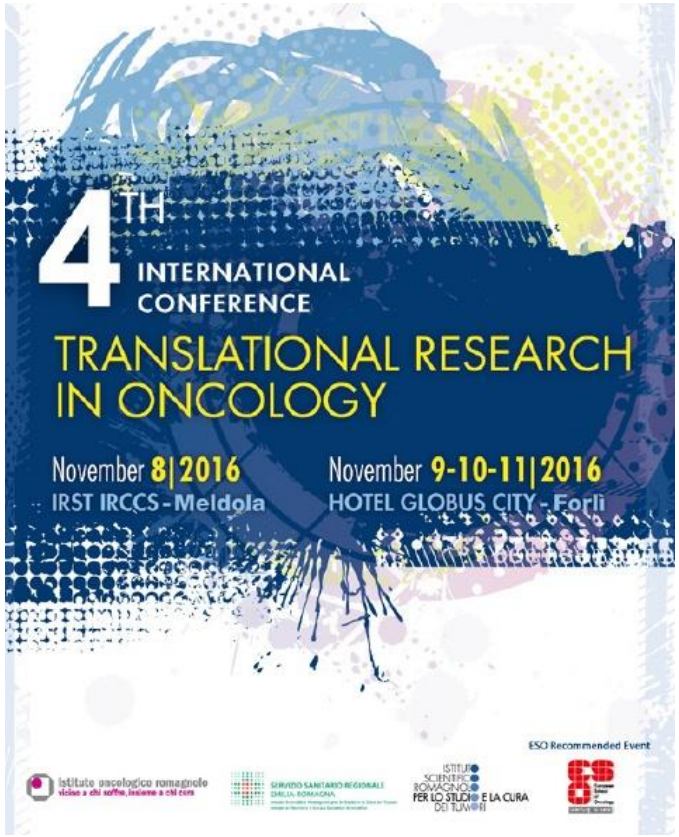
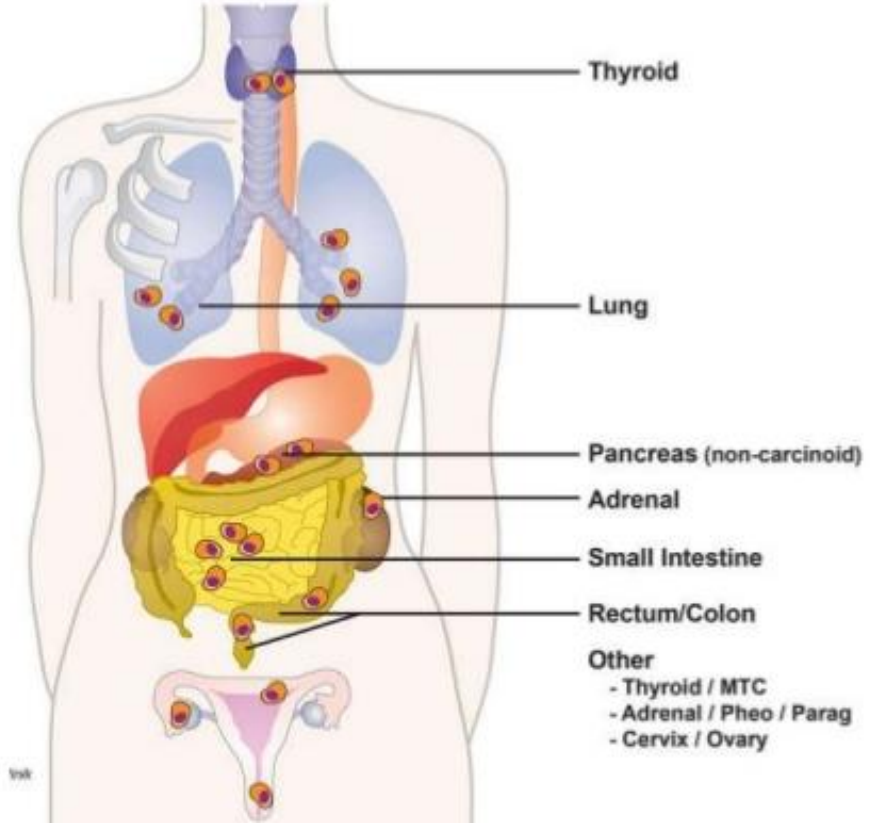


RADIONUCLIDE THERAPY AND ALLIED SCIENCE

President: Giovanni Paganelli
Chairman: Maria Salvato Baltimore USA
Domenico Barone Meldola Italy

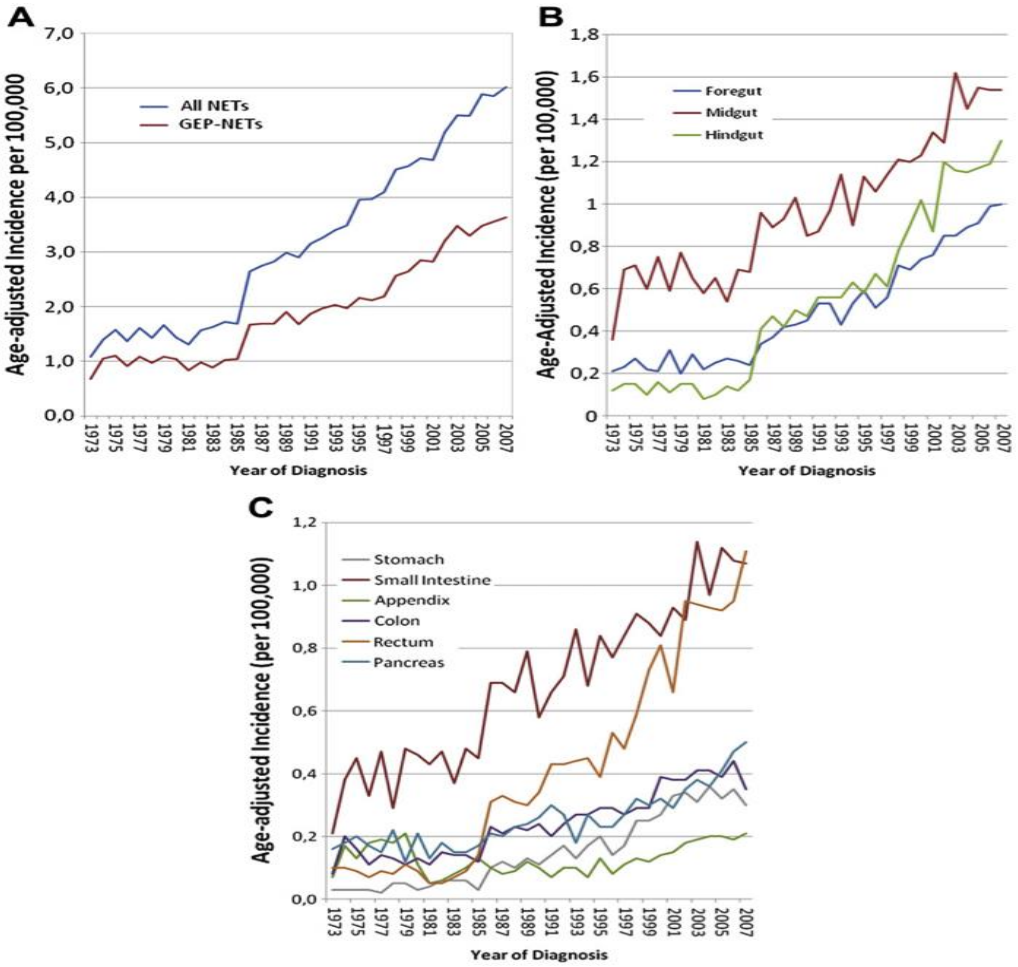
A New Proposal for Metabolic Classification of NENs

Stefano Severi **IRST Meldola Italy**



Neuroendocrine tumors are heterogeneous family of cancer with different prognosis according to histotypes and biological features

NETs: Incidence and Prognosis



GEP-NETs overall incidence has raised from 10 (1973-1977) to 36,5/million (2003 to 2007) in US.

In the most recent SEER registry analyses (SEER 17 up to 2007), 61.0% of all NETs were GEP-NETs, with highest frequencies in the rectum (17.7% of NETs), small intestine (17.3% of NETs) and colon (10.1% of NETs).

Pancreatic, gastric, and appendiceal sites accounted for 7.0%, 6.0%, and 3.1% of NETs, respectively.
Lawrence B et al. 2011

NETs incidence has increased between 1973 and 2007. The most substantial change in incidence over time occurred in small intestinal and rectal NETs, and these are now the most common GEP-NETs. Figure taken from Lawrence B. et al. Endocrinol Metab Clin N Am, 2011

Classification

The 2010 WHO classification is based on tumor volume, localization, cell proliferation index, local or vascular invasivity, presence of metastases and biological active hormone production

