Fondazione IRCCS Istituto Nazionale dei Tumori

Sistema Socio Sanitario
Regione Lombardia

UNIVERSITÀ DEGLI STUDI DI MILANO

4th Milan NET Conference

A meeting among active Italian Neuroendocrine Tumor Boards

Tuesday June 12th, 2018

Aula / Hall Gianni Bonadonna

Fondazione IRCCS Istituto Nazionale dei Tumori

Milano

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A meeting among active Italian Neuroendocrine Tumor Boards

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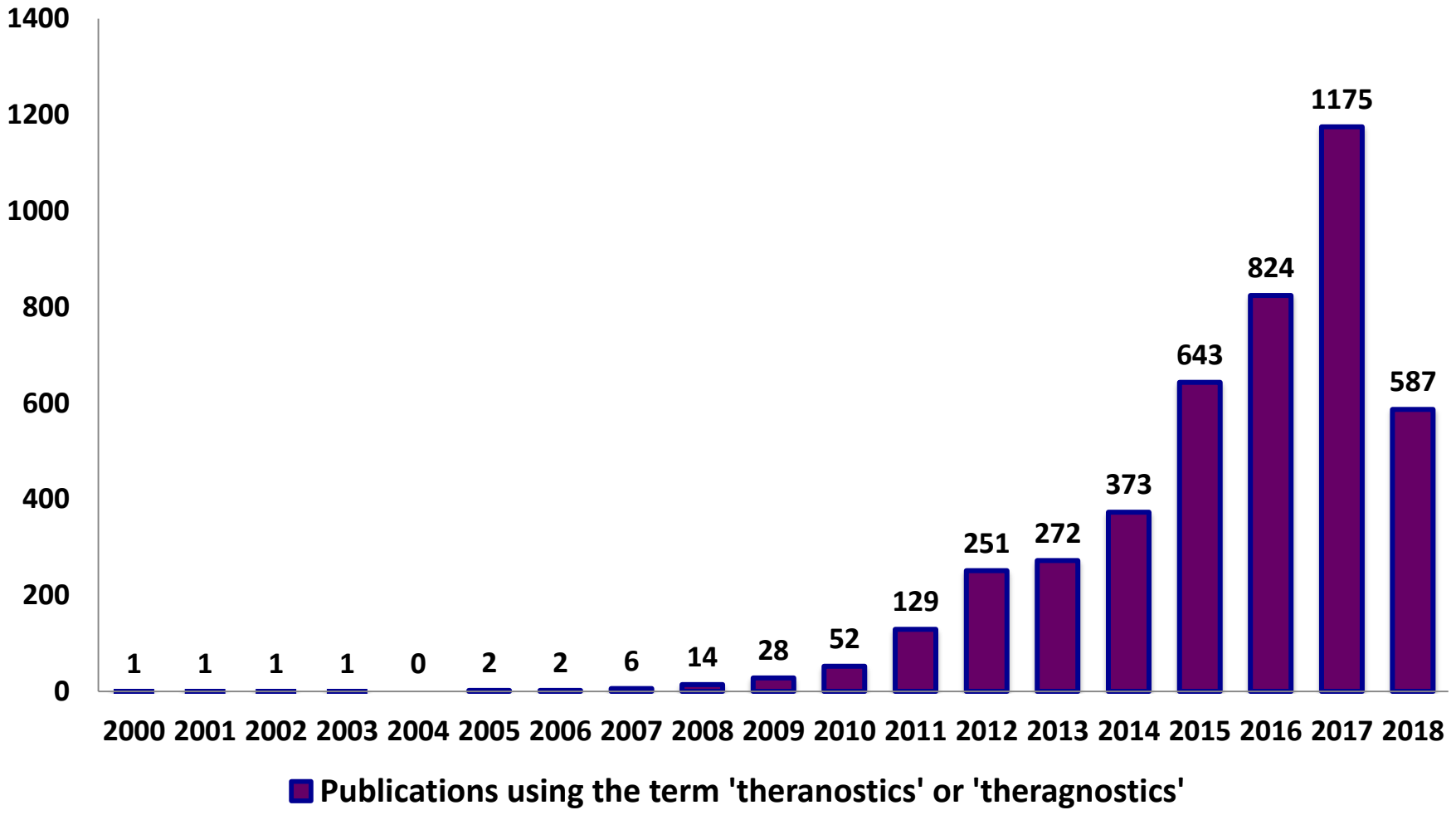
Theranostics in NET
Update and Novel Strategies

Aviral Singh MD, MSc

THERANOSTICS Center for Molecular Radiotherapy & Molecular Imaging

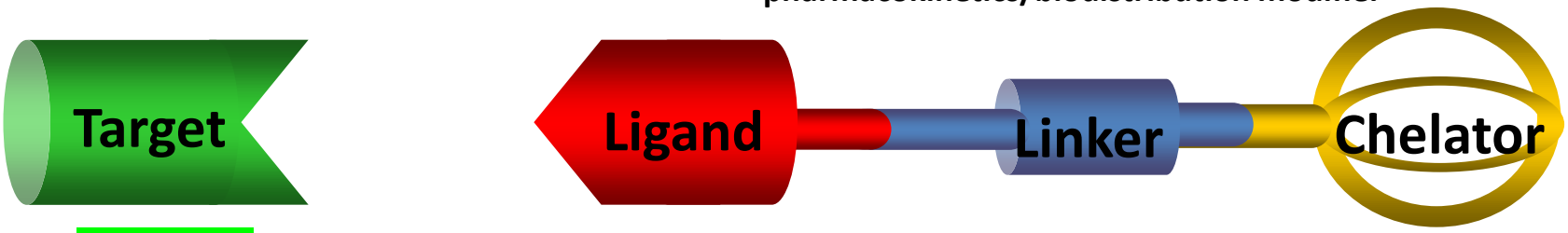
ENETS Center of Excellence, Zentralklinik Bad Berka, Germany

PubMed-derived number of publications per year including the term ‘theranostics’ or ‘theragnostics’ from 2000 to mid-2018 (search performed on June 11, 2018)



THERANOSTIC PAIRS
Targeted Molecular Imaging and Therapy
WE TREAT WHAT WE SEE

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
- ^{68}Ga, ^{44}Sc, ^{152}Tb, ^{64}Cu

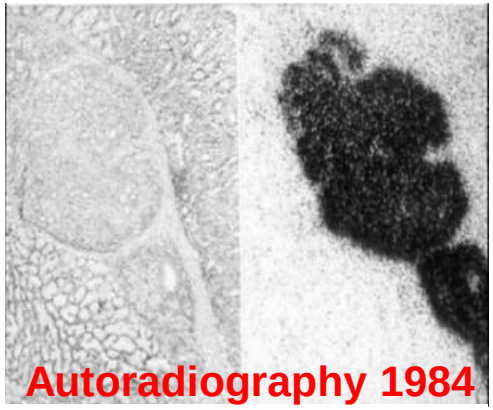
Cytotoxic Unit

- ^{90}Y, ^{177}Lu
- ^{225}Ac, ^{213}Bi

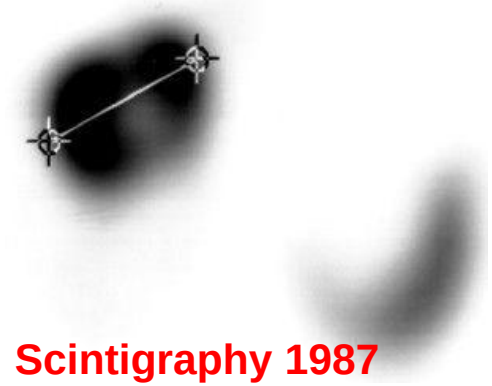
Courtesy Helmut Mäcke (modified)

PRRT: from bench to bedside to clinical approval

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

1994 • **First PRRT with high-dose ^{111}In-octreotide**

1996 • **First ^{90}Y-octreotide PRRT - Basel**

2000 • **First ^{177}Lu-octreotate PRRT - Rotterdam**

2012 • Phase III registration trial of ^{177}Lu-octreotate

NETTER-1 trial: First results reported at ESMO 2015

Approval of Lutathera by EMA (09/2017) & FDA (01/2018)

A landmark publication in Theranostics

The NEW ENGLAND JOURNAL of MEDICINE

EMA Approval in September 2017

FDA Approval in January 2018

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

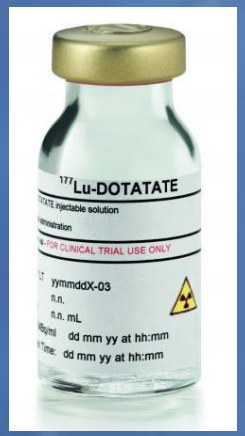
N Engl J Med 2017;376:125-35.

TRC

NETTER-1 Trial (AAA-III-01)

multicentre, stratified, open, randomized, phase III study

R



^{177}Lu-DOTATATE:

- 200 mCi x 4 cycles at q8 wks + Octreotide LAR 30 mg q4 wks

Compare PFS

Octreotide LAR:

- Octreotide LAR 60 mg q4 wks

Over 20 years from first clinical use in patients to drug approval !

Courtesy Lisa Bodei

NETTER-1 RCT Results in SI-NET

Long Progression-Free Survival

N = 229 (ITT)

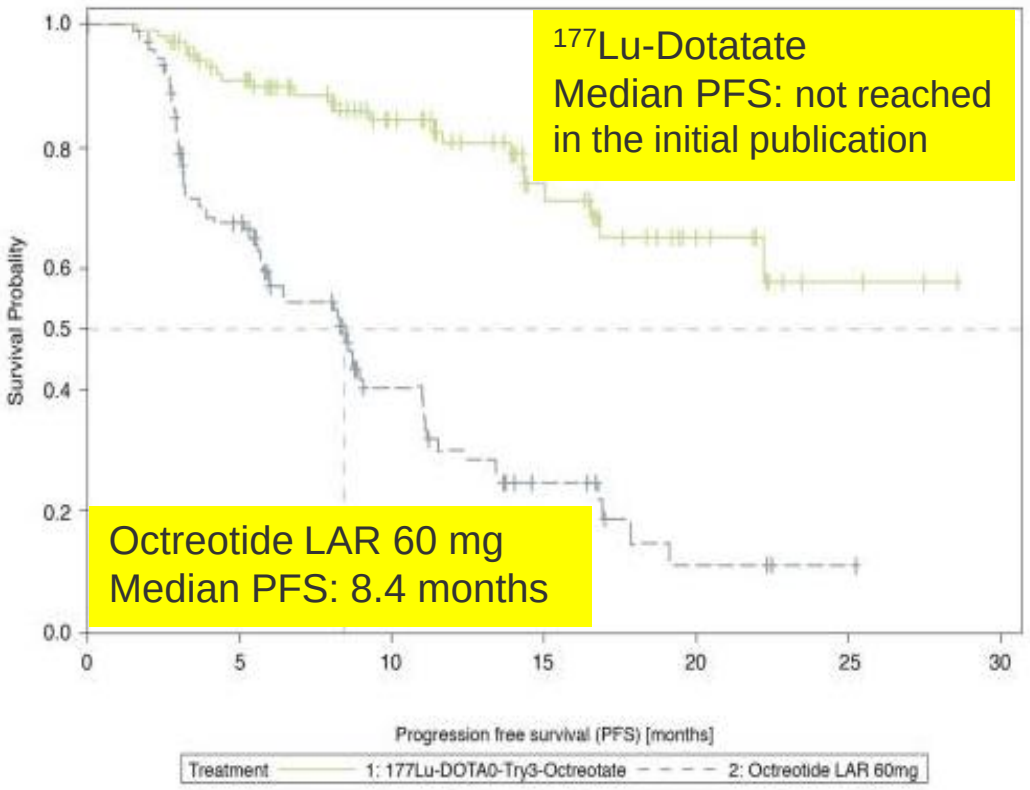
Number of events: 90

- ^{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

Median PFS
Lu-DOTATATE arm
Now reported: 28.4 mo

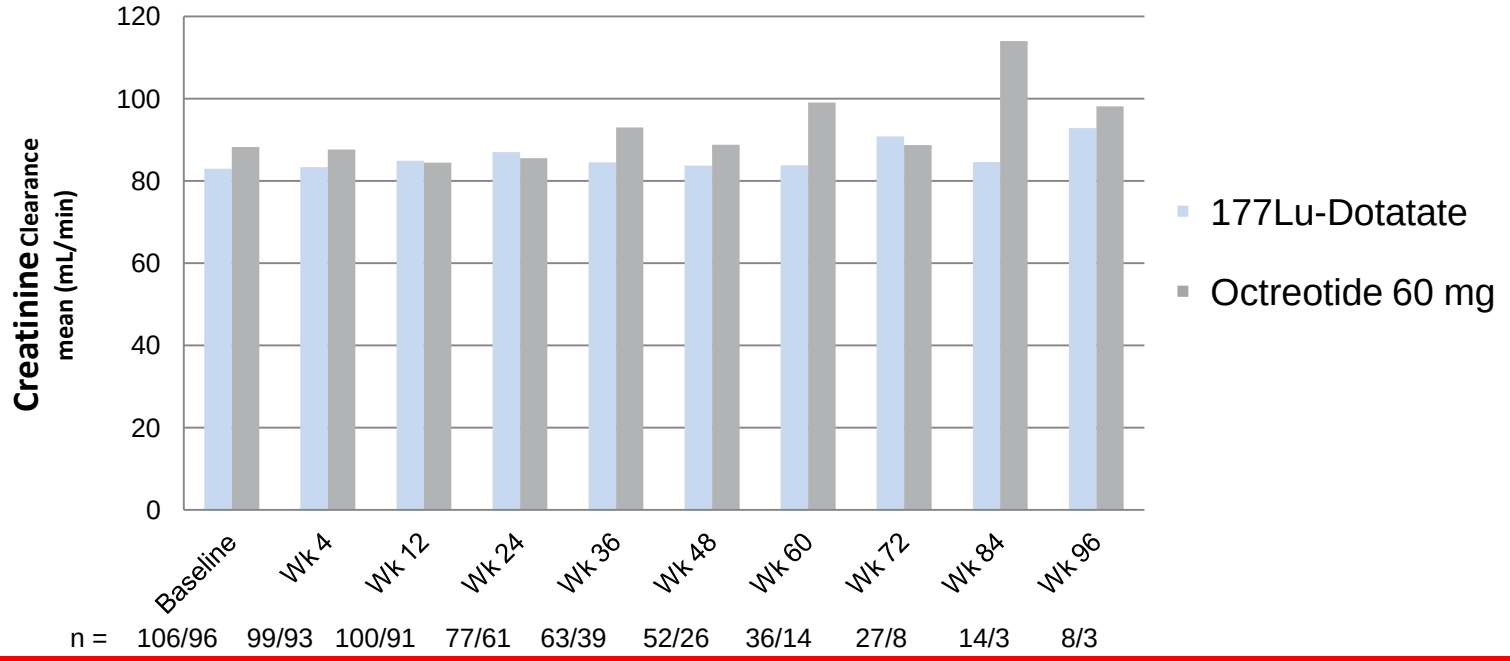


All progressions centrally confirmed and independently reviewed for eligibility (SAP)

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

Creatinine Clearance
Renal function remains stable over the 2-year observation period

	^{177}Lu-Dotatate (N = 111)	Octreotide LAR (N = 110)
	Grade 3/4	Grade 3/4
Creatinine increased	0%	0%



Lu-177 is not nephrotoxic!

Quality of life findings in the NETTER-1 Study

EORTC QLQC-30 G.I.SNET-21 questionnaires at baseline and every 12 weeks thereafter until progression

QoL scores were converted to a 100-point scale

Time to deterioration was defined as the time (in months) between randomization and the first QoL deterioration ≥10 points for each patient in the corresponding domain scale.

Time to QoL deterioration was significantly longer in the Lu-177 DOTATATE vs control arm for:

global health status (hazard ratio (HR) 0.406; p=0.0006)

physical functioning (HR 0.518; p=0.0147)

role functioning (HR 0.580; p=0.0298)

fatigue (HR 0.621; p=0.0297)

pain (HR 0.566; p=0.0247)

diarrhea (HR 0.473; p=0.0107)

disease related worries (HR 0.572; p=0.0176)

and body image (HR 0.425; p=0.0058)

DOI: 10.1200/JCO.2016.34.15_suppl.4005 Journal of Clinical Oncology 34, no. 15_suppl (May 20 2016) 4005-4005.

Quality of life findings in the NETTER-1 Study

- Treatment with ^{177}Lu-Dotatate is associated with **improvement in quality of life** in several key domains including global health and diarrhea.
- Non-statistically-significant improvement in QOL seen (more improvement/less worsening) observed with ^{177}Lu-Dotatate in most domains.
- No evidence of significantly decreased quality of life with ^{177}Lu-Dotatate observed in any domain.
- Limitation of study includes lack of blinding. Patients were aware of treatment assignment.

DOI: 10.1200/JCO.2016.34.15_suppl.4005 Journal of Clinical Oncology 34, no. 15_suppl (May 20 2016) 4005-4005.

The **COMPETE** study

Trial started in 2017

Controlled, **O**pen-label, **M**ulticentre study of **P**RRT with ^{177}Lu-**E**dotreotide compared to targeted molecular **T**herapy with **E**verolimus in neuroendocrine tumours of the **pancreas (P-NET) and midgut**

300 GEP-NET patients will be randomized 2:1 to receive either Targeted Radionuclide Therapy with ^{177}Lu-Edotreotide consisting of a maximum of four cycles (7.5 GBq ^{177}Lu-Edotreotide each), administered as an IV infusion at 3-month intervals for 9 months, or until diagnosis of progression (200 patients), or 10 mg Everolimus daily, administered orally as a tablet until diagnosis of progression (100 patients).

Study duration per patient will be 24 months.

Peptide Receptor Radionuclide therapy (ZBB)

As of March 31, 2018

Patients treated	**n = 1532**
Therapy cycles	**n = 5616**

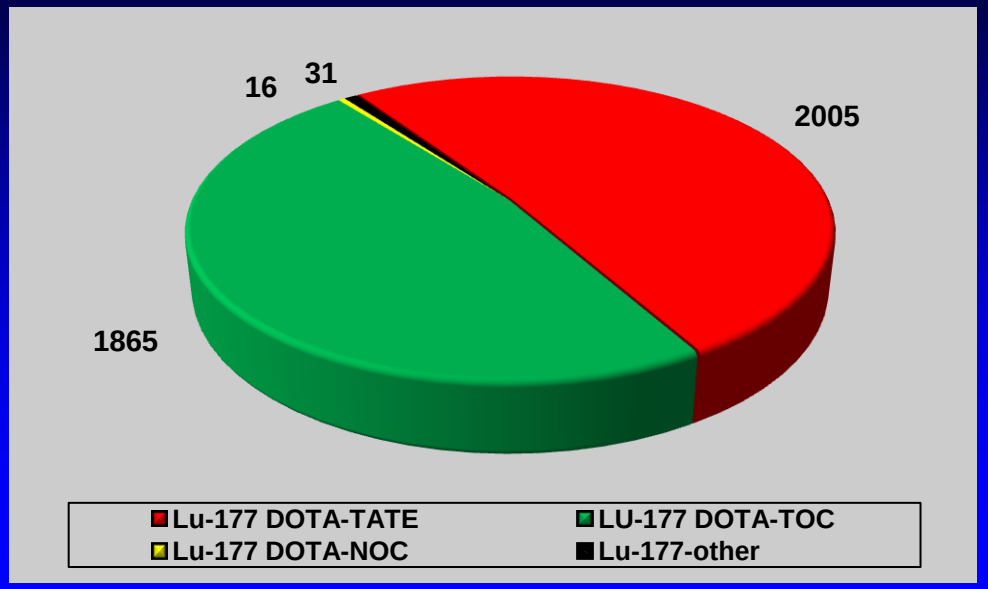
Lu-177	**n = 3917**
Y-90	**n = 1737**
Bi-213	**n = 1**

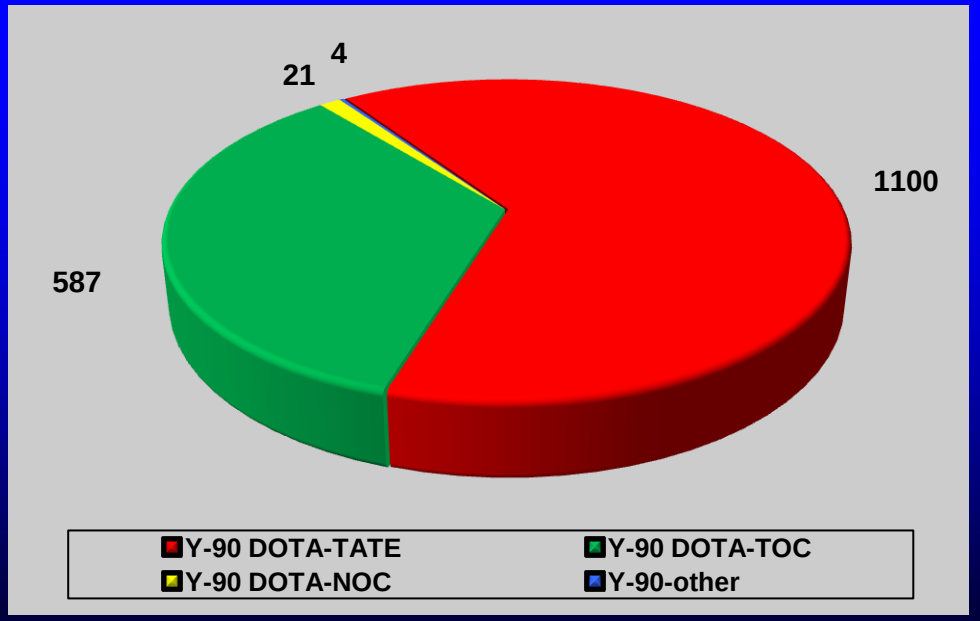
Somatostatin receptor positive neuroendocrine tumors

	Y-90	Lu-177
Mean	3,35 GBq	6.5 GBq
Max.	9,50 GBq	12.06 GBq

Age: 4 – 86 years

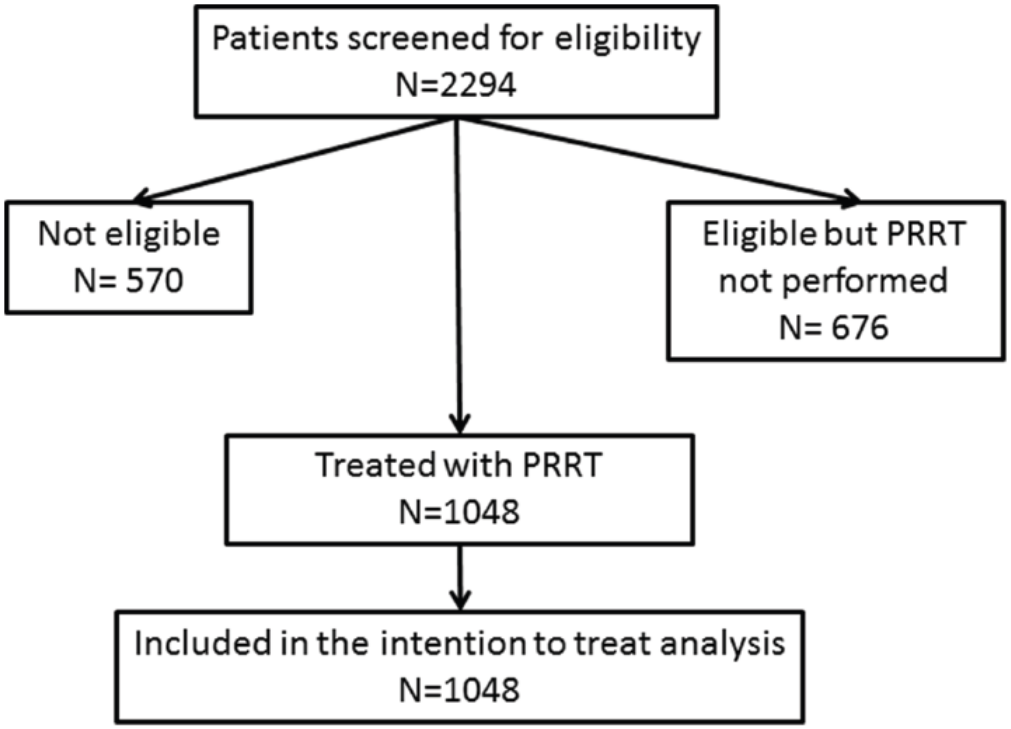
Median: 59.8 years





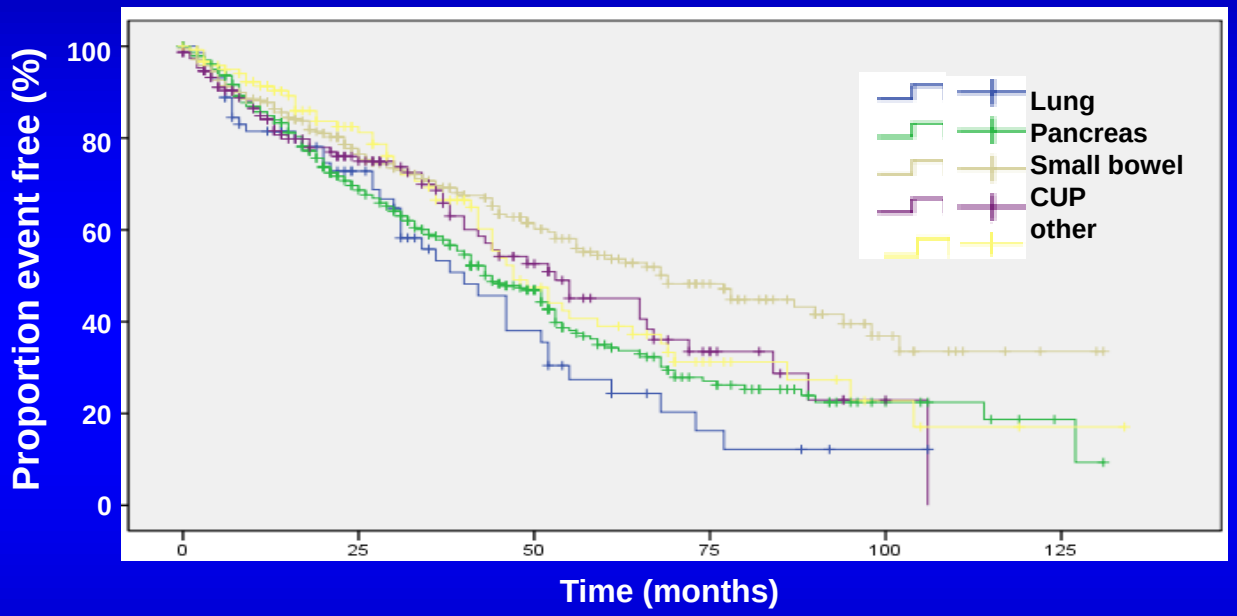
Results and adverse events of personalized peptide receptor radionuclide therapy with ^{90}Yttrium and ^{177}Lutetium in 1048 patients with neuroendocrine neoplasms

Richard P. Baum[1], Harshad R. Kulkarni[1], Aviral Singh[1], Daniel Kaemmerer[2], Dirk Mueller[1], Vikas Prasad[3], Merten Hommann[2], Franz C. Robiller[4], Karin Niepsch[1], Holger Franz[5], Arthur Jochems[6], Philippe Lambin[6,7] and Dieter Hörsch[8]



OVERALL SURVIVAL ACCORDING TO PRIMARY TUMORS

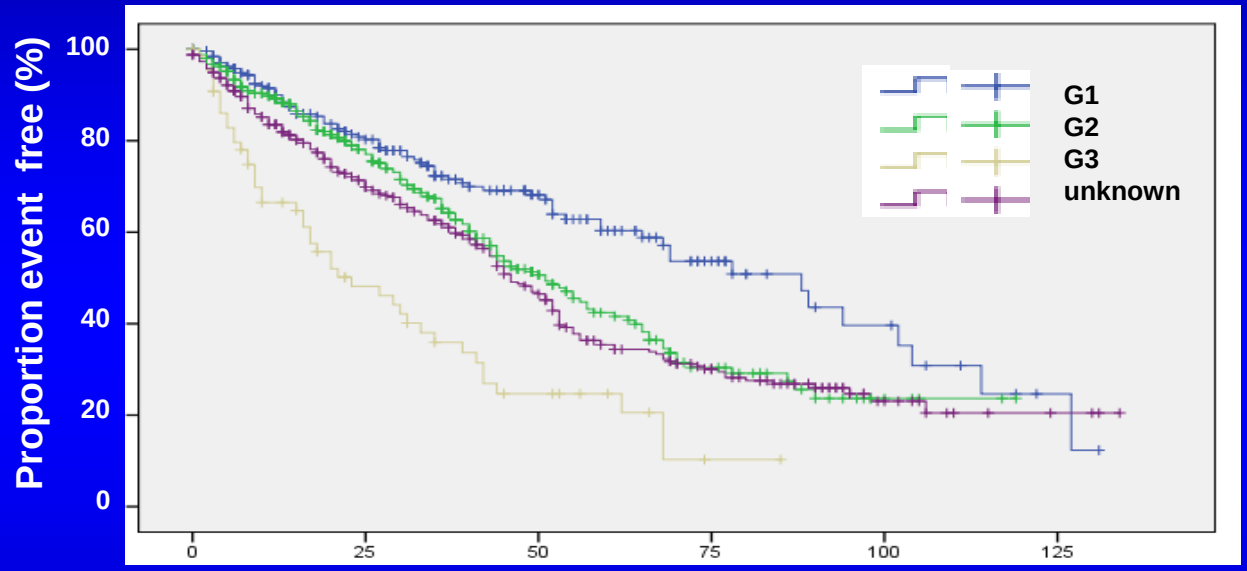
Patients with NENs of small intestinal origin (69 months 53.7-84.2 95% CI) had a better survival compared to other primary tumors



