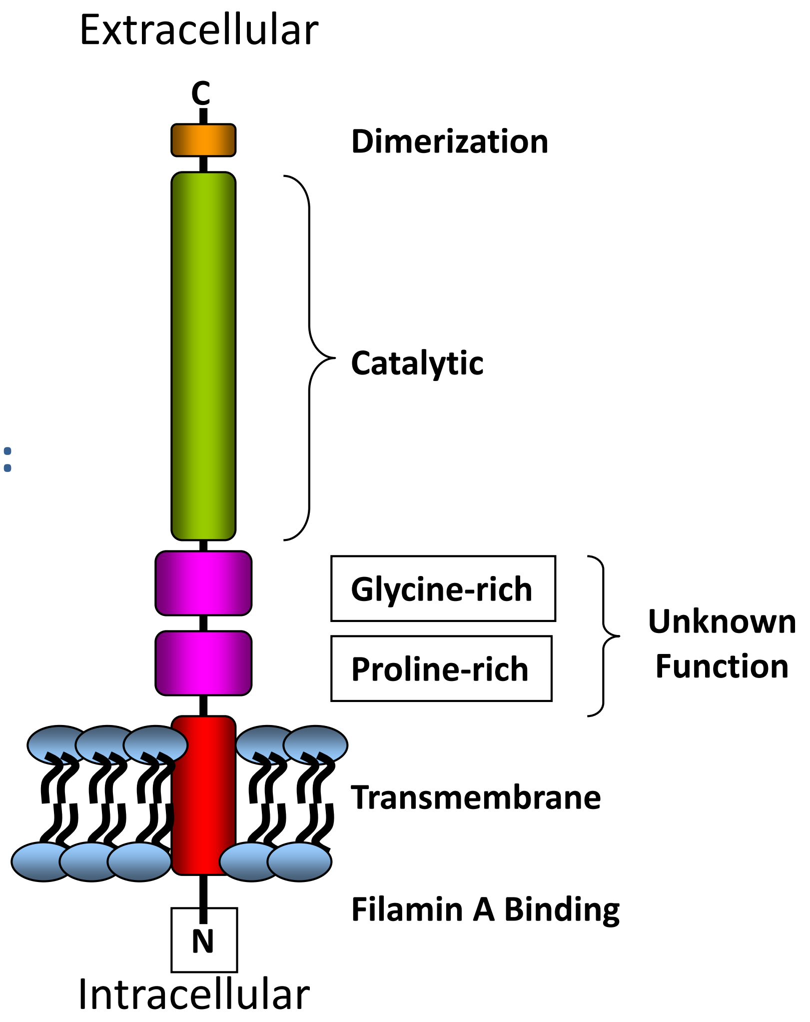


Theranostics of Prostate Cancer

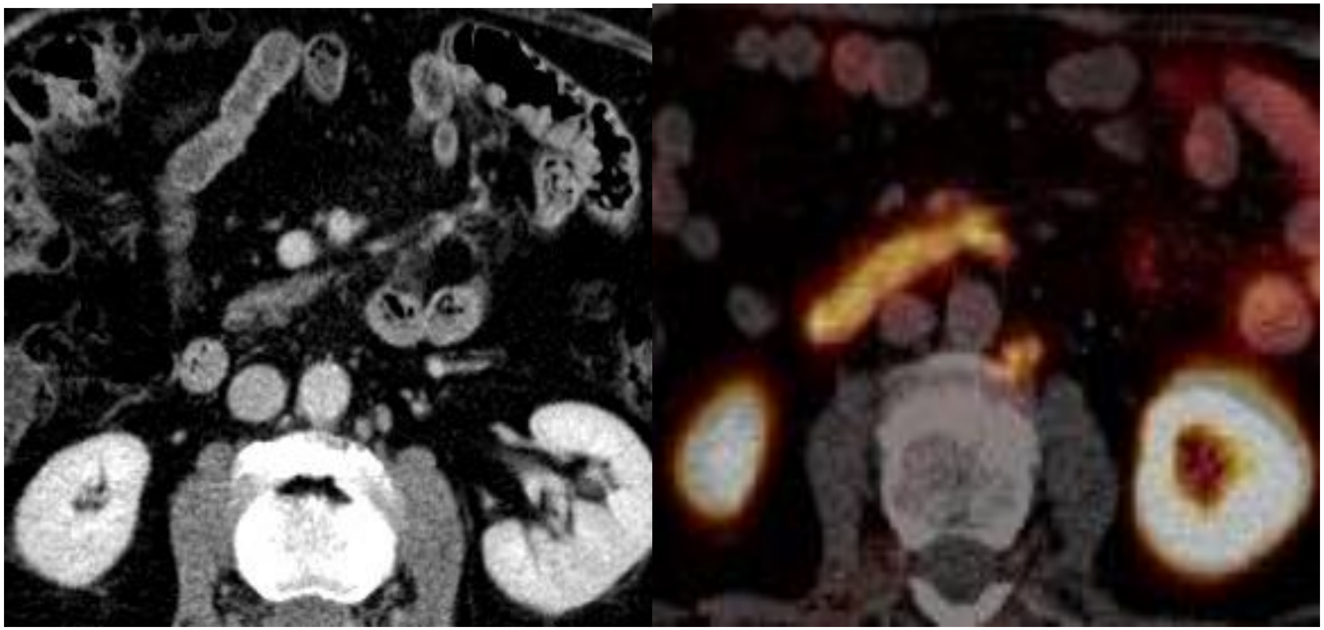
PSMA for Targeting Prostate Cancer

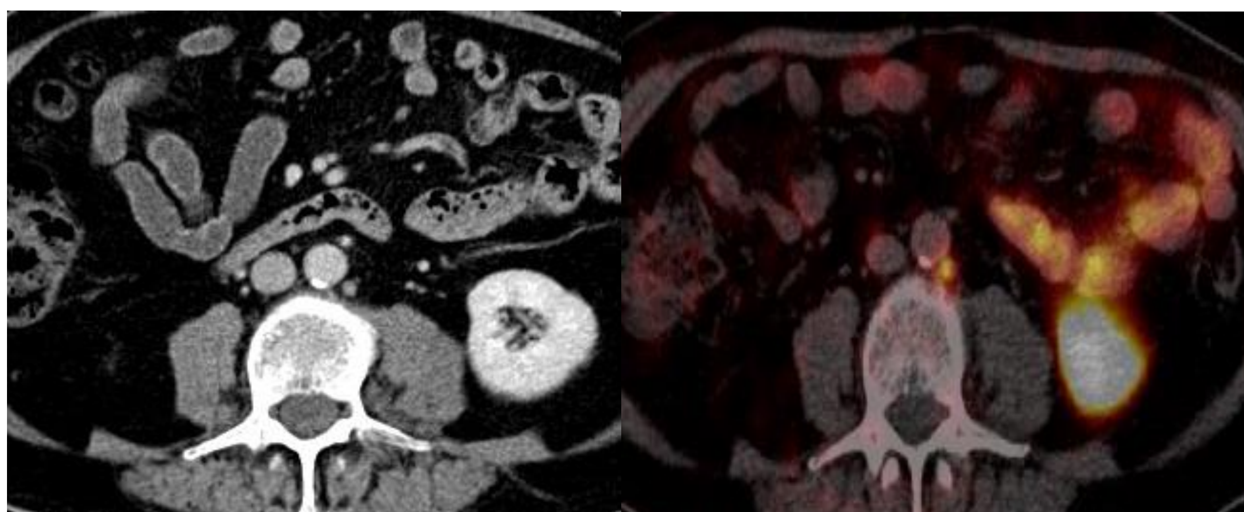
Henry N. Wagner: FDG – the molecule of the (last) century
Richard P. Baum: PSMA – the target of the next decade

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

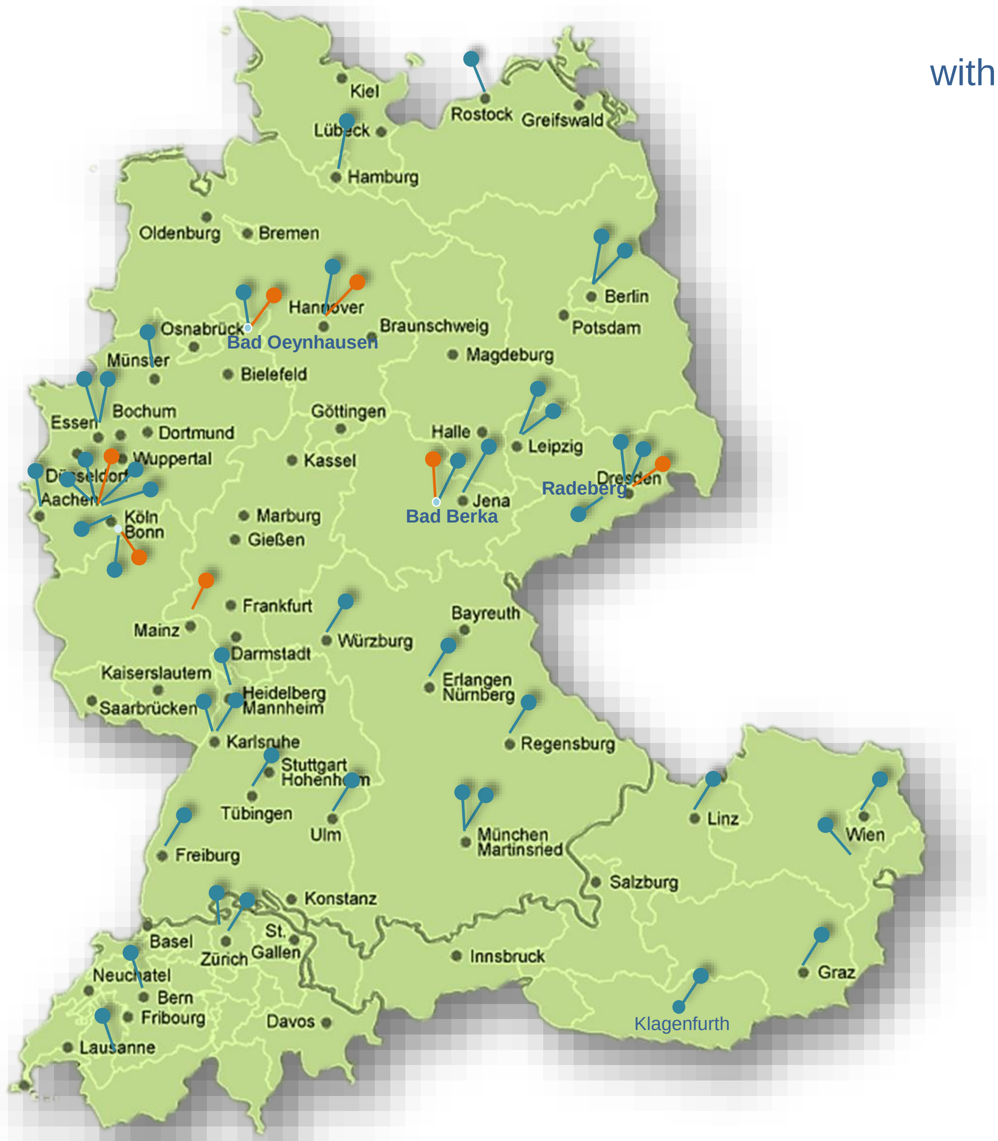


… none of these lesions is enlarged on *contrast-enhanced CT study (lymph node size 2-3 mm)*





