Peptide Receptor Radionuclide Therapy: Current Status and Future Perspectives

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SGH Postgraduate Medical Institute

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Singapore

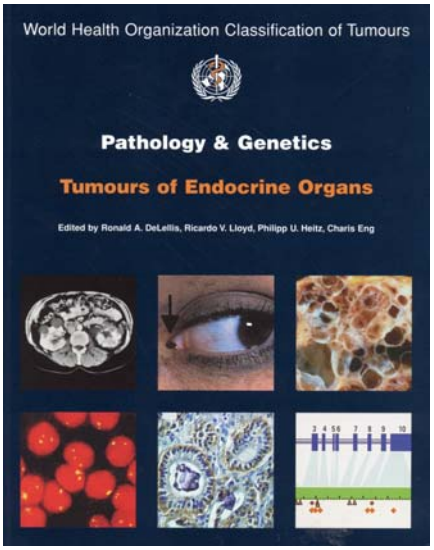
Selection of Patients

What must be known before PRRT?

- **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**

GEP-NETs:
> 40 Entities

Considering:
- Localization
- functional activity
- hereditery background



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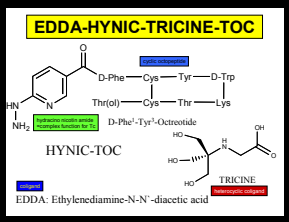
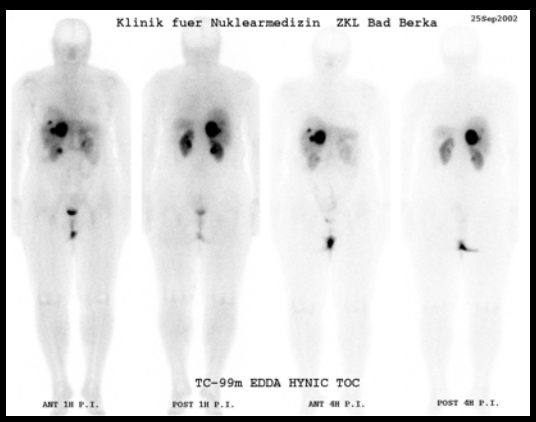
Molecular Diagnostic Imaging of SMS-R positive tumors

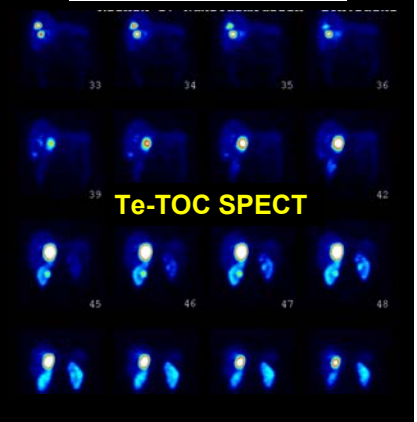
- NET of the intestine (foregut, midgut, hindgut) including bronchus carcinoid, GEP-NET
- Meningioma
- Aesthesioneuroblastoma
- Medullary thyroid cancer (MTC)
- Paraganglioma
- Pheochromocytoma
- Adrenal carcinoma
- Thymus cancer
- Hepatocellular carcinoma
- Merkel cell tumours (and many more….)

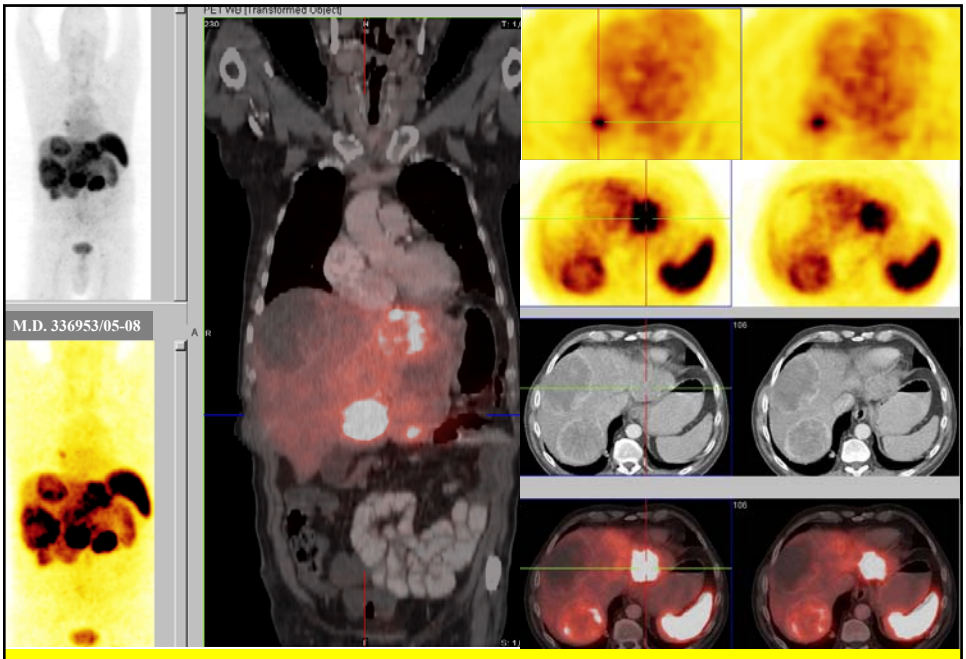
Tc-99m SMS Scintigraphy (Te-TOC) for Centers without PET

- Tc-99m Kit: simple, safe, fast, low costs
- Excellent image quality, 4-hr protocol
- Prediction of targeting for tumour therapy
- Commercially available (POLATOM, Poland)



