Principles of Theragnostics in Neuroendocrine Tumors: diagnosis and therapy with labelled peptides.

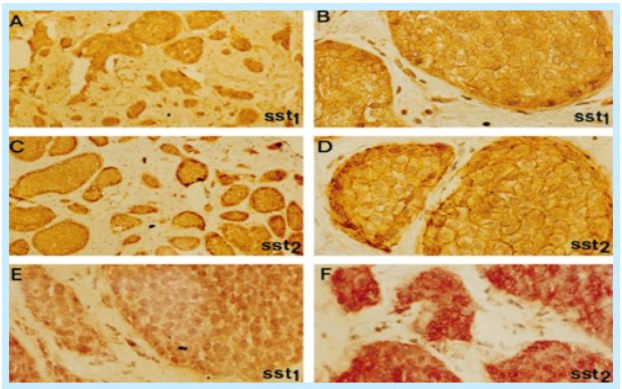
Prof . Giovanni Paganelli

Università di Ferrara

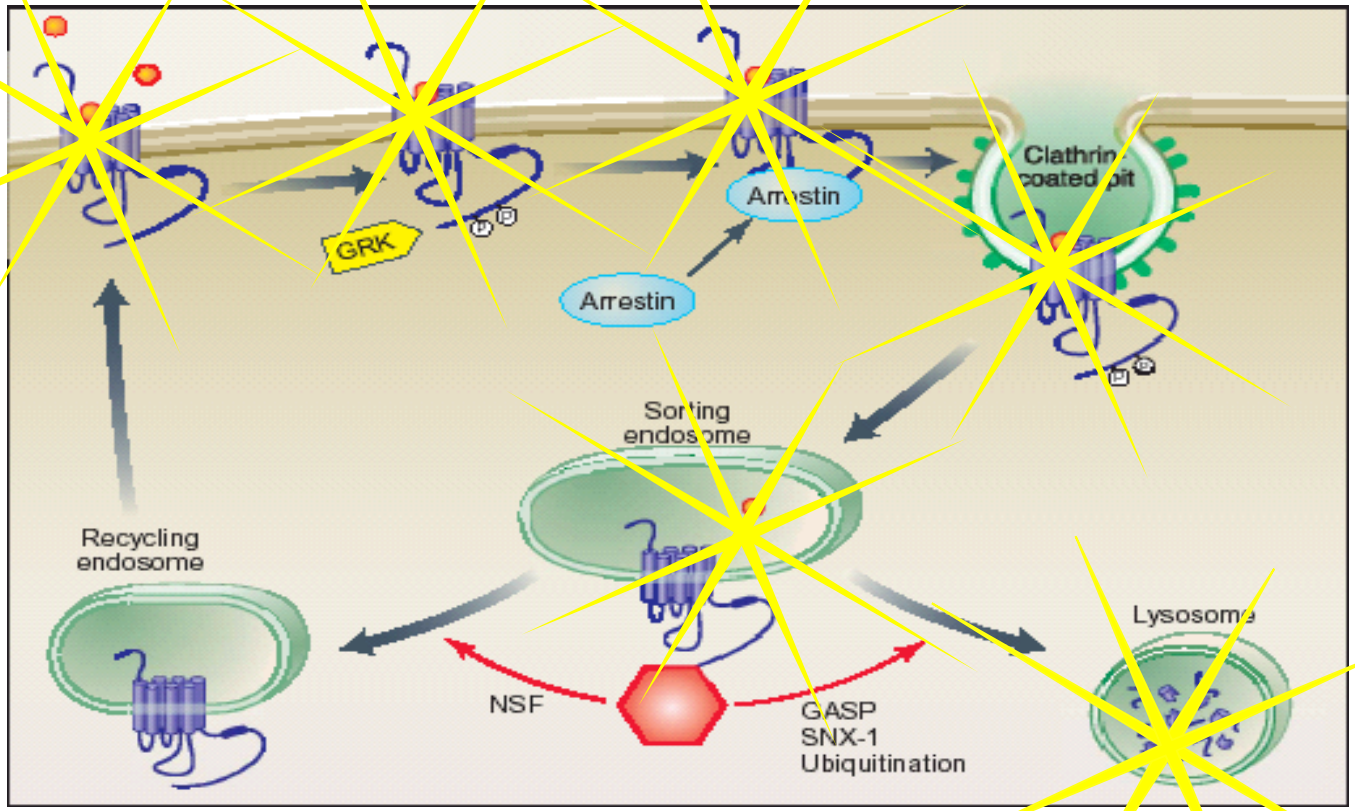
Direttore Medicina Nucleare IRST-IRCCS , Meldola.

Radiopeptide Therapy: Rationale and Basis for Radioligand Binding

Image courtesy of IRST-IRCCS, 100.26, pat. n°60.



Hofland LJ, et al. *J Clin Endocrinol Metab.* 1999;84(2):775-780.



Adapted from: Gray JA, Roth BL. *Science.* 2002;297(5581):529-531.

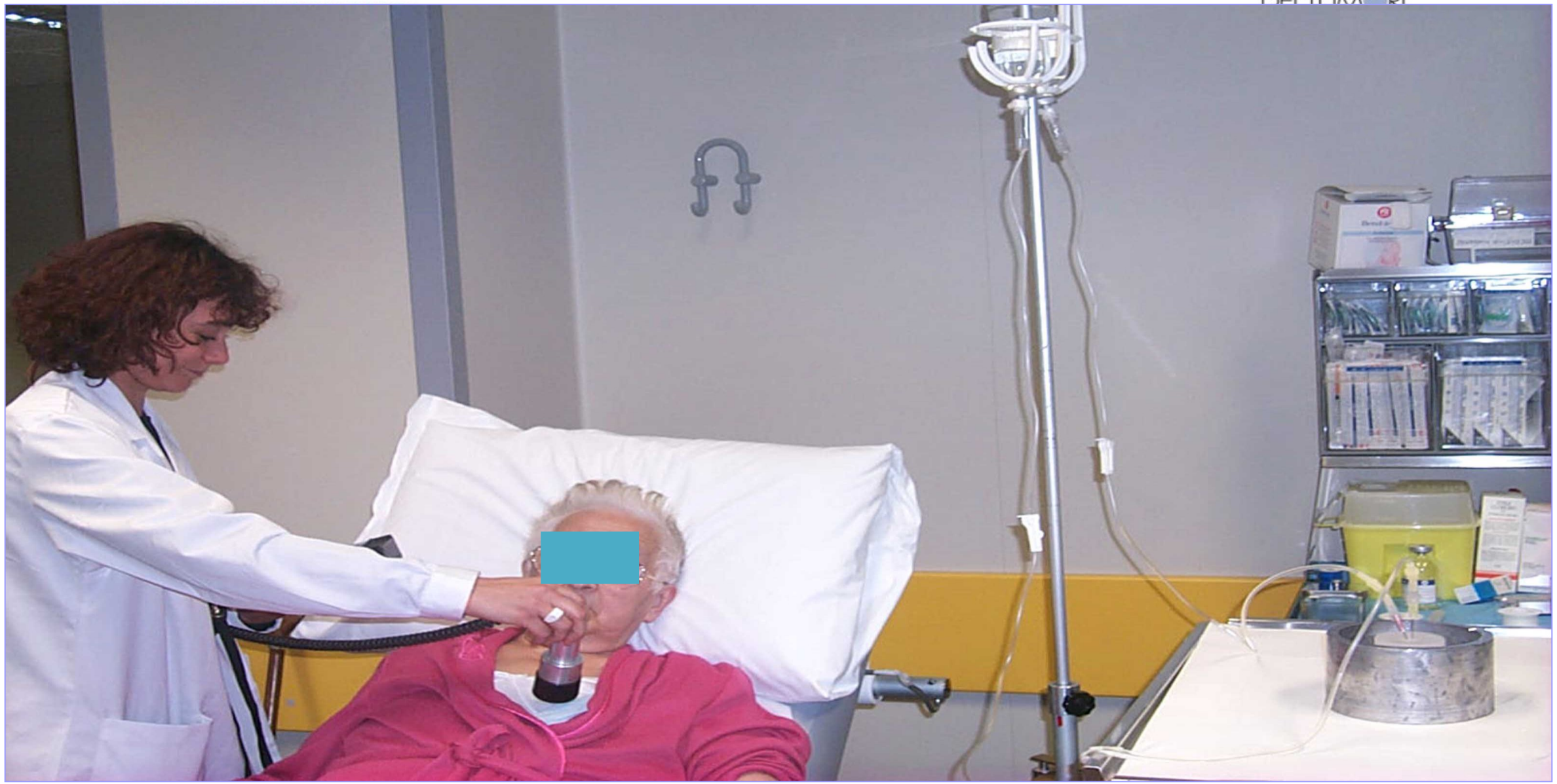
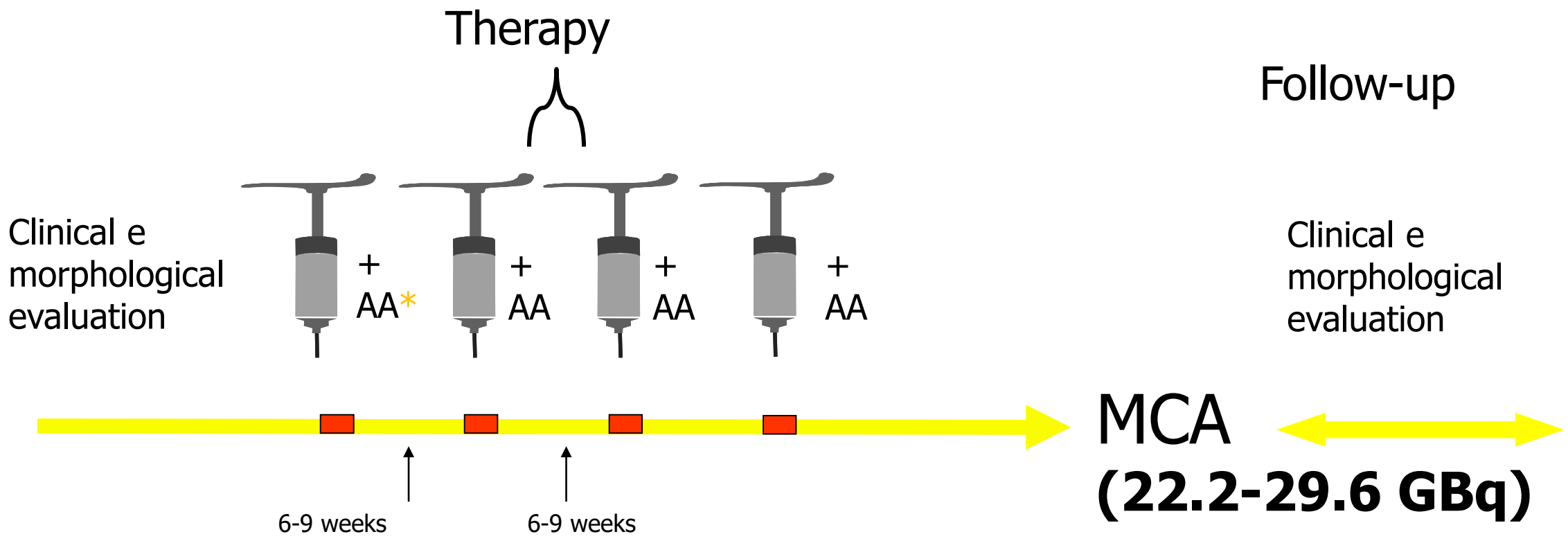


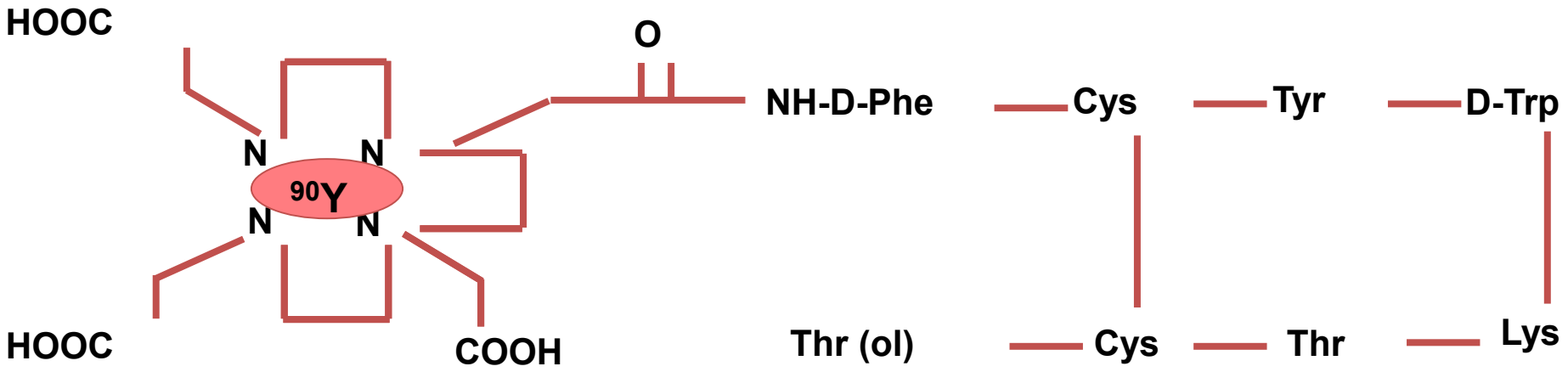
Image courtesy of Paganelli G.

^{177}Lu-DOTATATE therapy schedule



* Arginine 12.5 g in 500 ml saline before therapy
Arginine 12.5 g in 500 ml saline after therapy
Arginine 12.5 g in 500 ml saline b.i.d. up to two days after therapy

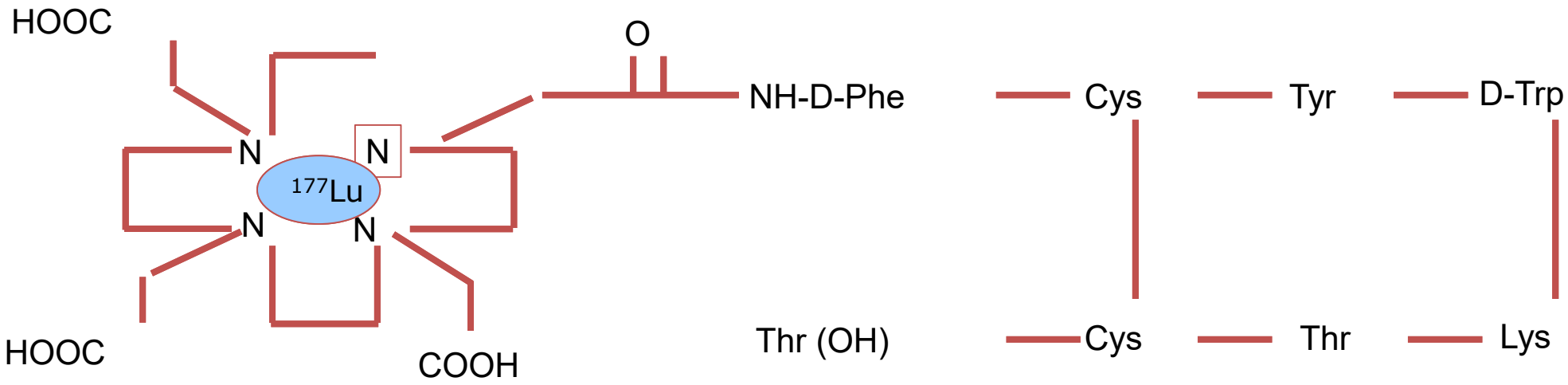
^{90}Y-DOTATOC
([90Y-DOTA0-Tyr3]-octreotide)3



Affinity (IC50, nM)				
sst_1	sst_2	sst_3	sst_4	sst_5
>10000	11 ± 1.7	389 ± 13	>10000	114 ± 29

Bodei L, et al. *Nuclear Oncology: Pathophysiology and Clinical Applications*. New York, New York: Springer New York; 2013.

