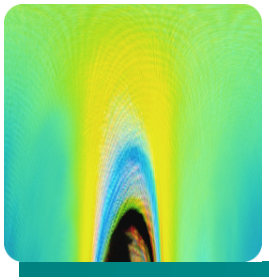
Heterogeneity of NETs and PRRT Strategies

Irene J. Virgolini

MORE Conference
September 4-6 2018
Varna, Bulgaria

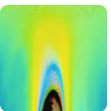


Tirol Kliniken GmbH
Landeskrankenhaus – Universitätskliniken Innsbruck
Medizinische Universität Innsbruck
Universitätsklinik für Nuklearmedizin
Direktor: Univ.-Prof. Dr. Irene J. Virgolini

Heterogeneity of NETs and PRRT Strategies

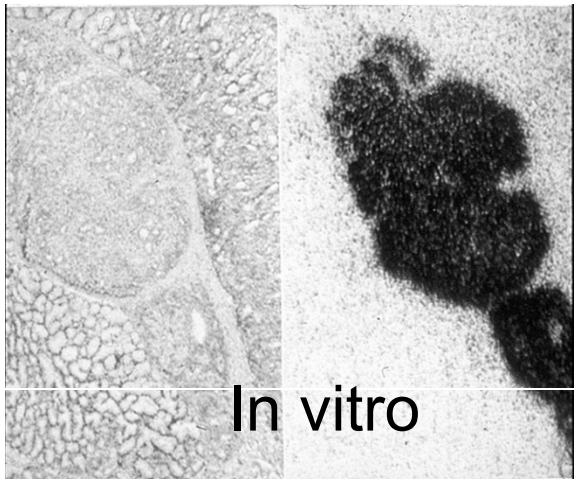
tirol kliniken

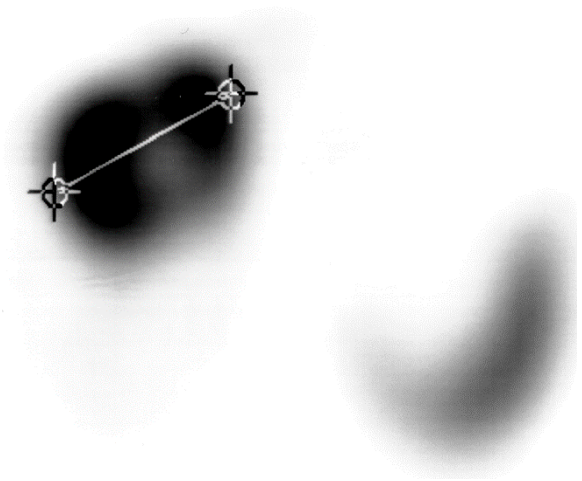
MEDIZINISCHE UNIVERSITÄT INNSBRUCK

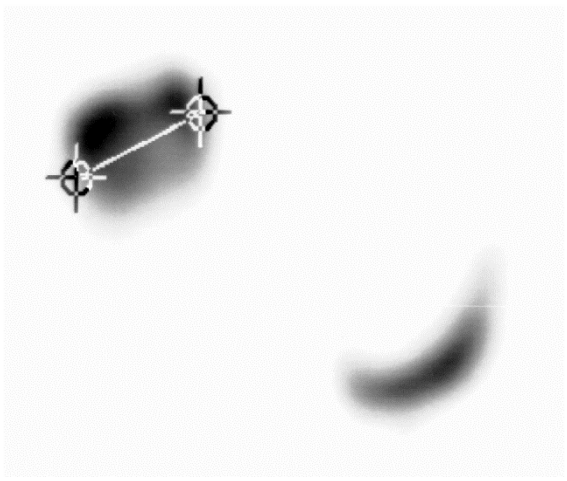


RADIOLABELLED OCTREOTIDE

1984	1987	1992
Autoradiography	**Scintigraphy**	**Radionuclide Therapy**
	6 mCi	**180 mCi**







Curtesy, Marion De Jong, Rotterdam

Peptide Receptor Radionuclide Therapy

PRRTs

1992 ^{111}In-OctreoScan
1995 ^{111}In-OctreoScan
1995 ^{90}Y-DOTA-Tyr^{3}-Octreotide
1996 ^{90}Y-DOTA-Tyr^{3}-Octreotide
1997 ^{90}Y-DOTA-Lanreotide
1997 ^{90}Y-DOTA-Tyr^{3}-Octreotide
1998-2003 ^{90}Y-DOTA-Lanreotide
1998 ^{90}Y-DOTA-Tyr^{3}-Octreotide
1998 ^{90}Y-DOTA-Tyr^{3}-Octreotide
1998 ^{90}Y-DOTA-Tyr^{3}-Octreotide
1999 ^{177}Lu-DOTA-Tyr^{3}-Octreotate
2000-2005 OctreoTher®
2003 ^{90}Y-DOTA-Tyr^{3}-Octreotate
2004 ^{67}Ga-DOTA-Tyr^{3}-Octreotide
2005 ^{177}Lu-DOTA-Lanreotide
2005 ^{90}Y-DOTA-Tyr^{3}-Octreotate
2012-2021 ^{177}Lu-DOTA-Tyr^{3}-Octreotate
2013 ^{213}Bi-DOTA-Tyr^{3}-Octreotide
2014 ^{177}Lu-DOTA-JR11
2017-2020 ^{177}Lu-OPS203 (DOTA-JR11)
2017 ^{177}Lu-DOTA-Tyr3-Octreotide

CENTERS

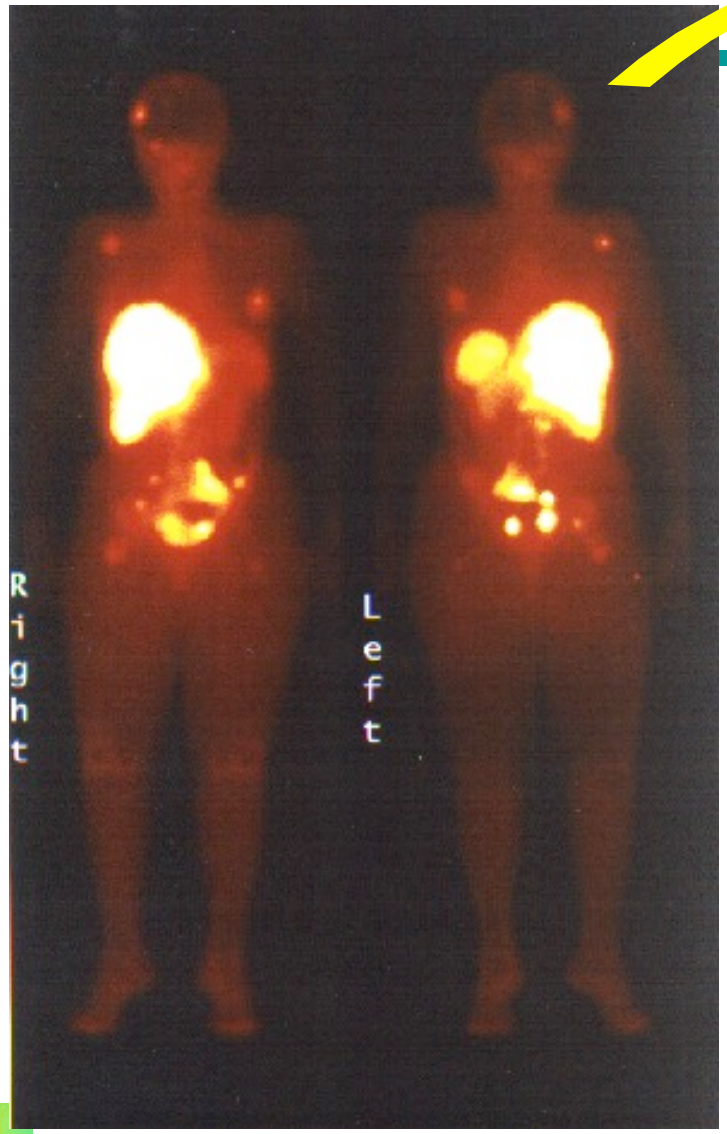
Krenning, Rotterdam
Virgolini, Vienna
Müller, Basle
Krenning, Rotterdam
Virgolini, Vienna
Virgolini, Vienna
„MAURITIUS“ (11 EU Centers)
Paganelli, Milan
Baum, Bad Berka
Riccabona, Innsbruck
Kwekkeboom, Rotterdam
NOVARTIS Multicenter Study
Müller, Basle
Knapp, Hannover
Virgolini, Innsbruck
Buscombe, London
NETTER-1, AAA Study
Haberkorn, Heidelberg
Wild, Basle
IPSEN Multicenter Study
COMPETE Multicenter Studie

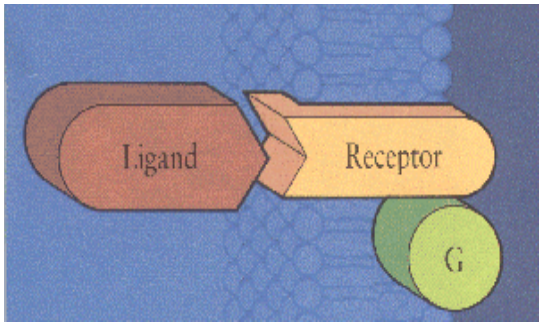
PRRT around the Globe Today

Physical Properties of Radionuclides

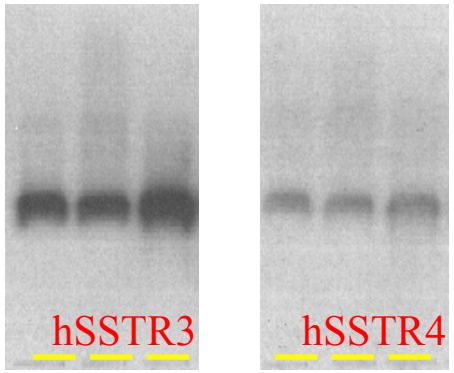
Radionuclide	$t_{1/2}$ (d)	energy (keV)	path length (mm)	Gamma (keV)
^{111}Indium	2.8	Auger electrons 14.7	<0.01	172 (90%) 247 (94%)
^{90}Yttrium	2.7	935	12	-
^{177}Lutetium	6.7	133	2.1	113 (6.6%) 208 (11%)
^{225}Actinium	10.0	5935 (8536 from 213Po daughter)	~ 0.1	218 (11%) from ^{221}Fr daughter, 440 (26%) from ^{213}Bi daughter

University of Vienna, 1995, OctreoScan in a patient with metastasized carcinoid tumour receiving high dose ^{111}In-DTPA-Octreotide (OctreoScan®, 200 mCi)





receptor studies



Northern Blotting

ENETS Guidelines

Neuro
endocrinology

Neuroendocrinology 2009;90:220–226
DOI: 10.1159/000225951

Received: August 27, 2008
Accepted after revision: January 27, 2009
Published online: August 28, 2009

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Peptide Receptor Radionuclide Therapy with Radiolabeled Somatostatin Analogs

Dik J. Kwekkeboom[a] Eric P. Krenning[a] Rachida Lebtahi[b] Paul Komminoth[c]
Beata Kos-Kudła[d] Wouter W. de Herder[e] Ursula Plöckinger[f]
and the Mallorca Consensus Conference participants

[a]Department of Nuclear Medicine, Erasmus University Medical Center, Rotterdam, The Netherlands; [b]Nuclear Medicine Department, Bichat Hospital, Paris, France; [c]Institute for Pathology, Stadtspital Triemli, Zürich, Switzerland; [d]Slaska Akademia Medyczna Klinika Endokrynologii, Zabrze, Poland; [e]Department of Internal Medicine, Section of Endocrinology, Erasmus MC, Rotterdam, The Netherlands; [f]Department of Hepatology and Gastroenterology, Campus Virchow-Klinikum, Charité-Universitätsmedizin Berlin, Berlin, Germany

Eur J Nucl Med Mol Imaging (2013) 40:800–816
DOI 10.1007/s00259-012-2330-6

GUIDELINES

The joint IAEA, EANM, and SNMMI practical guidance on peptide receptor radionuclide therapy (PRRNT) in neuroendocrine tumours

John J. Zaknun · L. Bodei · J. Mueller-Brand ·
M. E. Pavel · R. P. Baum · D. Hörsch · M. S. O'Dorisio ·
T. M. O'Dorisiol · J. R. Howe · M. Cremonesi ·
D. J. Kwekkeboom

Consequences from the NETTER-1 Trial

NANETS GUIDELINES

The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors

Jonathan R. Strosberg, MD, Thorvardur R. Halfdanarson, MD,† Andrew M. Bellizzi, MD,‡ Jennifer A. Chan, MD,§ Joseph S. Dillon, MD,|| Anthony P. Heaney, MD,¶ Pamela L. Kunz, MD,# Thomas M. O'Dorisio, MD,|| Riad Salem, MD,** Eva Segelov, MBBS, PhD, FRACP,†† James R. Howe, MD,‡‡ Rodney F. Pommier, MD,§§ Kari Brendtro,|||| Mohammad A. Bashir, MD,¶¶ Simron Singh, MD,## Michael C. Soulen, MD,*** Laura Tang, MD,††† Jerome S. Zacks, MD,‡‡‡ James C. Yao, MD,§§§ and Emily K. Bergsland, MD||||||*

(*Pancreas* 2017;46: 707–714)

ENETS Consensus Guidelines update for the management of distant metastatic disease.

Pavel et al. ; Neuroendocrinology 2016; 103:172-185; Hicks et al; Neuroendocrinology 2017: 105-295-309

... PRRT is in general recommended in G1/G2 NET after failure of medical therapy....

However, potential increasing toxicity, e.g. after prior chemotherapy or targeted therapy, needs to be considered.....and might justify an earlier use of PRRT...

ENETS Consensus Guidelines Update for the Management of Distant Metastatic Disease of Intestinal, Pancreatic, Bronchial Neuroendocrine Neoplasms (NEN) and NEN of Unknown Primary Site.

Pavel M, O'Toole D, Costa F, Capdevila J, Gross D, Kianmanesh R, Krenning E, Knigge U, Salazar R, Pape UF, Öberg K; Vienna Consensus Conference participants.

Neuroendocrinology. 2016;103(2):172-85. doi: 10.1159/000443167. Epub 2016 Jan 5.

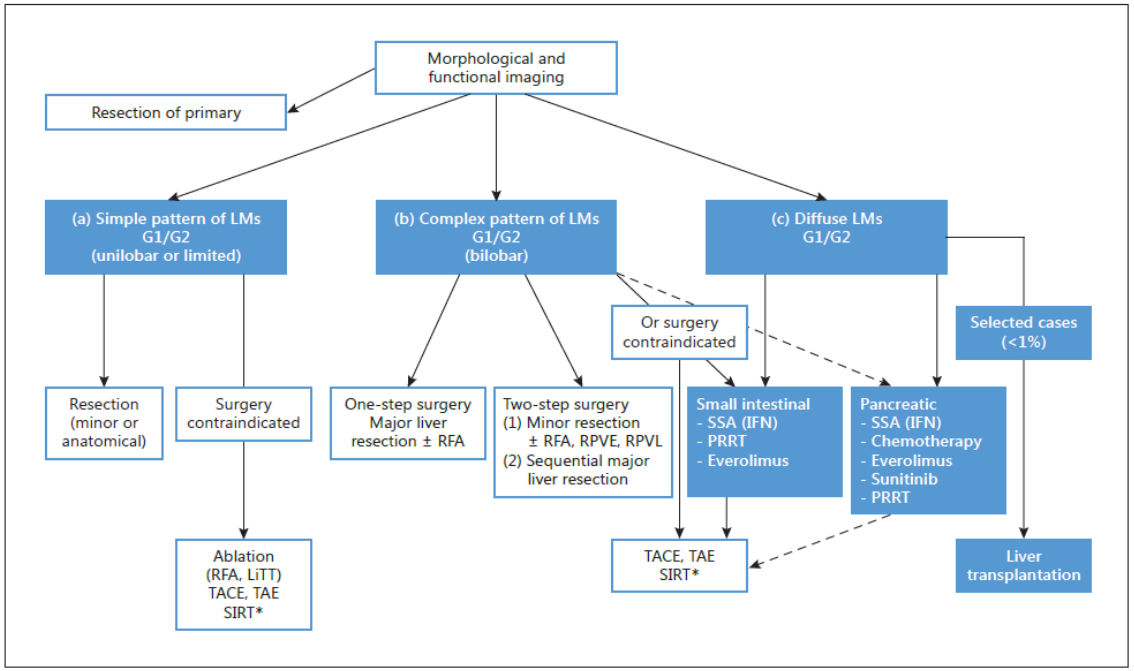


Fig. 1. Management of liver metastases without extrahepatic disease in G1/G2 NEN. * SIRT (selective internal radiation therapy) is still an investigational method. LiTT = Laser-induced thermotherapy; LMs = liver metastases; RFA = radiofrequency ablation; RPVE = right portal vein embolization; RPVL = right portal vein ligation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

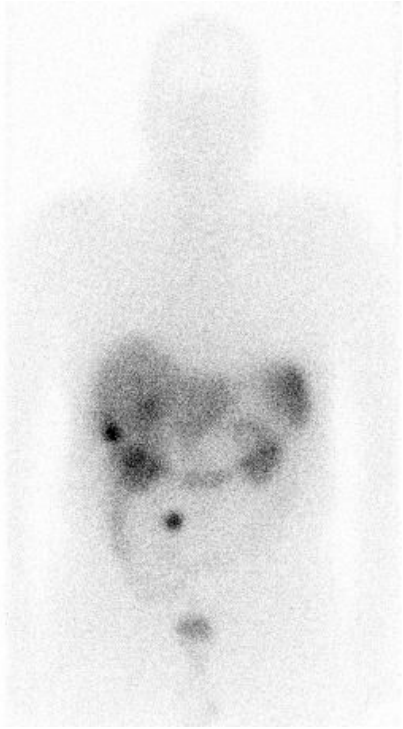
CONTENT

- Status of Radiopharmaceuticals
- Current Status of PRRT
  and Retreatment-PRRT
- Importance of Dual Tracer Imaging
- Long-term Side Effects
- New Indications (Non-NETs)
- Antagonists
- Combination Treatments

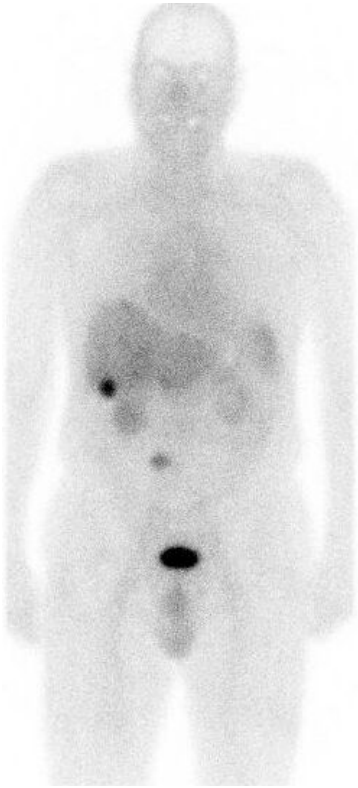
Status of Radiopharmaceuticals

Somatostatin Analogues – licensed Diagnostics 2018

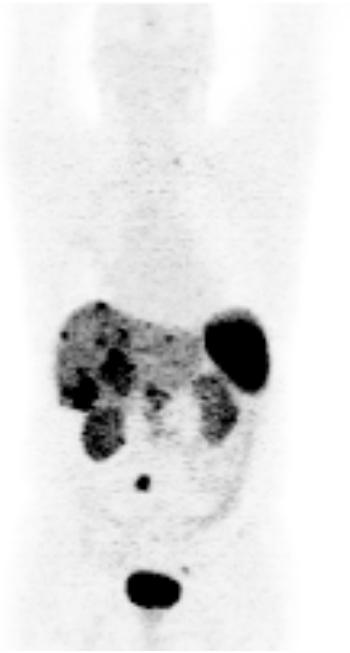
^{111}In-DTPA-Octreotid (OctreoScan®) 24h p.i.



^{99m}Tc-EDDA-HYNIC-TOC (Tektrotyde®) 4h p.i.



^{68}Ga-DOTA-TOC (Somakit TOC®) 1h p.i.