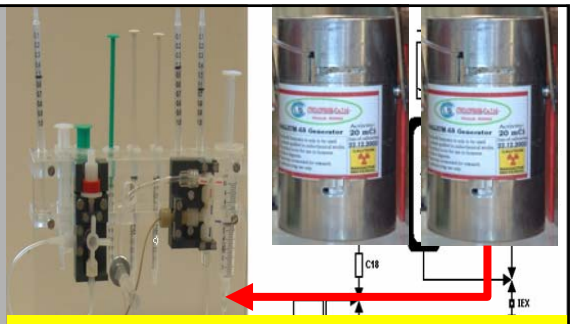




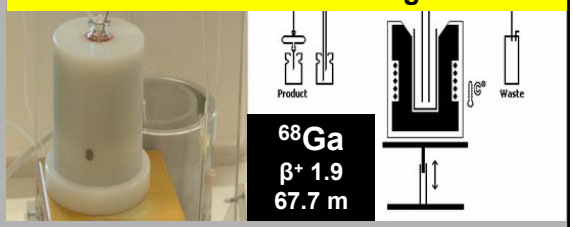


CUP (NET proven by liver biopsy), referrred for PRRT – bronchus carcinoid
Ga-68 receptor PET/CT – should become standard for all centers with PET

Ga-68 Generator System



Simultaneous use of several generators



Developed in close collaboration between

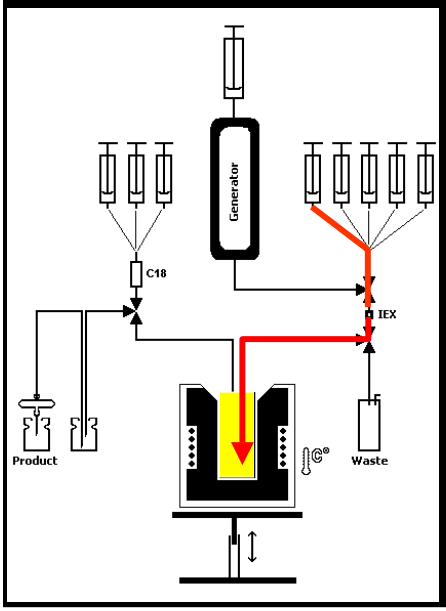
Radiopharmacy PET/CT Center,
Zentralklinik Bad Berka
and
Institute of Nuclear Chemistry
Johannes Gutenberg-Universität, Mainz, Germany

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

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

^{68}Ga-elution, purificaton
and synthesis module
First use July 2004

Radiopharmaceutical synthesis



97±2% ^{68}Ga @ t^{o} + 4 min
chemically and radiochemically pure

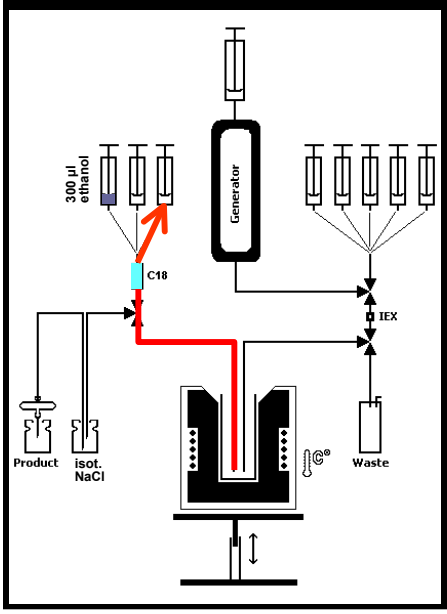
eluted directly into labelling vial,
containing appropriate amounts of precursor,
e.g. DOTA-TOC or DOTA-NOC,
and an appropriate volume of water,
without (or with) using buffer systems

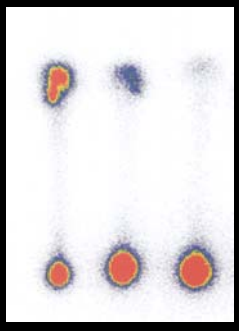
for syntheses of ^{68}Ga-labelled tracers
within 5 - 10 min
yields: 95 – 98% for ^{68}Ga-DOTA-NOC

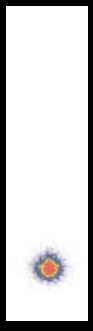
Specific activities:
35 MBq / µg DOTA-NOC
in 5 ml water only

> 450 MBq / µg DOTA-NOC
in 0.5 ml water + 1 M HEPES pH4

Radiopharmaceutical purification







Labelling kinetics (min)
1 5 10

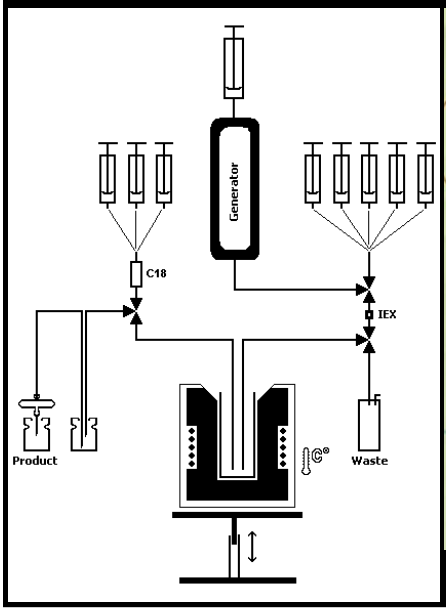
51.4% 85.2% 95%

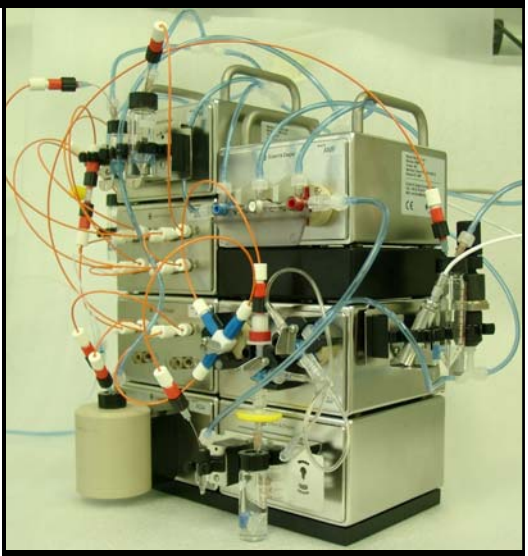
purified product after C18

100%

Quality control:
e.g. on silica gel impregnated glass fibre strips
(TLC alumina sheets SG 60 by MERCK)