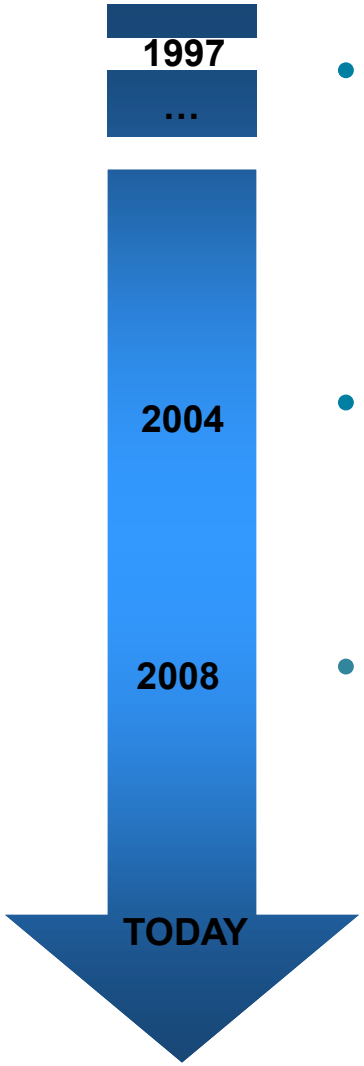
177Lu-DOTATATE ([177Lu-DOTA0-Tyr3]-octreotate)



Affinity (IC50, nM)				
sst_1	sst_2	sst_3	sst_4	sst_5
>10000	1.6 ± 0.4	>1000	523 ± 239	187 ± 50

Bodei L, et al. *Nuclear Oncology: Pathophysiology and Clinical Applications*. New York, New York: Springer New York; 2013.

PRRT: The IEO-IRST Experience



- **^{90}Y-DOTATOC:**
  - Dosimetry (^{111}In modelling)
  - Phase I studies
  - Efficacy
- **^{177}Lu-DOTATATE:**
  - Dosimetry
  - Phase I-II study
- **Safety and efficacy**
  - Phase II study of ^{177}Lu-DOTATATE in GEP NETs
  - FDG-PET in GEP NETs
  - Randomized trials

IEO/IRST, European Institute of Oncology/Istituto Scientifico per lo Studio e la Cura dei Tumori GEP NET, gastroenteropancreactic neuroendocrine tumor

Internal Dosimetry

- **Internal dosimetry deals with the determination of the amount and the spatial and temporal distribution of radiation energy deposited in tissue by radionuclides within the body**

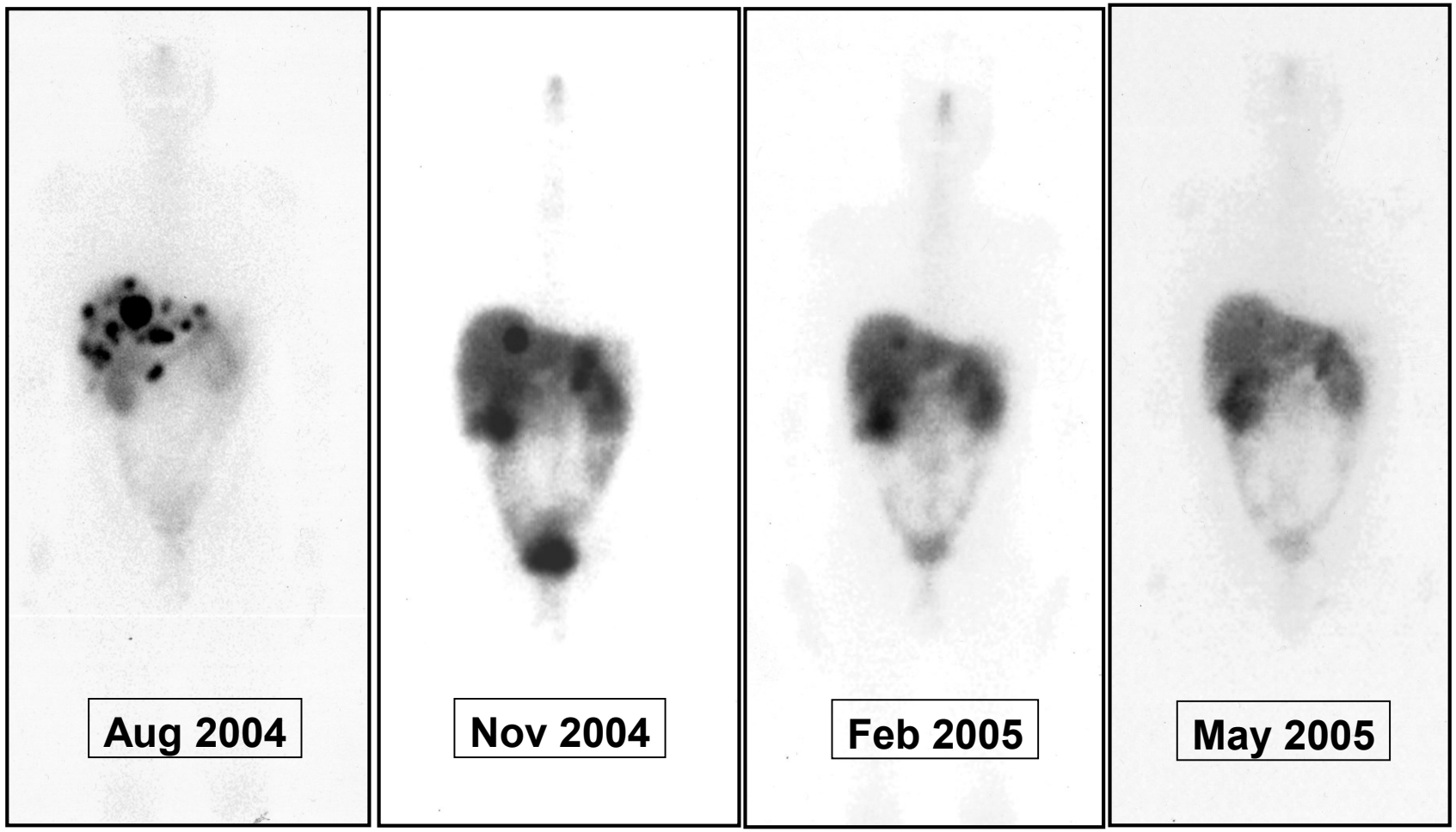
$$D = d\bar{E} / dm$$

$d\bar{E}$ = Mean energy imparted by ionizing radiation to matter

dm = Mass to which energy is imparted

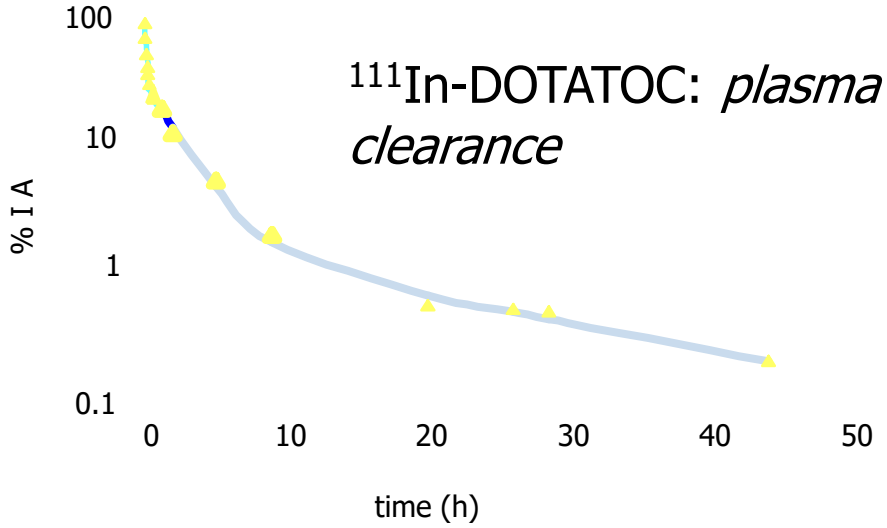
Zanzonico PB, et al. *J Nuncl Med.* 2000; 41(2):297-308.

Objective Response After 4 Cycles of PRRT

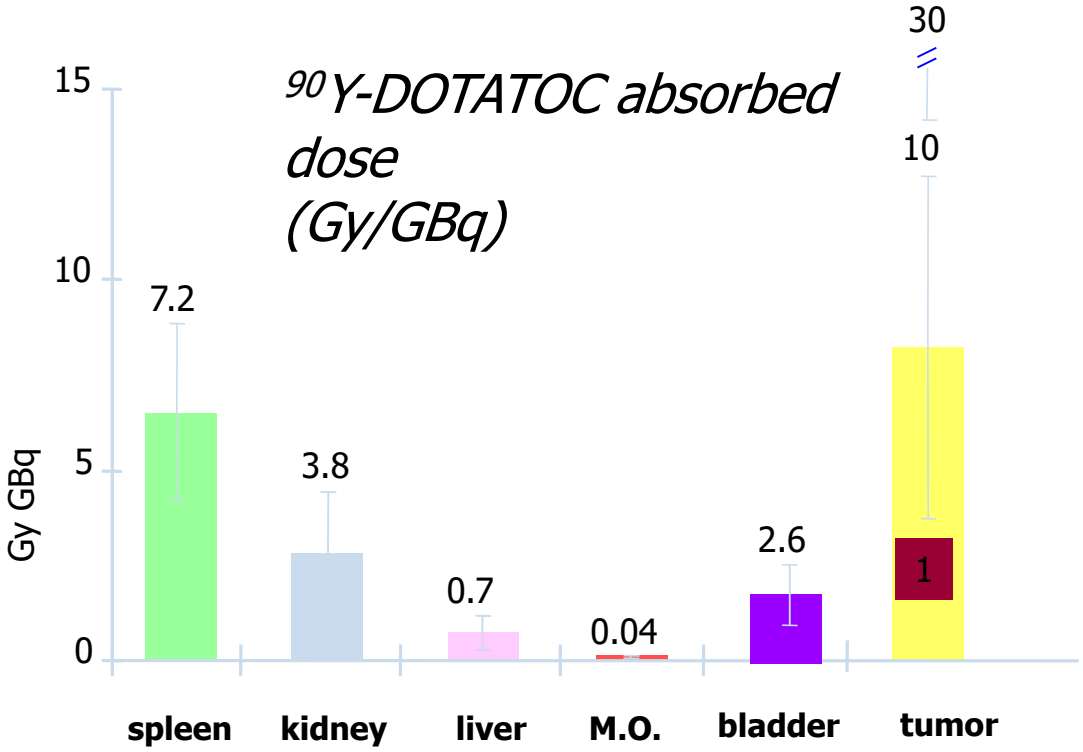


Images courtesy of Paganelli G.