NENs

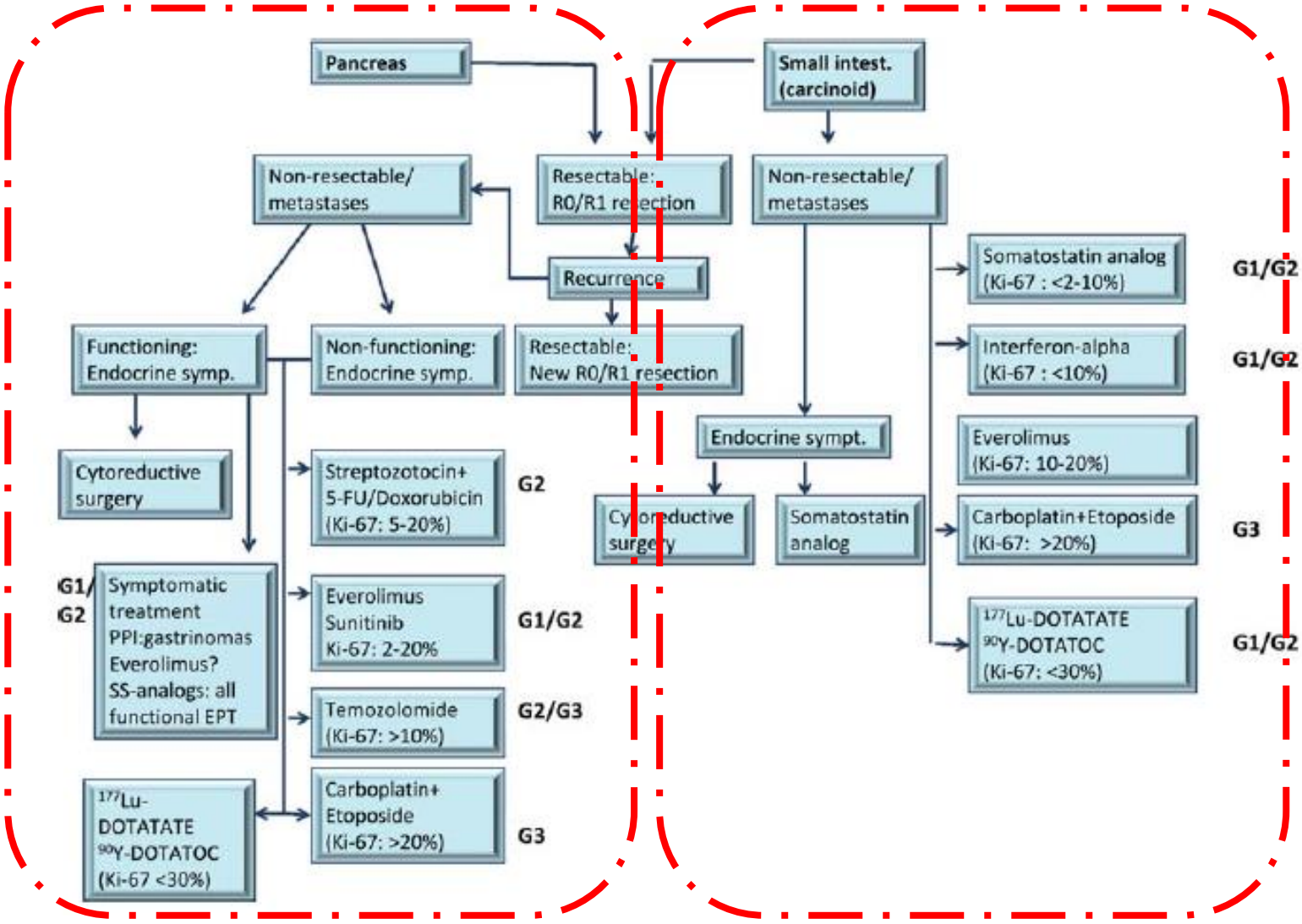
GRADING GEP-NETs
(ENETS - WHO)

G1≤2 mytosis /10hpf
<3% Ki67 index

G2 3 - 20 mytosis / 10hpf
3%-20% Ki67 index

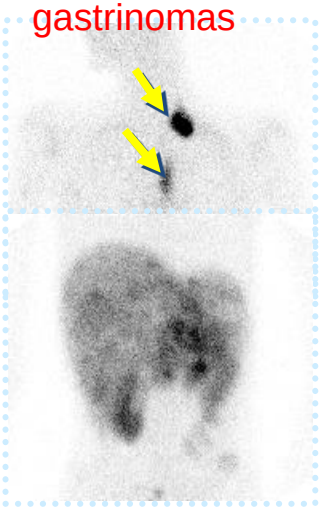
G3 >20 mytosis / 10hpf
>20% Ki67 index

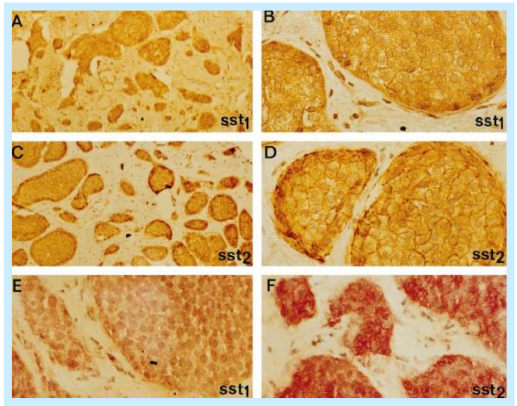
ESMO 2012 GEP-NETs Guide Line



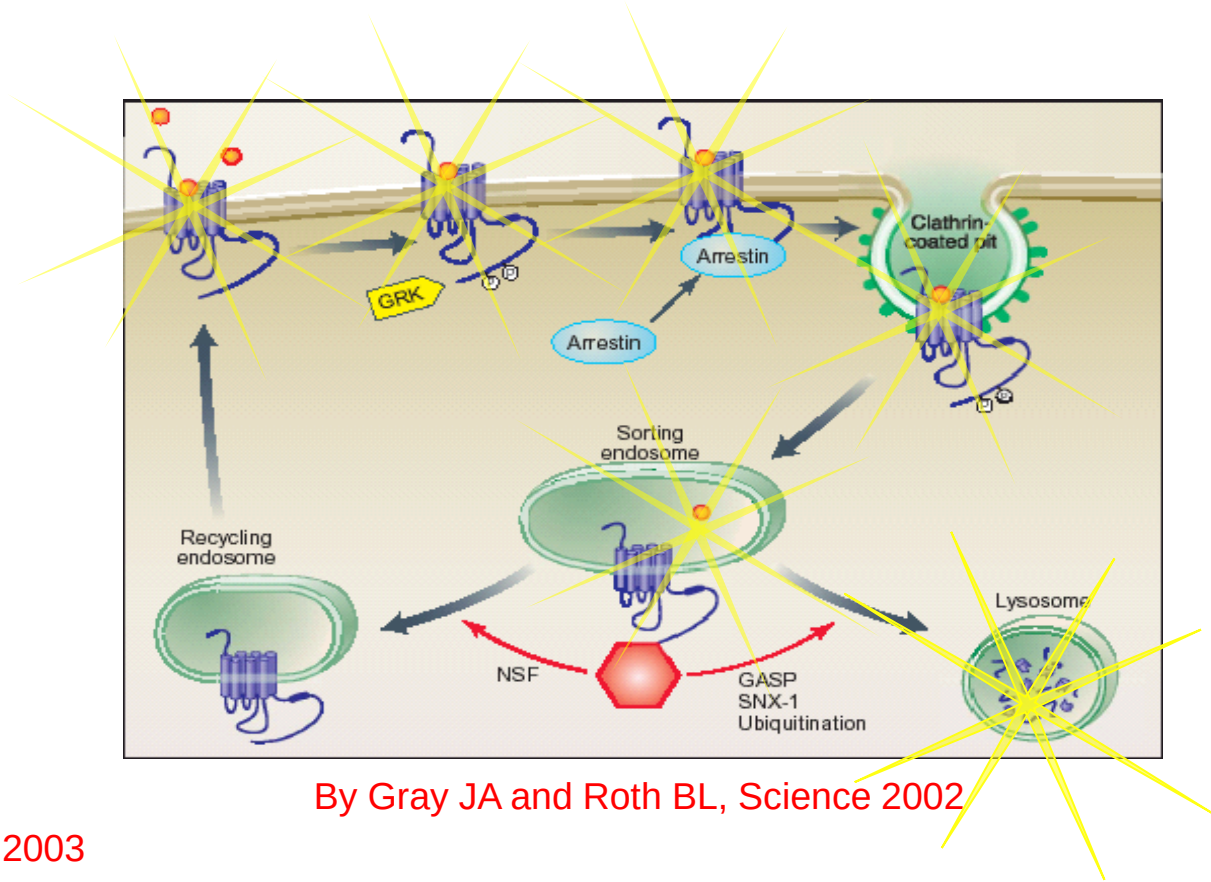
PRRT: rationale basis of the radioligand binding

Metastatic gastrinomas





Lamberts SWJ, Hofland LJ. Endocr Rev 2003



By Gray JA and Roth BL, Science 2002

PRRT: the IEO-IRST experience

1997

…

2004

2008

TODAY

^{90}Y-DOTATOC:

- Dosimetry (^{111}In modelling)
- Phase I studies
- Efficacy

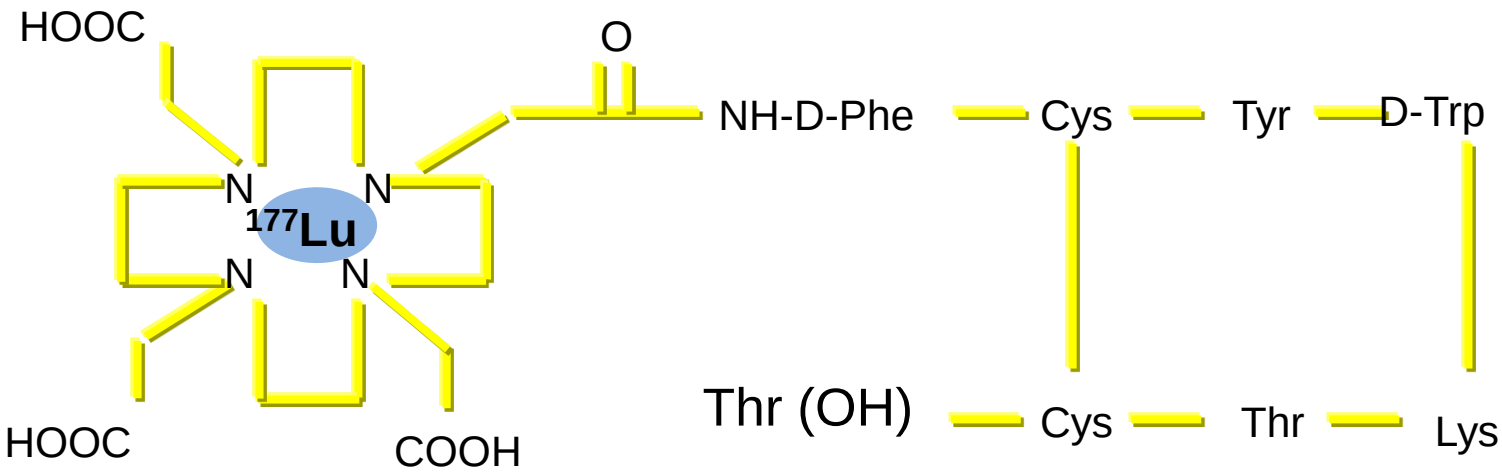
^{177}Lu-DOTATATE

- Dosimetry
- Phase I-II study

Safety and efficacy

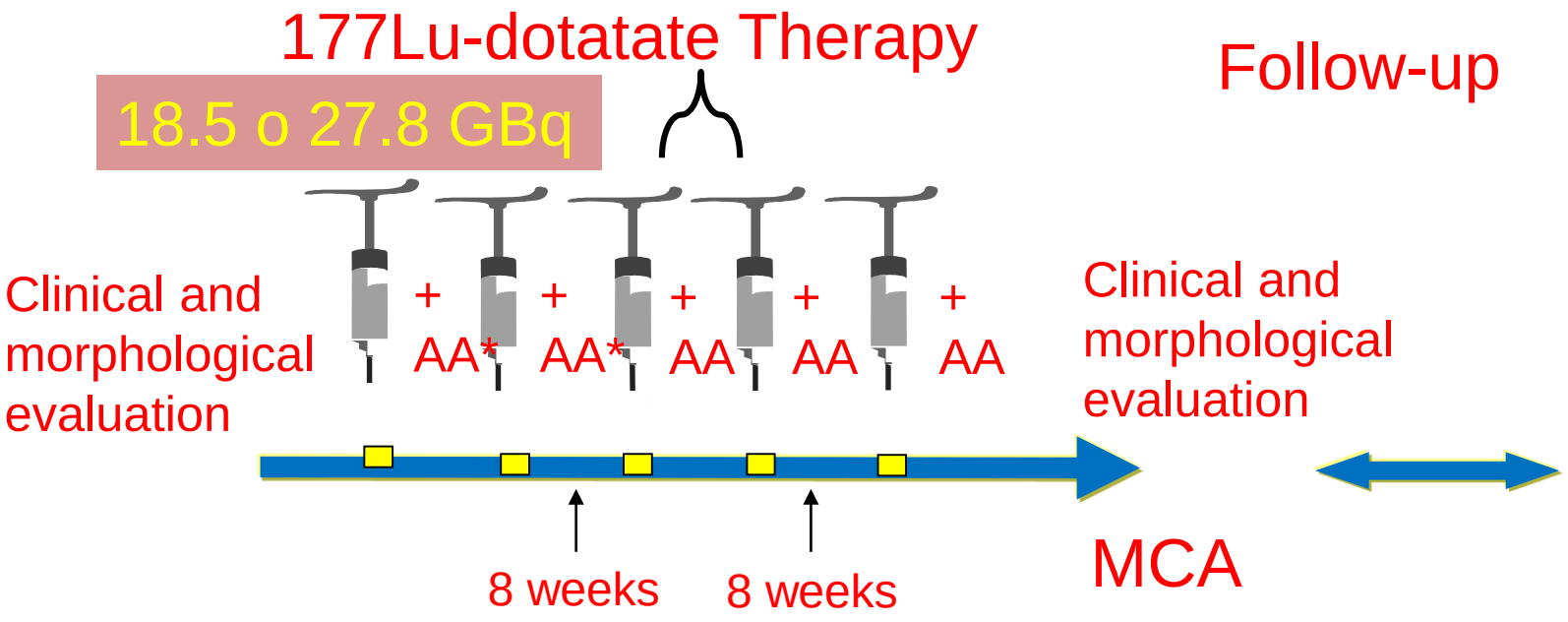
- Renal and Bone Marrow Toxicity
- Phase II study of ^{177}Lu-TATE in GEP-NETs
- FDG-PET in GEP NETs

[^{177}Lu-DOTA^{0}-Tyr^{3}]-octreotate (^{177}Lu-DOTATATE)



Affinity (IC_{50}, nM)				
sst$_1$	*sst*$_2$	*sst*$_3$	*sst*$_4$	*sst*$_5$
>10,000	1.6 ± 0.4	>1,000	523 ± 239	187 ± 50

Therapy scheme

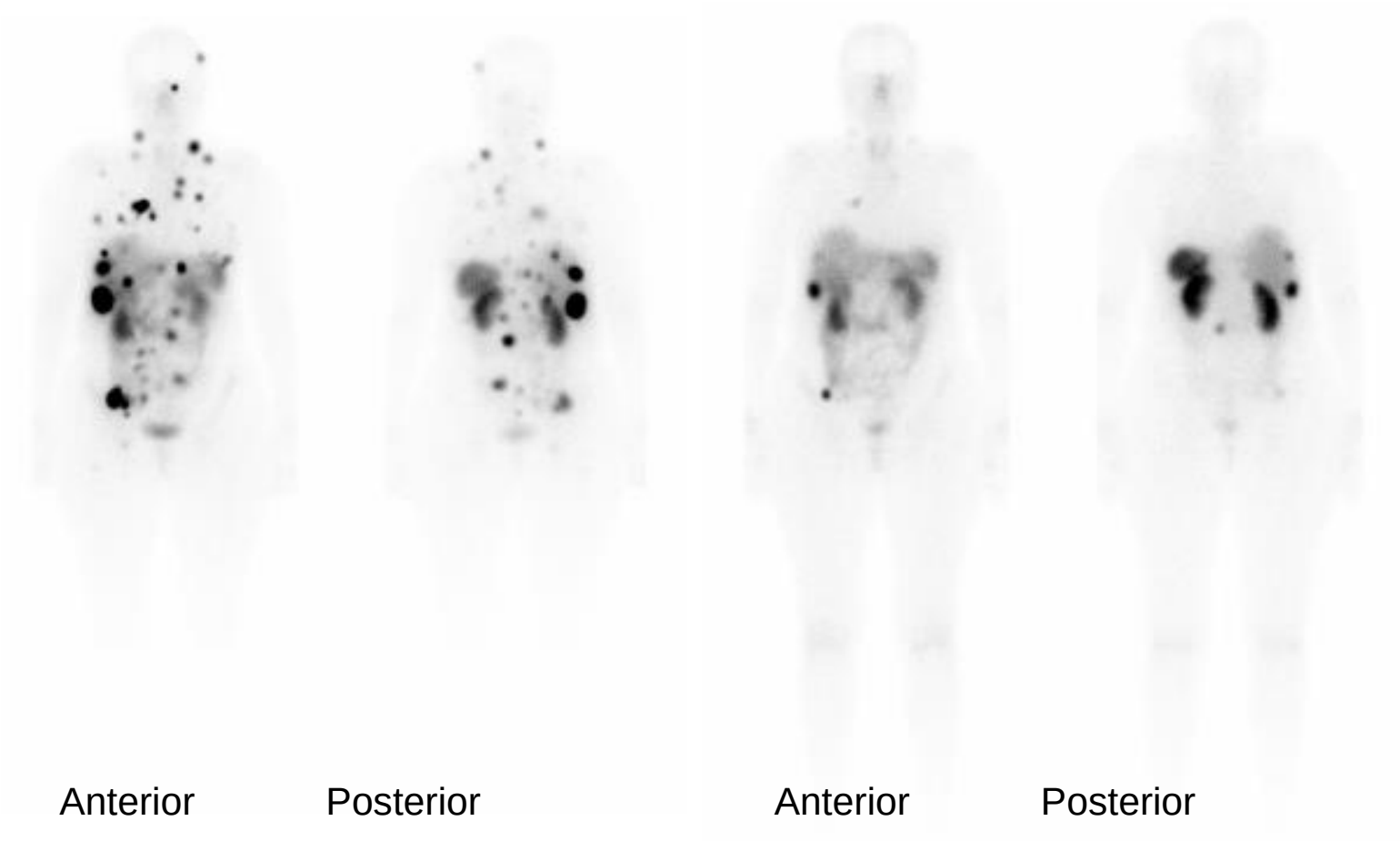


Lisine 70 MEq in 500 ml saline: 250 cc pre therapy and 250 cc in course of therapy
Lisine 70 MEq in 500 ml salina 3 ours after
Lisine 70 MEq in 500 ml salina x 2 the day after therapy.