Cylotron Installations in GER, CH and A



status summer 2014,
without warranty of completeness

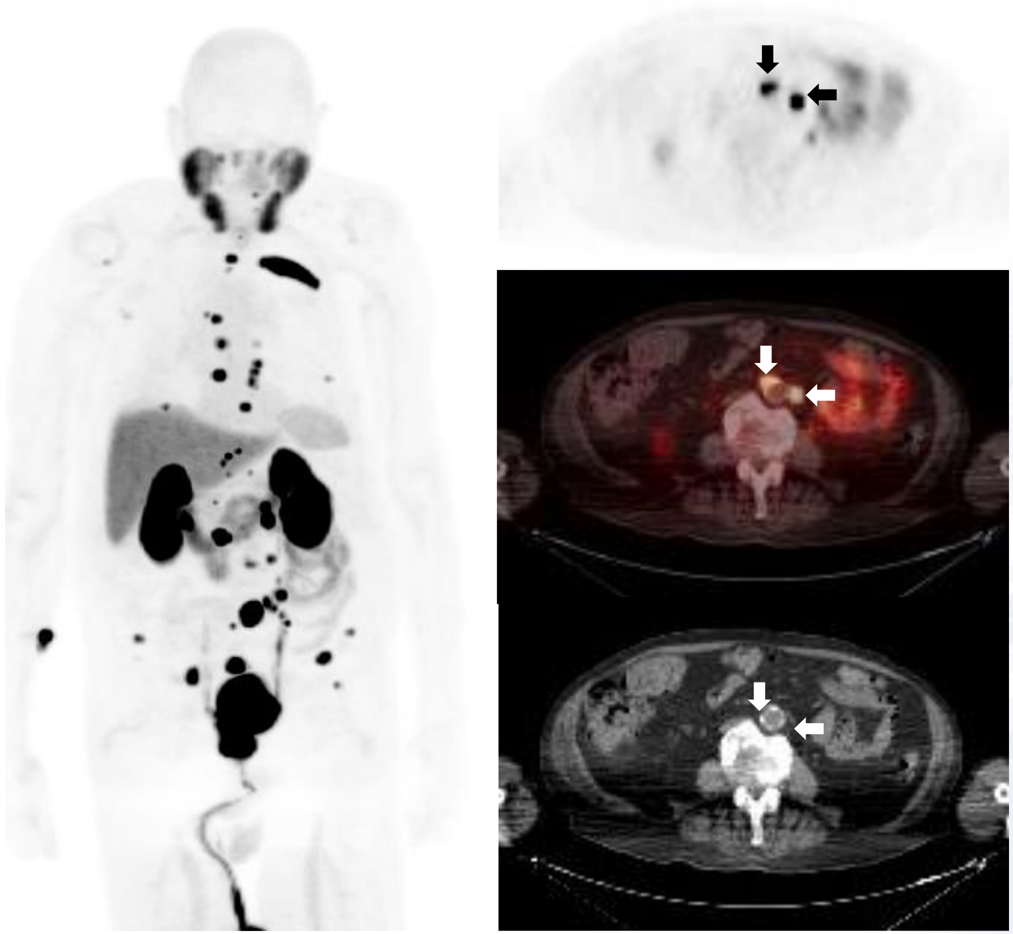
Germany
33 Installations
+ 8 planned installations
(2015/2016)

Swisse
4 installations

Austria
5 installations

Most of these sites (plus additional sites) produce Ga-68-radiopharmaceuticals for clinical application.

Next generation: F-18 DCFPyL metastatic castration-resistant prostate cancer



Highest SUV_{max}

- Bone = 102
- Lymph node = 100
- Primary = 72

Overall 4 x higher "unequivocal" lesion detection than CIM

(N = 9, avg. PSA = 8)

Courtesy: Martin Pomper, Steve Cho and Zsolt Szabo

SNM MI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

THERANOSTICS World Congress Ga-68 & PRRT

JOHNS HOPKINS MEDICINE

THERANOSTICS OF PROSTATE CANCER USING Lu-177 LABELED PSMA SMALL MOLECULES FIRST CLINICAL RESULTS

Richard P. Baum

Harshad R. Kulkarni, Christiane Schuchardt, Hans-J. Wester*

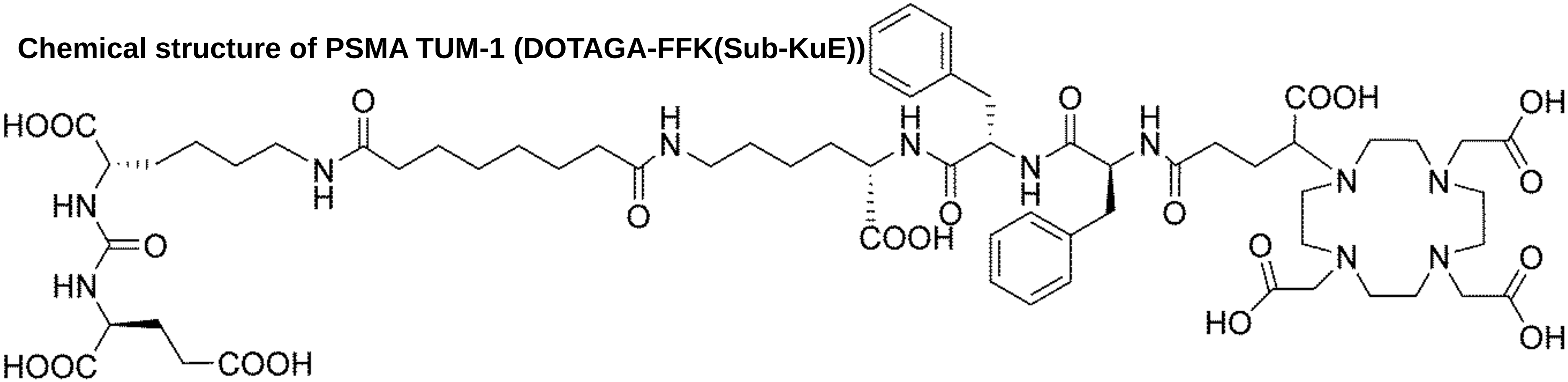
[1]THERANOSTICS Center for Molecular Radiotherapy & Molecular Imaging (PET/CT)

ENETS Center of Excellence, Zentralklinik Bad Berka, Germany

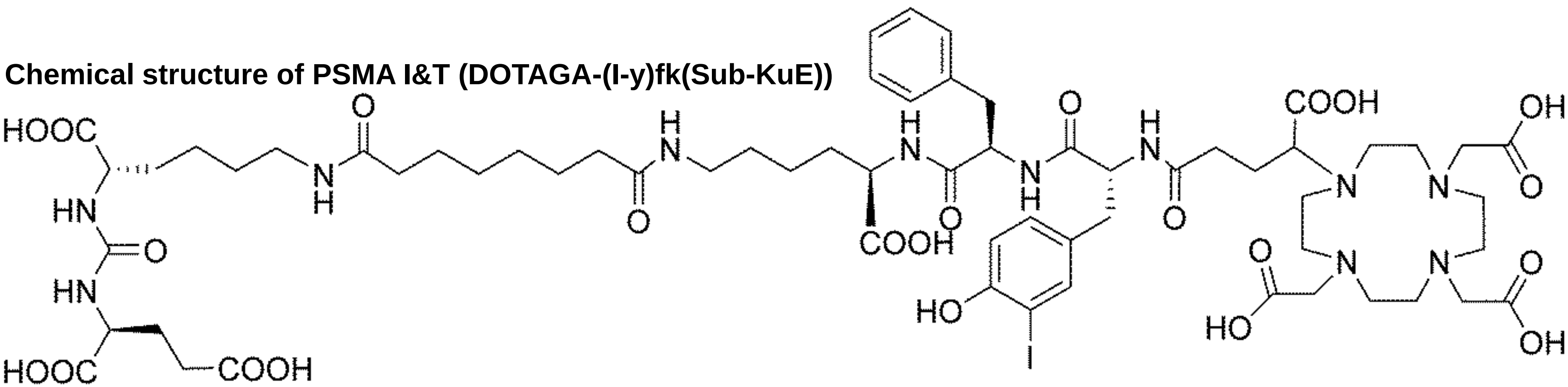
*Pharmaceutical Radiochemistry, Technical University, Munich, Germany

www.PRRTinfo.org richard.baum@zentralklinik.de

Chemical structure of PSMA TUM-1 (DOTAGA-FFK(Sub-KuE))



Chemical structure of PSMA I&T (DOTAGA-(I-y)fk(Sub-KuE))



The DOTAGA PSMA small molecules (PSMA TUM-1 and PSMA I&T) were labeled with Lu-177 at the Radiopharmacy of Zentralklinik Bad Berka and utilized after appropriate quality control (purity > 99 %)

mCRPC Patients‘ Characteristics

Mean Age = 71 +/- 7.4 years

Mean Gleason Score = 8 +/- 1

Previous Therapies

Total no. of patients	**95**
Antiandrogen therapy	**90**
Surgery	**72**
- Primary tumor not operated -	**23**
Radiotherapy (EBRT)	**68**
Chemotherapy	**42**
Other	**9 (hyperthermia, immunotherapy)**

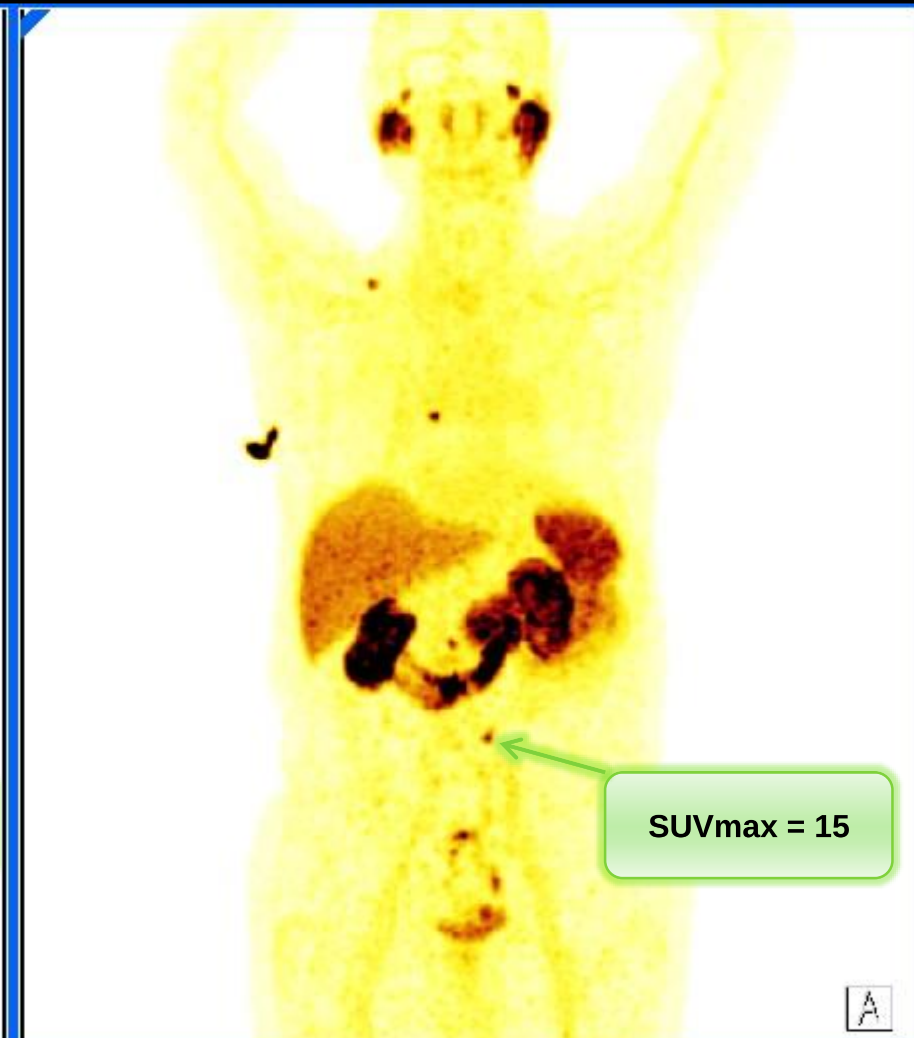
Disease status before PRLT: progressive disease in all patients