Post-processing combined with labelling …
… on an automated module





Eckardt & Ziegler AG, Berlin

Summary ^{68}Ge/Ga Generator

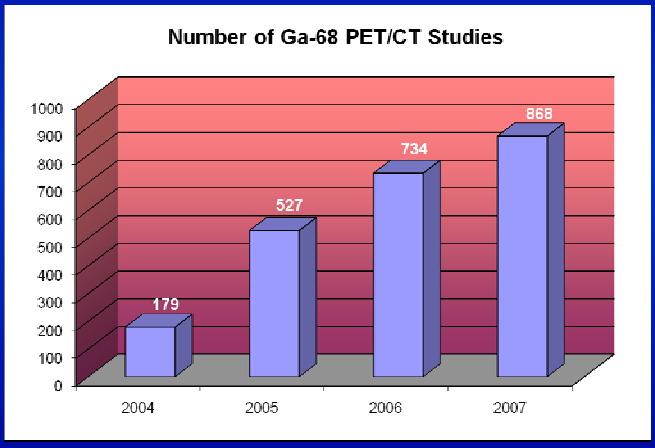
- Post-processing of ^{68}Ge/^{68}Ga radionuclide generators using cation exchange resin provides chemically and radiochemically pure ^{68}Ga
  97±2% within 4 min
  ready for on-line labelling

- Highest chemical purity guarantees for high labelling and overall product yields (e.g. ^{68}Ga-DOTA-conjugated octreotides) of 75±5% decay corrected

- Ready for injection – up to 8 patients per day can be studied
  easy handling in a nuclear medical environment
  easily to transfer to IAEA and other countries
  (in use already in Dehli/India and Santiago de Chile)

Significant step towards the routine medical use of the ^{68}Ge/Ga generator

Gallium-68 will become the Tc-99m for PET/CT!



Prediction by R.P. Baum (2004)

Ga-68 Receptor PET/CT

The Bad Berka Experience (>2,300 studies)

Receptor PET/CT using the Ga-68-labeled somatostatin analogue DOTA-NOC enables the molecular imaging of neuroendocrine tumours and their metastases with very high diagnostic sensitivity and specificty

Advantages:

- Semiquantitative, reproducible data (SUV) which can be used for selecting patients for PRRT and evaluation of therapy response
- fast protocol (60-90 min.), patient friendly, low radiation burden
- flexibility, daily use, lower (!) cost than Octreotide scintigraphy
- a new goldstandard for *in vivo* SMS receptor imaging

Comparative studies will probably allow to determine tumor and kidney dosimetry prior to subsequent PRRT using Y-90 or Lu-177-labeled somatostatin analogues.

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

SUV primary tumors (n = 400 patients)	Mean	Range
Primary tumours	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

Selection of Patients

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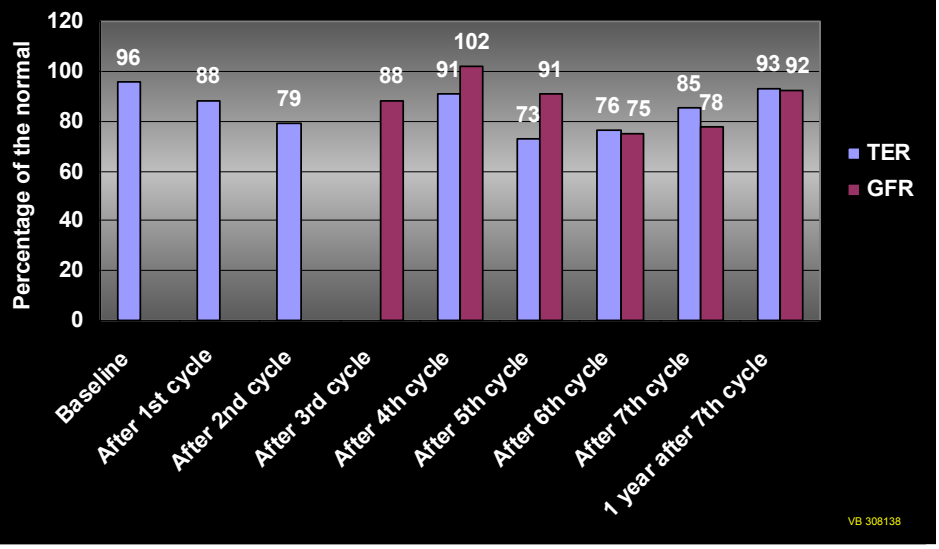
- Receptor density – ideally determined by receptor PET/CT (SUV) or scintigraphy
- **Kidney function –** MAG3 (TER), Tc-99m DTPA (GFR)
- Blood profile/chemistry

In patients without any predisposing risk factors, PRRT is safe.

Long term (5 years) follow-up of renal function after 7 cycles of Y-90 / Lu-177 DOTA-TATE (30.29 GBq)



VB 308138

Kidney Toxicity - Summary

- Effect of Y-90 on renal function is much more pronounced (detrimental) as compared to Lu-177
- The number of courses given to the patient is a very important parameter to be taken into consideration for assessing the affect of PRRT on kidney function
- Lower quantity of radioactivity for each therapy course can be administered while increasing the number of courses and the time interval between courses with almost similar (better?) results on the tumor but with

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Increased Hematological Toxicity

- Previous chemotherapy (e.g. cisplatinum, etoposide, streptotozin etc.)
- Previous external radiation therapy (large fields)
- Previous high-dose PRRT with Y-90
- Disseminated bone (marrow) involvement
- Decreased renal function

Peptide Receptor Radionuclide Therapy

How is it performed?