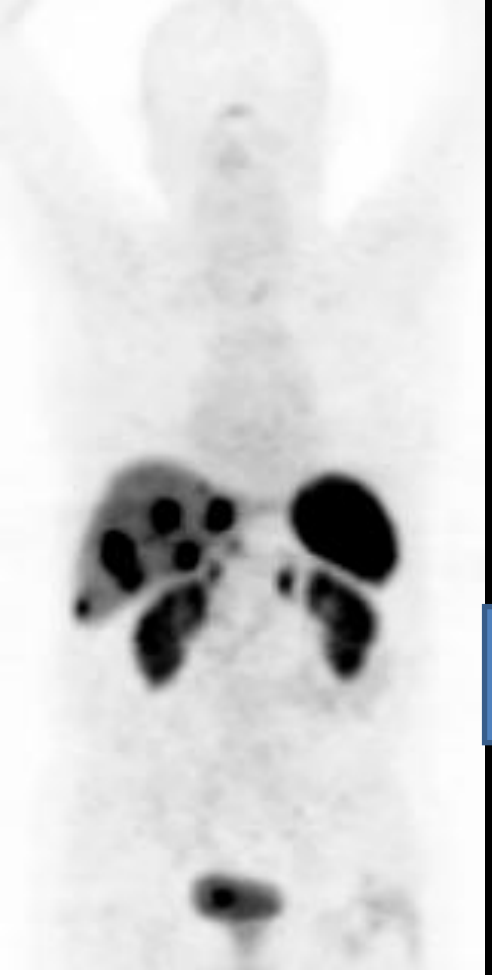
Number at risk:						
Total	1048	561	262	103	28	5
Lung	75	37	15	4	1	0
Pancreas	384	202	95	32	9	2
Small bowel	315	185	91	45	12	2
CUP	151	72	32	11	2	0
Other	123	65	29	11	4	1

OVERALL SURVIVAL ACCORDING TO TUMOR GRADE

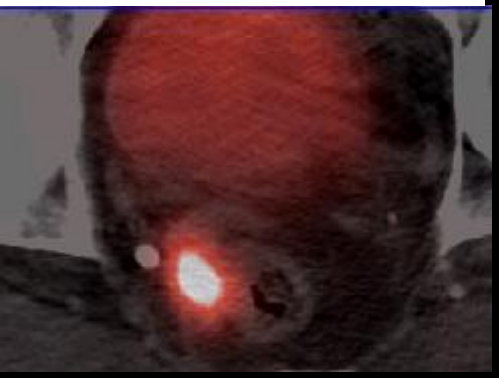
Patients with G1 NEN had a better survival (88 months 69.3-106.6 95% CI) compared to G3 NEN (23 months 10.8-35.2 95% CI)

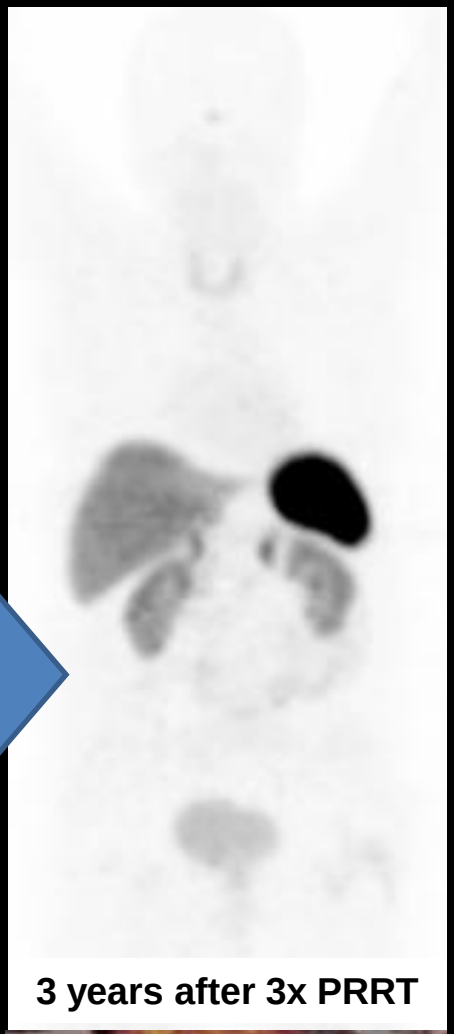


Number at risk:						
Total	1048	561	262	103	28	5
G1 (≤2%)	247	137	68	25	10	2
G2 (3-20%)	399	206	77	26	5	0
G3 (>20%)	67	24	10	1	0	0
unknown	335	194	107	51	13	3

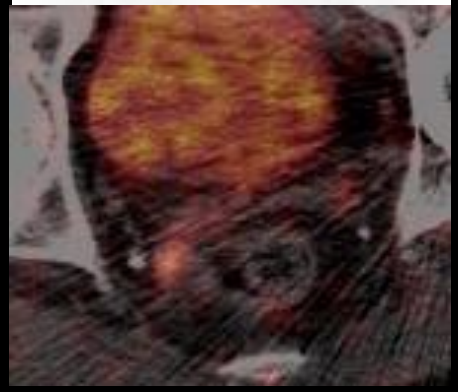


Pre-PRRT





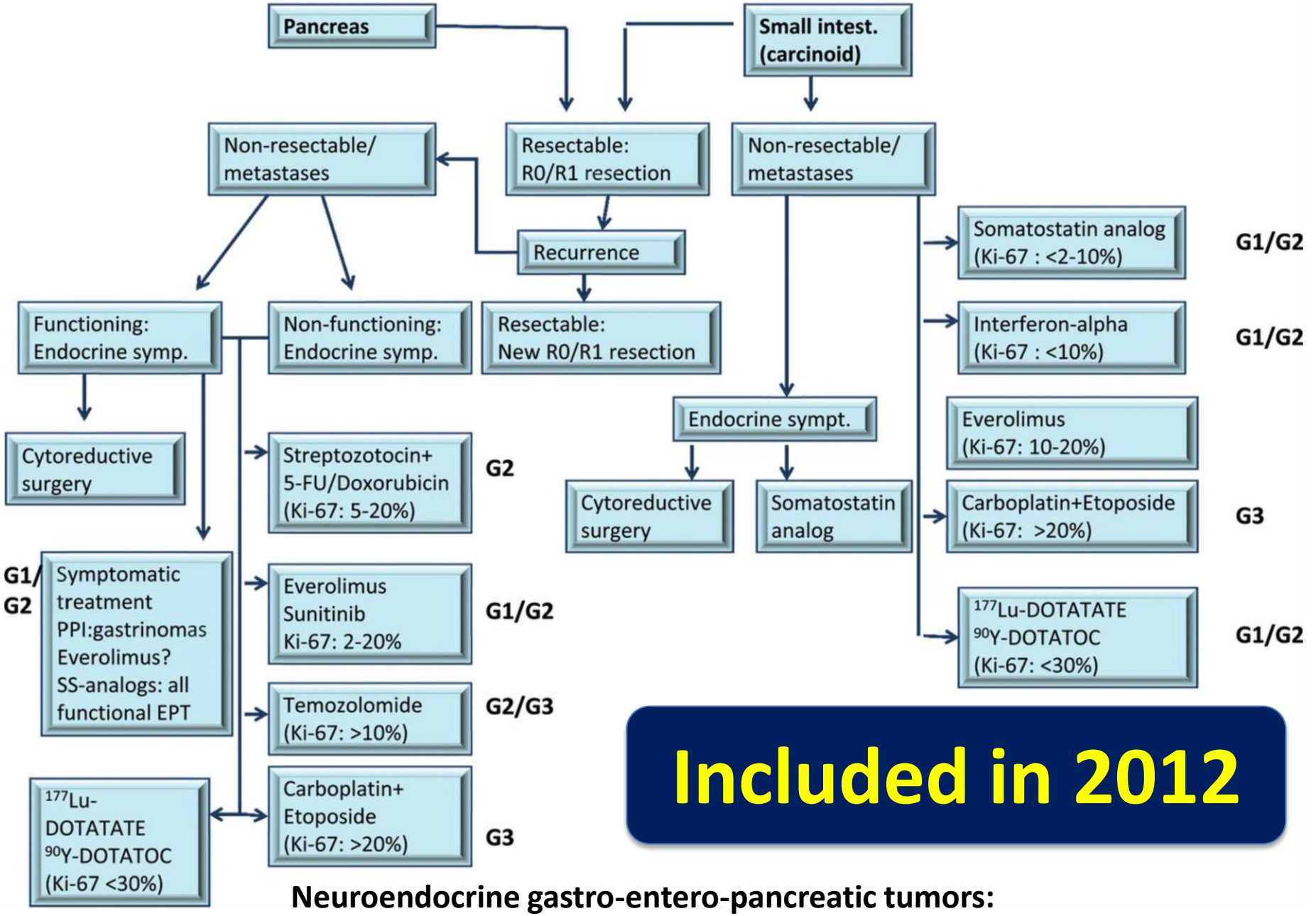
3 years after 3x PRRT



71 y-o patient

Well-differentiated, non-functioning neuroendocrine neoplasm of the rectum: persistent remission of multiple liver metastases 3 years after 3 PRRT cycles

The primary tumor also demonstrated a response to PRRT with decrease in size on CT and uptake on PET.

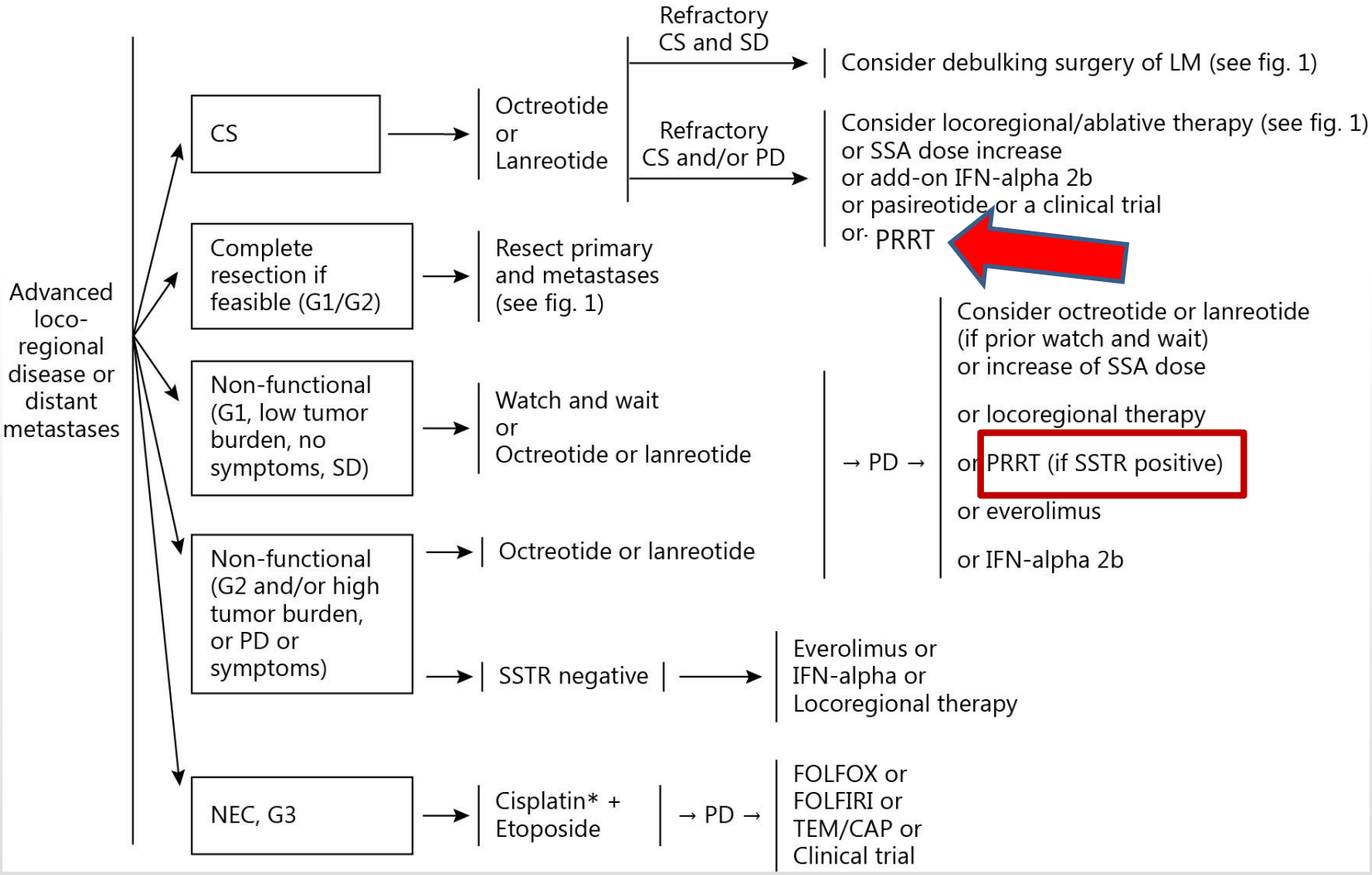


Neuroendocrine gastro-entero-pancreatic tumors:
ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Ann Oncol. 2012;23(suppl_7):vii124-vii130. doi:10.1093/annonc/mds295

ENETS Guidelines 2016

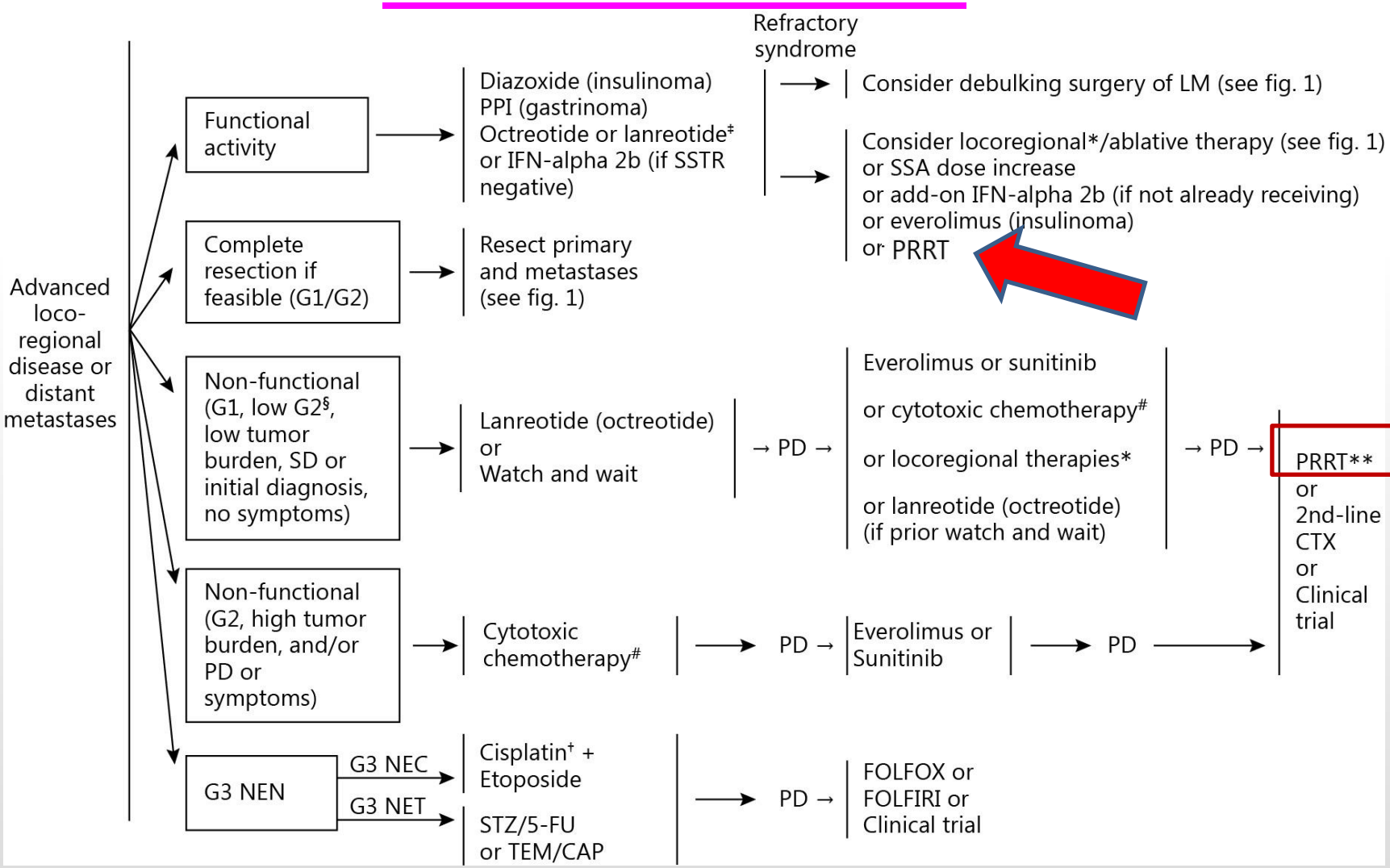
Intestinal NET



Pavel et al Neuroendocrinology 2016

ENETS Guidelines 2016

Pancreatic NET



Pavel et al Neuroendocrinology 2016

Peptide Receptor Radiotherapy – what does the future hold?

- **Combination therapies – PRRT+**
  - **PRCRT (PRRT + chemotherapy)**
  - **PRIT (PRRT + immunotherapy)**
  - **Surgery (neoadjuvant / adjuvant PRRT, use of intraoperative probes)**
  - **TACE (transarterial chemoembolization)**
  - **SIRT (selected internal radiation therapy)**
  - **RFA (radiofrequency ablation)**
  - **Kinase inhibitors**
  - **Radiosensitizers**

- **Targeted alpha radiation therapy (ART, e.g. Bismuth-213, Actinium-225)**
- **Novel radioisotopes for imaging and therapy (theranostic pairs - Sc-44/Sc-47, Cu-64/Cu-67, Tb-152/Tb-149, Tb-155/Tb-161)**
- **Novel targets (e.g. SSR antagonists, CXCR4, GLP, GIP)**
- **Liquid biopsy (pCR and gene analysis for better selection of patients for PRRT, prognostication of efficacy of therapy and of possible side effects)**
- **Radiomics (selection of patients for PRRT, prognostication of therapy effects)**

- **DUO-PRRT i.e., using Y-90 and Lu-177 labeled SSA in sequence**
- **TANDEM-PRRT i.e., using Y-90 and Lu-177 labeled SSA simultaneously**
- **Intra-arterial PRRT**
- **Improvements in dosimetry (personalized and predictive dosimetry)**

Long-term results and tolerability of tandem peptide receptor radionuclide therapy with $^{90}Y/^{177}Lu$-DOTATATE in neuroendocrine tumors with respect to the primary location: a 10-year study.

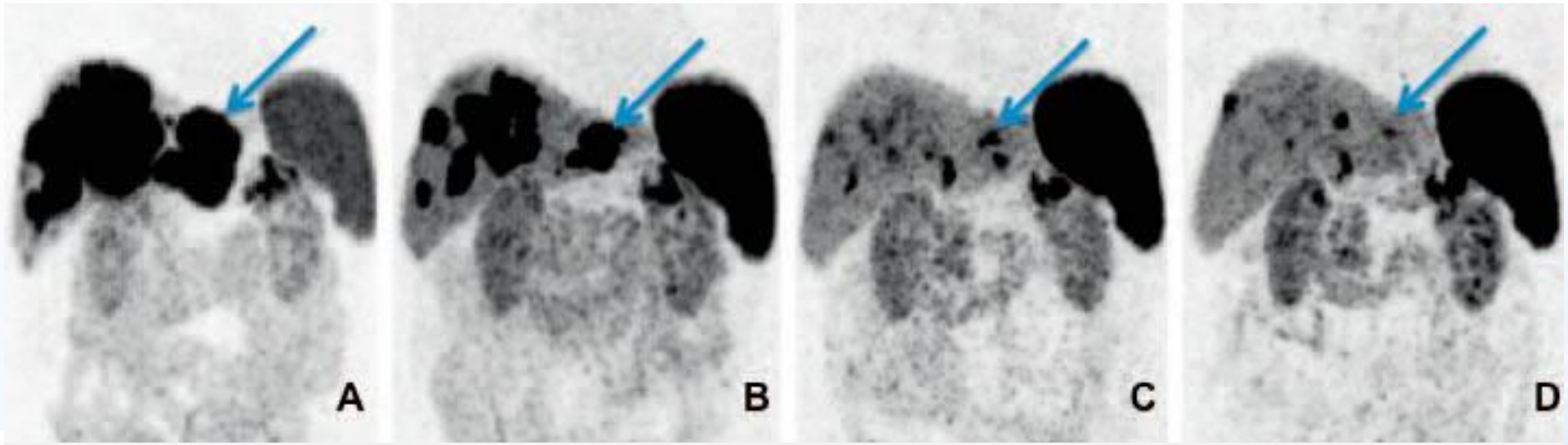
Ann Nucl Med. 2017 Jun;31(5):347-356.

Kunikowska J[1], Pawlak D[2], Bąk MI[3], Kos-Kudła B[4], Mikołajczak R[2], Królicki L[5].

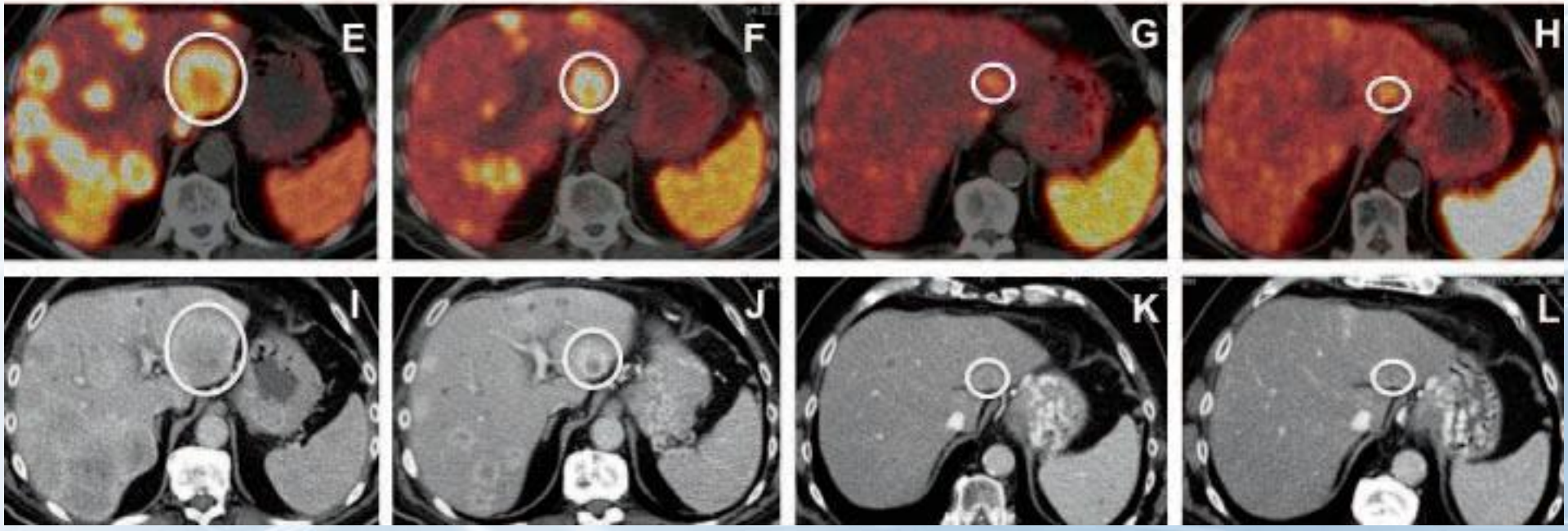
MATERIALS AND METHODS: 59 patients with disseminated NET were included in the study prospectively. 3-5 cycles of combined 1:1 $^{90}Y/^{177}Lu$-DOTATATE (total injected activity 11.1-16.65 GBq) with mixed amino acids for kidney protection were performed.

RESULTS: During a median follow-up of 75.8 months, the PFS was 32.2 months, and the OS was 82 months; 25 patients died. Depending on primary tumor's site, the PFS and the OS for pancreatic NET vs. small bowel, NET vs. large bowel, NET were 30.4 vs. 29.5 vs. 40.3 and 78.9 vs. 58.1 vs. 82.5, respectively. The observed 5-year overall survival was 63%, and a 2-year risk of progression was 39.4%. The following imaging response was observed: CR in 2%, PR in 22%, SD in 65%, and PD in 6% patients. The disease control rate was 89%. The objective response rate was 24%. The **PRRT** was well tolerated by all patients. One patient (2%) revealed MDS, and one patient (2%) grade 3 nephrotoxicity. No other grade 3 and 4 hematological or renal toxicity was observed.

CONCLUSIONS: These results indicated the **tandem** $^{90}Y/^{177}Lu$-DOTATATE therapy for patients with disseminated/inoperable NET as highly effective and safe, considering long-term side effects. In the majority of patients, clinical improvement was observed.



72M with WD functional pNEN – glucagonoma - (G2, Ki-67 10%) with extensive LM
4 cycles of PRRT (DUO–PRRT: 1st with Y-90, subsequent 3 with Lu-177)
Result: PR (*molecular as well as objective*)

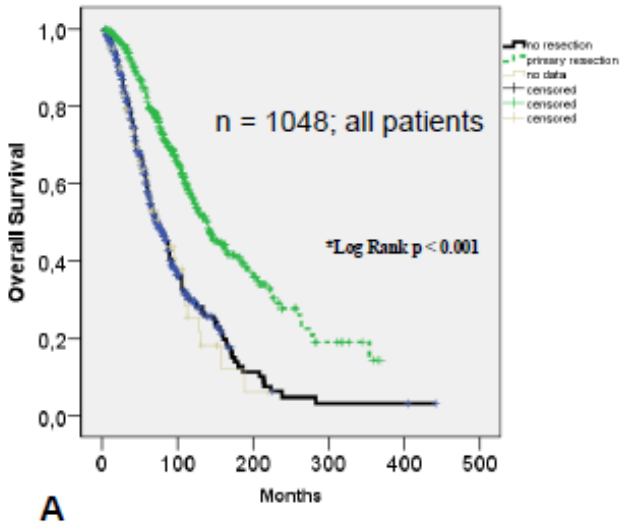


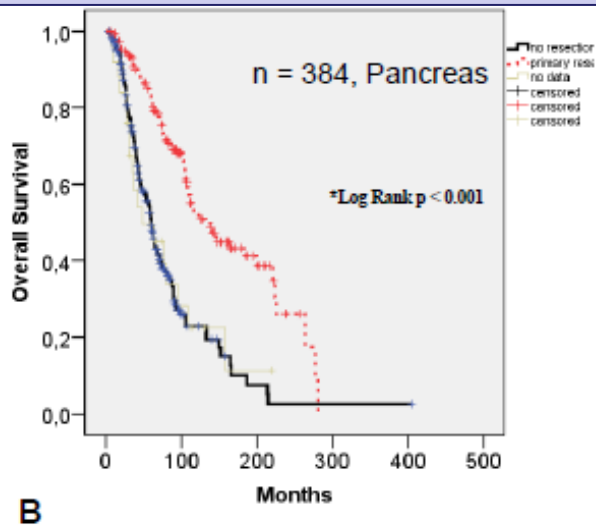
Primary Tumor Resection Results in Superior Overall Survival after Peptide-Receptor-Radionuclide-Therapy (PRRT) in Advanced Neuroendocrine Neoplasms.

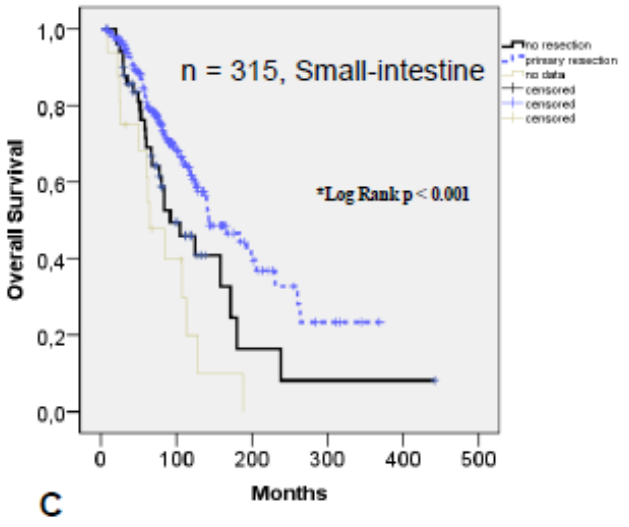
D. Kaemmerer[1], M. Twrznik[1], M. Hommann[1], D. Hörsch[2], RP. Baum[3]

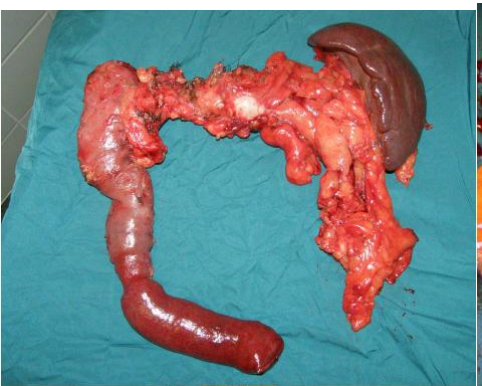
[1]Department of General and Visceral Surgery, Zentralklinik Bad Berka, Germany,
[2]Department of Internal Medicine, Gastroenterology and Endocrinology, Zentralklinik Bad Berka, Germany,
[3]THERANOSTICS Center for Molecular Radiotherapy and Molecular Imaging / Center for PET, Zentralklinik Bad Berka, Germany.

