Peptide Receptor Radionuclide Therapy (PRRNT)
of Neuroendocrine Tumors:
The Bad Berka Approach

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prrtinfo.org

ENETS Center of Excellence Awarded March 2011
Zentralklinik Bad Berka

☐ **Internal Medicine, Endocrinology, Gastroenterology, OncologyThoracic, Abdomino/Visceral and General SurgeryInterventional RadiologyNuclear Medicine & Molecular Imaging (PET/CT Center including a specialized nuclear medicine ward, medical physics and GMP radiopharmaceutical facilities/radiopharmacy center „THERANOSTIK"**

☐ **>1200 NET patient visits/year**

PET/CT Center & NM Department

Nuclear Medicine Ward (22 beds for RN treatment)

Multidisciplinary Team at Zentralklinik Bad Berka

1 - DR. MERTEN HOMMAN, HEAD, ABDOMINAL/VISCERAL AND GENERAL SURGERY
2 - DR. ALEXANDER PETROVICH, CHIEF, INTERVENTIONAL RADIOLOGY
3 - DR. RICHARD P. BAUM, CHAIRMAN & CLINICAL DIRECTOR, CENTER FOR MOLECULAR IMAGING & THERAPY
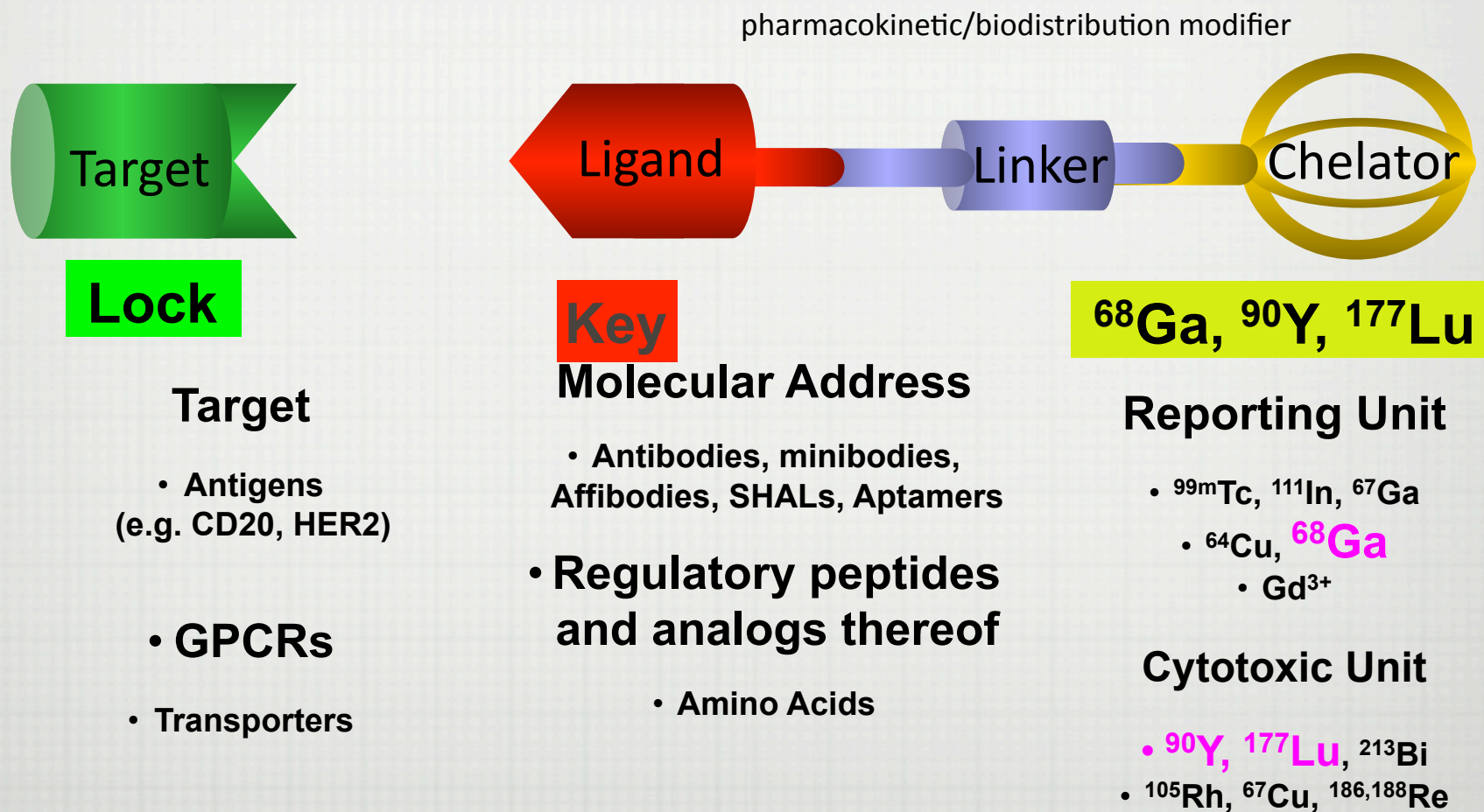4 - DR. DIETER HOERSCH, HEAD, INT. MEDICINE, ENDOCRINOLOGY, GASTROENTEROLOGY, ONCOLOGY

Targeted Molecular Imaging and Therapy
THERANOSTICS
The Key-Lock Principle

Schematic Representation of a Drug for Imaging and Targeted Therapy

pharmacokinetic/biodistribution modifier

Target   **Ligand**   **Linker**   **Chelator**

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

Target

- Antigens (e.g. CD20, HER2)

- GPCRs

- Transporters

Molecular Address

- Antibodies, minibodies, Affibodies, SHALs, Aptamers

- **Regulatory peptides and analogs thereof**

- 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)

PRRT – The Bad Berka Concept

- **Dedicated multidisciplinary team** of experienced NET specialists

- **Selection of patients** for PRRT based on Bad Berka Score (BBS) i.e. clinical aspects / molecular features: progressive tumors,uncontrolled symptoms despite maximum conventional therapy / high SMS-receptor expression (determined by receptor PET/CT)

- **Individualized therapy plan** for each patient – no formal clinical trial

- **Frequent cycles** (4-6, up to 9) applying low or intermediate doses of radioactivity: long term low dose, not short term high dose concept

- **Combined use** of Y-90 and Lu-177 (in sequence, in few concurrent)

- **Intra-arterial PRRT** (e.g. for inoperable large primary tumors)

- **Standardized evaluation** before therapy and systematic restaging

- All clinical data are entered into a **prospective clinical database**

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

- **SUV on receptor PET/CT (referrals: OctreoScan K.S.)**

- **Renal function (GFR and TER / creatinine & BUN)**

- **Hematological status (blood counts)**

- Liver involvement

- Extrahepatic tumor burden

- Ki-67 index / tumor grade

- FDG status (glucose hypermetabolism of tumors/mets)

- Tumor dynamics (doubling time, new lesions)

- Karnofsky performance index

- Weight loss

- Time since first diagnosis

- Functional activity of tumor

- Previous therapies

Treatment decisions based on Ga-68 SMS receptor PET/CT
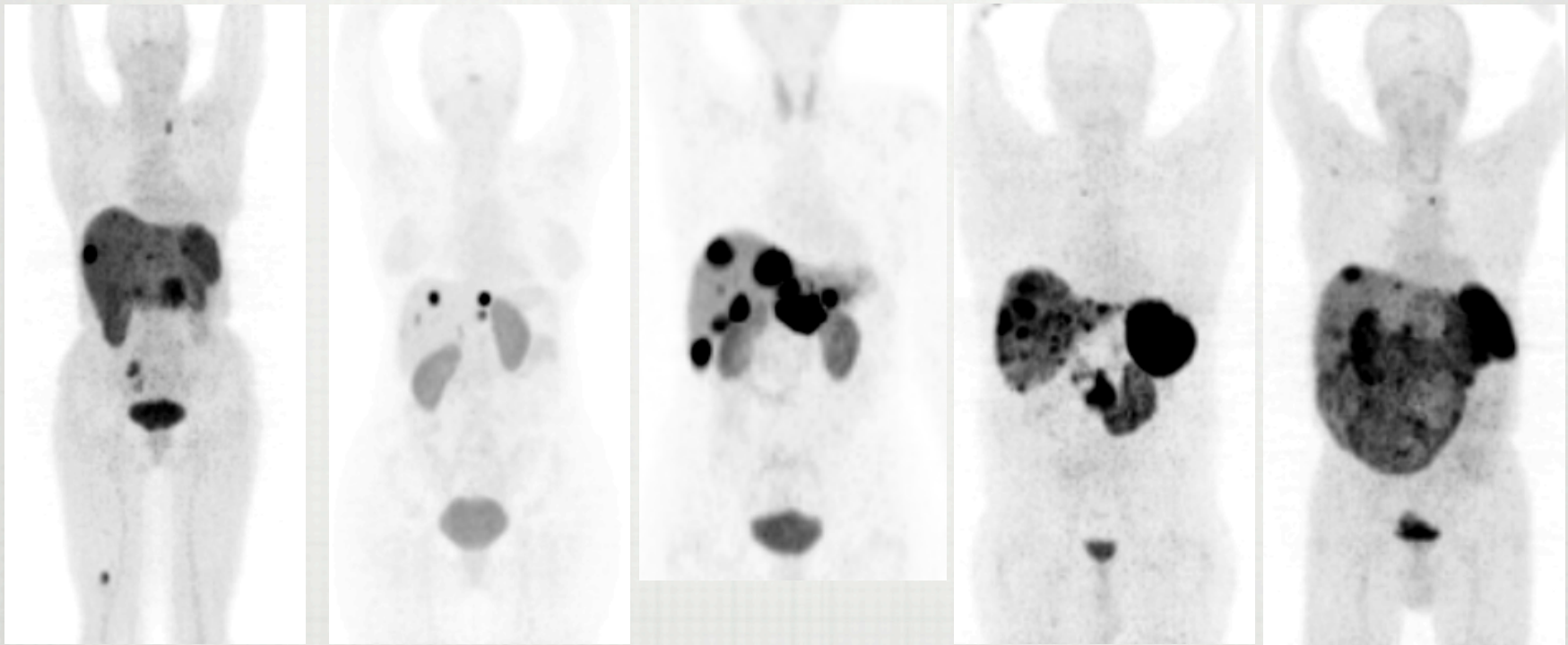
Molecular and Metabolic Imaging For Patient Selection

