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Special Symposium

Integrating targeted treatments with tumor biology and molecular imaging in the current and future management of gastrointestinal NETs

Peptide Receptor Radionuclide Therapy of NETs

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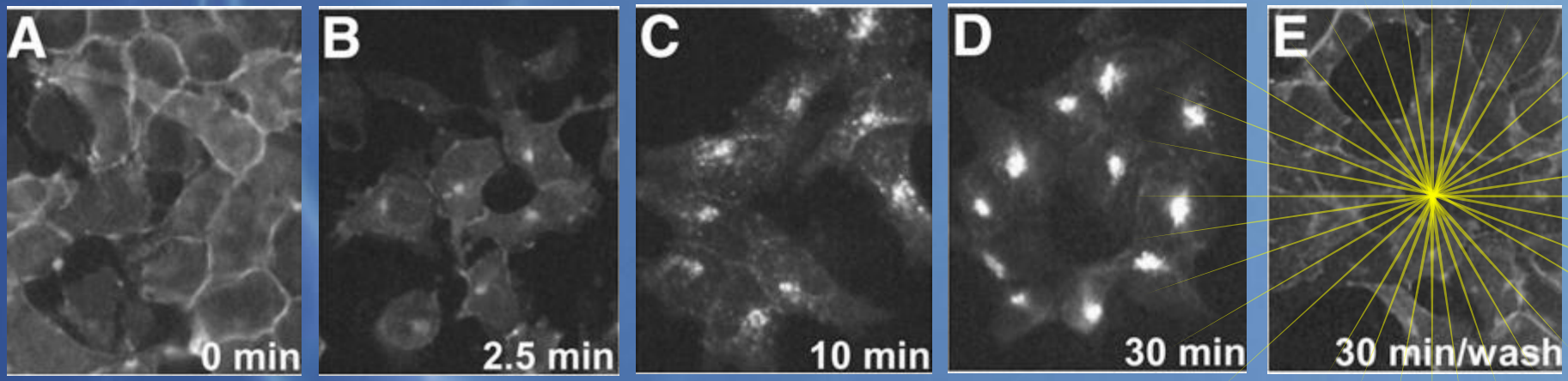
IEO
Istituto Europeo di Oncologia