^{90}Y-DOTATOC: biodistribution and dosimetry



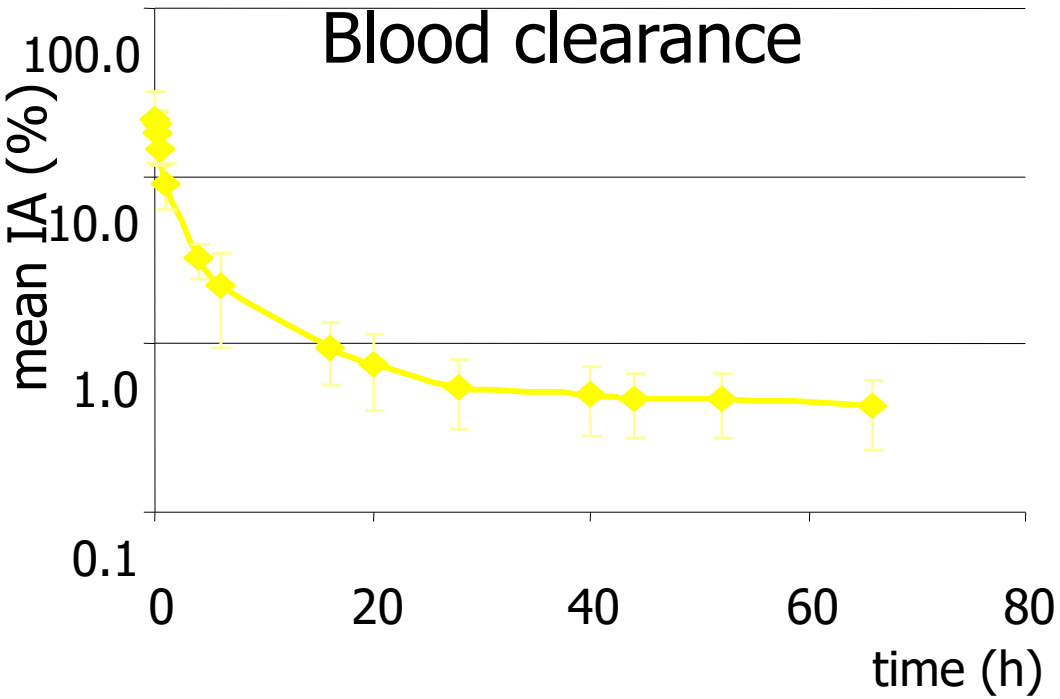
^{111}In-DOTATOC: *plasma clearance*



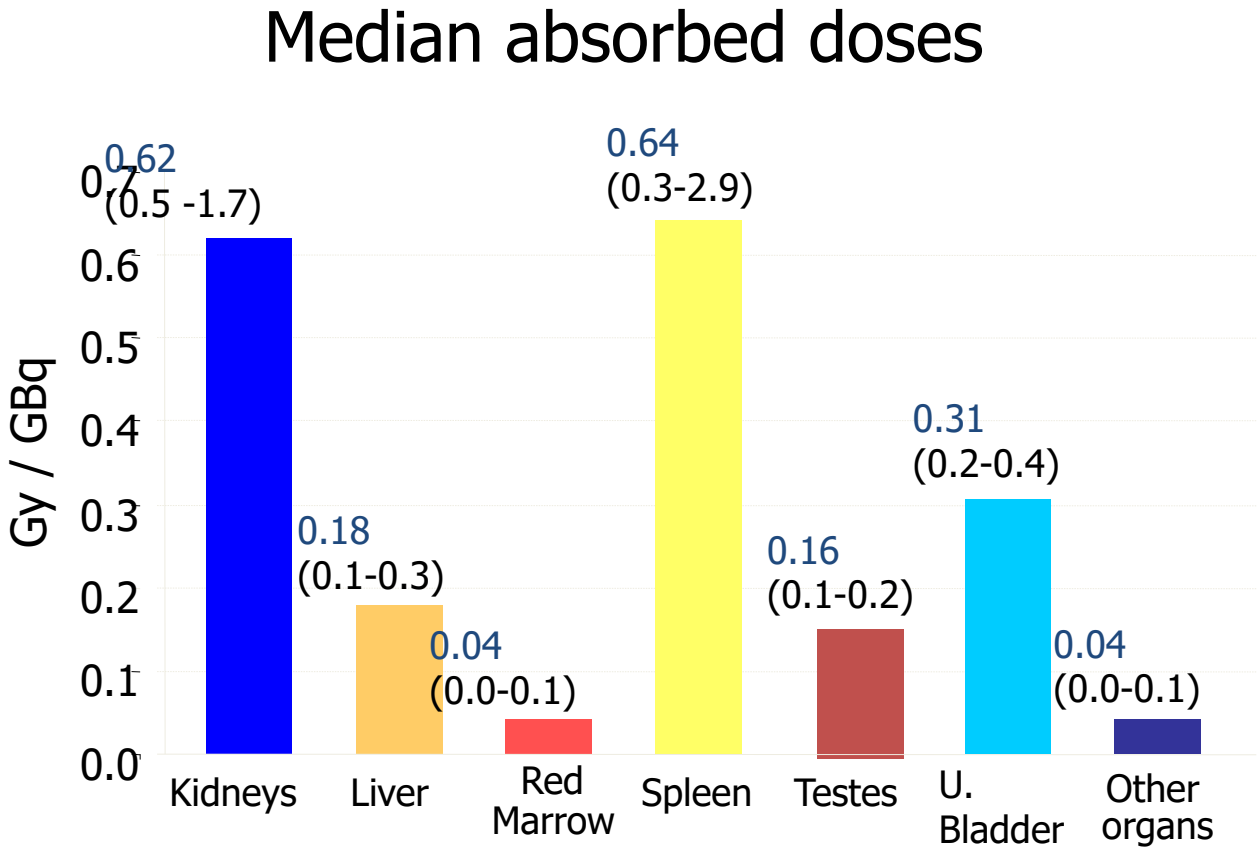
Cremonesi M et al. Eur J Nucl Med 1999

Cremonesi M et al. J Nucl Med 2006

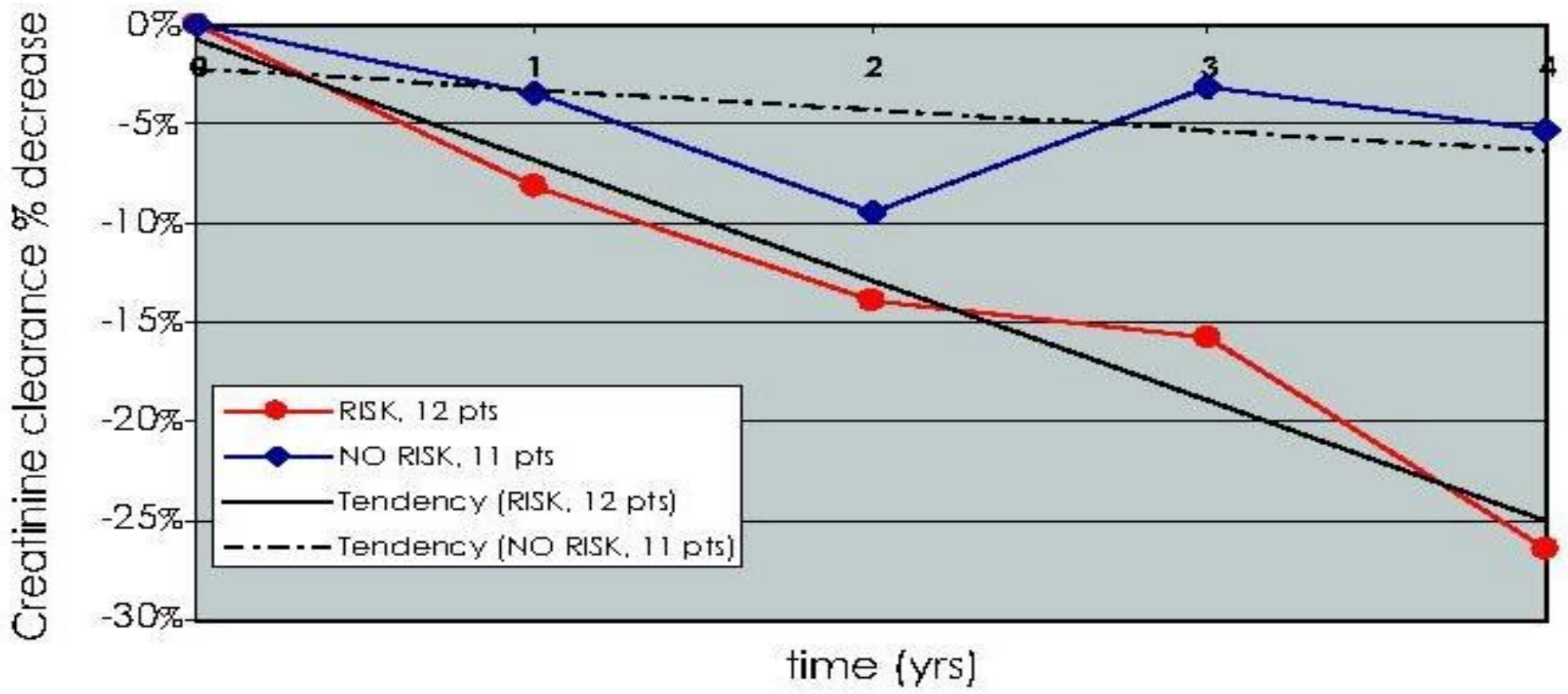
^{177}Lu-DOTATATE:biodistribution and dosimetry



Tumours (0.6 – 56) Gy/GBq



Different median creatinine clearance course in risk (red line, tendency continuous line) and no risk (blue line, tendency dotted line) patients treated with 90Y-DOTATOC over 4 years of follow-up (R2=0.9598)



Bodei L., Cremonesi M, G. Paganelli et al. "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". Eur J Nucl Med Mol Imaging 2008

^{90}Y or ^{177}Lu..?

Which is more appropriate?

Possible combinations?

Timing? (which first; Δt)

dosimetry ↓

Comparison of

^{177}Lu-DOTATATE vs. ^{90}Y-DOTATATE

through a retrospective study

^{90}Y versus ^{177}Lu

Half-Life = 64 h (2.6 d)

Emission: pure β^- emitter

$E_{\beta max}$ = 2.27 MeV

Range = 11 mm

Chemical form = C.F. $^{90}YCl_3$

Half-Life = 6.64 d

Emission: β^-, γ emitter

$E_{\beta max}$ = 0.5 MeV

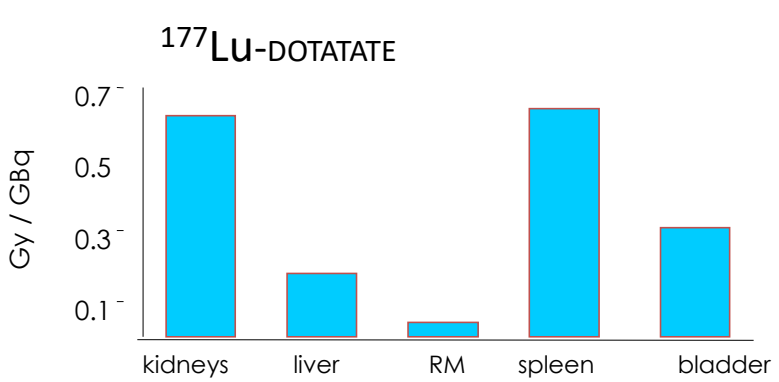
Range = 2 mm

Chemical form = $^{177}LuCl_3$

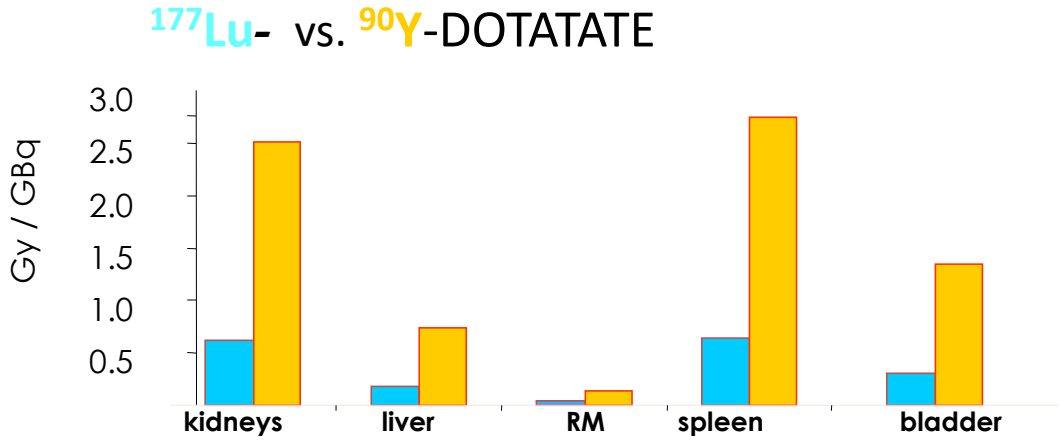
main γ emissions = 160 KeV

202 KeV

absorbed doses: ^{177}Lu vs. ^{90}Y



177Lu-TATE Tumours: (0.6 – 56) Gy/GBq

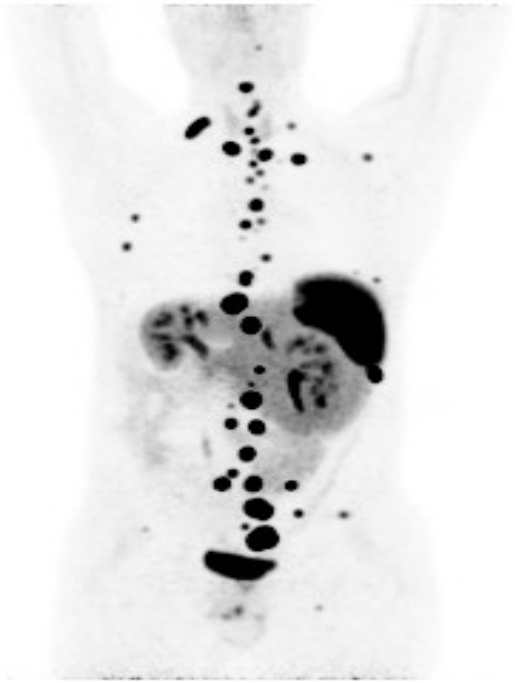


90Y- TATE: Tumours: (2.2–180) Gy/GBq

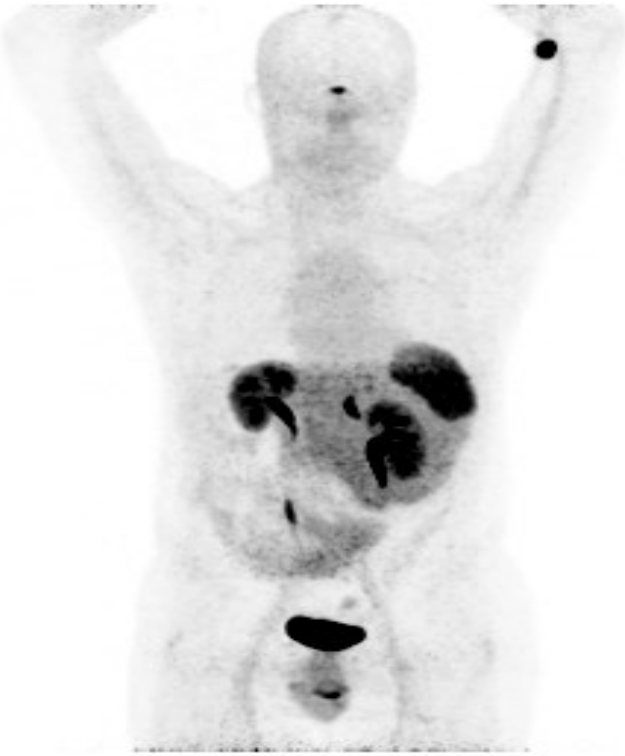
NORMAL ORGANS $\frac{^{90}Y}{^{177}Lu} \sim 4$ TUMOURS $\frac{^{90}Y}{^{177}Lu}$ 2.1 (∅< 2cm)… …4.5 (∅> 2cm)

Benefit/risk balance remains to be established for each patient **based on the TUMOUR / KIDNEY dose ratio**

Patient With Bone Marrow Metastases From a Pancreatic G2 NET Treated With PRRT With 177Lu-DOTATATE (25 GBq)



Basal 68Ga-DOTATOC PET-CT

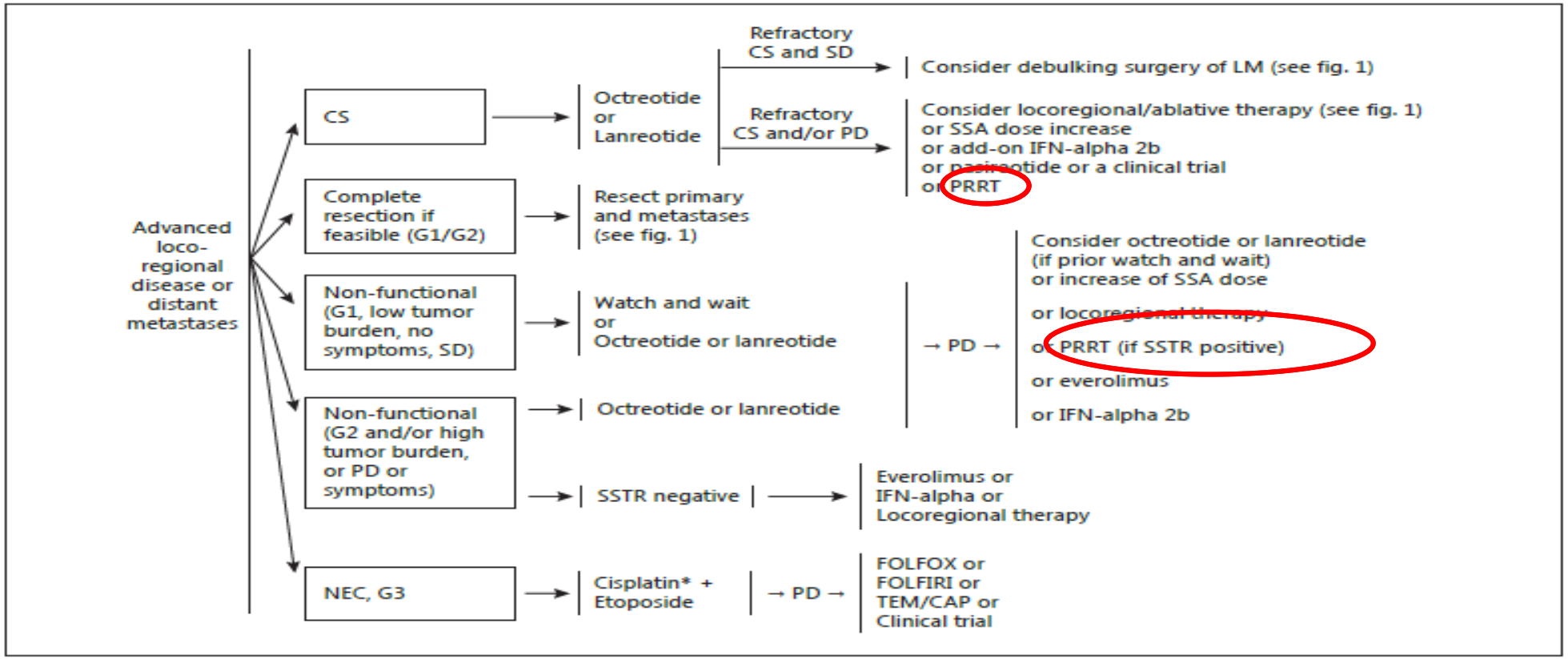


Final 68Ga-DOTATOC PET-CT

Images courtesy of Paganelli G.

ENETS Consensus Guidelines 2016: Midgut NEN

Therapeutic Algorithm for the Management of (Midgut) NEN With Advanced Locoregional Disease

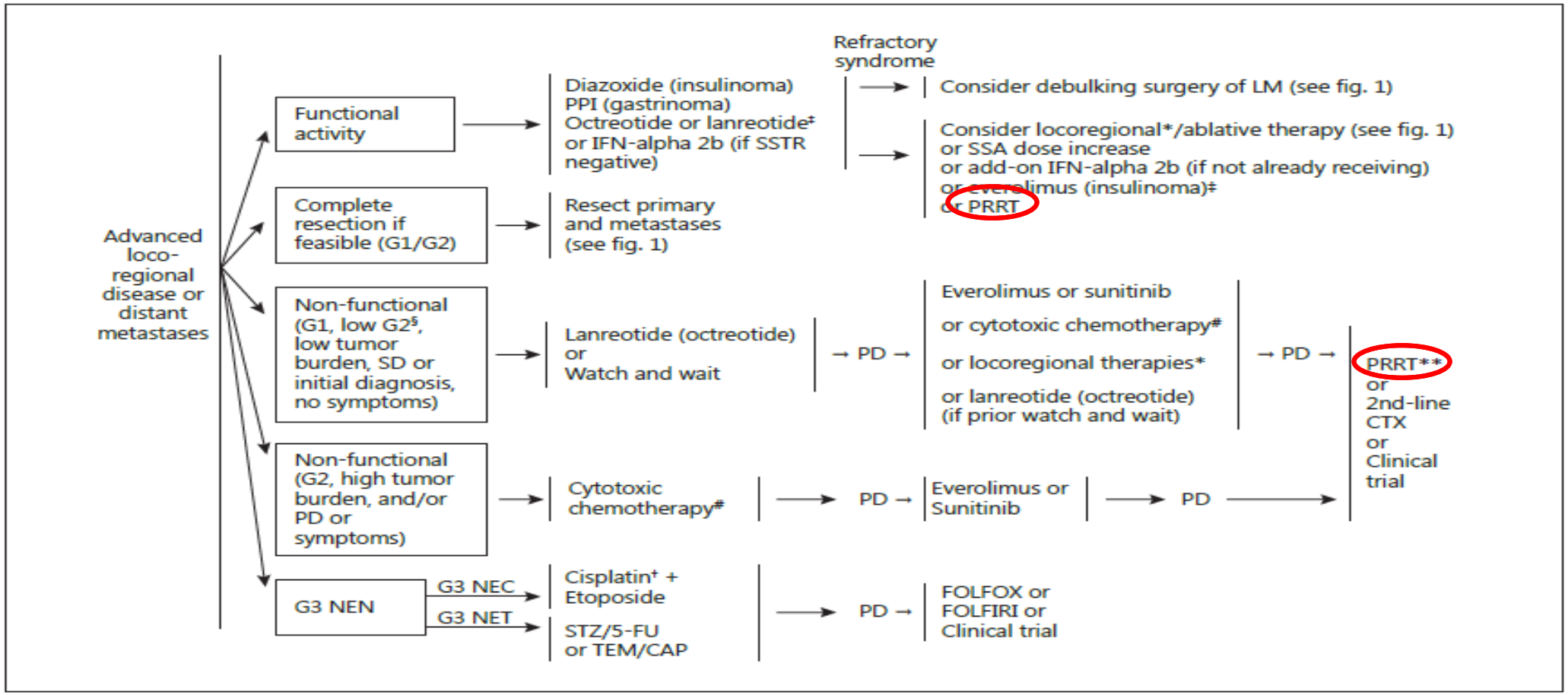


CS, carcinoid syndrome; G, grade; LM, liver mestasis; NEN, neuroendocrine neoplasm; NEC, neuroendocrine carcinoma; PD, disease progression; SD, stable disease; SSA, somatostatin analogue; SSTR, somatostatin receptor

Pavel M, et al. *Neuroendocrinology.* 2016;103(2):172-185.