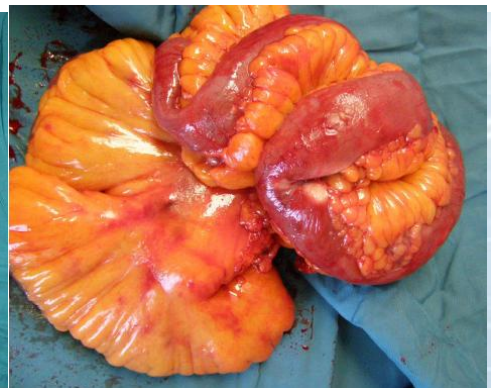
Presented at ENETS 2017







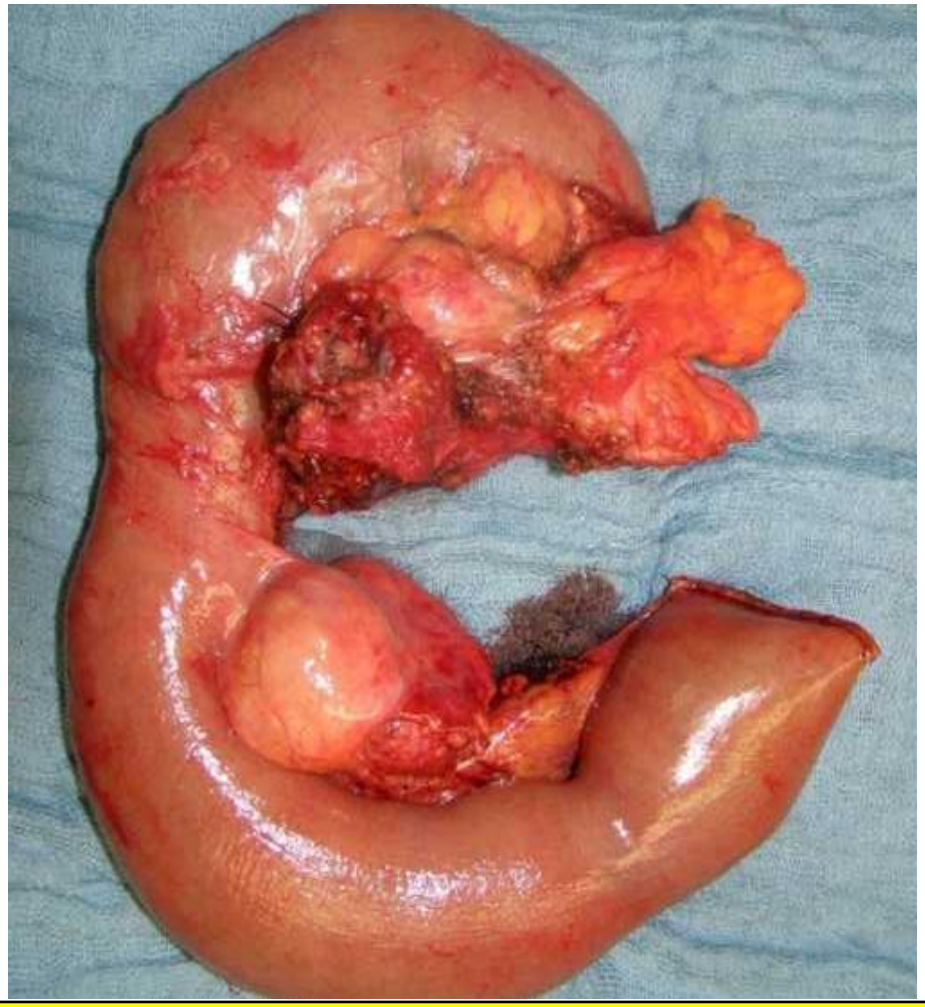


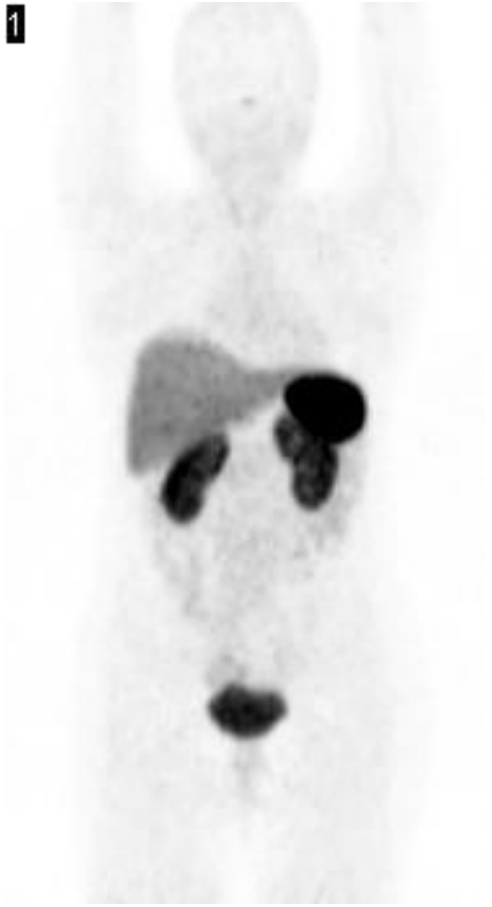


After surgery of the primary tumor, pts. have a better survival following PRRT.

These effects may result from selection bias, however, there are strong indicators for clinical practice that primaries should be removed when feasible.

Whipple‘s Operation – Complete Resection of Pancreatic NET after Neoadjuvant PRRT





Histology revealed nearly total tumor necrosis typical for radiation necrosis

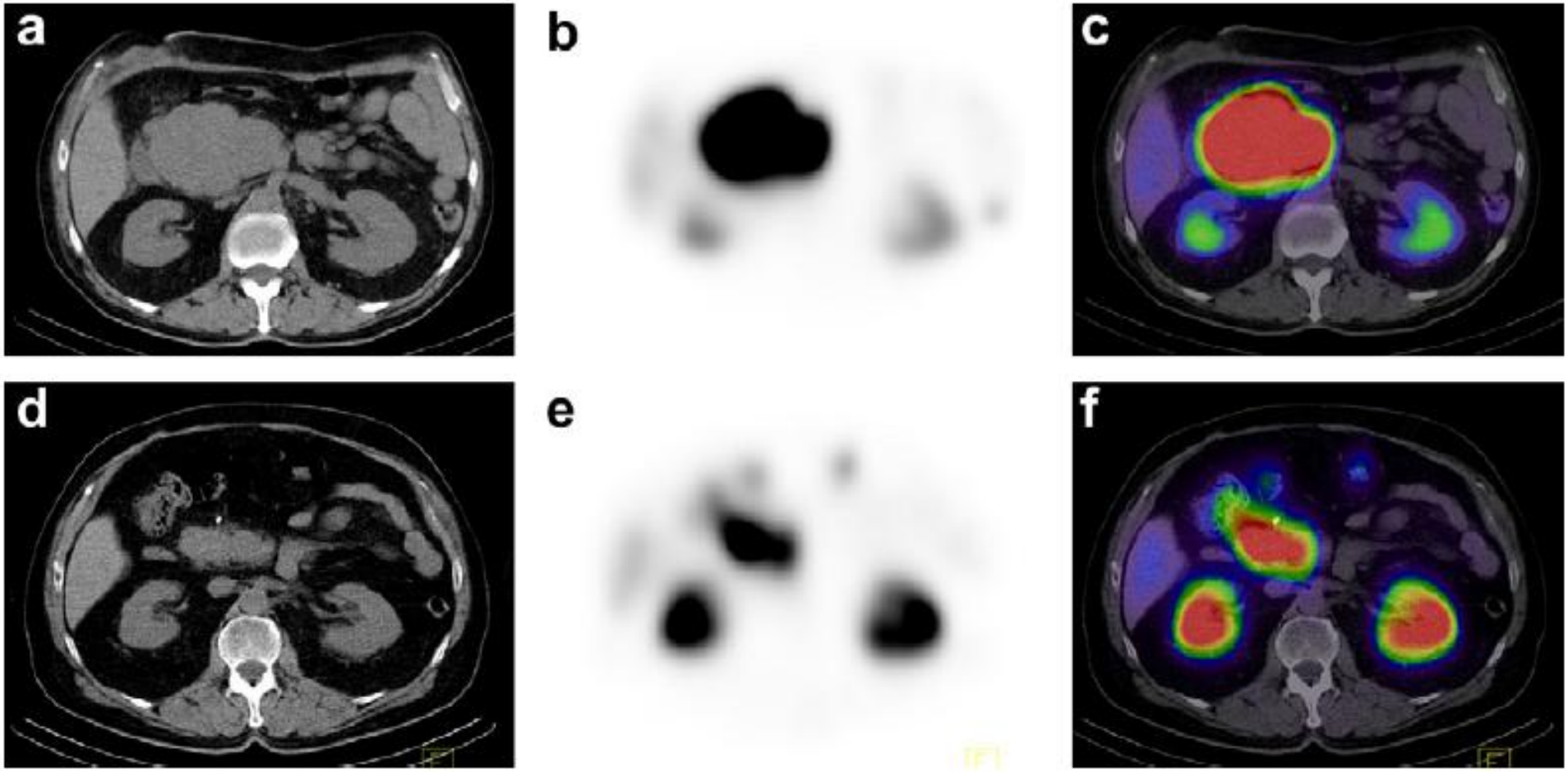
Follow-up at 10 years: Complete Remission

The potential for induction peptide receptor chemoradionuclide therapy to render inoperable pancreatic and duodenal neuroendocrine tumours resectable

T.W. Barber [a,*,1], M.S. Hofman [a,b,1], B.N.J. Thomson [b,c,2], R.J. Hicks [a,b,1]

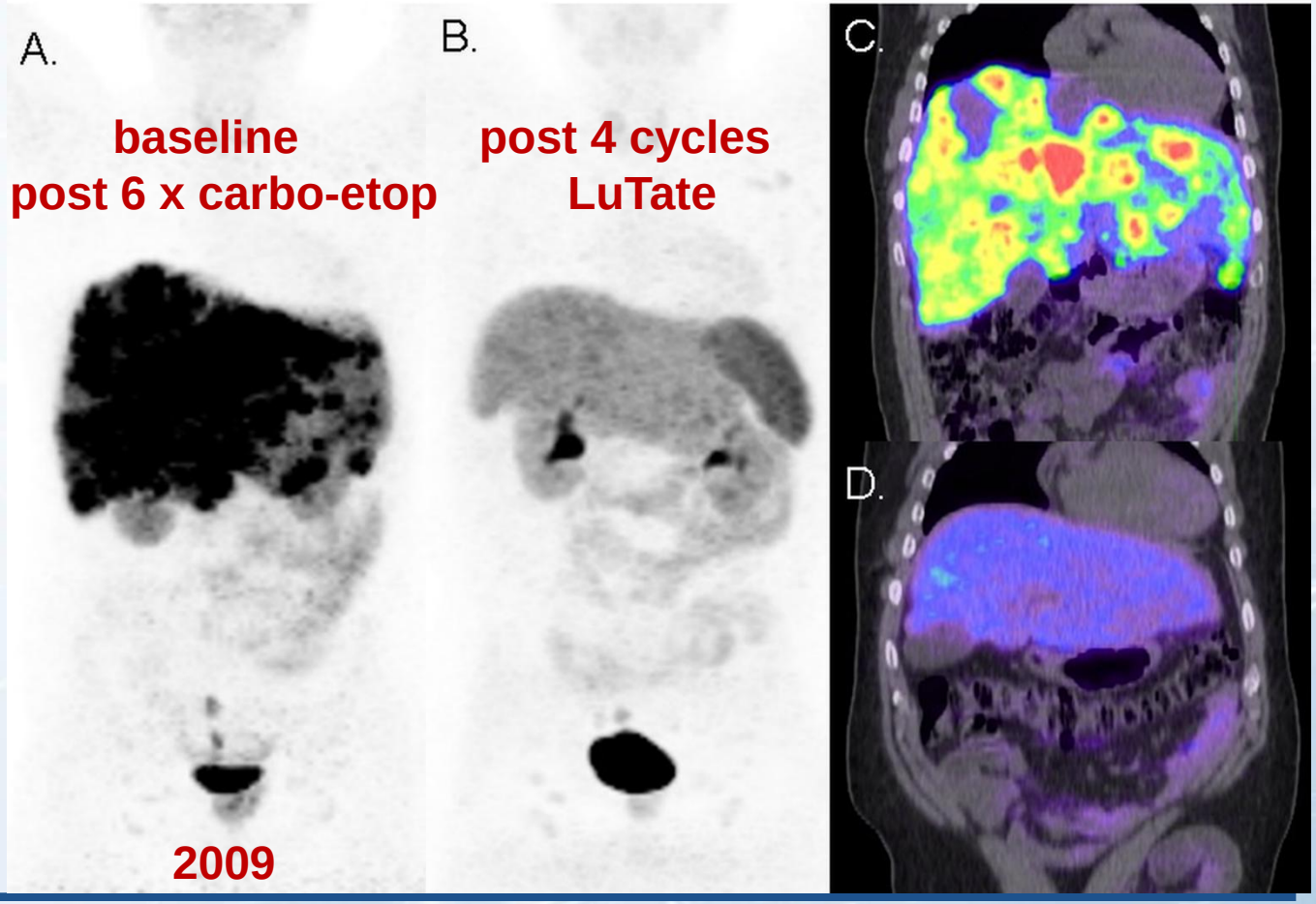
EJSO 38 (2012) 64–71

PRCRT using 177Lu-octreotate (LuTate) with concurrent 5FU chemotherapy in patients with inoperable primary pancreatic and duodenal neuroendocrine tumours (NETs) can be effective and may play a role as neoadjuvant therapy in this patient group.



Response to LuTate PRCRT in ENETS G3 NEN

- 46yo with rectal NET | Ki-67=40%
- Progressed following 6 cycles of carbo-etoposide chemo



Near complete response

Courtesy: Prof. Michael Hofman, Australia

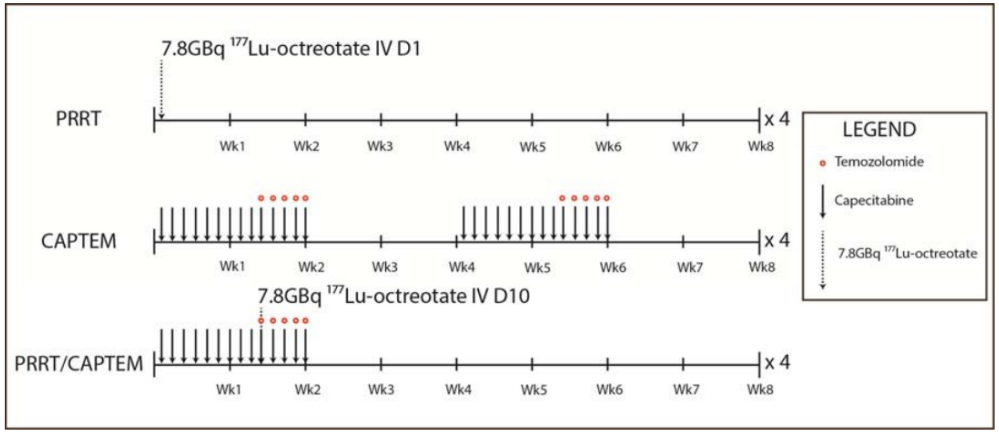
PeptideReceptorChemoRadioTherapy (PRCRT)

Australia Leading the Way: RCT of PRCRT

Cohort A: pancreatic NETs: Lu-177 DOTATATE+CAPTEM vs. CAPTEM (control)

Cohort B: small bowel NETs: Lu-177 DOTATATE+CAPTEM vs. Lu-DOTATATE (control)

CONTROL NETs Treatment Plan



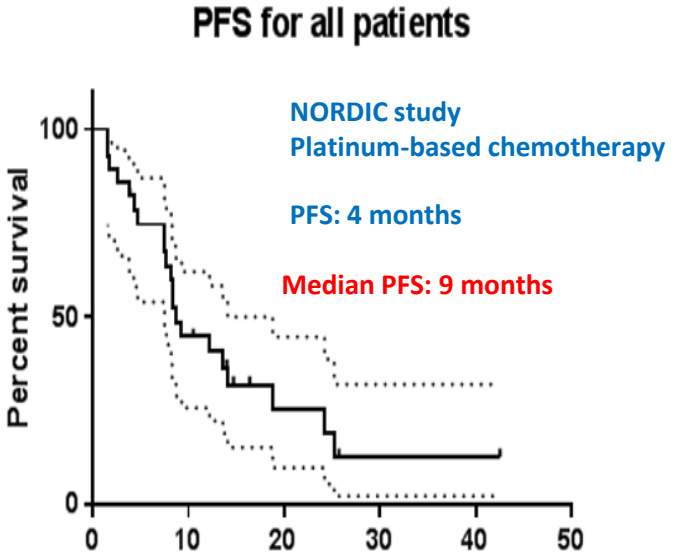
Note: For CAPTEM alone one cycle is shown in this diagram. Each 8 week CAPTEM alone cycle includes 2 weeks CAPTEM followed by a 2 week break then another 2 weeks CAPTEM followed by a 2 week break.

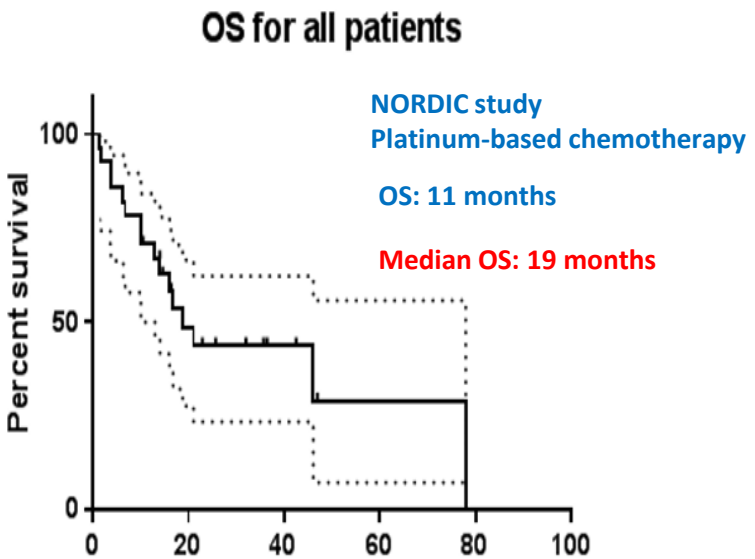
State	Site	Principal Investigator
NSW	Royal North Shore Hospital	A/Prof Nick Pavlakis
NSW	St George Hospital	Dr Katrin Sjoquist
WA	Fiona Stanley Hospital	Dr David Ransom
SA	The Queen Elizabeth Hospital	Dr Gabrielle Cehic
QLD	Royal Brisbane and Women's Hospital	Dr David Wyld
VIC	Peter MacCallum Cancer Centre	Prof Rod Hicks

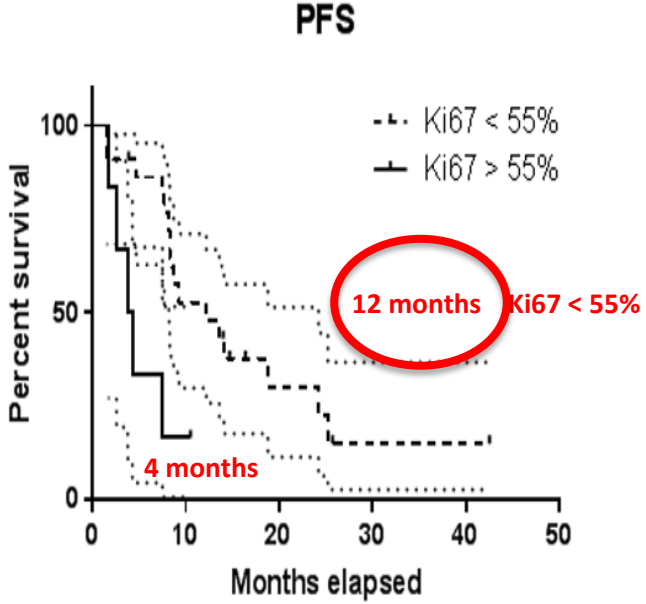
AGITG
AUSTRALASIAN GASTRO-INTESTINAL TRIALS GROUP

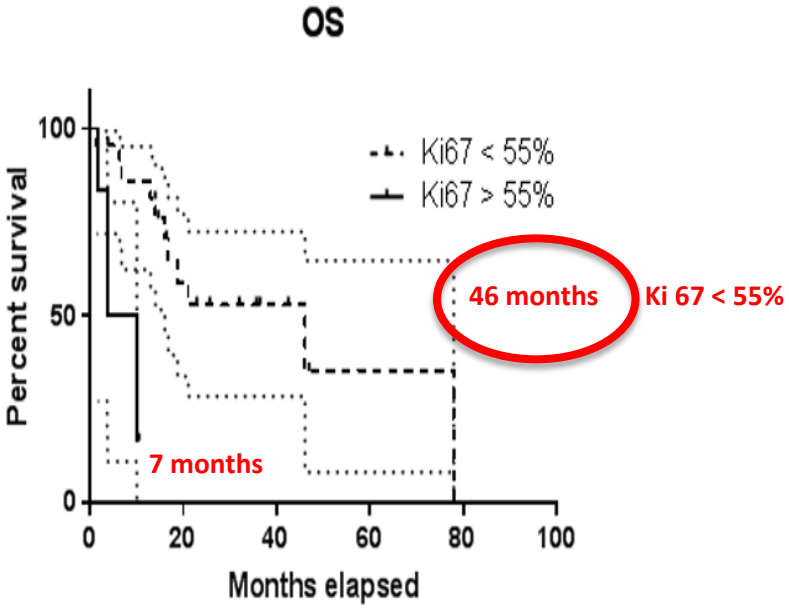
PRRT of G3 NEN: Progression Free Survival (PFS) and Overall Survival (OS)

Median follow-up = 29 months. 16 patients died (Ki-67 ≤55% = 11; Ki-67 >55% = 5).







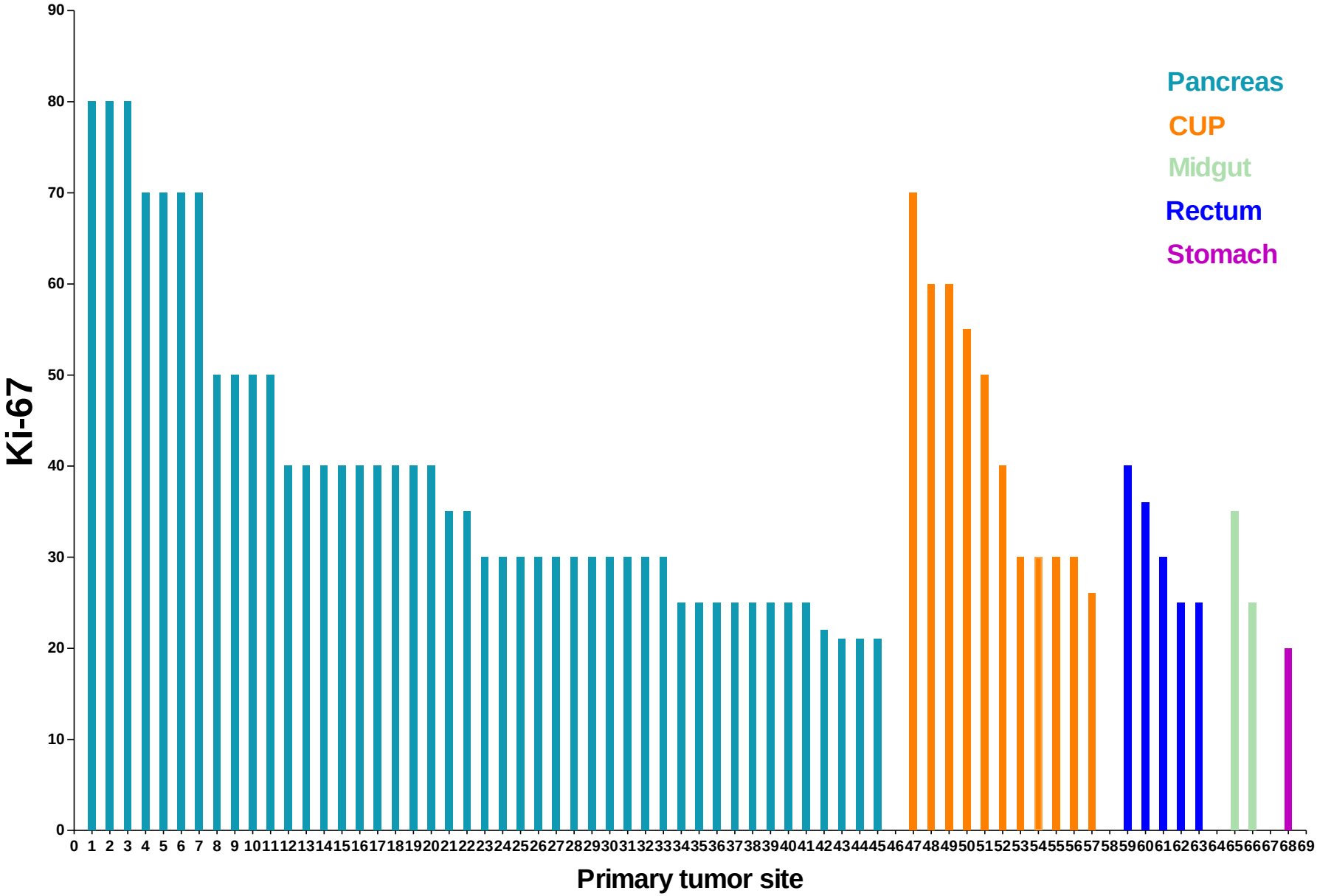


Ping Thang S et al. EJNMMI 2017

Sorbye H et al. Ann Oncol. 2013;24:152-60

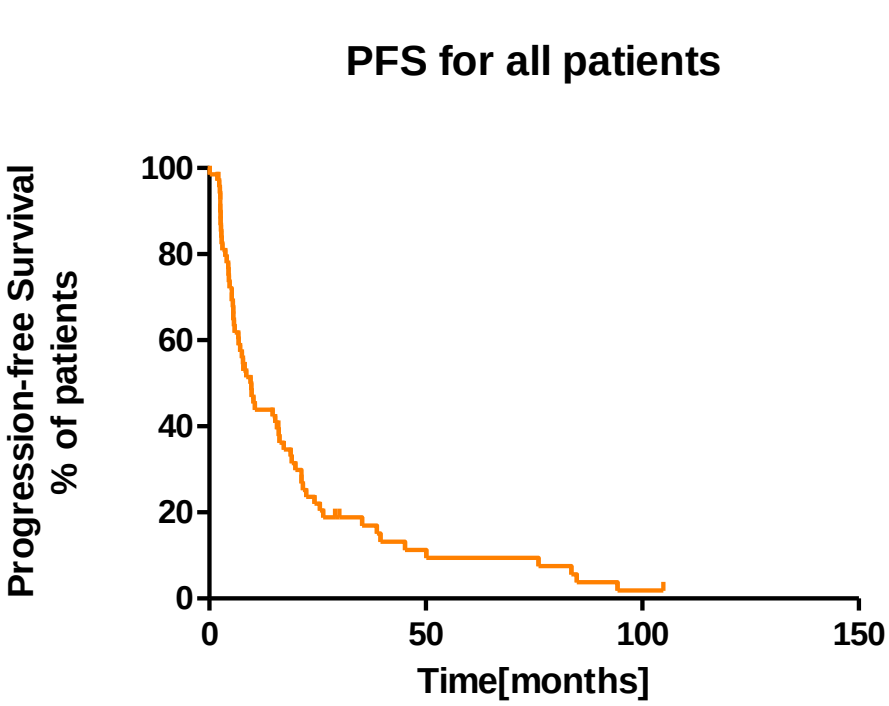
Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms

Primary tumor to Ki-67% profile in 64 patients treated at Zentralklinik Bad Berka