Disclosure slide

- No Conflicts of Interest to declare

PRRT: rationale

radioligand internalization



Agonist induced internalization and recycling of sst_2 receptor in HEK293 cells

Adapted to Waser B et al. J Nucl Med 2009

Efficacy: radioactivity concentration in tumor

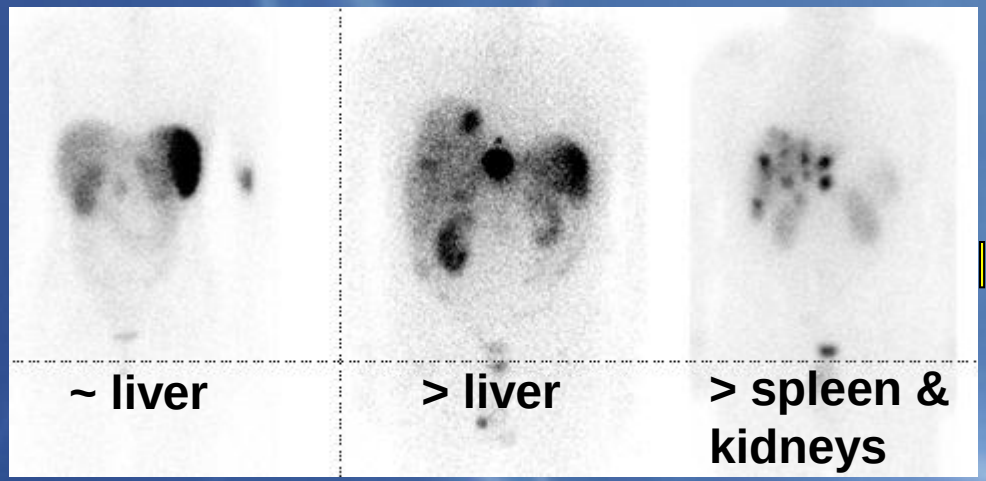
PRRT

Receptor affinity of radiopeptide

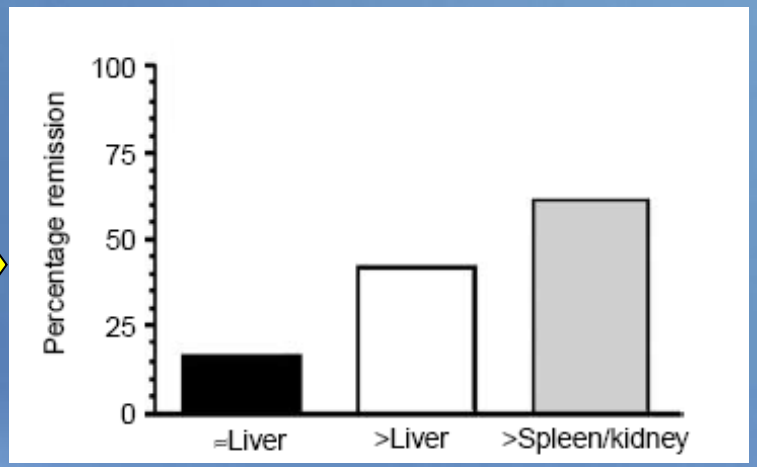
Peptides	hsst 1	hsst 2	hsst 3	hsst 4	hsst 5
DOTA-TOC	>10,000 (7)	14±2.6 (6)	880±324 (4)	>1,000 (6)	393±84 (6)
DOTA-[Tyr^3]-octreotate	>10,000 (3)	1.5±0.4 (3)	>1,000 (3)	453±176 (3)	547±160 (3)

Reubi JC et al. Eur J Nucl Med 2000

Receptor density on tumor vs normal organs



Grade 1 *Grade 2* *Grade 3*



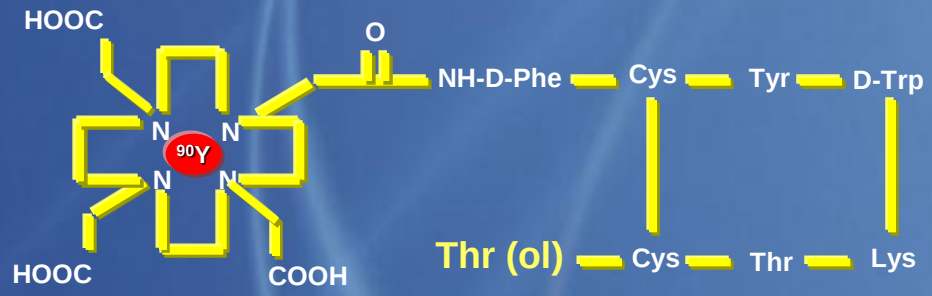
Kwekkeboom D et al Endocrine Rel Cancer 2010

Pharmacokinetics: rapid plasma clearance and renal excretion

Bodei L. et al. J Endocrinol Invest 2009

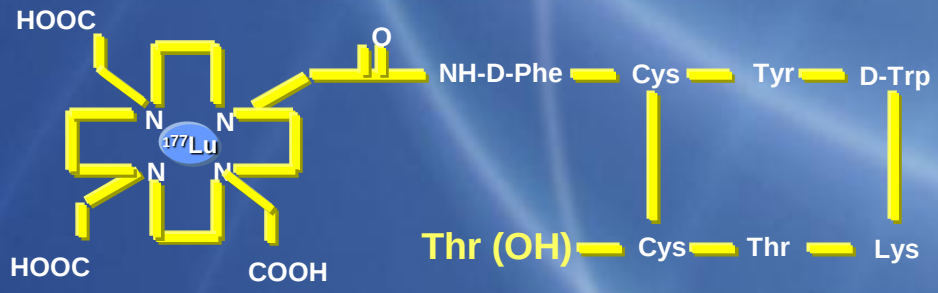
Radiopeptides

[^{90}Y-DOTA]-Tyr^3-octreotide or **^{90}Y-DOTATOC** or **^{90}Y-edotreotide**



^{90}Y characteristics	
Beta particle max energy	2.3 MeV
Max range	11 mm
Half-life	64 hrs

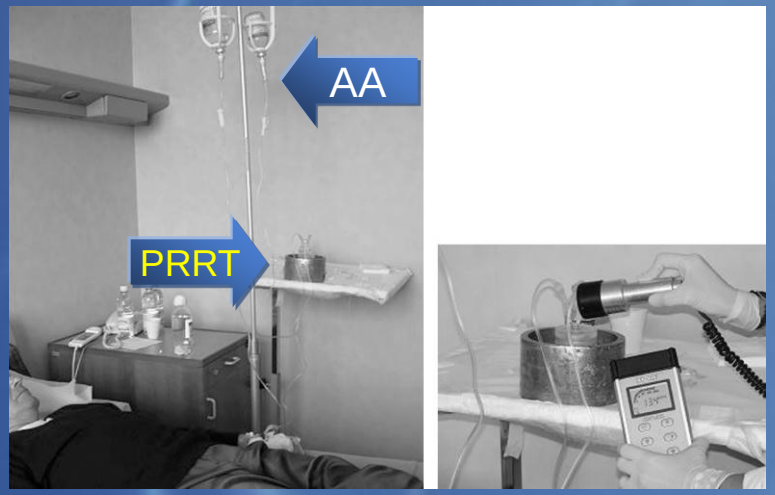
[^{177}Lu-DOTA]-Tyr^3,Thr^8-octreotide or **^{177}Lu-DOTATATE or Lutathera**