ENETS Consensus Guidelines 2016: Pancreatic NEN

Therapeutic Algorithm for the Management of Pancreatic NEN With Advanced Locoregional Disease and/or Distant Metastases



CXT, chemotherapy

Pavel M, et al. *Neuroendocrinology.* 2016;103(2):172-185.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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,

Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-135.

Conference Report

Neuroendocrinology

Neuroendocrinology 2017;105:295–309
DOI: 10.1159/000475526

Received: December 12, 2016
Accepted after revision: April 6, 2017
Published online: April 13, 2017

ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Neoplasms: Peptide Receptor Radionuclide Therapy with Radiolabelled Somatostatin Analogues

Rodney J. Hicks[a] Dik J. Kwekkeboom[b] Eric Krenning[c] Lisa Bodei[d]
Simona Grozinsky-Glasberg[e] Rudolf Arnold[f] Ivan Borbath[g] Jaroslaw Cwikla[h]
Christos Toumpanakis[i] Greg Kaltsas[j] Philippa Davies[i] Dieter Hörsch[k] Eva Tiensuu Janson[l]
John Ramage[m] all other Antibes Consensus Conference participants

"Current guidelines place it as an option after other tratments have failed…However, in the future, in certain situations, PRRT may well be considered earlier in the treatment pathway"

Hicks RJ, et al. *Neuroendocrinology.* 2017;105(3):295-309.

The NETTER Study: Trial Design

229 Patients With Midgut NETs

^{177}Lu-DOTATATE group, 116 patients

^{177}Lu-DOTATATE

7.4 GBq every **8** weeks

+

Octreotide LAR

30 mg every 4 weeks

Control group, 113 patients

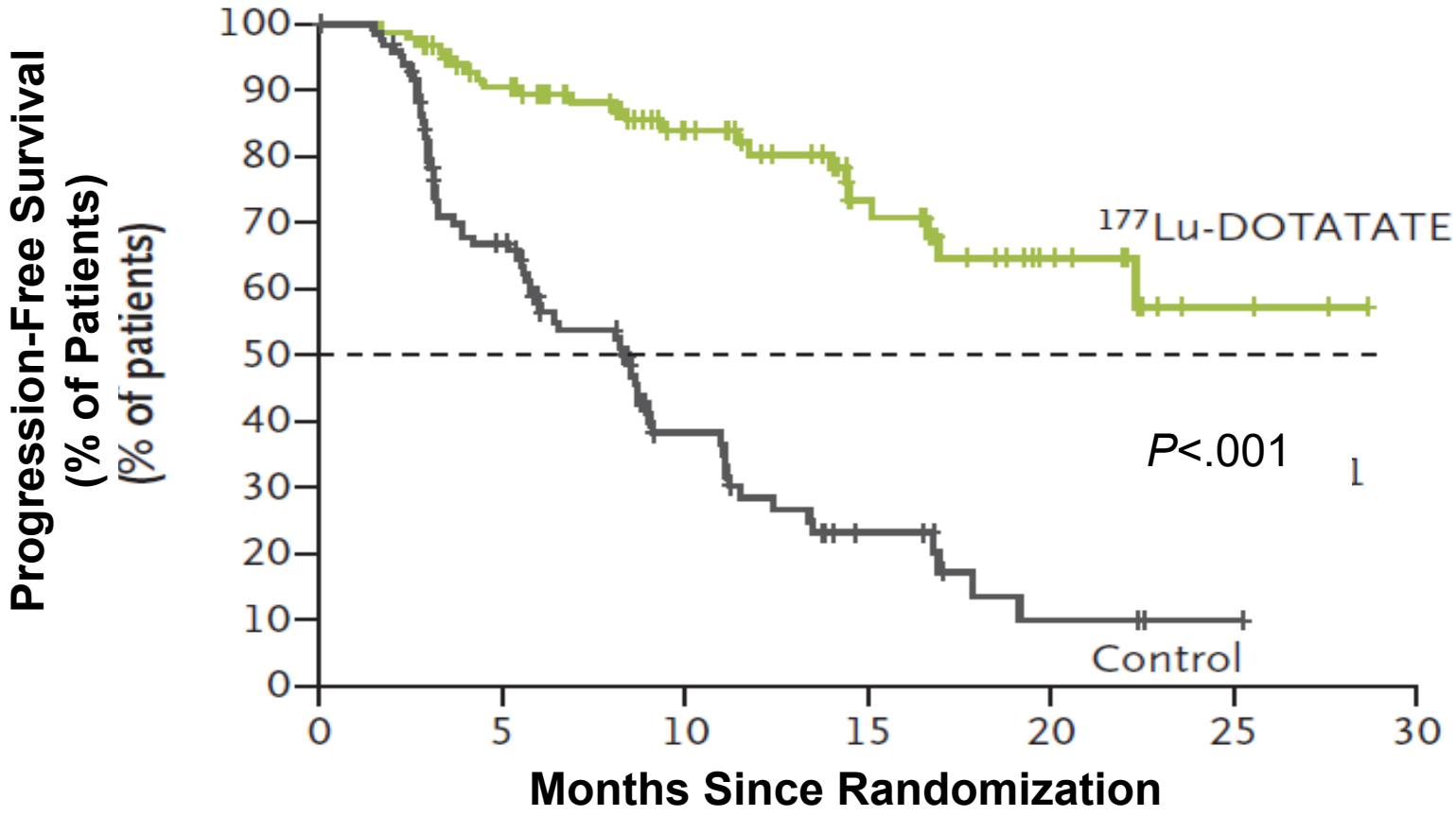
Octreotide LAR

60 mg every 4 weeks

Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-135.

The NETTER Study: Results

PFS

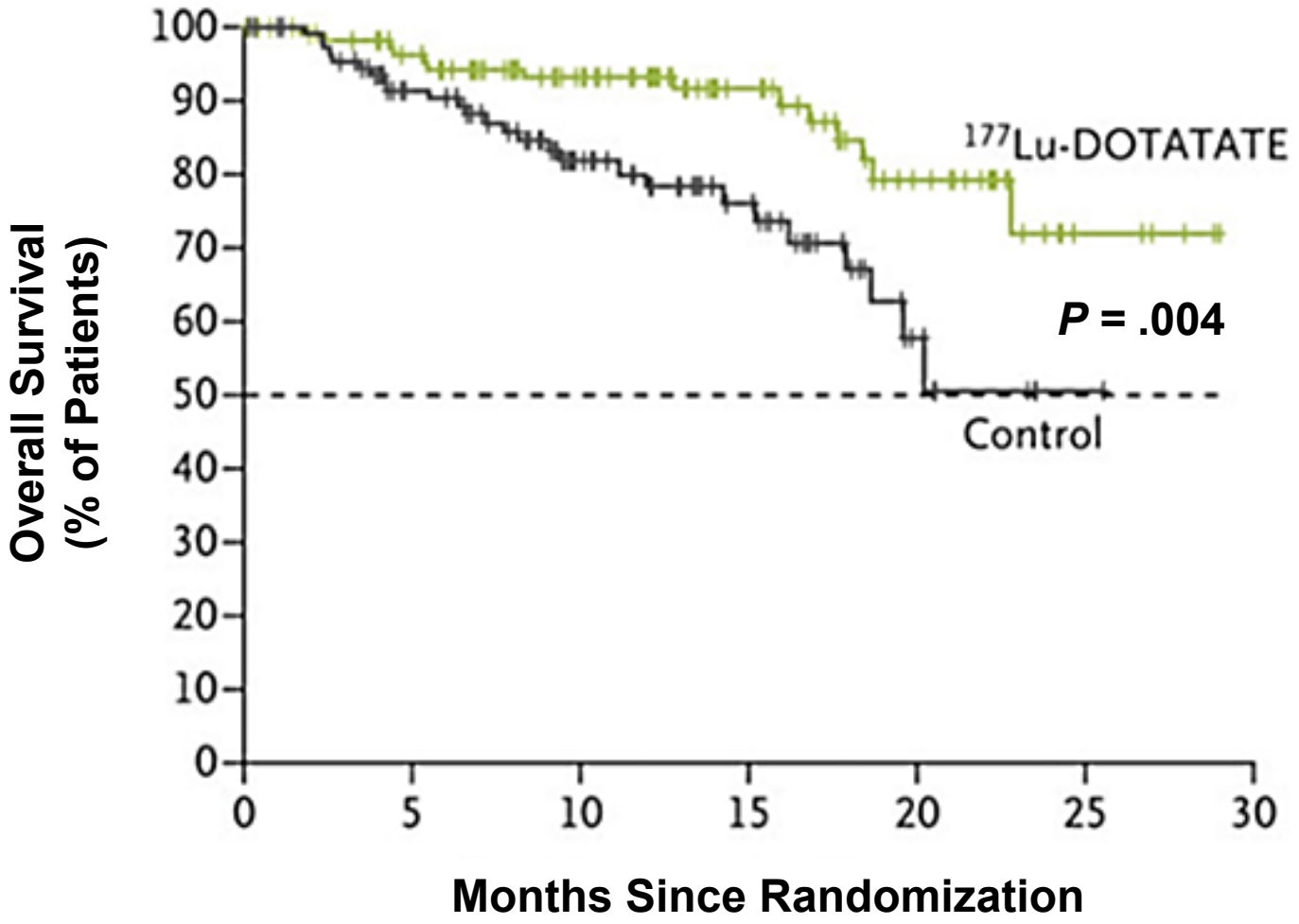


PFS, progression-free survival

Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-135.

The NETTER Study: Results

OS (Interim Analysis)



OS, overall survival

Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-135.

The NETTER Study: Health-Related Quality of Life

Time to QoL deterioration (TTD)

^{177}Lu-DOTATATE group

Global health status 28.8 months

Physical functioning status 25.2 months

Control group

Global health status 6.1 months

Physical functioning status 11.5 months

QoL, quality of life

Strosberg J, et al. *J Clin Oncol.* 2018;36(25):2578-2584.

The NETTER Study: Adverse Events

Safety Population (Cont'd)

Event	^{177}Lu-DOTATATE Group (N = 111)		Control Group (N = 110)		*P* Value
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade
Blood disorders					
Thrombocytopenia	28 (25)	2 (2)	1 (1)	0	<.001
Anemia	16 (14)	0	6 (5)	0	.04
Lymphopenia	20 (18)	10 (9)	2 (2)	0	<.001
Leukopenia	11 (10)	1 (1)	1 (1)	0	.005
Neutropenia	6 (5)	1 (1)	1 (1)	0	.12
Musculoskeletal disorders					
Musculoskeletal pain	32 (29)	2 (2)	22 (20)	1 (1)	.16
Nutrition disorders					
Decreased appetite	20 (18)	0	9 (8)	3 (3)	.04
Nervous system disorders					
Headache	18 (16)	0	5 (5)	0	.007
Dizziness	12 (11)	0	6 (5)	0	.22

Strosberg J, et al. *N Engl J Med.* 2017;376(2):125-135.

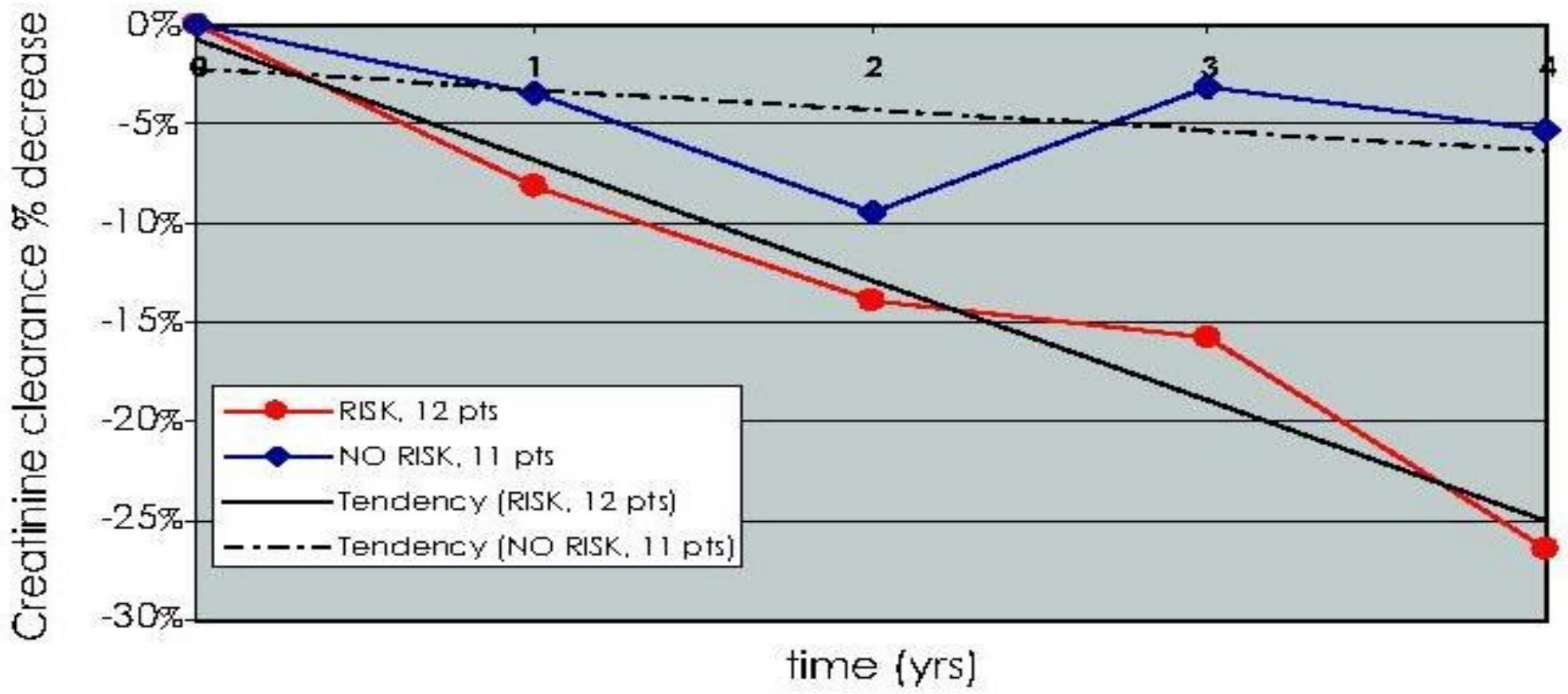
Risk Factors for Bone Marrow and Kidney Toxicity

Risk Factors for Bone Marrow and Kidney Toxicity

- Diabetes
- Hypertension
- Previous chemotherapy
- Previous PRRT

Bodei L…Paganelli G. *Eur J Nucl Med Mol Imaging.* 2008;35(10):1847-1856.