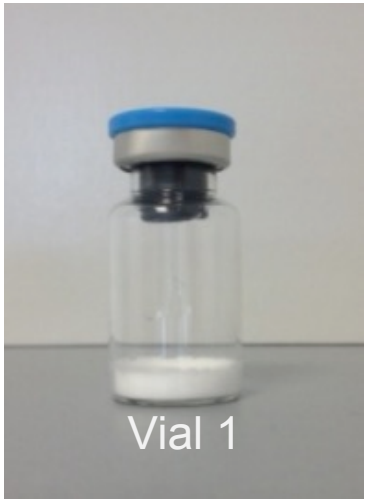


Imaging time point over the last 2 decades

Somatostatin Analogues – licensed Diagnostics 2018

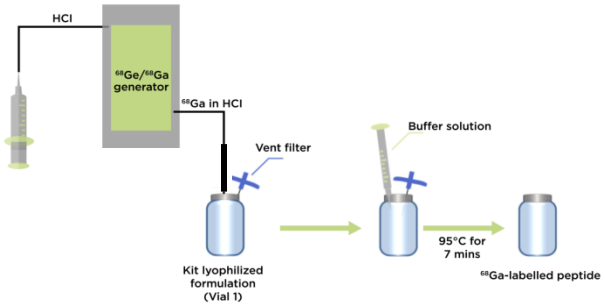
Kit-based preparation of ^{68}Ga-DOTA-TOC SomaKit TOC® / NeoSPOT™

^{68}Gallium kit	
Vial-1 Lyophilized formulation	**Vial-2 Reaction buffer**



EU: SomaKit TOC®
kit for radiopharmaceutical preparation [^{68}Ga]-Edotreotide
US: NETSPOT™
kit for radiopharmaceutical preparation [^{68}Ga]-Oxodotreotide (DOTATATE)

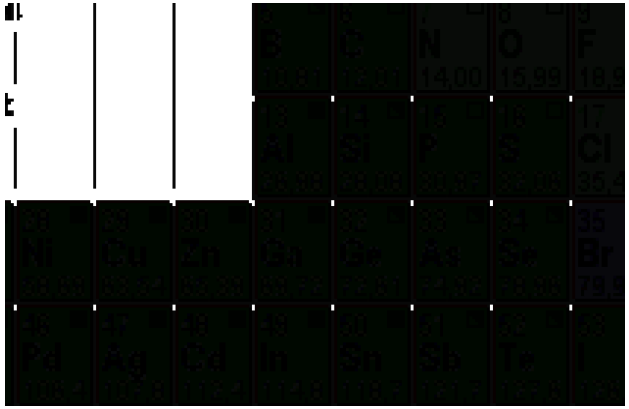
- Qualified / chemically controlled materials
- Reproducible composition, GMP produced
- Standardized, simple labelling procedure



$^{68}Ge/^{68}Ga$ Generator

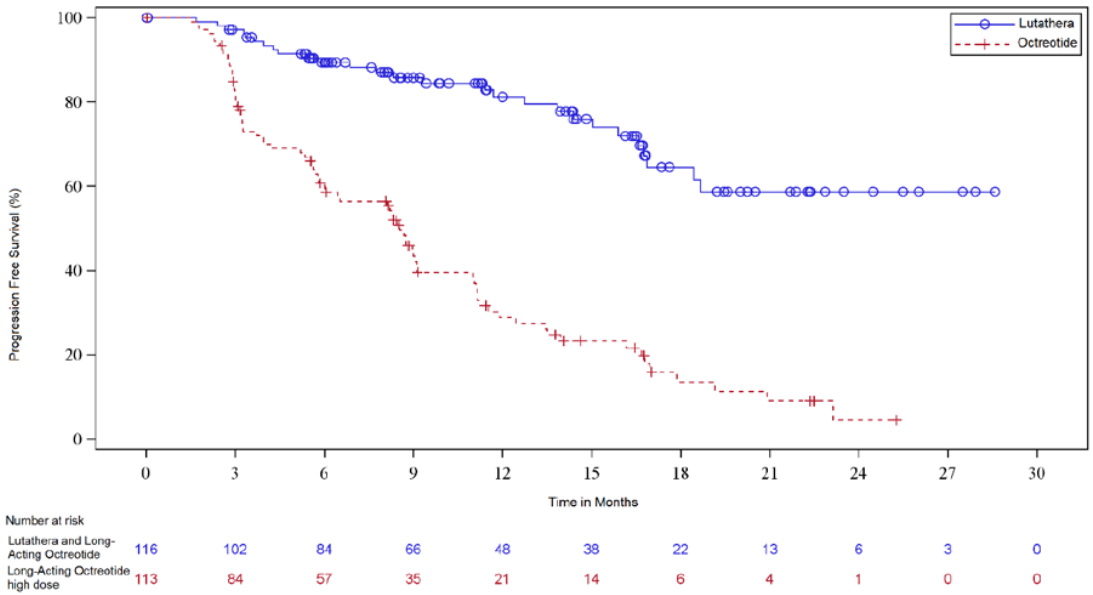
Galliapharm®-Marketing Authorisation in Europe

Registered as „a medicinal product which allows direct, simplified preparation of ^{68}Ga-radiopharmaceuticals in combination with licensed kits“



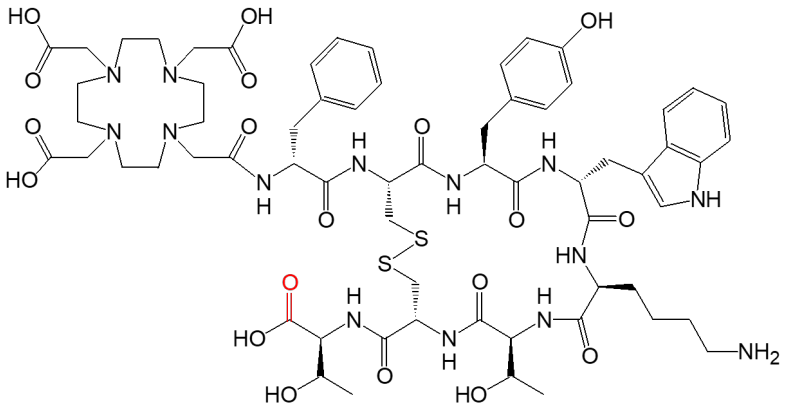
- Halflife of mother : 270.8 days
  - **Decay: 100%ec**
- Halflife of daughter: 67.6 minutes
  - **Decay : 89.2% ß+**

Somatostatin Analogues – licensed Therapeutics
Lutathera®



^{177}Lu-DOTATATE (Oxodotreotide)

Advanced Accelerator Applications



DOTATATE

Current Status of PRRT and Retreatment-PRRT

Netter 1: Progression-Free Survival

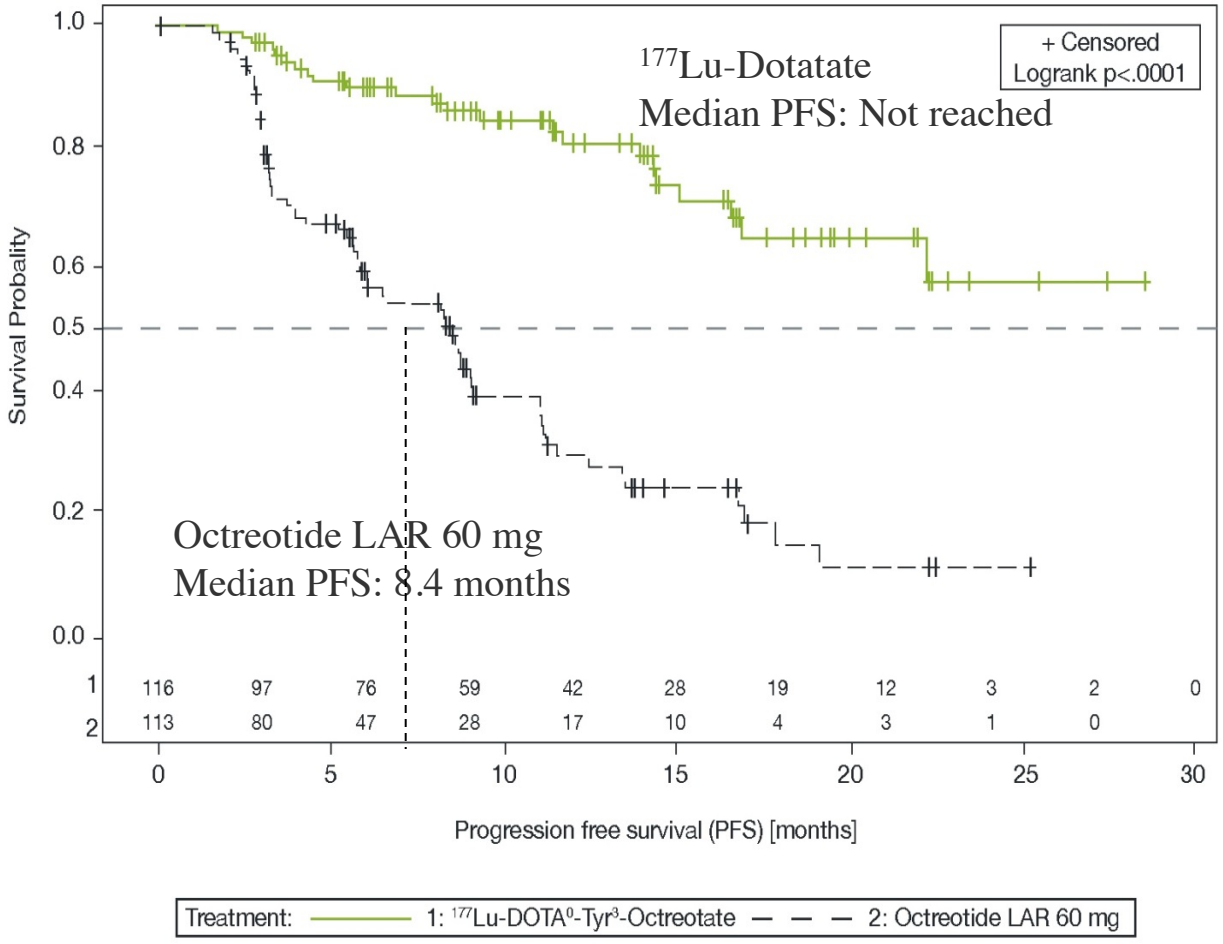
- **Primary Objective**

In the Lutathera arm, TTP was significantly higher compared to the Octreotide LAR arm (p<0.0001) with a median TTP not reached for Lutathera and 8.7 months for Octreotide LAR [95% CI: 6.4-11.1 months].

17 patients treated with Lutathera had a centrally assessed tumor progression at the cut-off date compared to 58 patients treated with Octreotide LAR.

Hazard ratio: **0.21**
[0.13 – 0.33]
p < 0.0001

79% reduction in the risk of disease progression/death



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

Innsbruck – 1998 to 2018
Somatostatin-Analogs for PRRT

1. **^{90}Y-DOTA-Tyr^{3}-Octreotide**
   binds with high affinity to hSSTR 2 and 5

2. **^{177}Lu-DOTA-Tyr^{3}-Octreotate**
   binds with higher affinity to hSSTR2

3. **^{90}Y- ^{177}Lu-DOTA-Lanreotide**
   binds to a broader spectrum of SSTR (hSSTR 2,3,4,5), and produces thus a higher soft tissue and bone marrow dose – indicated only if dosimetry with octreotide analogs gives no satisfactory tumour dose

^{90}Y versus ^{177}Lu

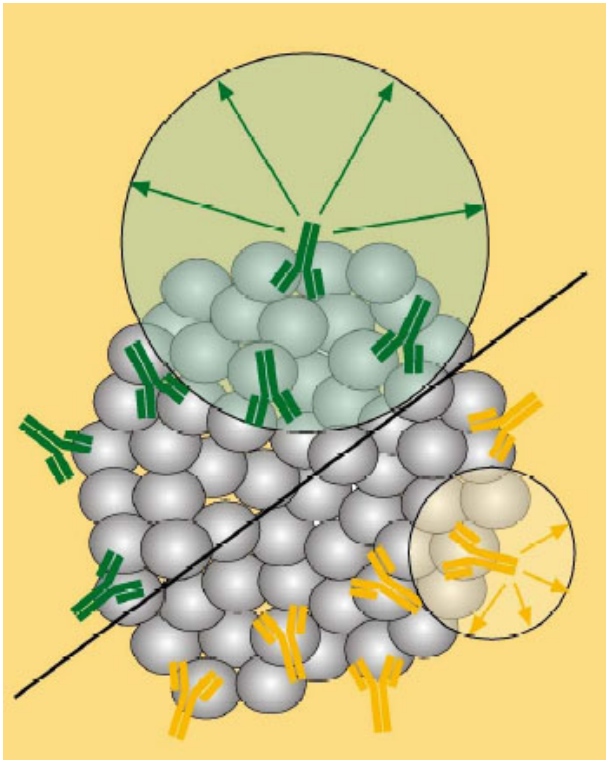
Y-90

ß$^-$ max. 2280 keV

high energy
pure beta emitter

max. tissue penetration
12 mm

tumour lesions
> 1 g
inhomogenous tumours
(no micrometastases)



● ^{90}Y ● ^{177}Lu

Lu-177

ß$^-$ max. 498 keV
γ 208 keV

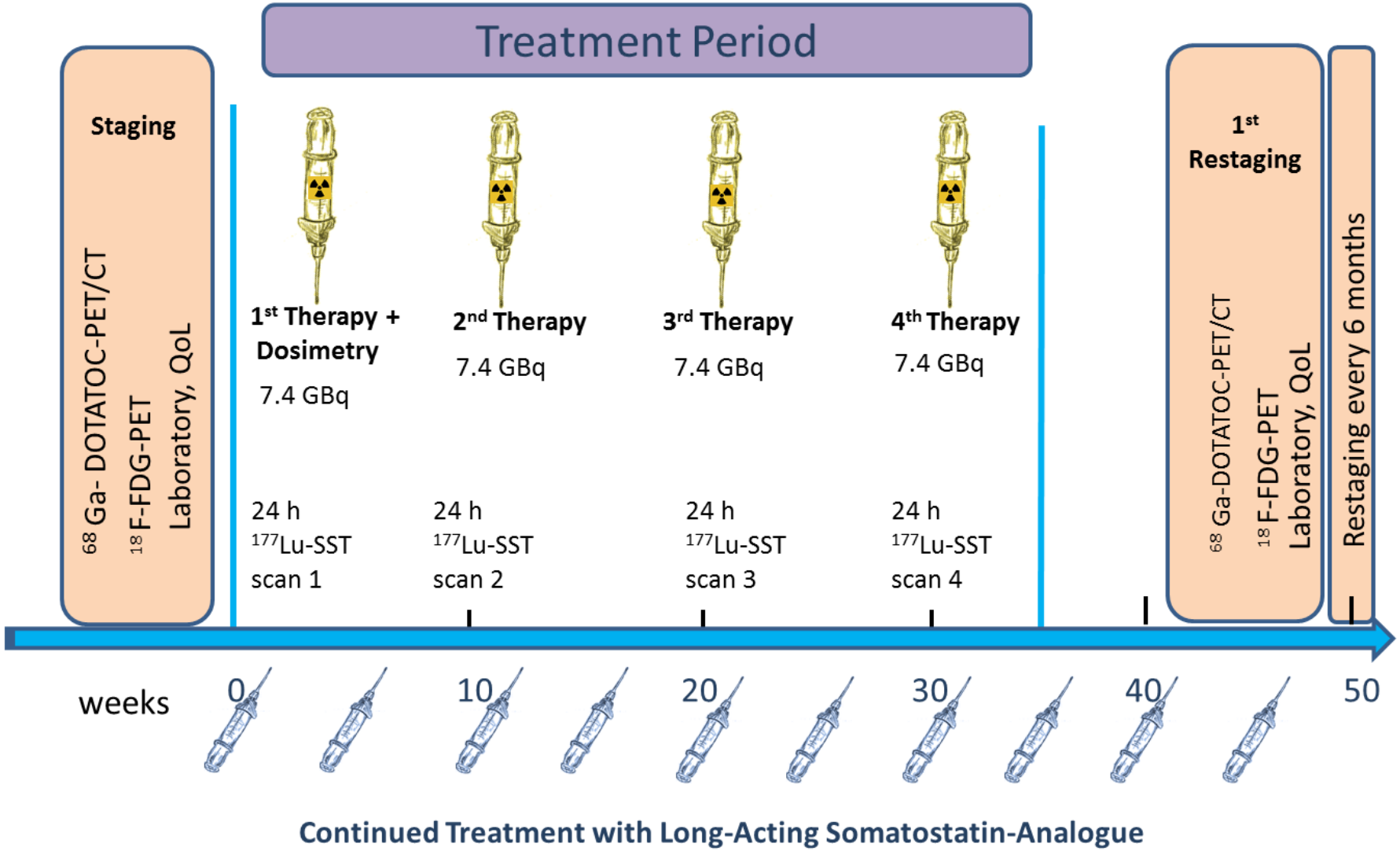
low energy

max. tissue penetration
2 mm

small tumour lesions
micrometastases
< 1 g

INNSBRUCK - PRRT Treatment Scheme (2004-2018)

(Individually Adapted Doses and Time Intervals Depending on Tumor Stage, Age, Tracer Uptake, Biochemical Response, Karnofsky Index, QoL)



^{68}Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT.

Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Von Guggenberg E, Bale R, Virgolini IJ.

J Nucl Med. 2007 Apr;48(4):508-18.

The aim of this study was to evaluate the diagnostic value of a new somatostatin analog, ^{68}Ga-labeled 1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid-d-Phe(1)-Tyr(3)-octreotide (^{68}Ga-DOTA-TOC), for PET in patients with known or suspected neuroendocrine tumors. PET was compared with conventional scintigraphy and dedicated CT.

METHODS: **Eighty-four patients** (48 men, 36 women; age range, 28-79 y; mean age +/- SD, 58.2 +/- 12.2 y) were prospectively studied. For analysis, patients were divided into 3 groups: detection of unknown primary tumor in the presence of clinical or biochemical suspicion of neuroendocrine malignancy (n = 13 patients), initial tumor staging (n = 36 patients), and follow-up after therapy (n = 35 patients). Each patient received 100-150 MBq ^{68}Ga-DOTA-TOC. Imaging results of PET were compared with (99m)Tc-labeled hydrazinonicotinyl-Tyr(3)-octreotide (^{99m}Tc-HYNIC-TOC) and ^{111}In-DOTA-TOC. CT was also performed on every patient using a multidetector scanner. Each imaging modality was interpreted separately by observers who were unaware of imaging findings before comparison with PET. The gold standard for defining true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) results was based on all available histologic, imaging, and follow-up findings.

RESULTS: PET was TP in 69 patients, TN in 12 patients, FP in 1 patient, and FN in 2 patients, indicating a sensitivity of 97%, a specificity of 92%, and an accuracy of 96%. The FP finding was caused by enhanced tracer accumulation in the pancreatic head, and the FN results were obtained in patients with a tumor of the gastrointestinal tract displaying liver metastases. ^{68}Ga-DOTA-TOC showed higher diagnostic efficacy compared with SPECT (TP in 37 patients, TN in 12 patients, FP in 1 patient, and FN in 34 patients) and diagnostic CT (TP in 41 patients, TN in 12 patients, FP in 5 patients, and FN in 26 patients). This difference was of statistical significance ($P < 0.001$). However, the combined use of PET and CT showed the highest overall accuracy.

CONCLUSION: ^{68}Ga-DOTA-TOC PET shows a significantly higher detection rate compared with conventional somatostatin receptor scintigraphy and diagnostic CT with clinical impact in a considerable number of patients.

^{68}Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT.

Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Von Guggenberg E, Bale R, Virgolini IJ.

J Nucl Med. 2007 Apr;48(4):508-18.

TABLE 5

Comparison of 3 Imaging Modalities: PET, SPECT, and CT

Parameter	PET (%)	SPECT (%)	CT (%)
Sensitivity	97 (69/71)	52 (37/71)	61 (41/67)
Specificity	92 (12/13)	92 (12/13)	71 (12/17)
Accuracy	96 (81/84)	58 (49/84)	63 (53/84)

Number of patients is in parentheses.

^{68}Ga-DOTA-Tyr3-octreotide PET in neuroendocrine tumors: comparison with somatostatin receptor scintigraphy and CT.

Gabriel M, Decristoforo C, Kendler D, Dobrozemsky G, Heute D, Uprimny C, Kovacs P, Von Guggenberg E, Bale R, Virgolini IJ.