^{177}Lu characteristics	
Beta particle max energy	0.5 MeV
Max range	2 mm
Gamma 1 energy	113 KeV (6%)
Gamma 2 energy	208 KeV (11%)
Half-life	6.7 days

Bodei L. et al. J Endocrinol Invest 2009

Peptide Receptor Radionuclide Therapy (PRRT)



Systemic administration

Baseline

Clinical and morphological evaluation

Follow-up

Clinical and morphological evaluation

MCA*

*maximum cumulative administrable activity

≥ 6-9 weeks ≥ 6-9 weeks

Bodei, Paganelli 2006

What we learned from 18 yrs of clinical trials of PRRT

despite the lack of homogeneity among studies

EFFICACY

- ✓ Tumor shrinkage
- ✓ Symptom relief and QoL improvement
- ✓ Biomarker reduction
- ✓ Impact on survival

TOLERABILITY

- ✓ Generally well tolerated
- ✓ Generally mild acute side effects:
  - AA-related: nausea, vomiting
  - PRRT-related: fatigue, mild hair loss (Lu-tate), rare exacerbation of syndromes
- ✓ Chronic and permanent effect on kidney, BM, (testes)
  - Generally mild if necessary precautions are taken

Kwekkeboom DJ et al. JNM 2005
Bodei L et al. Eur J Nucl Med Mol Imaging 2004
Bodei et al. J Endocrinol Invest 2009
Kwekkeboom DJ et al. Endocrine Rel Cancer 2010
Brans B et al. Eur J Nucl Med 2007
Cremonesi M et al. Q J Nucl Med Mol Imaging 2011

^{90}Y-octreotide: response in GEP-NETs

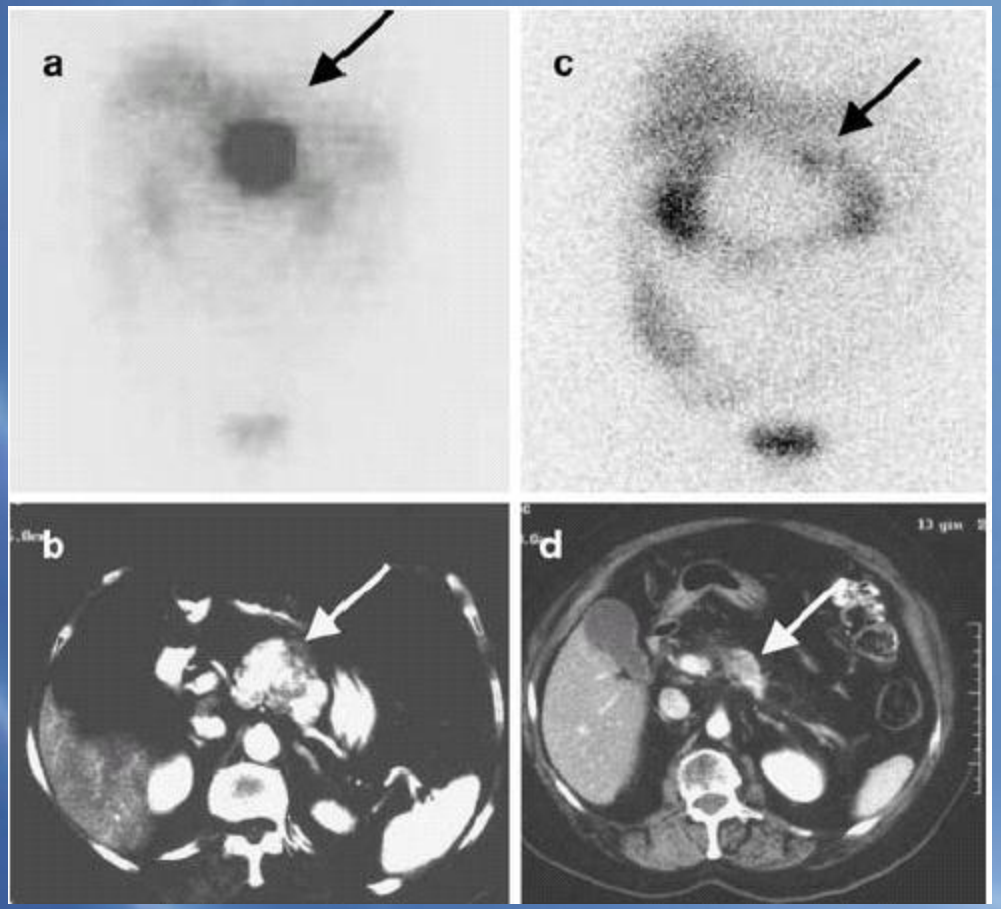
	Waldherr *et al.* (2002)[14]
Tumor type	Mainly GEPNETs
Number of patients	39
Phase	II
Cumulative dose of radioactivity (GBq/m²)	7.40
Radioactivity dose per cycle (MBq/m²)	1,850
Number of cycles	4
Progressive disease at start (%) GEPNETs	100
Complete remission (%)	5
Partial remission (%)	18
Stable disease (%)	69
Number of patients with GEPNET	37
Complete remission (%)	3
Partial remission (%)	19
Stable disease (%)	70
Progressive disease (%)	8
Median time to progression	NA
Renal toxic effects (%)	3 (grade 2)
Median follow-up (months)	6.0