Different median creatinine clearance course in risk (red line, tendency continuous line) and no risk (blue line, tendency dotted line) patients treated with 90Y-DOTATOC over 4 years of follow-up (R2=0.9598)



Bodei L., Cremonesi M, G. Paganelli et al. "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". Eur J Nucl Med Mol Imaging 2008

GEP NETs: SSTR2 Positive

Risk factors for kidney and bone marrow toxicity

No Risk factors

Risk Factors

^{177}Lu 750 mCi in 5 cycles

^{177}Lu 500 mCi in 5 cycles

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori
Istituto di Ricovero e Cura a Carattere Scientifico

ISTITUTO SCIENTIFICO ROMAGNOLO PER LO STUDIO E LA CURA DEI TUMORI

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-014-2735-5

ORIGINAL ARTICLE

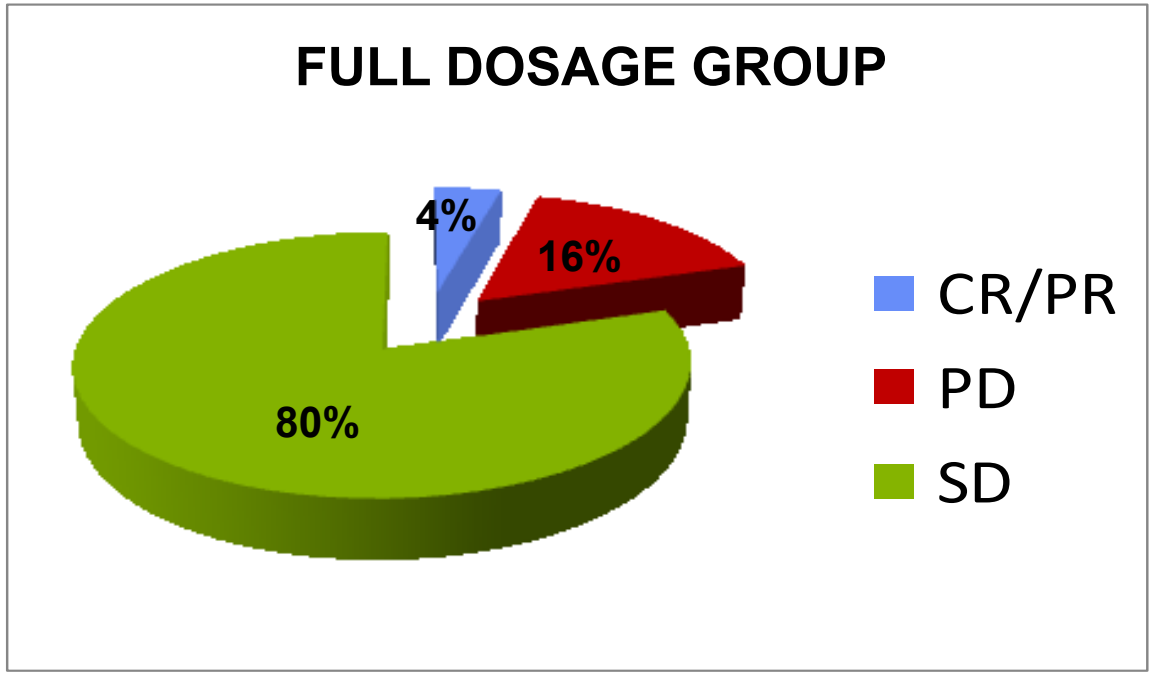
177 Lu-Dota-octreotate radionuclide therapy of advanced gastrointestinal neuroendocrine tumors: results from a phase II study

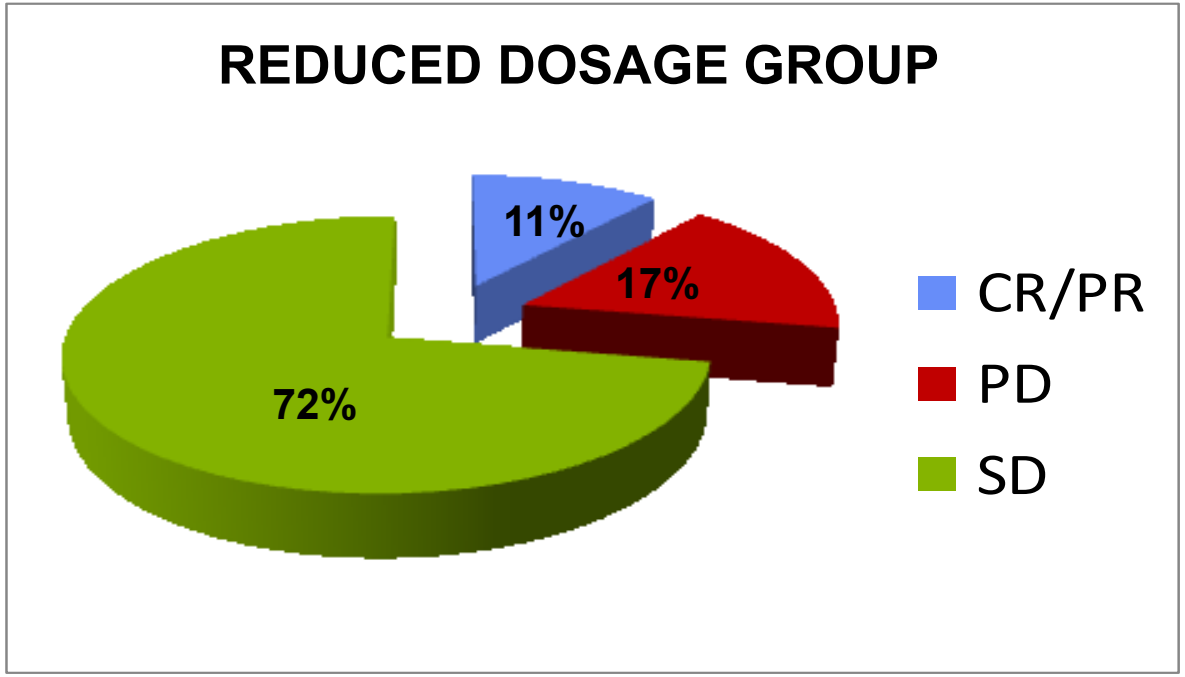
Giovanni Paganelli · Maddalena Sansovini · Alice Ambrosetti · Stefano Severi · Manuela Monti · Emanuela Scarpi · Caterina Donati · Annarita Ianniello · Federica Matteucci · Dino Amadori

Similar population of NETTER-1 Trial

Paganelli G, et al. *Eur J Nuc Med Mol Imaging.* 2014;41(10):1845-1851.

Results



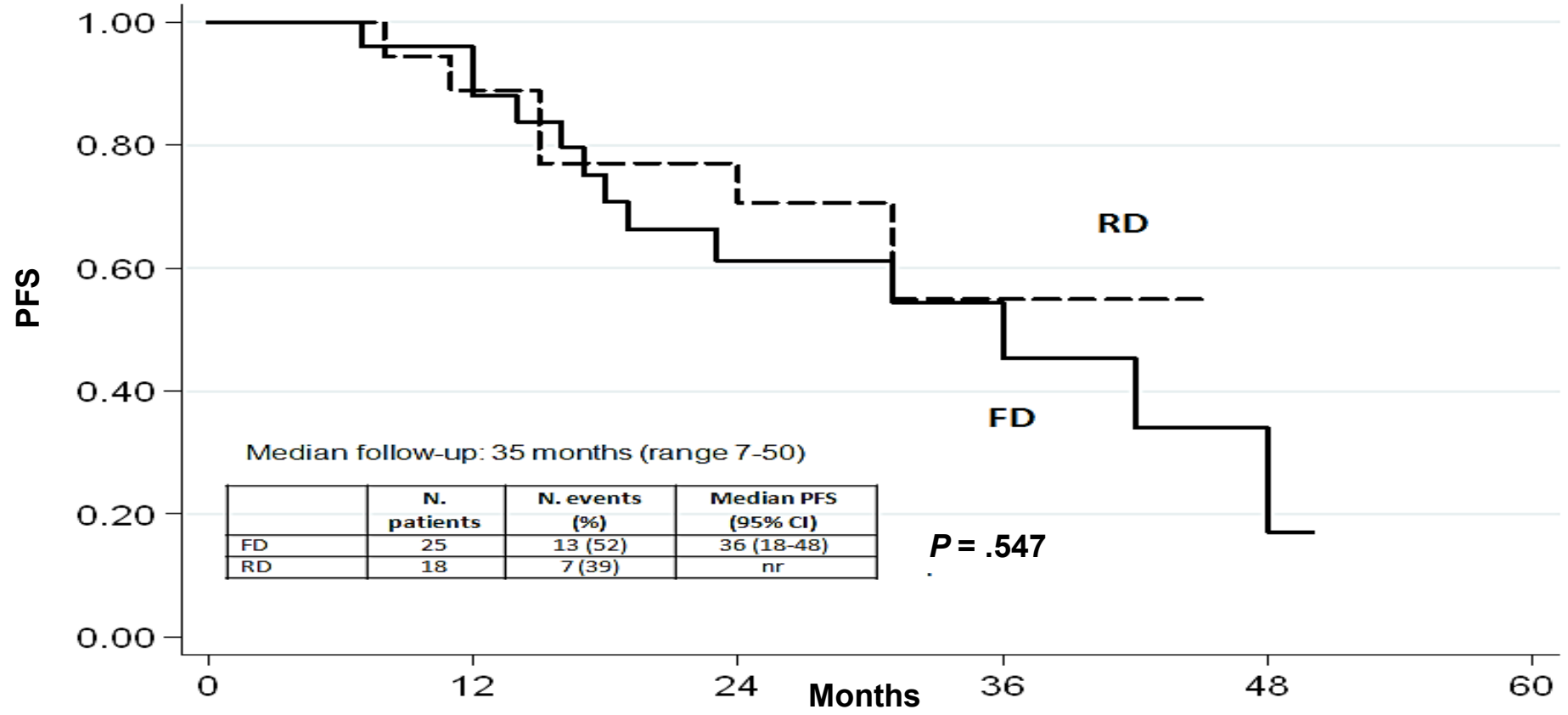


25 patients received 25.5 GBq

18 patients received 17.8 GBq

Paganelli G, et al. *Eur J Nuc Med Mol Imaging.* 2014;41(10):1845-1851.

Median PFS in Relation to the FD/RD Group

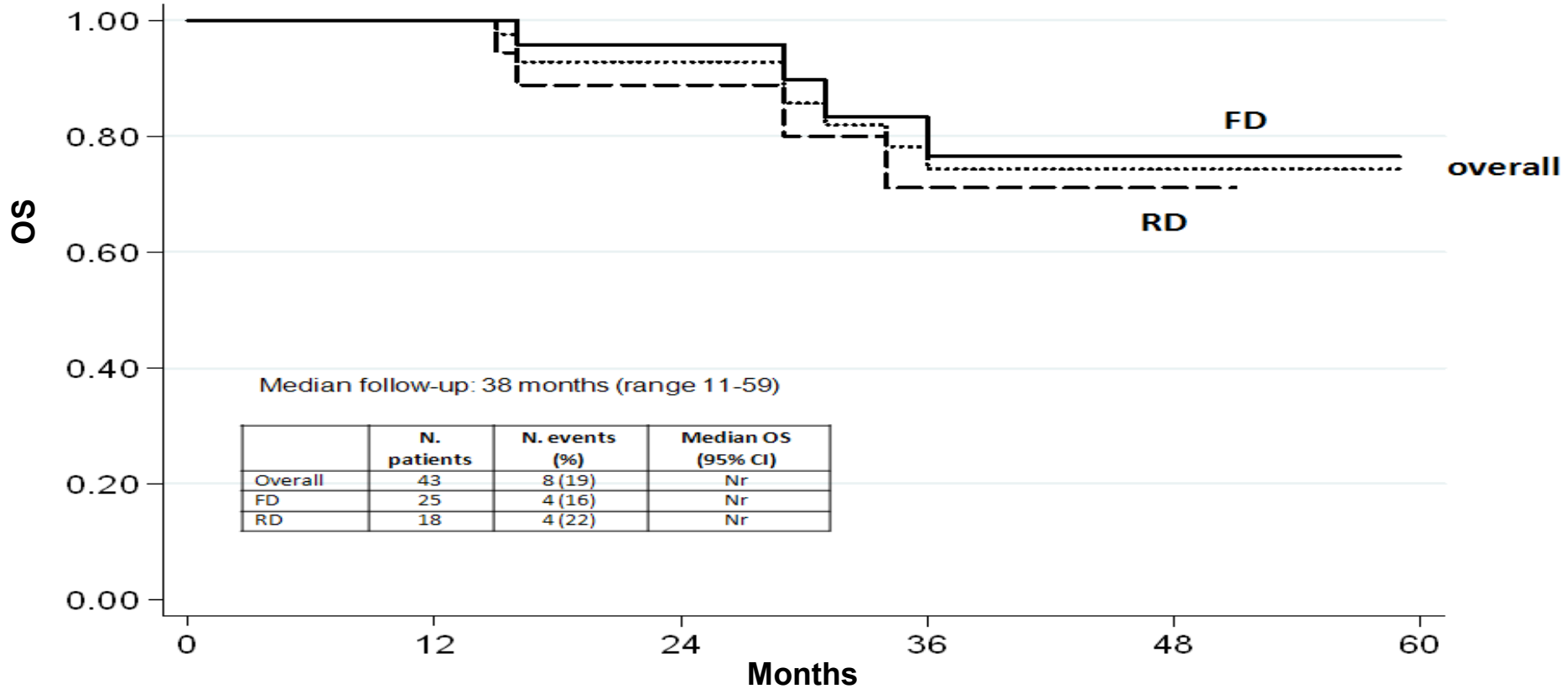


	N. patients	N. events (%)	Median PFS (95% CI)
FD	25	13 (52)	36 (18-48)
RD	18	7 (39)	nr

P = .547

Paganelli G, et al. *Eur J Nuc Med Mol Imaging.* 2014;41(10):1845-1851.

Median OS of the Entire Population and in Relation to the FD/RD Group



	N. patients	N. events (%)	Median OS (95% CI)
Overall	43	8 (19)	Nr
FD	25	4 (16)	Nr
RD	18	4 (22)	Nr

Paganelli G, et al. *Eur J Nuc Med Mol Imaging.* 2014;41(10):1845-1851.

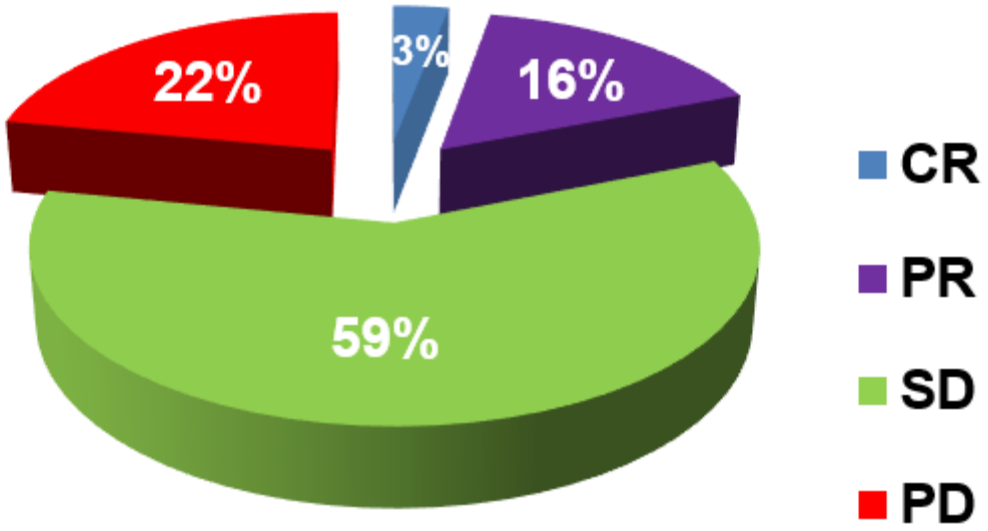
Results: pNET G1-G2

Patients With Disease Progression	60
No risk factors	28
With risk factors	32

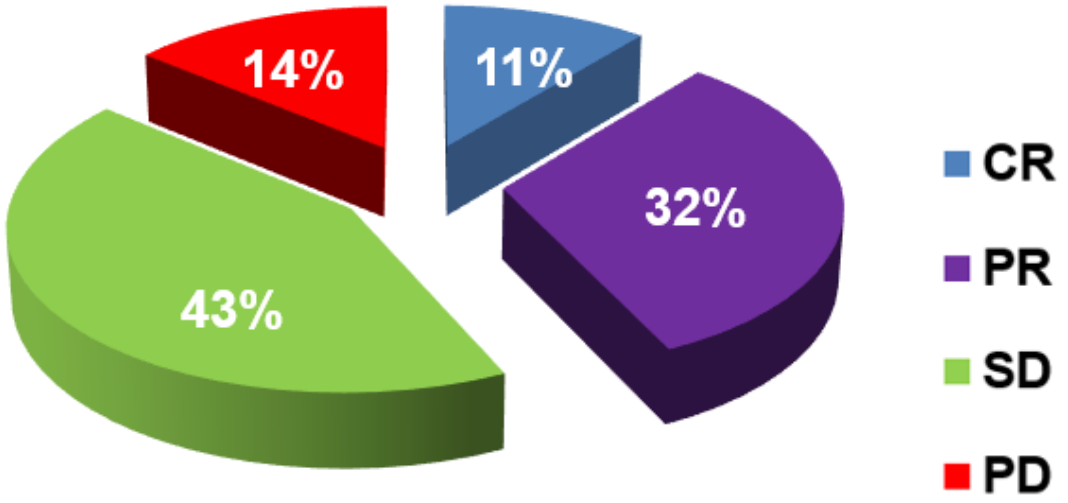
Sansovini M, et al. *Eur J Nucl Med Mol Imaging*. 2017;44(3):490-499.