Flip-Flop phenomenon:

FDG positive, receptor negative neuroendocrine tumor

F-18 FDG
SUV_{max} 15.9

Ki-67 > 30%

Poorly differentiated neuroendocrine carcinoma

Patient not suitable for PRRT

Ga-68 DOTA-NOC
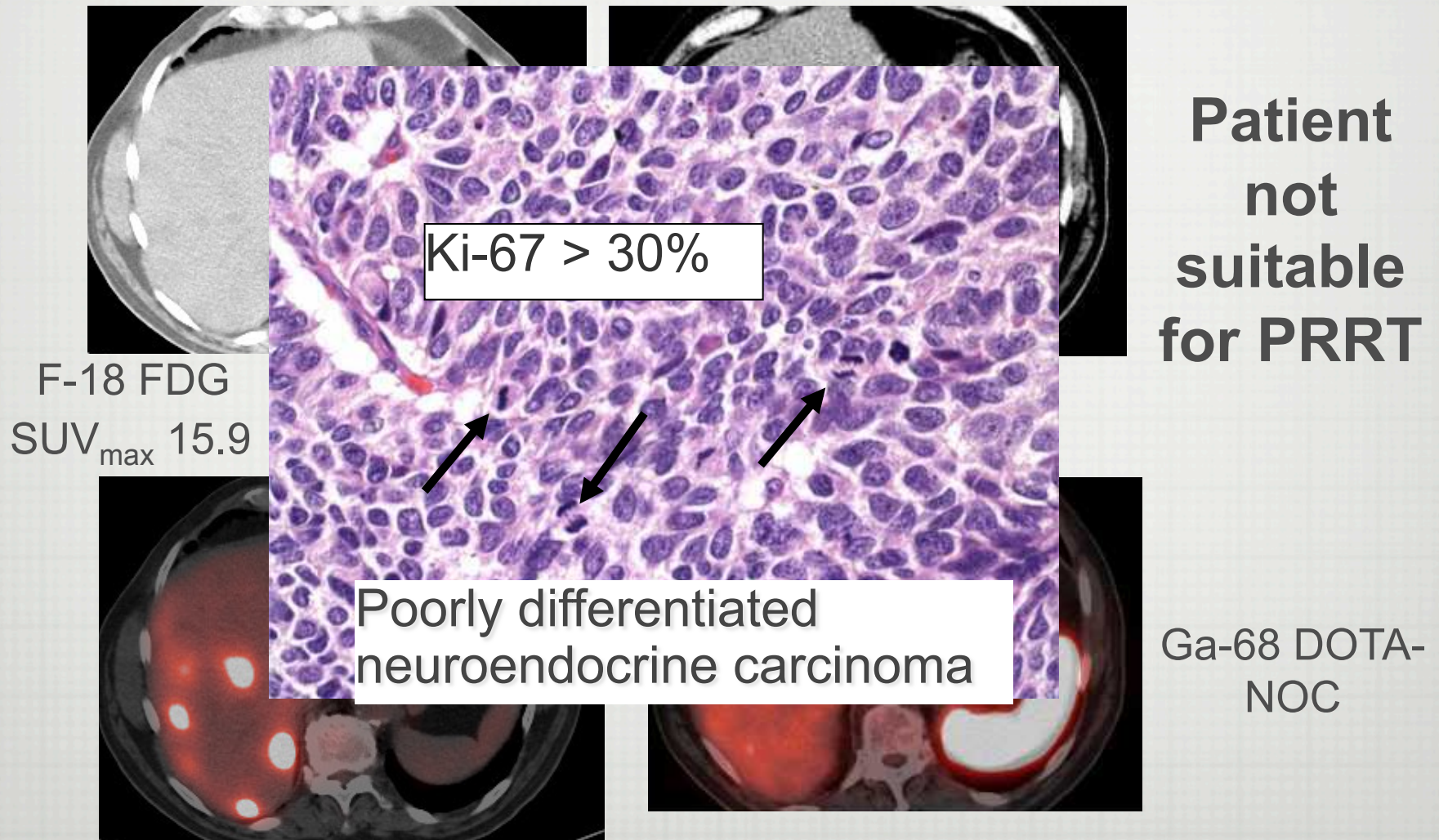
Selection of Patients
What must be known before PRRT to be effective?

- ☐ Histology / immunohistochemistry
  - grading, proliferation rate (Ki-67), CgA, Synaptophysin, hormone production (e.g. glucagon, gastrin, insulin)

- ☐ Receptor density – ideally determined by receptor PET/CT (or otherwise by OctreoScan)

- ☐ Kidney function – MAG3 (TER), Tc-99m DTPA

- ☐ Blood profile/chemistry – RBC, WBC, PLT, Crea, BUN

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

SUV in primary tumors and metastases (n = 1,400 studies)	Mean	Range
Primary tumors	19.2	8.2 – 109
Liver mets	20.9	3.3 - 105
Lymph node mets	9.5	4.2 – 152
Bone mets	13.6	3.0 – 20.4
Brain mets	12.3	4.6 – 17.2
Lung mets	2.3	1.6 – 5.6
Abdominal mets	14.8	5.8 – 34.1

Ga-68 DOTA-*NOC*

Retrocrural LN-Mets

SUV 152

Eur J Nucl Med Mol Imaging (2007)
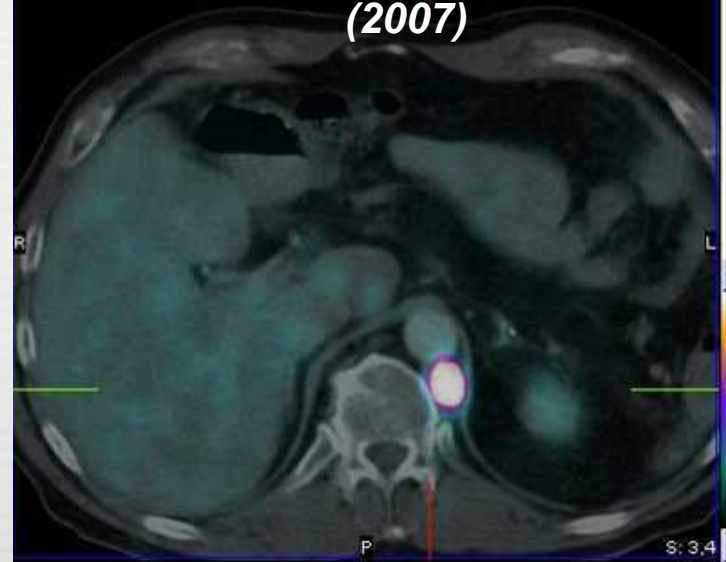
Pancreas NET, status post left resection of pancreas, extirpation of liver metastasis (S2), splenectomy. MRI revealed retrocrural lesion of 2.2 cm in Ø. LAR 20 mg 4 wks before..
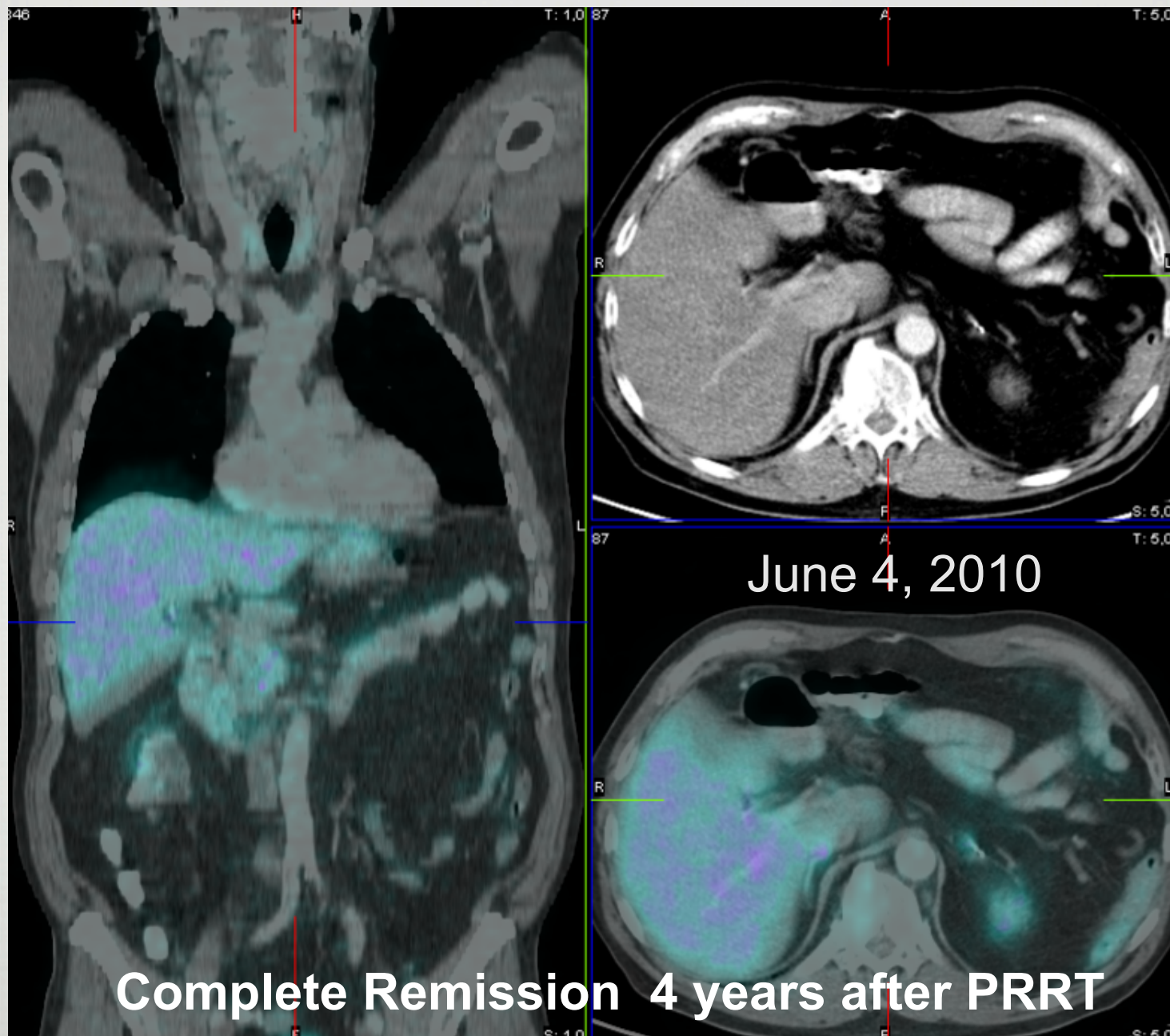
June 4, 2010