Ga-68 PSMA PET

Nearly complete regression of lymph node metastases post PRLT

Pre-PRLT - 02 - 22.09.2014

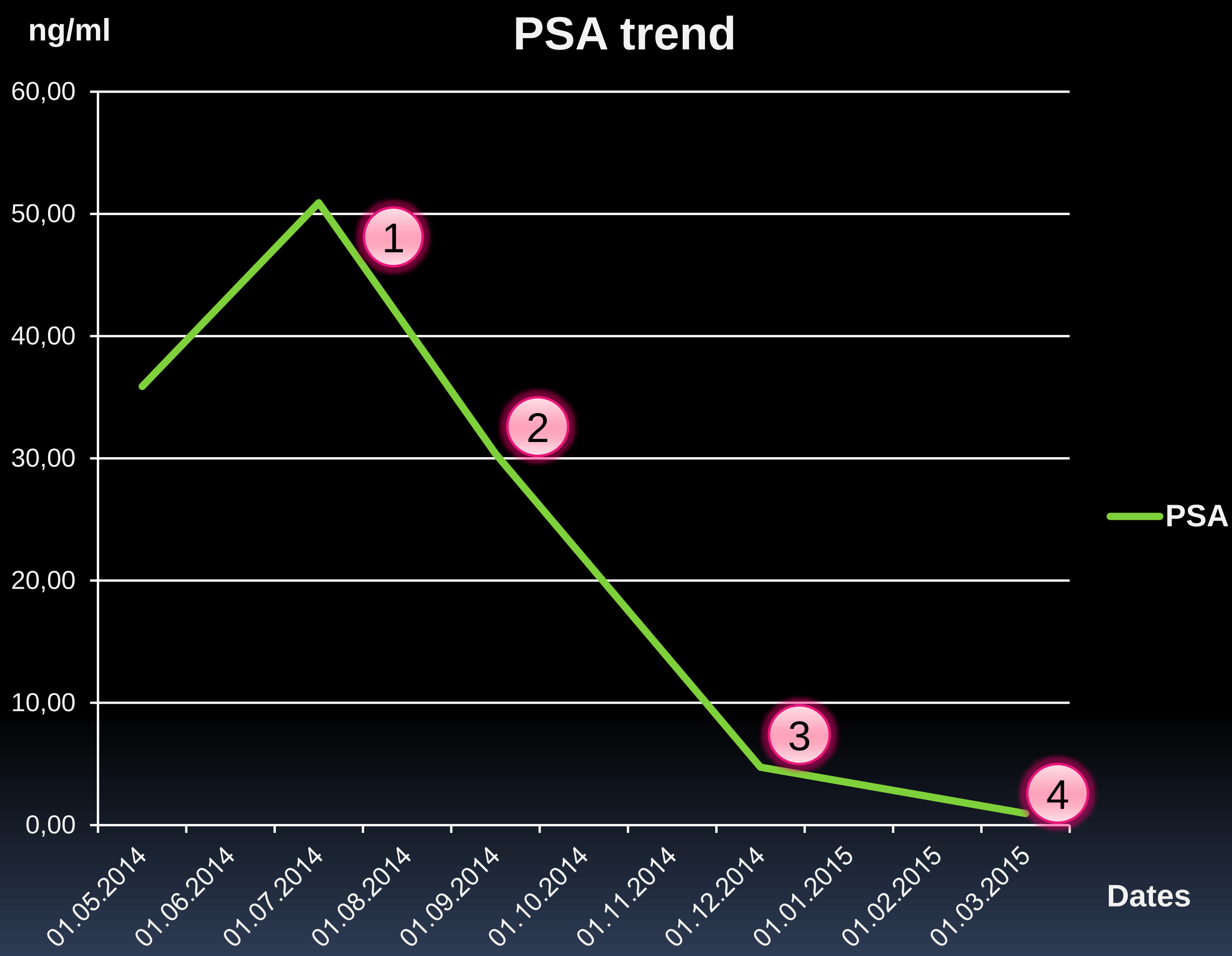
Pre-PRLT - 04 - 03.03.2015



PSA trends with RLT
Continuous drop of PSA after PRLT (biochemical response)

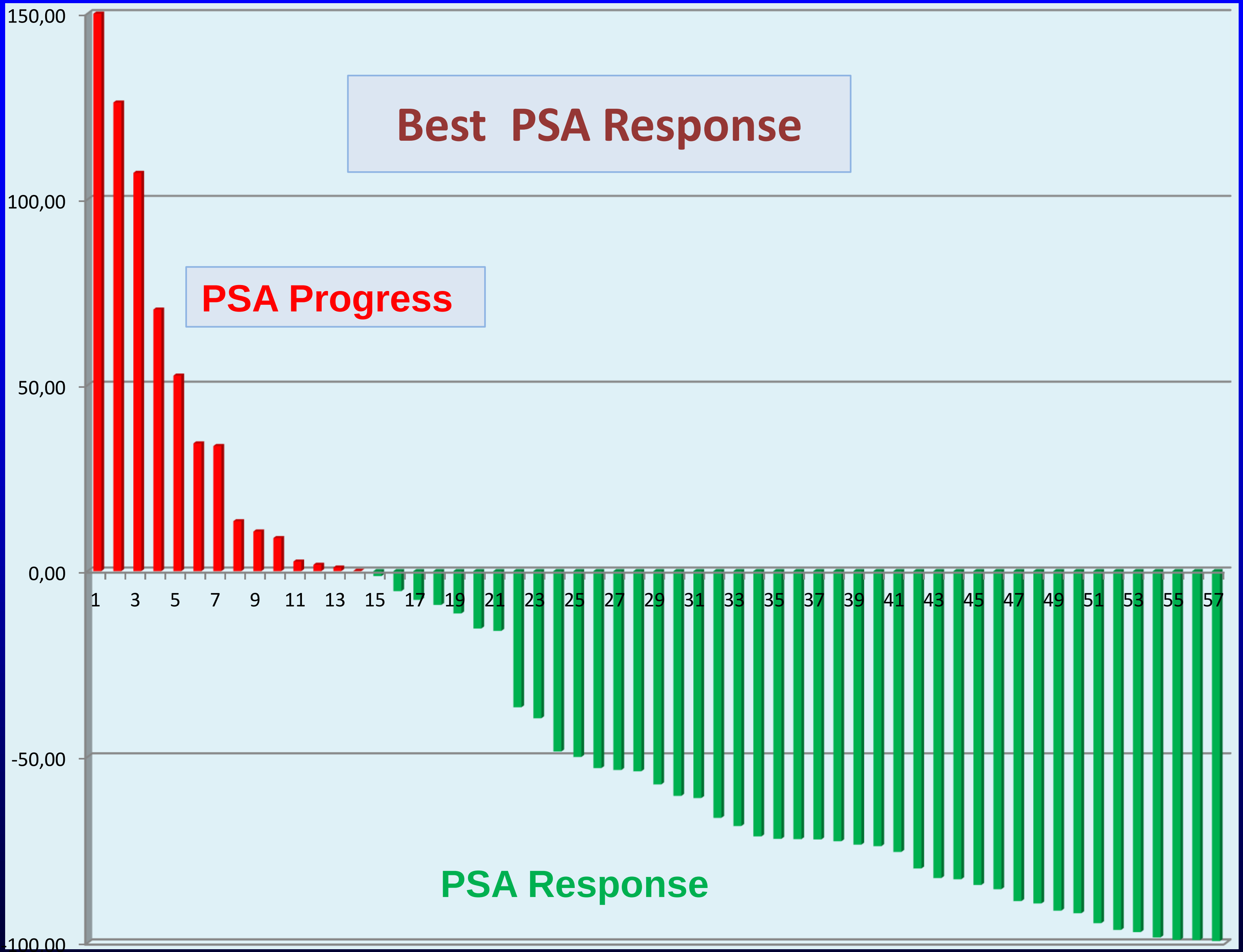
Date	PSA
30.05.2014	35.89
13.07.2014	50.91
21.09.2014	30.39
08.12.2014	4.73
01.03.2015	0.95

Date	PRLT No.
16.07.2014	1
23.09.2014	2
09.12.2014	3
04.03.2015	4



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

Best PSA response in 57 patients (represented as percentage change of pre-therapy value)



PRLT

Metastatic,
Moderately Differentiated Prostate Adenocarcinoma

Low PSA with extensive bone and lymph node metastases

Excellent Response to Therapy

Moderately differentiated prostate adenocarcinoma

with extensive lymph node and multiple bone metastases

Date of diagnosis: Dec-2010
Initial tumor classification cT2c cN0 cM0, Gleason 7b (4 + 3), G2b
iPSA value 11.4 ng / mL, prostate volume 52 ml

12/2010 - 02/2011	commencement of androgen blockade (Trenantone + Casodex)
02-04/2011	image-guided radiotherapy of prostate, GD 76 Gy (5 x 2 Gy/week) PSA after IGRT = 0.05 ng/ml
07/2014	Progressive Disease: multiple bone and lymph node metastases on Ga-68 PSMA PET/CT; PSA 10.8 ng/ml
Since 07/2014	GnRH therapy (3 months Eligard depot) and Bicalutamide 50 mg
07-11/2014	pain and consolidation irradiation C3 - T3 (GHD 35Gy 5 x 2.5 Gy/week) and left shoulder (GHD 36Gy, 5 x 3 Gy/week)

Secondary diagnoses

Arterial hypertension, 3-vessel coronary artery disease, obesity, hypercholesterolemia, right THR (12/2013), avascular necrosis right (MRI 01/2012), dorsiflexion right, DD Peroneusläsion; demyelinating axonal polyneuropathy of unknown origin, pathological fracture BWK 12 after fall (11/2011), central renal cyst right (Ø 3.4 x 3.2 cm), hypoacusis, osteoporosis, glaucoma

Peptide Receptor Radio-Ligand Therapy

Cycle	Date	Therapy agent	Activity (MBq)	Route
1	08-Oct-2014	Lu-177 PSMA	5400	IV
2	05-Jan-2015	Lu-177 PSMA	6000	IV
3	20-Mar-2015	Lu-177 PSMA	4900	IV
Cumulative administered activity: 16.3 GBq (441 mCi) of Lu-177				
IV: intravenous				

Current Tumor Status

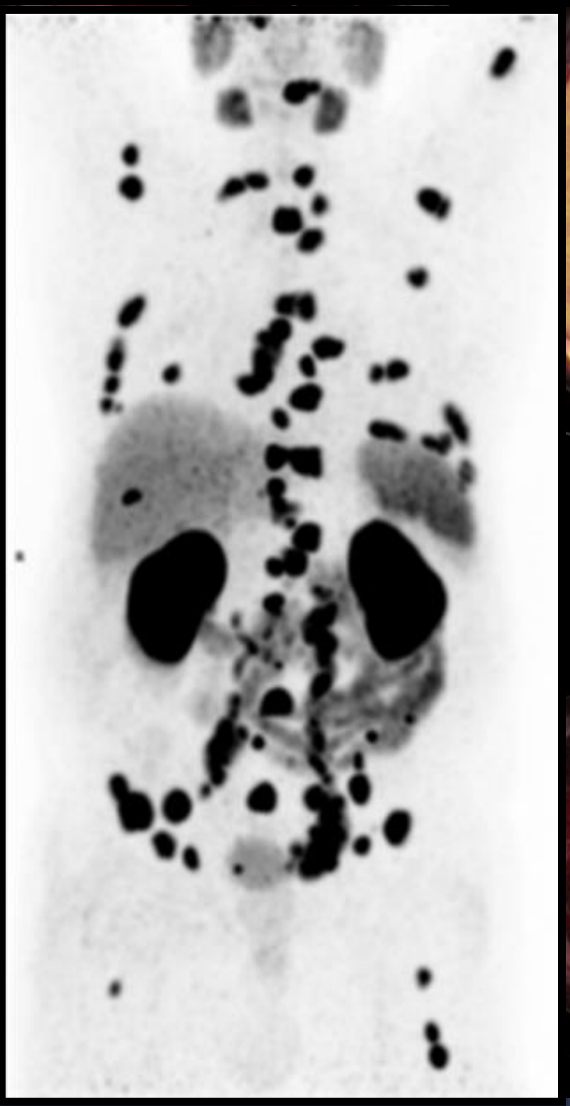
Partial Remission (RECIST and PERCIST)

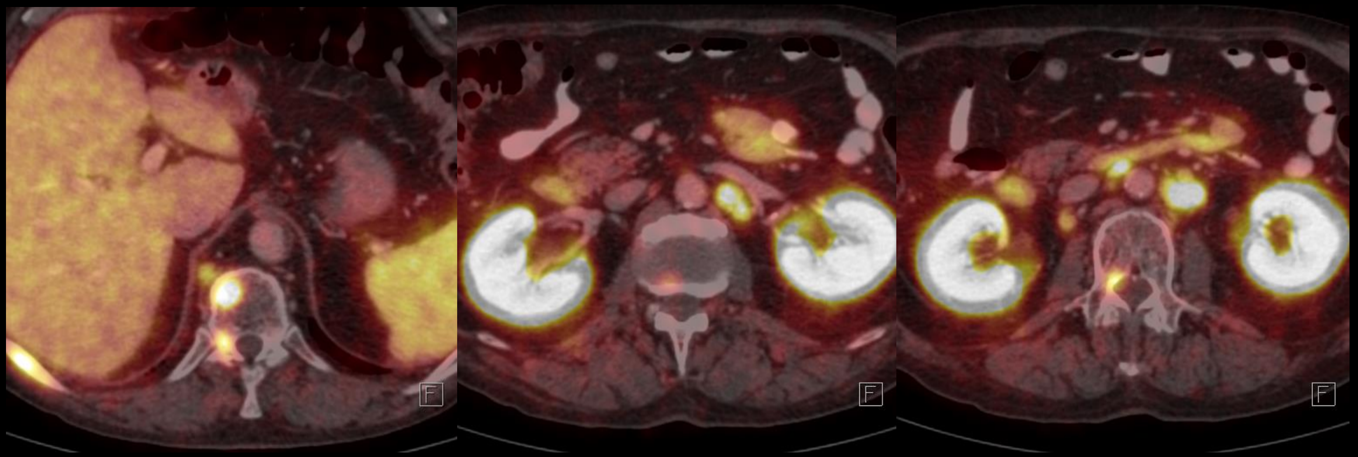
Near complete resolution of PSMA expression in known lesions