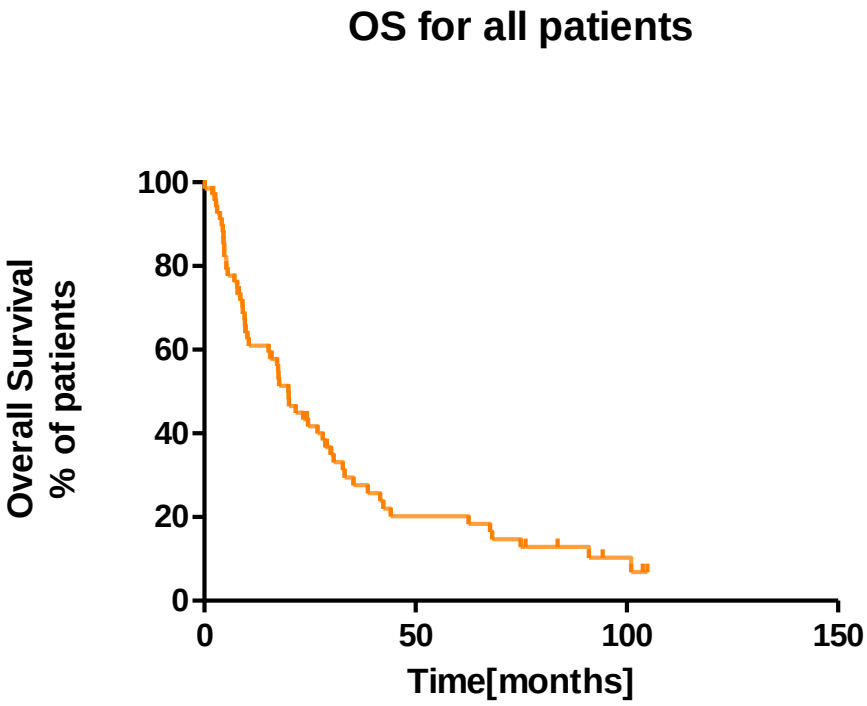


ZBB unpublished data

Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms
Survival Analysis in 64 patients treated at Zentralklinik Bad Berka



Median PFS = 9.6 months
 # deaths/events=63

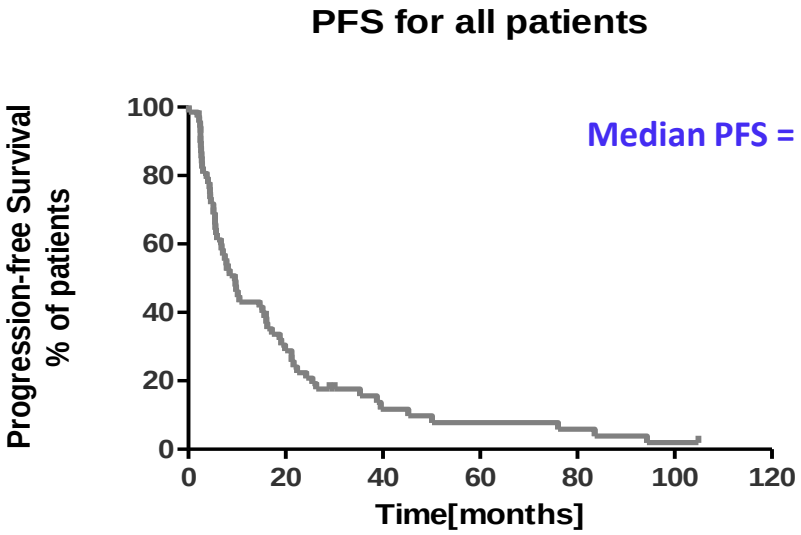


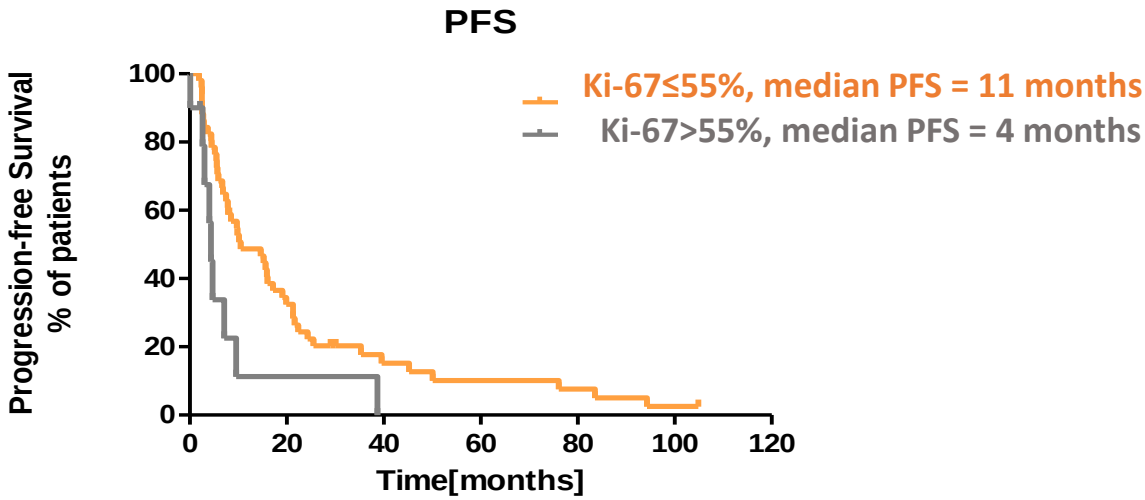
Median OS = 19.9 months
 # deaths/events=56

In G3 NEN patients median progression-free (PFS) and overall survival (OS) were 9.6 and 19.9 months, respectively, with a median follow-up time of 94.3 months (range 0.1-104.9 months).

Unpublished data

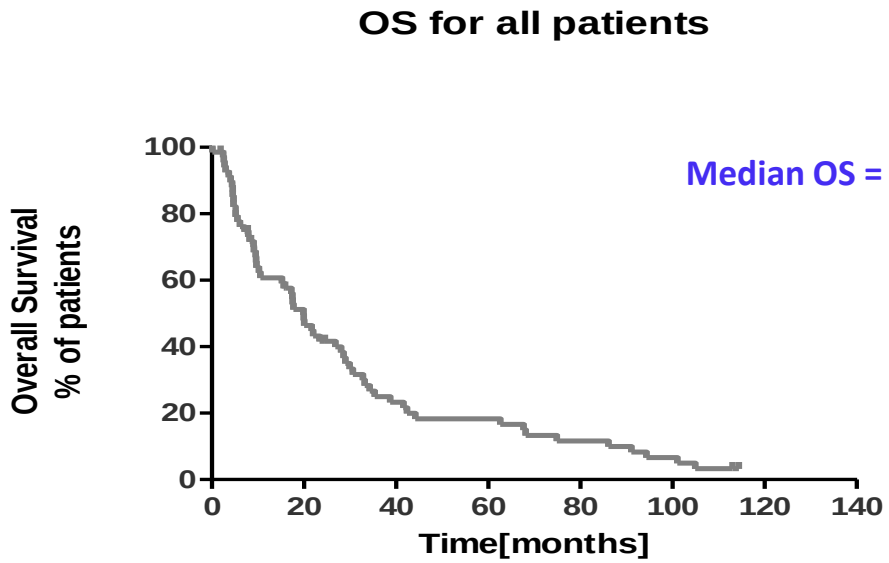
Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms
Survival Analysis in 64 patients treated at Zentralklinik Bad Berka

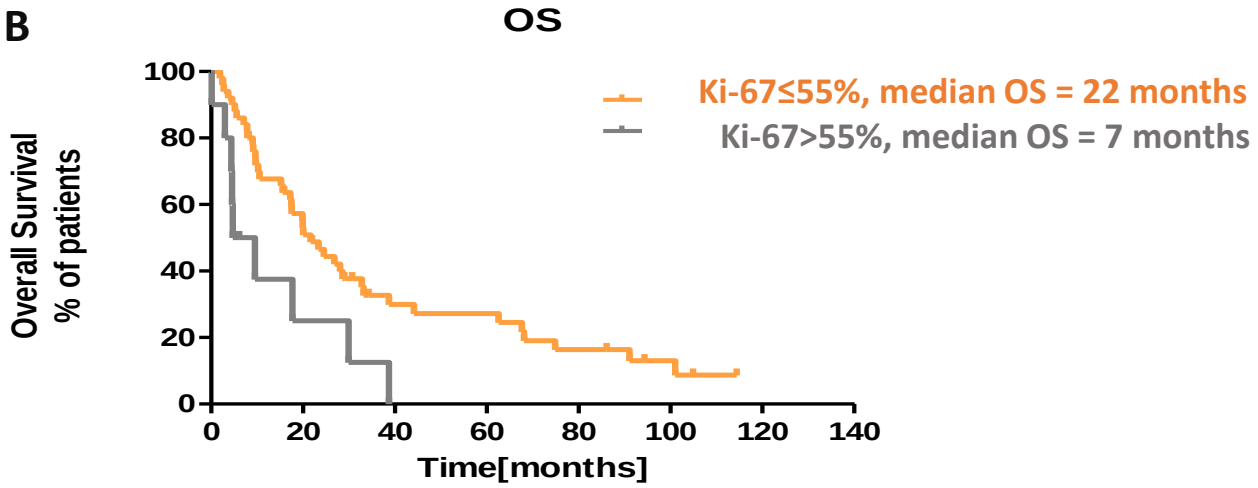




ZBB unpublished data

Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms
Survival Analysis in 64 patients treated at Zentralklinik Bad Berka

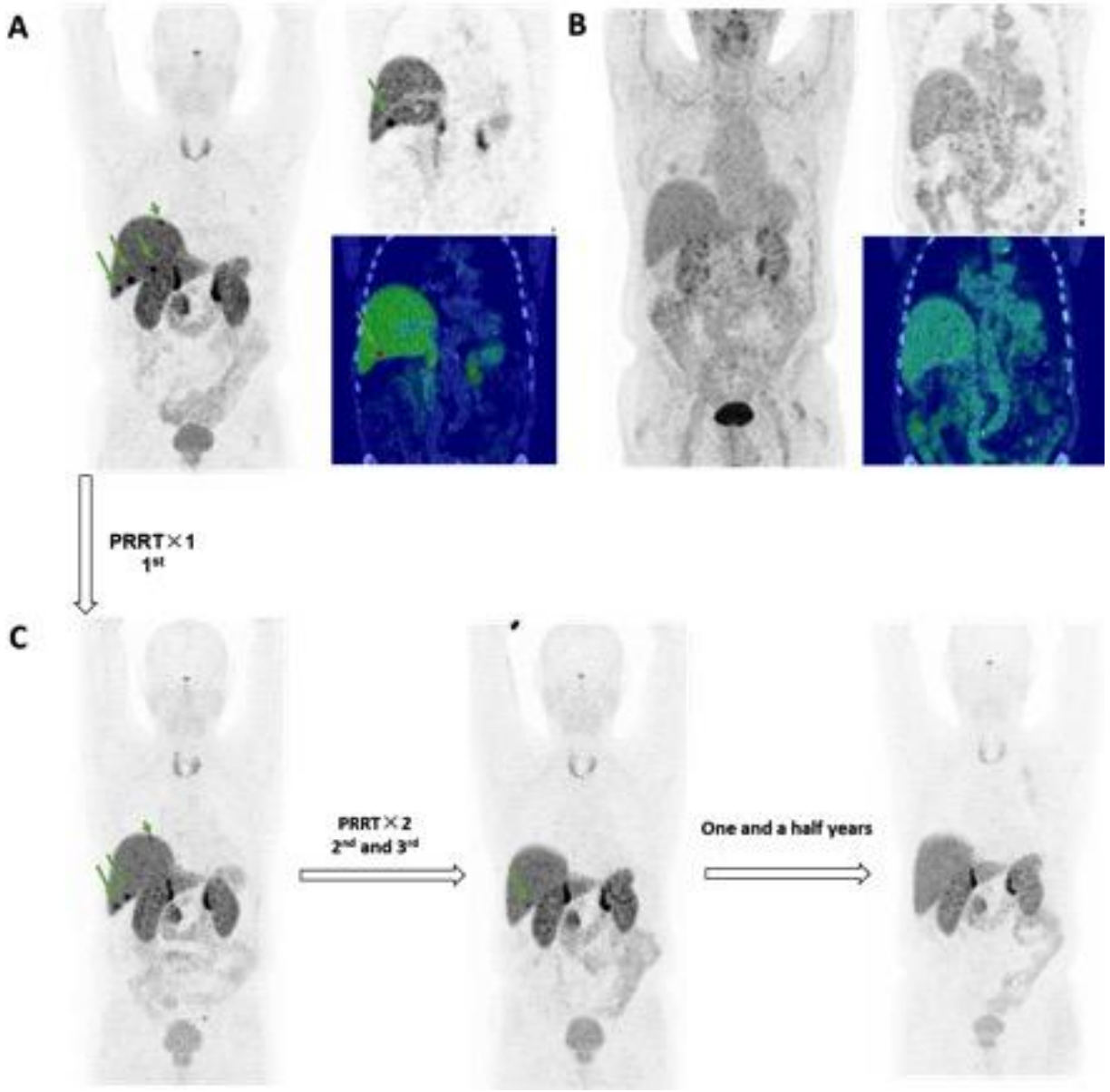




ZBB unpublished data

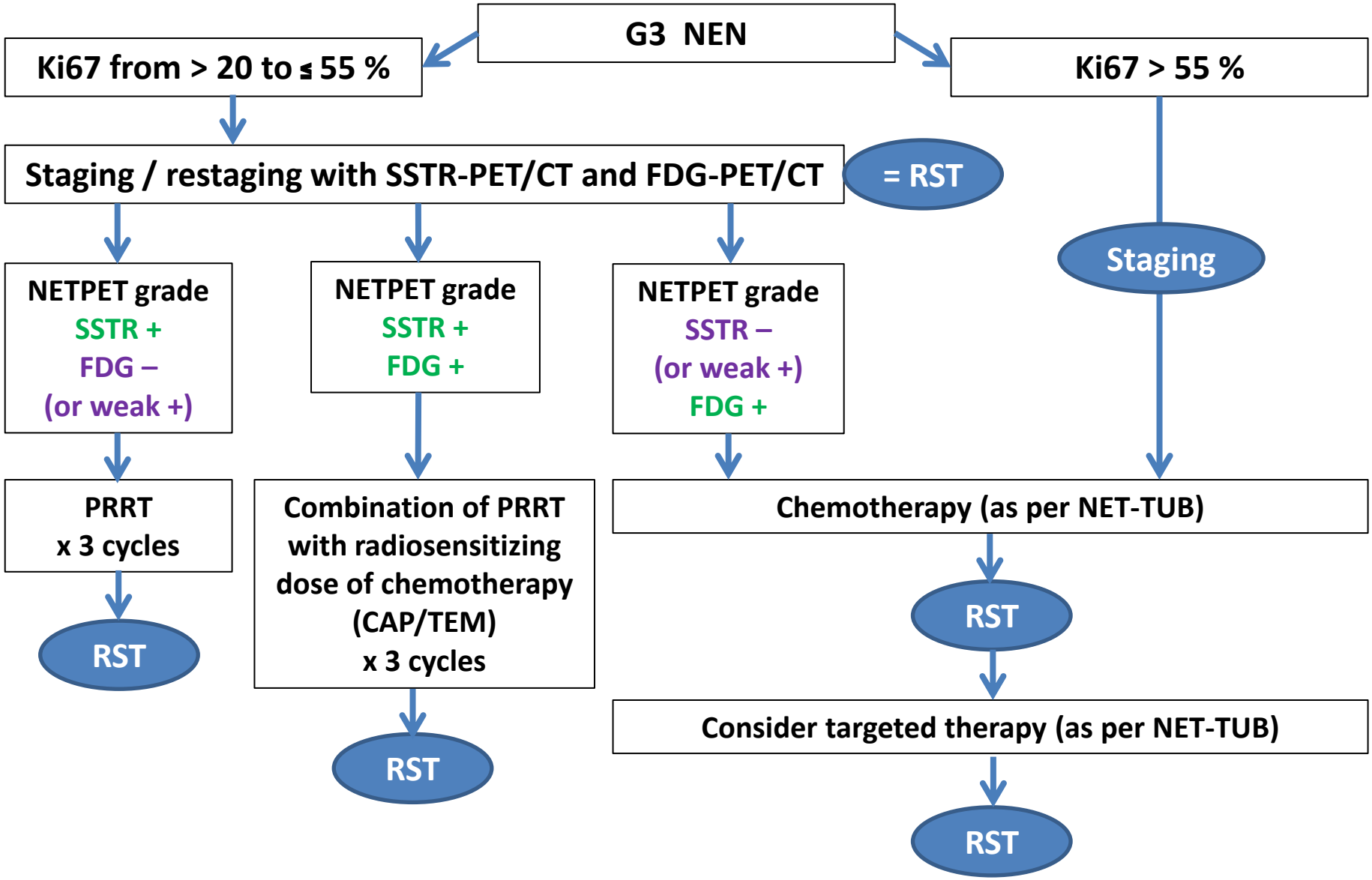
Peptide Receptor Radionuclide Therapy in Grade 3 Neuroendocrine Neoplasms

71 F with metastatic p-NEN Ki-67 25%



ZBB unpublished data

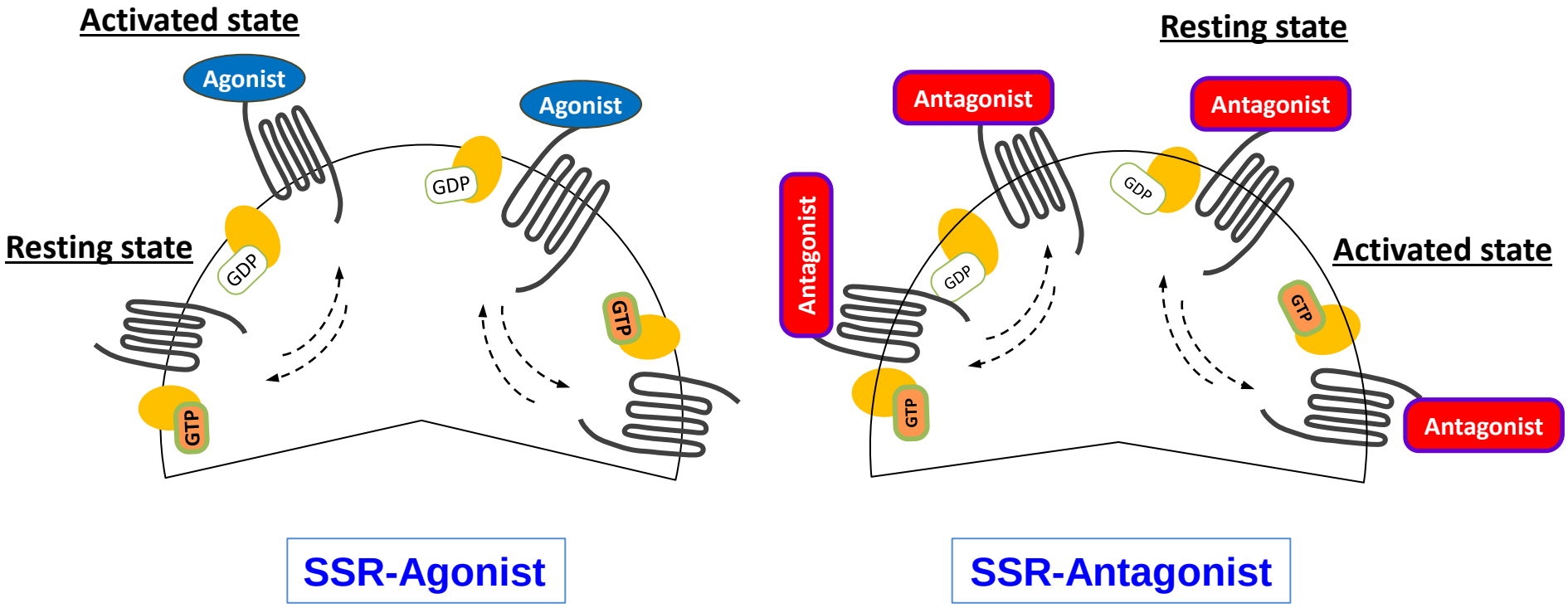
Suggestive treatment decision algorithm for G3-NEN



Symptomatic treatment of functional NEN with SSA, PPI, H2-antagonist, etc. as clinically indicated

Tumor-cell binding capacity of SSR-Agonist compared to SSR-Antagonist

Antagonists target more binding sites on a tumor cell as they bind to somatostatin receptors (SSR) independent of the activation site of the receptor (the degree of G-protein phosphorlation).

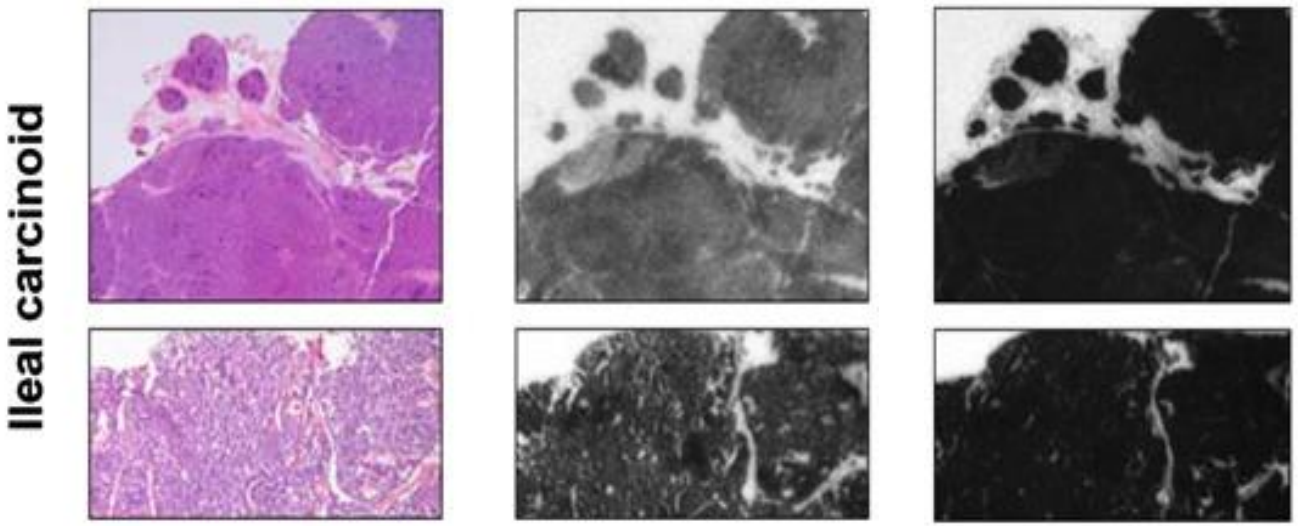


Adapted from Leo J. Hofland and Steven W. J. Lamberts,
Endocrine Reviews 2003

Somatostatin Receptor Antagonist

- Higher tumor uptake — Fani M. et al. JNM 2012
- Longer tumor retention time — Wild D. et al. JNM 2014

- Higher renal uptake



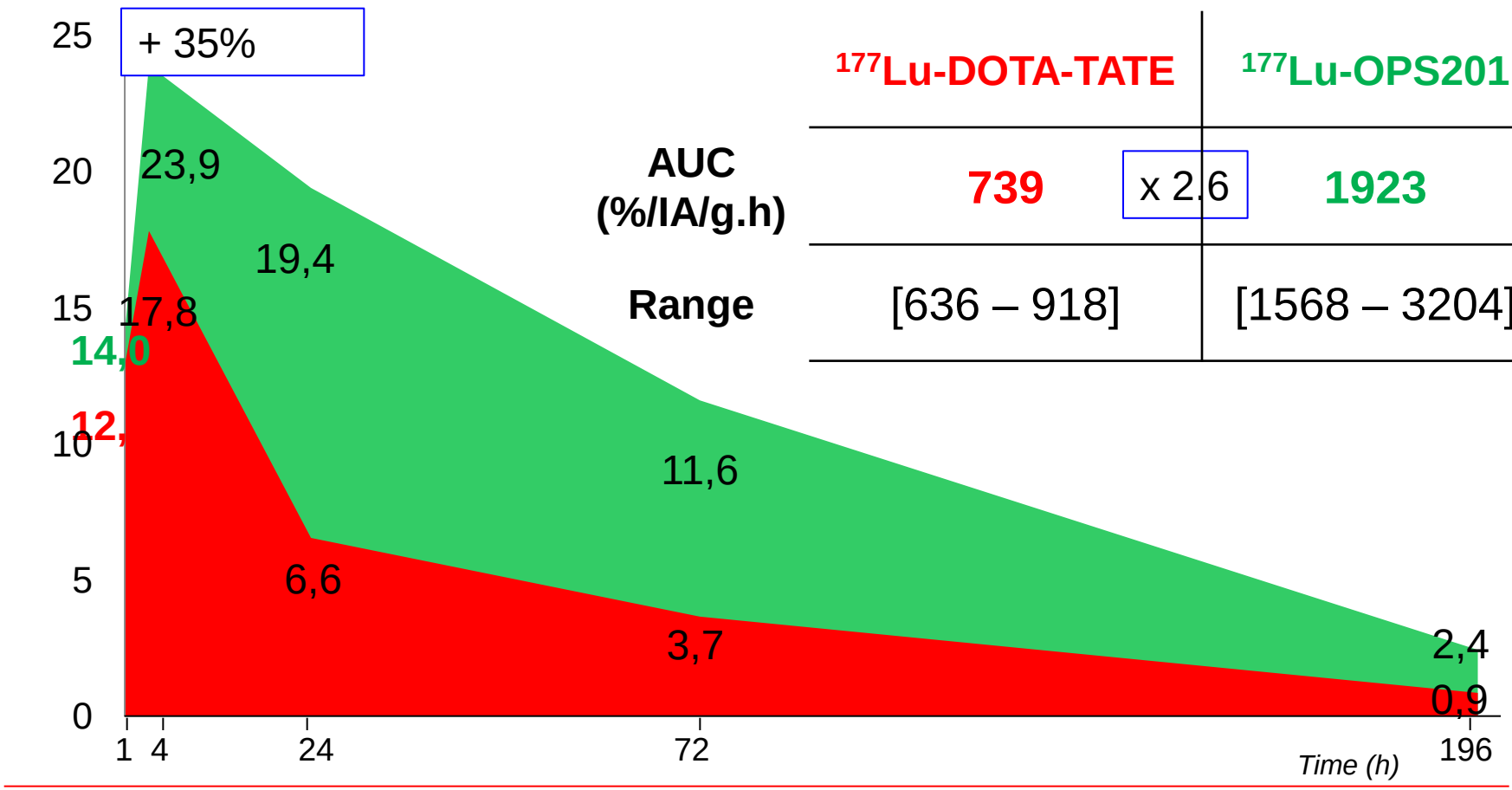
^{177}Lu-DOTA-TATE — Agonist

^{177}Lu-DOTA-BASS — Antagonist

Cescato R. et al. JNM 2011

Courtesy: G. P. Nicolas

Tumor Dose *(Tumor Time Activity Curve)*



	^{177}Lu-DOTA-TATE		^{177}Lu-OPS201
AUC (%/IA/g.h)	**739**	x 2.6	**1923**
Range	[636 – 918]		[1568 – 3204]

2.6 times longer tumor residence time results in higher tumor dose with Lu-177-OPS201 than with Lu-177-DOTA-TATE.
The uptake is 35% higher for OPS201 in comparison to DOTA-TATE.