Complete Remission 4 years after PRRT

Patient Evaluation Before PRRT

☐ Receptor density determined by receptor PET/CT:

☐ Semiquantitative measurement by SUV (Standardized Uptake Values)

☐ How accurate are SUV?

mmunohistochemical Validation of Somatostatin-Receptor PET/CT As In-Vivo Method For Quantification Of Receptor Density On Neuroendocrine Tumors

Luisa Goetze[1], Vikas Prasad[2], Daniel Kaemmerer[3],
Merten Hommann[3], Lupp Amelie[1], Joerg Saenger[4],
Stefan Schulz[1] and Richard P. Baum[2]

[1] Department of Pharmacology, University Hospital, Jena, Germany
[2] Dept. of Nuclear Medicine/PET Centre, Zentralklinik Bad Berka, Germany
[3] Department of General and Visceral Surgery, Zentralklinik Bad Berka, Germany
[4] Department of Pathology, Zentralklinik Bad Berka, Germany

EANM 2010

Method

Ileum NET

IHC Scoring
for SSTR1-5

Ga-68 DOTA-SMS PET/ CT in 34 histologically documented GEP NET patients	44 surgical specimens generated	Lesions (n=14) > 1.5 cm on PET/CT were selected to avoid partial volume effect on the semi-quantitative parameters
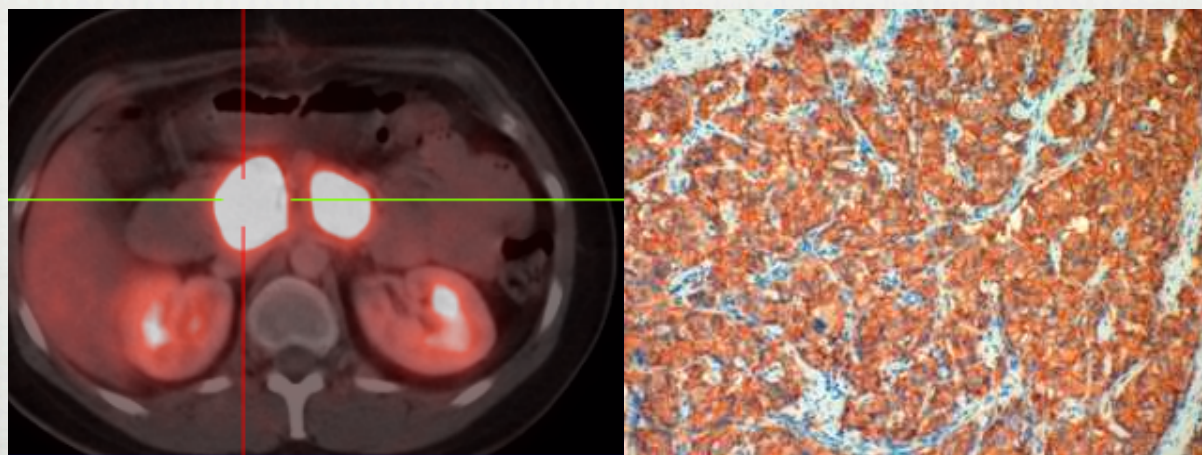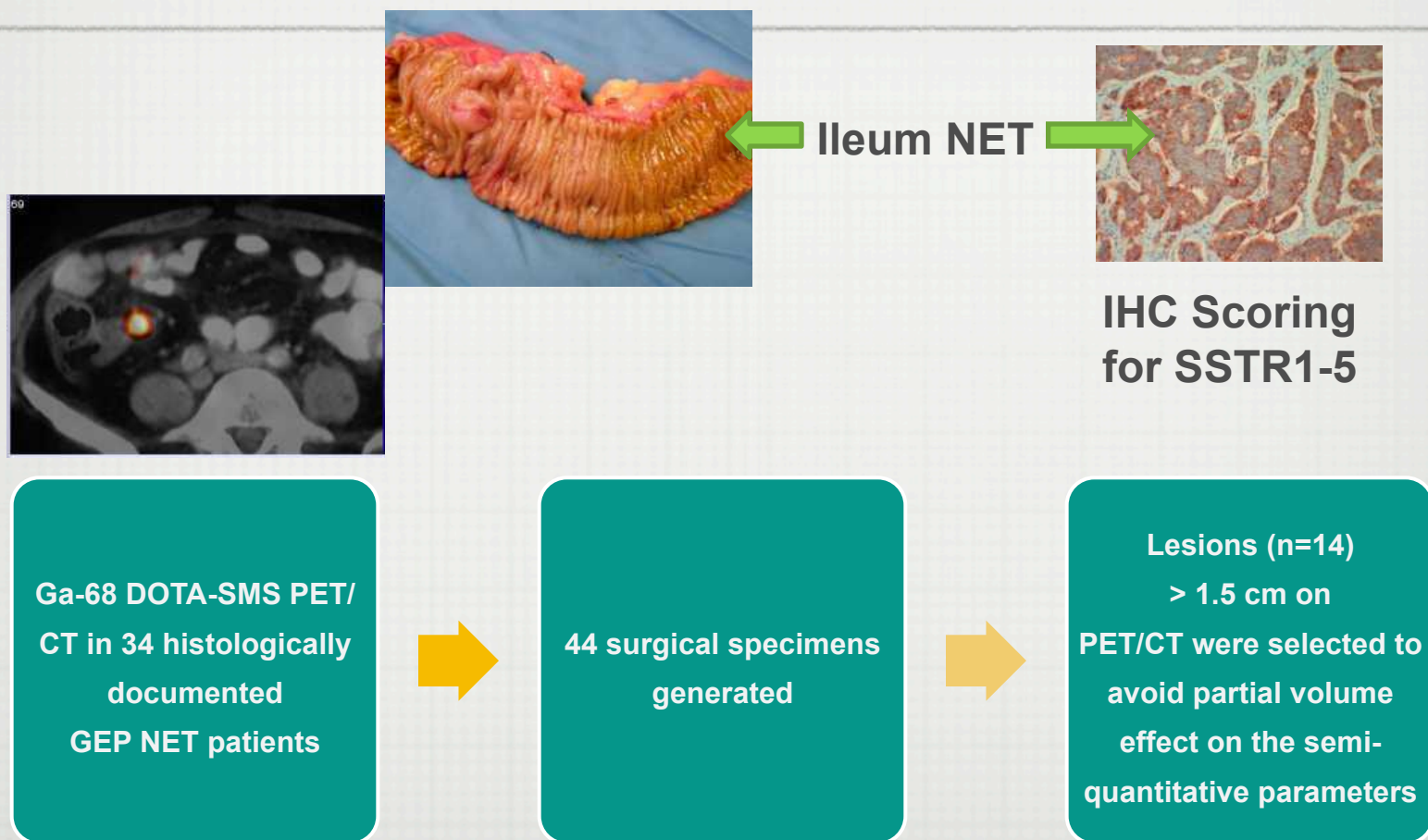
Receptor PET/CT imaging using Ga-68 DOTANOC results in accurate estimation of somatostatin receptor density in vivo.

SSTR1

p<0.05

| IRS Score for SSTR 2A proportional to SUVmax and SUVmean | IRS Score for SSTR 5 proportional to SUVmax | SSTR3 | SSTR4 |

p>0.05

No significant correlation between the IRS score for SSTR1, SSTR3 and SSTR4 with the semiquantitative parameters

What must be known before PRRT to avoid possible toxicity?

☐ Histology / immunohistochemistry
  - grading, proliferation rate (Ki-67), CgA, Synaptophysin,
    hormone production (e.g. glucagon, gastrin, insulin)

☐ Receptor density – ideally determined by
  receptor PET/CT (SUV) or scintigraphy

☐ ***Kidney function – MAG3 (TER), Tc-99m DTPA***

☐ ***Blood profile/chemistry – RBC, WBC, PLT, Crea, BUN***

PRRT is part of the ENETS Consensus GL!