Results: pNET G1-G2

REDUCED DOSAGE GROUP



FULL DOSAGE GROUP



CR, complete response; PR, partial response

Sansovini M, et al. ***Eur J Nucl Med Mol Imaging.*** **2017;44(3):490-499.**

Results: pNET G1-G2

REDUCED DOSAGE GROUP

32 patients had 18.5 GBq (range 11.1-21.4)

DCR 78.1%

Median PFS 21.7 months (range 18.1-48.2)

Median OS 63.8 months (range 28-NR)

FULL DOSAGE GROUP

28 patients had 25.9 GBq (range 22.2-29.2)

DCR 85.7%

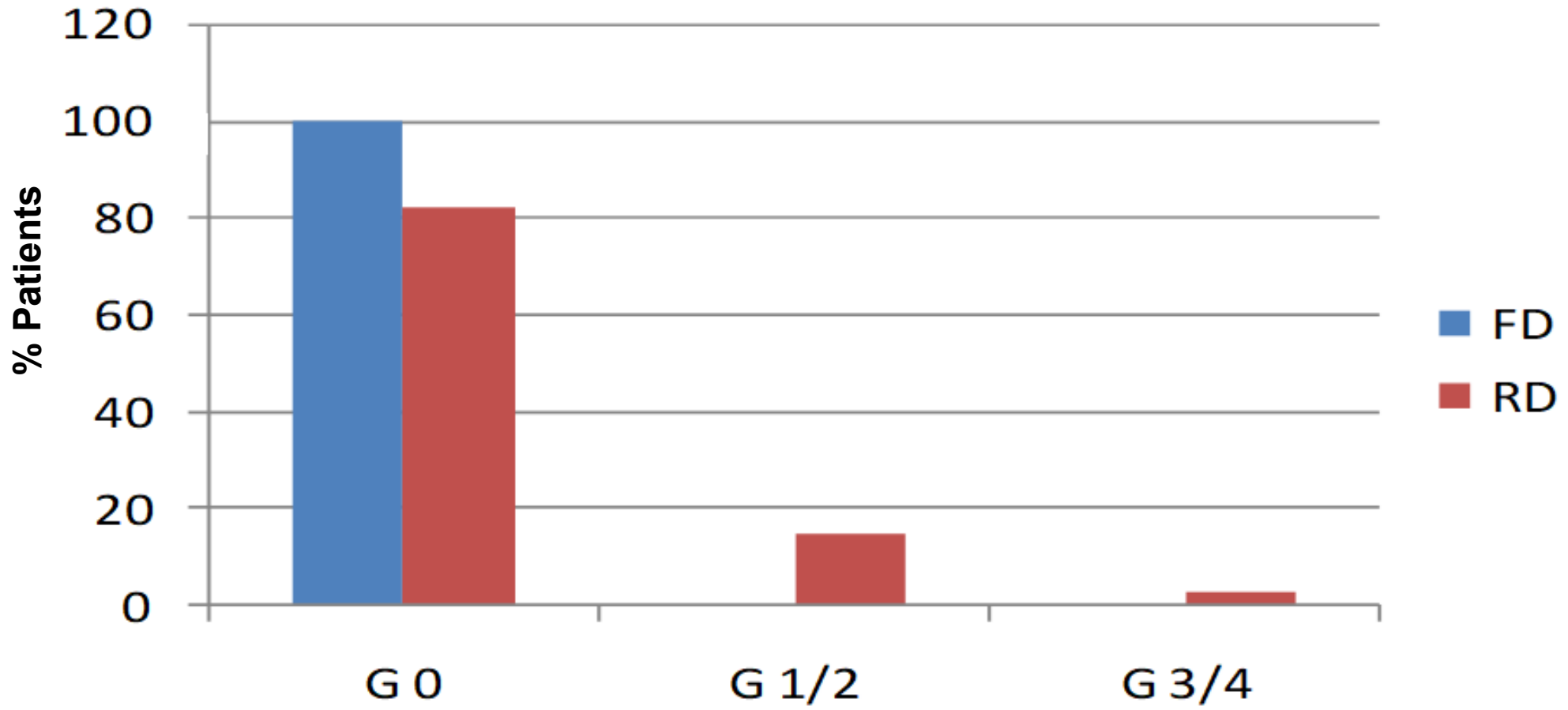
Median PFS 53.4 months (range 20.1-68.7)

Median OS not reached

DCR, disease-control rate; NR, not reached

Sansovini M, et al. *Eur J Nucl Med Mol Imaging*. 2017;44(3):490-499.

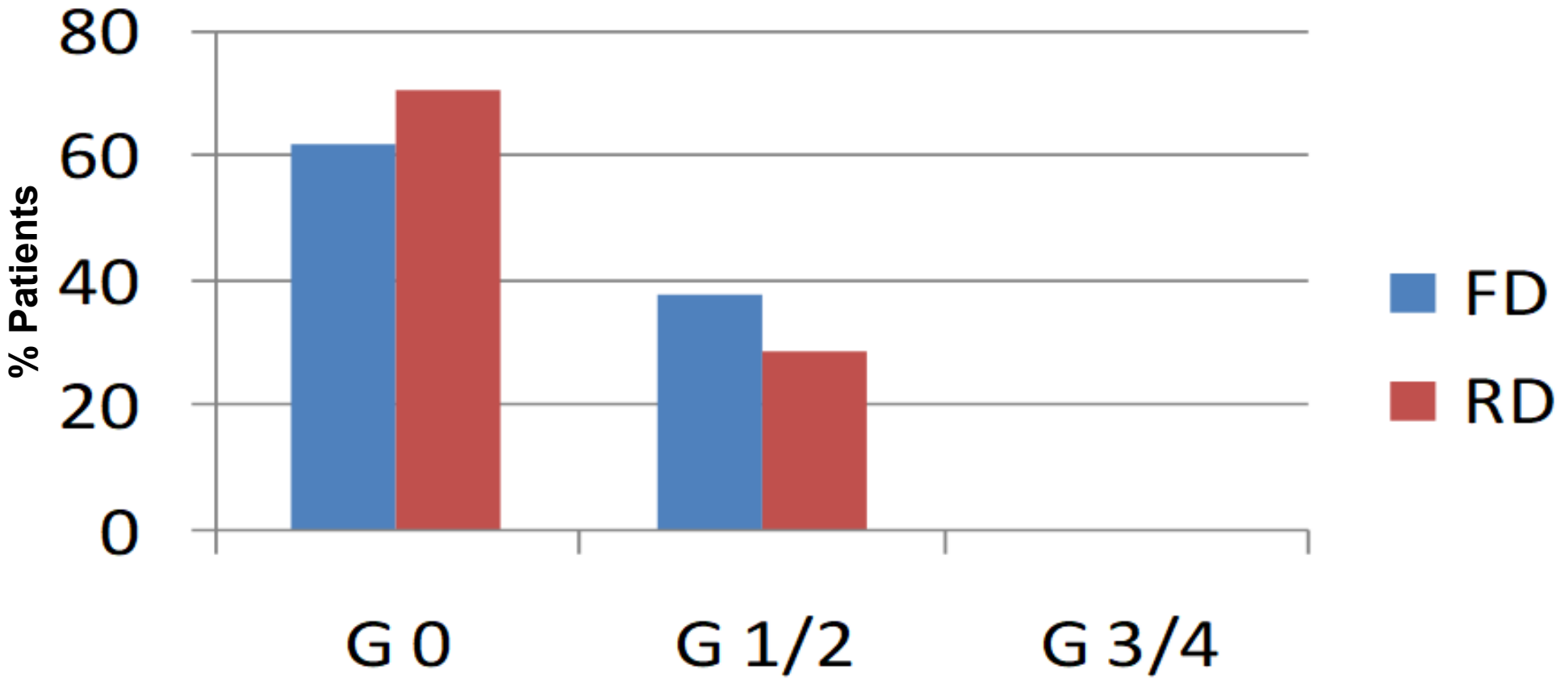
Renal Toxicity



FD, full dose; RD, reduced dose

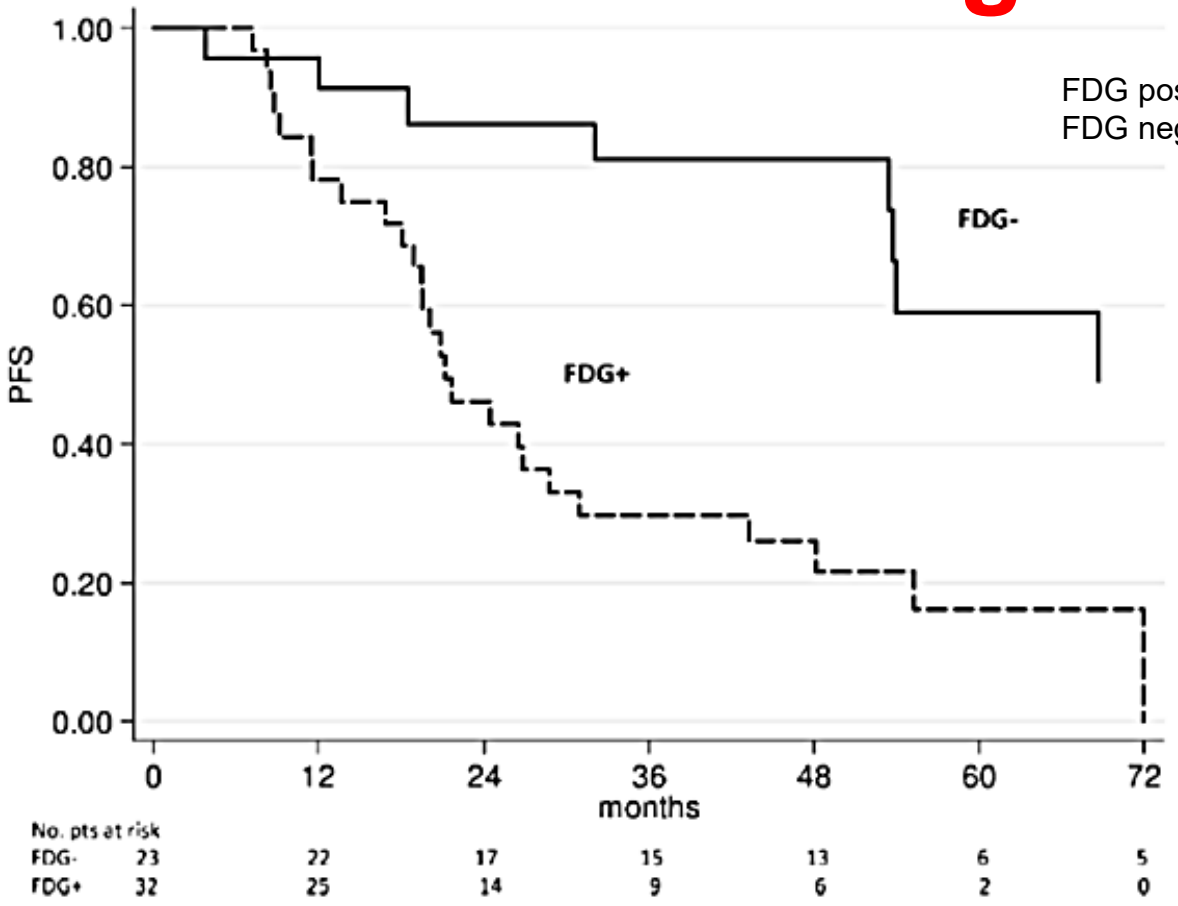
Sansovini M, et al. *Eur J Nucl Med Mol Imaging*. 2017;44(3):490-499.

Bone Marrow Toxicity



Sansovini M, et al. *Eur J Nucl Med Mol Imaging*. 2017;44(3):490-499.

PFS According to FDG PET



FDG positive: **Median PFS 21.2** months (95% CI 18.1-28.7)
FDG negative: **Median PFS 68.7** months (95% CI 53.4-not reached)
P<.0002

Sansovini M, et al. *Eur J Nucl Med Mol Imaging.* 2017;44(3):490-499.

Role of FDG-PET

FDG-PET With a Prognostic Purpose in NETs

Predictive Value of ^{18}F-FDG PET and Somatostatin Receptor Scintigraphy in Patients with Metastatic Endocrine Tumors

Etienne Garin[1,2], Florence Le Jeune[1], Anne Devillers[1], Marc Cuggia[3], Anne-Sophie de Lajarte-Thirouard[4], Catherine Bouriel[1], Eveline Boucher[5], and Jean-Luc Raoul[2,5]

JNM The Journal of Nuclear Medicine

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 50 • No. 6 • June 2009

Imaging, Diagnosis, Prognosis

^{18}F-Fluorodeoxyglucose Positron Emission Tomography Predicts Survival of Patients with Neuroendocrine Tumors

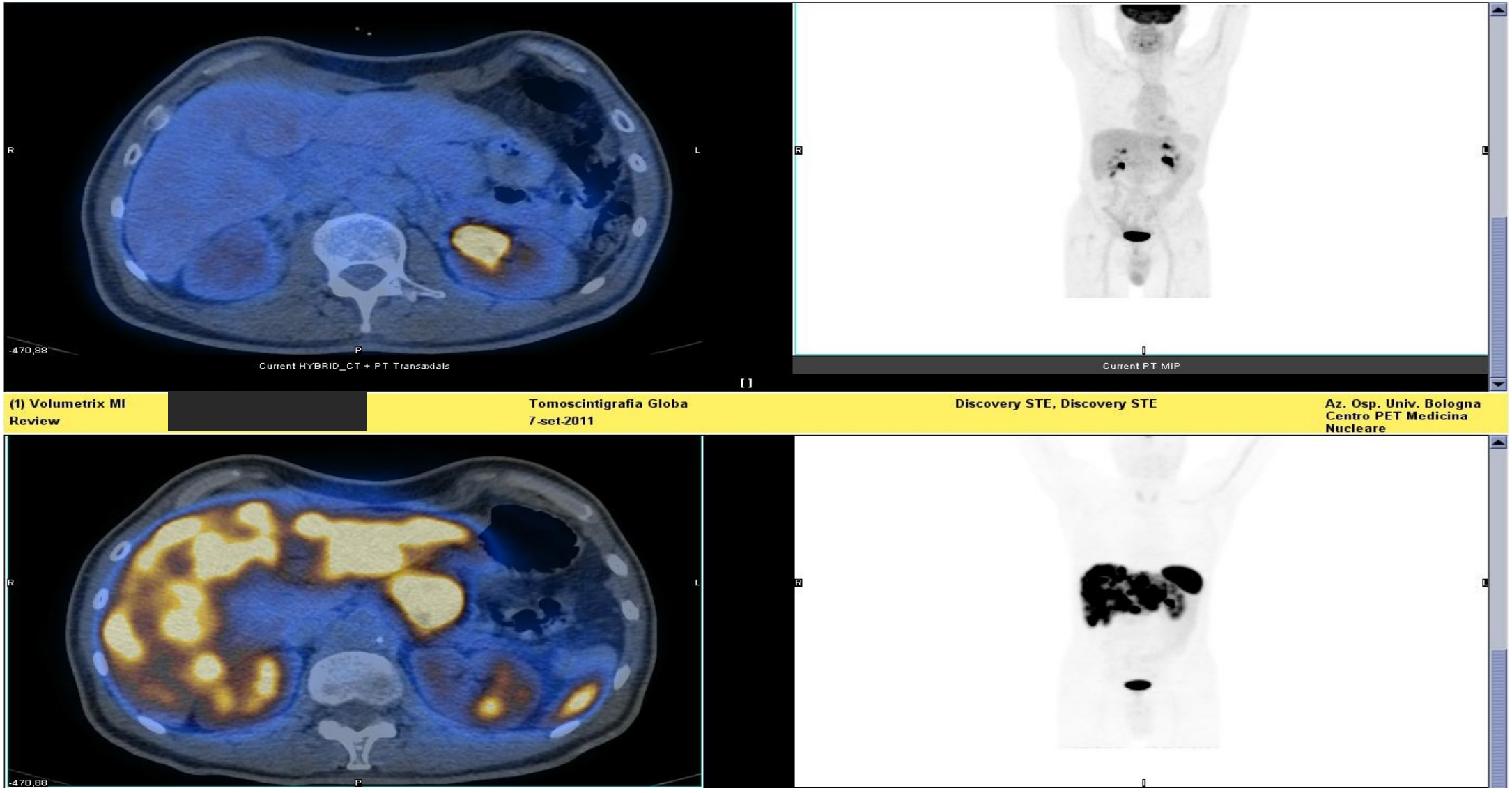
Tina Binderup[1,2], Ulrich Knigge[2,3], Annika Loft[1], Birgitte Federspiel[4], and Andreas Kjaer[1,2]