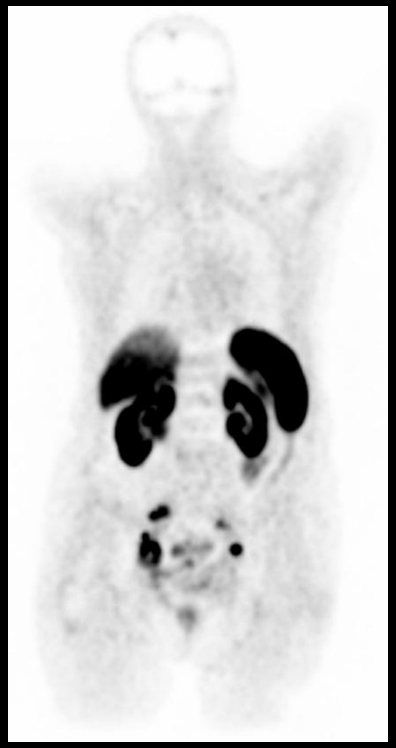
University Hospital Basel

Courtesy: G. P. Nicolas

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

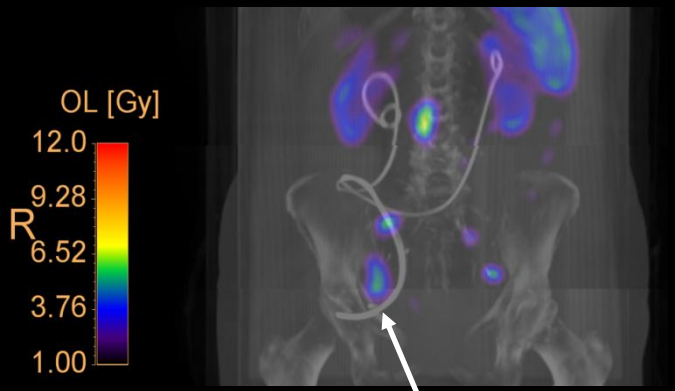
Patient with NEC (G3) of the bladder with lymphnode and uterus metastases,
shows progression after surgery and treatment with Somatostatin analogues

^{68}Ga-DOTA-TATE PET



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

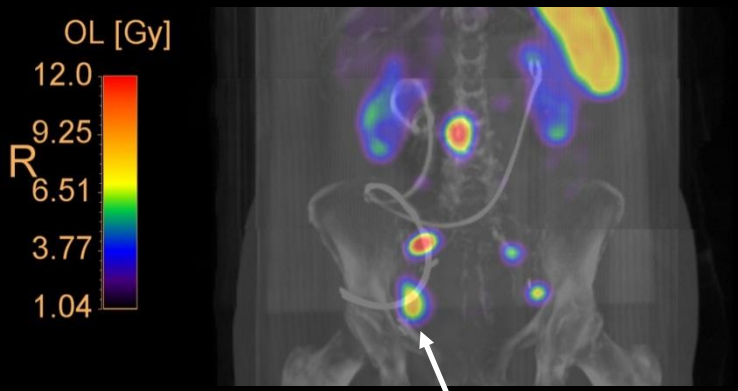
^{177}Lu-DOTA-TATE (Agonist)
Isodose curves based on
3D voxel dosimetry analysis



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

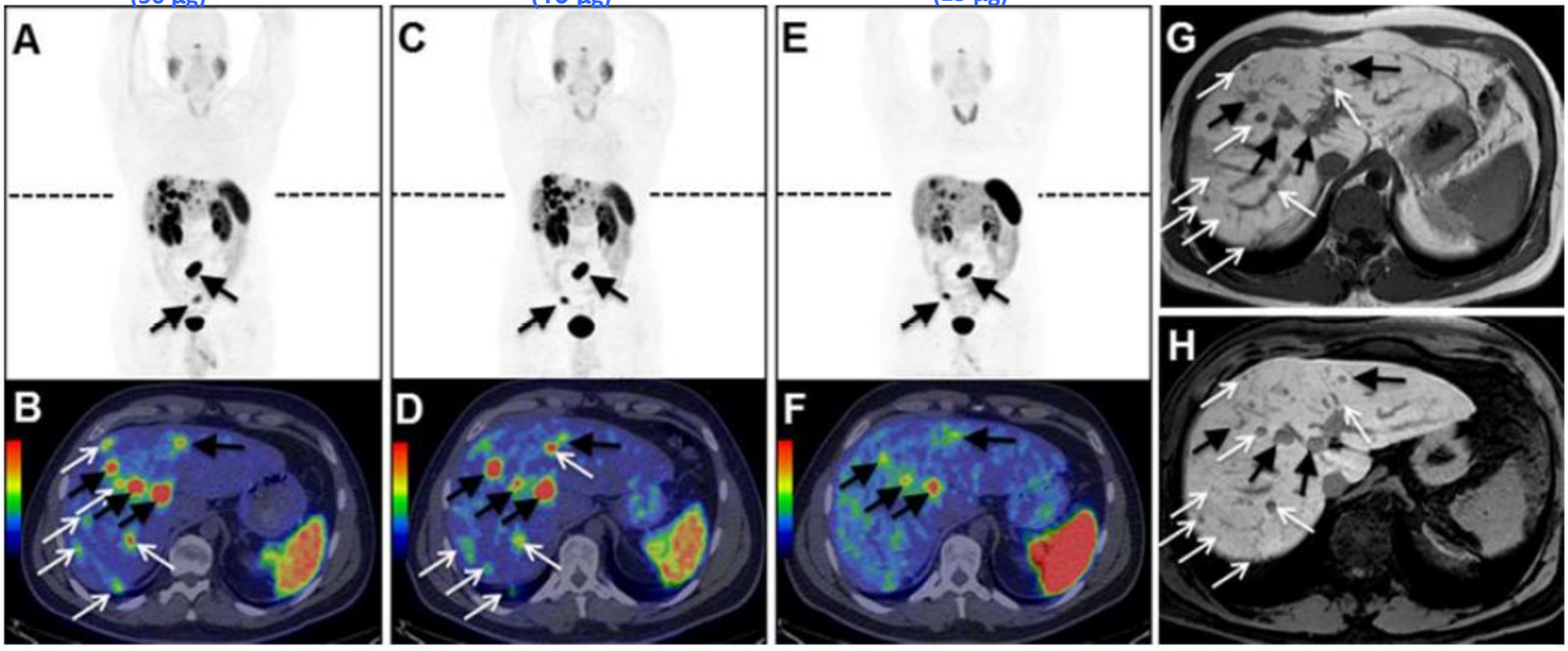
UNIVERSITÄTS KLINIKUM FREIBURG

D. Wild et al. J Nucl Med 2014;55:1248-52

Comparison of ^{68}Ga-OPS202 (^{68}Ga-NODAGA-JR11) and ^{68}Ga-DOTATOC (^{68}Ga-Edotreotide) PET/CT in Patients with Gastroenteropancreatic Neuroendocrine Tumors: Evaluation of Sensitivity in a Prospective Phase II Imaging Study

Guillaume P. Nicolas[1,2], Nils Schreiter[3,4], Felix Kaul[1,2], John Uiters[4,5], Hakim Bouterfa[6], Jens Kaufmann[6], Tobias E. Erlanger[7], Richard Cathomas[8], Emanuel Christ[2,9], Melpomeni Fani[1,10], Damian Wild[1,2]

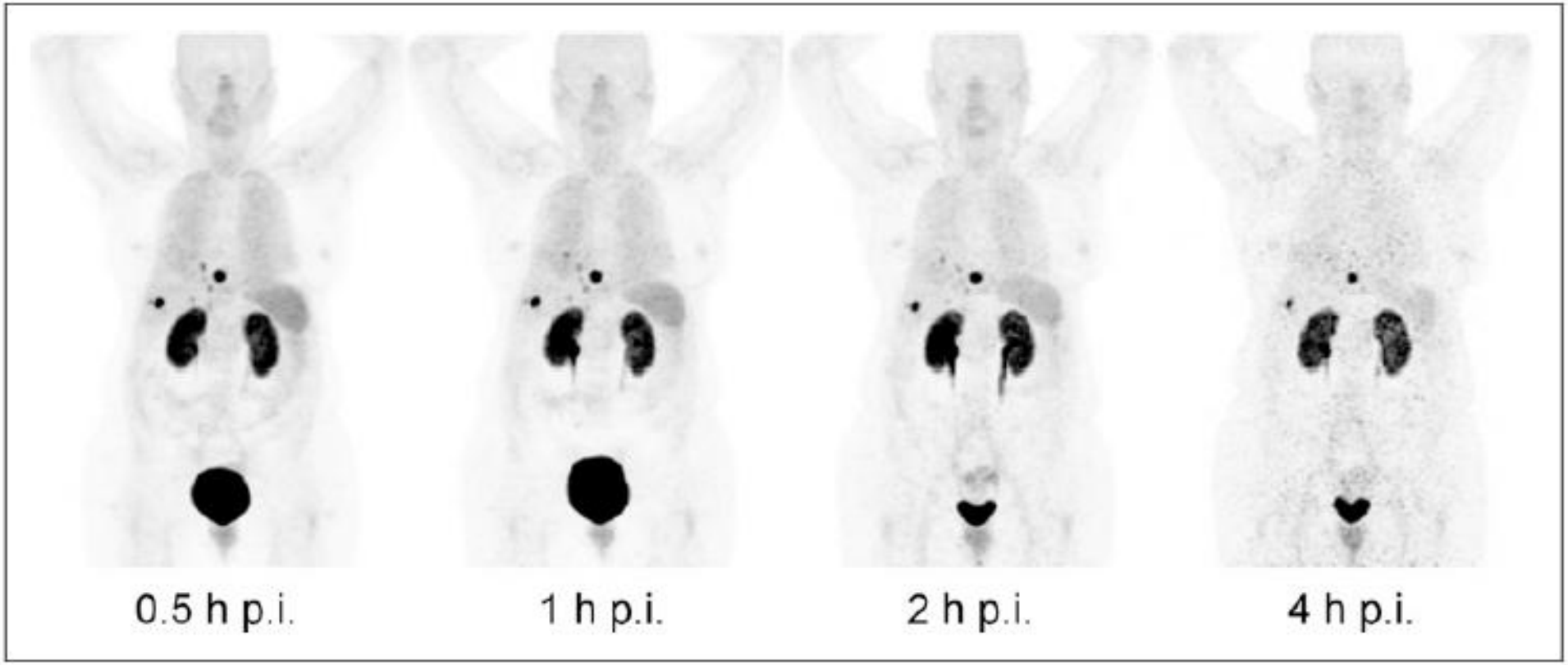
J Nucl Med. 2018 Jun



THE JOURNAL OF NUCLEAR MEDICINE • Vol. 59 • No. 6 • June 2018

Safety, Biodistribution, and Radiation Dosimetry of ^{68}Ga-OPS202 in Patients with Gastroenteropancreatic Neuroendocrine Tumors: A Prospective Phase I Imaging Study

Guillaume P. Nicolas[1,2], Seval Beykan[3], Hakim Bouterfa[4], Jens Kaufmann[4], Andreas Bauman[5], Michael Lassmann[3], Jean Claude Reubi[6], Jean E.F. Rivier[7], Helmut R. Maecke[8], Melpomeni Fani[1,5], and Damian Wild[1,2]



First-in-human PET/CT imaging of somatostatin receptor expressing tumors with the novel somatostatin receptor antagonist ^{68}Ga-NODAGA-LM3 – a comparison with ^{68}Ga-DOTATOC PET/CT

A. Singh[1], H. R. Kulkarni[1], T. Langbein[1], D. Müller[1], S. Senftleben[1], M. Fani[2], H. Maecke[3], R. P. Baum[1]

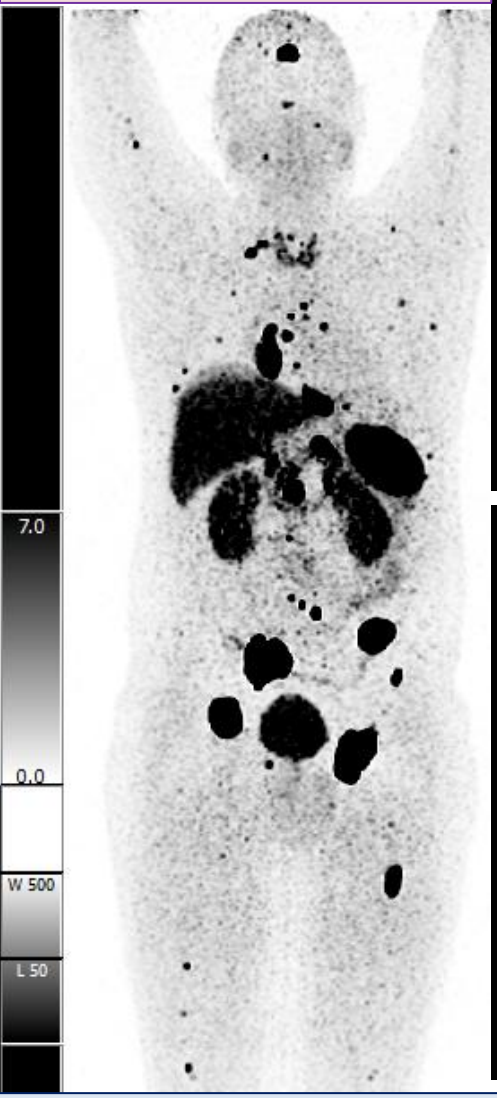
[1]Theranostics Center for Molecular Radiotherapy, Zentralklinik Bad Berka, Germany

[2]Division of Radiopharmaceutical Chemistry, University Hospital of Basel, Switzerland

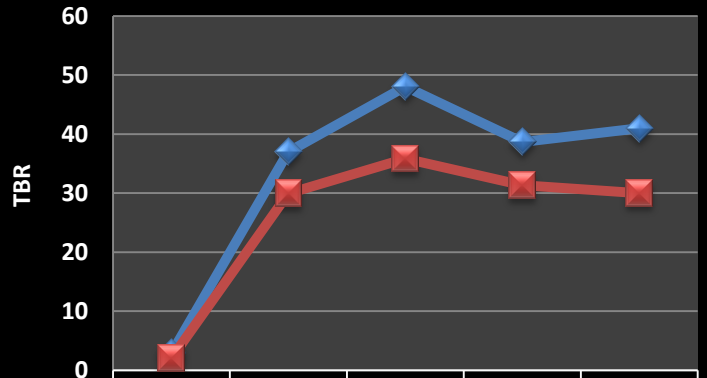
[3]Department of Nuclear Medicine, University Hospital Freiburg, Germany

Data presented at EANM 2017

Ga-68 DOTATOC PET/CT
(30-Jan-2017)

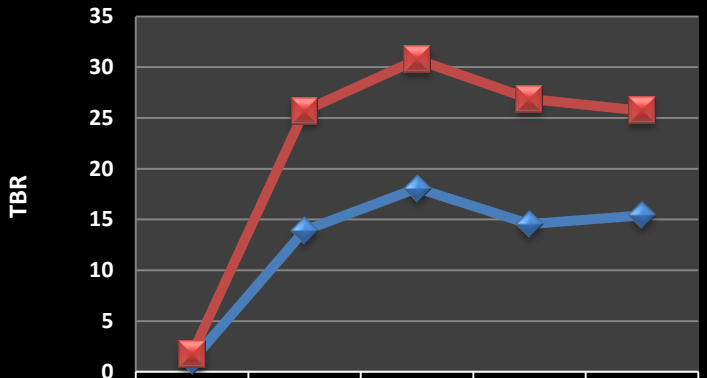


TBR (TL/liver) NODAGA-LM3 vs DOTATOC



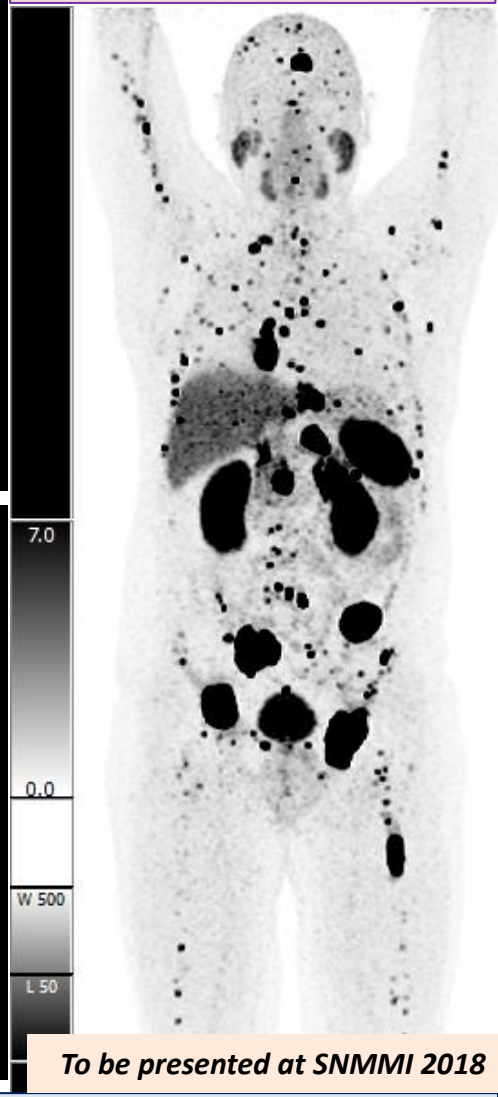
	TL1	TL2	TL3	TL4	TL5
LM3 - RT (liver)	2,88	37	48,03	38,67	40,97
DOTATOC - RT (liver)	2,02	29,96	35,86	31,32	29,98

TBR (TL/kidney) NODAGA-LM3 vs DOTATOC



	TL1	TL2	TL3	TL4	TL5
LM3 - RT (kidney)	1,08	13,92	18,07	14,55	15,41
DOTATOC - RT (kidney)	1,74	25,7	30,76	26,86	25,71

Ga-68 NODAGA-LM3 PET/CT
(20-Mar-2017)



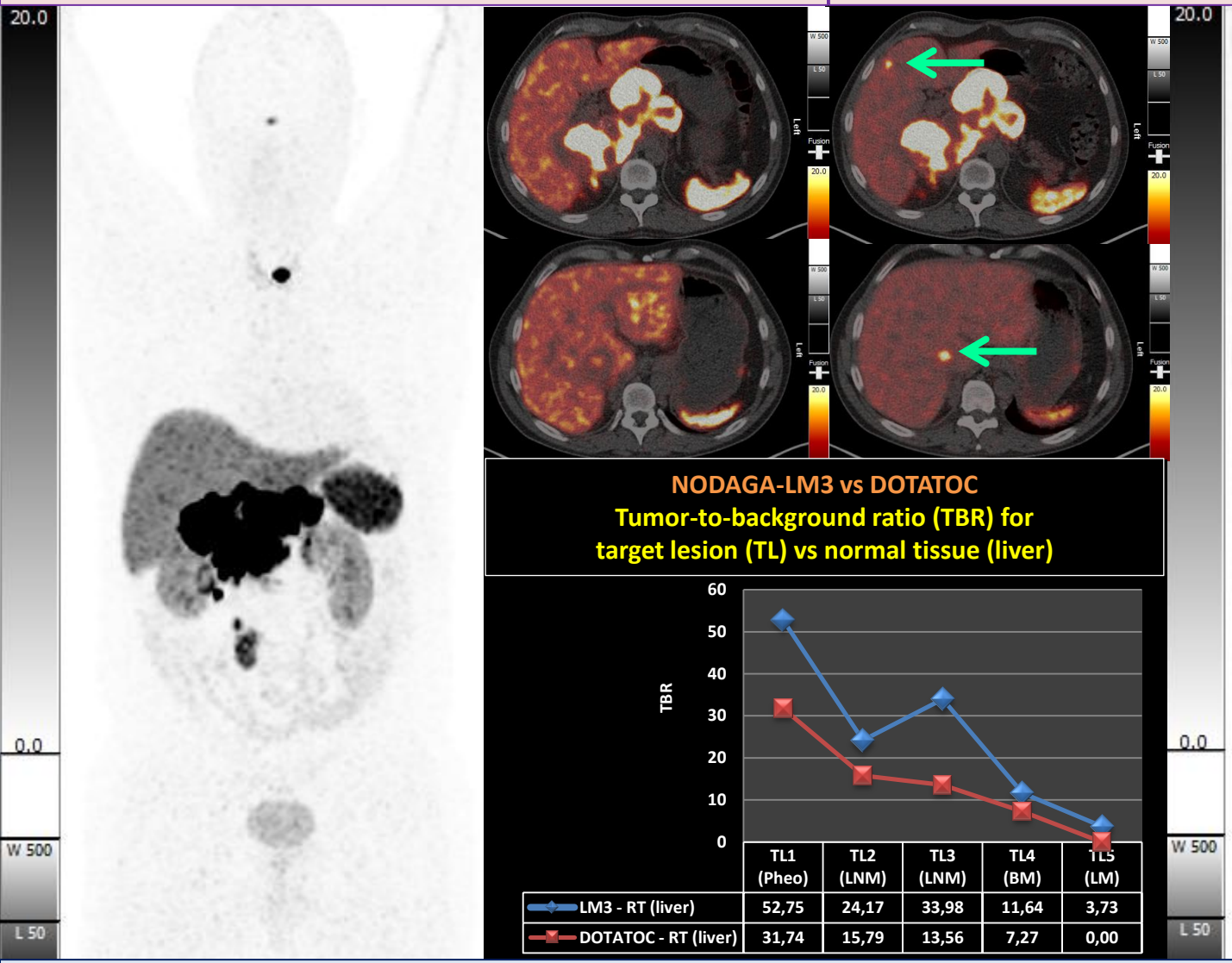
To be presented at SNMMI 2018

In a patient with metastatic paraganglioma, general higher tumor-to-background ratio (TBR) of target lesion (TL) versus normal tissue on Ga-68 NODAGA-LM3 PET/CT compared to that on Ga-68 DOTATOC PET/CT, allowed detection of >140 osseous metastases amongst others.

The lower TBR for kidneys warrants further dosimetry studies of NODAGA-LM3.

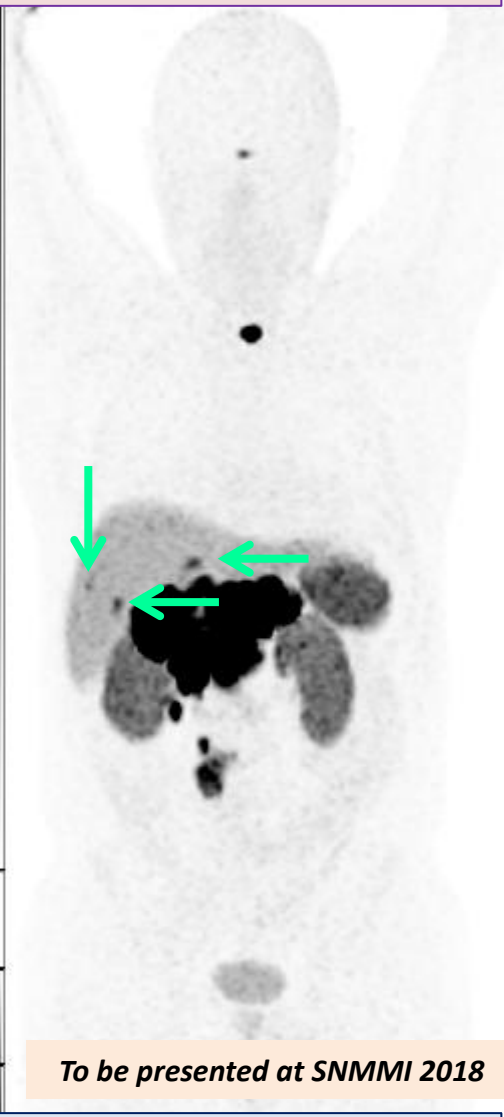
3 extra liver metastases detected by Ga-68 NODAGA-LM3 PET/CT vs Ga-68 DOTATOC PET/CT

Ga-68 DOTATOC PET/CT (24-Jul-2017) | Ga-68 NODAGA-LM3 PET/CT (02-Aug-2017)



NODAGA-LM3 vs DOTATOC
Tumor-to-background ratio (TBR) for target lesion (TL) vs normal tissue (liver)

	TL1 (Pheo)	TL2 (LNM)	TL3 (LNM)	TL4 (BM)	TL5 (LM)
LM3 - RT (liver)	52,75	24,17	33,98	11,64	3,73
DOTATOC - RT (liver)	31,74	15,79	13,56	7,27	0,00



To be presented at SNMMI 2018

In a patient with metastatic malignant pheochromocytoma, the higher tumor-to-background ratio (TBR) of target lesion (TL) versus normal liver tissue on Ga-68 NODAGA-LM3 PET/CT compared to Ga-68 DOTATOC PET/CT, allowed detection of additional liver metastases

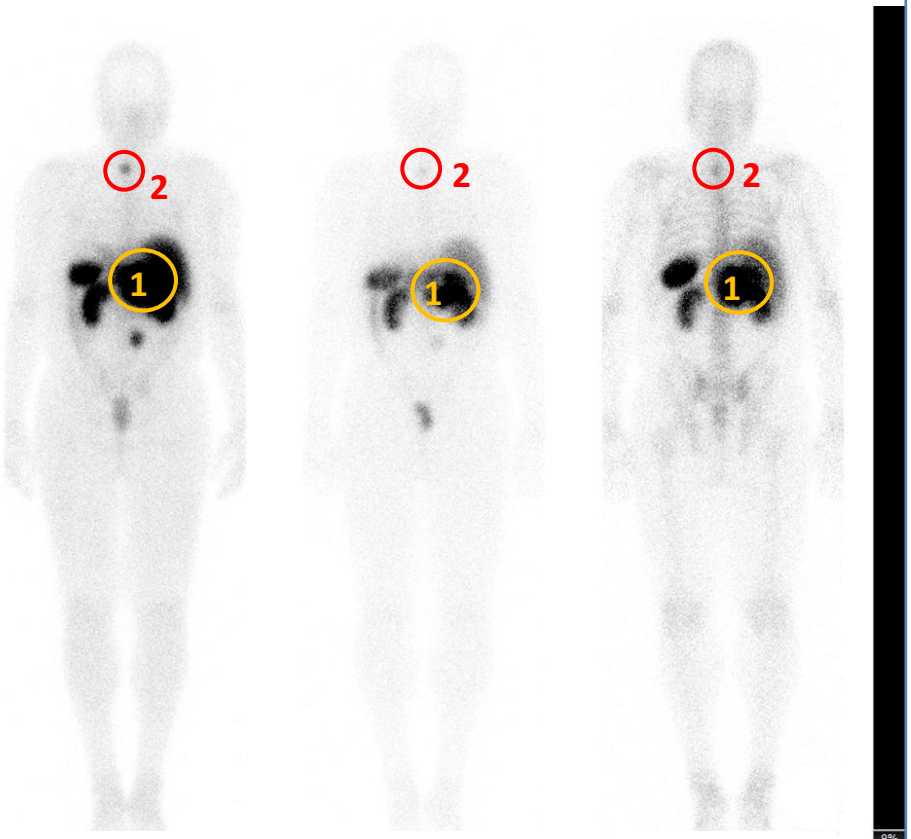
RRT Dosimetrie: ^{177}Lu DOTA-LM3 und ^{177}Lu DOTATOC

Presented at DGN 2017

Ziel | Methodik | **Ergebnisse** | Schlussfolgerung

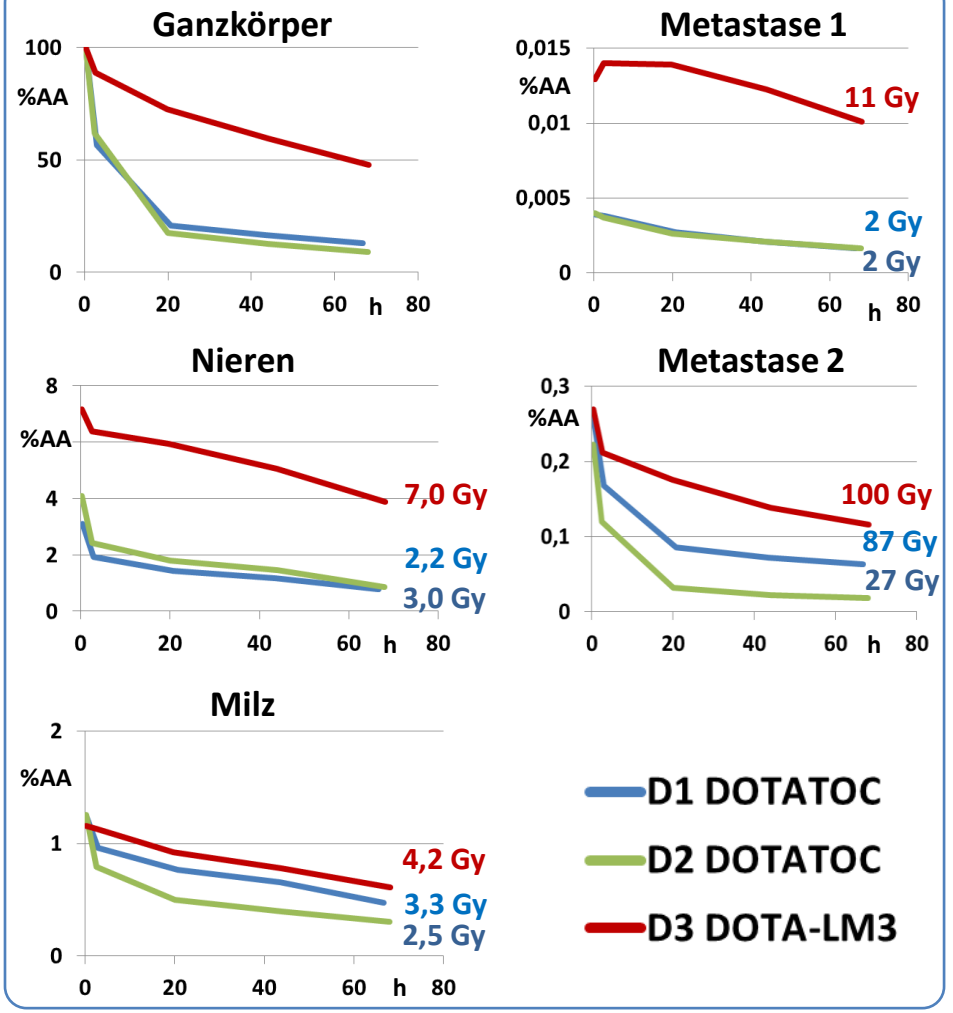
^{177}Lu DOTATOC und ^{177}Lu DOTA-LM3 im *gleichen Patienten*

GK Szintigraphie 24h p.i. posterior



16.10.2017	31.07.2017	16.06.2015
5,4 GBq	8 GBq	7 GBq
^{177}Lu DOTA-LM3	^{177}Lu DOTATOC	^{177}Lu DOTATOC
Dosimetrie 3	Dosimetrie 2	Dosimetrie 1