- Choice of peptide (DOTA-TATE or DOTA-TOC)
- Choice of radionuclide (Lu-177, Y-90)
- Kidney protection (lysine, arginine, Rotterdam protocol)
- Tumor and organ dosimetry (posttreatment scan
- Monitoring of toxicity (follow-up)

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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	-
^{111}Indium*	2.8	auger electrons 14.7	<0.01	172 (90%) 247 (94%)

*not suitable for therapy

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: Relation to Chemotherapy

Table 3. Results and Side Effects of Chemotherapy in Patients With Neuroendocrine Tumors Compared With the Present Study

Regimen	Tumor Types	No. of Patients	PR and CR (%)	Median Response Duration (months)	Hematologic Toxicity Grade 3 and 4 (%)	Nausea and Vomiting (%)	Other Major Side Effects	Study
Doxorubicin	Carc	33	21*	4	NA	NA	—	Moertel[20]
FU	Carc	19	26*	3	NA	NA	—	Moertel[20]
STZ + FU	Carc	43	33*	7	NA	NA	—	Moertel[20]
STZ	NEP	42	36*	17	0	83	Renal toxicity, 29%; liver failure, 2%	Moertel et al[21]
STZ + FU	NEP	42	63*	17	29	85	Renal toxicity, 31%	Moertel et al[21]
STZ + FU	NEP	33	45*	7	25	81	Diarrhea, 33%; renal insufficiency, 7%	Moertel et al[22]
STZ + doxorubicin	NEP	36	69*	20	5	80	Diarrhea, 5%; renal insufficiency, 4%; heart failure, 9%	Moertel et al[22]
STZ + doxorubicin	NEP	16	6	> 18	19	NA	Diarrhea, 19%; cardiac toxicity, 19%	Cheng and Saltz[23]
DTIC	Carc	15	13	4	NA	NA	—	Van Hazel et al[24]
DTIC	Carc	56	16	3	29	88	Diarrhea, 23%	Bukowski et al[25]
DTIC	Carc/NEP	7	14	NA	NA	0	—	Ritzel et al[26]
FU + IF-A	Carc/NEP	24	21	13	42	NA	Diarrhea, 8%	Andreyev et al[27]
Mitoxantrone	Carc	35	9	14	32	26	—	Neijt et al[28]
Paclitaxel	Carc/NEP	24	4	3	61	63	Diarrhea, 54%; neurologic toxicity, 61%	Ansell et al[29]
^{177}Lu-octreotate	Carc/NEP	131	28	> 36	< 2	31	Renal insufficiency, 1%; liver failure, 1%	Present study

Abbreviations: PR, partial remission; CR, complete remission; DTIC, dimethyltriazenoimidazole carboxamide; FU, fluorouracil; STZ, streptozocin; Carc, carcinoids; NEP, neuroendocrine pancreatic tumors; NA, not available; IF-A, interferon alpha; ^{177}Lu-octreotate, [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate.
*Response evaluation including biochemical responses and physical examination for evaluation of hepatomegaly.

Kwekkeboom et al, J Clin Oncol 2005;23:2754-2762

Erasmus MC

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 43 • No. 5 • May 2002

Tumor Response and Clinical Benefit in Neuroendocrine Tumors After 7.4 GBq ^{90}Y-DOTATOC

Christian Waldherr, MD[1]; Miklos Pless, MD[2]; Helmut R. Maecke, PhD[3]; Tilmann Schumacher, MD[1]; Armin Crazzolara, MD[1]; Egbert U. Nitzsche, MD[1]; Andreas Haldemann, MD[4]; and Jan Mueller-Brand, MD[1]

[1]PET Center, Institute of Nuclear Medicine, University Hospital, University of Basel, Basel, Switzerland; [2]Department of Oncology, University Hospital, University of Basel, Basel, Switzerland; [3]Institute of Radiological Chemistry, University Hospital, University of Basel, Basel, Switzerland; and [4]Oncology Institute of Southern Switzerland, Bellinzona, Switzerland

Tumor Response (WHO Standard Criteria)

Tumor type	Progression before treatment	CR	PR	SD	Progressive disease within or after treatment	Overall tumor response	CR, PR, SD
EPT (n = 13)	13 (100%)	1	4	6	2	38%	11 (85%)
Intestinal NET (n = 12)	12 (100%)	—	1	11	—	8%	12 (100%)
Bronchial NET (n = 3)	3 (100%)	—	—	3	—	0%	3 (100%)
NET of unknown origin (n = 9)	9 (100%)	—	2	6	1	22%	8 (89%)
Others (n = 2)	2 (100%)	1	—	1	—	50%	2 (100%)
All (n = 39)	39 (100%)	2	7	27	3	23%	36 (92%)

CR = complete remission; PR = partial remission; SD = stable disease; EPT = endocrine pancreatic tumor; NET = neuroendocrine tumor.

PRRT - SEQUENTIAL USE OF Y-90 & LU-177

Y-90 DOTA-TOC has been most frequently used for the treatment of metastatic neuroendocrine tumors *(Waldherr et al., Paganelli et al.)*.

Lu-177 DOTA-TATE has shown very promising results in somatostatin receptor (SSTR) positive GEP tumors *(Kwekkeboom et al.)*.

Few data exist on the use of Y-90 DOTA-TATE for PRRT of NET, none on the sequential use of Y-90 and Lu-177 DOTA-TATE.

Our strategy is to study

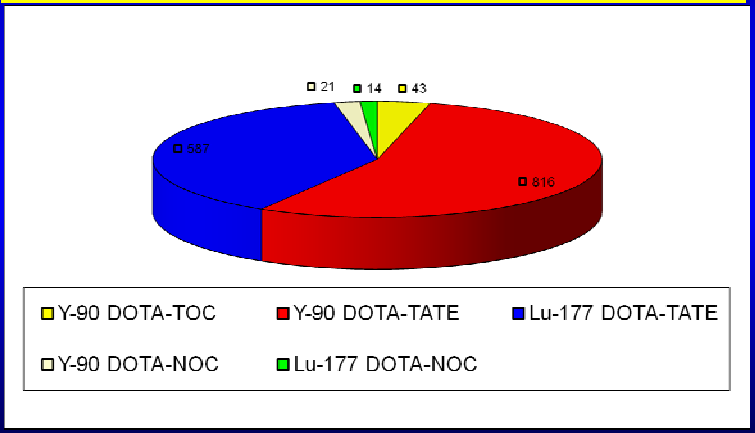
- the therapeutic efficacy and

- to evaluate the short and longterm adverse effects

of PRRT using the somatostatin analogue octreotate labeled with Y-90 or Lu-177 in patients with *progressive*, metastasized neuroendocrine tumors (mostly with large tumor burden).