Clinical Cancer Research

Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

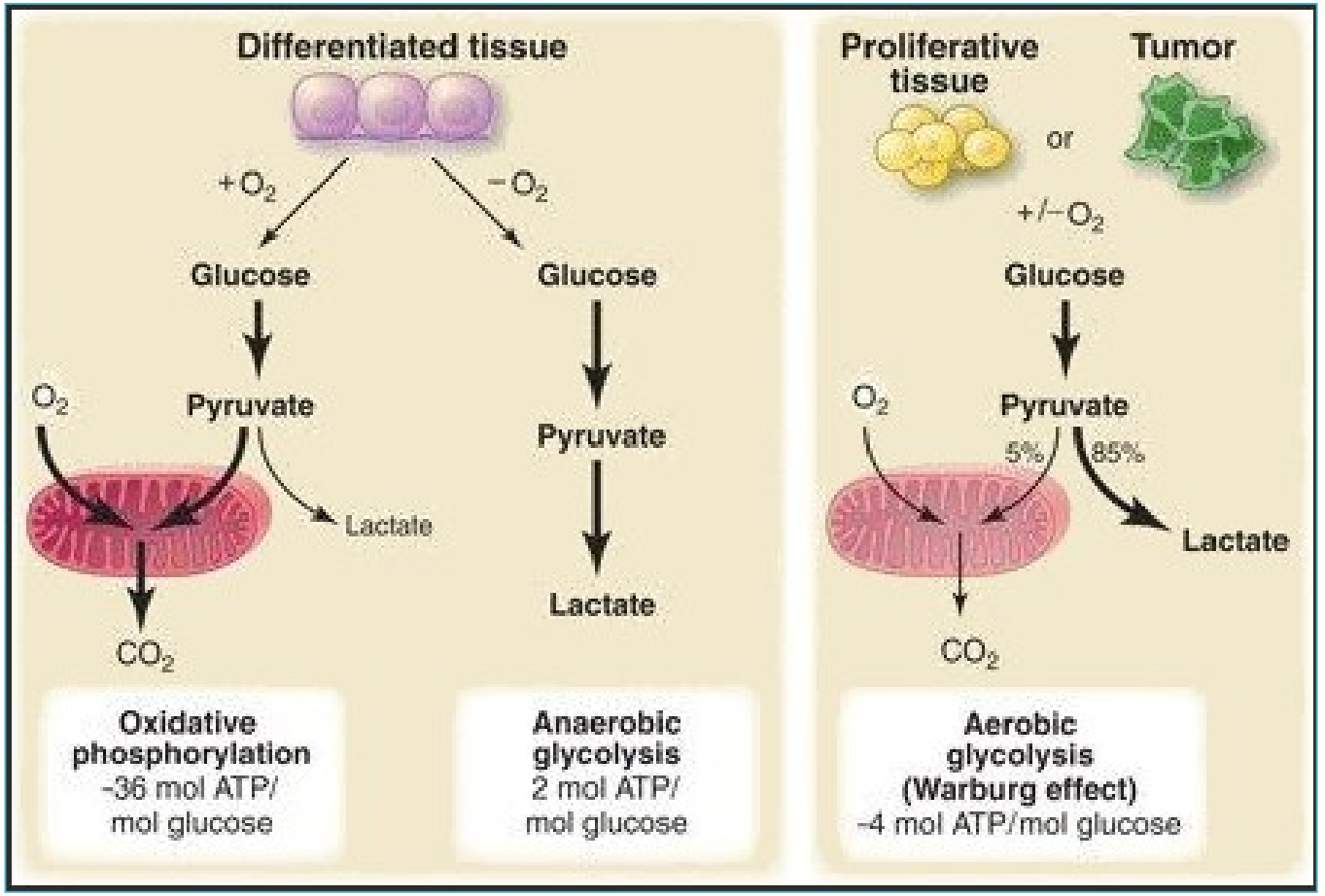
Garin E, et al. *J Nucl Med.* 2009;50(6):858-864.

FDG-PET–Negative and PET-CT ^{68}Ga–Positive scan



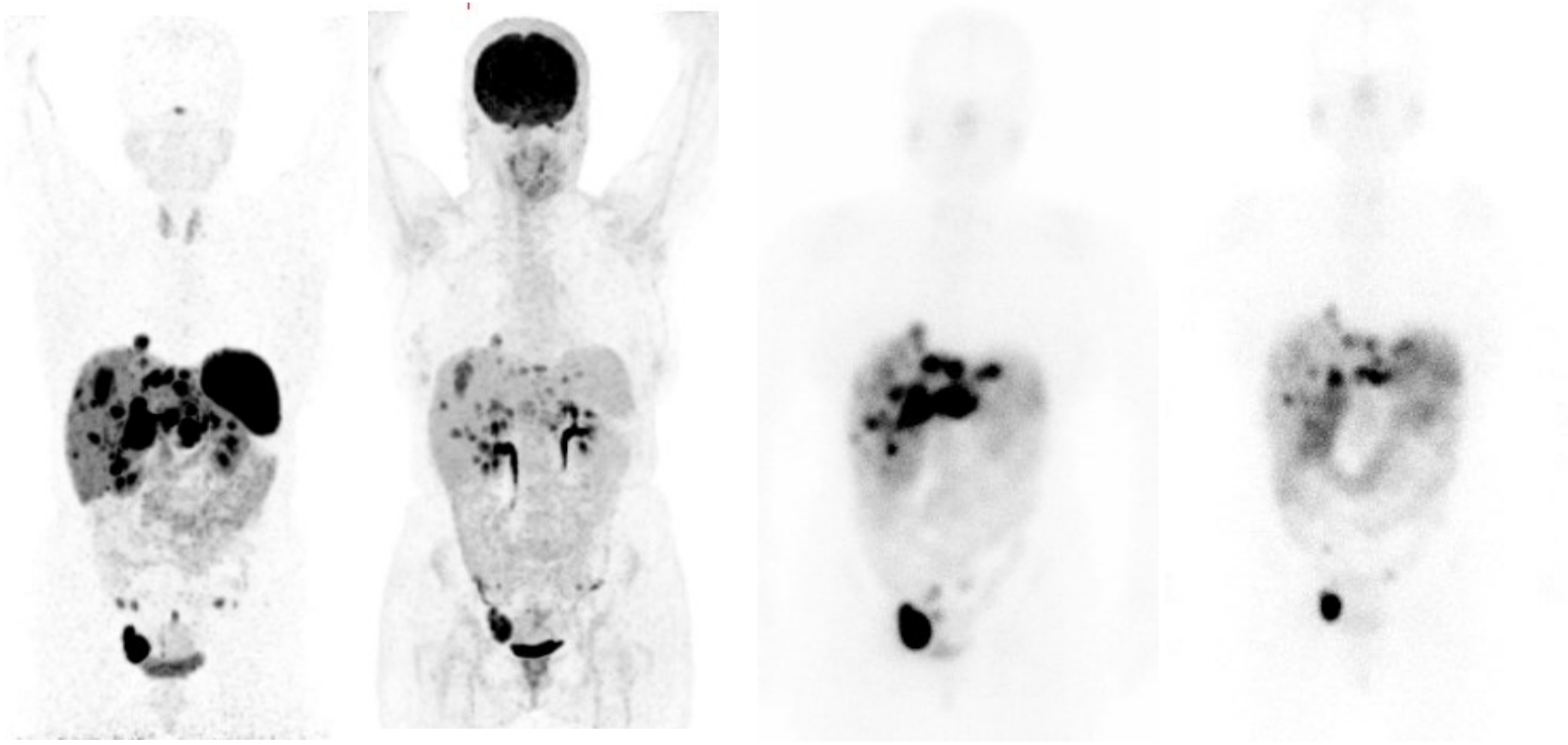
Images courtesy of Azienda-Ospedaliero-Universitaria di Bologna.

Warburg Effect



Vander Heiden MG, et al. *Science.* 2009;324(5930):1029-1033.

Midgut NET, Ki67<3% FDG PET +



Baseline ^{68}Ga PET

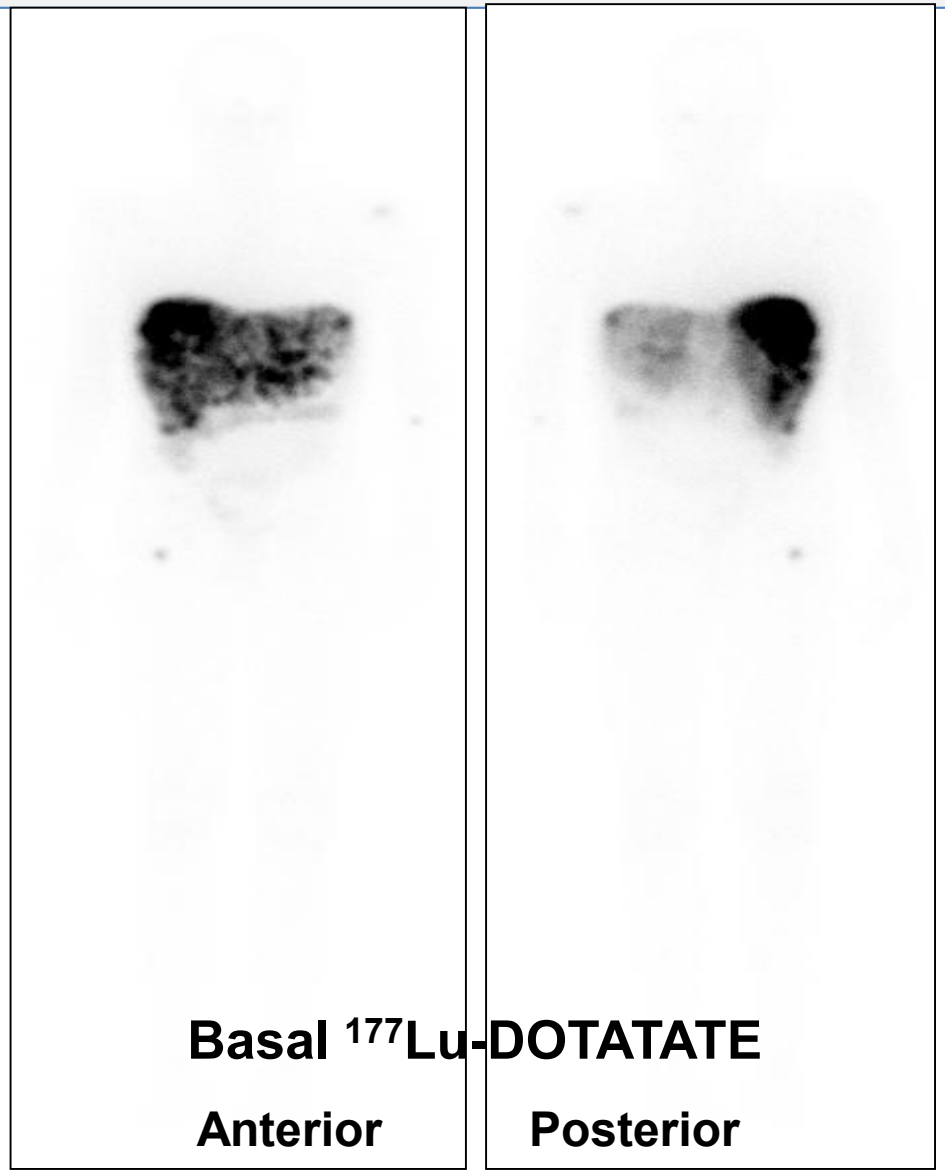
Baseline FDG PET

^{177}LU DOTATATE 1° WB

^{177}LU DOTATATE 4° WB

Images courtesy of Paganelli G.

Liver Metastases From Unknown NET (FDG-ve)