^{177}Lu Dotatate; Total Body

I Cycle

IV Cycle

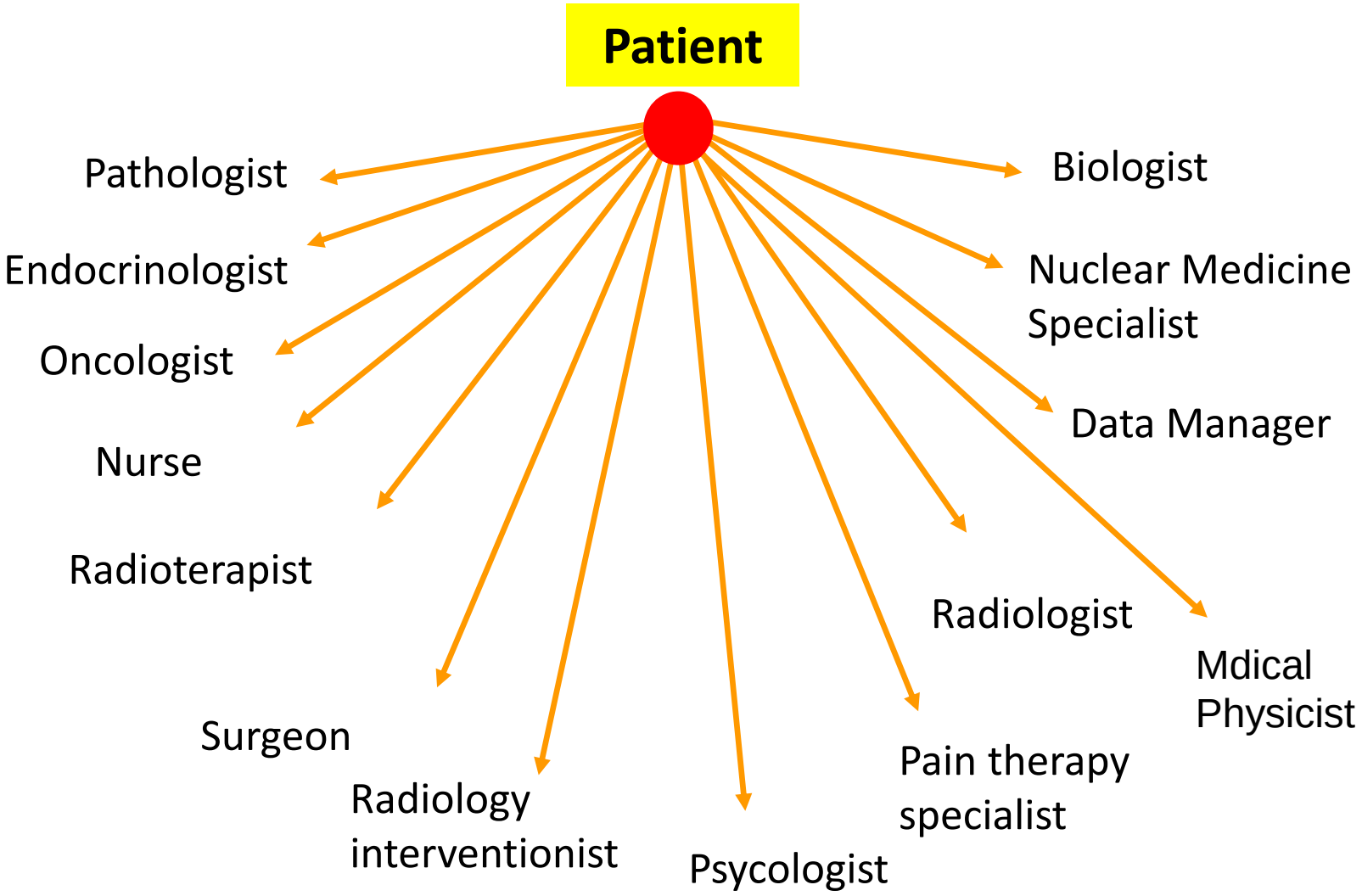


Anterior Posterior Anterior Posterior

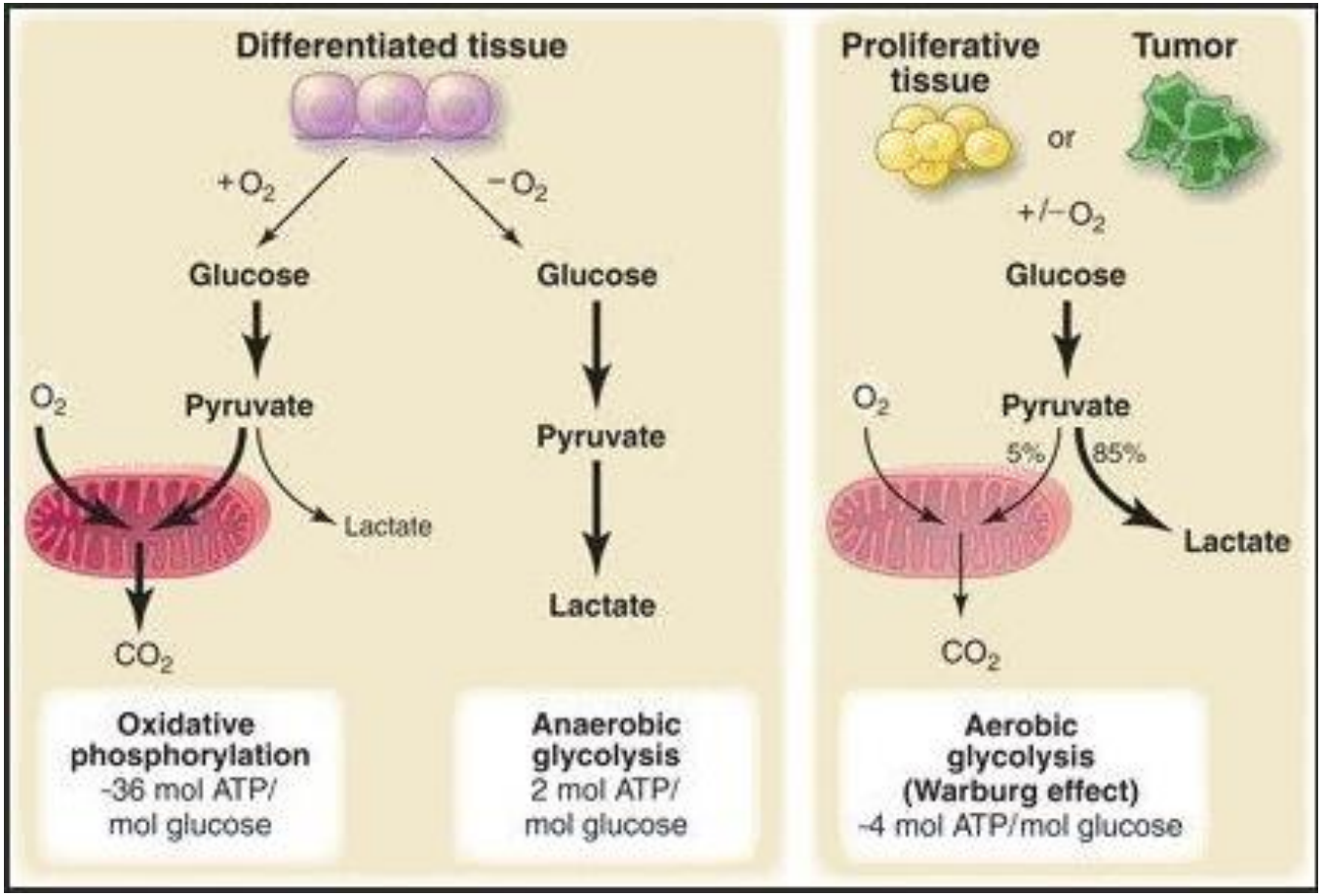
Overall Response: PRRT and other therapies

Treatment	Tumor type	N. Patients	PR + CR	PFS/OS	Reference
STZ+ Doxorubicin+FU	p-NET	84	39%	PFS 18m OS 37m	Kouvaraki (2004)
Temozolomide	p-NET	53	34%	PFS 14m OS 35m	Kulke (2009)
Temozolomide + Capecitabine	p-NET	30	70%	PFS 18m	Strosberg (2010)
Everolimus	p-NET	207	5%	11m	Yao (2011)
Sunitinib	p-NET	86	9%	11m	Raymond (2011)
^{177}Lu-DOTATATE	midgut / p-NET	310	30% p-NET 44%	PFS 33m OS 46m	Kwekkeboom (2008)
177Lu DOTATATE IRST	p-NET	52	29%	29 m	Sansovini et al Neuroendo2013

Multidisciplinary team of NENs



Warburg Effect



FDG – PET with a prognostic purpose in NET

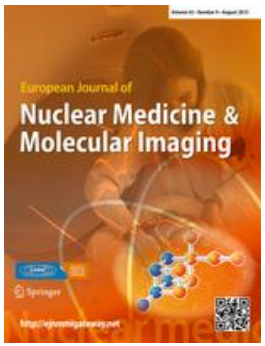
Published OnlineFirst January 26, 2010; DOI: 10.1158/1078-0432.CCR-09-1759

Clinical Cancer Research

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]



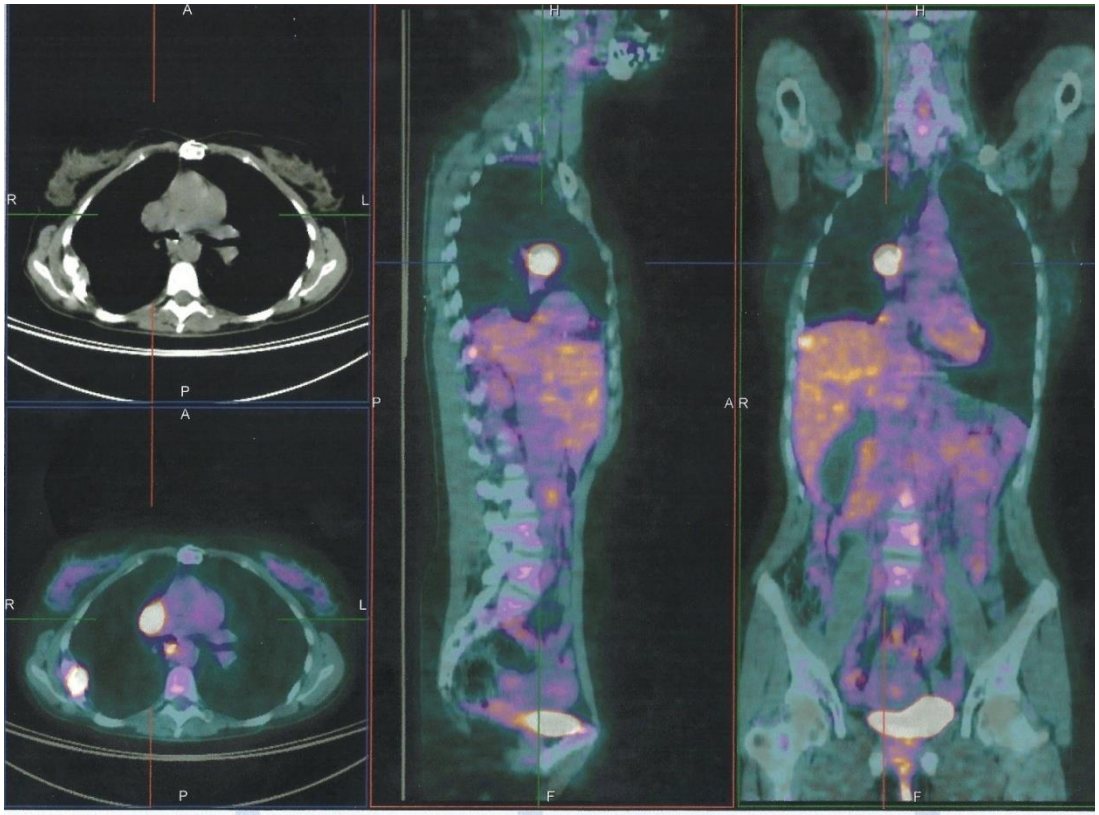
Eur J Nucl Med Mol Imaging
DOI 10.1007/s00259-013-2369-z