Treatment Plan

Continuation of therapy

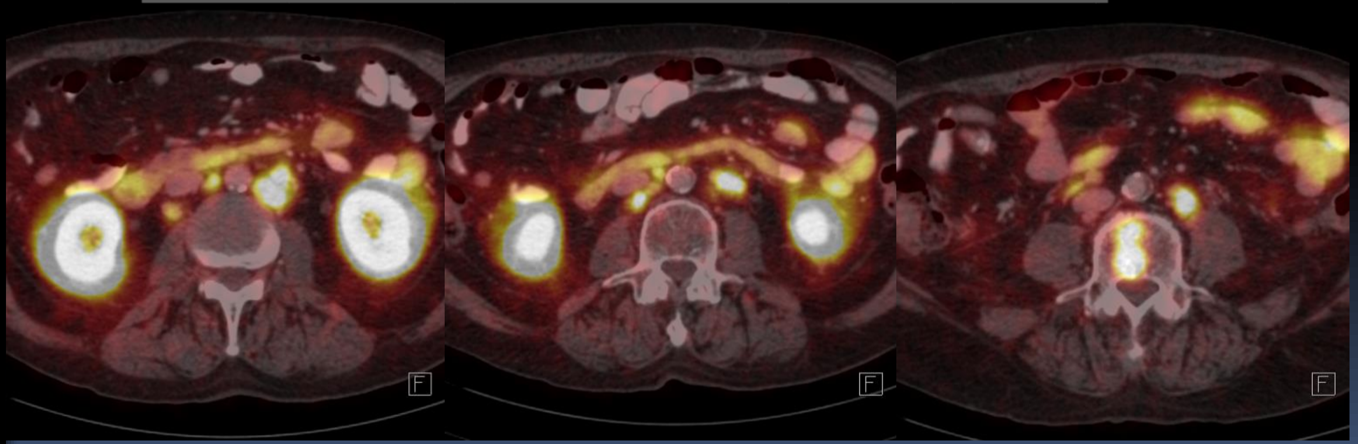
Ga-68 PSMA PET/CT
Jul-2014

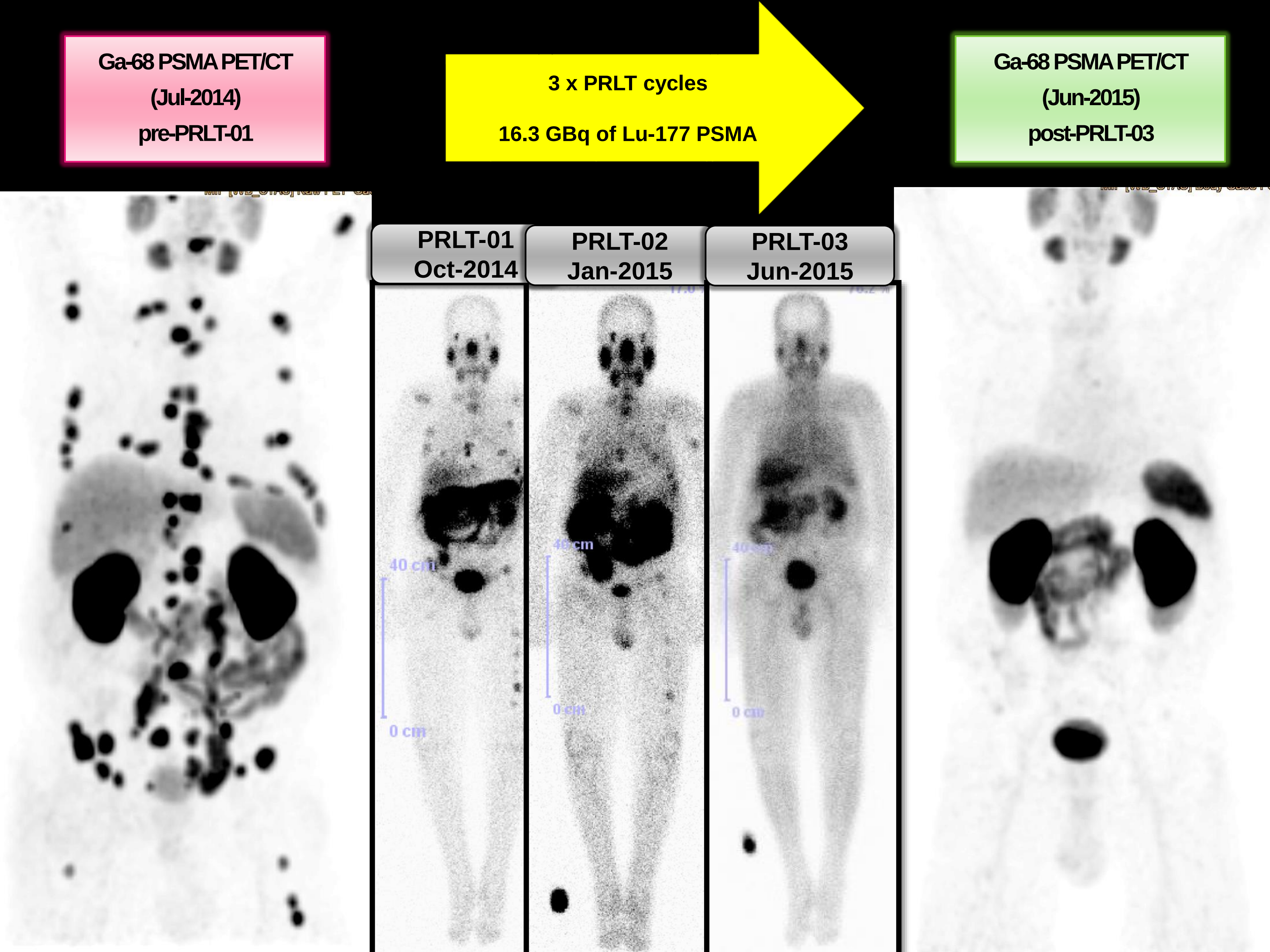




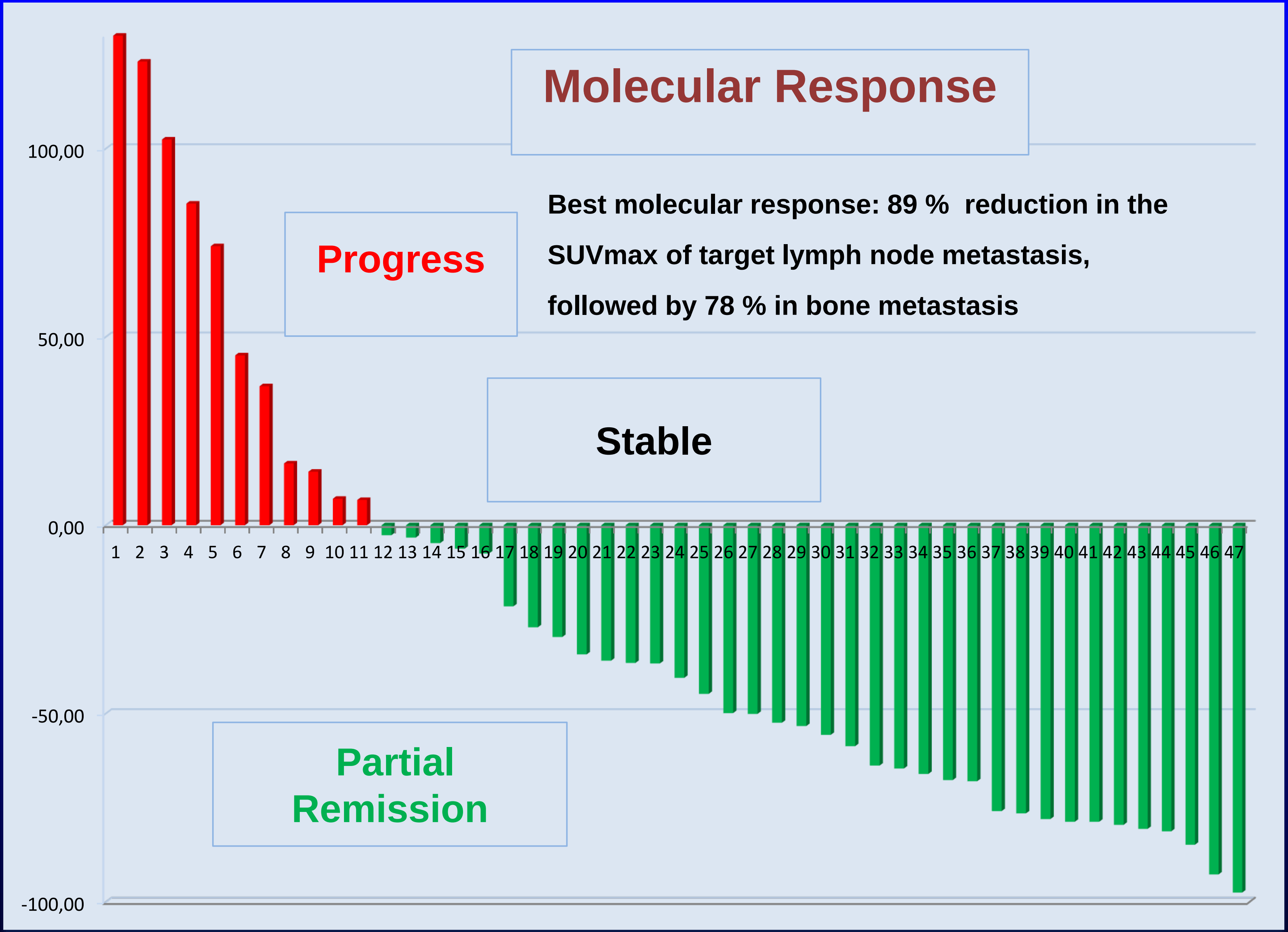
EXTENSIVE METASTASES

!!! PSA = 0.05 ng/ml !!!




Ga-68 PSMA PET/CT
(Jul-2014)
pre-PRLT-01
3 x PRLT cycles
16.3 GBq of Lu-177 PSMA
Ga-68 PSMA PET/CT
(Jun-2015)
post-PRLT-03
PRLT-01
Oct-2014
PRLT-02
Jan-2015
PRLT-03
Jun-2015
40 cm
0 cm
40 cm
0 cm
40 cm
0 cm

Best molecular response : percentage change in the SUV_{max} on ^{68}Ga-PSMA PET/CT