	Bodei *et al.* (2003)[18]	Valkema *et al.* (2006)[19]	
Tumor type	Mixed	Neuroendocrine	
Number of patients	40	60 (58 with GEPNETs)	
Cumulative dose of radioactivity	5.92–11.00 GBq	8.20–14.90 GBq/m² (4 equal doses) or 7.20–12.90 GBq/m² (single dose escalation)	
Dose of radioactivity per cycle	2.96–5.55 GBq	0.73–3.80 GBq/m² (4 equal doses) or 3.60–9.30 GBq/m² (single dose escalation)	
Number of cycles	2	4 (4 equal doses) or 2–3 (single dose escalation)	
Response criteria	WHO	SWOG	
Patients with progressive disease (GEPNET) at start	NA	47 of 58 (76%)	
Complete response (%)	3	NA	
Partial response (%)	18	NA	
Stable disease (%)	45	NA	
Progressive disease (%)	33	NA	
Number of patients with GEPNET	20	58	
Complete response (%)	0	0	
Partial response (%)	30	9	
Stable disease (%)	50	62	
Progressive disease (%)	20	24	
Median time to progression (months)	10	29	
		End-stage renal failure in 3% of patients	
Other toxic effects	NA	MDS in 2% of patients Liver failure in 2% of patients	
Follow-up duration	Median 19 months	18 months after first cycle (planned)	

Adapted from van Essen, M. et al. Nat. Rev. Endocrinol 2009

Pancreatic VIP-oma

After 14 GBq ^{90}Y-DOTATOC



Bodei L, Eur J Nucl Med Mol Imaging 2004

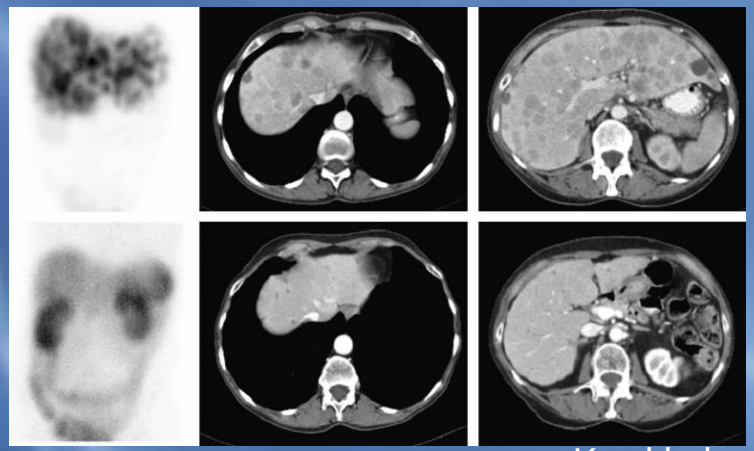
^{177}Lu-octreotate: response in 310 GEP-NET pts

3 months after last cycle

Table 2. Tumor Responses in Patients With GEPNETs, 3 Months After the Last Administration of ^{177}Lu-Octreotate (n = 310)