Uptake



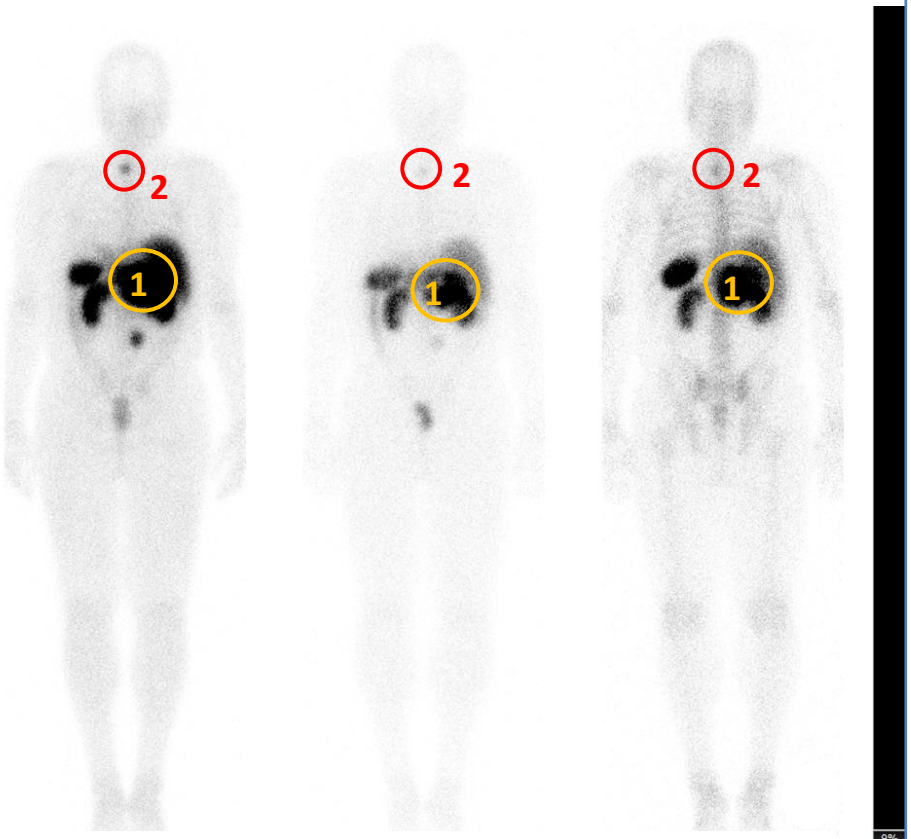
RRT Dosimetrie: ^{177}Lu DOTA-LM3 und ^{177}Lu DOTATOC

Presented at DGN 2017

Ziel | Methodik | **Ergebnisse** | Schlussfolgerung

^{177}Lu DOTATOC und ^{177}Lu DOTA-LM3 im *gleichen Patienten*

GK Szintigraphie 24h p.i. posterior



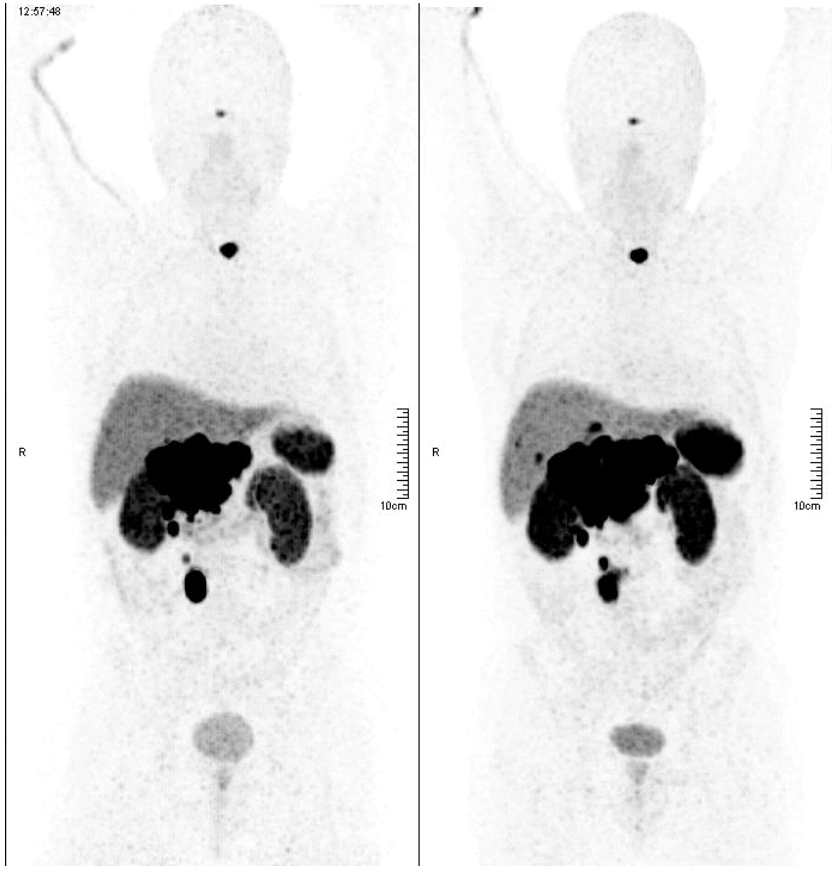
16.10.2017
5,4 GBq
^{177}Lu DOTA-LM3
Dosimetrie 3

31.07.2017
8 GBq
^{177}Lu DOTATOC
Dosimetrie 2

16.06.2015
7 GBq
^{177}Lu DOTATOC
Dosimetrie 1

^{68}Ga NODAGA-LM3 PET/CT

28. Feb 2018 | **02. Aug 2017**



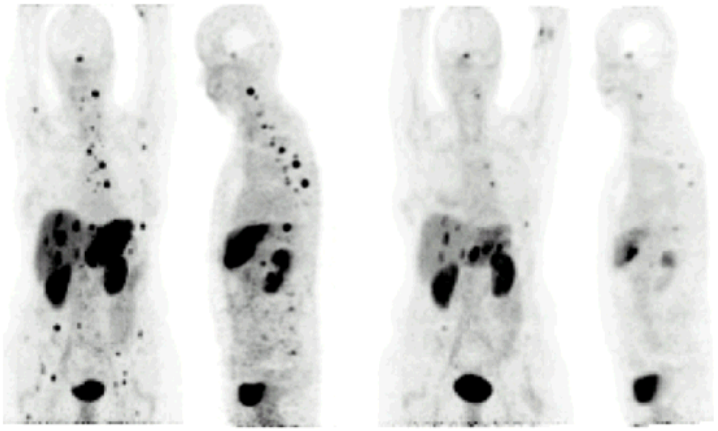
- **Higher accumulation of the Antagonist ^{177}Lu DOTA-LM3 in metastases**
  - **50% longer residence times**
- **However, higher mean absorbed organ doses with ^{177}Lu DOTA-LM3**
  - ➢ **4x higher renal dose / 6x higher splenic dose**

→ **PRRT with SSTR Antagonist appears promising,**
While higher tumor doses are achievable
➢ **4x higher doses in liver metastases**

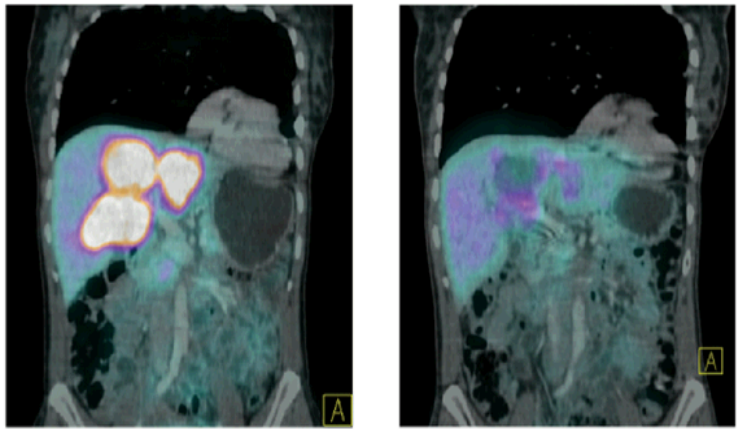
→ **Further studies with variable peptide amounts in direct comaprison, as well as larger patient groups need to be studied.**

Intra arterial alpha- (IA) PRRT

Remarkable responses to Bi-213-DOTATOC observed in tumors resistant to previous therapy with Y-90/Lu-177-DOTATOC



Case I: Shrinkage of liver lesions and bone metastases after i.a. therapy with 11 GBq Bi-213-DOTATOC

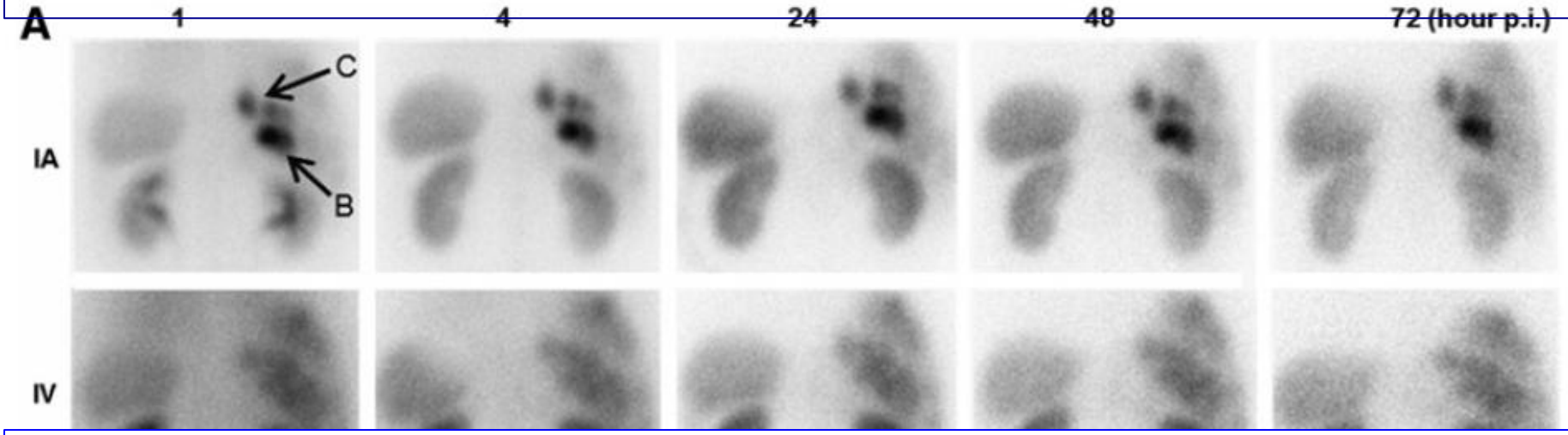


Case II: Response of multiple liver lesions after i.a. therapy with 14 GBq Bi-213-DOTATOC

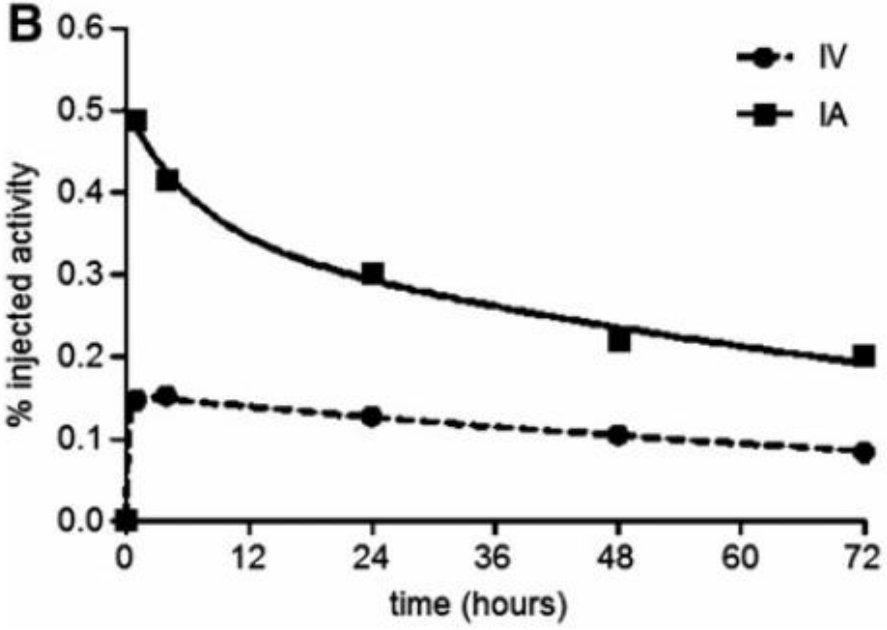
2012 SNMMI Image of the Year Morgenstern A et al

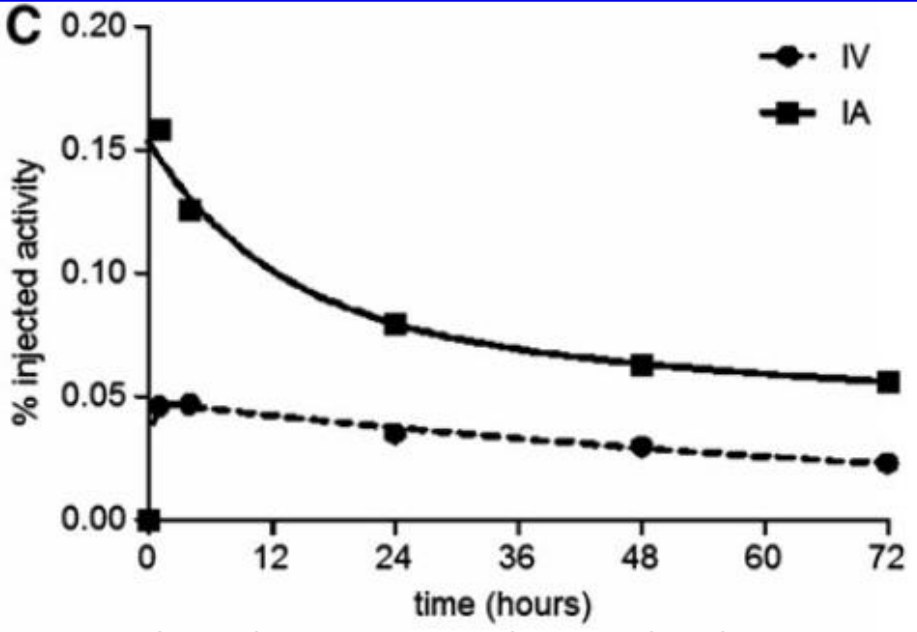
SNM 59th Annual Meeting, June 9-13, 2012

Intraarterial versus intravenous studies



2.4 fold increase in liver metastases uptake with intra-arterial administration compared to that of intravenous administration of In-111 DTPAOC



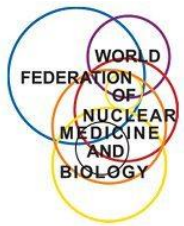


- Pool et al. Cancer Biother Radiopharm 2014.

Intra-arterial PRRT of neuroendocrine liver metastases (NELM): experience in over 50 patients and long term follow-up

Aviral Singh MD, MSc
THERANOSTICS Center for Molecular Radiotherapy & Molecular Imaging
ENETS Center of Excellence, Zentralklinik Bad Berka, Germany

Presented at the 13th ICRT at the 12th WFNMB
April 20, 2018



Intra-arterial (I.A.) PRRT at ZBB – tumor entities

SSTR expressing tumors

GEP-NEN (n)

- **Pancreatic**
  - 41
- **Midgut**
  - Duodenum (1)
  - Jejunum (1)
  - Ileum (4)

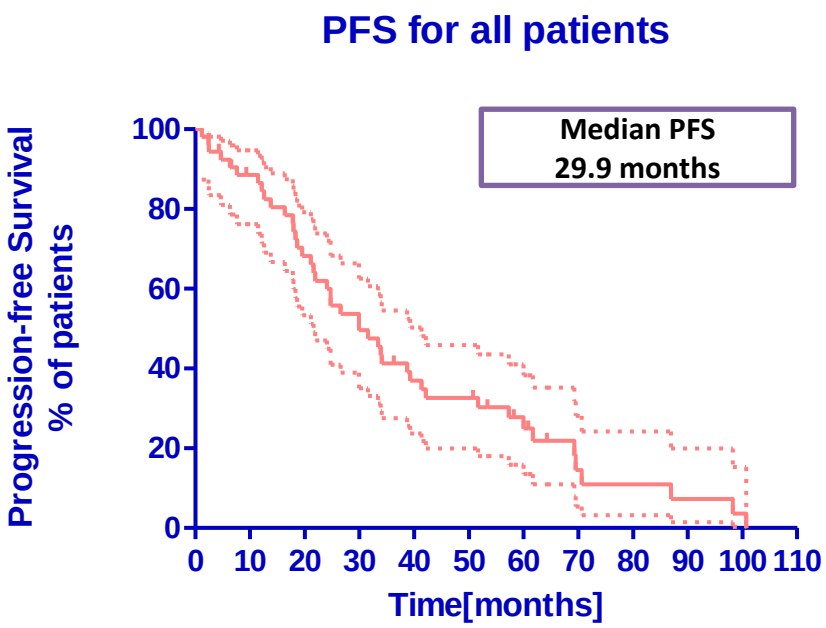
Others (n)

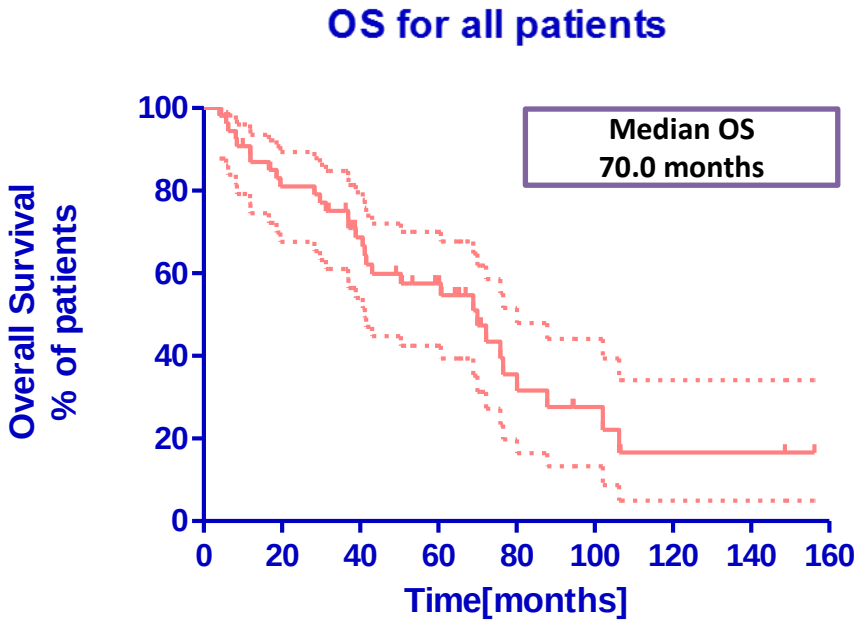
- **CUP**
  - 2
- Meningioma (1)
- Glomus (2)
- Nasopharyngeal (1)
- Adrenal (1)
- Paraganglioma (1)
- Pheochromocytoma (1)

Total 56 patients treated
Long-term follow-up in 55 patients

I.A. PRRT at ZBB – Survival analysis for 55 patients

Median progression-free (PFS) and overall survival (OS) were 29.9 and 70.0 months, respectively, with a median follow-up time of 94.6 months (range 4.0-156.2 months).



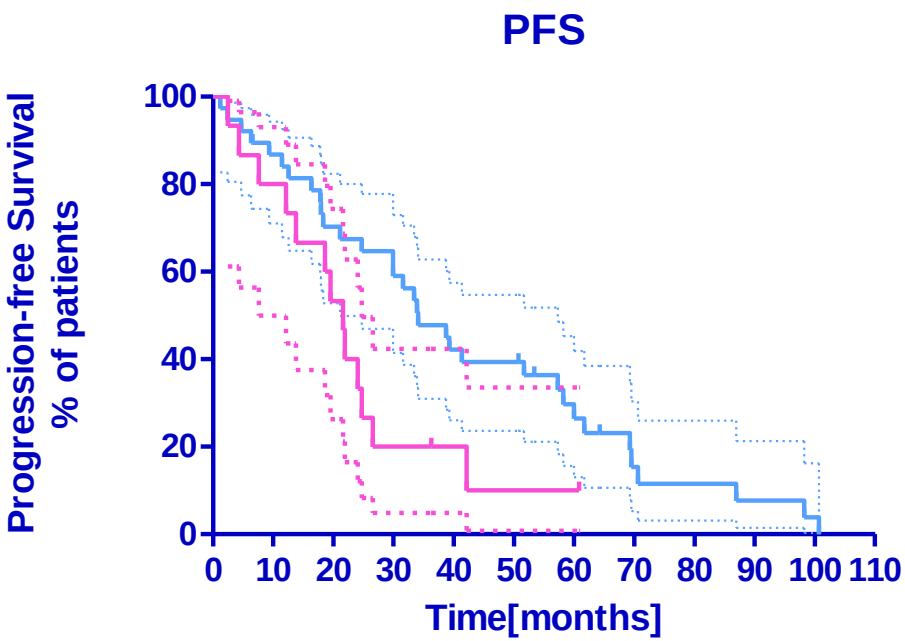


Median PFS = 29.9 months
 # deaths/events=45

Median OS = 70.0 months
 # deaths/events=34

- **34/55 (56.4%) patients died with a median follow-up 94.6 months (mean ± SD, 50.6±34.7 months, range 4.0-156.2 months).**

I.A. PRRT at ZBB – Survival analysis for patients with hepatic metastases only *versus* patients with hepatic as well as extrahepatic metastases - PFS

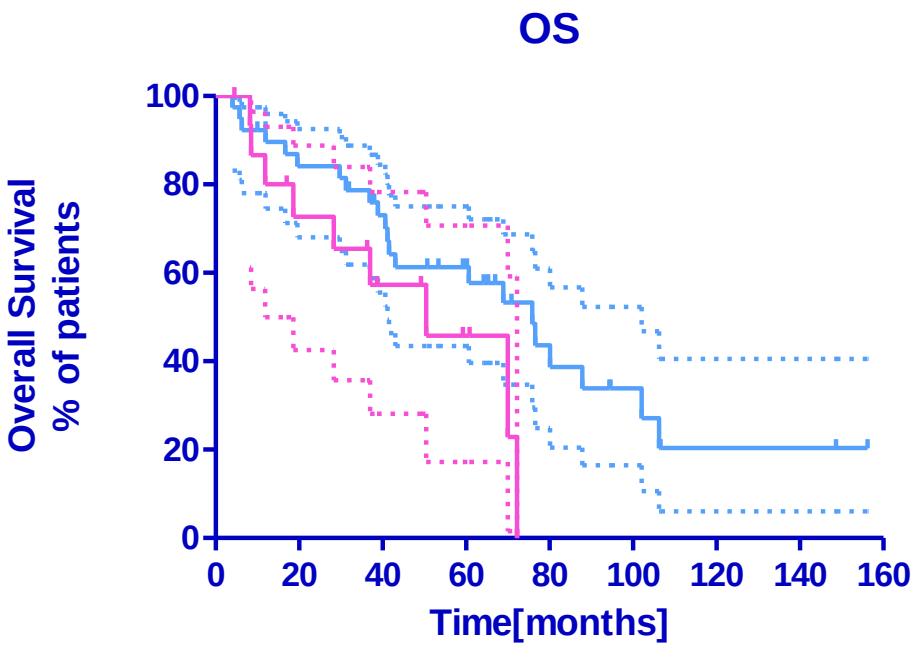


Liver metastasis	34.07
Distant metastasis	21.63
Ratio	1.575
95% CI of ratio	1.048 to 2.101

For patients with liver metastases only, the median PFS was 33.4 months (n=39).

For patients with additional distant metastases, the median PFS was 21.9 months (n=16).

I.A. PRRT at ZBB – Survival analysis for patients with hepatic metastases only *versus* patients with hepatic as well as extrahepatic metastases – median OS



Hepatic metastases — OS = 75.8

Hepatic + extrahepatic metastases — OS = 50.5

(p = 0.0980)

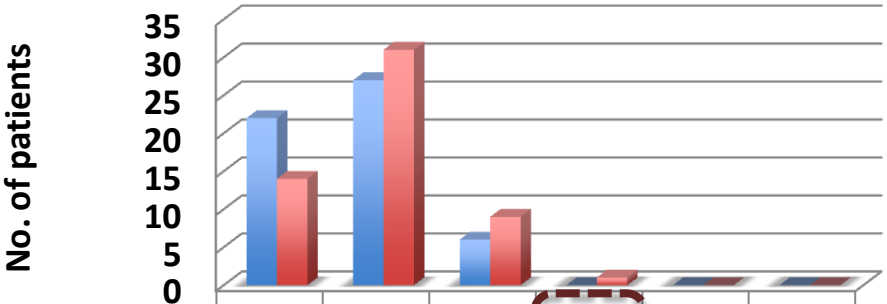
Median survival	
Liver metastasis	75.83
Distant metastasis	50.47
Ratio	1.502
95% CI of ratio	1.042 to 1.963

For patients with liver metastasis only, the median OS was 76 months (n=39).

For patients with additional distant metastases, the median PFS was 50 months (n=16).

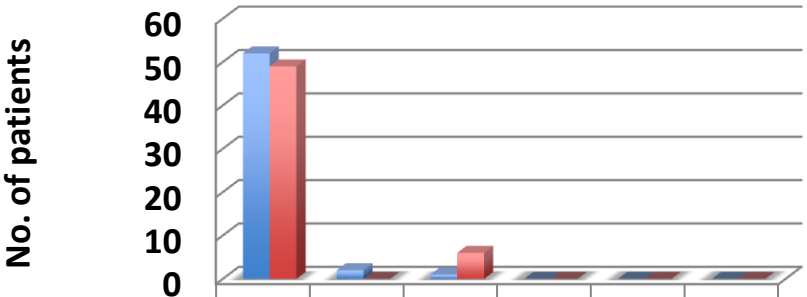
Safety profile - Anemia

Anemia



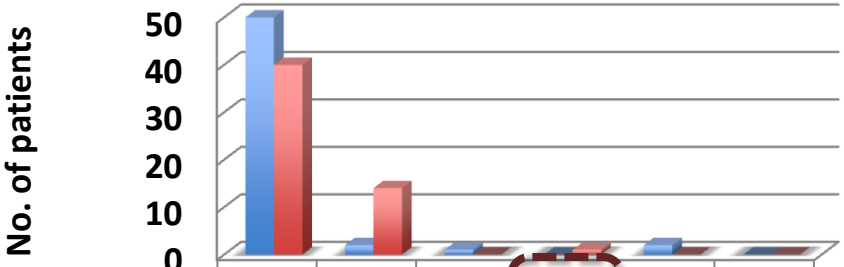
	G0	G1	G2	G3	G4	G5
Pre-PRRT	22	27	6	0	0	0
Post-PRRT	14	31	9	1	0	0

Leukocytopenia



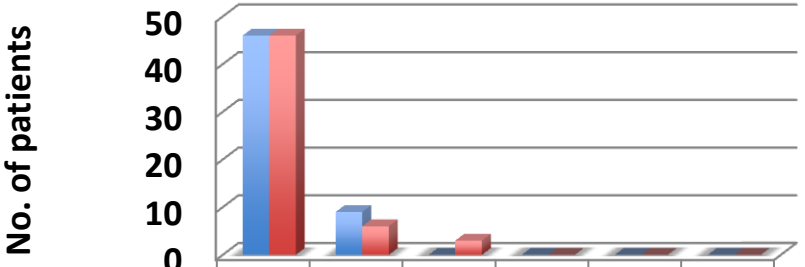
	G0	G1	G2	G3	G4	G5
Pre-PRRT	52	2	1	0	0	0
Post-PRRT	49	0	6	0	0	0

Thrombocytopenia



	G0	G1	G2	G3	G4	G5
Pre-PRRT	50	2	1	0	2	0
Post-PRRT	40	14	0	1	0	0

Creatinine



	G0	G1	G2	G3	G4	G5
Pre-PRRT	46	9	0	0	0	0
Post-PRRT	46	6	3	0	0	0

eGFR, MAG3 Renogram based TER, LFT were all within acceptable normal limits

Clinical Case – 23 M university student with NPCa

Nonkeratinizing, undifferentiated nasopharyngeal carcinoma (Schmincke-Regaud type, EBV-associated) with lymph node, extensive hepatic and polytopic osseous metastases

First diagnosis February 2016
Tumor classification cT2b cN2 pM1oss G3, stage IVa (UICC 2009)

05/2015	Initial symptoms: hearing loss of right ear, recurrent tympanic effusions despite insertion of a tympanic drainage, tubal aeration disorder
10/2015	Tubal dilatation right
11/2015	Pain cervico-thoracic region, ultrasound multiple lymphadenopathy. No therapy.
02/2016	Progressive obstruction of nasal breathing due to nasopharyngeal SOL
12.02.16	Panendoscopy with Bx: histological nasopharyngeal carcinoma
03/2016	CT: left cervical lymph node metastases
03 - 05/16	Combined radiochemotherapy: EBRT: tumor in the nasopharynx + locoregional LN + cervical sheath Chemotherapy: with mitomycin and 5-FU Premature discontinuation of chemotherapy (Fever and pneumonia)
04/2016	F-18 FDG-PET/CT: 6th left rib metastasis
05/2016	6th left rib section resection (R1), histological MTS from nasopharyngeal carcinoma
06/16 – 01/17	Atezolizumab (checkpoint inhibitor / PD-L1 ligand) - Progressive Disease
10/2016	EBRT of a metastasis in T7
03 - 06/17	Cetuximab (chimeric mAb against epidermal growth factor receptor (EGFR) – Progressive Disease

Clinical Case – 23 M university student with NPCa

03/2017 IHC showed expression of PSMA (Hamburg)