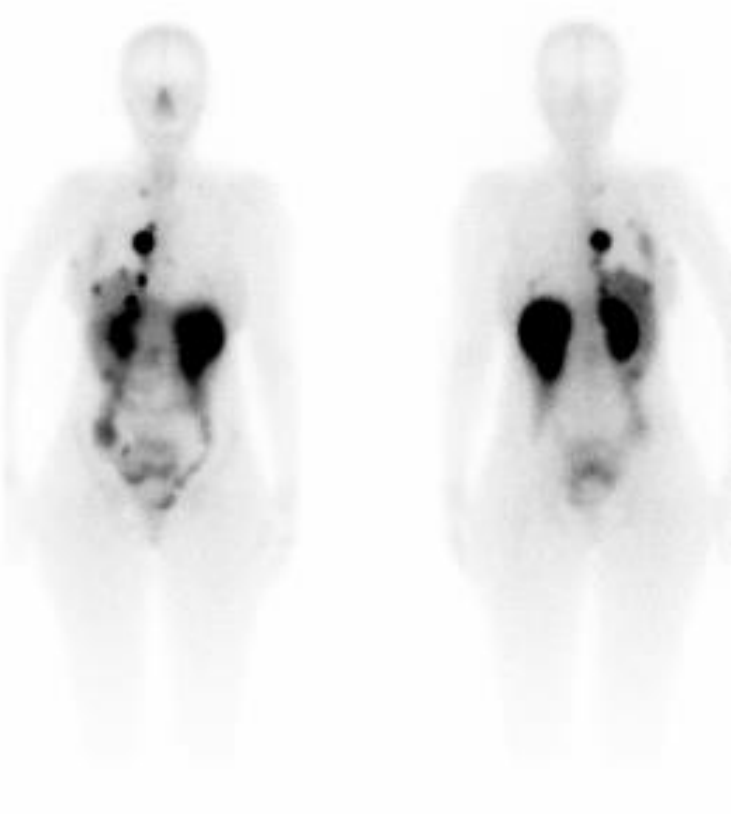
ORIGINAL ARTICLE

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

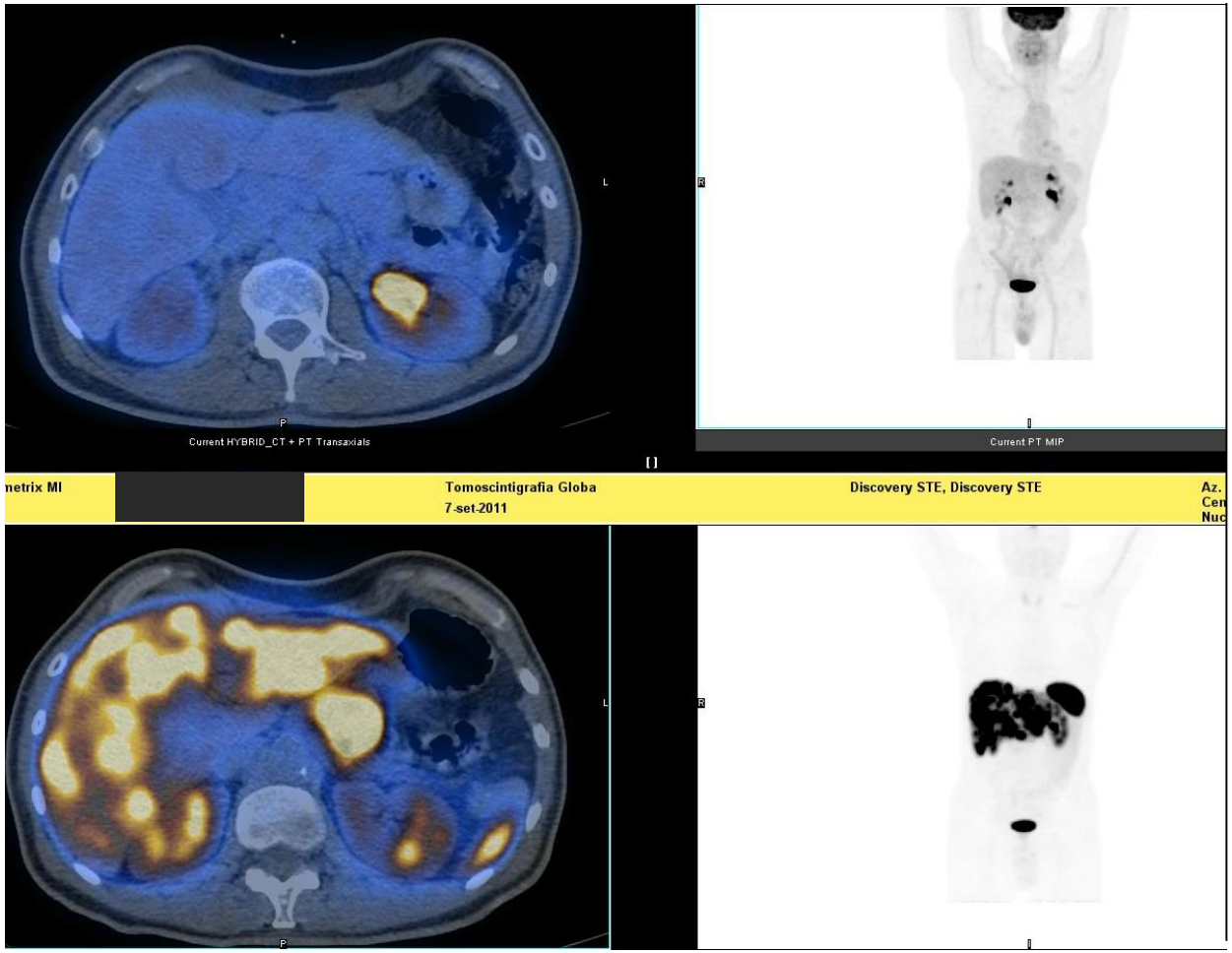
PET-CT FDG e TB post terapia con ^{177}Lu-Dotatate





FDG PET

Post 177Lu-Dotatate TB



FDG PET

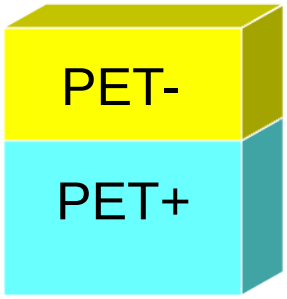
68Ga PET

Ki67 5 %

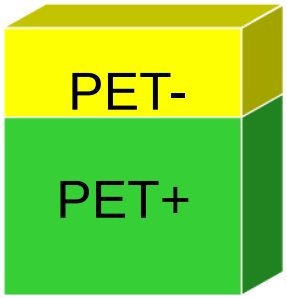
"METABOLIC CLASSIFICATION"

FDG PET+ Ve

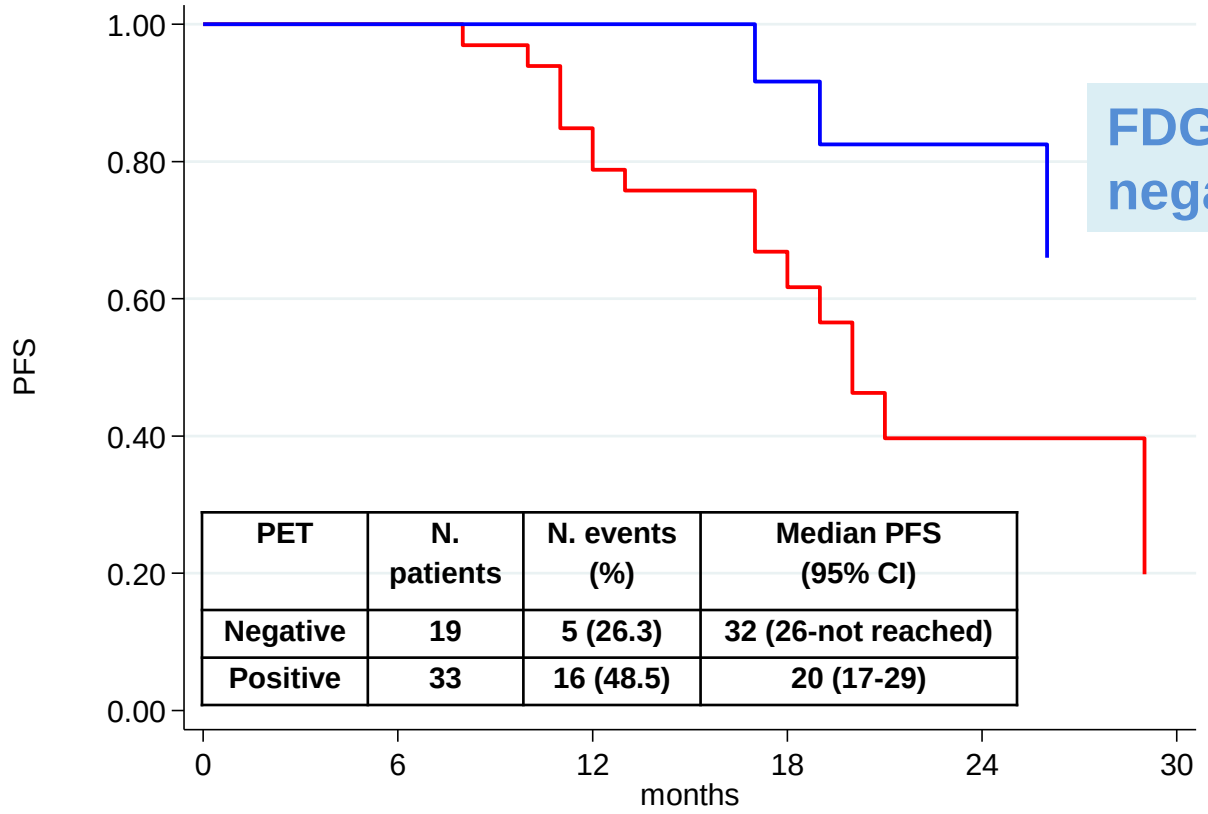
57% G1



66% G2



Median PFS according to FDG PET (n=52)