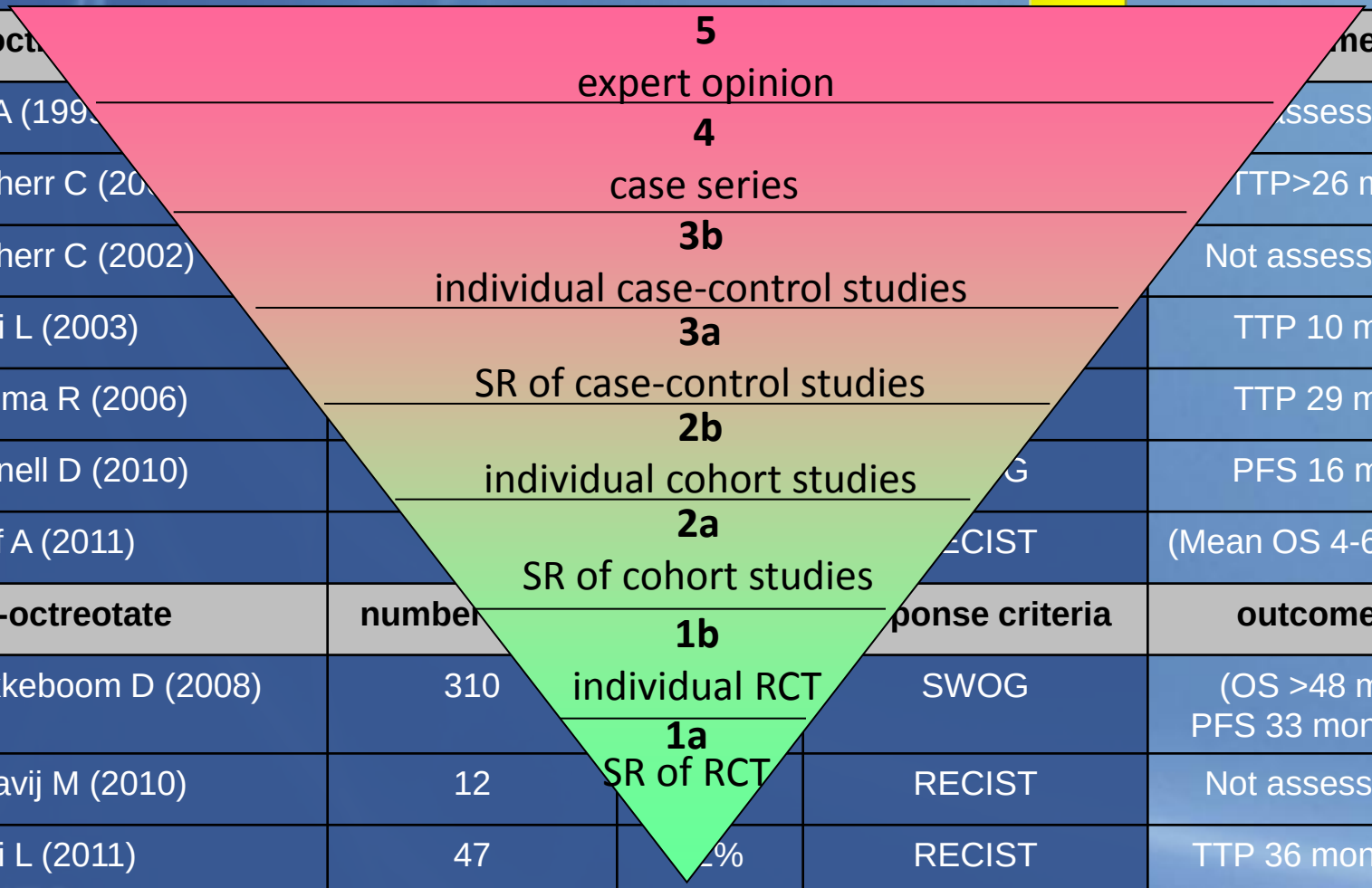
	Response										
	CR		PR		MR		SD		PD		
Tumor Type	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	Total No. of Patients
Carcinoid	1	1	41	22	31	17	78	42	37	20	188
Nonfunctioning pancreatic	4	6	26	36	13	18	19	26	10	14	72
Unknown origin			10	32	3	10	7	23	11	36	31
Gastrinoma			5	42	4	33	2	17	1	8	12
Insulinoma			3	60			1	20	1	20	5
VIPoma			1	50					1	50	2
Total	5	2	86	28	51	16	107	35	61	20	310