J Nucl Med. 2007 Apr;48(4):508-18.

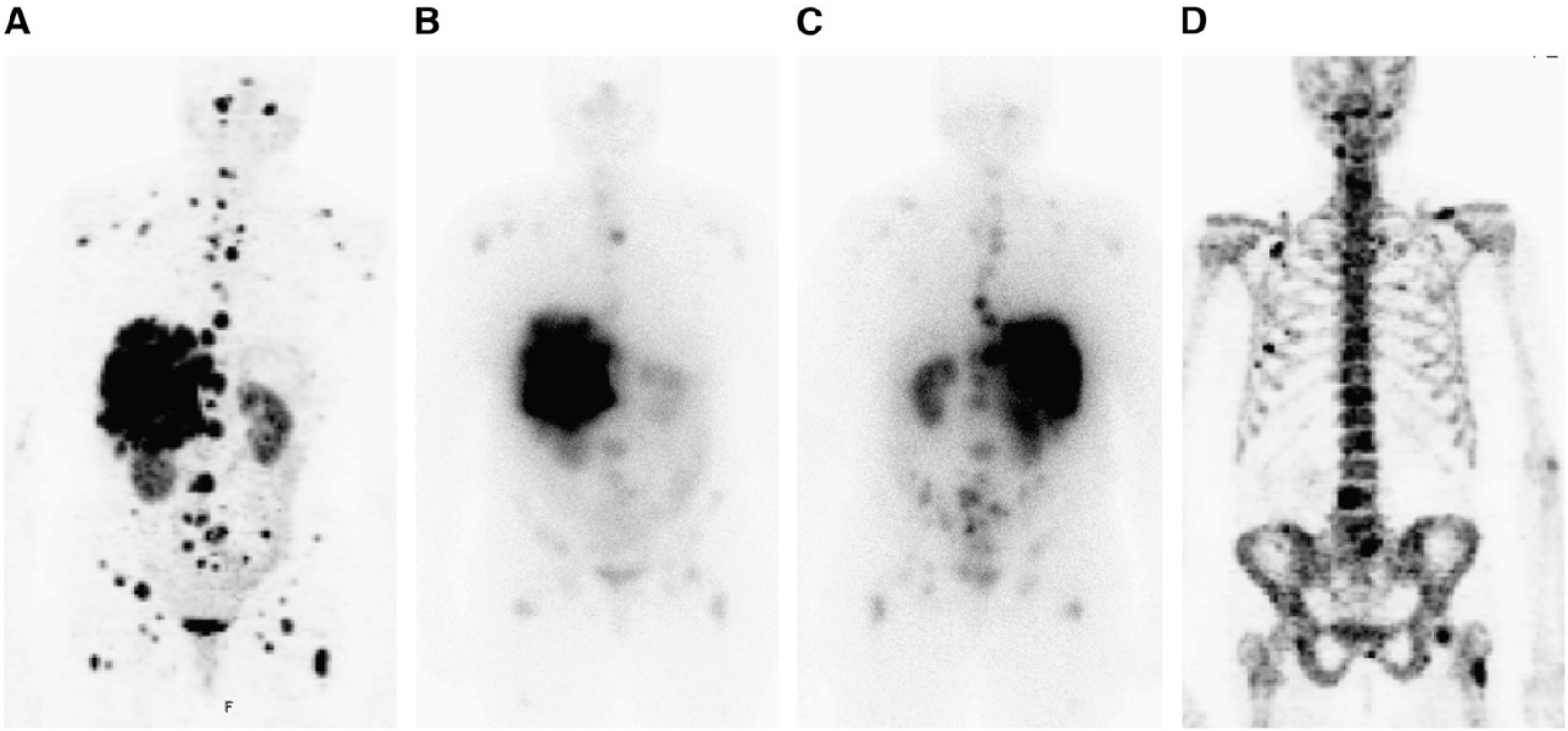
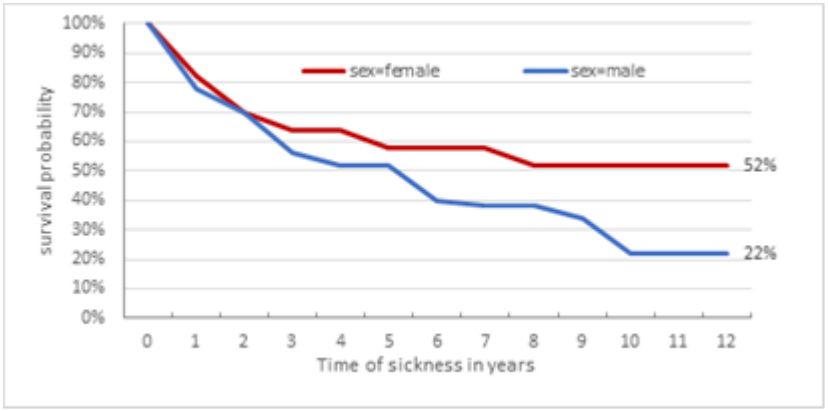
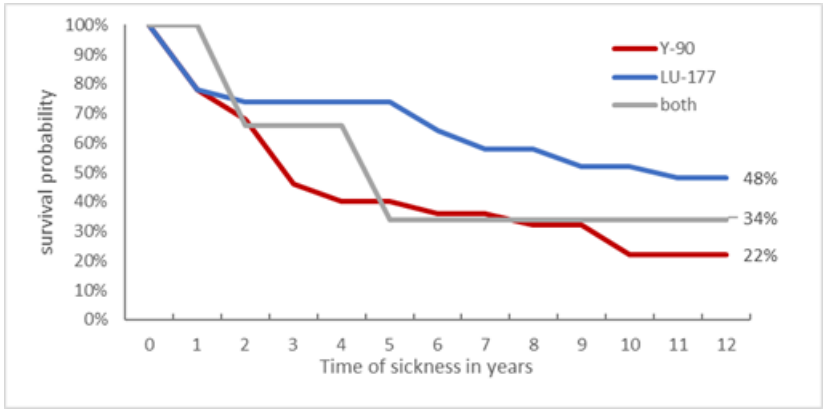


FIGURE 2. A 56-y-old woman with multiple liver and lymph node metastases was referred for restaging after surgery and chemotherapy. CT presented these tumor lesions; however, it was negative for bone lesions. Beside the visceral metastases, some additional osteoblastic and osteolytic bone metastases were clearly depicted with ^{68}Ga-DOTA-TOC (A). Only some of these bone metastases were delineated by conventional scintigraphy (B, anterior view; C, posterior view). Osteoblastic bone lesions were confirmed by ^{18}F-Na-fluoride PET (D). Retrospective CT analysis after image fusion revealed some of these bone metastases.

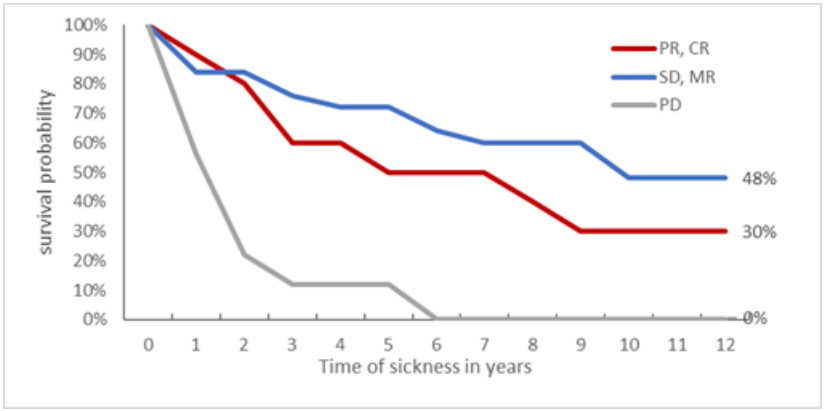
More Than 12-Year Follow-Up of PRRT at Innsbruck

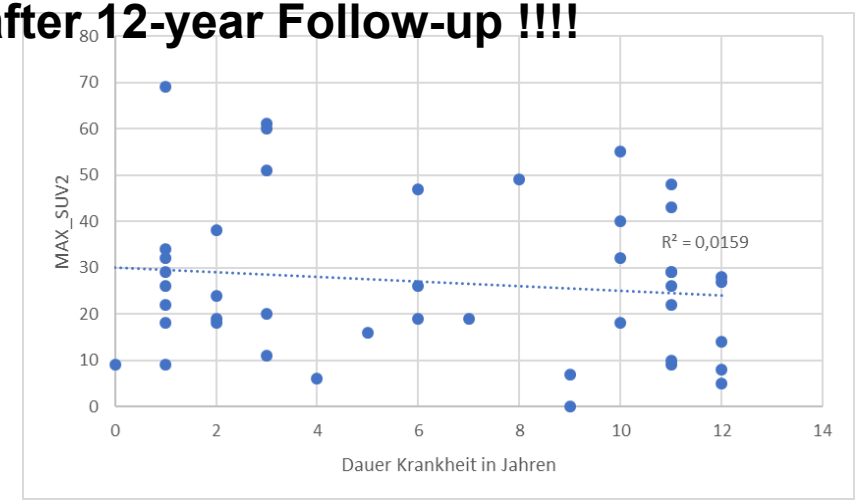
Gabriel M, Nilica B, Kaiser B, Virgolini IJ.
J Nucl Med. 2018 Aug 16. pii: jnumed.118.215376. doi: 10.2967 [Epub ahead of print]





34% (12/44) patients are alive after 12-year Follow-up !!!!





Eur J Nucl Med Mol Imaging (2010) 37:2004–2010
DOI 10.1007/s00259-010-1512-3

GUIDELINES

Procedure guidelines for PET/CT tumour imaging with ^{68}Ga-DOTA-conjugated peptides: ^{68}Ga-DOTA-TOC, ^{68}Ga-DOTA-NOC, ^{68}Ga-DOTA-TATE

Irene Virgolini · Valentina Ambrosini · Jamshed B. Bomanji · Richard P. Baum · Stefano Fanti · Michael Gabriel · Nikolaos D. Papathanasiou · Giovanna Pepe · Wim Oyen · Clemens De Cristoforo · Arturo Chiti

Eur J Nucl Med Mol Imaging (2017) 44:1588–1601
DOI 10.1007/s00259-017-3728-y

GUIDELINES

Guideline for PET/CT imaging of neuroendocrine neoplasms with ^{68}Ga-DOTA-conjugated somatostatin receptor targeting peptides and ^{18}F–DOPA

Murat Fani Bozkurt[1] · Irene Virgolini[2] · Sona Balogova[3,4] · Mohsen Beheshti[5,6] · Domenico Rubello[7] · Clemens Decristoforo[2] · Valentina Ambrosini[8] · Andreas Kjaer[9] · Roberto Delgado-Bolton[10] · Jolanta Kunikowska[11] · Wim J. G. Oyen[12] · Arturo Chiti[13] · Francesco Giammarile[14] · Stefano Fanti[8]

SPECIAL CONTRIBUTION

Appropriate Use Criteria for Somatostatin Receptor PET Imaging in Neuroendocrine Tumors

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Summary Treatment Results in NETs

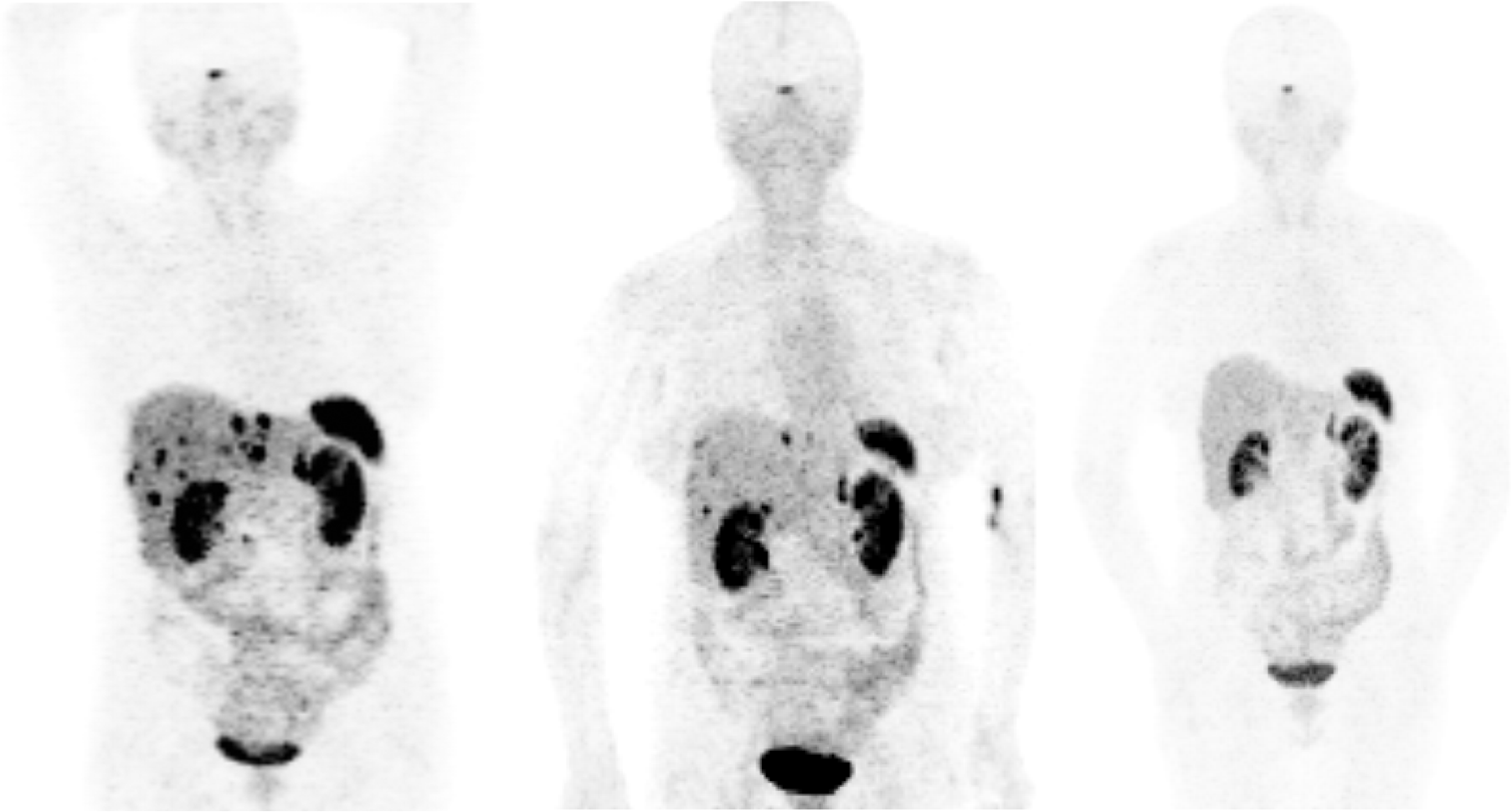
(from all major centers, mostly retrospective studies)

- Problem : Assessment of Results

Overall Response:	~80%
Stable Disease/Minor Response:	~55%
Complete/Partial Remission:	~25%
Progressive Disease:	~20%

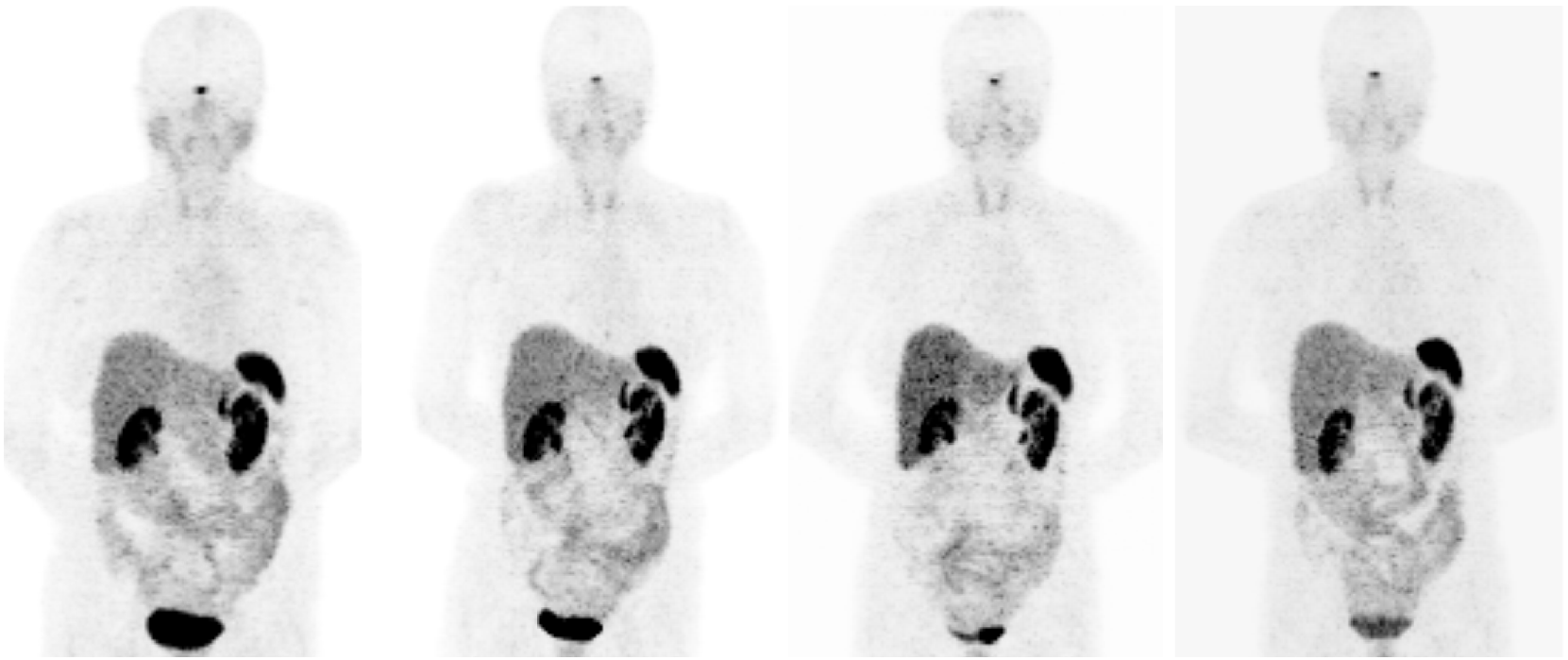
Progression Free Survival: ~ 2 years (median)

^{68}Ga-DOTA-TOC PET. Long-Term Follow-up of PRRT (5 cycles ^{90}Y-DOTA-TOC, 10 GBq, acc. dose; 4 cycles ^{177}Lu-DOTA-TATE; 29 GBq acc. dose) in a 56 year old female patient with pancreatic NET with liver metastases (1)



10/2005 07/2006 11/2006

^{68}Ga-DOTA-TOC PET. Long-Term Follow-up of PRRT (4 cycles ^{90}Y-DOTA-TOC, 10 GBq, acc. dose; 4 cycles ^{177}Lu-DOTA-TATE; 29 GBq acc. dose) in a 59 year old female patient with pancreatic NET with liver metastases (2)

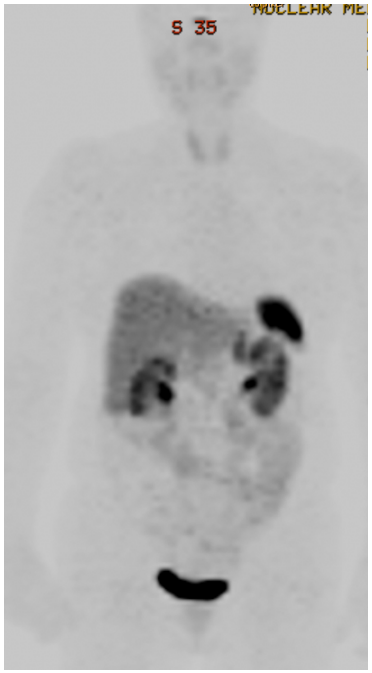


09/2007 03/2008 09/2008 03/2009

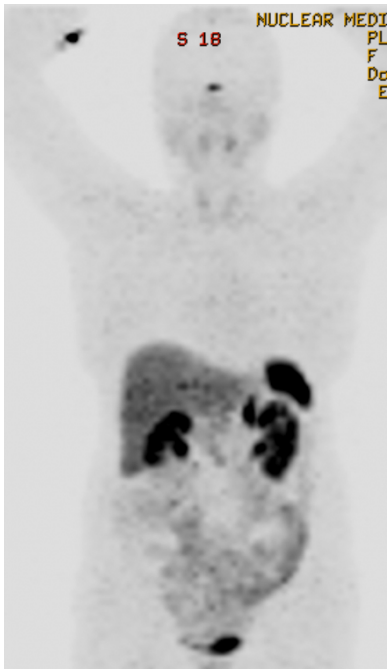
In addition to PRRT, the patient received long-acting octreotide over the years. Complete remission is documented over the last 3 years, no side effects.