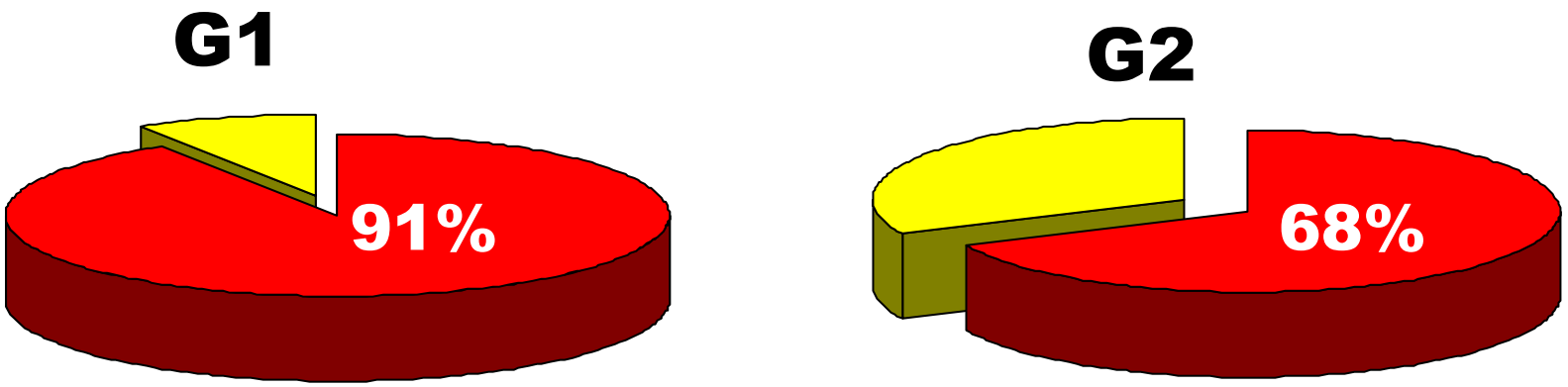
PET	N. patients	N. events (%)	Median PFS (95% CI)
Negative	19	5 (26.3)	32 (26-not reached)
Positive	33	16 (48.5)	20 (17-29)

FDG PET negative

FDG PET positive

In PET+ cases we had

In **G1** patients DCR 91% PFS n.r.
In **G2** patients DCR 68% PFS 19 months.



PFS analysis was statistically significant

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

ORIGINAL ARTICLE

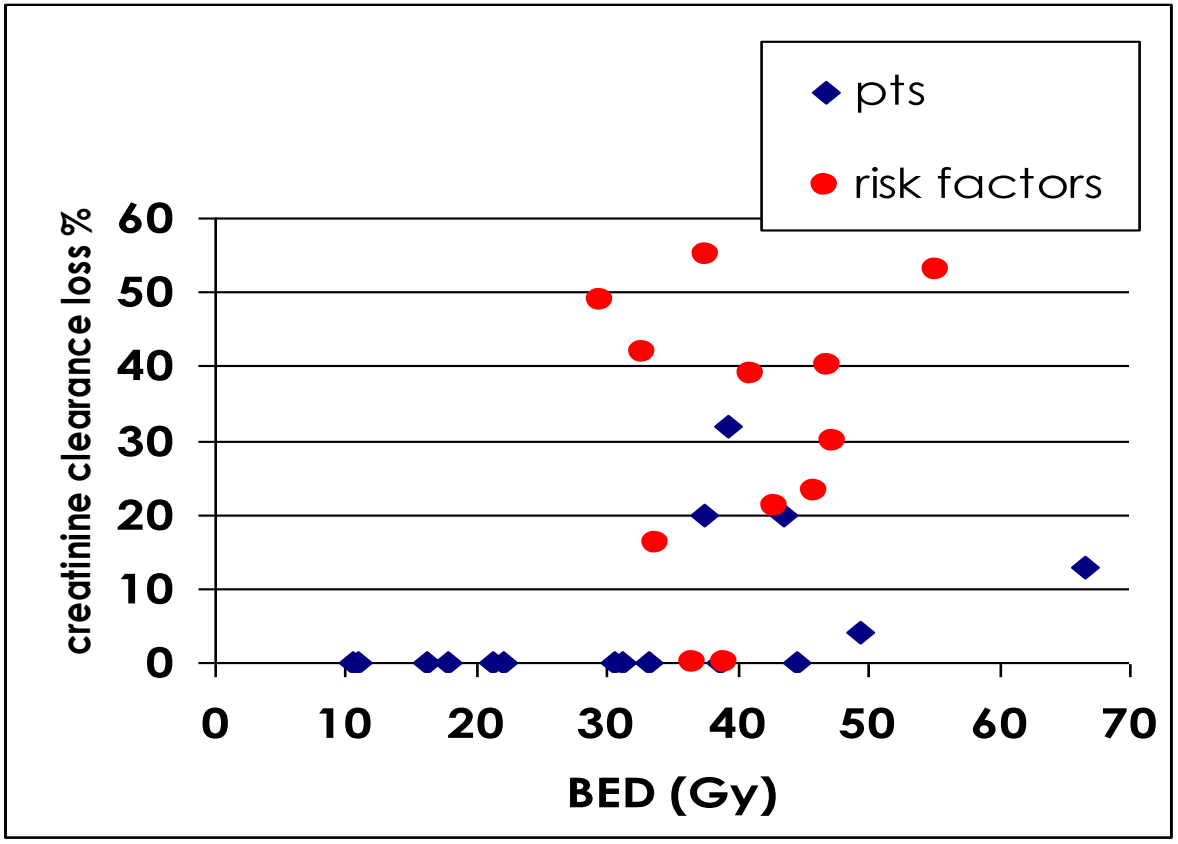
Long-term evaluation of renal toxicity after peptide receptor radionuclide therapy with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE: the role of associated risk factors

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

Creatine Clearance % Decrease vs BED and Risk factors



BED threshold of 28 Gy in patients with Risk Factors

BED threshold of 40 Gy in patients without Risk Factors

Neuro endocrinology

Neuroendocrinology (DOI:10.1159/000348394)
(Accepted, unedited article not yet assigned to an issue)

Advanced Release: February 2, 2013

Received: June 27, 2012
Accepted after revision: January 28, 2013

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

GEP-NETs SSTR2 Positive

Risk factors for Kidney and Bone Marrow toxicity

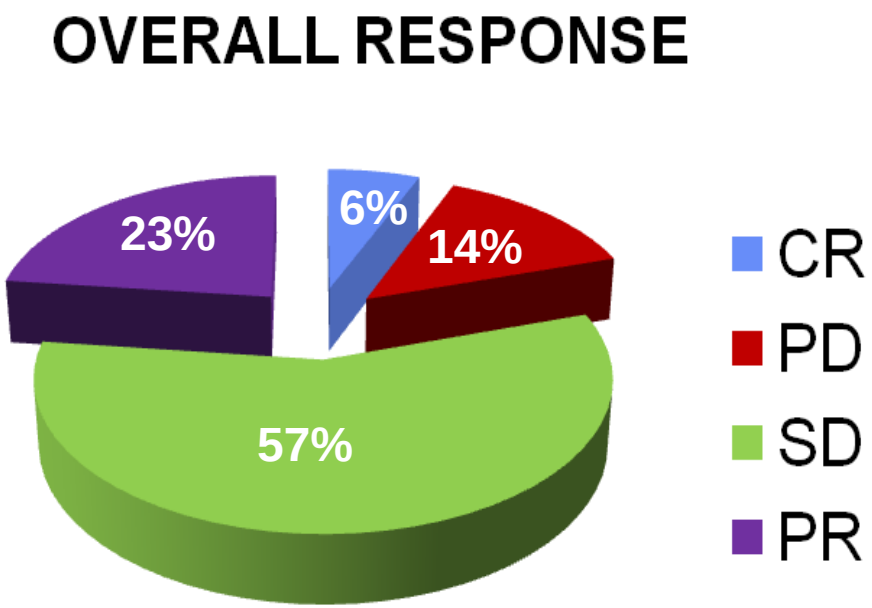
No Risk factors

Risk Factors

^{177}Lu 750mCi in 5 cycles

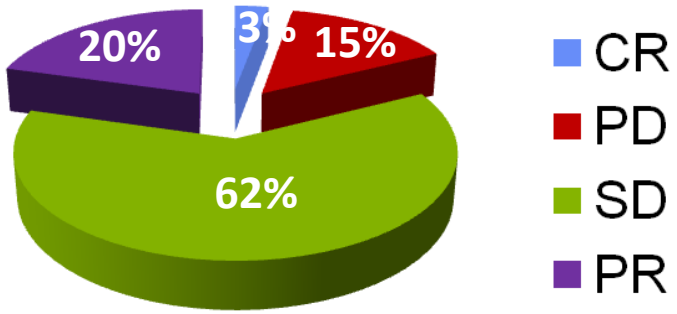
^{177}Lu 500 mCi in 5 cycles

Results in 65 Pancreatic patients



Median PFS 35 months (22-54)
Median OS nr

REDUCED DOSAGE GROUP



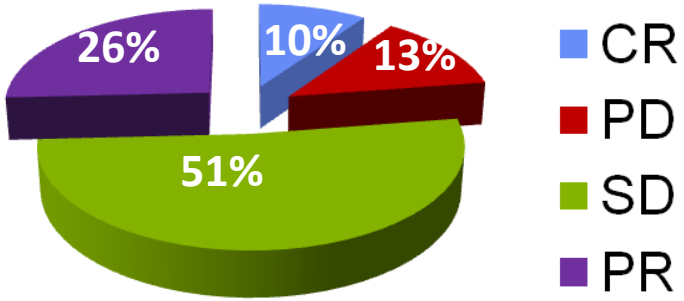
34 patients had 17.8 GBq
(range 11.1-19.9)

DCR 85%

Median PFS 25 mesi (20-nr)

Median OS 50 (28-nr)

FULL DOSAGE GROUP



31 patients had 25.5 GBq
(range 20.7-27.8)