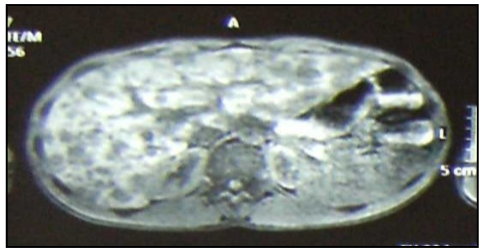


Basal ^{177}Lu-DOTATATE

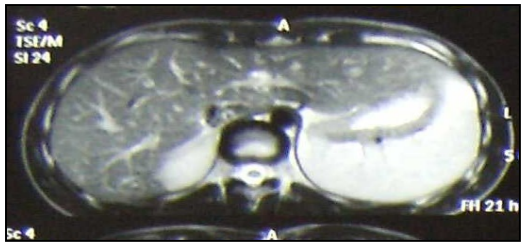
Anterior

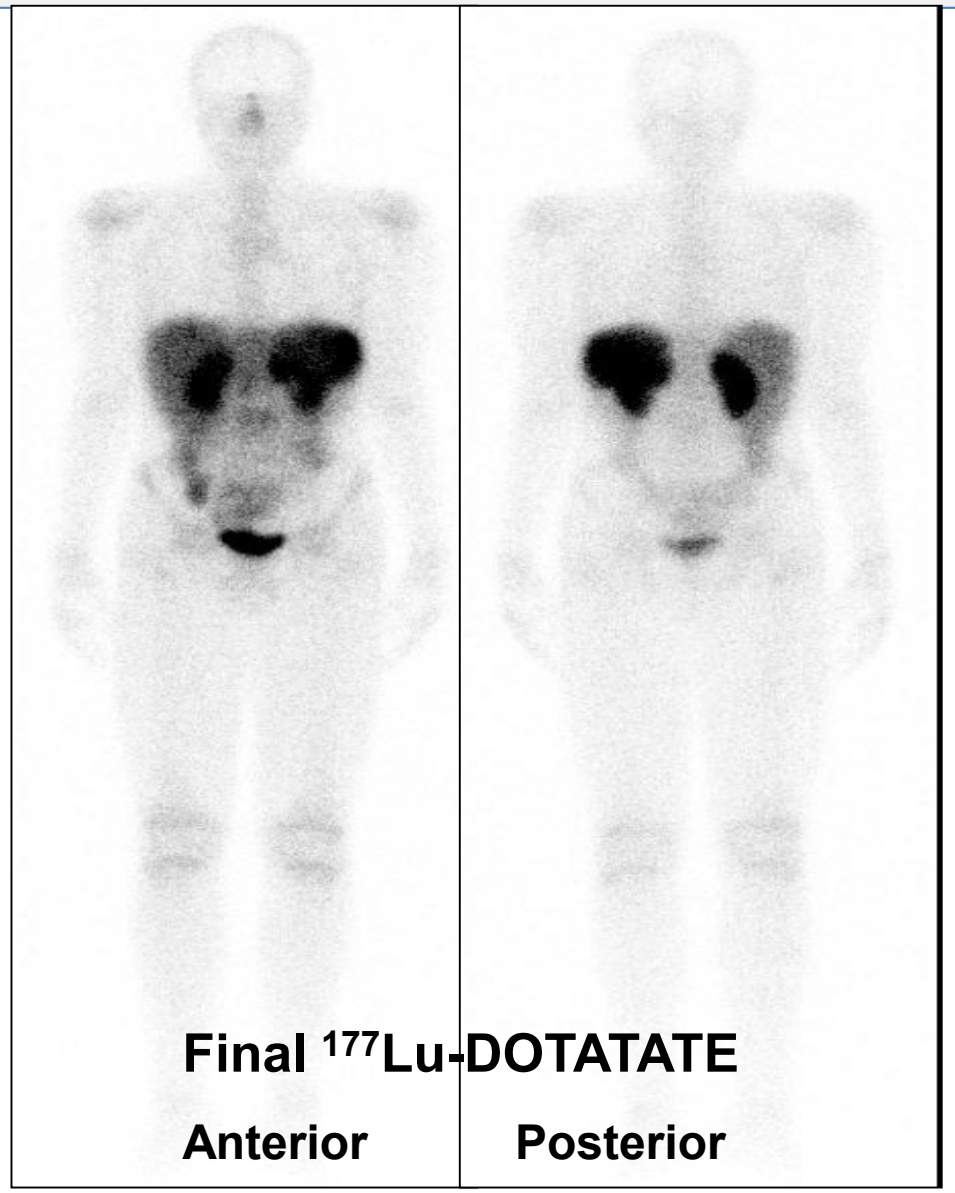
Posterior

Basal MRI



Final MRI





Final ^{177}Lu-DOTATATE

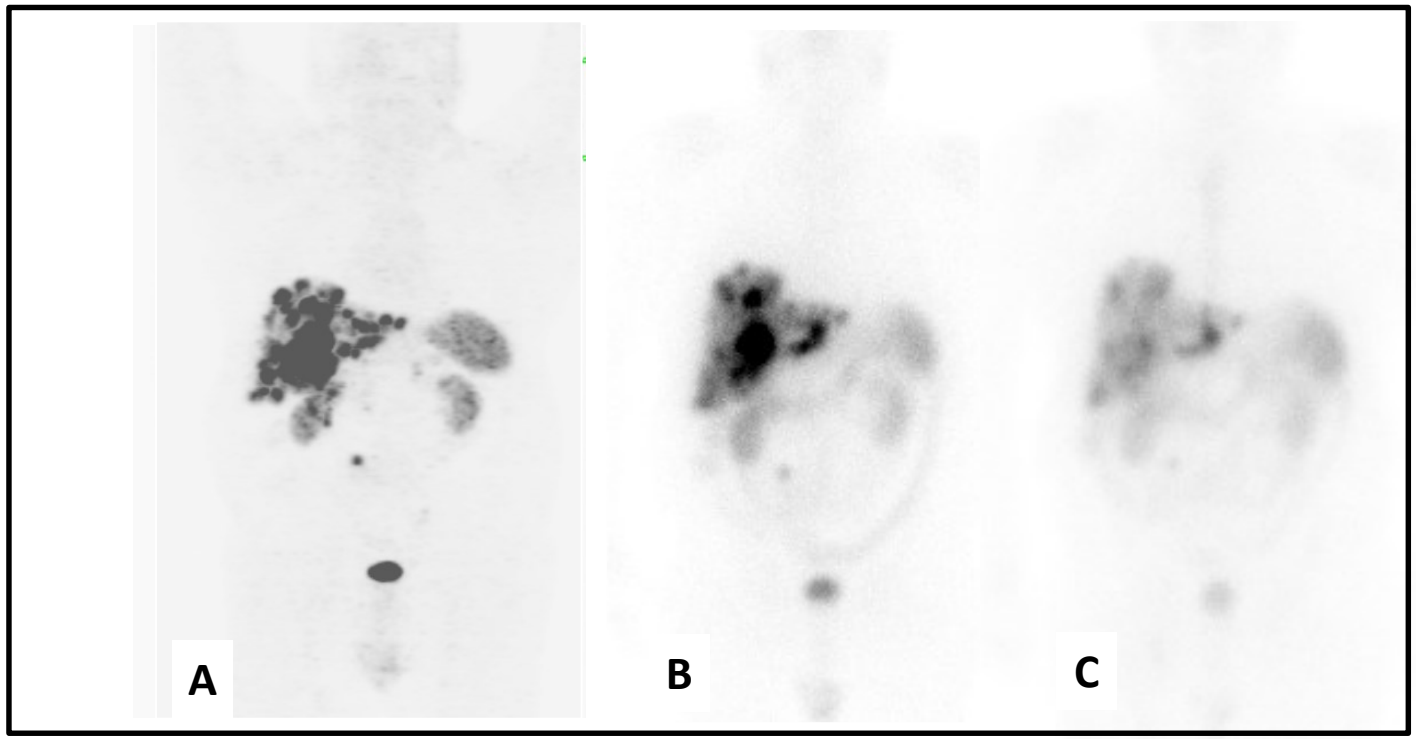
Anterior

Posterior

IEO S189/104

Images courtesy of Paganelli G.

Patient With GI NEN, Ki67 = 30%



A. Positive ^{68}Ga-PET (negative FDG) in liver and intestinal sites prePRRT
B. Whole-body scintigraphy after 1st cycle of Lu-PRRT
C. Whole-body scintigraphy after 4th cycle of Lu-PRRT

Cumulative activity administered: 22.2 GBq ^{177}Lu-DOTATATE

Nicolini S, et al. *Eur J Nucl Med Mol Imaging.* 2018;45(6):923-930.

FDG-PET With a Prognostic Purpose in NETs

Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-013-2369-z

Eur J Nucl Med Mol Imaging. 2013 Jun;40(6):881-8. doi: 10.1007/s00259-013-2369-z. Epub 2013 Feb 27.

ORIGINAL ARTICLE

Role of ^{18}FDG PET/CT in patients treated with ^{177}Lu-DOTATATE for advanced differentiated neuroendocrine tumours

Stefano Severi · Oriana Nanni · Lisa Bodei · Maddalena Sansovini · Annarita Ianniello · Stefania Nicoletti · Emanuela Scarpi · Federica Matteucci · Laura Gilardi · Giovanni Paganelli

Severi S, et al. *Eur J Nucl Med Mol Imaging.* 2013; 40(6):881-888.

Eur J Nucl Med Mol Imaging (2017) 44:490–499
DOI 10.1007/s00259-016-3533-z

CrossMark

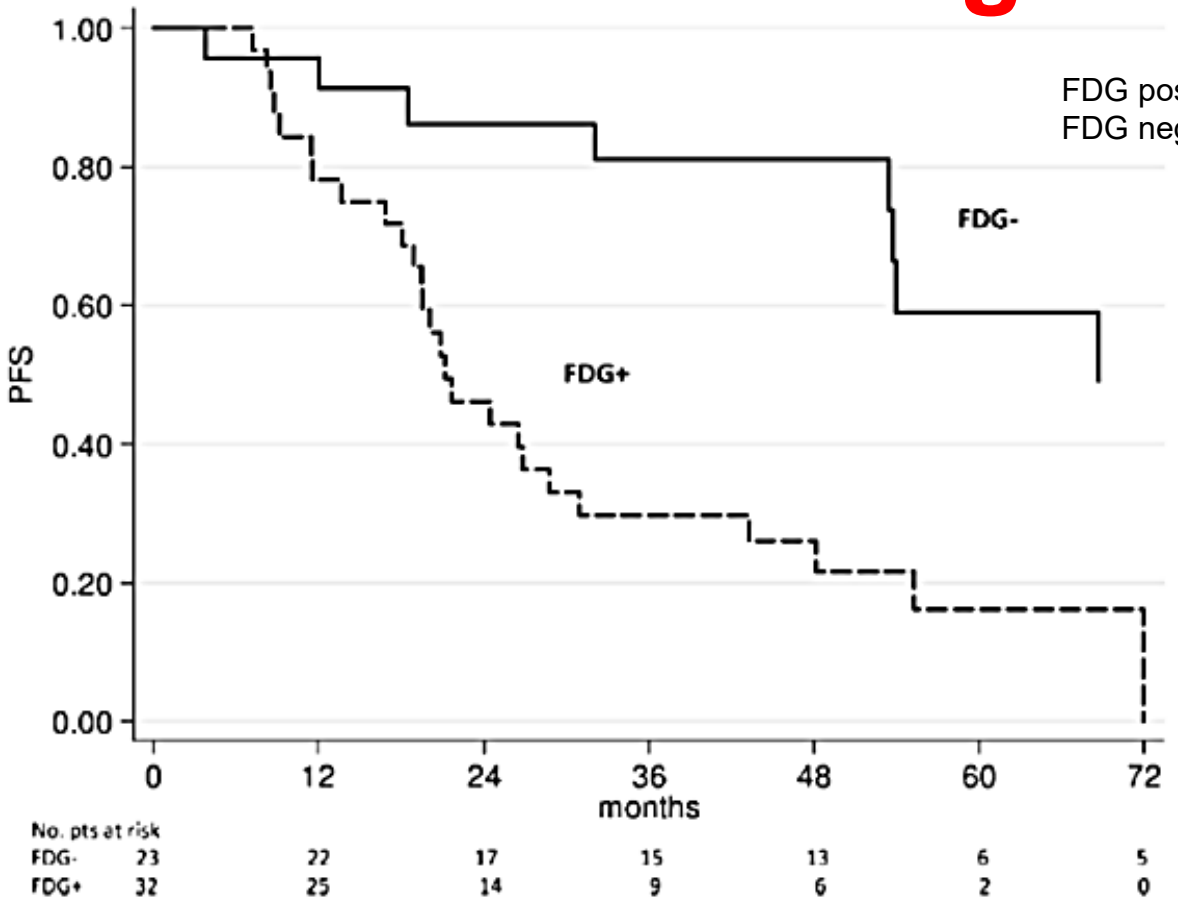
ORIGINAL ARTICLE

Long-term follow-up and role of FDG PET in advanced pancreatic neuroendocrine patients treated with ^{177}Lu-D OTATATE

Maddalena Sansovini[1] · Stefano Severi[1] · Annarita Ianniello[1] · Silvia Nicolini[1] · Lorenzo Fantini[1] · Emilio Mezzenga[2] · Fabio Ferroni[3] · Emanuela Scarpi[4] · Manuela Monti[4] · Alberto Bongiovanni[5] · Sara Cingarlini[6] · Chiara Maria Grana[7] · Lisa Bodei[7] · Giovanni Paganelli[1]

Sansovini M, et al. *Eur J Nucl Med Mol Imaging.* 2017;44(3):490-499.

PFS According to FDG PET



FDG positive: **Median PFS 21.2** months (95% CI 18.1-28.7)
FDG negative: **Median PFS 68.7** months (95% CI 53.4-not reached)
P<.0002

Sansovini M, et al. *Eur J Nucl Med Mol Imaging.* 2017;44(3):490-499.

Multivariate Analysis Related to PFS and Median OS

	PFS		mOS	
	HR (95% CI)	*P*	HR (95% CI)	*P*
FDG (positive vs negative)	5.15 (1.42-18.75)	.013	5.08 (0.85-30.42)	.075
Tumor burden (score 2 vs 1)	3.03 (0.92-9.99)	.188	4.12 (0.41-40.96)	.477
Tumor burden (score 3 vs 1)	2.55 (0.75-8.71)		3.98 (0.38-41.95)	
Hepatic lesions (grade 1 vs grade 0)	1.54 (0.30-7.80)	.871	1.76 (0.13-22.92)	.910
Hepatic lesions (grade 2 vs grade 0)	1.31 (0.31-5.49)		1.54 (0.15-15.99)	
Cumulative activity (RA vs FA)	0.85 (0.41-1.76)	.658	2.32 (0.75-7.16)	.144
After backward stepwise procedure				
FDG (positive vs negative)	4.27 (1.88-9.69)	.0005	4.89 (1.35-17.65)	.015
Cumulative activity (RA vs FA)	1.18 (0.60-2.34)	.627	3.17 (1.08-9.34)	.0361

FA, full activity; mOS, median overall survival; RA, reduced activity

Sansovini M, et al. *Eur J Nucl Med Mol Imaging.* 2017;44(3):490-499.

**"The presence of increased glycolytic activity of 18FDG tends to increase with tumor grade and has been shown to predict poor survival in NEN ...
It may be a more powerful prognostic marker than conventional measures including the percentage of cells staining for Ki-67... "**

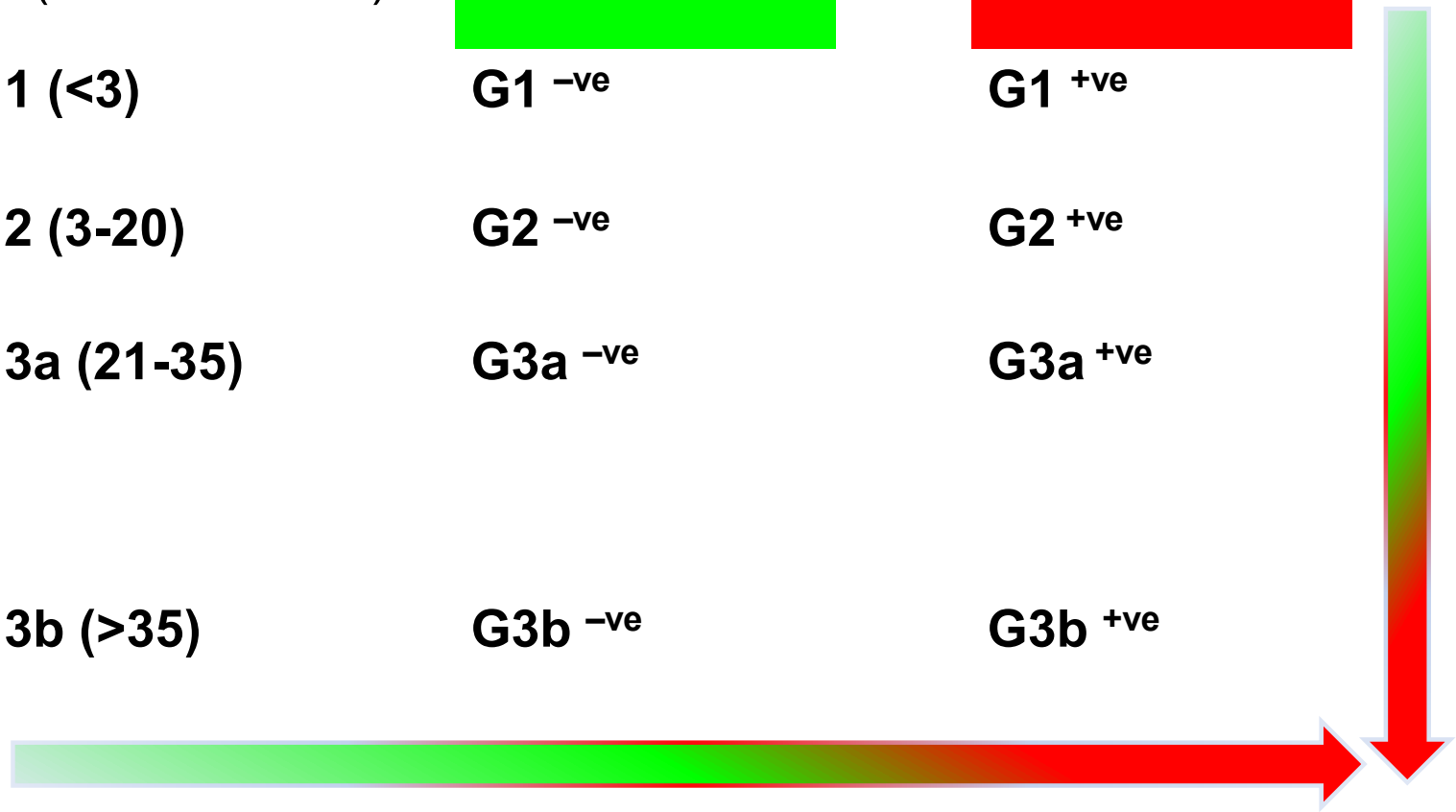
**"Studies combining PRRT with radiosensitizing chemotherapy …
Peptide Receptor Chemoradionuclide Therapy (PRCRT), have shown that is feasible with minimal incremental toxicity ...
The rationale ... in strongest for higher grade NEN"**

and FDG +ve (Paganelli)

Hicks RJ, et al. *Neuroendocrinology.* 2017;105(3):295-309.

GRADING PROPOSAL FOR NET

GRADE (KI 67 index %)	PET FDG NEGATIVE	PET FDG POSITIVE
1 (<3)	G1 –ve	G1 +ve
2 (3-20)	G2 –ve	G2 +ve
3a (21-35)	G3a –ve	G3a +ve
3b (>35)	G3b –ve	G3b +ve



Randomized Studies at IRST

- **The LU-P-PET randomized trial**

GEP NETs SSTR2-Positive G1-G2, G3 (<35%)

FDG PET

NEGATIVE: LU-NET

^{177}Lu 700 mCi vs ^{177}Lu 500 mCi

POSITIVE: LU-CAS

^{177}Lu 750 mCi + Cap vs
750 mCi ^{177}LuDotatate

Take Home Messages

- **Stop “one fits all” concept in PRRT!**
- **More intensive therapy protocols in FDG PET+ ve cases**
- **Randomized trials needed**


Thank You