RADIOPEPTIDE THERAPY (ZKL BAD BERKA)

Total number of patients treated **n = 475**
Total number of treatment sessions **n = 1400**
(as of January 31, 2008)

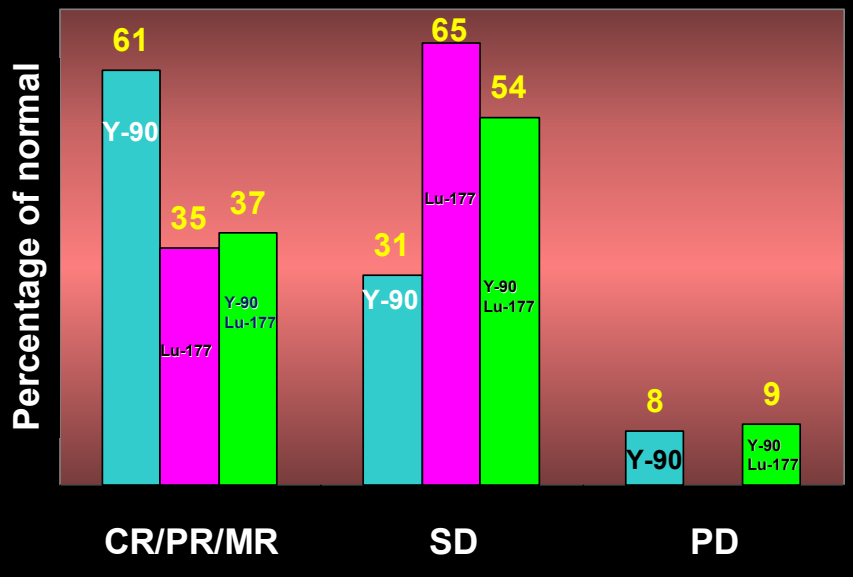


Yttrium-90 **n = 816**
Lutetium-177 **n = 587**

Age: **4 – 81 years**
mean 59 years

RESPONSE TO PRRT – DIFFERENT TREATMENT REGIMENS BAD BERKA

Highest response rate was observed with Y-90 followed by Lu-177 + Y-90 and Lu-177 DOTA-TATE alone



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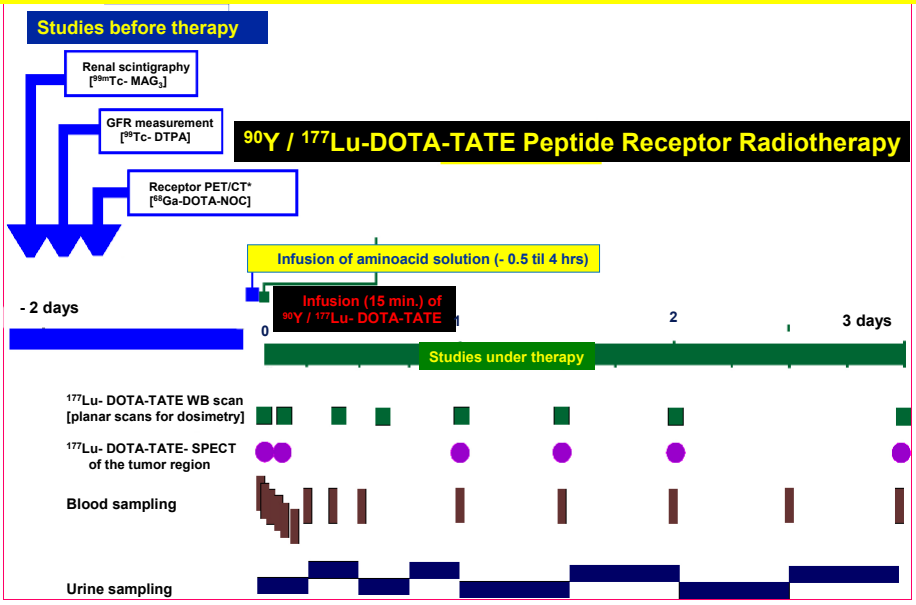
- Monitoring of toxicity (follow-up)

BAD BERKA PROCEDURE FOR PRRT

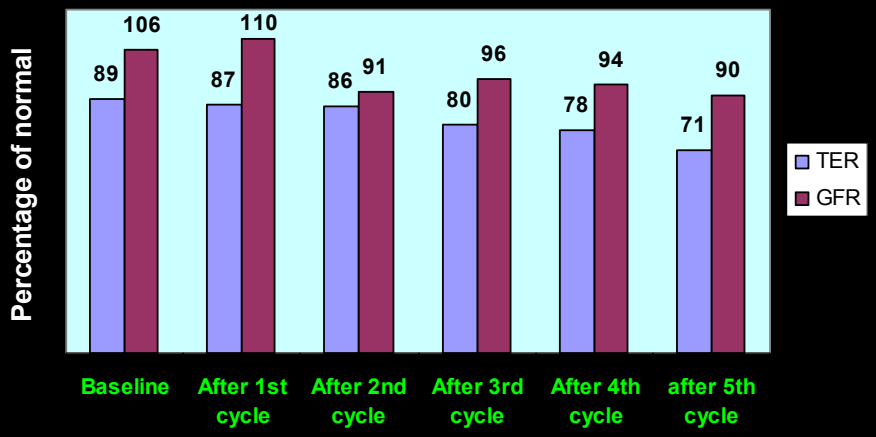


* Since July 2004. Previously, Tc-99m EDDA Hynic TOC (planar & SPECT) was performed.
In selected patients, also F-18 FDG and / or F-18 fluoride PET/CT is performed as well as MRI of the liver / bones

LONG TERM FOLLOW-UP AFTER 5 CYCLES OF PRRT

The results in 35 patients having received more than 5 cycles of PRRT show a mean fall in TER / GFR of 18% / 16%, respectively.