^{68}Ga-DOTA-TOC PET. Long-Term Follow-up of PRRT (5 cycles ^{90}Y-DOTA-TOC, 10 GBq, acc. dose; 4 cycles ^{177}Lu-DOTA-TATE; 29 GBq acc. dose) in a 61 year old female patient with pancreatic NET with liver metastases (3)

^{68}Ga-68-DOTATOC

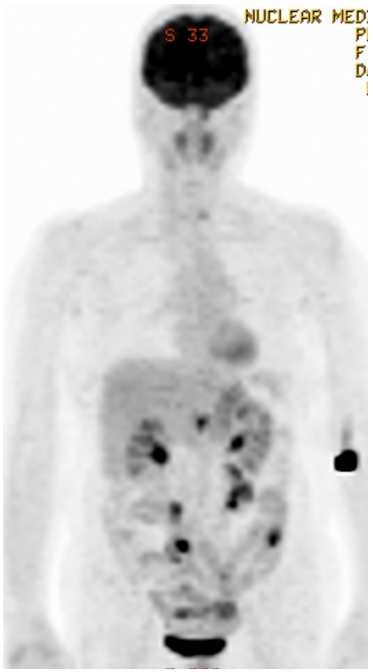


March 2010

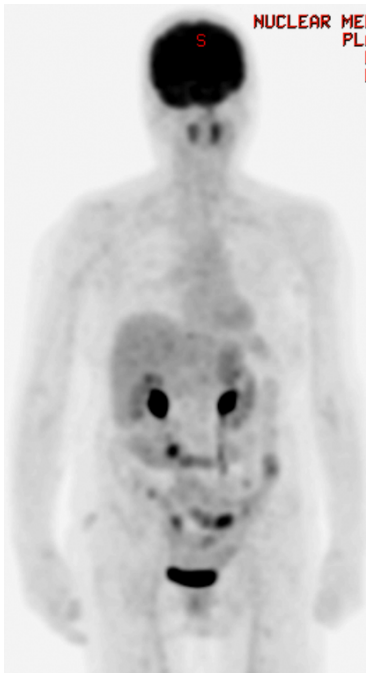


May 2011

^{18}F-FDG



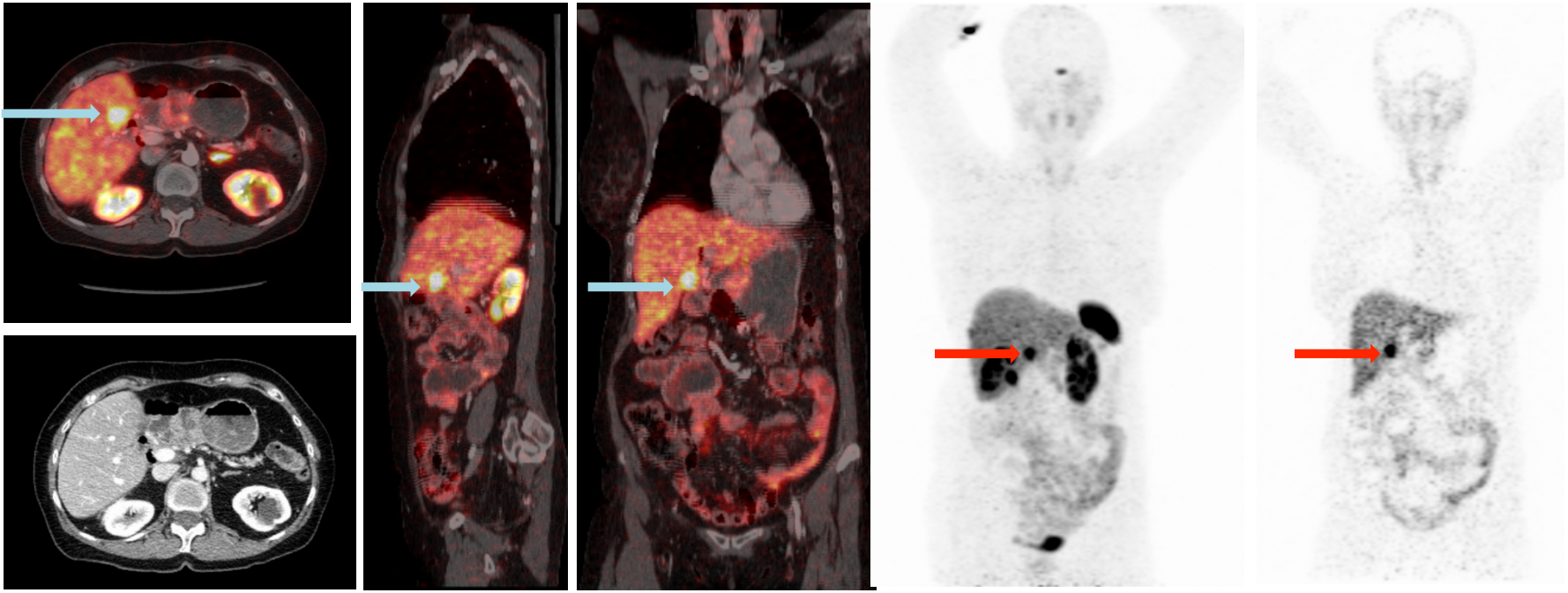
March 2010



May 2011

Complete Remission over 5 years!

^{68}Ga-DOTA-TOC PET. Long-Term Follow-up of PRRT (5 cycles ^{90}Y-DOTA-TOC, 10 GBq, acc. dose; 4 cycles ^{177}Lu-DOTA-TATE; 29 GBq acc. dose) in a 61 year old female patient with pancreatic NET with liver metastases (4)

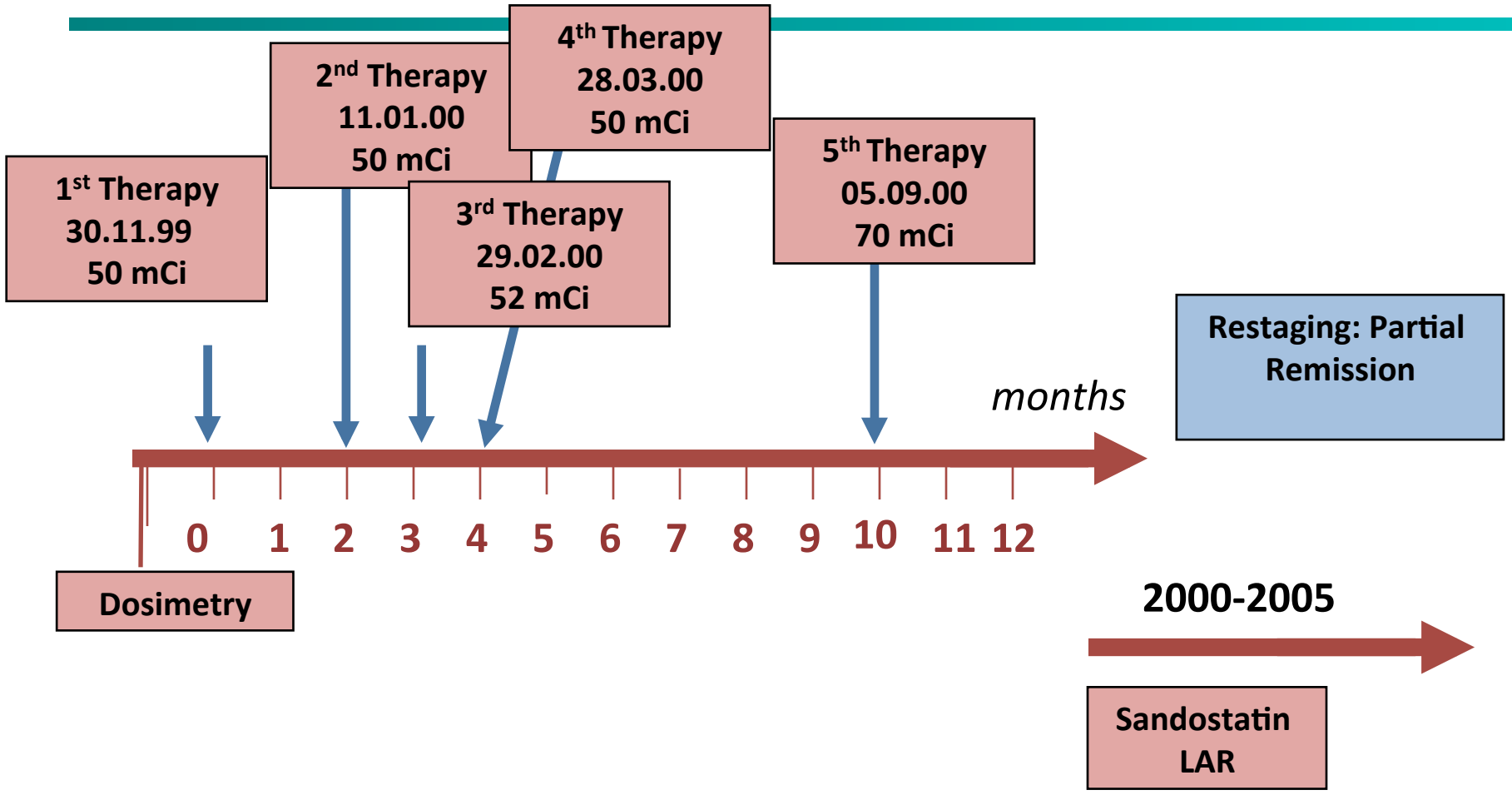


Tumor recurrence in May 2011: a single liver metastasis in segment 4b (arrow)

→ 3rd Treatment Period with ^{177}Lu-DOTA-TATE (17 GBq acc. dose) + RFA

→ 2015 & 2017: ^{68}Ga-DOTA-TOC PET/CT complete remission

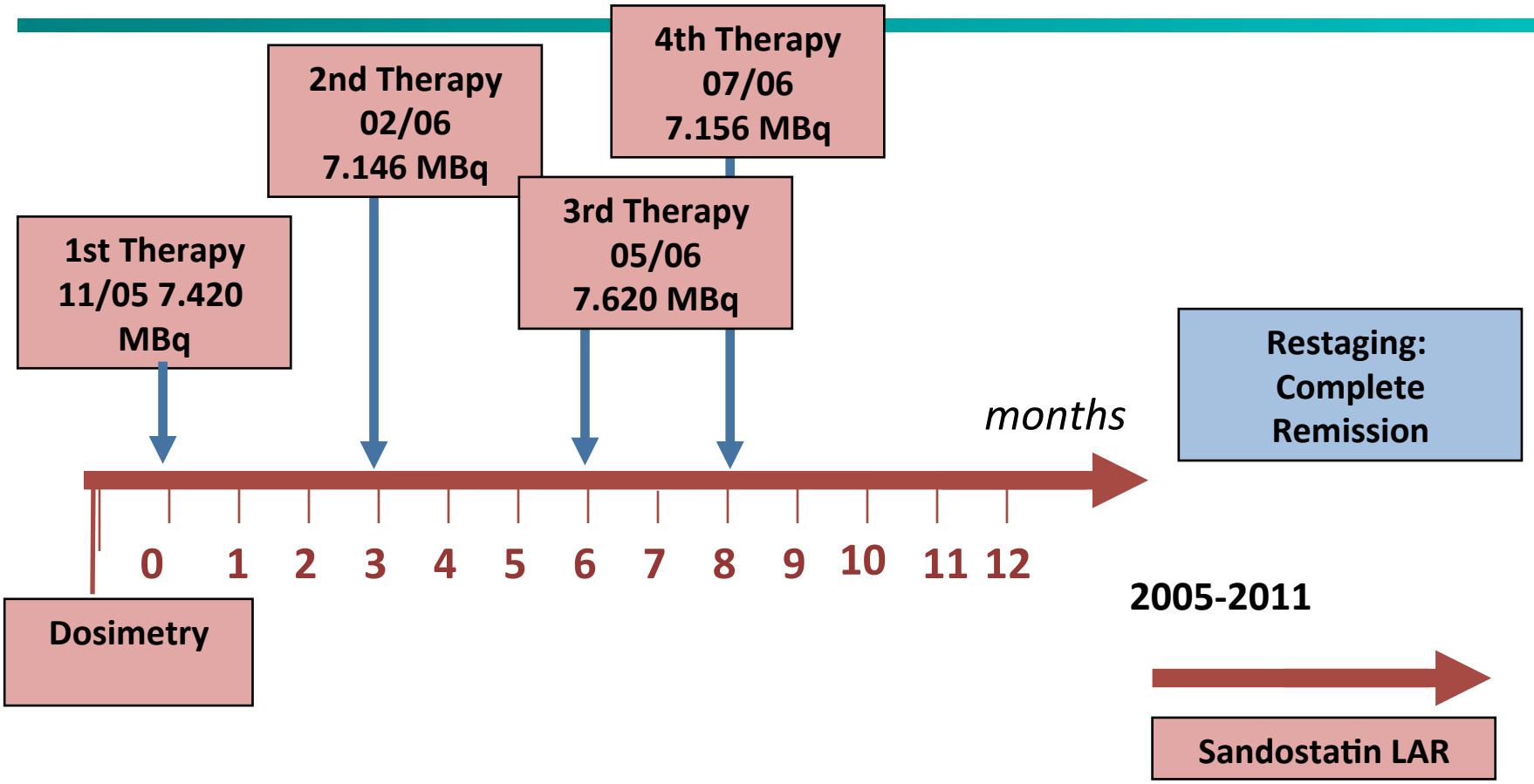
2000 Peptide Receptor Radionuclide Therapy First Treatment Period with ^{90}Y-DOTATOC I



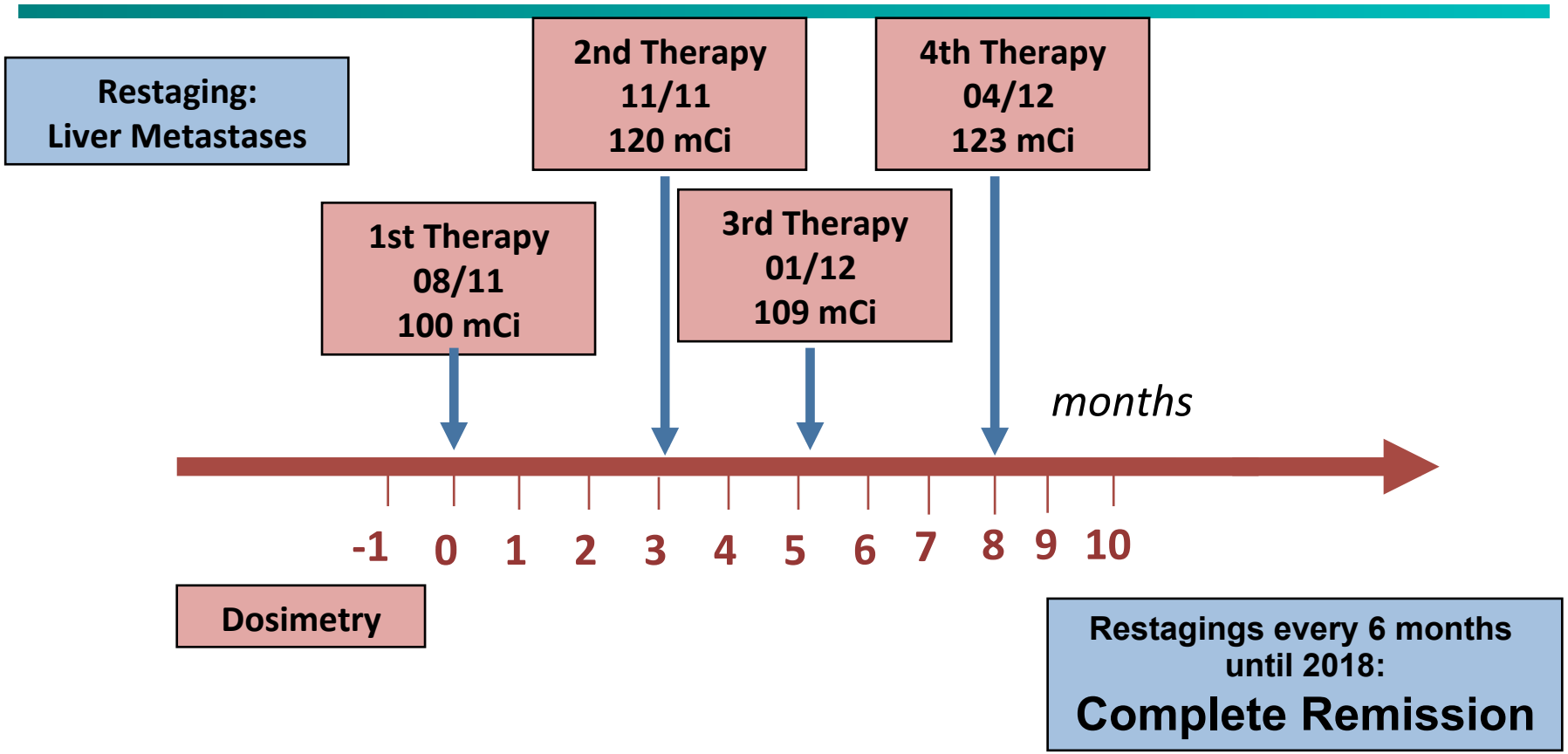
2005

Peptide Receptor Radionuclide Therapy Second Treatment Period with ^{177}Lu-DOTATATE

II



2011/12 Peptide Receptor Radionuclide Therapy Third Treatment Period with ^{177}Lu-DOTATATE III



^{68}Ga-DOTA-TOC versus ^{68}Ga-DOTA-Lanreotide (82 patients)

Somatostatin receptor PET in neuroendocrine tumours: ^{68}Ga-DOTA0,Tyr3-octreotide versus ^{68}Ga-DOTA0-lanreotide.
Putzer D, Kroiss A, Waitz D, Gabriel M, Traub-Weidinger T, Uprimny C, von Guggenberg E, Decristoforo C, Warwitz B, Widmann G, Virgolini IJ.
Eur J Nucl Med Mol Imaging. 2013 Feb;40(3):364-72.

Multiparametric PET imaging in thyroid malignancy characterizing tumour heterogeneity: somatostatin receptors and glucose metabolism.
Traub-Weidinger T, Putzer D, von Guggenberg E, Dobrozemsky G, Nilica B, Kendler D, Bale R, Virgolini IJ.
Eur J Nucl Med Mol Imaging. 2015 Dec;42(13):1995-2001.