☐ **Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumours**

> **Neuroendocrinology 2006; 84: 155-215**

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

> **Neuroendocrinology 2008; 87 (1): 8-39**

www.neuroendocrine.net

Radiopeptide Therapy Cycles
Zentralklinik Bad Berka 1999 - 2010
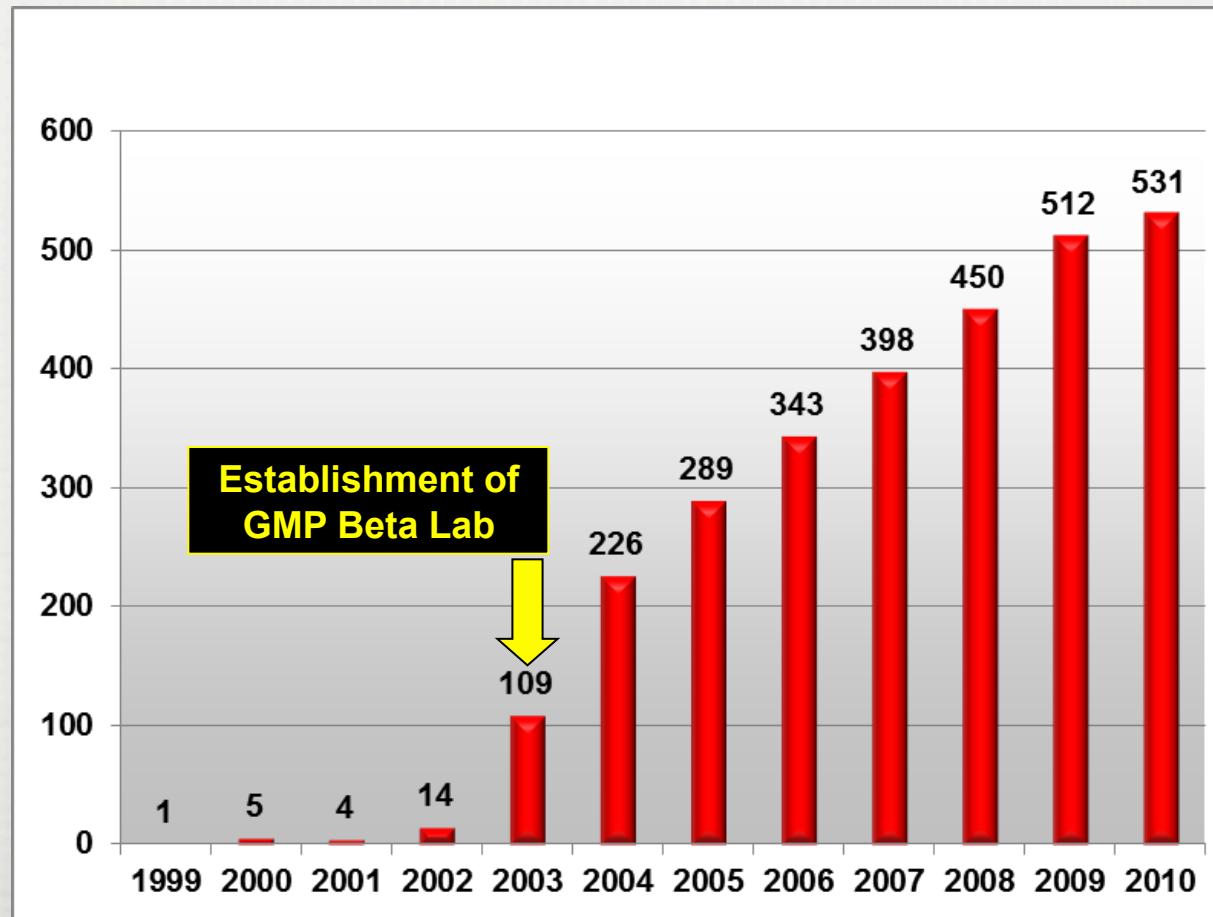
Radiopeptide therapy (ZKL Bad Berka)

Patients treated   n = 883

Therapy cycles   n = 2829

Lu-177 n = 1511

Y-90 n = 1318

Age: 4 – 84 years

Median: 59 years

As of 31. December 2010
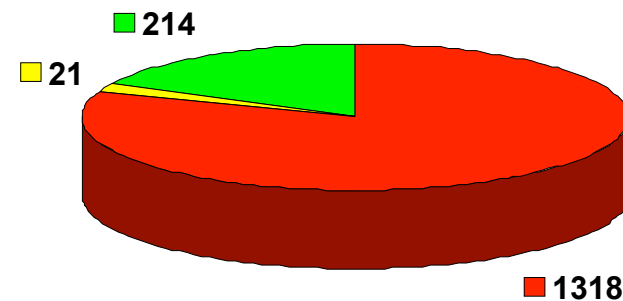
Y-90 DOTA-TATE — 1318
Y-90 DOTA-NOC — 21
Y-90 DOTA-TOC — 214
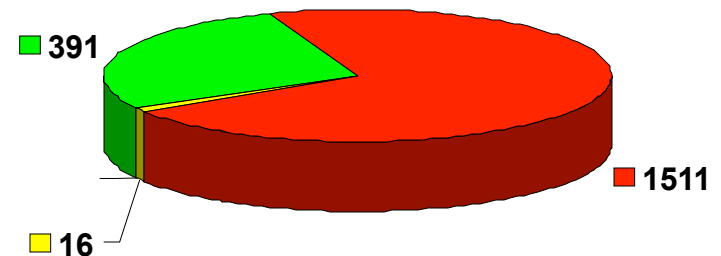
Lu-177 DOTA-TATE — 1511
Lu-177 DOTA-NOC — 16
Lu-177 DOTA-TOC — 391

Our youngest patient treated by PRRT (metastatic hepatoblastoma)

PRRNT – Worldwide Request 2008
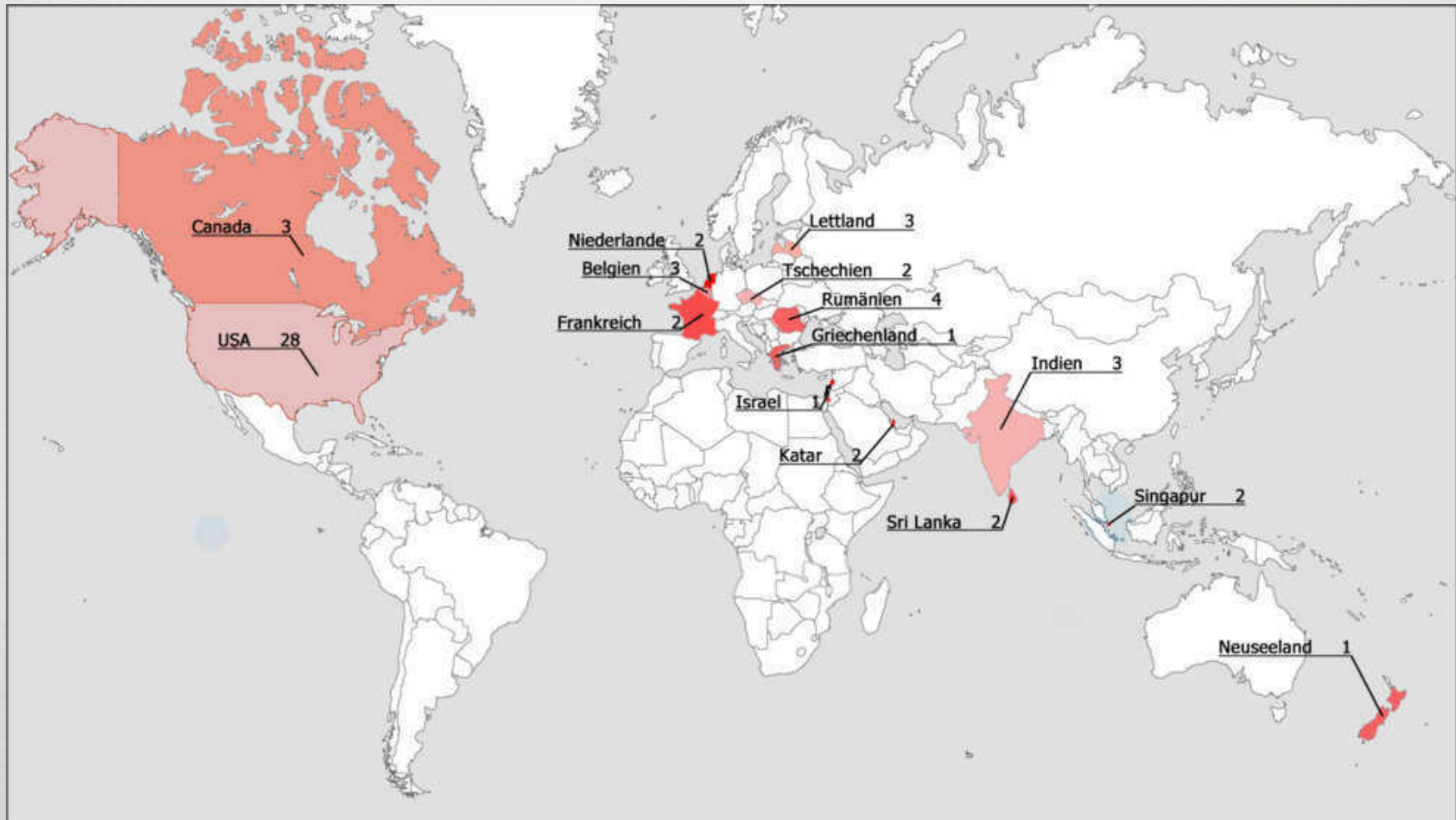
Physical Properties of Radionuclides Used for PRRT