only 43% of all patients with documented progressive disease before PRRT



Kwekkeboom et al. J Clin Oncol 2008
van Essen et al. Acta Oncologica 2007

Clinical results of PRRT

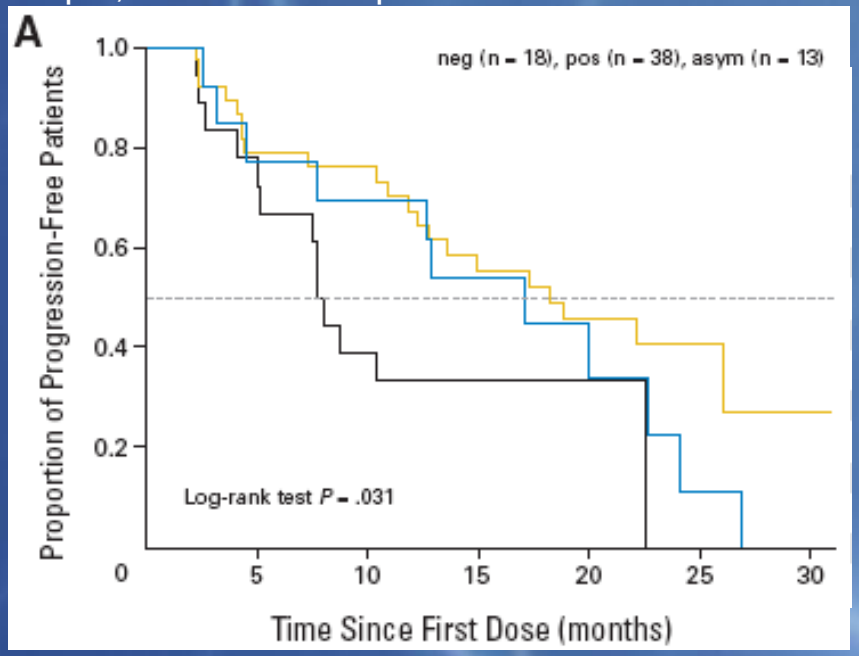


^{90}Y-oct				me
Otte A (199				ssessed
Waldherr C (20				TTP>26 m
Waldherr C (2002)				Not assessed
Bodei L (2003)				TTP 10 m
Valkema R (2006)				TTP 29 m
Bushnell D (2010)			G	PFS 16 m
Imhof A (2011)			ECIST	(Mean OS 4-60 m)
^{177}Lu-octreotate	**numbe**		**ponse criteria**	**outcome**
Kwekkeboom D (2008)	310		SWOG	(OS >48 m) PFS 33 months
Garkavij M (2010)	12		RECIST	Not assessed
Bodei L (2011)	47	2%	RECIST	TTP 36 months