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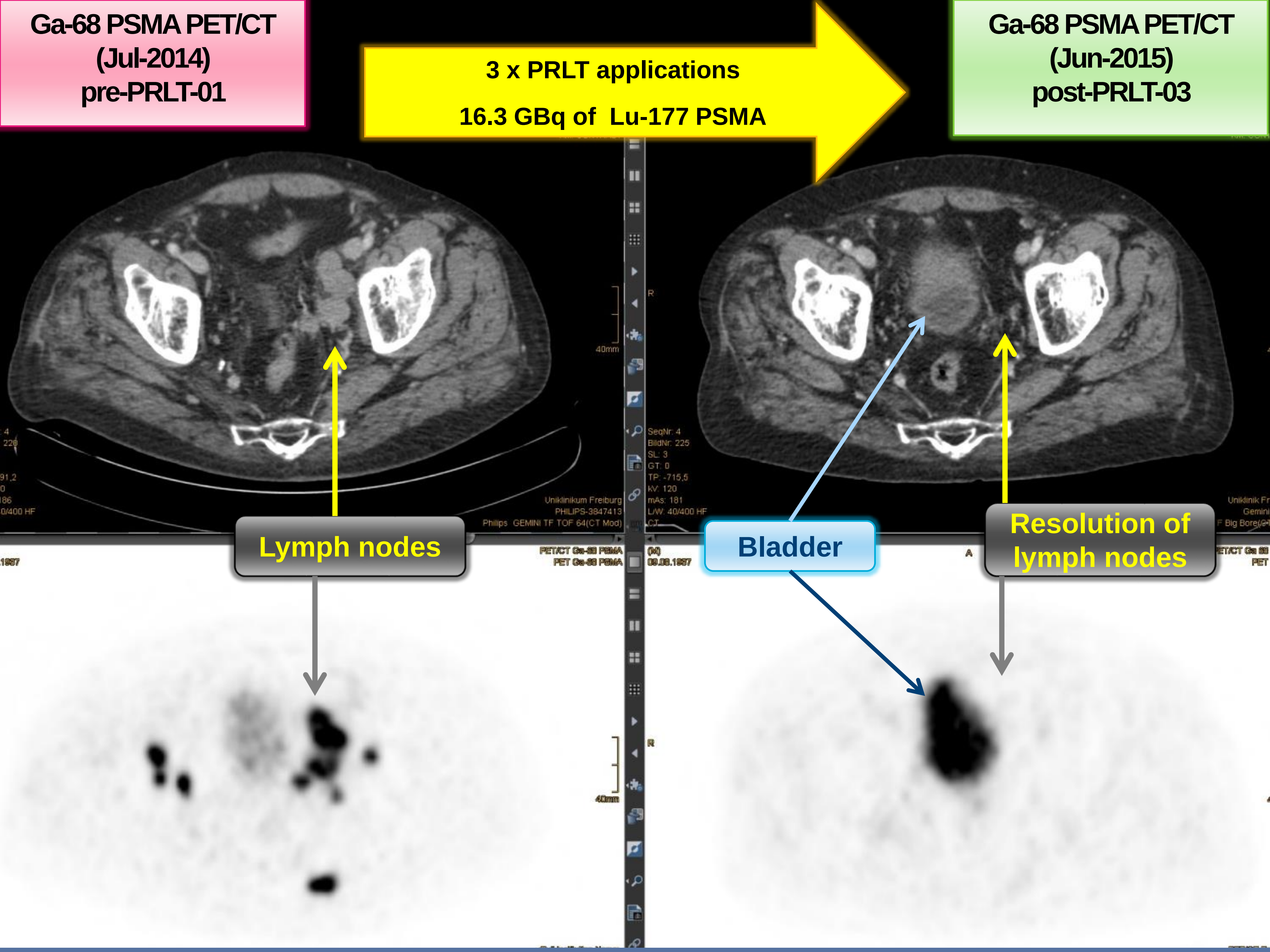
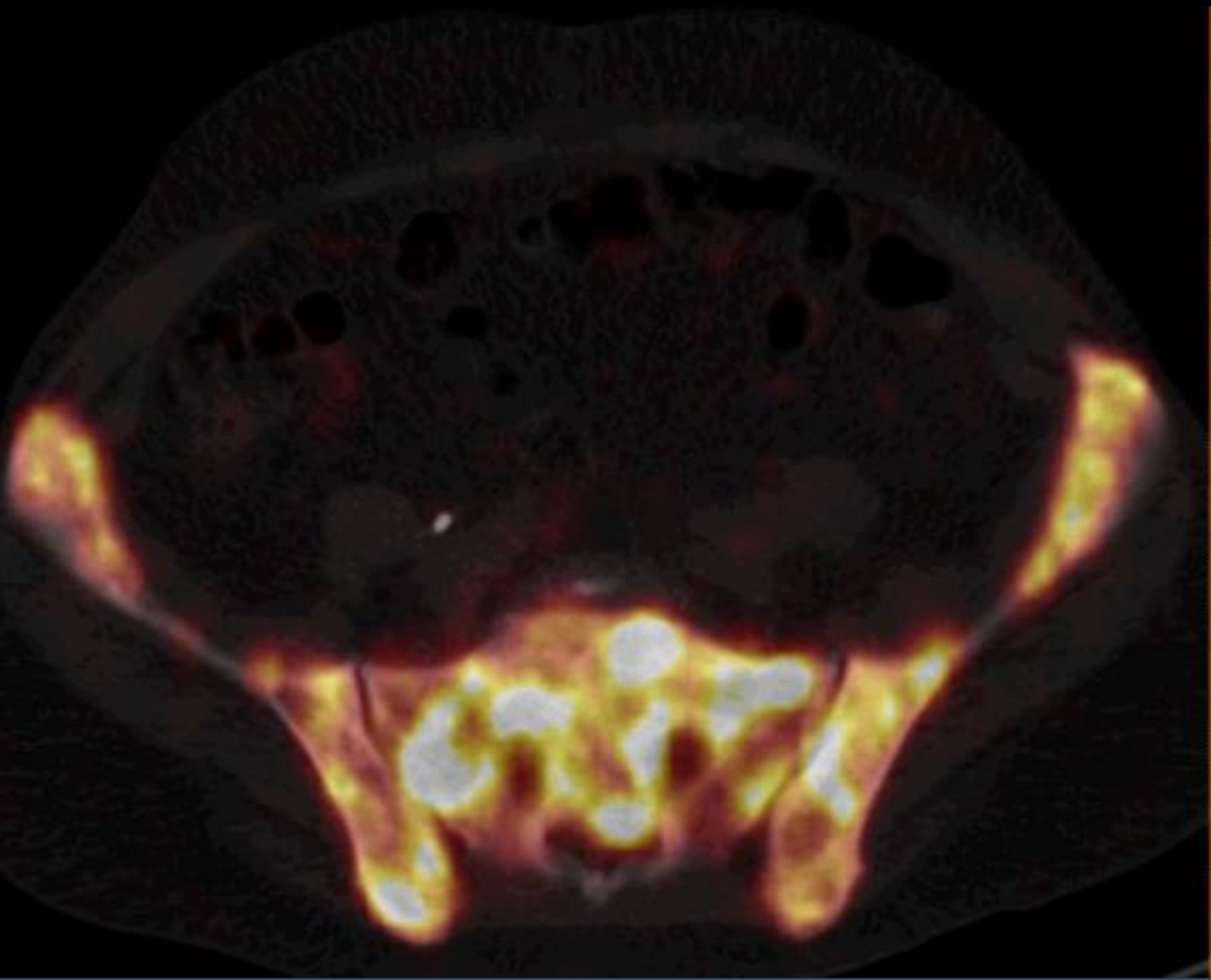

Ga-68 PSMA PET/CT
(Jul-2014)
pre-PRLT-01
3 x PRLT applications
16.3 GBq of Lu-177 PSMA
Ga-68 PSMA PET/CT
(Jun-2015)
post-PRLT-03
Lymph nodes
Bladder
Resolution of lymph nodes

Lu-177 PSMA PRLT

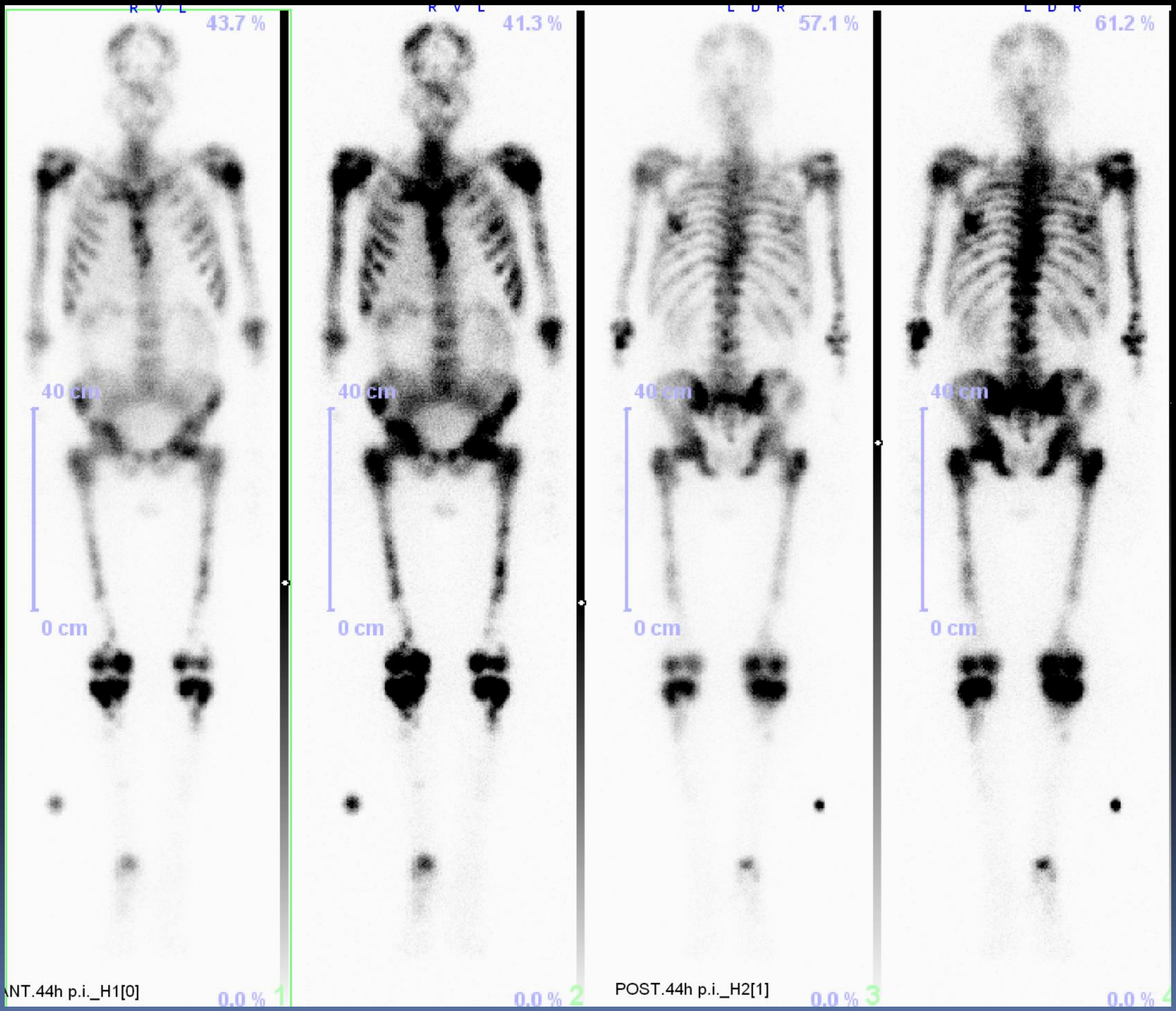
mCRPCa

Extensive skeletal metastases
No significant myelosuppression

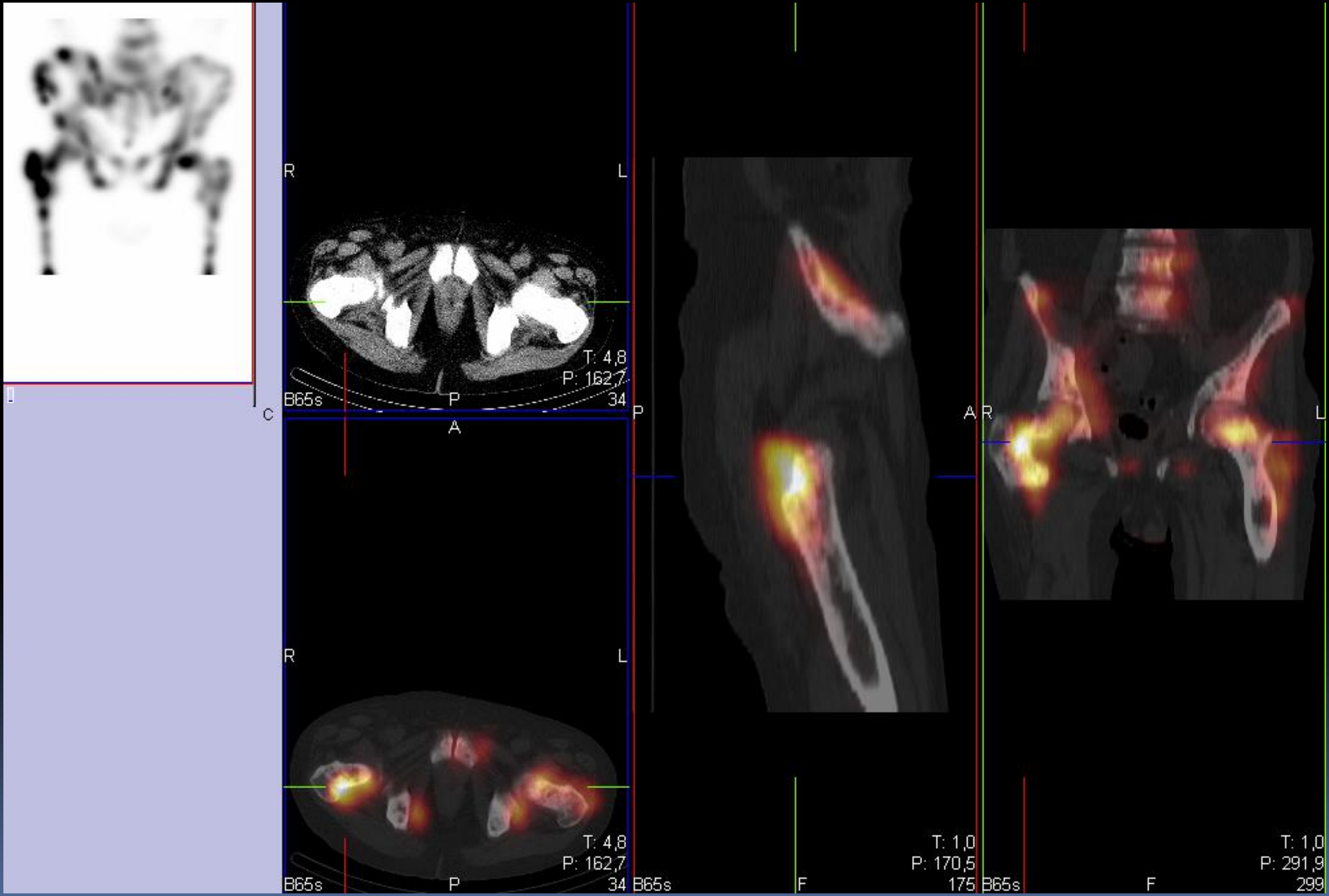
Ga68 PSMA PET/CT Pre-PRLT-01



PRLT-02 Lu-177 PSMA WB Planar images
44 h p.i.