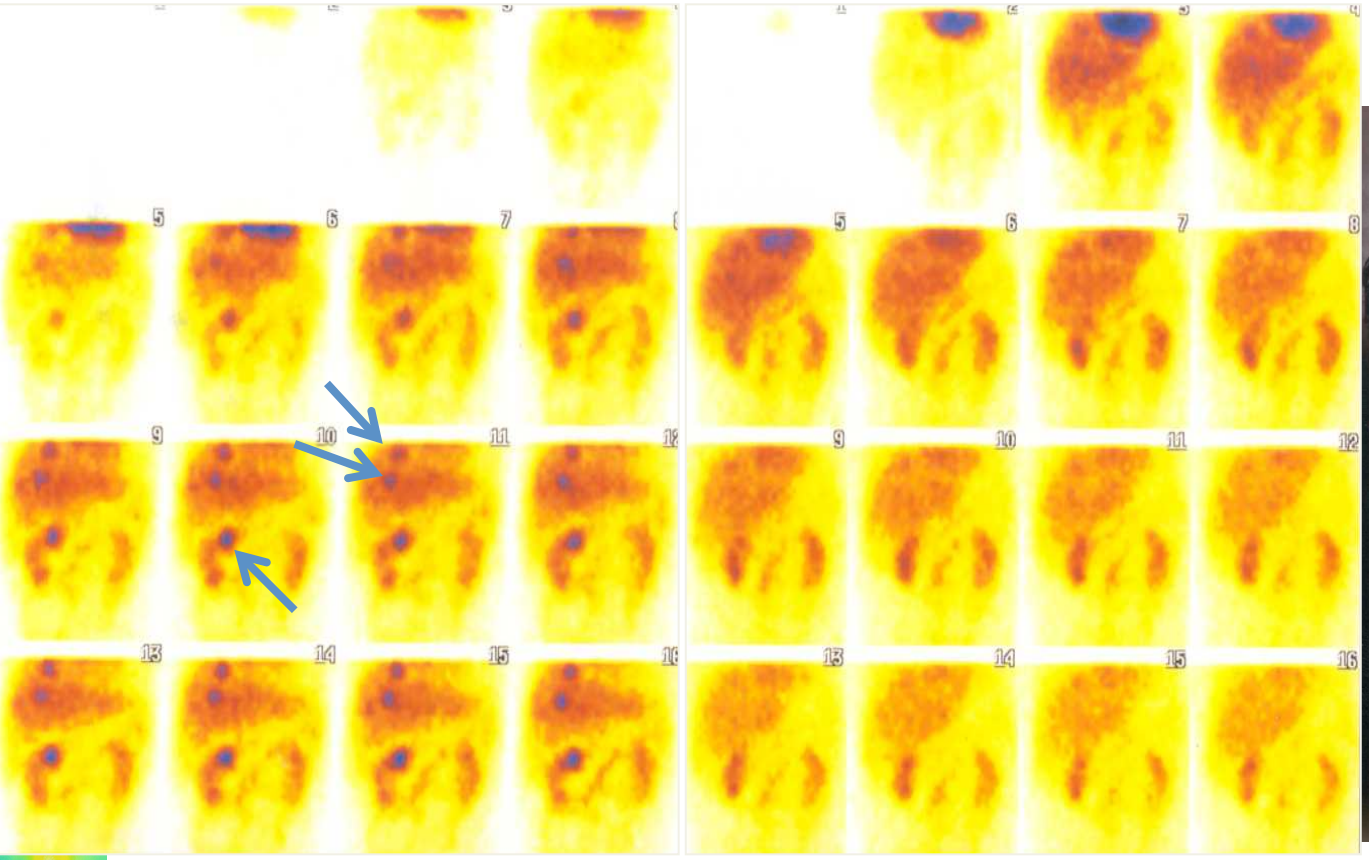
	Increased Octreotide Uptake	Faint Octreotide Uptake	No Octreotide Uptake
Increased Lanreotide Uptake	12	3	4
Faint Lanreotide Uptake	13	14	9
No Lanreotide Uptake	7	6	14
Sum	32	23	27

Response to Treatment with Yttrium 90-DOTA-Lanreotide of a Patient with Metastatic Gastrinoma

Maria Leimer, Amir Kurtaran, Peter Smith-Jones, Markus Raderer, Ernst Havlik, Peter Angelberger, Friedrich Vorbeck, Bruno Niederle, Christian Herold and Irene Virgolini

Departments of Nuclear Medicine, Oncology, Biomedical Engineering and Physics, Radiology, and Surgery, University of Vienna; and the Department of Radiochemistry, Research Center Seibersdorf, Aus

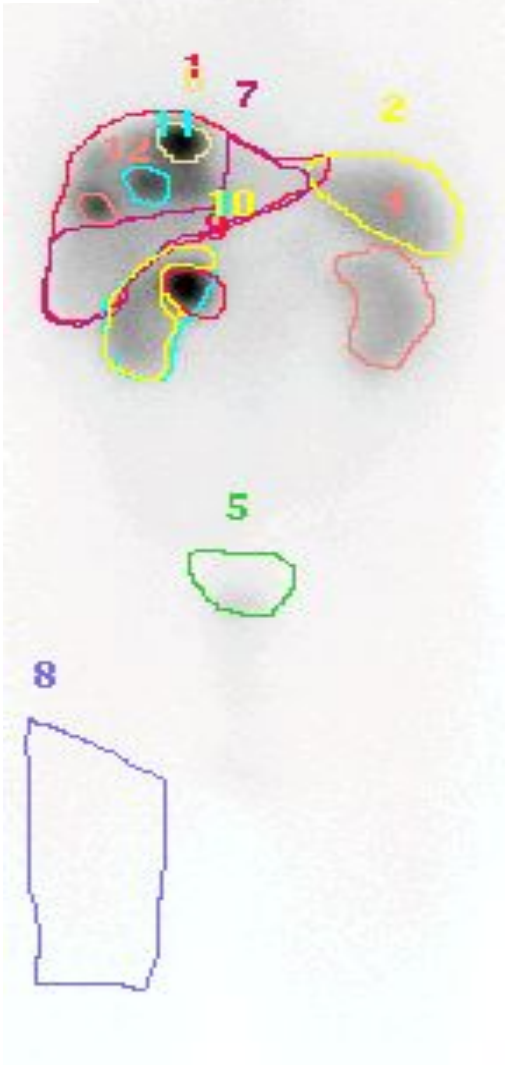
J Nucl Med 1998; 39:2090–2094



^{111}In-DOTA-TOC Dosimetry

- Estimation of Benefit / Risk
- Estimation of Tumour Dose
- Estimation of Organ Dose

1997	^{90}Y-DOTA-Lanreotide	4x25 mCi
1999-2001	^{90}Y-DOTATOC	10x50 mCi
2005	^{177}Lu-DOTATATE	26 GBq




September 2018

Status on Re-treatment

In patients with relapse after ^{90}Y-DOTATOC treatment

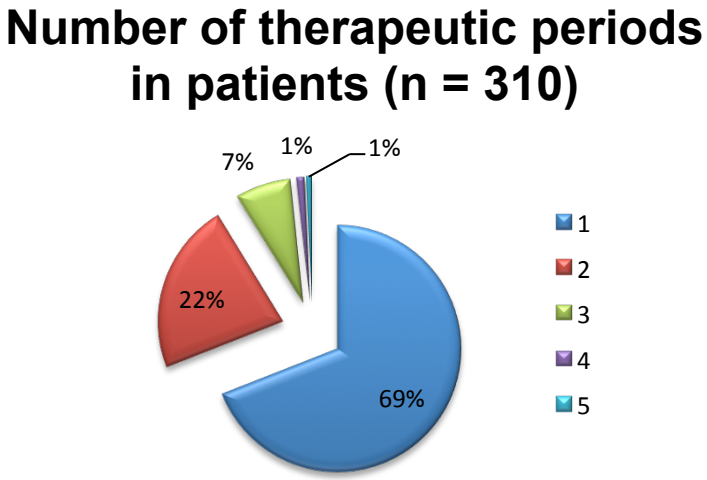
(multiple) re-treatment

is feasible, safe, and efficacious

- Virgolini I; Innsbruck Team.
  Peptide receptor radionuclide therapy (PRRT): clinical significance of re-treatment? Eur J Nucl Med Mol Imaging. 2015;42:1949-54.

Innsbruck Treatment Regimen

therapeutic cycles (= single application) performed with a maximum interval of 10 weeks summarized as one **therapeutic period**



Number of therapeutic periods	Number of patients	Percent
1	214	69%
2	69	22%
3	22	7%
4	3	1%
5	2	1%

Results Innsbruck (PERSIST)

Patients with ^{68}Ga-SSTR-PET/CT Follow-up

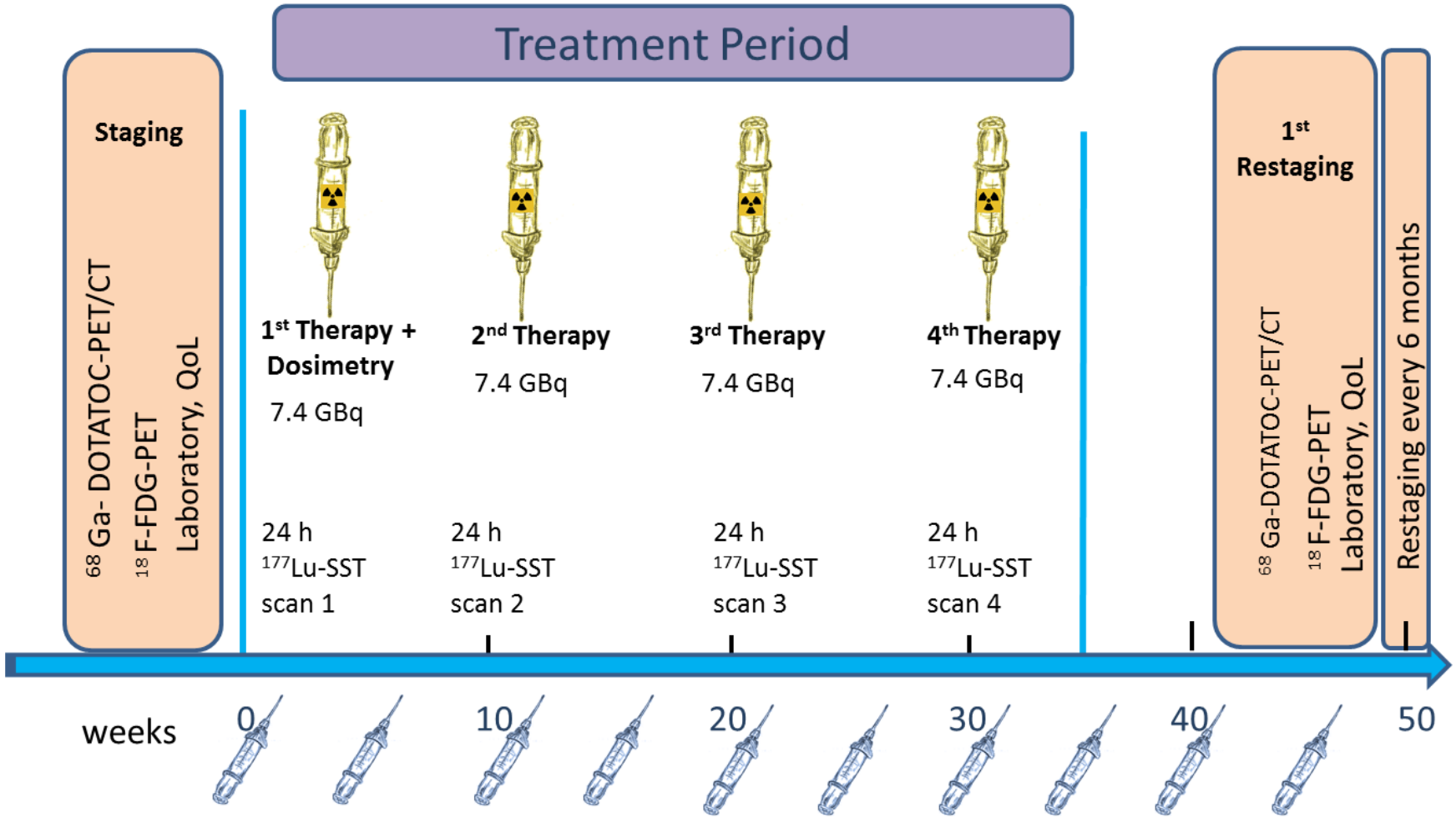
Treatment Response	Median Survival (months)	Median Time to Progression (months)
Partial / Minor Remission	40.25 ± 17.75 NS	**26.70 ± 9.9** p<0.01
Stable Disease	31.40 ± 15.06 p<0.001	**19.48 ± 7.13**
Progressive Disease	7.87 ± 3.62	

Overall survival: 3 - 80 months (median 23.26 ± 17.55)

Importance of Dual Tracer Imaging

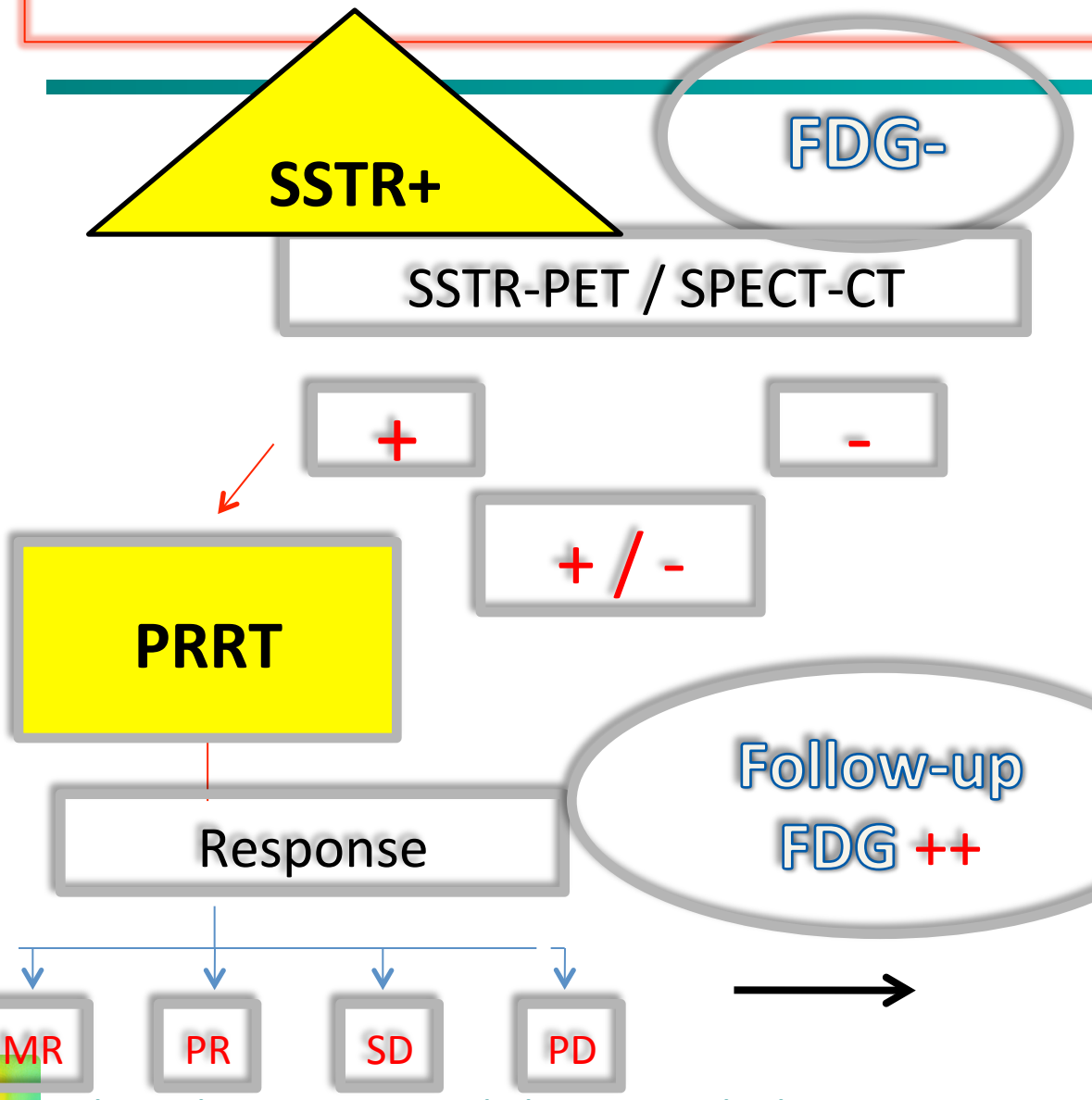
INNSBRUCK - PRRT Treatment Scheme (2004-2018)

(Individually Adapted Doses and Time Intervals Depending on Tumor Stage, Age, Tracer Uptake, Biochemical Response, Karnofsky Index, QoL)



Continued Treatment with Long-Acting Somatostatin-Analogue

Management of NET: Role of FDG?



treatment options :

-Chemotherapy

- mTOR inhibitors:
Rapamycin (Everolimus)

- Tyrosine kinase inhibitors
(Sunitinib)

- ^{131}I-miBG?

-Angiogenesis inhibitors
(Bevacizumab)

Direct comparison of ^{68}Ga-DOTA-TOC and ^{18}F-FDG PET/CT in the follow-up of patients with neuroendocrine tumour treated with the first full peptide receptor radionuclide therapy cycle.

Nilica B, Waitz D, Stevanovic V, Uprimny C, Kendler D, Buxbaum S, Warwitz B, Gerardo L, Henninger B, Virgolini I, Rodrigues M.

Eur J Nucl Med Mol Imaging. 2016 Aug;43(9):1585-92. doi: 10.1007/s00259-016-3328-2. Epub 2016 Feb 27.

PURPOSE

To determine the value of ^{68}Ga-DOTA-TOC and ^{18}F-FDG PET/CT for initial and follow-up evaluation of patients with neuroendocrine tumour (NET) treated with peptide receptor radionuclide therapy (PRRT).

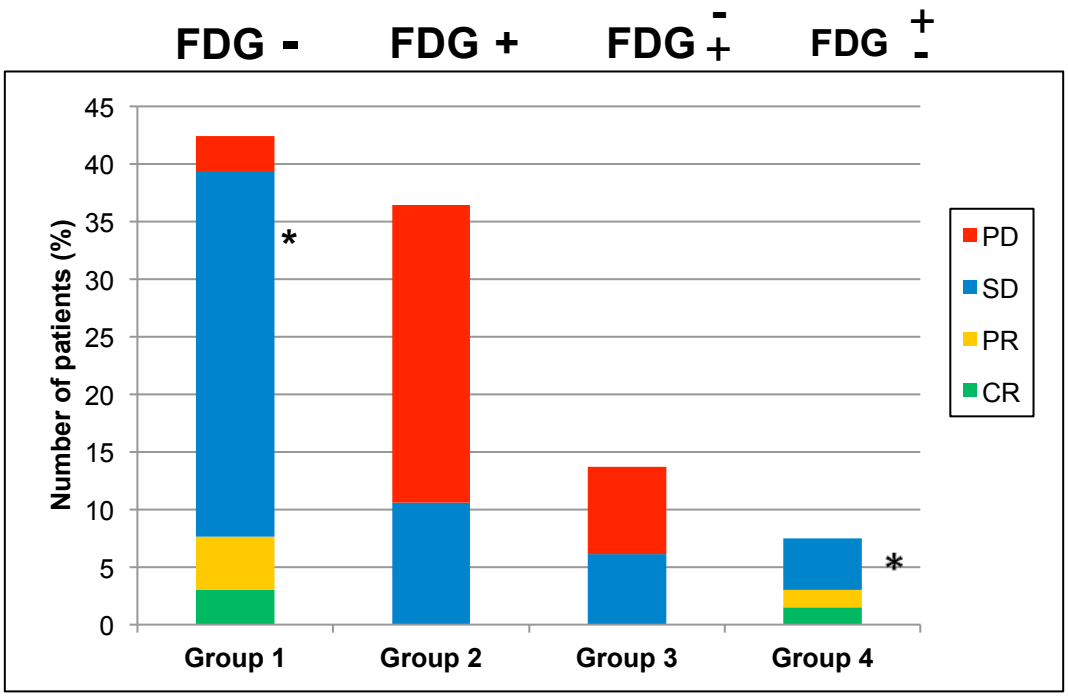
METHODS

CONCLUSION

In NET patients, the presence of ^{18}F-FDG-positive tumours correlates strongly with a higher risk of progression. Initially, patients with ^{18}F-FDG-negative NET may show ^{18}F-FDG-positive tumours during follow-up. Also patients with grade 1 and grade 2 NET may have ^{18}F-FDG-positive tumours. Therefore, ^{18}F-FDG PET/CT is a complementary tool to ^{68}Ga-DOTA-TOC PET/CT with clinical relevance for molecular investigation.

2) were ^{18}F-FDG-positive initially but ^{18}F-FDG-negative during follow-up (group 4).^{18}F-FDG PET showed more and/or larger metastases than ^{68}Ga-DOTA-TOC PET in five patients of group 2 and four patients of group 3, all with progressive disease. In three patients with progressive disease who died during follow-up tumour SUV_{max} increased by 41 - 82 % from the first to the last follow-up investigation.