Radionuclide	$t_{1/2}$ (d)	energy (keV)	path length (mm)	gamma (keV)
^{177}Lutetium	6.7	133	2	113 (6.6%) 208 (11%)
^{90}Yttrium	2.7	935	12	-

Bad Berka Procedure for PRRT

Studies before therapy

Renal scintigraphy [^{99m}Tc- MAG$_3$]

GFR measurement [^{99}Tc- DTPA]

Receptor PET/CT* [^{68}Ga-DOTA-NOC]

^{90}Y / ^{177}Lu-DOTA-TATE Peptide Receptor Radiotherapy

Infusion of aminoacid solution (- 0.5 until 4 hrs) plus Gelofusine

Infusion (15 min.) of ^{90}Y / ^{177}Lu- DOTA-TATE

- 2 days   0   1   2   3 days

Studies under /after therapy, dosimetry

^{177}Lu- DOTA-TATE WB scan [planar scans for dosimetry]

^{177}Lu- DOTA-TATE- SPECT of the tumor region
Blood sampling

Urine sampling

* Since July 2004. Previously, Tc-99m EDDA Hynic TOC (planar & SPECT) was performed.
In selected patients, also F-18 FDG and / or F-18 fluoride PET/CT is performed as well as MRI of the liver / bones
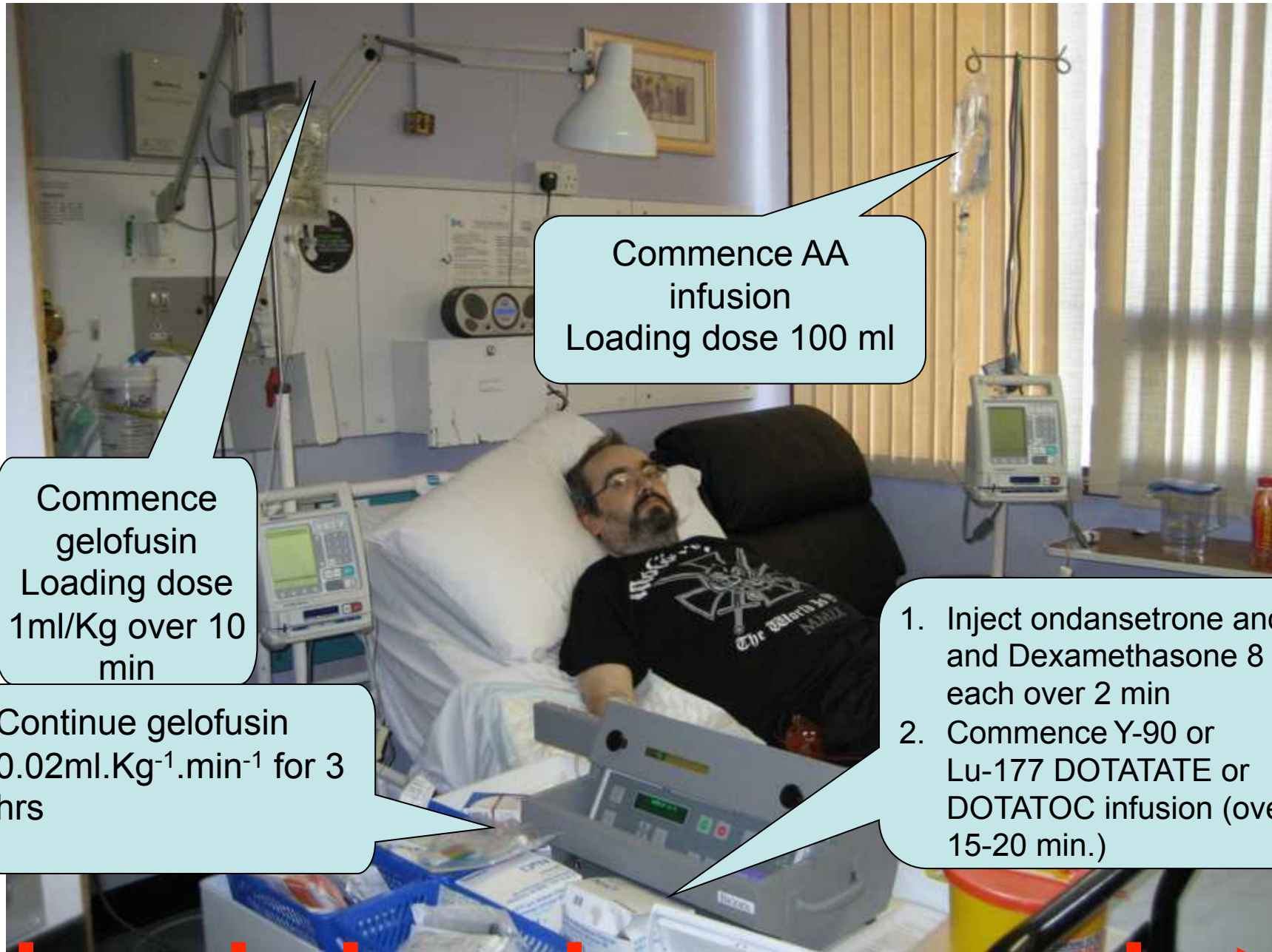
Lutetium-177 DOTATATE PHARMACOKINETICS