PRLT-02 SPECT/CT
44 h p.i.



Blood Results

	Dat-Zeit:	09.04.2015 07:46		06.04.2015 17:54		11.01.2015 16:44	
	Fall-Nr:	7407630892		7407630892		7407619781	
	Auftrag-Nr:	3119514		3118563		3041665	
	Einsender:	D3NUK		D3NUK		D3NUK	
		Blutbild					
	Hämoglobin	6.60	--	7.10	-	7.50	-
	Hämatokrit	0.34	-	0.35	-	0.39	-
	MCHC	19.7		20.2		19.4	
	MCH	1.7		1.8		1.7	
	MCV	87		87		85	
RBC	Erythrozyten	3.86	-	4.02	-	4.53	
WBC	Leukozyten	7.3		5.9		7.5	
Platelets	Thrombozyten	214		219		197	
	Reti-abs			53.9		82.4	+
	Reti-rel			1.34		1.82	
	Reti-Häm-Äquiv			1.96		2.28	+
	Reti-Prod-Index			0.7		1.2	
	IRF			17.5	+	12.1	
	LFR			82.5	-	87.9	
	Baso-AD					0	
	Eo-AD					2	
	Neutro-AD					61	
	Lymph-AD					24	-
	Mono-AD					14	+
	Diff-manuell			s.u.			
	Eo-MD			1			
	Seg-MD			87	++		
	Lymph-MD			10	-		
	Mono-MD			2			
	Neutrophile abs			5.1		4.6	

No evidence of PRLT induced hematotoxicity

Nuklearmedizin 2015; 54: 197–203
http://dx.doi.org/10.3413/Nukmed-0751-15-06
received: June 16, 2015
accepted in revised form: August 18, 2015

Haematopoietic toxicity of radium-223 in patients with high skeletal tumour burden

M. Miederer[1]; C. Thomas[2,3]; J. Beck[4]; C. Hampel[2]; C. Krieger[1]; P. E. Baqué[1]; A. Helisch[1]; M. Schreckenberger[1]

[1]Department of Nuclear Medicine, University Medical Center Mainz, Germany; [2]Department of Urology, University Medical Center Mainz, Germany; [3]Department of Urology, University Medical Center Frankfurt, Germany; [4]Department of Internal Medicine III (Haematology, Oncology, Pneumology), University Medical Center Mainz, Germany

For ^{223}Ra treatment in patients with late stages and high tumour burden haematologic toxicity must be expected and close follow-up of blood counts is mandatory.

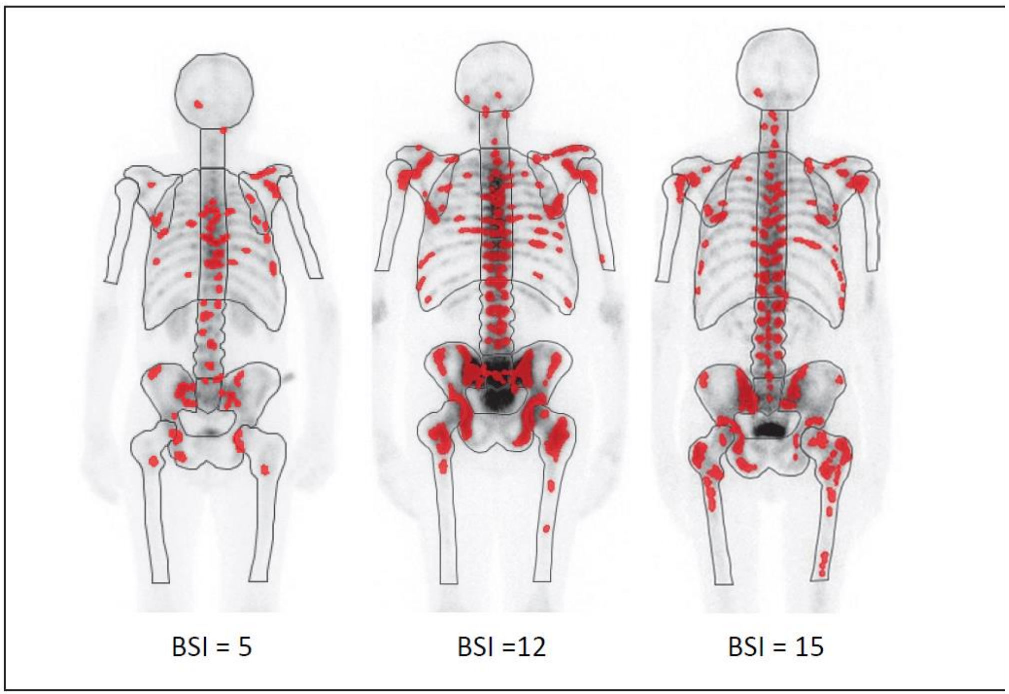
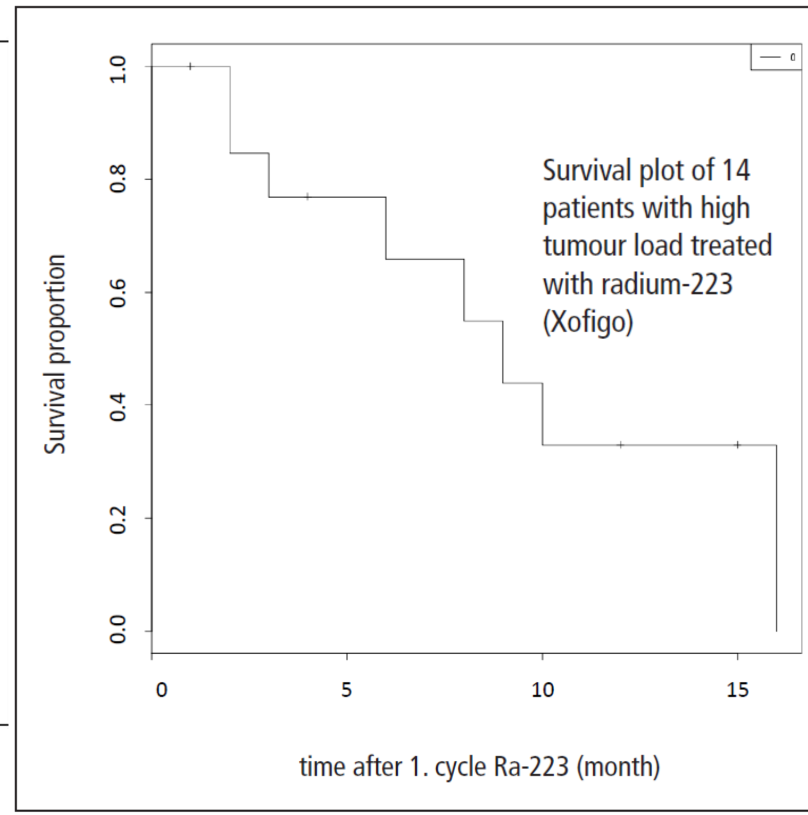


Fig. 1 Representative patients with high tumour load quantified by BSI (bone scan index)