06/2017 Ga-68 PSMA PET/CT: multiple PSMA-avid hepatic and osseous lesions

07/2017 Dosimetry with Lu-177 PSMA-617 - insufficient for radioligand therapy

Ga-68 DOTATOC-PET/CT: intense SSTR expression of multiple hepatic, skeletal and lymph node metastases

Initiation of PRRT with Lu-177 DOTATOC

08 - 09/17 EBRT to right pelvis (GHD 45 Gy), 6th left rib (GHD 45 Gy), OS heads b/l (GHD 5 x 5 Gy)

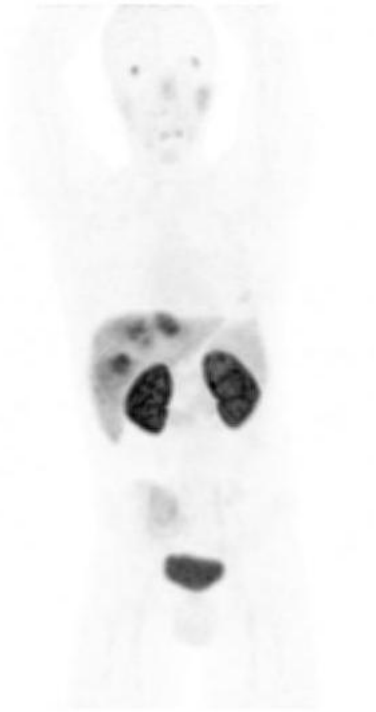
Associated clinical conditions

Sialadenopathy secondary to percutaneous radiotherapy
Anemia G1 (persistent before PRRT; DD iron deficiency, DD thalassemia minor)
Thrombocytopenia G1

Clinical Case – 23 M university student with NPCa

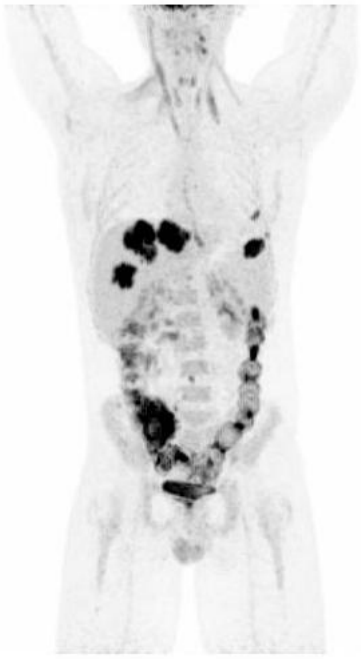
Pre-RNT receptor status and metabolic activity assessment

09.06.2017



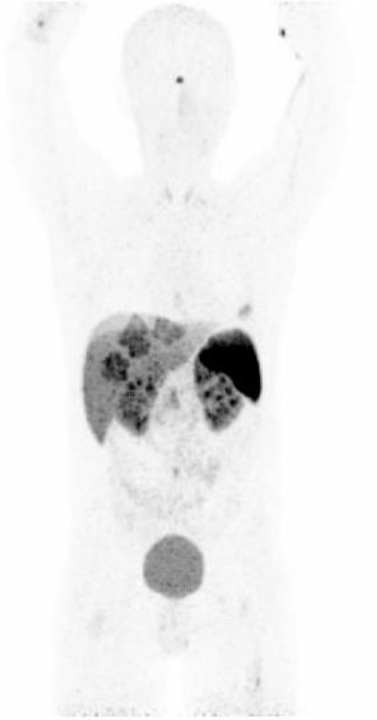
PSMA receptor expression (Hamburg)

24.07.2017



FDG-avid disease (ZBB)

25.09.2017



SSTR receptor expression (ZBB)

Clinical Case – 23 M university student with NPCa

RNT approach and regimen

Dosimetry to assess feasibility of PSMA radio ligand therapy

Application of 1900 MBq Lu-177 PSMA on 03.07.2017 (Dosimetry)

PRRT

Application of 10000 MBq Lu-177 DOTATOC on 24.07.2017 (1st course)

Application of 8800 MBq Lu-177 DOTATOC on 26.09.2017 (2nd course + Xeloda)

Application of 5800 MBq Y90 DOTATOC on 06.12.2017 (3rd course) intraarterial

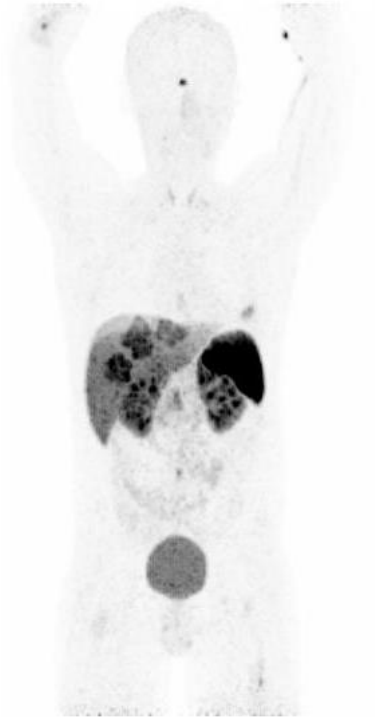
Application of 6800 MBq Lu-177 DOTATOC on 26.03.2018 (4th course + Xeloda)

Cumulatively administered activity 31.4 GBq (848.6 mCi) Y-90 / Lu-177

Clinical Case – 23 M university student with NPCa

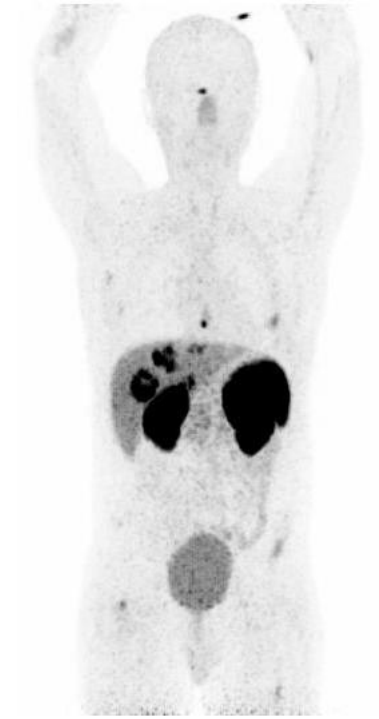
Restaging with Ga-68 DOTATOC associated with PRRT

25.09.2017



Pre PRRT - 2

05.12.2017



Pre-PRRT - 3
(intra-arterial planned)

Intra-arterial PRRT planned to treat liver metastases

Clinical Case – 23 M university student with NPCa

RNT approach and regimen

Dosimetry to assess feasibility of PSMA radio ligand therapy

Application of 1900 MBq Lu-177 PSMA on 03.07.2017 (Dosimetry)

PRRT

Application of 10000 MBq Lu-177 DOTATOC on 24.07.2017 (1st course)

Application of 8800 MBq Lu-177 DOTATOC on 26.09.2017 (2nd course + Xeloda)

Application of 5800 MBq Y90 DOTATOC on 06.12.2017 (3rd course) intraarterial

Application of 6800 MBq Lu-177 DOTATOC on 26.03.2018 (4th course + Xeloda)

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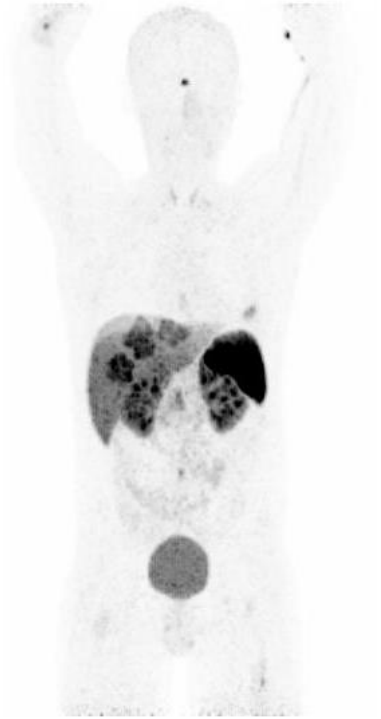
Clinical Case – 23 M university student with NPCa

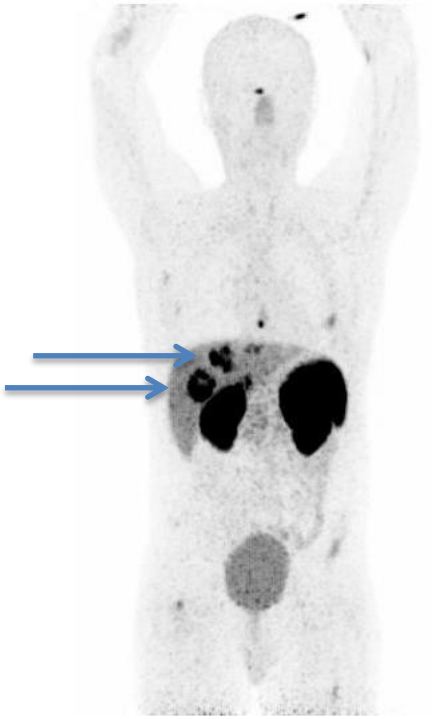
Restaging with Ga-68 DOTATOC associated with PRRT

25.09.2017



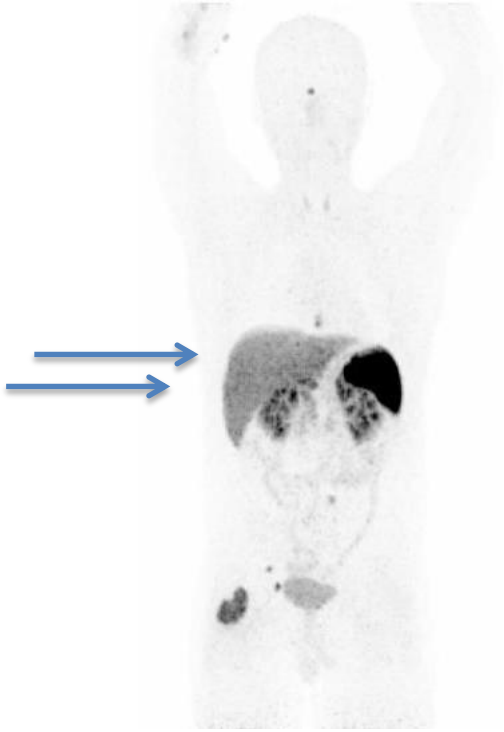
Pre PRRT - 2

05.12.2017



Pre-PRRT - 3
(I.A. PRRT planned)

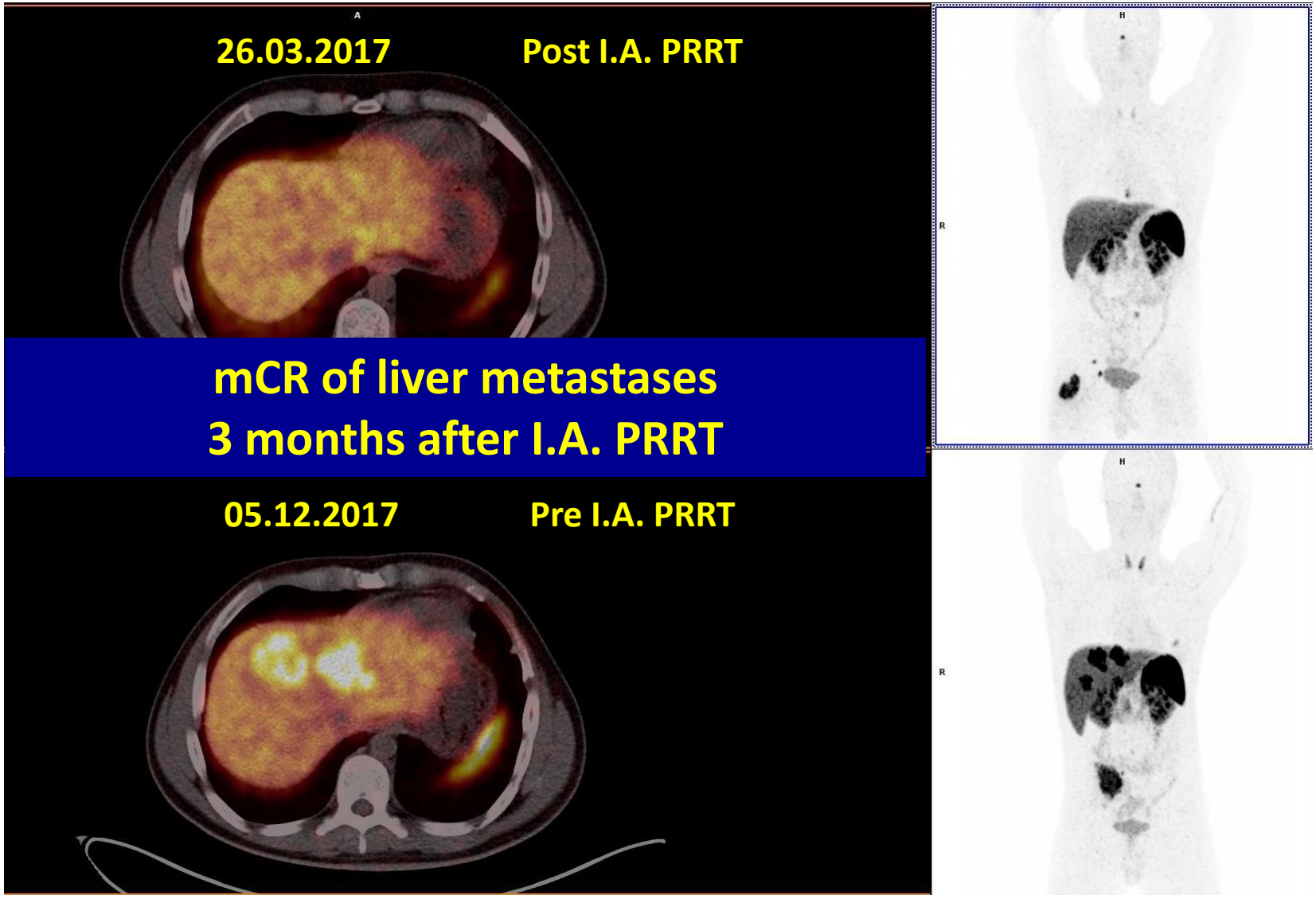
26.03.2017



Pre-PRRT – 4
(mCR of liver metastases
3 months after I.A. PRRT)

Clinical Case – 23 M university student with NPCa

Ga-68 DOTATOC assessment of response to I.A. PRRT



Clinical Case – 23 M university student with NPCa

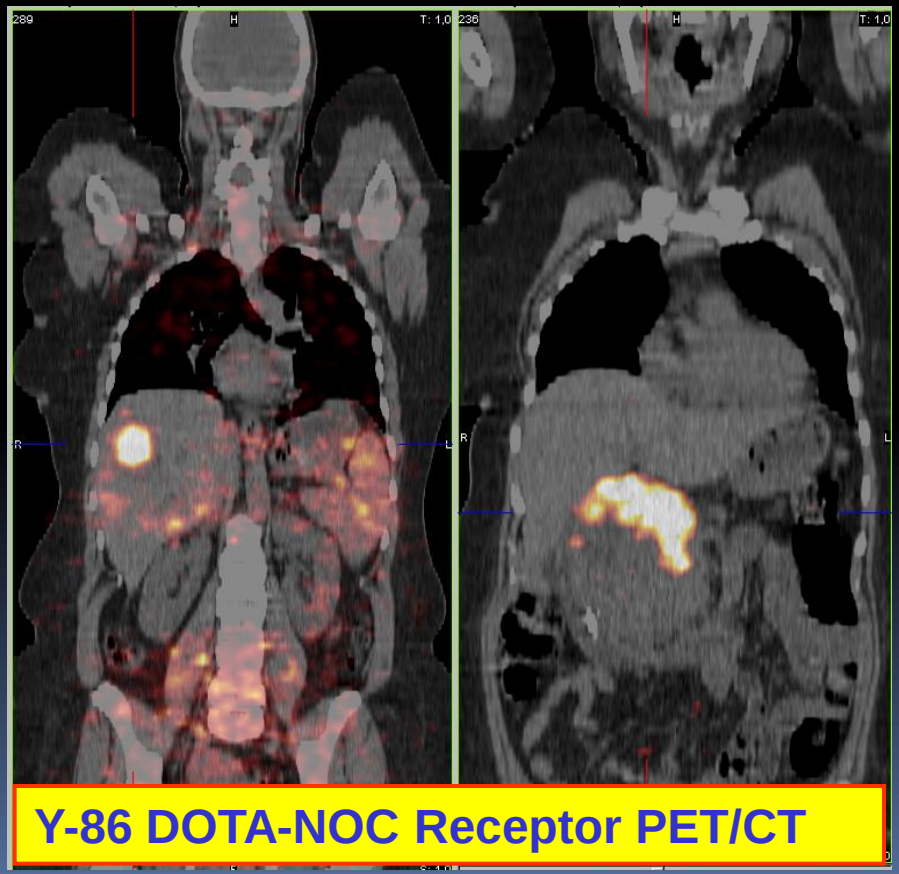
Laboratory parameter following I.A. PRRT

Parameter	Pre-PRRT (23.07.2017)	Post I.A. PRRT (25.03.2018)
Hemoglobin	6.7 --	7.1 -
Leukocytes	13.2 +	3.9 -
Thrombocytes	216	100 -
Creatinine	72.3	69.9
eGFR	>60	>60
Bilirubin	3	4
AST	0.52	0.47
ALT	0.28	0.33
GGT	3.28 ++	0.77
ALKP	2.45 +	1.99
LDH	6.38 +	3.56
Albumin	38	45
Total protein	66	75
INR	1.25 +	1.06

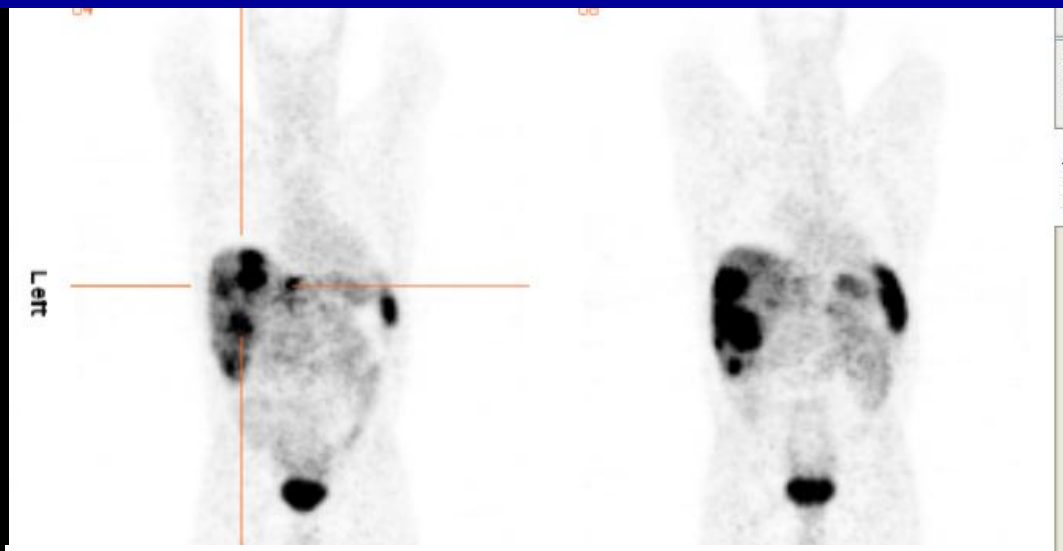
Dosimetry Perspectives - New Isotopes

Pre-therapeutic organ and tumor dosimetry using receptor PET/CT and longer lived positron emitters, e.g. **Sc-44,Cu-64 Tb-152** 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.

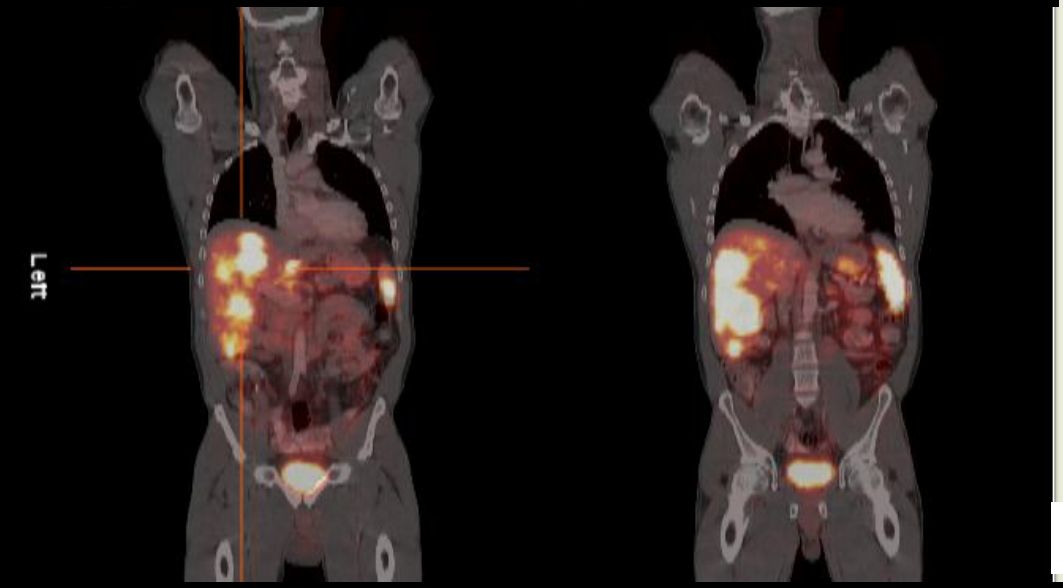


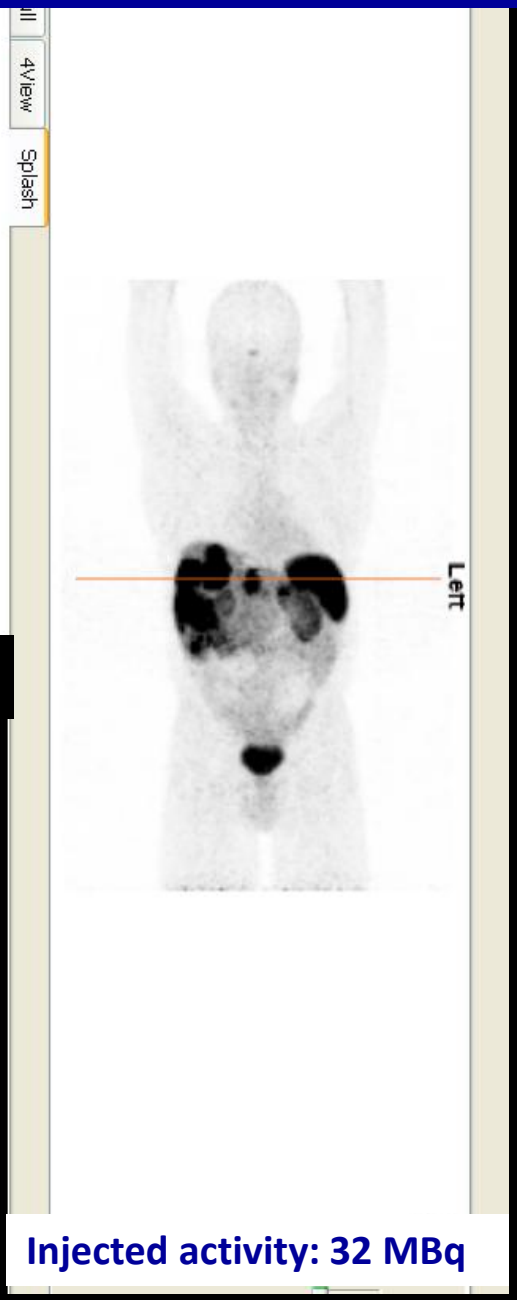
Sc-44 ($t_{1/2}$ 3.9 hrs) from Titanium-44 generator ($t_{1/2}$ >60 years)



First use of Scandium-44 SR-PET/CT in 2009

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





Injected activity: 32 MBq

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

Sc-44 DOTATOC PET/CT – collaboration between PSI and ZBB

CANCER BIOTHERAPY AND RADIOPHARMACEUTICALS
Volume 32, Number 4, 2017

DOI: 10.1089/cbr.2016.2173

Original Article

First-in-Human PET/CT Imaging of Metastatic Neuroendocrine Neoplasms with Cyclotron-Produced ^{44}Sc-DOTATOC: A Proof-of-Concept Study

Aviral Singh,[1] Nicholas P. van der Meulen,[2,3] Cristina Müller,[3] Ingo Klette,[1] Harshad R. Kulkarni,[1] Andreas Türler,[2,4] Roger Schibli,[3,5] and Richard P. Baum[1]

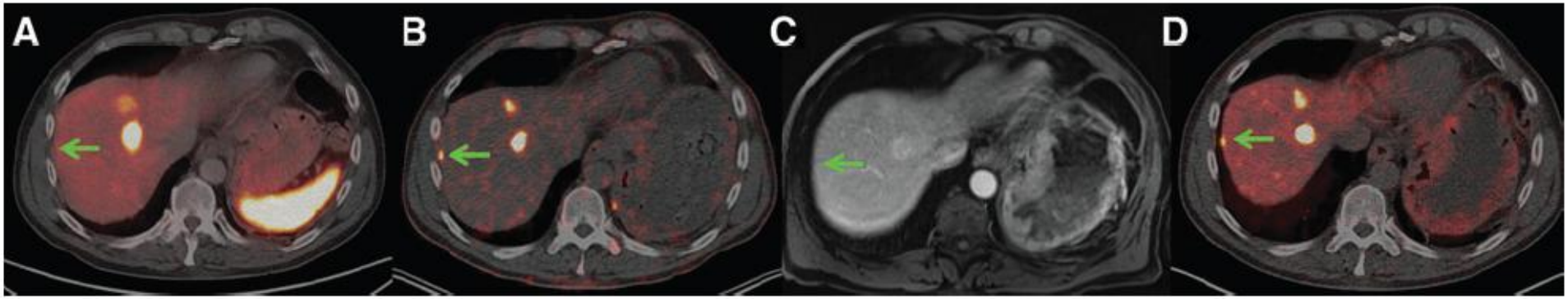
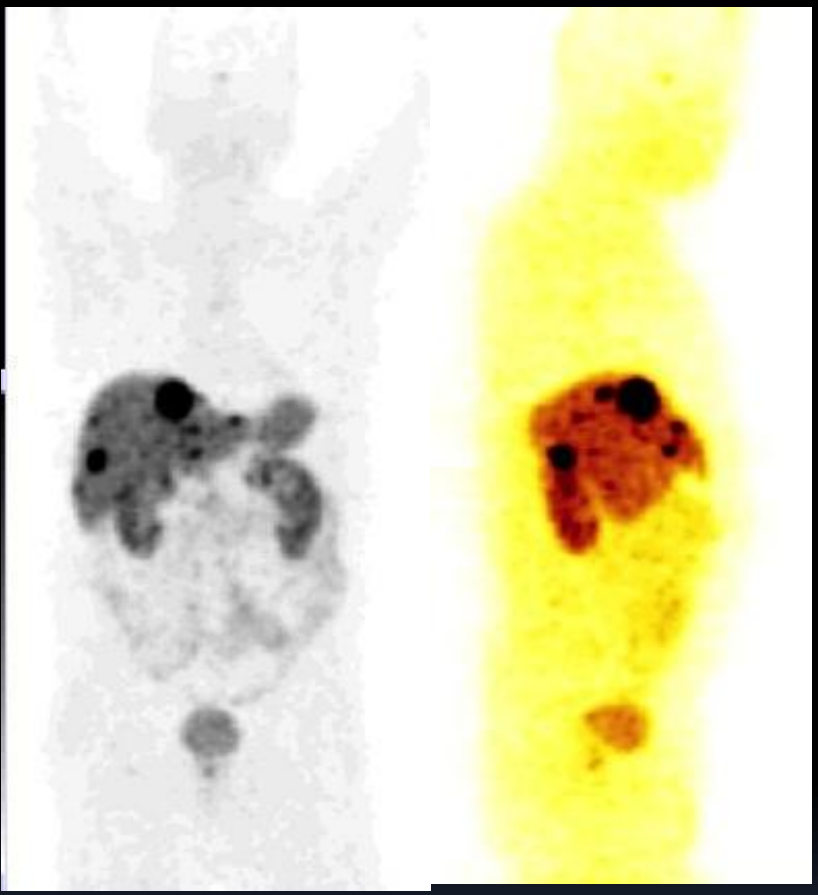


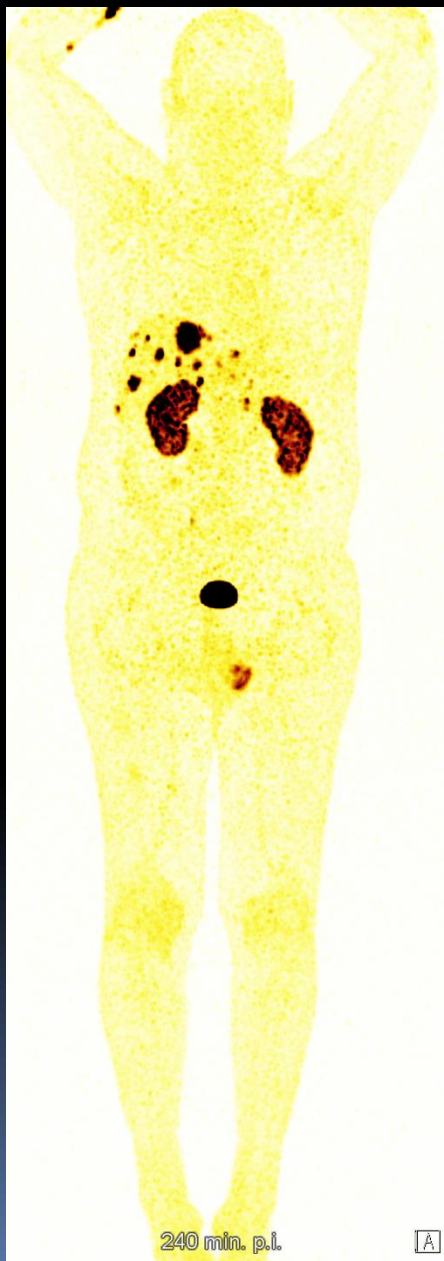
FIG. 5. Comparison of serial images of the transverse section of liver, representing the lesion in segment VIII (*green arrow*), obtained by PET/CT imaging of Patient 2 using somatostatin analogs. (**A**) Nine months before the ^{44}Sc-based PET/CT scan, the lesion was not detected on the PET/CT image obtained with ^{68}Ga-DOTATOC PET/CT; (**B**) the lesion was detected on PET/CT images performed with ^{44}Sc-DOTATOC, but (**C**) it was not seen on a concurrent MRI performed within 24 hours of ^{44}Sc-based PET/CT scan; (**D**) 9 months later, the lesion was detected on PET/CT images obtained with ^{68}Ga-DOTATOC.