DCR 87%

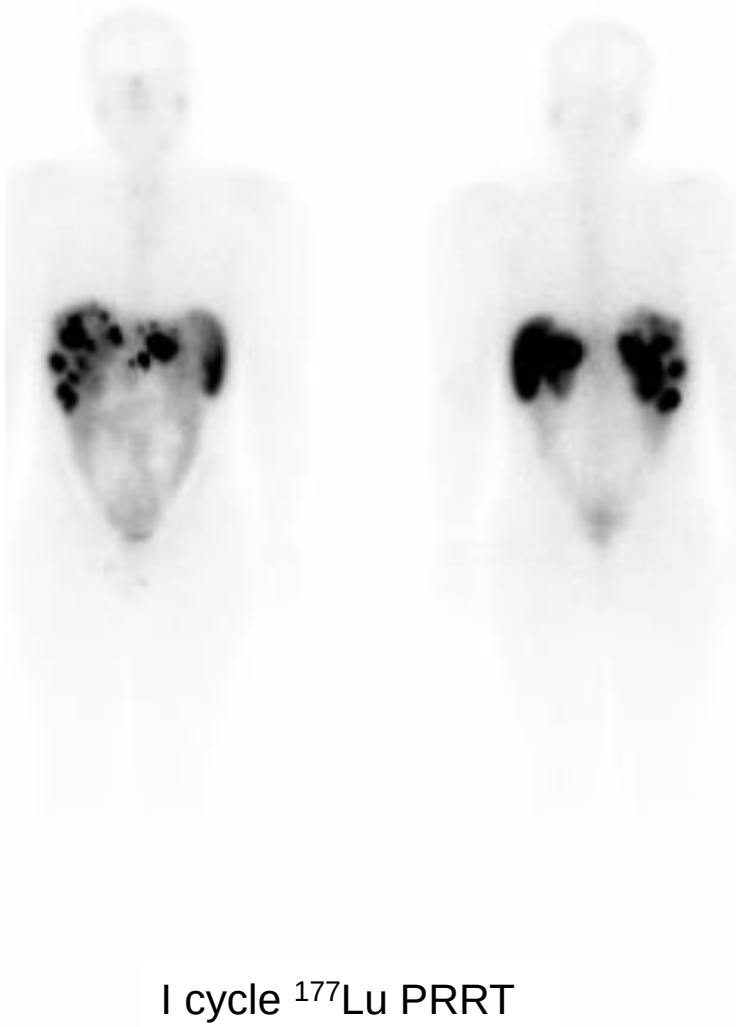
Median PFS 46 mesi (26-69)

Median OS nr

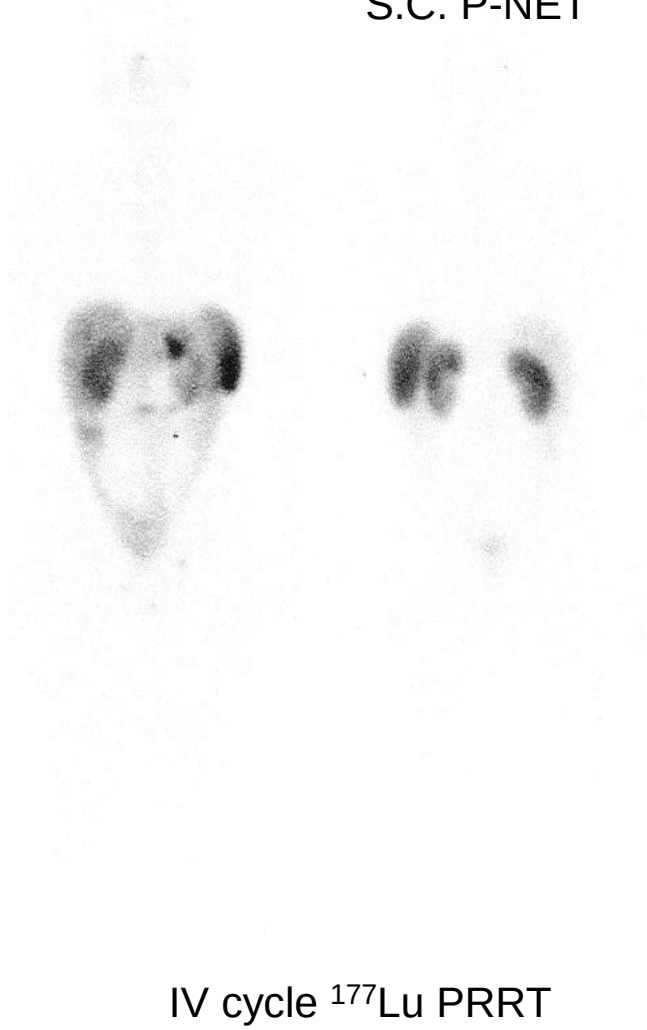
No major haematological toxicity. One G3 kidney toxicity in a patient with risk factors

Toxicity	Overall (%)			FD Group (%)			RD Group (%)		
	G1	G2	G3	G1	G2	G3	G1	G2	G3
WBC	10 (15)	5 (8)	0	2 (6)	5 (16)	0	8 (23)	0	0
PLT	12 (18)	1 (2)	0	5 (16)	0	0	7 (21)	1 (3)	0
HB	18 (28)	4 (6)	0	10 (32)	2 (6)	0	8 (23)	2 (6)	0
CREATININE	4 (6)	1 (2)	1 (2)	0	0	0	4 (12)	1 (3)	1 (3)

S.C. P-NET

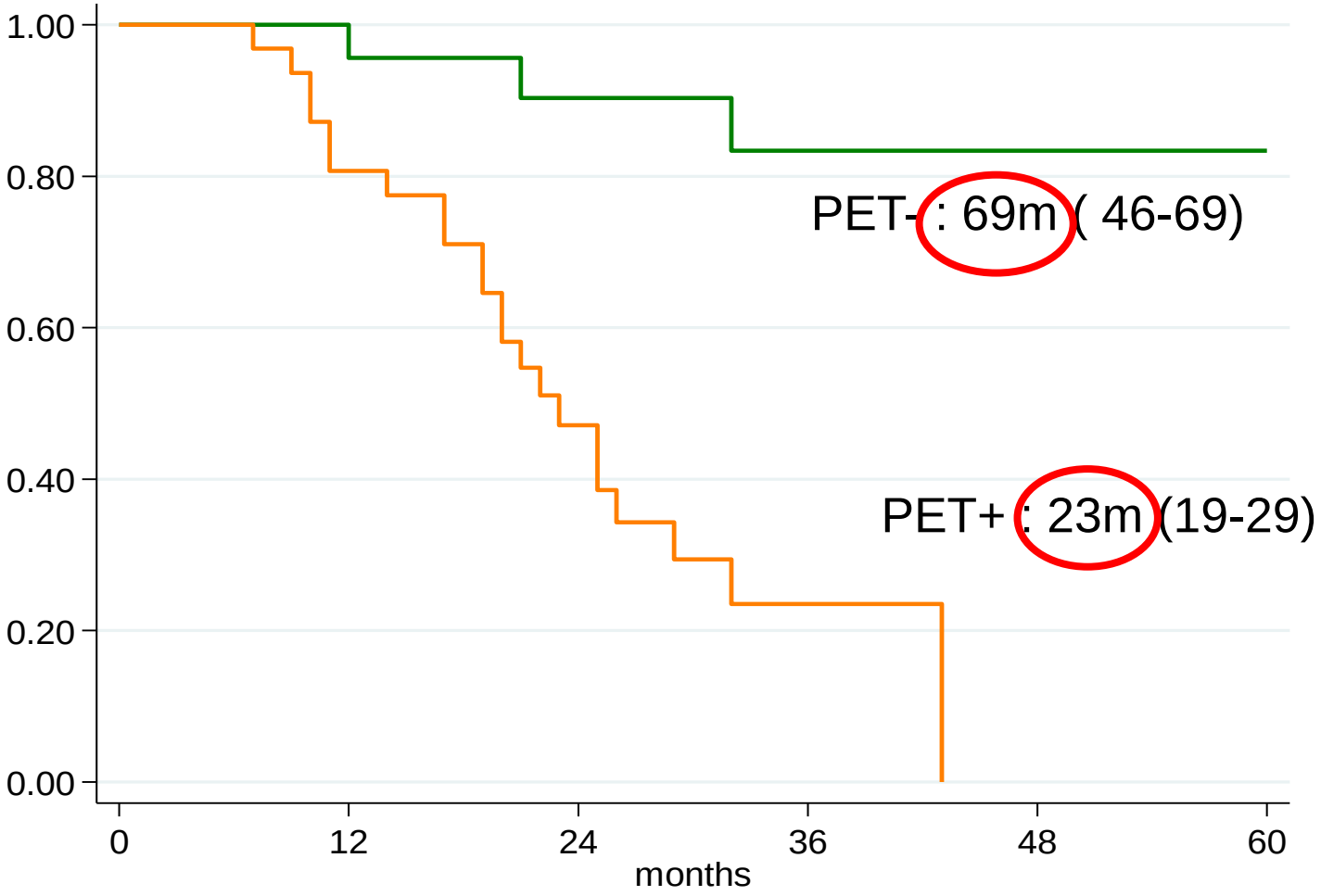


I cycle ^{177}Lu PRRT
6.4GBq 19/6/2012



IV cycle ^{177}Lu PRRT
6.4GBq 18/12/2012

Median PFS according to FDG-PET in p-NET



p < 0.0001

Fase II prospective Protocol: High Grade Ki67 GEP-NENs patients treated with 177Lu-Dotatate to evaluate activity and toxicity

- 26 consecutive patients with Ki67 >15% treated with 4-5 cycles 177Lu dotatate therapy 6 ± 2 weeks apart
- Reduced dosage for patients with factors
- 20/26 patients had FDG PET positive

26 High Ki67 Grade GEP-NENs patients

Median follow-up: 30 months (range 3-69)

	n. pts	DCR	Median PFS (95% CI)	p	Median OS (95% CI)	p
Overall	**26**	**16 (61%)**	**18.4 m. (7.1-26.3)**	**-**	**36.6 (16.3-55.8)**	**-**
Ki67 15-35%	**16**	**13 (81%)**	**20.9 m. (10.8-28.0)**		**52.9 (17.1-68.9)**	
Ki67 >35%	**10**	**3 (19%)**	**6.8 m. (2.1-27.0)**	**0.050**	**12.6 (3.4-55.8)**	**0.054**

177Lu-DOTATATE PRRT ASSOCIATED WITH METRONOMIC CAPECITABINE IN PATIENTS AFFECTED BY AGGRESSIVE GEP-NENs (LuX).