None of the patients developed significant renal toxicity.



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DOSIMETRY

CANCER BIOTHERAPY & RADIOPHARMACEUTICALS
Volume 22, Number 3, 2007

DOI: 10.1089/cbr.2006.325

Results of Individual Patient Dosimetry in Peptide Receptor Radionuclide Therapy with ^{177}Lu DOTA-TATE and ^{177}Lu DOTA-NOC

Christiane Wehrmann, Stefan Senftleben, Carolin Zachert, Dirk Müller, and Richard P. Baum
Department of Nuclear Medicine/Center for P.E.T., Zentralklinik Bad Berka, Bad Berka, Germany

Patient dosimetry in radioreceptor therapy using ^{177}Lu DOTA-NOC and ^{177}Lu DOTA-TATE

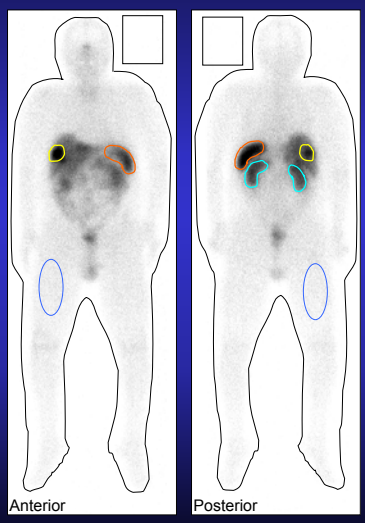
AIM | METHODS | RESULTS | CONCLUSIONS

Dosimetry → MIRD-Scheme

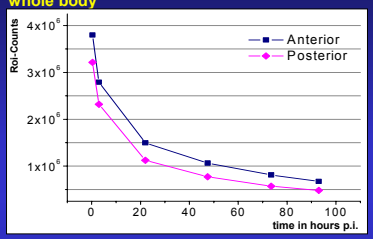
Serial planar whole body scans

Scan time:
direct p.i.
3h p.i.
24h p.i.
48h p.i.
72h p.i.
(96h p.i.)

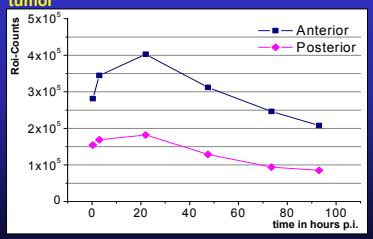
Regions of: Interest (ROI)
organs
(liver, kidneys, spleen...)
whole body
tumor
normal tissue



whole body



tumor



Department of Nuclear Medicine / Center for P.E.T. — Zentralklinik Bad Berka, Germany

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- Tumor and organ dosimetry (posttreatment scan)
- **Monitoring of toxicity** (follow-up)

Monotoring for Toxicity

(Re-staging)

- **Laboratory tests**

  Hematology, liver enzymes, renal parameters (creatinine, BUN).

  The lab tests were repeated at monthly intervals between the therapy cycles by the caring physicians and sent to our institution.

- **Kidney function** (GFR + TER MAG3 always before next PRRT)

RESTAGING OF PATIENTS

Restaging was always performed before the next therapy cycle by

- Ga-68 DOTA-NOC PET/CT (with oral & i.v. contrast)
- Renal scintigraphy (Tc-99m MAG 3) with TER measurements
- GFR measurements (Tc-99m DTPA)
- Laboratory tests (hematology, liver enzymes, renal parameters)
- Tumor markers (chromogranin, serotonin, glucagon, gastrin etc.)
- MRI of the abdomen / spine (in selected cases)
- FDG-PET/CT (in selected cases)
- F-18-Fluoride-PET/CT (in selected cases)

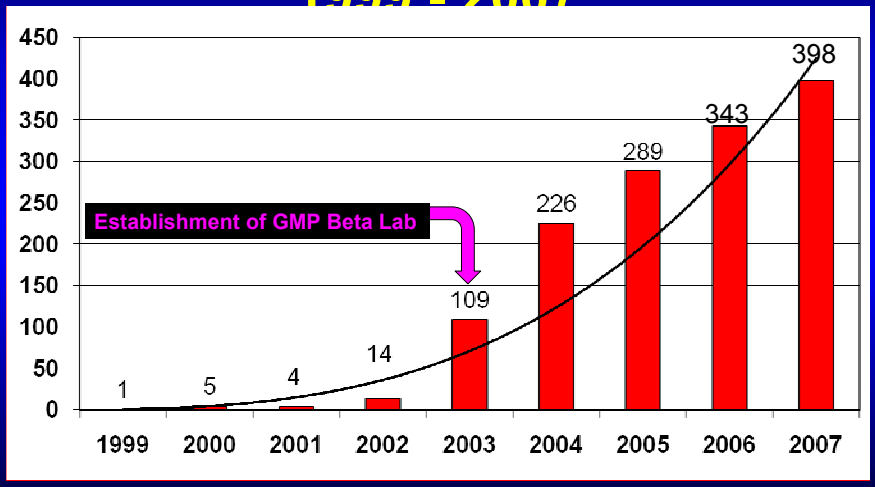
The lab tests were also performed at monthly intervals between therapy cycles by the caring physicians and sent to our institution.

All data are entered into a database containing 270 single items.