| 30m | 1h | 2h | 4h | 24h | 48h | 5d |
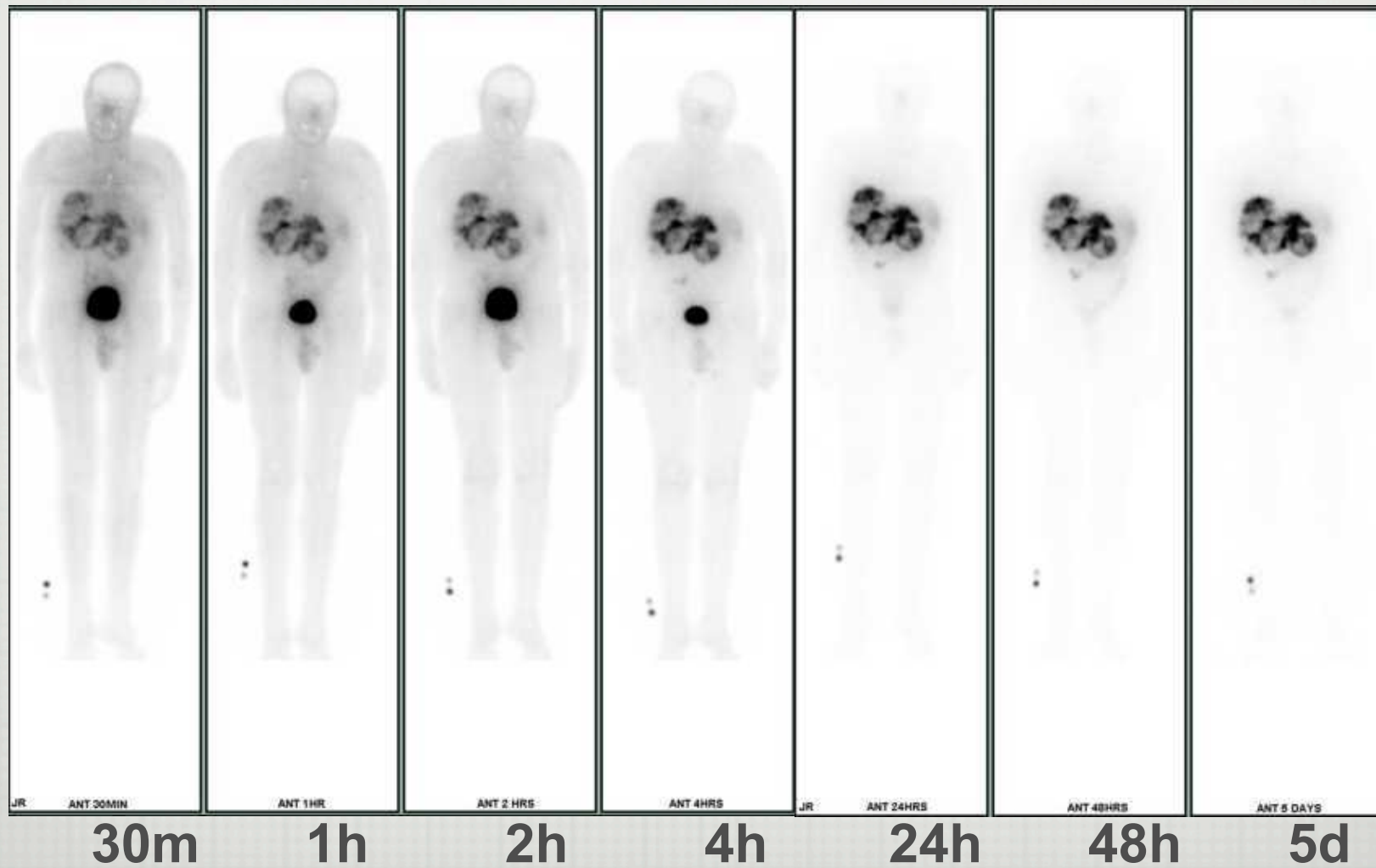
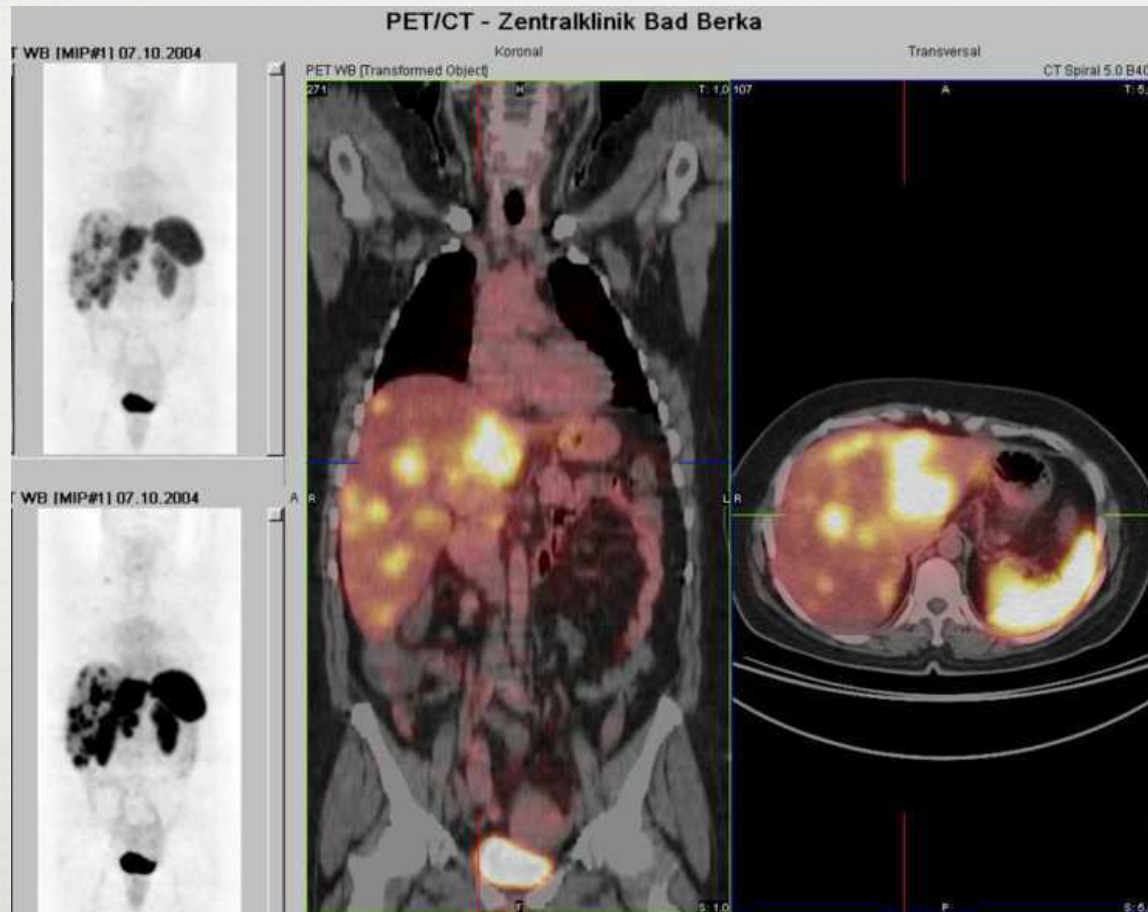# In patients without any predisposing risk factors, PRRT is safe.
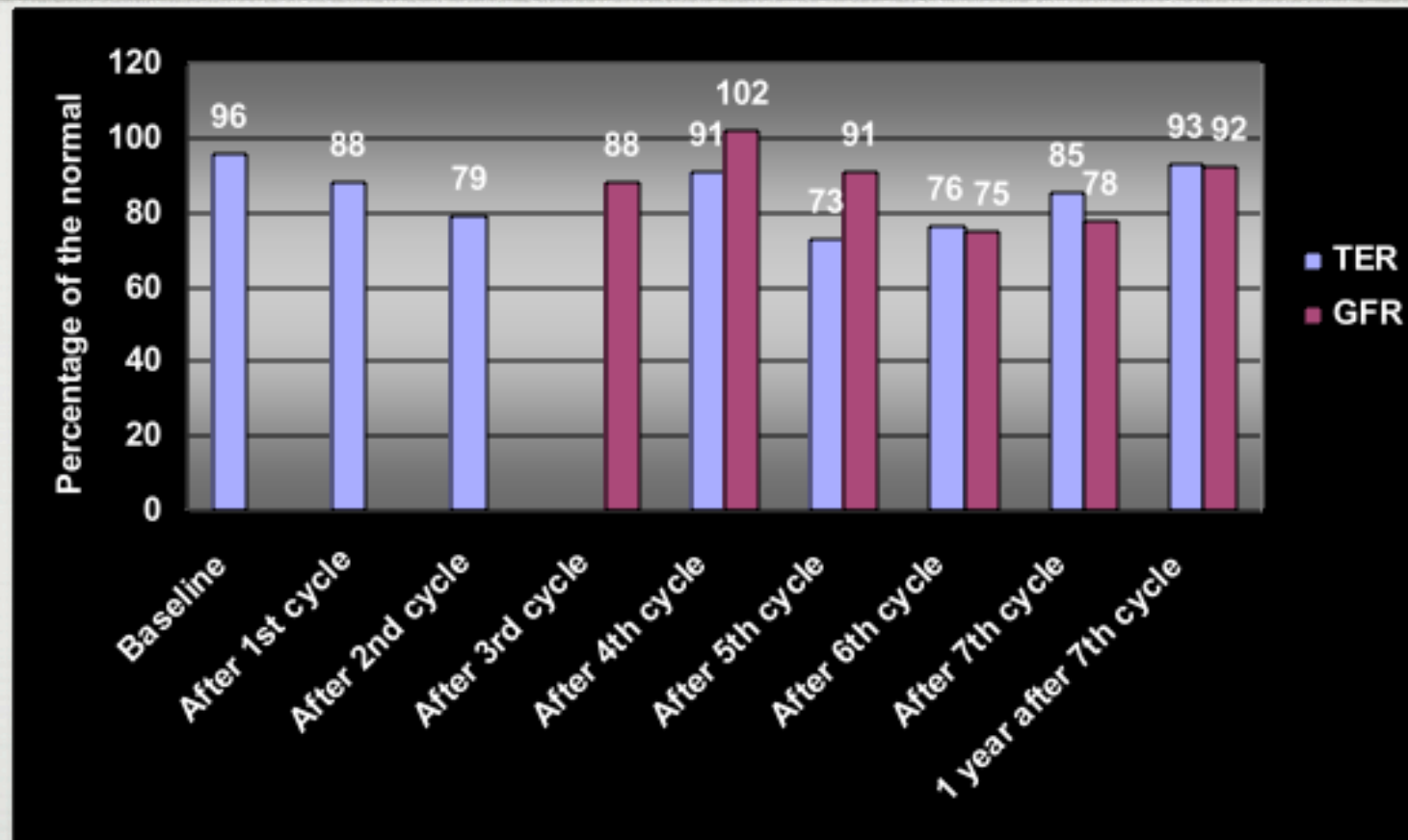
LONG-TERM FOLLOW-UP (5 YEARS) OF RENAL FUNCTION AFTER 7 CYCLES
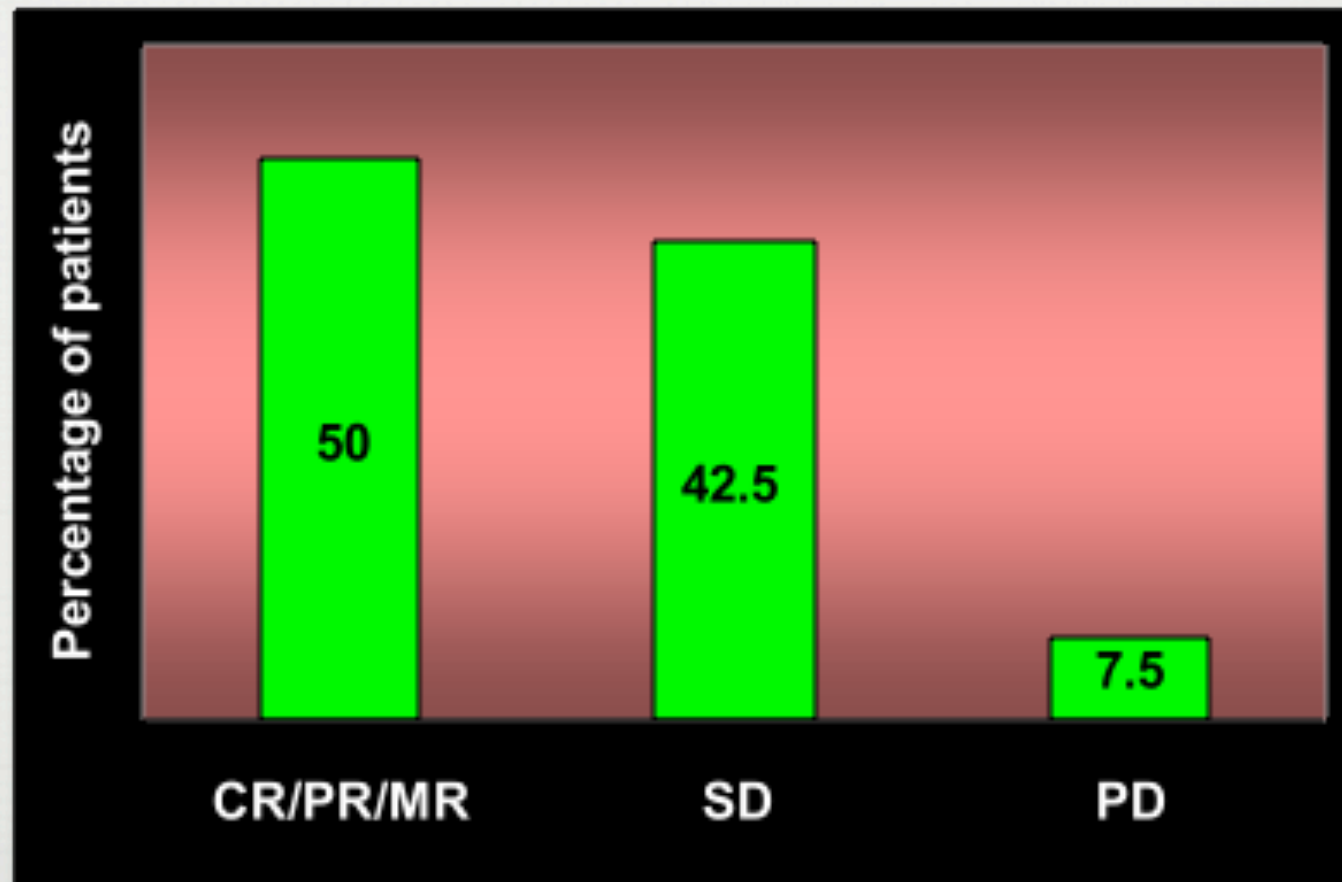OF Y-90 / LU-177 DOTA-TATE (30.29 GBQ)