^{18}F-FDG PET/CT findings and disease course

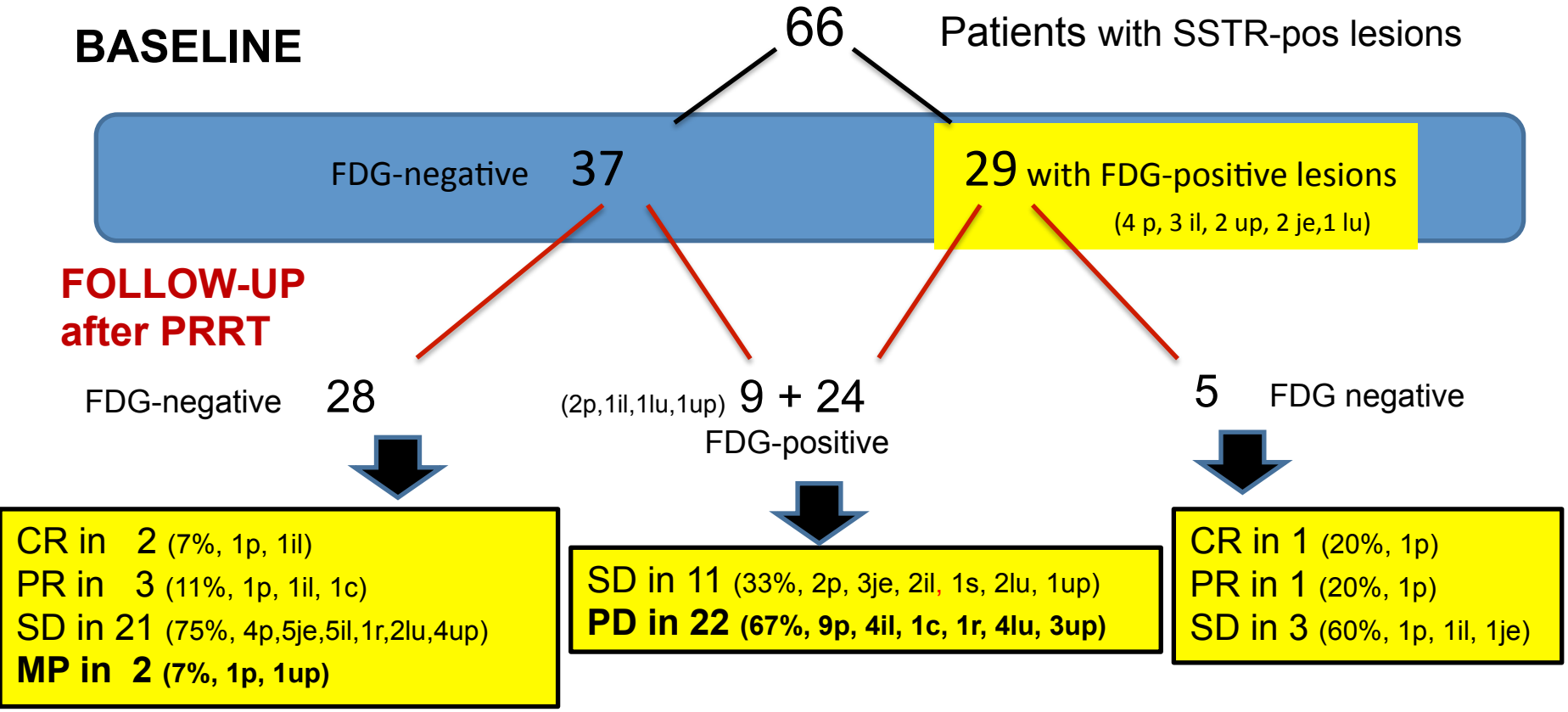


G1, FDG-negative initially and during follow-up; **G2**, FDG-positive initially and during follow-up; **G3,** FDG-negative initially, but FDG-positive during follow-up; **G4**, FDG-positive initially, but FDG-negative during follow-up

* $p<0.05$ as compared with G2

^{68}Ga-DOTA-TOC PET/CT and ^{18}F-FDG PET in the Follow-up of 66 NET Patients treated by PRRT

(28 females, 38 males, median age 57.2 a; median follow-up: 34.5 months)
primary: 20 pancreas (p), 15 ileum (il), 9 jejunum (je), 8 lung (lu), 2 colon (c), 2 rectum (r), 1 stomach (s), 9 unknown (up)



CR: complete remission, PR: partial remssion
SD: stable disease, MP: minor progression
PD: progressive disease (>25% RECIST)

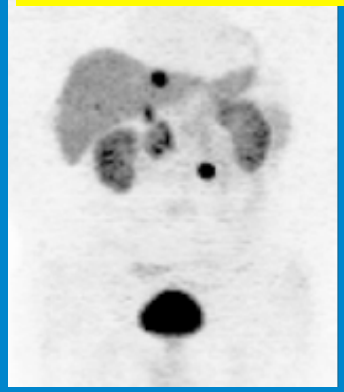
Eur J Nucl Med Mol Imaging. 2016 Aug;43(9):1585-92. doi: 10.1007/s00259-016-3328-2. Epub 2016 Feb 27

Male, 64 a, NET G2 in the pancreatic head

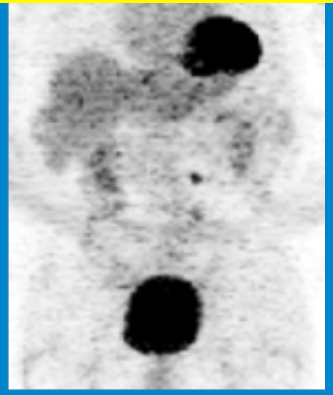
Initial evaluation

Follow-up

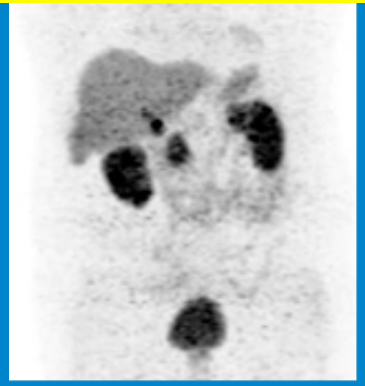
PATIENT WILL PROFIT FROM „Wait and See-Strategy“



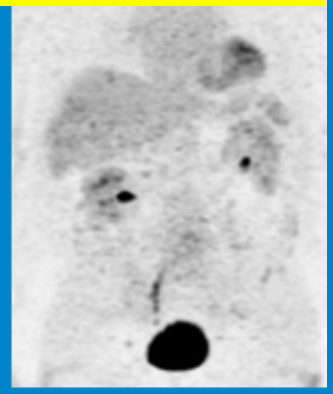
^{68}Ga-DOTA-TOC-PET



^{18}F-FDG-PET



^{68}Ga-DOTA-TOC-PET

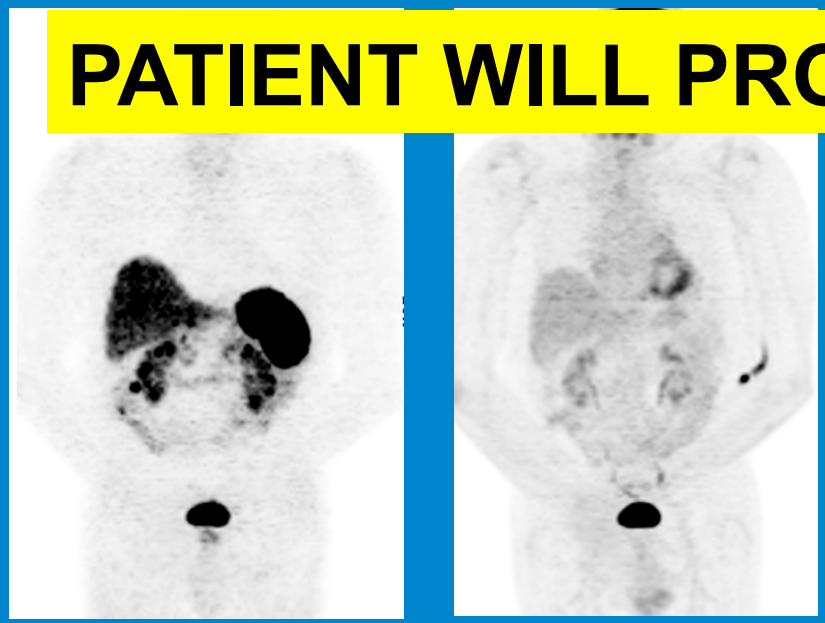


^{18}F-FDG-PET

^{68}Ga-DOTA-TOC PET/CT-positive while ^{18}F-FDG-PET/CT-positive initially but converted to ^{18}F-FDG-PET/CT-negative during follow-up (partial remission)

Male, 75 a, NET G1 in the ileum

Initial evaluation



^{68}Ga-DOTA-TOC-PET ^{18}F-FDG-PET

Follow-up

^{68}Ga-DOTA-TOC-PET ^{18}F-FDG-PET

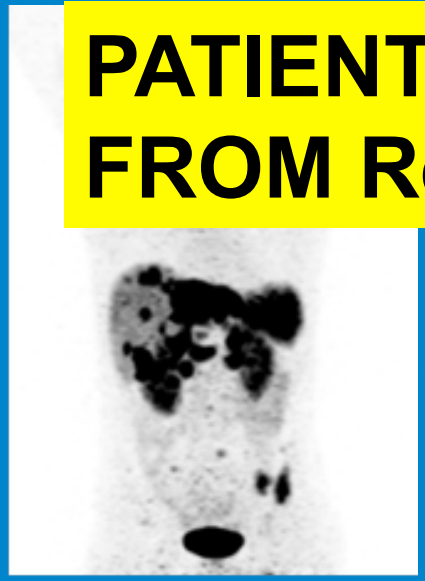
PATIENT WILL PROFIT FROM Re-PRRT !

Positive ^{68}Ga-DOTA-TOC (progressive disease) while ^{18}F-FDG-PET/CT negative initially and during follow-up

Male, 32 a, NET G2 in the pancreatic tail

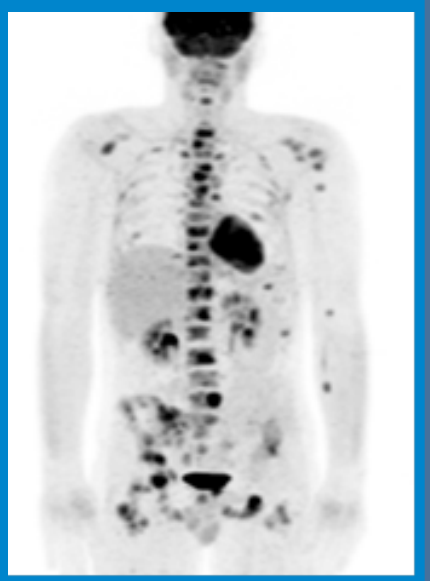
Initial evaluation

PATIENT WILL NOT PROFIT FROM Re-PRRT (alone) !



^{68}Ga-DOTA-TOC-PET ^{18}F-FDG-PET

Follow-up



^{68}Ga-DOTA-TOC-PET ^{18}F-FDG-PET

Positive ^{68}Ga-DOTA-TOC and ^{18}F-FDG PET/CT initially and during follow-up (progressive disease)

EFFICIENCY of PRRT: RESPONSE PREDICTORS

1.) EXTEND OF TUMOR DISEASE

(liver involvement, bone involvement)

2.) Functional Imaging:

- ^{68}Ga-SSTR-PET + ^{18}F-FDG-PET, Ki-67 Index
- **G1 (neuroendocrine tumour) Ki 67 ≤ 2%**
- **G2 (neuroendocrine tumour) Ki 67 3 - 20%**
- **G3 (neuroendocrine carcinoma) Ki 67 > 20%**

3.) KARNOFSKY SCORE

Investigation of receptor radionuclide therapy with ^{177}Lu-DOTATATE in patients with GEP-NEN and a high Ki-67 proliferation index.

Nicolini S, Severi S, Ianniello A, Sansovini M, Ambrosetti A, Bongiovanni A, Scarpi E, Di Mauro F, Rossi A, Matteucci F, Paganelli G.

Eur J Nucl Med Mol Imaging. 2018 Feb 1. doi: 10.1007/s00259-017-3925-8. [Epub ahead of print]

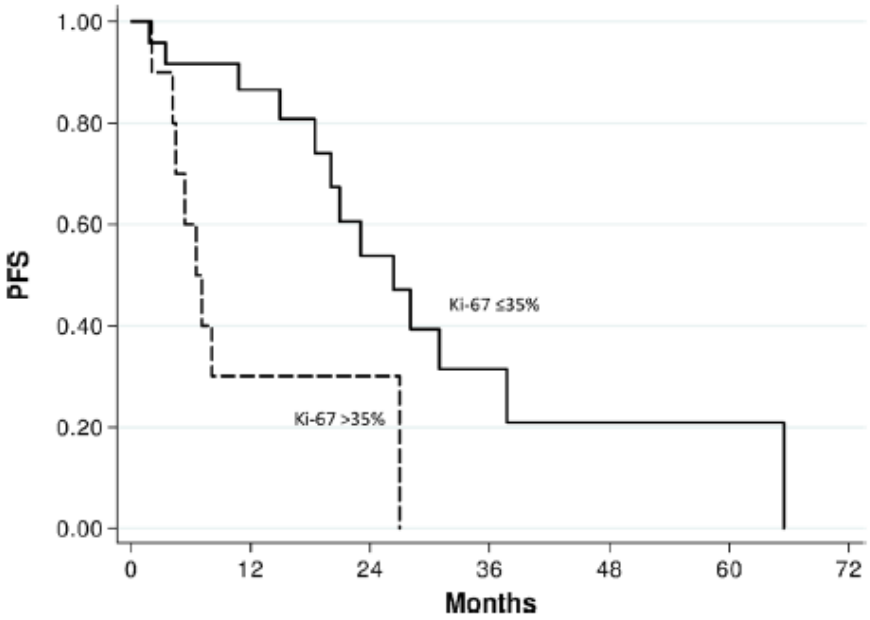


Fig. 1 Progression-free survival (PFS) in relation to Ki-67 proliferation index. Patients with a Ki-67 index of ≤35% had a significantly longer PFS (median PFS 26.3 months) than those with a Ki-67 index of >35% (median PFS 6.8 months; $p = 0.005$)

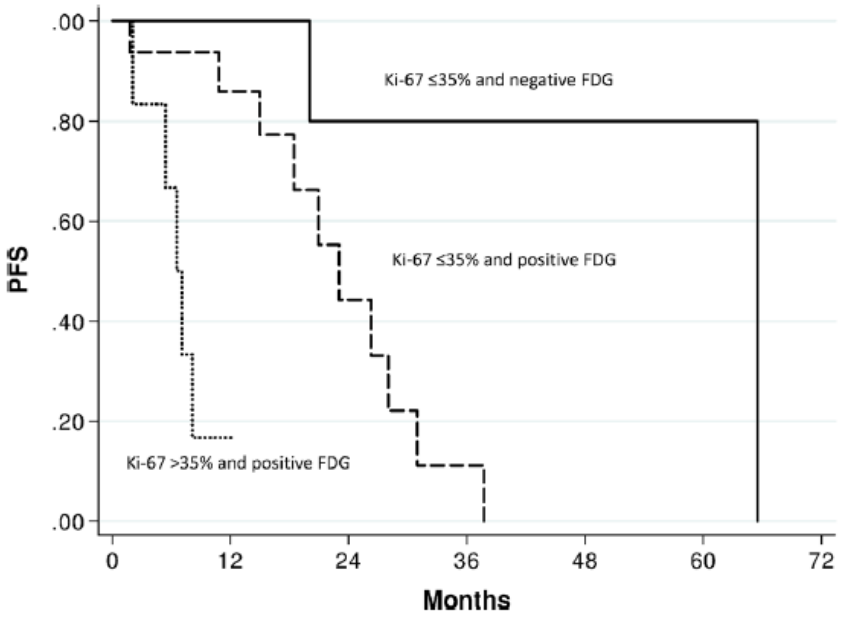


Fig. 3 Median progression-free survival (PFS) in relation to Ki-67 proliferation index and FDG PET results. Considering patients with a Ki-67 index of ≤35%, FDG-negative patients had a median PFS of 65.5 months (95% CI 20.0–65.5 months), while FDG-positive patients had a median PFS of 23.0 months (95% CI 14.9–31.0) ($p = 0.039$). Patients with a Ki-67 index of >35% were all FDG-positive and showed a median PFS of 6.8 months (95% CI 2.1–27.0 months)

Peptide receptor radionuclide therapy (PRRT) in European Neuroendocrine Tumour Society (ENETS) grade 3 (G3) neuroendocrine neoplasia (NEN) - a single-institution retrospective analysis.

Thang SP, Lung MS, Kong G, Hofman MS, Callahan J, Michael M, Hicks RJ.

Eur J Nucl Med Mol Imaging. 2018 Feb;45(2):262-277.

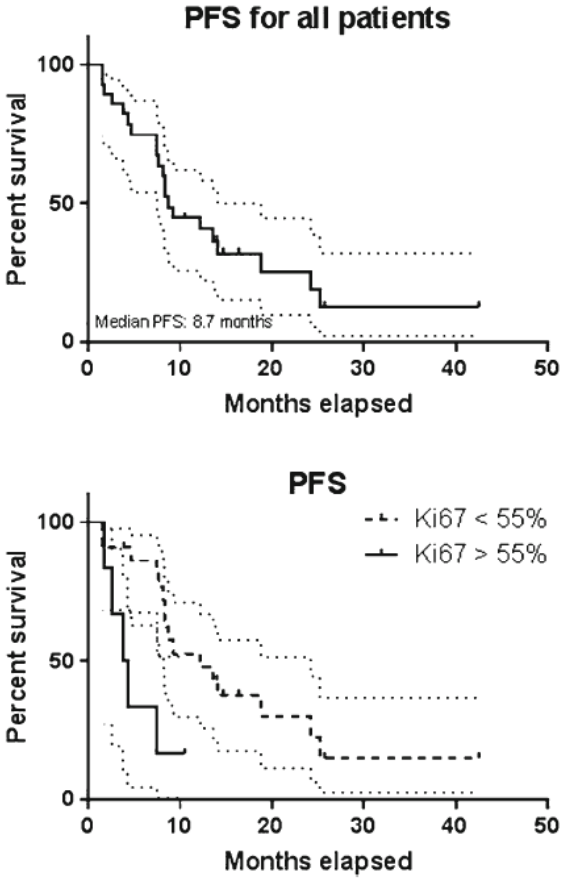


Fig. 4 Kaplan–Meier curves for progression free survival (PFS) months from the start of treatment

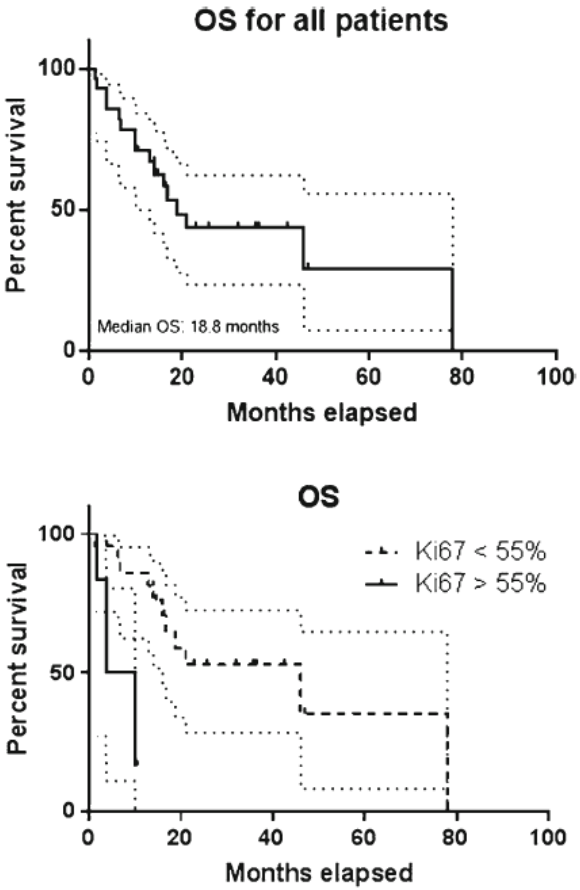


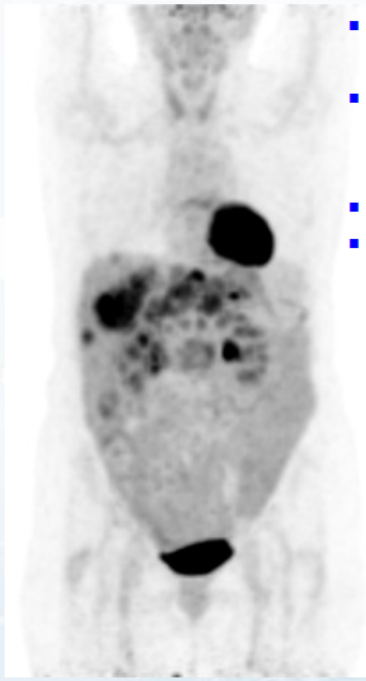
Fig. 5 Kaplan–Meier curves for overall survival (OS) months from the start of treatment

Peptide Receptor Chemotherapy (PRCRT) and Dosimetry

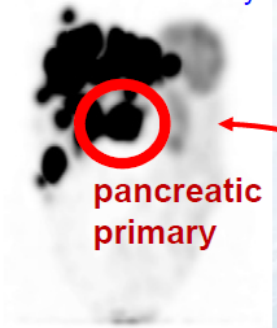
Prof. Michael Hofman Nuclear Medicine Update 2017, August 17th-19th, 2017

How would you treat this patient?