Phase: I-II n. IRST 100.19

- **38** pts. enrolled, (2 whithdrawn for early toxicity)
- **17** concluded the PRRT protocol, **19** are ongoing
- no kidney or bone marrow toxicity ≥G2
  (personalized PRRT and capecitabine dosage)
- 17 pts. (WHO Grading : 4 G1, 10 G2, 3 G3),
  The post therapy result was **10 SD, 7 PR**

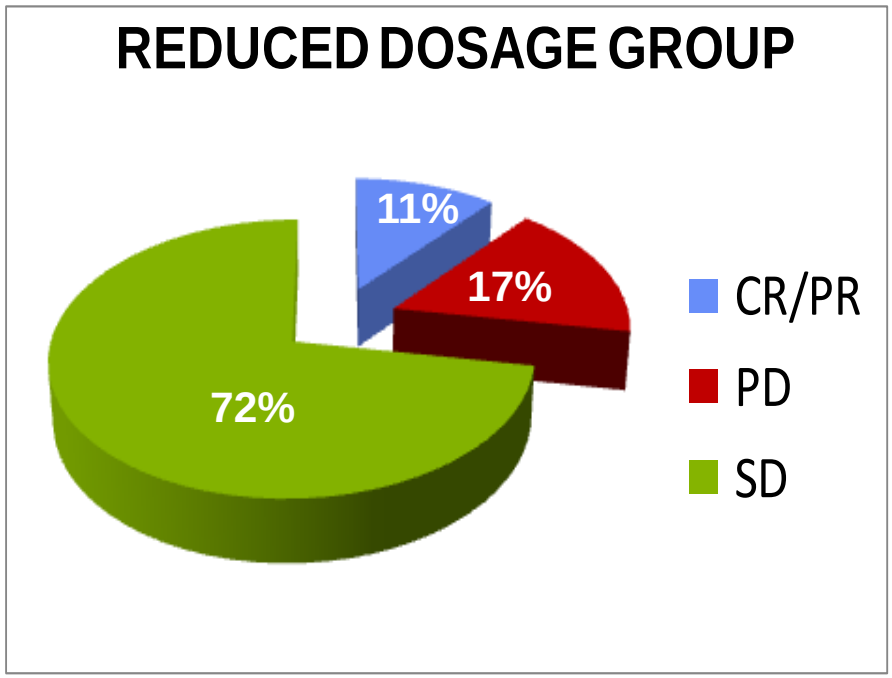
Preliminary scintigraphic results

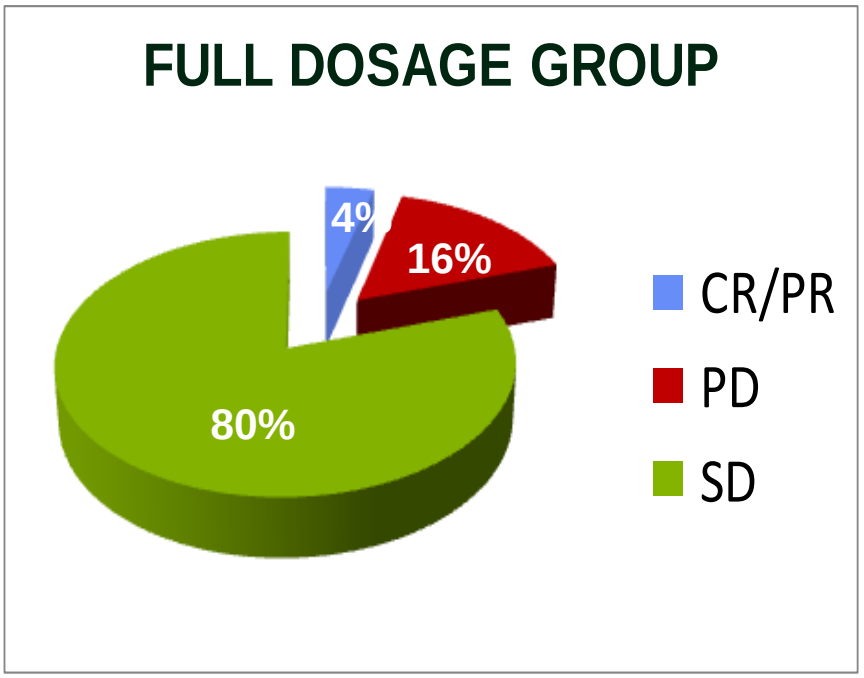
GRADING PROPOSAL FOR GEP-NENs

GRADE (KI 67 index)	PRRT	PRRT + Chemo
G 1 (<5%)	**G1 –ve**	**G1 +ve**
G 2a (6-15%)	**G2a –ve**	**G2a +ve**
G 2b (15-35%)	**G2b –ve**	**G2b +ve**
G 3a (36-55%)	**G3a –ve**	**G3a +ve**
G 3b (>55%)	**G3b –ve**	**G3b +ve**


Thanks for your attention

43 gastrointestinal patients (GI-NETs)





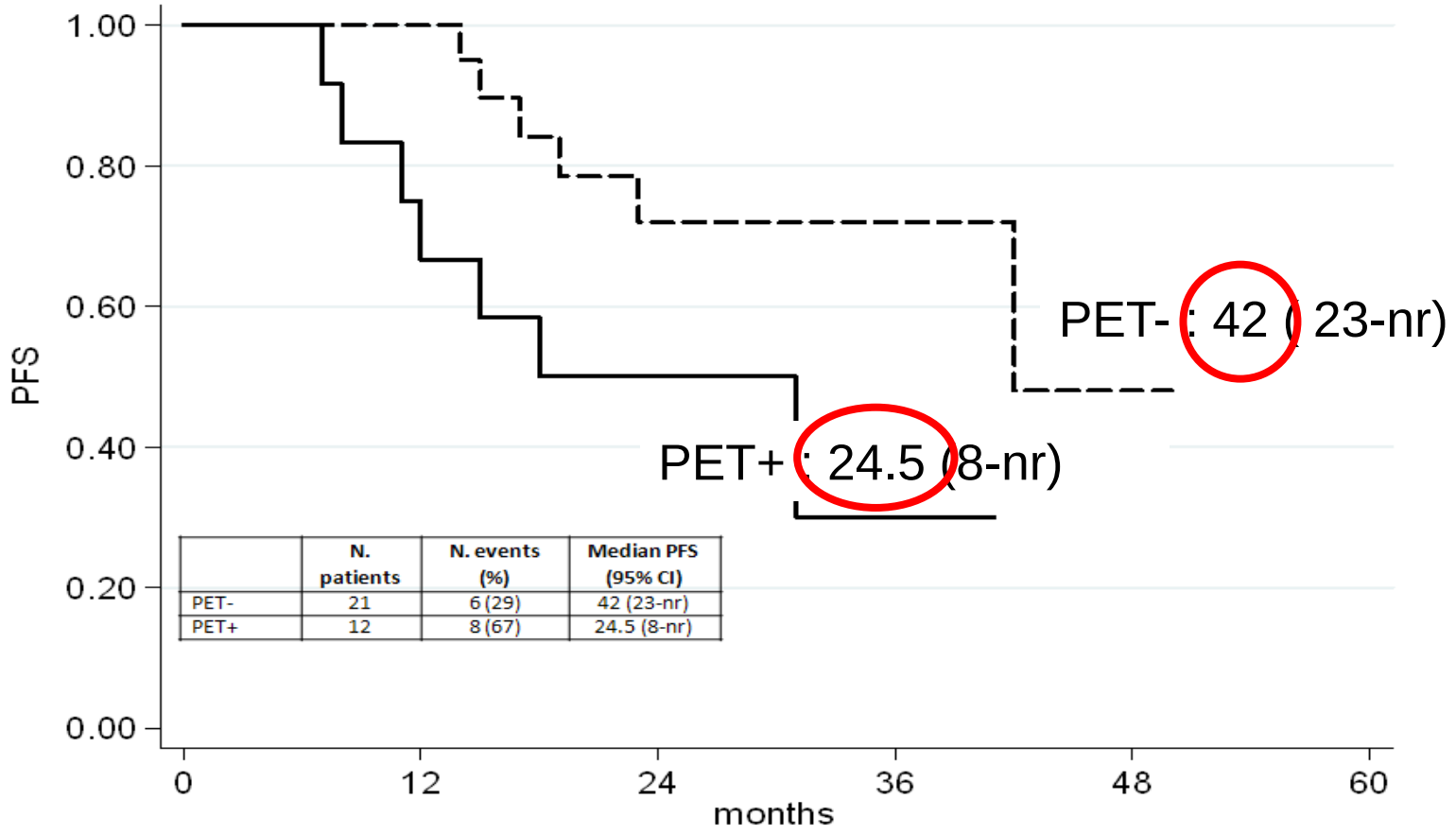
18 patients had 17.8 GBq

DCR 83%

25 patients had 25.5 GBq

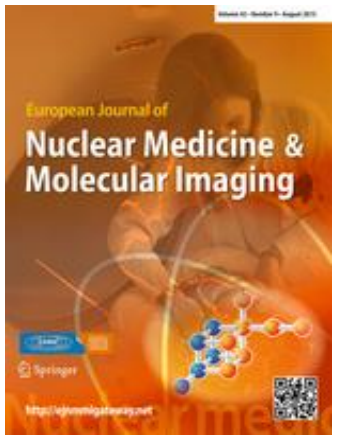
DCR 84%

Median PFS according to FDG PET 43pz. GI-NETs



	N. patients	N. events (%)	Median PFS (95% CI)
PET-	21	6 (29)	42 (23-nr)
PET+	12	8 (67)	24.5 (8-nr)

p = 0.025



Eur J Nucl Med Mol Imaging. 2016 May;43(5):839-51.
doi: 10.1007/s00259-015-3250-z. PMID: 26596723

ORIGINAL ARTICLE

Measurement of circulating transcripts and gene cluster analysis predicts and defines therapeutic efficacy of Peptide Receptor Radionuclide Therapy (PRRT) in neuroendocrine tumors.

Bodei L., Kidd M. , Modlin IM. , Severi S., Drozdov I., Nicolini S., Kwekkeboom D., Krenning EP., Baum RP., Paganelli G..

The predictive quotient (a combination of circulating gene cluster analysis and grading) accurately predicted PRRT efficacy.

Blood gene transcript levels accurately identified PRRT responders and non-responders, while CgA was non-informative.

Circulating BIOMARKERS in GEP-NET

Protocol Code: IRSTB056

Circulating Endotelial Cells as marker of vascular damage and altered endothelial turnover and a large pannel of **miRNA** involved in GEP-NETs will be evaluated to test a possible use as predittive or prognostic factors.

Sampling will be done at baseline, in course of therapy, during the follow up and variation of response will also tested in relation to FDG PET response.