First-in-human Sc-44 DOTATOC PET/CT

^{68}Ga-DOTATOC PET



^{44}Sc-DOTATOC PET



No significant uptake

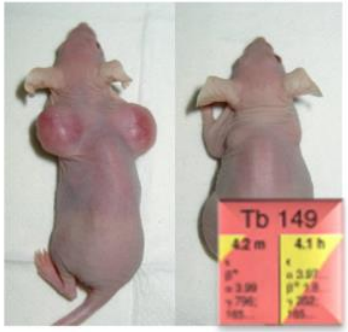
- pituitary gland
- salivary glands
- normal liver
- intestines

Excellent tracer uptake in metastases

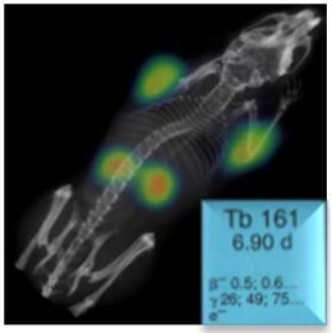
High tumor-to-background ratio

Terbium: the Swiss Army knife of Nuclear Medicine

^{149}Tb-therapy



^{161}Tb-therapy & SPECT

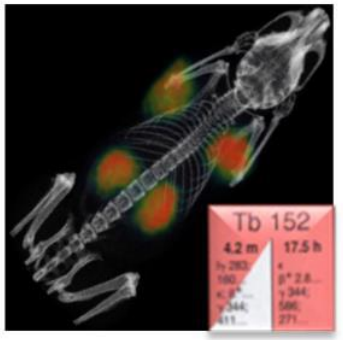


CERN ISOLDE

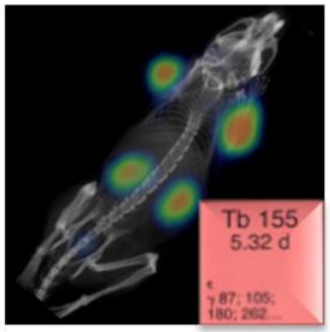
NEUTRONS FOR SCIENCE

PAUL SCHERRER INSTITUT PSI

^{152}Tb-PET



^{155}Tb-SPECT



Müller et al. **2012**, J Nucl Med 53:1951.

Potential for diagnosis, pre-therapeutic dosimetry and radionuclide therapy

^{152}Tb/^{177}Lu-DOTANOC: Equal Tissue Distribution

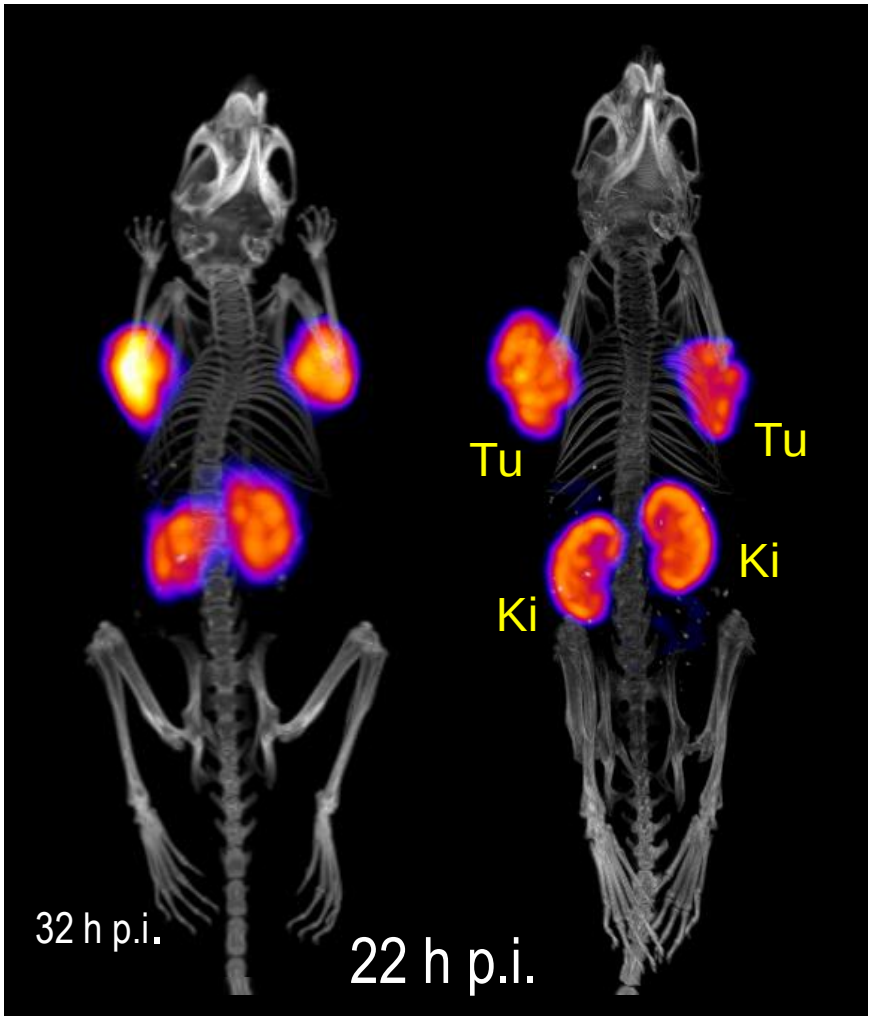
^{152}Tb-DOTANOC PET/CT

Tb 152
17.5 h
ε
β^+ 2.8…
γ 344;
586;
271…

Injection: 47 MBq, 4.7 nmol

Scan time: 20 min (in vivo)

G8 PET/CT Scanner



^{177}Lu-DOTANOC SPECT/CT

Lu 177
6.71 d
β^- 0.5…
γ 208; 113…
g
σ 1000

Injection: 47 MBq, 4.7 nmol

Scan time: 4 h (post-mortem)

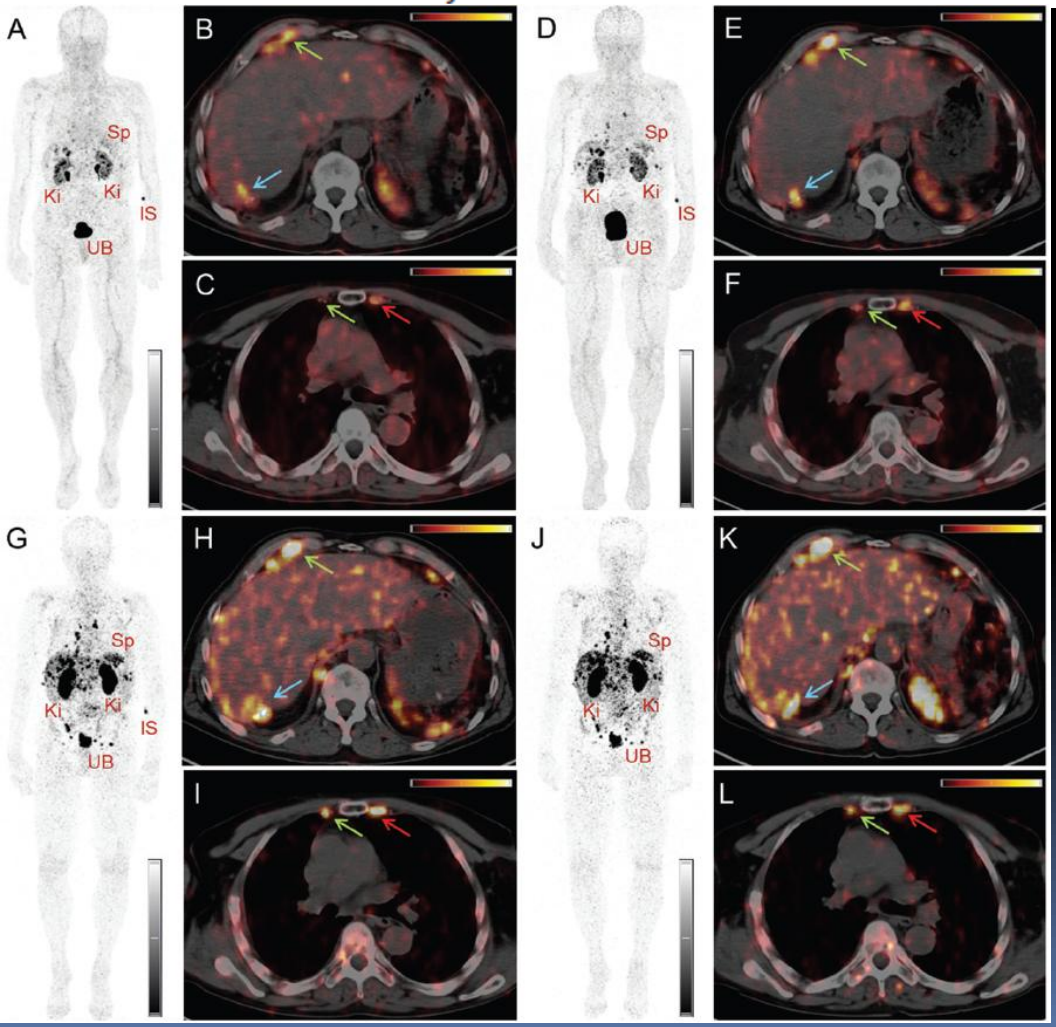
NanoSPECT/CT Scanner

Müller et al. **2016** EJNMMI Research 6:35.

Published on 21 August 2017.
Dalton Transactions
DOI: 10.1039/c7dt01936j

Clinical evaluation of the radiolanthanide terbium-152: first-in-human PET/CT with ^{152}Tb-DOTATOC

Richard P. Baum, †[a] Aviral Singh,*†[a] Martina Benešová,[b,c] Christiaan Vermeulen,[b] Silvano Gnesin,[d] Ulli Köster,[e] Karl Johnston,[f] Dirk Müller,[a] Stefan Senftleben,[a] Harshad R. Kulkarni,[a] Andreas Türler,[g,h] Roger Schibli,[b,c] John O. Prior,[d] Nicholas P. van der Meulen[b,g] and Cristina Müller *[b,c]



A unique, multi-disciplinary study in which ^{152}Tb was investigated from the production to the first-in-human clinical application.

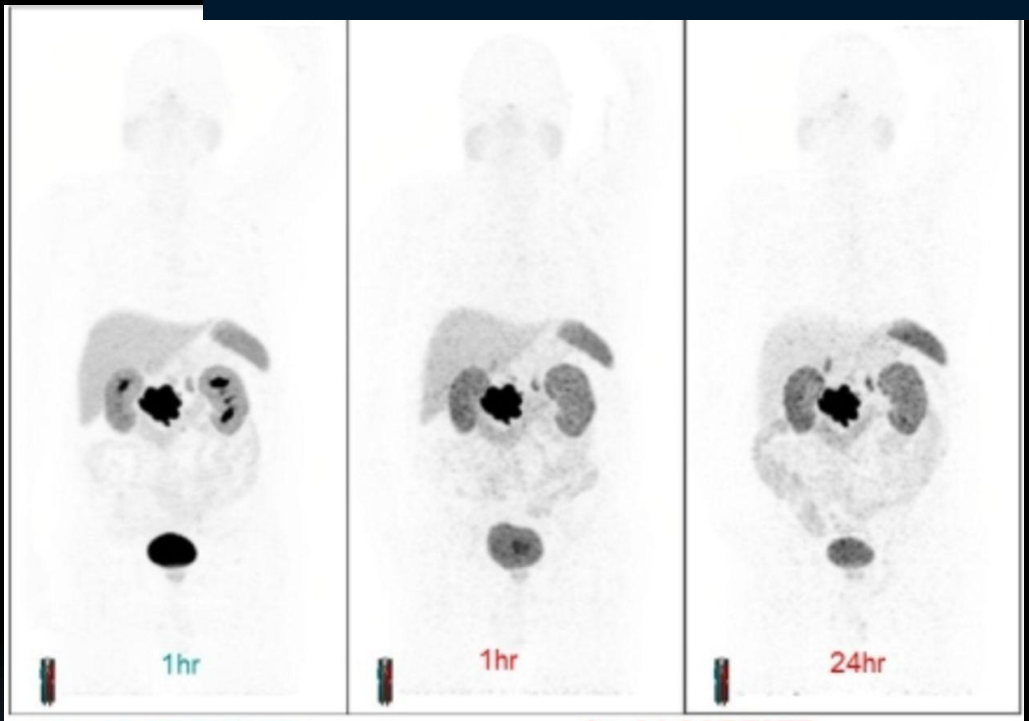
PET/CT imaging using ^{152}Tb-DOTATOC in a patient with SI-NEN, allowed the visualization of even small lymph node and bone metastases.

Due to the considerably longer half-life of ^{152}Tb ($T_{1/2}$ = 17.5 h) this novel radionuclide would be particularly interesting for performing predictive dosimetry prior to radionuclide therapy.

First-Time-in-Human Trial of Cu-64 MeCOSAR-octreotate (CuSARTATE) for Imaging and Dosimetry Estimation in Neuroendocrine Tumor (NET)

Rodney Hicks[8,4], Price Jackson[4], Robert Ware[4], Elizabeth Drummond[5], Peter Roselt[4], Wayne Noonan[4], Roger Price[6], Charmaine Jeffrey[6], Jason Callah

DIAGNOSTIC APPLICATION & PREDICTIVE DOSIMETRY



	Ga-68 DOTATATE 60min	Cu-64 SARTATE 60min	Cu-64 SARTATE 24hr
Tumour/Liver SUV Ratio	22:1	29:1	45:1

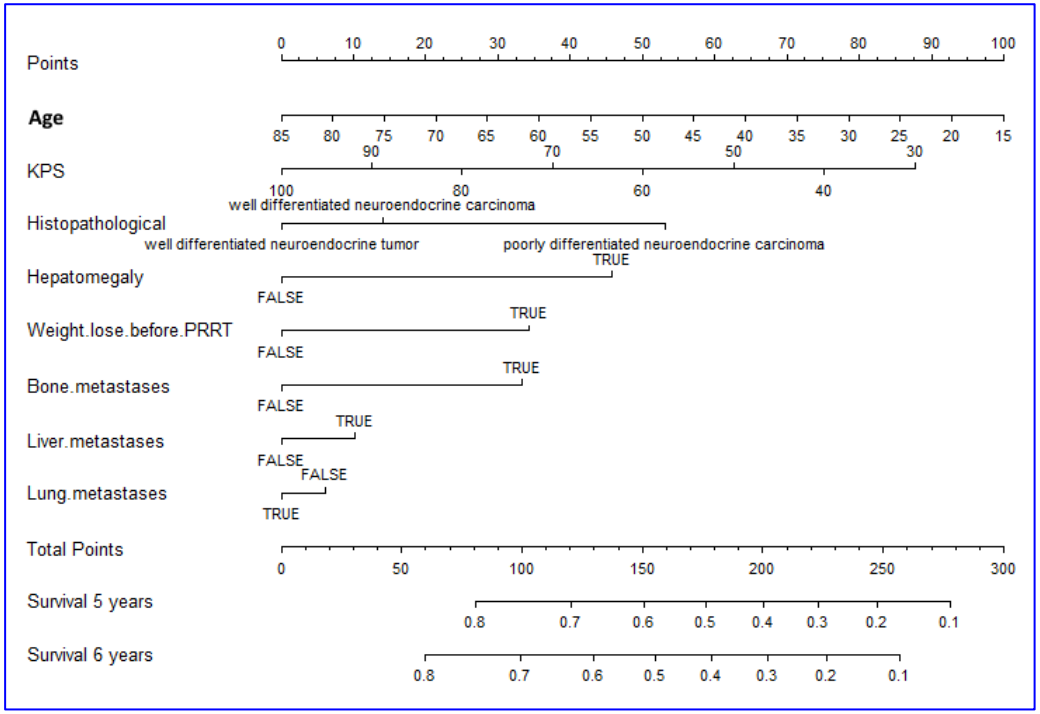
Presented at SNMMI 2016; JNM 2016;57(2)26

"The high-retention of tracer in lesions, accompanied by progressive liver and kidney clearance, provides improved imaging contrast at late time-points. This supports use of CuSARTATE for both staging and prospective dosimetry estimation, especially for Cu-67 SARTATE therapy. The long half-life of Cu-64 makes distribution of GMP product feasible to sites without onsite Ga-68 tracer production capability."

PO-0696 A predictive nomogram for decision support for patients with pancreatic neuroendocrine tumors

A. Jochems[1], R. Baum[2], A. Singh[2], K. Niepsch[2], H. Kulkarni[2], P. Lambin[1]

ESTRO 36, Vienna 2017



Nomogram of the model PRRT of pancreatic NEN.

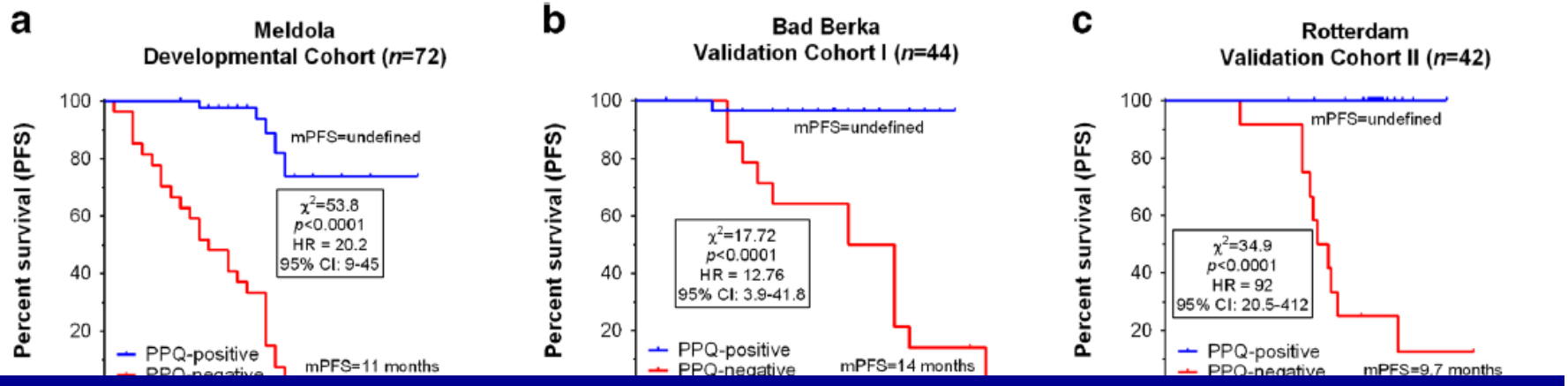
The nomogram is based on a proportional hazards cox regression. A number of points can be looked up for each variable, the total points can be summed up and mapped to the survival scores on the bottom of the nomogram. The predictive value of each variable is proportional to the points score line length associated with the variable.

PRRT genomic signature in blood for prediction of ^{177}Lu-octreotate efficacy

European Journal of Nuclear Medicine and Molecular Imaging
https://doi.org/10.1007/s00259-018-3967-6

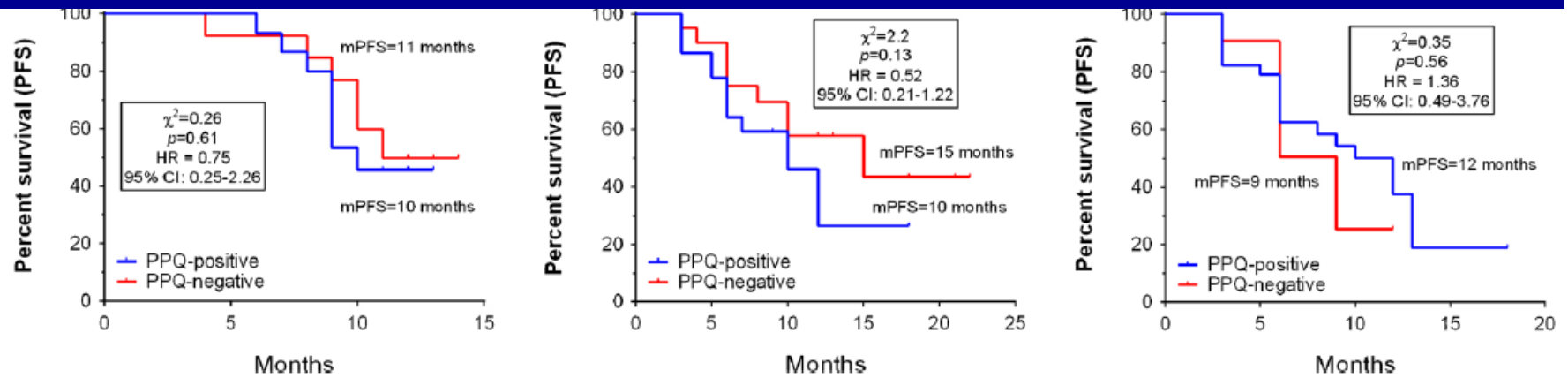
Lisa Bodei[1,2] · Mark S. Kidd[3] · Aviral Singh[4] · Wouter A. van der Zwan[5] · Stefano Severi[6] · Ignat A. Drozdov[3] · Jaroslaw Cwikla[7] · Richard P. Baum[2,4] · Dik J. Kwekkeboom[2,5] ·

PRRT



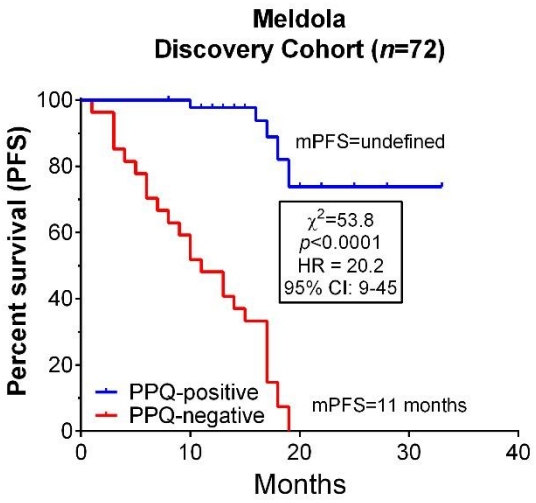
- **Strategies to identify PRRT efficacy prior to therapy**
- **Individual assessment of therapy response afer PRRT**

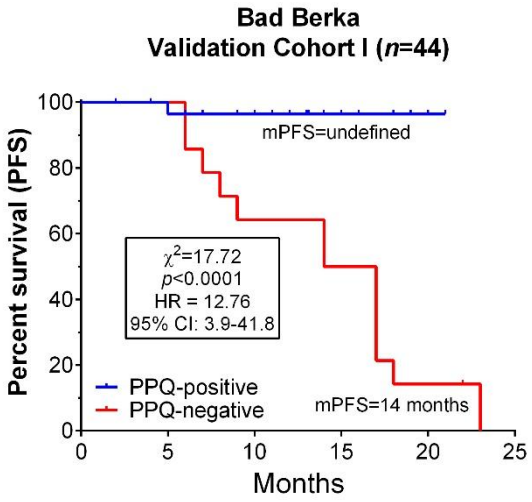
No PRRT

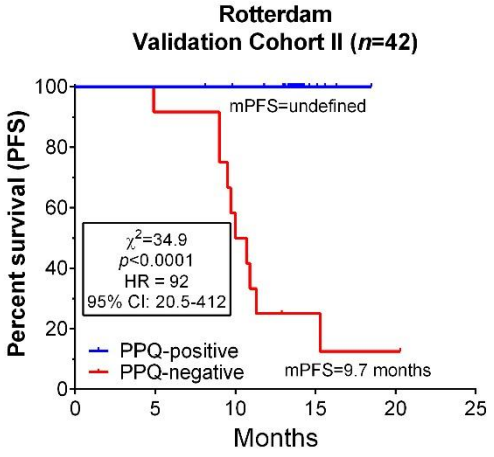


Prediction accuracy of NETest in different validation cohorts

PRRT

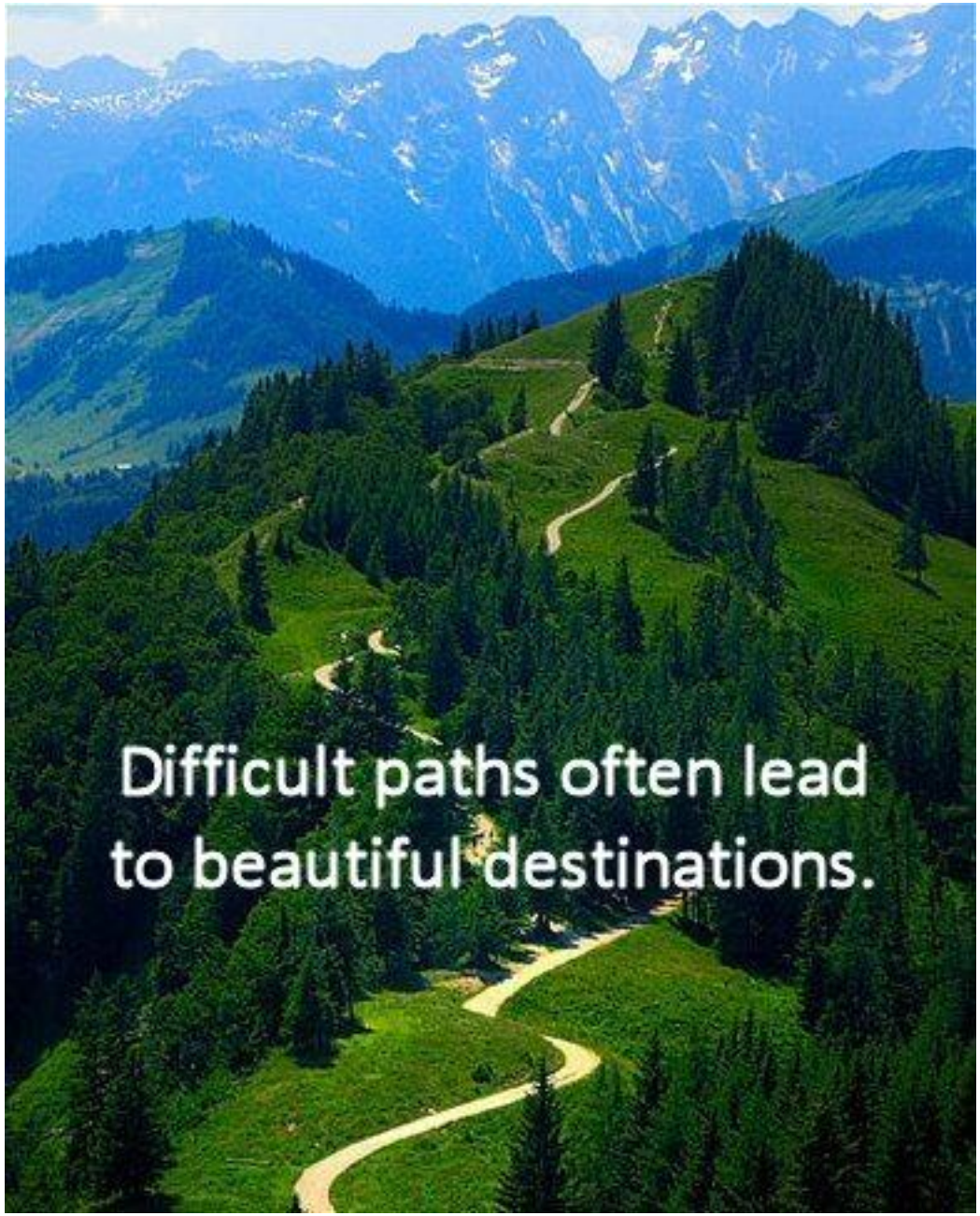






The predictive quotient is 95% accurate

Courtesy Lisa Bodei


Difficult paths often lead
to beautiful destinations.

Thank you for your attention

5th

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