2 days after PRTT…

Pancreatic NET, extensive liver mets

Female (PhD), 35 years old, active researcher in biology

Results – Overall Response ZKL Bad Berka

Patients with Progressive GEP NET before PRRT

Response to PRRT after 3 cycles

Impact on the clinical status of the patient

☐ **Improvement** of clinical symptoms in 85
- diarrhea
- flushing
- pain

☐ **Octreotide** doses before/after PRRT: 75 % less or no Oct

☐ **Weight gain** of 5 % or more in underweight pts. in 95 %

☐ **Improvement in Karnofsky** performance scale

☐ **Improvement of health state** score

Progression Free Survival After the First Cycle of PRRT
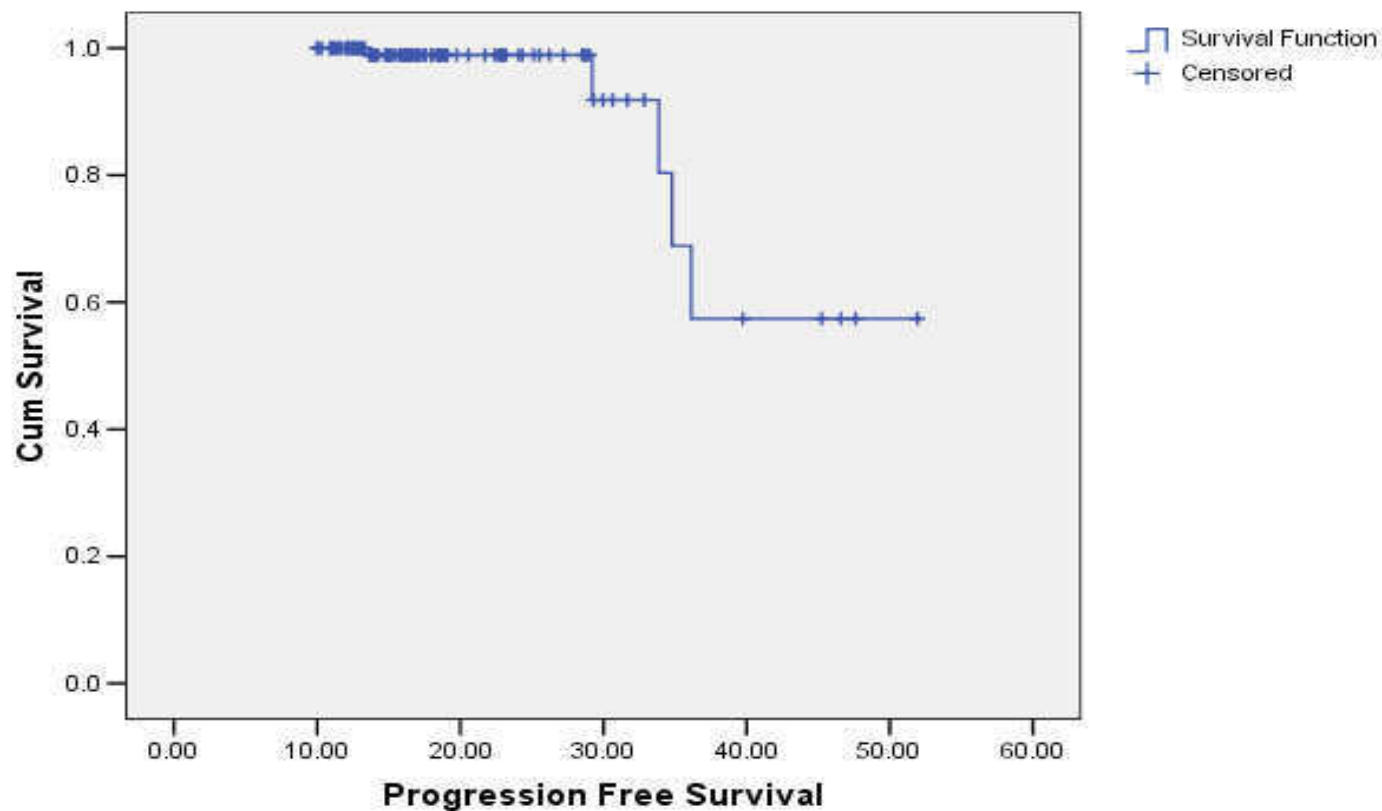
Overall **mean progression free survival** (PFS) in 124 patientsafter the first cycle of PRRT **(median is not achieved)** was 44 months

DUO-PRRT (Y-90/Lu-177 DOTATATE)
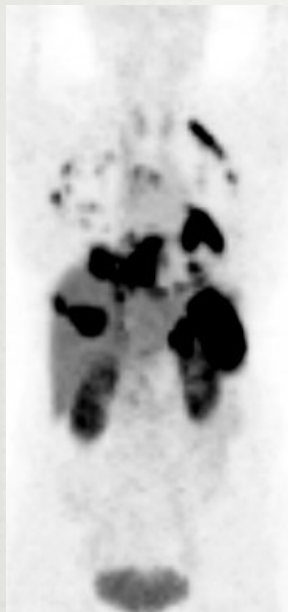## of Metastatic Mediastinal NET
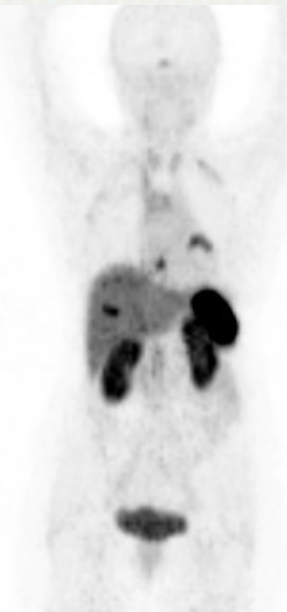

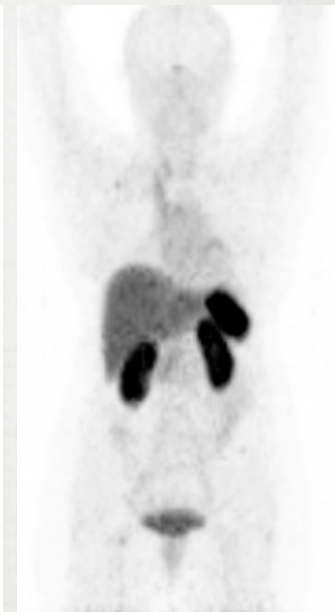| March 2006	June 2006	Oct. 2006	April 2007	Oct. 2007
before PRRT-1 4 GBq Y-90 SUV 15.8	3-mo after PRRT-1 SUV 8.4	before PRRT-2 4.5 GBq Lu-177 SUV 9.3	before PRRT-3 5.5 GBq Lu-177 SUV 6.9	6-mo after PRRT-3 SUV 3.4

Persisting Remission in August 2010!

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


Combined Y-90 / Lu-177 DOTA-TATE PRRT

Survival Function

Overall Survival

Median: 59 months

**Results ZKL Bad Berka**
Analysis of 415 NET Patients
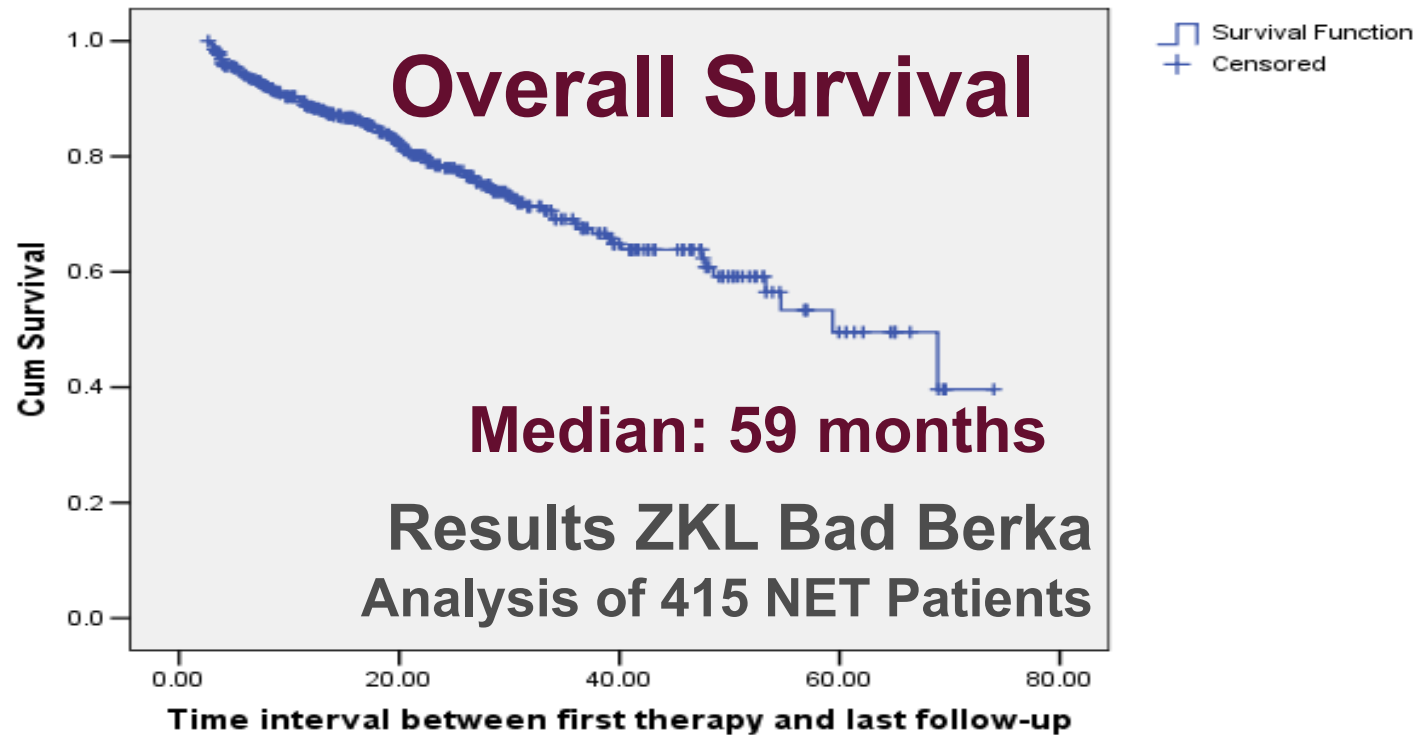
New Avenues to Improve PRRT in Future