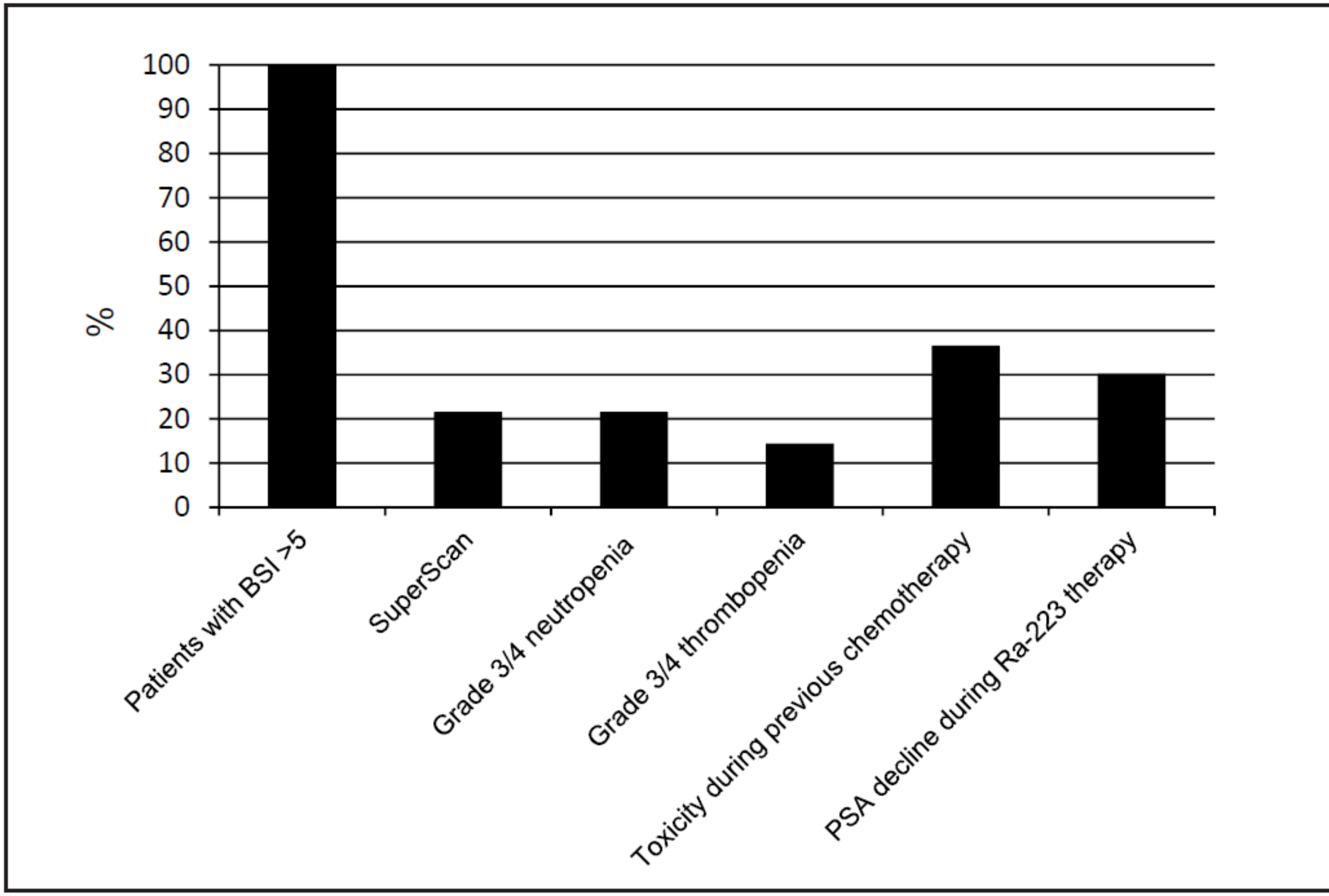
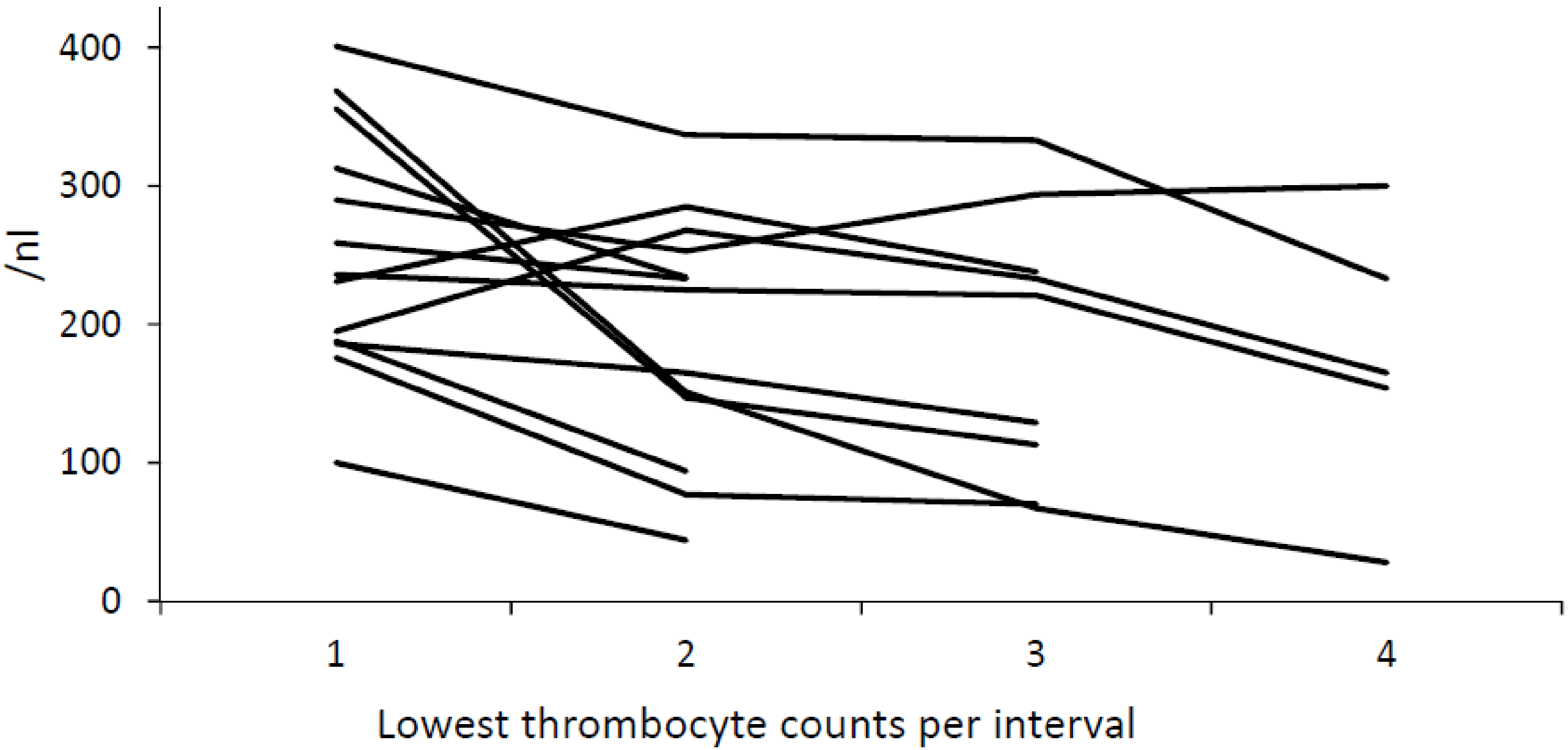
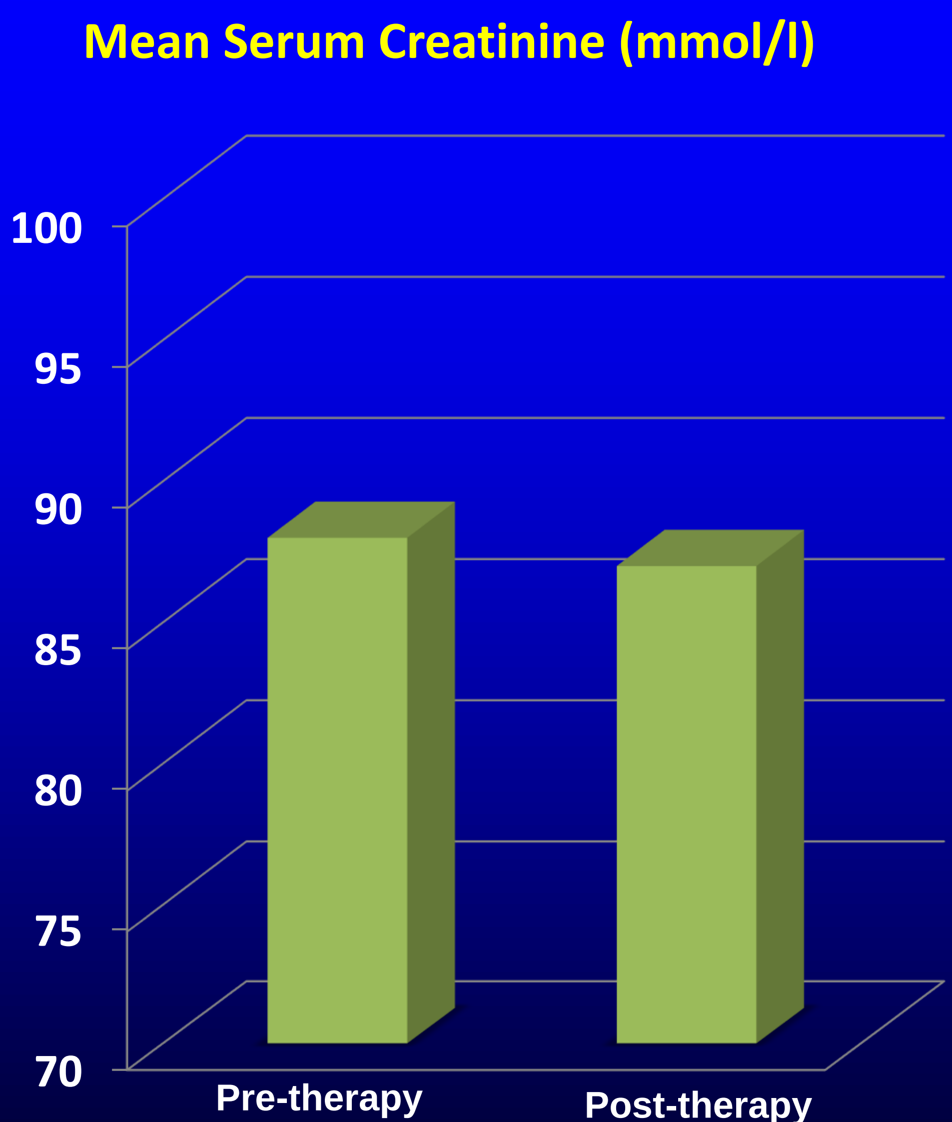


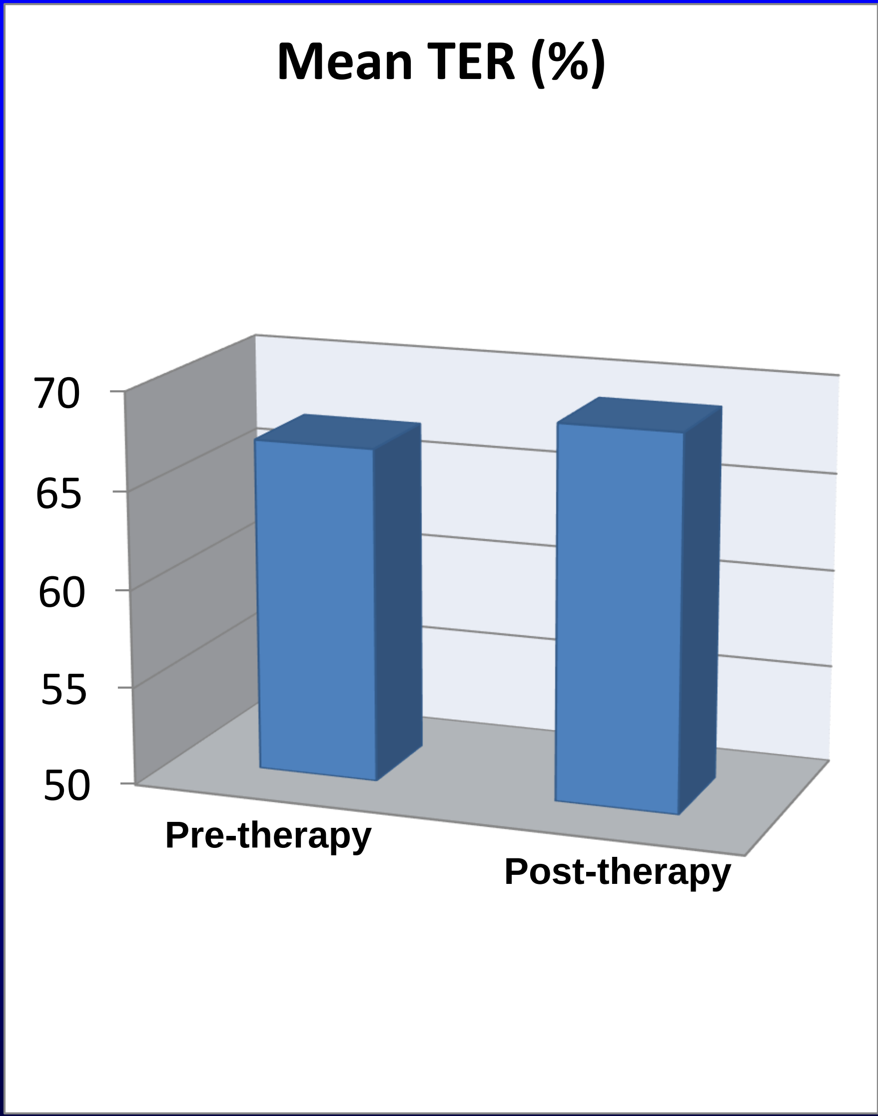
Fig. 5 Percentage of patients with certain imaging parameters, grade 3 or 4 toxicity, signs of previous toxicity and biochemical response during therapy

Fig. 6 Radium-223 therapy, development of blood cell counts (X-axis: **1**: baseline; **2**: 1–4 weeks after 1st cycle; **3**: 1–4 weeks after 2nd cycle; **4**: 1–16 weeks after 3rd cycle)
a) neutrophils; **b**) thrombocytes



Lu-177 PSMA - Effect on Renal Function





No renal toxicity ($p>0.05$)

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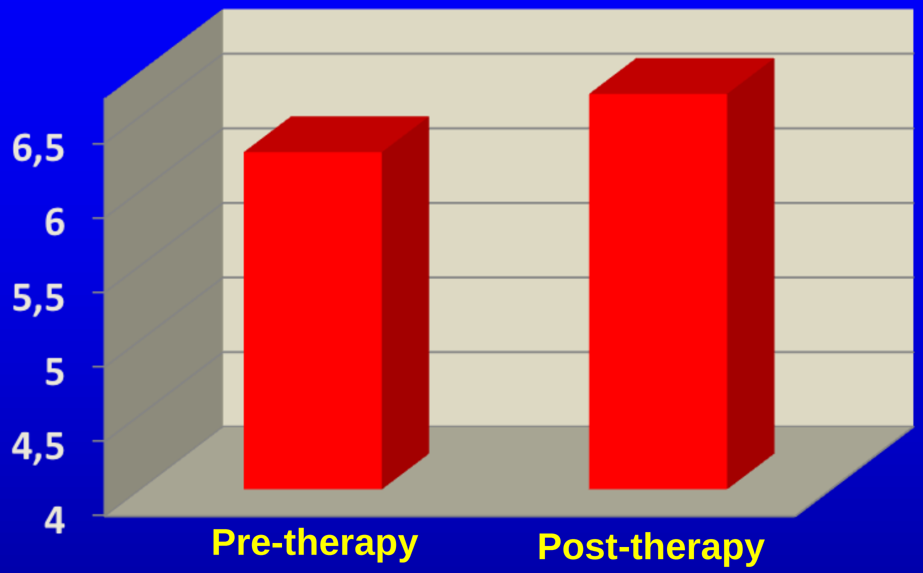
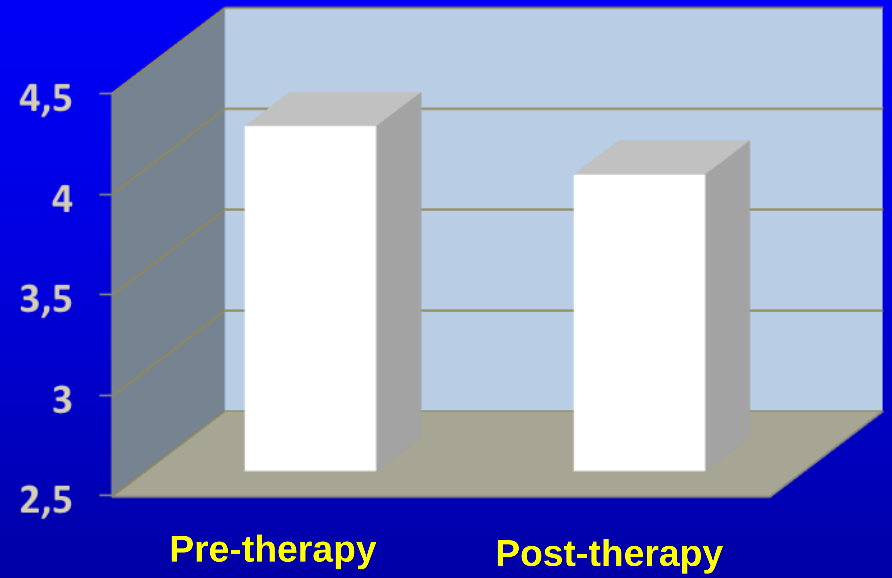
Lu-177 PSMA Effect on Hematological Function