Results

- statistical analysis
- clinical results

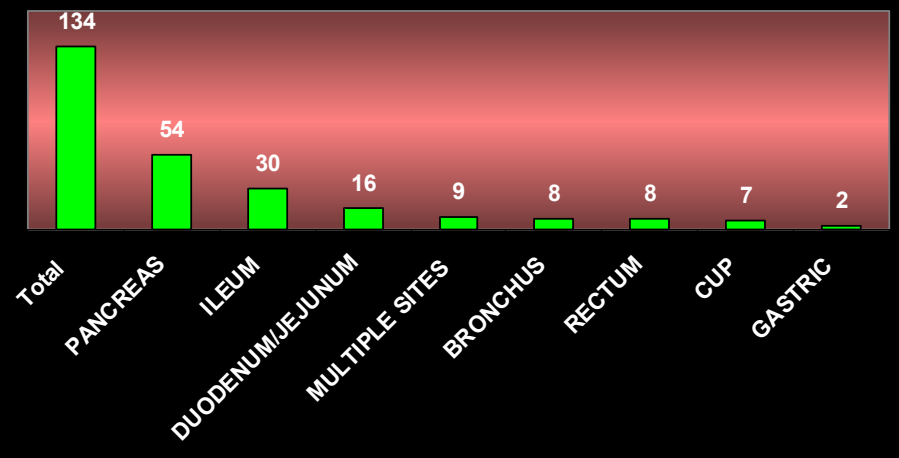
RADIOPEPTIDE THERAPY COURSES 1999 - 2007



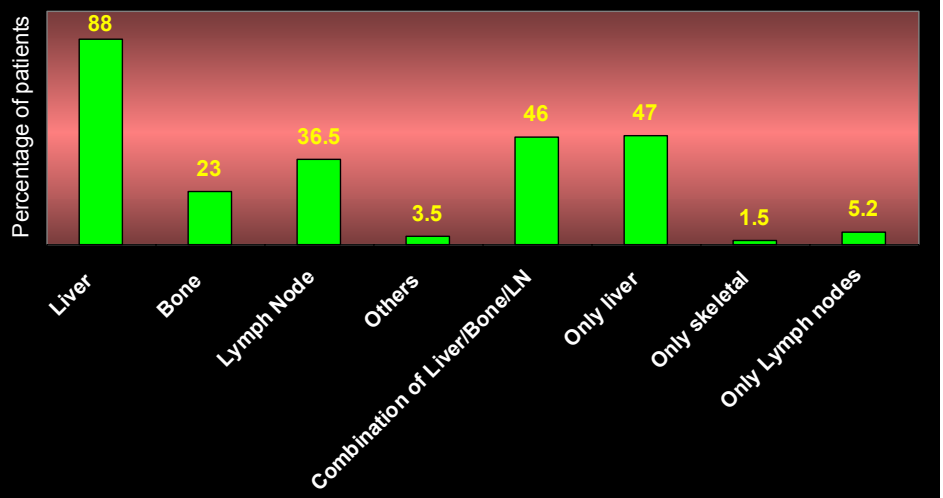
PATIENTS' DATA

- In total, 475 patients were treated with Y-90 / Lu-177 DOTA-TATE (overall 1,400 treatment courses as of January 31, 2008)
- Mean age: 58.1 years (4 - 81 years), 258 male, 217 female
- All patients were selected based on high SST-R expression as proven by Ga-68 DOTA-NOC receptor PET/CT
- Only progressive GEP NET patients treated with at least 3 cycles of PRRT were included in this analysis
- Assessment of therapy response was done after 3 cycles
- Three different groups were analyzed: PRRT using Y-90 (n=80), Lu-177 (n=19) and combined use of Y-90 & Lu-177 labeled DOTA-TATE (n=43)
- The average cumulative radioactivity administered was 10 GBq Y-90, 16 GBq Lu-177, and 12 GBq Lu-177 / Y-90 DOTA-TATE, respectively

DIFFERENT NET SUBTYPES TREATED WITH PRRT



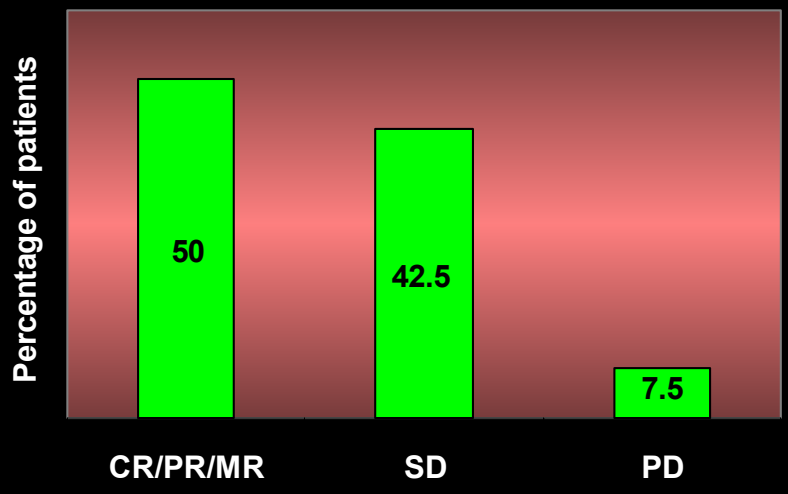
SITES OF METASTASES



RESULTS – OVERALL RESPONSE

Progressive GEP NET (n=134)

Response to PRRT after 3 cycles



PRRT – THE BAD BERKA CONCEPT

- **Selection of patients** based on clinical aspects (progressive tumours or uncontrolled symptoms despite maximum conventional therapy) and SMS-receptor expression (determined by **PET/CT**)

- **Frequent** (4-6, up to 8) **cycles** of low (2 GBq) or intermediate high (3-4 GBq) therapies: **long term low dose,** not short term, high dose
- **Combined use** of Y-90 and Lu-177 (in sequence)
- **Intra-arterial PRRT** for inoperable primary tumors

- **Standardized evaluation** before therapy and **systematic restaging**
- All clinical data are entered into a systematic **prospective database**
- The **management** of the patient during PRRT is controlled by the nuclear medicine physician in cooperation with other specialists