Dr Michael Hofman



FDG PET/CT



InTate SPECT/CT

- Individualised
- All sites of disease can targeted
- Very high uptake predicts response ORR >80-90%
- Well tolerated
- Limited availability

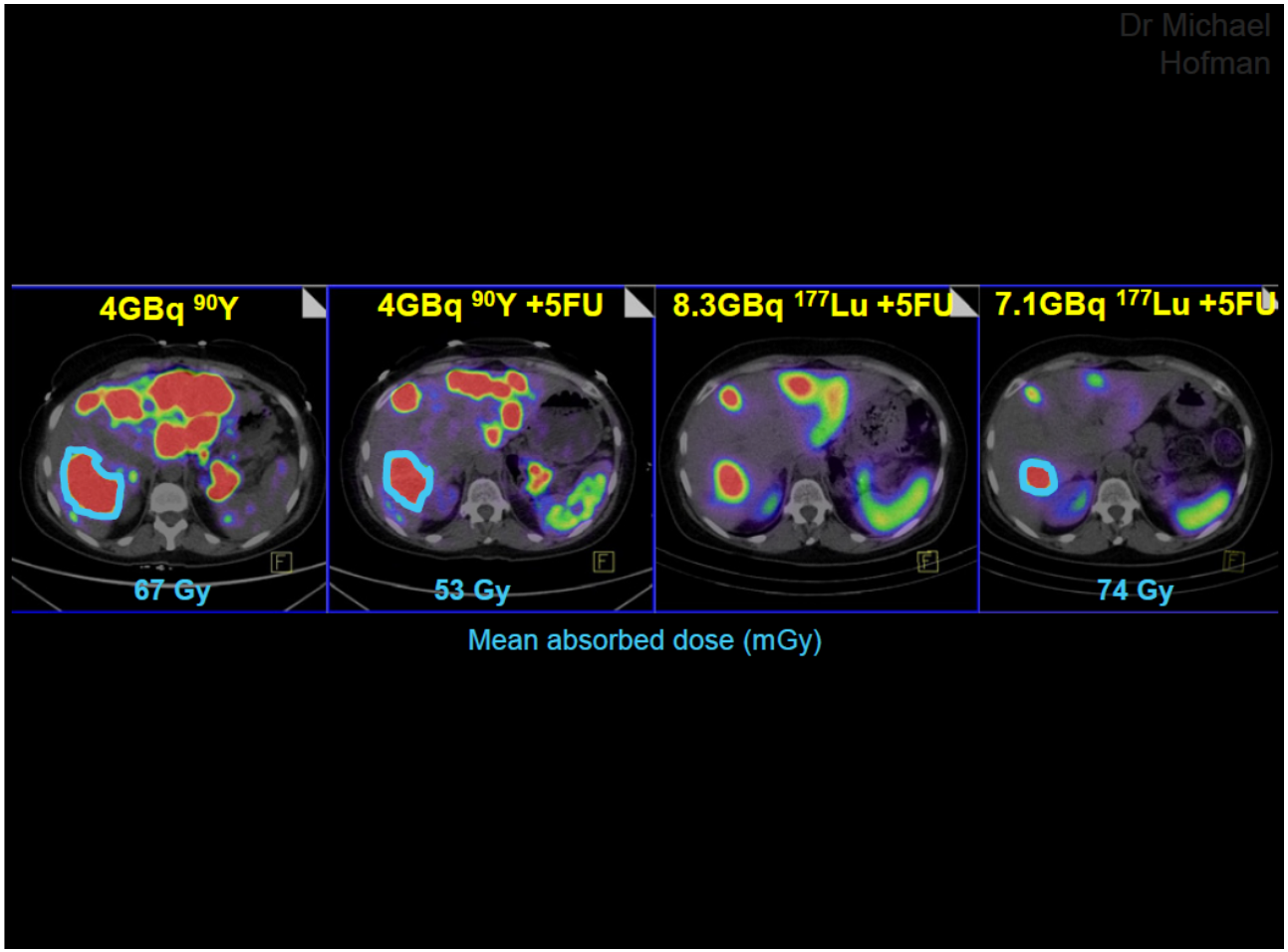
Which therapy?

- Chemotherapy
  - unable to predict response in individual
  - toxicity
- Everolimus
- Sunitnib
  - Phase 3 RCT
  - Low ORR sunitnib & everolimus
  - Modest "PFS" benefit
- Liver directed: TACE / SIRspheres
- surgical debulking
- SSA therapy
  - No hormonal symptoms
  - Low ORR
  - Can be used in combination
- PRRT
- PRCRT

ENETS Grade 2 Ki,67 18% (pancreatic)
RUQ pain. Progressive disease

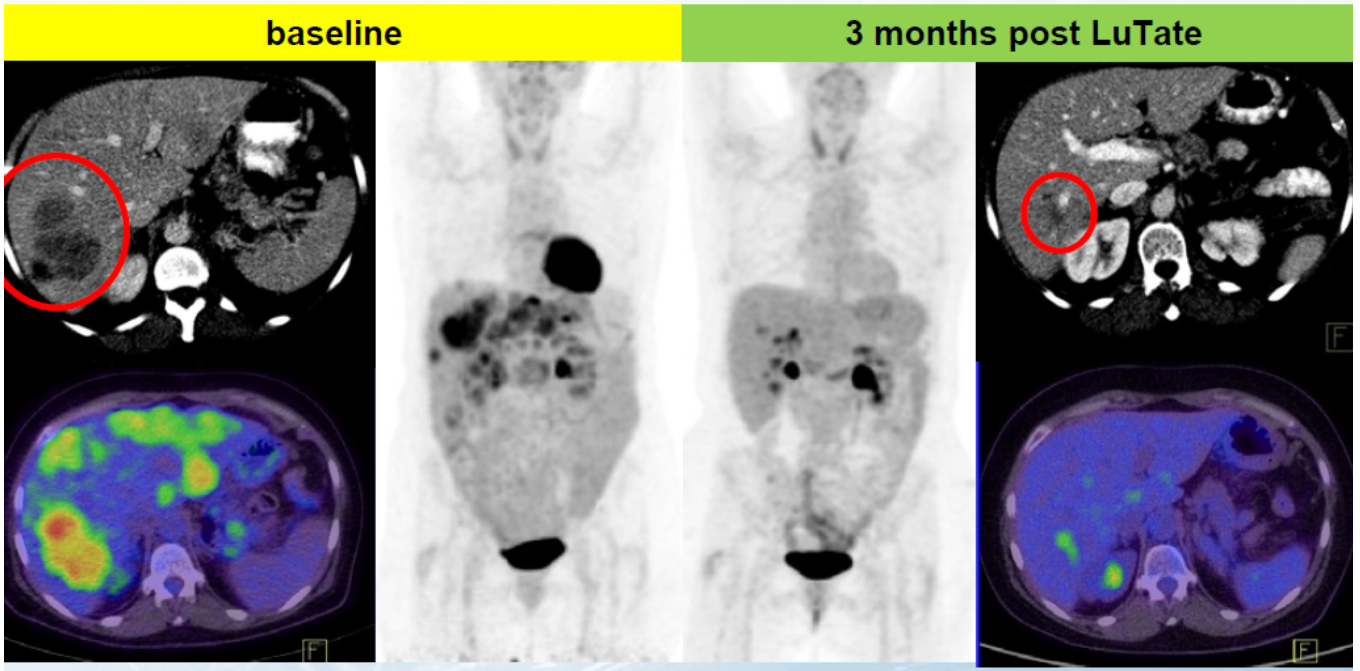
Peptide Receptor Chemotherapy (PRCRT) and Dosimetry

Prof. Michael Hofman Nuclear Medicine Update 2017, August 17th-19th, 2017



Peptide Receptor Chemotherapy (PRCRT) and Dosimetry

Dramatic response on FDG and CECT

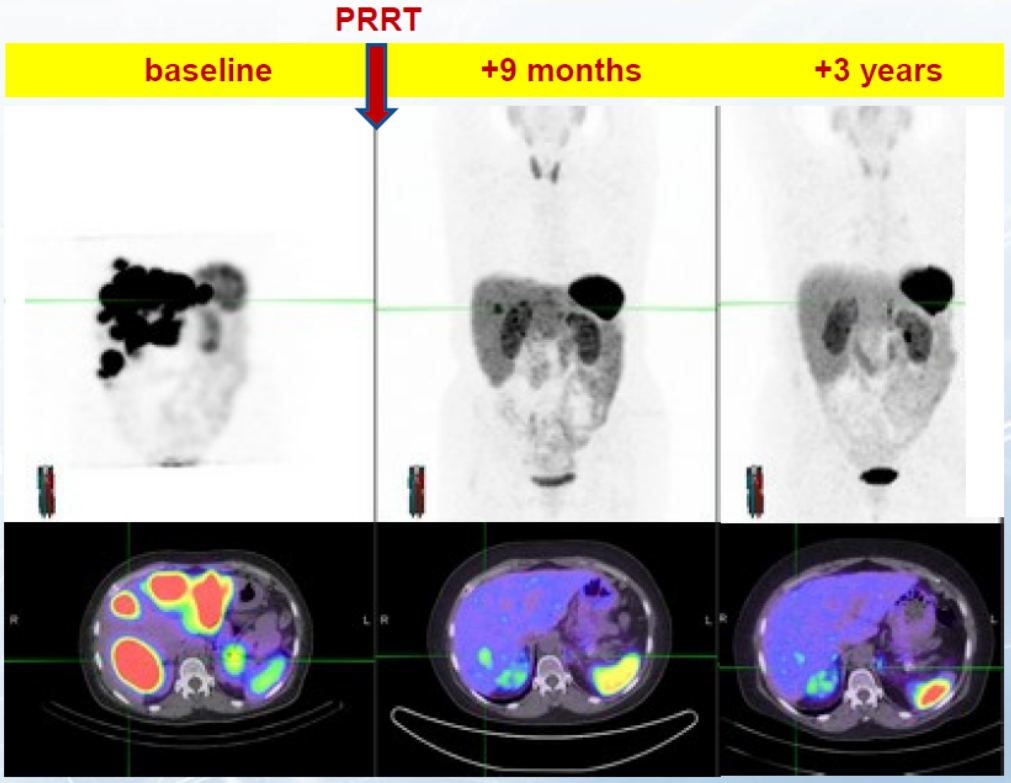


Response: >95% reduction in tumour burden

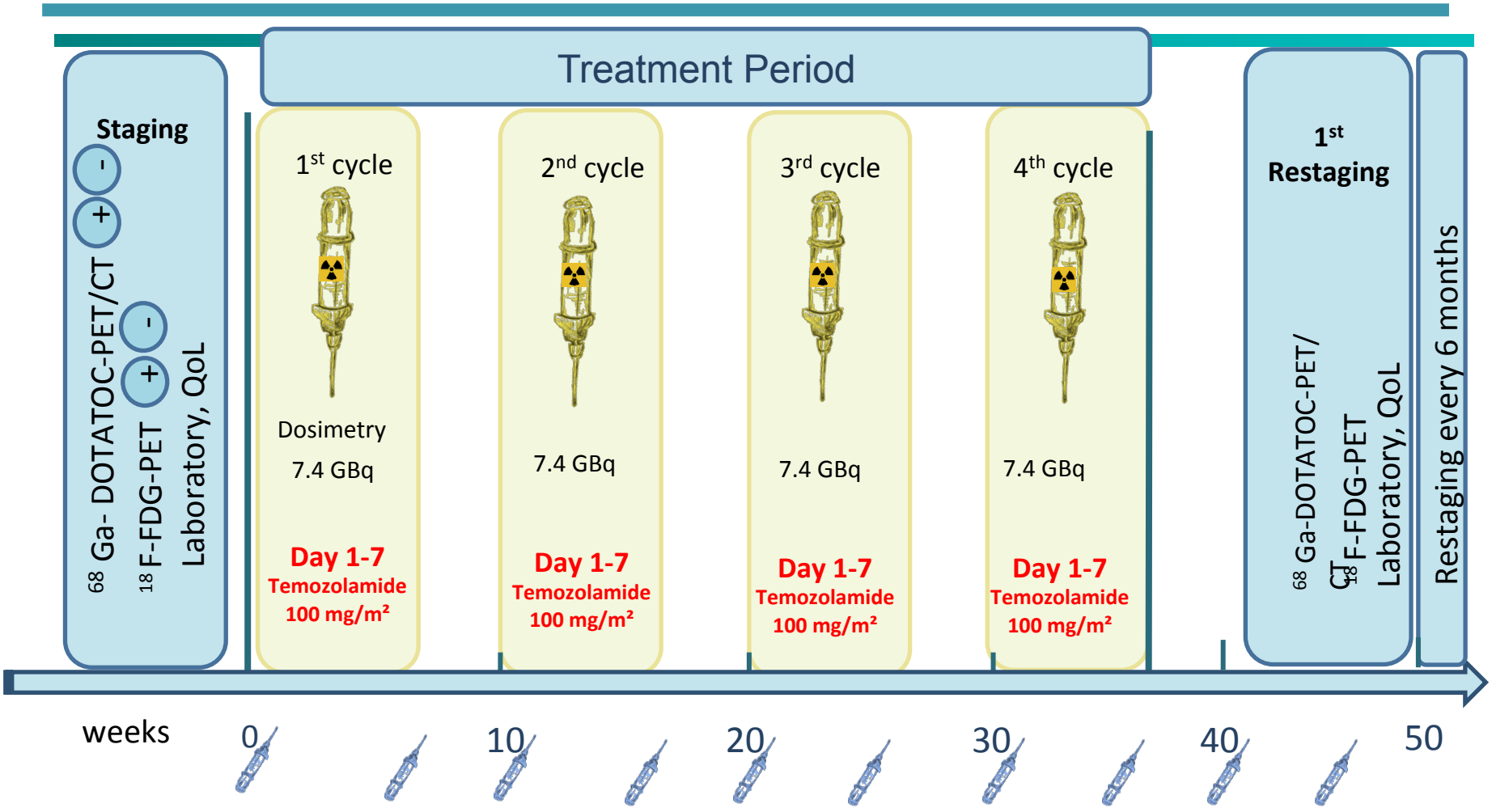
Peptide Receptor Chemotherapy (PRCRT) and Dosimetry

Prof. Michael Hofman Nuclear Medicine Update 2017, August 17th-19th, 2017

Durable response



PRRT + Radiosensibilization with Low-Dose Temozolamide in G3 SSTR- and FDG-PET/CT positive NETs



Continued Treatment with Long-Acting Somatostatin-Analogue

Nuclear Medicine Department, Medical University Innsbruck

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OF RADIOPHARMACEUTICAL
AND MOLECULAR THERAPY
FOUNDED 2009

Retrospective WARMTH Study: Multicenter Analysis of ^{68}Ga-Somatostatin Receptor and ^{18}F-FDG-PET/CT (Dual-Tracer Imaging) in Neuroendocrine Tumor Patients Treated With Peptide Receptor Radionuclide Therapy

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Inclusion Criteria

- Metastatic neuroendocrine tumor
- No concomitant other cancer (being treated)
- PRRT using ^{177}Lu-DOTATOC / TATE
- ECOG 0-2
- GFR > 40 mg/dl and Creatinine < 2 mg/dl
- WBC ≥ 2 x 10^3/µl; Plt ≥ 70 x 10^3/µl
- AST or ALT ≤ 2.0 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases)
- At least 3-year follow-up from the time of the first therapy cycle, or the patient died within this time
- Baseline Dual-Tracer Imaging and repeated Dual-Tracer Imaging in the follow-up

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Primary and Secondary Objectives

Primary Objective

The primary objective of this retrospective multicenter study is to determine and compare the value of ^{68}Ga-DOTA-TOC (or ^{68}Ga-DOTANOC or ^{68}Ga-DOTATATE, if applicable) and ^{18}F-FDG-PET/CT for initial and follow-up evaluation of NET patients treated and possibly retreated by PRRT. Furthermore, it is aimed to evaluate whether possible changes in tumor ^{18}F-FDG-uptake correlate with the course of the disease.

Secondary Objective

Progression Free Survival is defined as the time between first cycle of ^{177}Lu- DOTA-TATE therapy and occurrence of documented progression or death from any cause. Clinical and laboratory toxicities and all adverse events are documented and graded per common toxicity criteria of adverse events (CTCAE).

The study workflow will be divided in three phases

1. Data collection in an Excel table in each centre – Monitoring Process
2. Sending the anonymised data to Department of Nuclear Medicine, Medical University Innsbruck (Ethical Approval X / 2018)
3. Transferring the data from excel tables to a main SPSS table for statistical analysis (IAEA)
4. Statistical analysis (IAEA / Medical University of Innsbruck)

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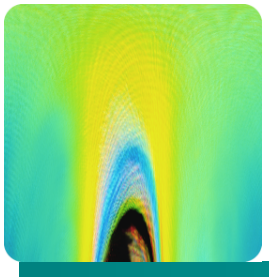
AND MOLECULAR THERAPY
FOUNDED 2009

Participating Centers

Hojjat Ahmadzadehfar (Bonn, Germany)
Richard Baum (Bad Berka, Germany)
CS Bal (Chandigarh, India)
Partha Choudhury (Delhi, India)
Michael Sathekge (Pretoria, South Africa)
Giovanni Paganelli (Meldola, Italy)
Michael Hofman (Melbourne, Australia)
Harvey Turner (Perth, Australia)
Irene Virgolini (Innsbruck, Austria)
Alexander Haug, Marcus Hacker (Vienna, Austria)
Kalevi Kairemo (Helsinki, Finland)
Levent Kabasakal (Istanbul, Turkey)
Diana Paez, Olga Morozowa (IAEA Vienna, Austria)
Feng Wang (Nanjing, China)
Omar Alonso (Montevideo, Uruguay)

Other WARMTH centers to be defined



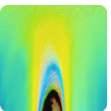
Tirol Kliniken GmbH
Landeskrankenhaus – Universitätskliniken Innsbruck
Medizinische Universität Innsbruck
Universitätsklinik für Nuklearmedizin
Direktor: Univ.-Prof. Dr. Irene J. Virgolini