☐ **DUO-PRRT** (already routine at our center for over **7** years)

☐ **TANDEM-PRRT** (concurrent Lu-177/Y-90 PRRT Kunikowska et al.)

☐ **Intra-arterial PRRT** (> 50 i.a. treatments up to now)

☐ **Combined PRRT** (in combination with other treatment modalities)

   - TACE, SIRT, RFA (Hörsch et a. ASCO 2010)

   - chemotherapy (e.g. Capecitabine, Doxorubicin)

   - kinase inhibitors (e.g. Sunitinib, Sorafenib)

   - antibodies (e.g. Bevacizumab)

☐ **Improved peptides** (e.g. antagonists)

☐ Intra-operative use of probes after PRRT with Lu-177

☐ Improved dosimetry and radioprotection

Future Improvement:
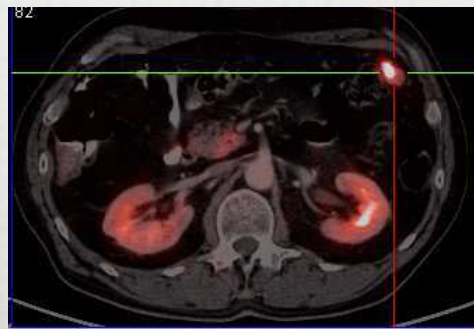# Intra-arterial PRRT
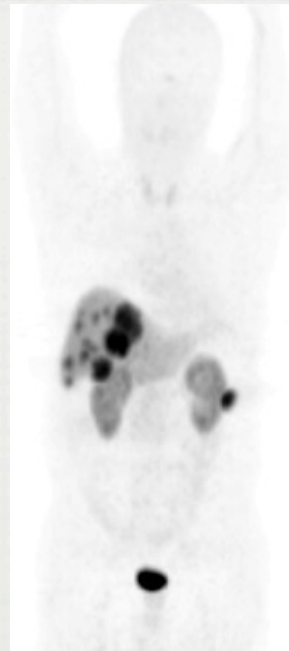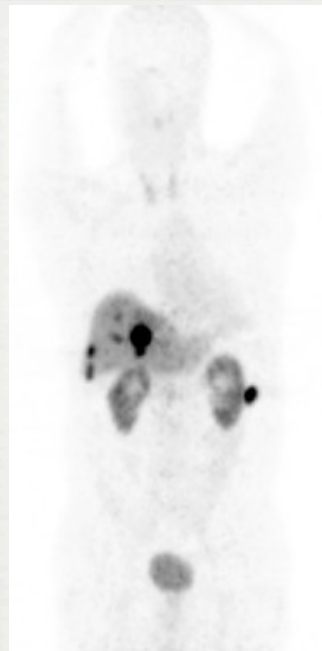
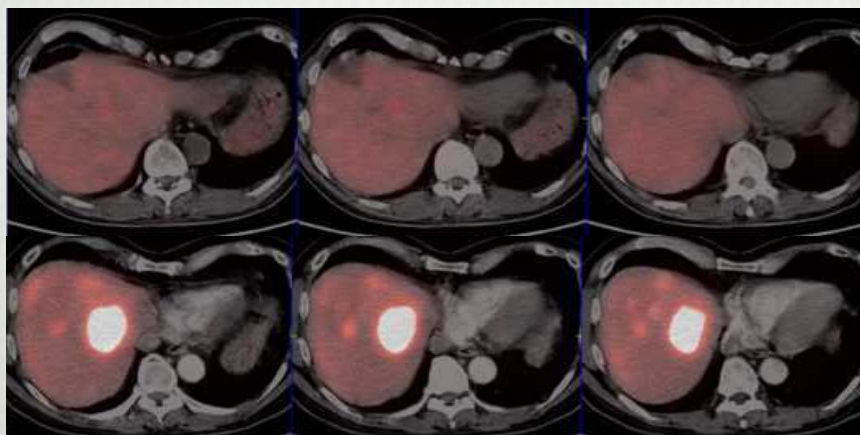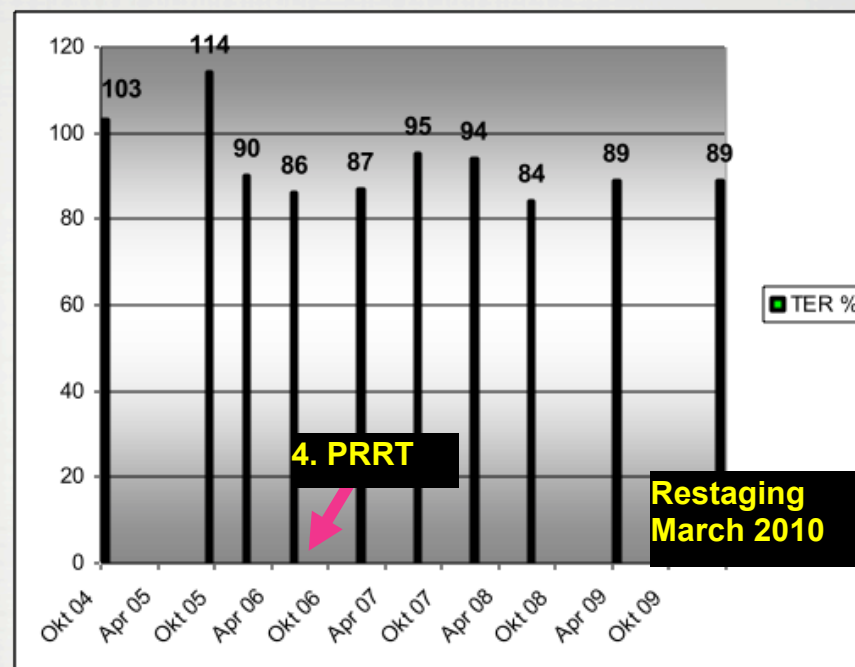pre 1. PRRT   post 2. PRRT   post 3. PRRT

**Regression
of liver and paracolic
metastases
after 3 PRRT
cycles**   BW 32 84 24

Restaging 5 years after 1st PRRT

42 months after 4th PRRT cycle
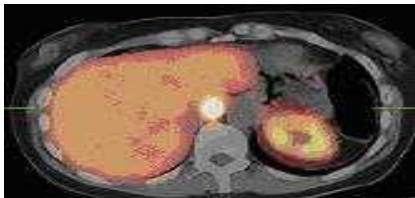
Patient cured!

before 1st PRRT

Summary and Conclusions

☐ **PRRT is effective** – even for very advanced case
   - Median overall survival (n=415 patients) from start of treatment: 59 months
   - PRRT leads to significant **improvement of clinical symptoms**
   - Cure is rarely possible - **but excellent palliation** can be achieved
   - In progressive NETs, **sequential (DUO)** or **concurrent (TANDEM)** PRRT is most effective (**highest CR / PR / SD rate**)

☐ Significant kidney damage **can be reduced** (or avoided) by extending the treatment intervals and by using lower therapy activities more frequently **(Bad Berka protocol)** as up to _10 courses given_ over several years were tolerated very well by most patients (no end stage renal insufficiency).

☐ PRRT should only be performed at **specialized centres**, NET patients need **highly individualized interdisciplinary** treatment and long term care.

International Symposisum Molecular Diagnosis and Therapy of Cancer in Nuclear Medicine The Future is now! May 2-3, 2008.

Second Announcement

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

THERANOSTICS – On the Way to
Personalized Medicine
CONGRESS VENUE: ZENTRALKLINIK BAD BERKA, GERMANY

JUNE 23 – 26, 2011 REGISTER NOW!

www.1stWorldCongress-Ga-68.de

Early Bird Registration	**April 29, 2011**
Late Registration	**June 16, 2011**

Post-Congress: June 27 - 29, 2011

Training School on

PET Radionuclide Generators ^{68}Ge / ^{68}Ga and ^{44}Ti / ^{44}Sc

Institute of Nuclear Chemistry

Johannes Gutenberg University Mainz