SUMMARY AND CONCLUSIONS

- PRRT is an effective therapy – even for very advanced cases – and leads to a significant improvement of clinical symptoms
- Cure is rarely possible - but good palliation can be achieved
- In patients with progressive NET, combined sequential Y-90 / Lu-177 PRRT is most effective (highest percentage of PR and SD)

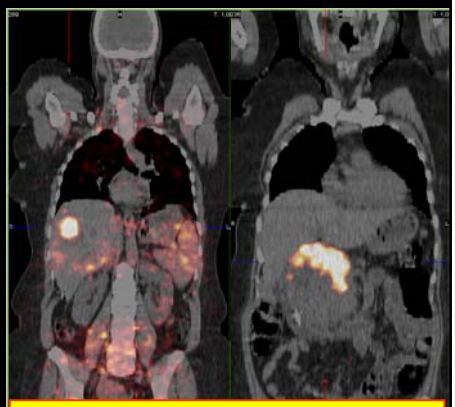
- Significant kidney damage can be reduced (avoided) by extending the treatment intervals and by using lower therapy activities more frequently as up to 8 courses given over several years were tolerated very well by most patients (no end stage renal insufficiency).

- PRRT should only be performed at specialized centres as NET patients are frequently very ill patients (multimorbidity) and need interdisciplinary treatment and long term care

Future Perspectives

Pre-therapeutic organ and tumor dosimetry using receptor PET/CT and longer lived positron emitters, e.g. Sc-44, Y-86 Cu-64 or Cu-61 and comparison with Ga-68 results.

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



Y-86 DOTA-NOC Receptor PET/CT

Molecular imaging of bombesin receptors in various tumors by Ga-68 AMBA PET/CT: First results

R. P. Baum[1], V. Prasad[1], N. Mutloka[1], M. Frischknecht[2], H. R. Maecke[2], J. C. Reubi[3]

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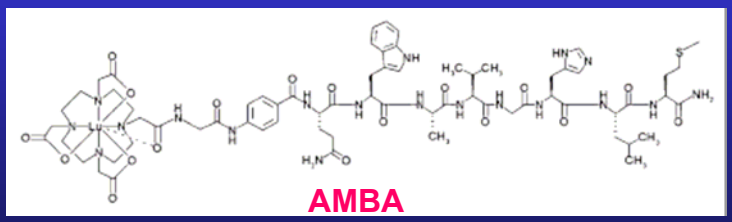
54th Annual Meeting Society of Nuclear Medicine



AMBA

2 - 6 June, 2007 Washington, D.C.

A novel molecular imaging agent for diagnosis of recurrent HER2 positive breast cancer.

First time in human study using an In-111 or Gallium-68 labeled Affibody molecule

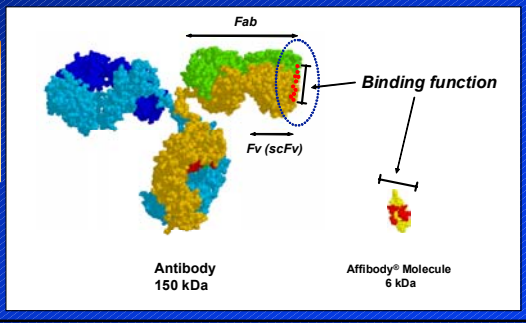
R. P. Baum, A. Orlova, V. Tolmachev*, J. Feldwisch**

Dept. of Nuclear Medicine / PET Center, Zentralklinik Bad Berka, Germany
**Affibody AB, Bromma, Sweden*

9th Congress of WFNMB

9th CONGRESS OF WORLD FEDERATION OF NUCLEAR MEDICINE AND BIOLOGY
October 22-27, 2006 COEX Seoul, Korea

Global Harmonization and New Horizon of Nuclear Medicine



Seoul, Korea October 23, 2006

Coworkers:

MDs: A. Niesen, C. Zachert, V. Prasad, M. Kupfer, J. Breitling

Radiochemistry: R. Wortmann, I. Klette, S. Müller

Technicians: P. Katzemann and coworkers

Nurses: M. Wieditz, B. Schneiting and coworkers

Med. Physics / Dosimetry: S. Senftleben, C. Wehrmann

Secretary / Logistics: A. Cihar

Collaboration: Helmut Mäcke, Basel; Jean Claude Reubi, Bern; Frank Rösch, Mainz; Jeong JM, Seoul

….and thanks to many colleagues for excellent cooperation

Thank you!

National Flower of Singapore

Vanda Miss Joaquim

Botanic Garden, March 3rd, 2008

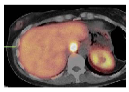
First Announcement

www.event-pet-zentralklinik-badberka.de

10 Years Anniversary PET and Nuclear Medicine Bad Berka (1998-2008)

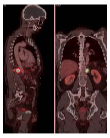
International Symposium

Molecular Diagnosis and Therapy of Cancer in Nuclear Medicine
The future is now!



May 2-3, 2008

Symposium Venue
Zentralklinik Bad Berka GmbH
Robert-Koch-Allee 9
99437 Bad Berka
Germany



Preliminary Program/Topics

- PET/CT and PET/MRI - the next decade
- New radioisotopes for diagnosis and therapy produced by powerful cyclotrons and new generators
- Molecular radiopharmaceuticals - what is in the pipeline?
- Novel clinical applications for PET/CT
- Molecular radioligand therapy of cancer - novel concepts
- Radioimmunotherapy - proven and new indications
- Peptide receptor radionuclide therapy - from a niche indication (NET) to broader application?
- Intraarterial radioembolisation of primary and secondary liver tumors
- Radionuclide therapy of brain tumors
- Molecular radiation therapy planning (MRTP)
- Nuclear medicine in developing countries: a quantum leap in one decade

We are happy to invite you to take part in the **10 Years Anniversary PET and Nuclear Medicine Bad Berka** meeting at the Zentralklinik Bad Berka – near Weimar, the most beautiful and charming cultural capital city of Europe in 1999.

For further information please contact:
www.event-pet-zentralklinik-badberka.de

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