Long-term Side Effects

PRRT
versus Targeted Agents

tirol kliniken

MEDIZINISCHE UNIVERSITÄT INNSBRUCK



Eur J Nucl Med Mol Imaging (2008) 35:1847–1856
DOI 10.1007/s00259-008-0778-1

ORIGINAL ARTICLE

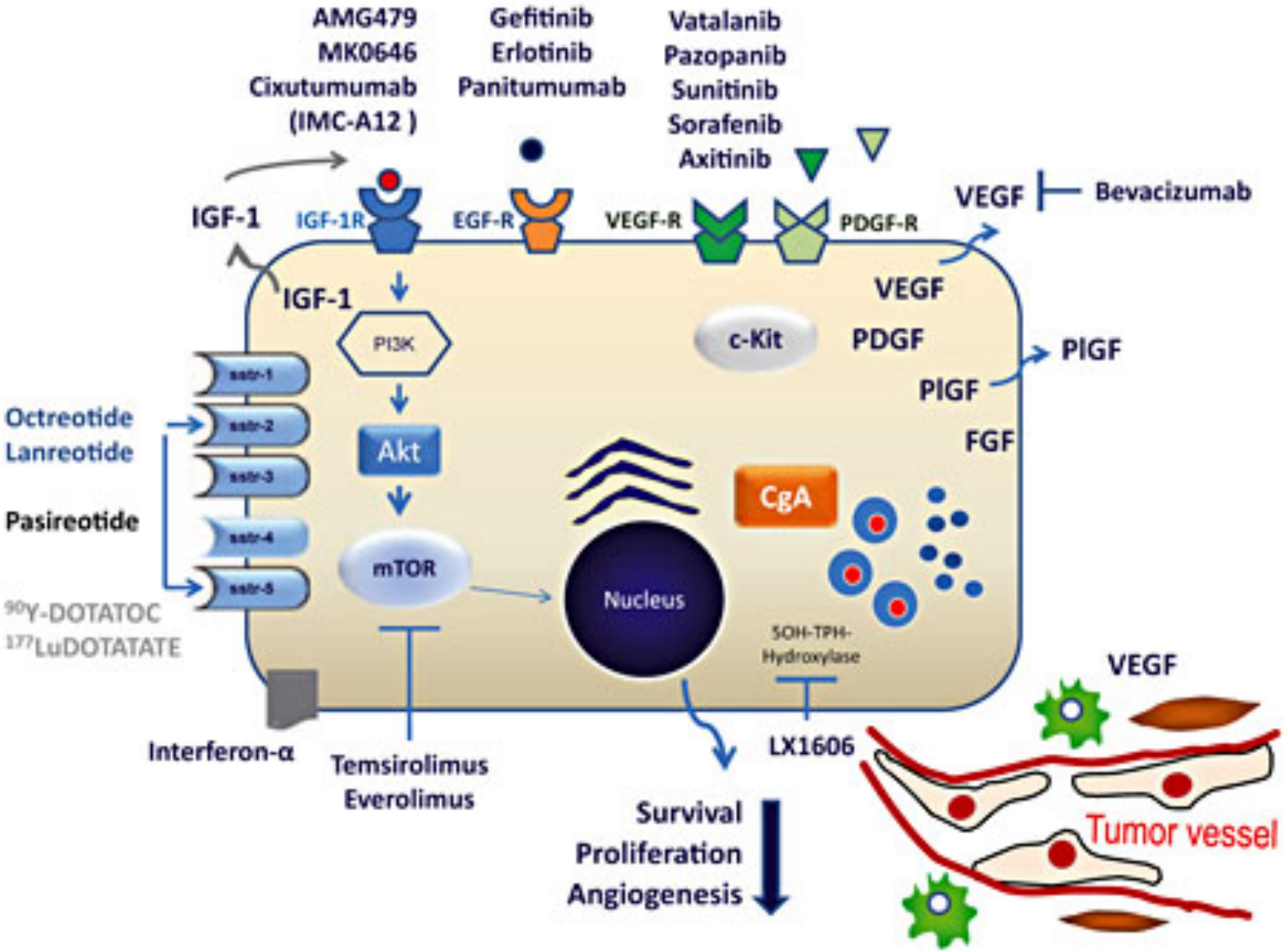
Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE: the role of associated risk factors

Lisa Bodei · Marta Cremonesi · Mahila Ferrari · Monica Pacifici · Chiara M. Grana · Mirco Bartolomei · Silvia M. Baio · Maddalena Sansovini · Giovanni Paganelli

Risk factors for kidney and bone marrow toxicity:
diabetes, hypertension, previous chemotherapy, previous PRRT

PRRT vs. Targeted Agents

- Efficiency (long-term)
- Side Effects
  - -Kidneys
  - Bone marrow
- Quality of Life


AMG479
MK0646
Cixutumumab
(IMC-A12)
Gefitinib
Erlotinib
Panitumumab
Vatalanib
Pazopanib
Sunitinib
Sorafenib
Axitinib
IGF-1
IGF-1R
EGF-R
VEGF-R
PDGF-R
VEGF
Bevacizumab
IGF-1
PI3K
c-Kit
PDGF
PIGF
PIGF
FGF
ssbr-1
ssbr-2
ssbr-3
ssbr-4
ssbr-5
Octreotide
Lanreotide
Pasireotide
Akt
mTOR
Nucleus
CgA
5OH-TPH-
Hydroxylase
90Y-DOTATOC
177LuDOTATATE
Interferon-α
Temsirolimus
Everolimus
LX1606
Survival
Proliferation
Angiogenesis
VEGF
Tumor vessel

PRRT vs. Targeted Agents

TABLE 4
Randomized Controlled Trials for Treatment of Advanced NETs (*64*)

Study	Trial name	Year	Tumor type	Intervention	Control	Median PFS (mo)	HR (95% CI)
Rinke et al. (*58*)	PROMID	2009	Midgut	Octreotide LAR (30 mg/4 wk)	Placebo	14 vs. 6	0.34 (0.20–0.59)
Caplin et al. (*59*)	CLARINET	2014	Pancreatic, midgut, hindgut	Lanreotide (120 mg/4 wk)	Placebo	NR at 24 vs. 18	0.47 (0.30–0.73)
Pavel et al. (*60*)	RADIANT-2	2011	NET + carcinoid syndrome	Everolimus (10 mg/d)*	Placebo*	16 vs. 11	0.77 (0.59–1.00)
Yao et al. (*61*)	RADIANT-3	2011	Pancreatic	Everolimus (10 mg/d)*	Placebo*	11 vs. 5	0.35 (0.27–0.45)
Yao et al. (*62*)	RADIANT-4	2016	Nonfunctioning lung/ gastrointestinal tract	Everolimus (10 mg/d)*	Placebo*	11 vs. 4	0.48 (0.35–0.67)
Raymond et al. (*63*)		2011	Pancreatic	Sunitinib (37.5 mg/d)*	Placebo*	11 vs. 6	0.42 (0.26–0.66)
Strosberg et al. (*45*)	NETTER-1	2017	Midgut	[^{177}Lu-DOTA^{0}-Tyr^{3}] octreotate (7.4 GBq × 4 cycles)	Octreotide LAR, 60 mg/mo	NR vs. 8	0.21 (0.13–0.34)

*With continuation of somatostatin analog therapy.
PFS = progression-free survival (intervention vs. control); HR = hazard ratio for disease progression and (disease-related) death; LAR = long-acting and repeatable; NR = not reached.

Somatostatin Receptor 2-Targeting Compounds
Smit Duijzentkunst DA, Kwekkeboom DJ, Bodei
J Nucl Med. 2017 Sep;58(Suppl 2):54S-60S. doi: 10.2967/jnumed.117.191015. L3.

Sunitinib malate for the treatment of pancreatic neuroendocrine tumors.

Raymond E, Dahan L, Raoul JL, Bang YJ, Borbath I, Lombard-Bohas C, Valle J, Metrakos P, Smith D, Vinik A, Chen JS, Hörsch D, Hammel P, Wiedenmann B, Van Cutsem E, Patyna S, Lu DR, Blanckmeister C, Chao R, Ruszniewski P.

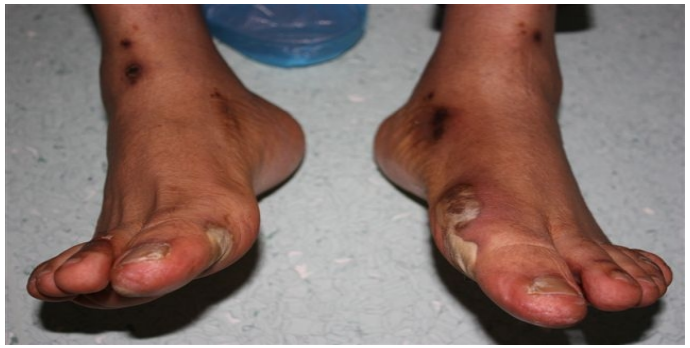
N Engl J Med. 2011 Feb 10;364(6):501-13. doi: 10.1056/NEJMoa1003825.

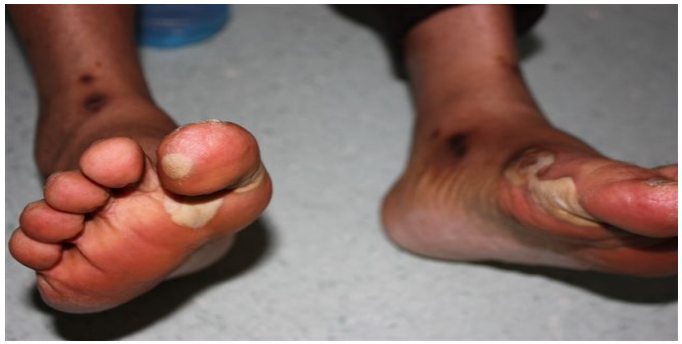
Table 3. Common Adverse Events in the Safety Population.*

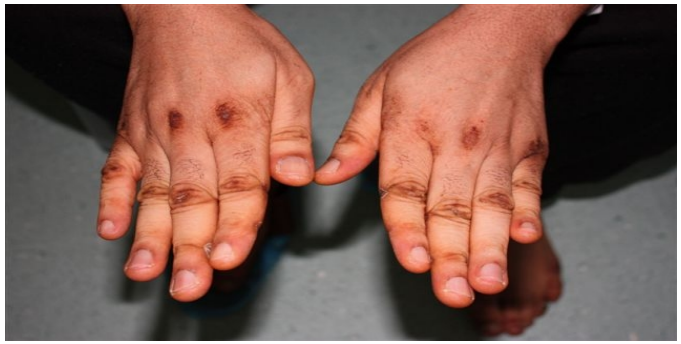
Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	number of patients (percent)					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar–plantar erythro-dysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0
Dysgeusia	17 (20)	17 (20)	0	4 (5)	4 (5)	0
Epistaxis	17 (20)	16 (19)	1 (1)	4 (5)	4 (5)	0
Headache	15 (18)	15 (18)	0	11 (13)	10 (12)	1 (1)
Insomnia	15 (18)	15 (18)	0	10 (12)	10 (12)	0
Rash	15 (18)	15 (18)	0	4 (5)	4 (5)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)	4 (5)	4 (5)	0
Mucosal inflammation	13 (16)	12 (14)	1 (1)	6 (7)	6 (7)	0
Weight loss	13 (16)	12 (14)	1 (1)	9 (11)	9 (11)	0
Constipation	12 (14)	12 (14)	0	16 (20)	15 (18)	1 (1)
Back pain	10 (12)	10 (12)	0	14 (17)	10 (12)	4 (5)

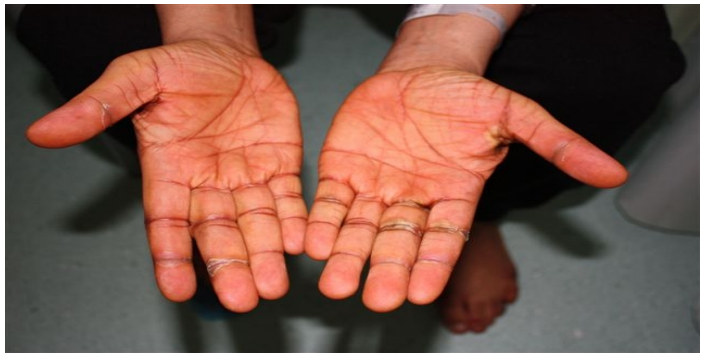
* Adverse events were defined on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. Events listed are those of any grade that occurred in more than 15% of patients in either group.

Side Effects
„hand food syndrome“









Combination Therapy

	SST-Analog	Combination	Indication	Center
1	^{177}Lu-DOTATATE	Nivolumab®	SCLC	Georgetown
2	^{111}In-Pentetreotide	^{131}I-MIBG	NET	Iowa
3	^{90}Y-DOTATOC	^{131}I-MIBG	NET	Iowa
4	^{111}Lu-DOTATATE	Capecitabine	GEP NET	Meldola
5	^{177}Lu-DOTATATE	Temozolomide Capecitabine	GEP NET	Australasia
6	^{177}Lu-DOTATATE	^{177}Lu-DOTATATE i.a.	GEP NET	Quebec

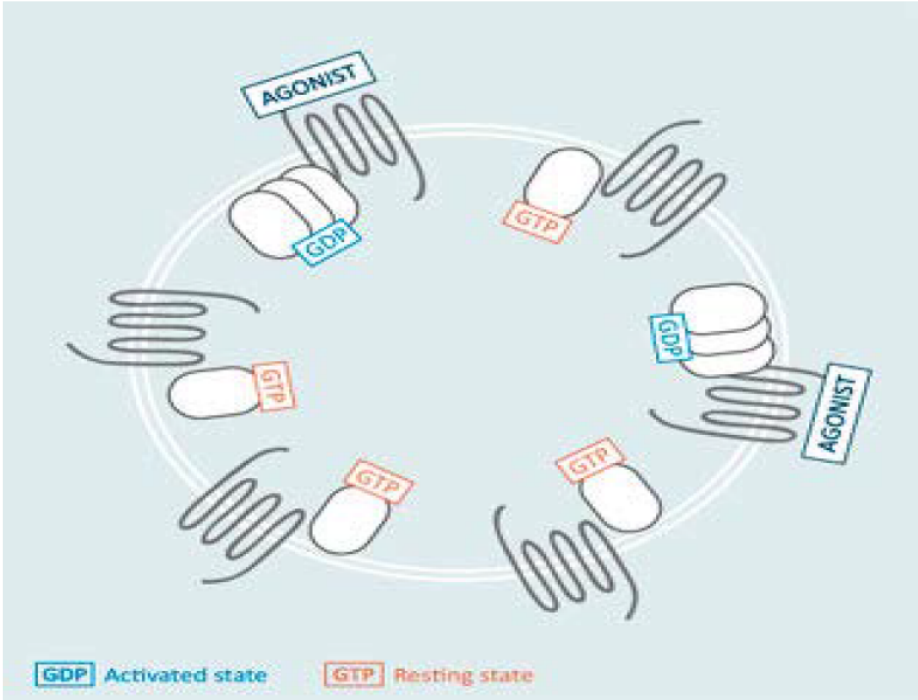
Antagonists

^{177}Lu OPS201 Trial for Metastatic Neuroendocrine Tumour

Lenzo N., Cardaci J, Meyrick D, Henderson A, Crouch J, Yeo S, Turner H

Theranostics Australia 2016

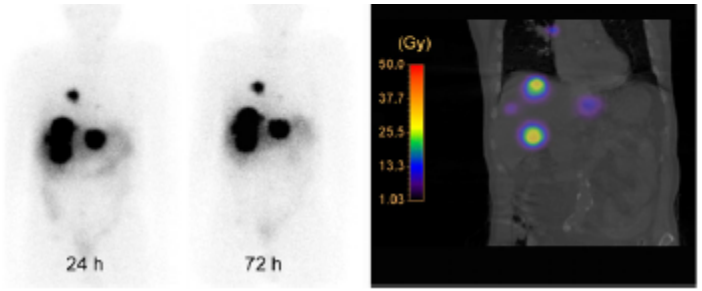
Somatostatin Receptor Agonists Vs Antagonists



^{177}Lu-DOTA-JR11 versus ^{177}Lu-DOTA-TATE

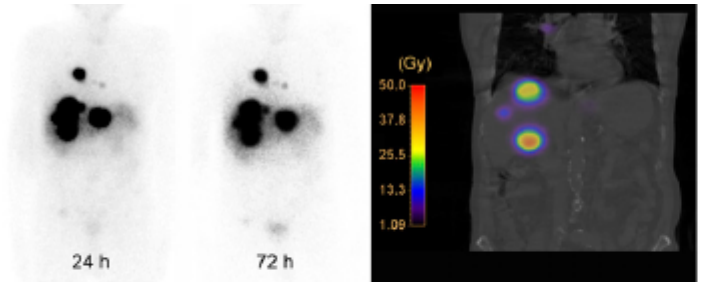
Patient with a NE tumour of the lung; Injected dose: ~1000 MBq (<200µg peptide)
Kidney protection with Arg/Lys infusion

^{177}Lu-DOTA-TATE
Agonist



Tumour dose (Gy/GBq) 16-29
T/K ratio 11-20
T/BM ratio 162-294

^{177}Lu-DOTA-JR11
Antagonist



Tumour dose (Gy/GBq) 5.6-13
T/K ratio 3.9-9.0
T/BM ratio 57-133

^{177}Lu-DOTA-JR11

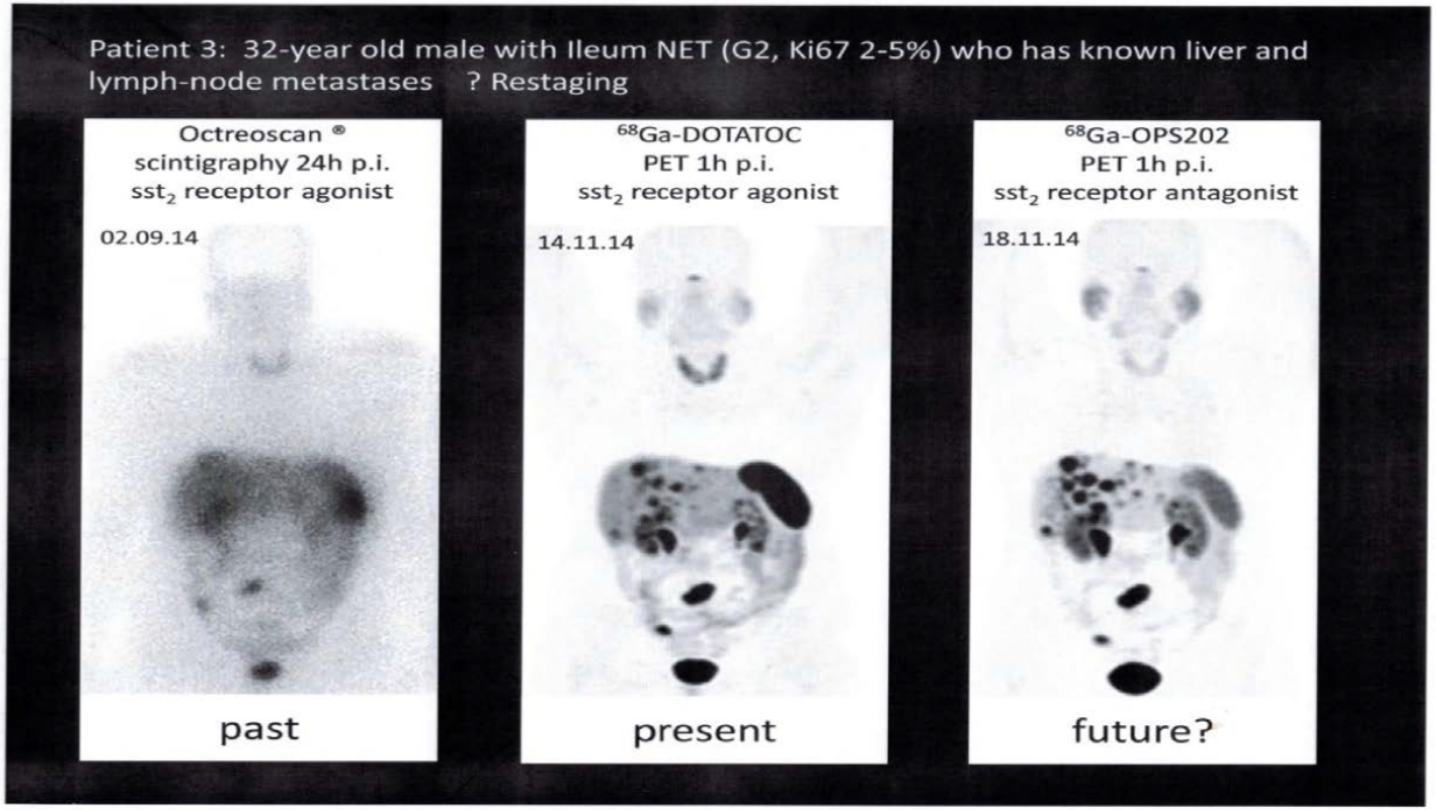
⇒ **longer intratumoural residence time**
⇒ **higher tumour uptake**
⇒ **higher tumour dose**
⇒ **higher tumour to kidney ratio**
⇒ **higher tumour to bone marrow ratio**

Wild D, et al. JNM, 2014, 55:1-5

^{177}Lu OPS201 Trial for Metastatic Neuroendocrine Tumour

Lenzo N., Cardaci J, Meyrick D, Henderson A, Crouch J, Yeo S, Turner H

Theranostics Australia 2016



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FOUNDED 2009

14th ICRT

(International Conference on Radiopharmaceutical Therapy)

August 21-25, 2019, Nanjing, China

Thank you!