Mean RBC Count

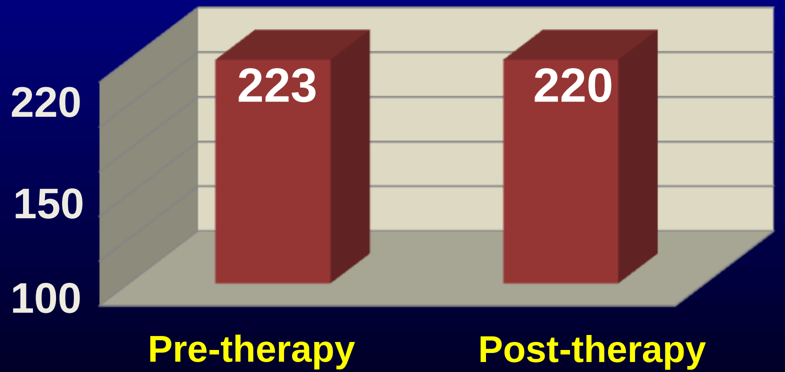


Mean WBC Count



No hematological toxicity ($p>0.05$)

Mean Platelet Count



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Title: **Lutetium-177 PSMA Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy**

Short-running title / foot line: ^{177}Lu-PSMA: Safety and Efficacy

Authors: Richard P. Baum[1*], Harshad R. Kulkarni[1*], Christiane Schuchardt[1], Aviral Singh[1], Martina Weineisen[2], Stefan Wiessalla[1], Margret Schottelius[2], Dirk Mueller[1], Ingo Klette[1], Hans-Jürgen Wester[2]

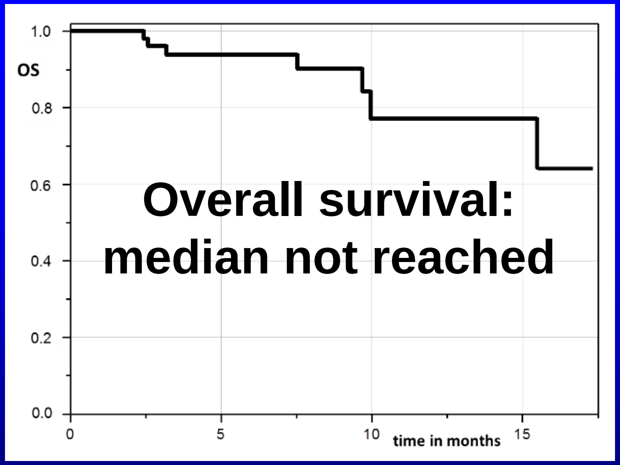
J Nucl Med – published ahead of print January 21, 2016

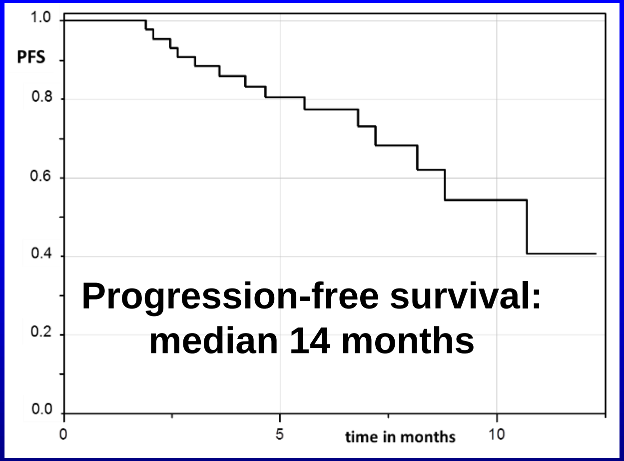
Chemotherapy/hormonal therapy survival benefit

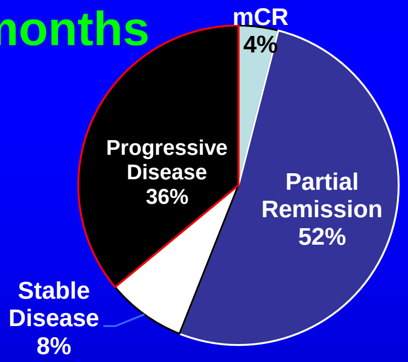
- Docetaxel: 2.5 Mo
- Cabazitaxel: 2.4 Mo
- Abiraterone: 3.9 Mo
- Enzalutamide: 4.8 Mo
- Radium 223: 3.6 Mo

Efficacy of PRLT (n=96 patients) with FU after 2-7 cycles)

- Number of therapy cycles of Lu-177 PSMA radioligand therapy (PRLT): 241
- Mean follow-up: 12 months (3 – 25)
- Mean administered radioactivity per cycle 5.8 GBq (range 2 – 9.7), number of cycles 2 - 7
- NO hematological, renal or salivary toxicity; improvement in QoL and pain score in all patients
- Response after 2 - 7 PRLT cycles: 3 mCR (molecular complete remission), 15 PR, 3 SD, 7 PD
- Dosimetry: Significantly higher tumor dose (14 – 36.2 mGy/MBq) than kidneys (0.2 – 2.4)
- Number of deaths: 7 (median OS not reached), median PFS : 14 months







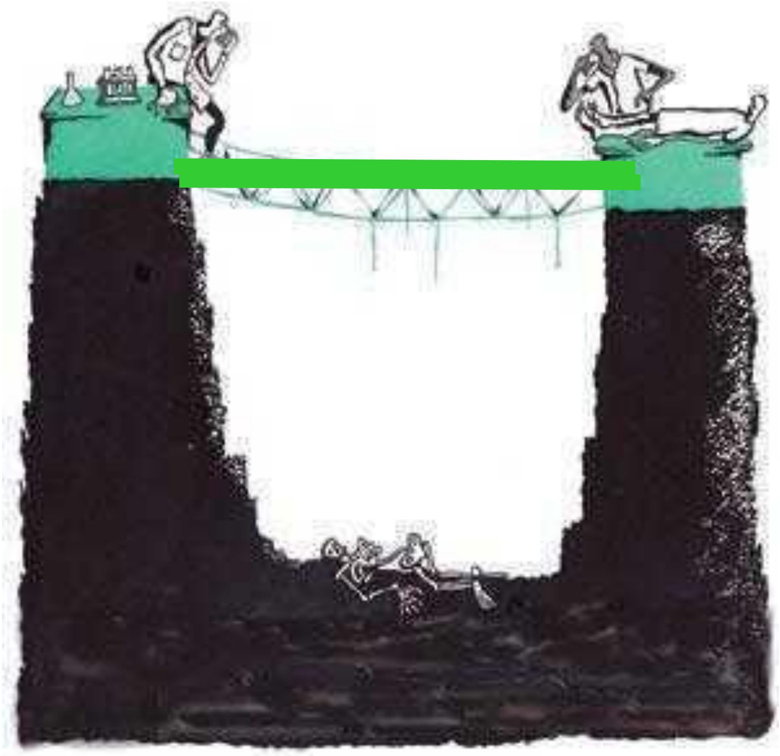
Remissions 56 %
Stable Disease 8 %
Responders 72 %
Non-responders 28 %

The next 10 years – what we need and where to go
A vision

- PET/CT: technical improvements (higher sensitivity, better resolution..)
- New isotopes for imaging (Sc-44, Cu-64)
- New isotopes for therapy (Re-188, Tb-161, Bi-213, Ac-225)
- New peptides (JR 11, CXCR4, and many more to come)
- New indications (lung, breast, colon…)
- Improved dosimetry
- Interface novel imaging/therapy and biomarker strategies
    - immunohistochemistry
    - quantitative mRNA analysis (RT-qPCR)
    - [liquid biopsy]

Translational Research: Crossing the Valley of Death

from CERN to bedside



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

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- Aviral Singh
- Christiane Schuchardt
- Ingo Klette
- Karin Niepsch

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WELCOME TO
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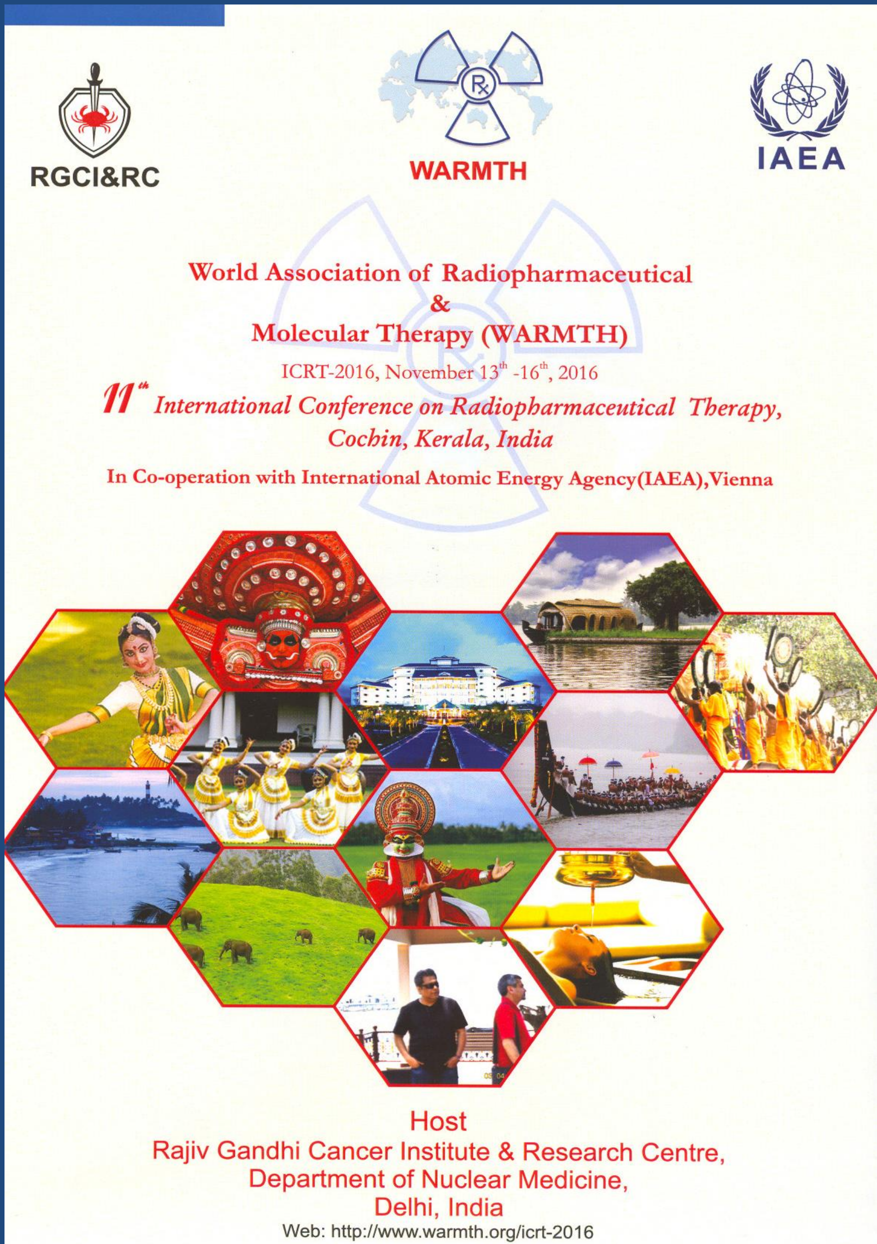
Invitation to WARMTH ICRT in Kerala, India, Nov. 13-16, 2016



Medical Radiology

Radiation Oncology

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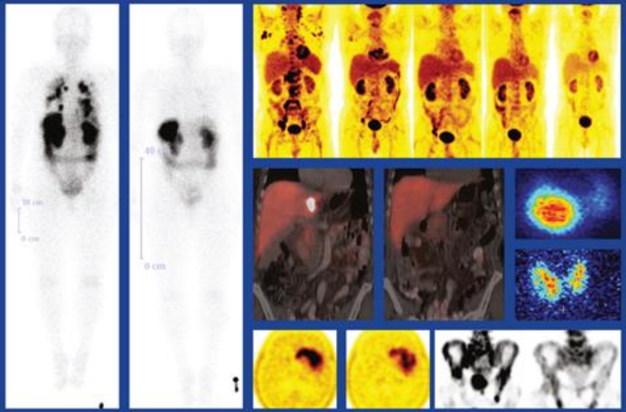

Springer

The First Car - 1886

2015 – F 015 – The self driving luxury

Year… - Concept

Start by doing what's necessary,
Then do what's possible,
Suddenly you are doing the impossible.

- St. Francis of Assisi

What we need is more people who specialize in the impossible

- Theodore Roethke

Thank you!