Symptom Relief

^{90}Y-octreotide

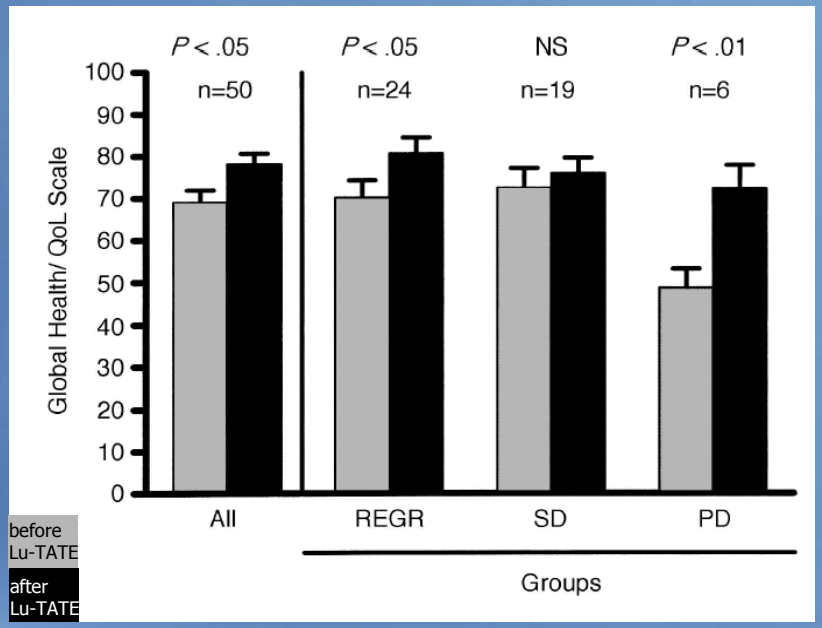
90 pts, MCA 13.3 GBq



Bushnell et al. J Clin Oncol 2010

^{177}Lu-octreotate

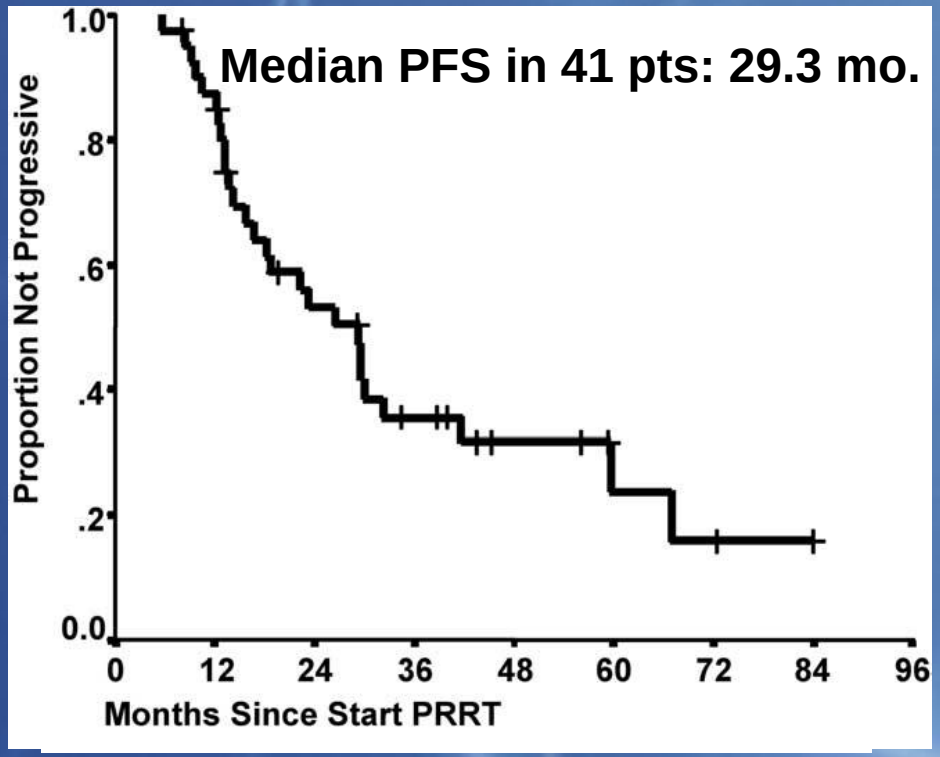
50 pts, MCA 22.2-29.6 GBq



Teunissen et al. J Clin Oncol 2004

Impact on survival

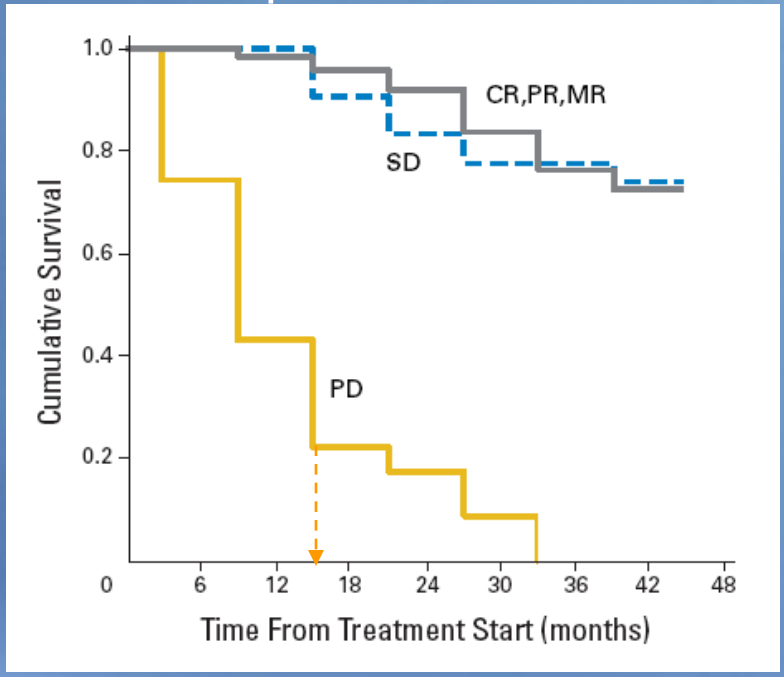
^{90}Y-octreotide



Valkema et al Semin Nucl Med 2006

^{177}Lu-octreotate

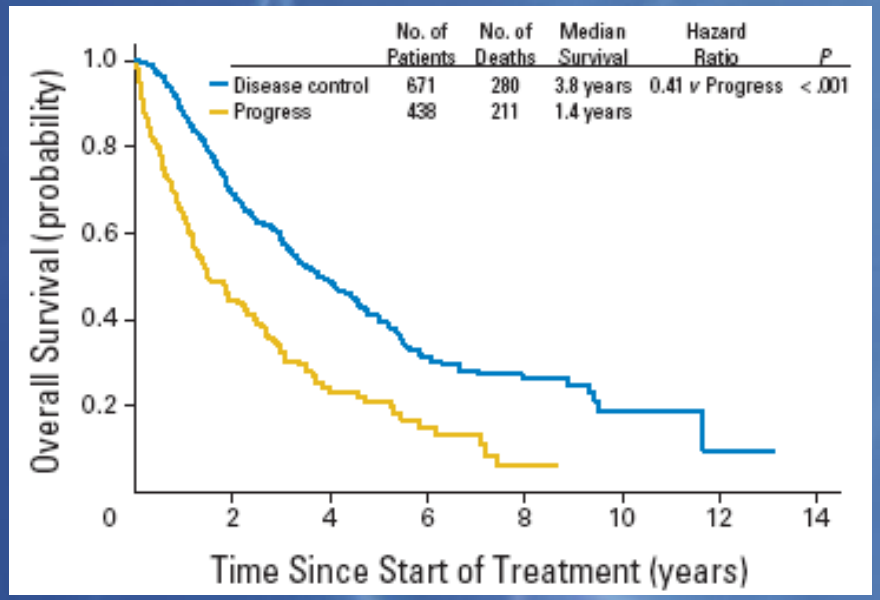
OS in 282 pts

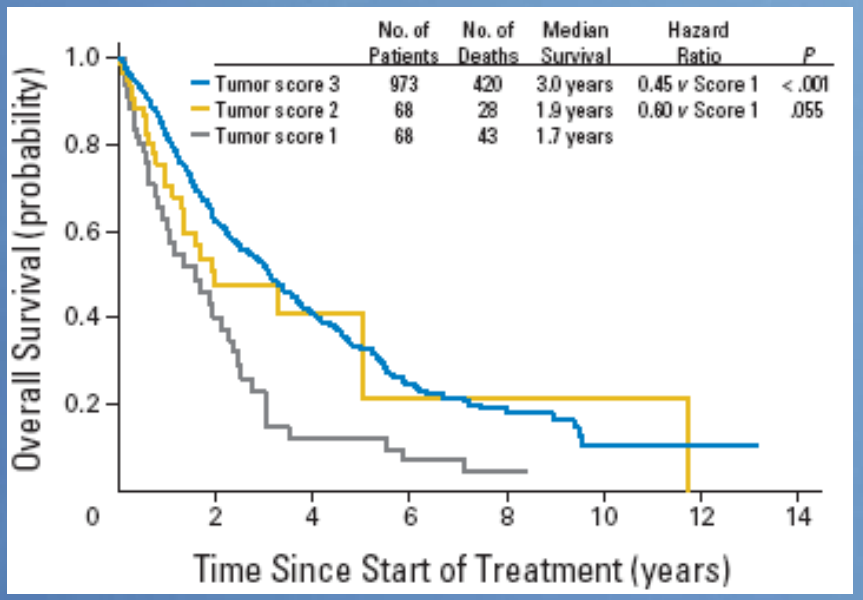


Modified from Kwekkeboom DJ et al. JCO 2008

Median PFS 33 mo.

Impact on survival: ^{90}Y-octreotide





Disease control and a high tumor uptake are associated with longer survival from time of first PRRT

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Imhof A et al. J Clin Oncol 2011

Impact on survival: comparison of ^{177}Lu-tate with other treatments

Study	Study Population	No. of Patients	Median OS From Referral (months)	Median OS From Diagnosis (months)
Clancy et al[9]	WDEC	137		72
	This study	310		128
	WDEC, Alk Phos < 127	67	51	
	This study	139	> 48	
	WDEC, Alk Phos > 127	46	19	
	This study	167	37	
Janson et al[10]	Carcinoid	256		92
Idem, update		304		115
	This study	188		155
Quaedvlieg et al[5]	Dutch patients with carcinoid liver metastases at diagnosis	58		43
	This study	100		97
Chu et al[12]	PNET with liver metastases	29	25	
	This study	76	44	
Mazzaglia et al[11]	Carcinoid liver metastases	35	47	82
	This study	172	> 48	154
	PNET liver metastases	18	35	54
	This study	76	44	94
Gupta et al[13]	Carcinoid liver metastases	69	34	
	This study	172	> 48	
	PNET liver metastases	54	23	
	This study	76	44	
Ho et al[14]	Carcinoid/PNET liver metastases	46	33	
	This study	276	45	

^{177}Lu-octreotate

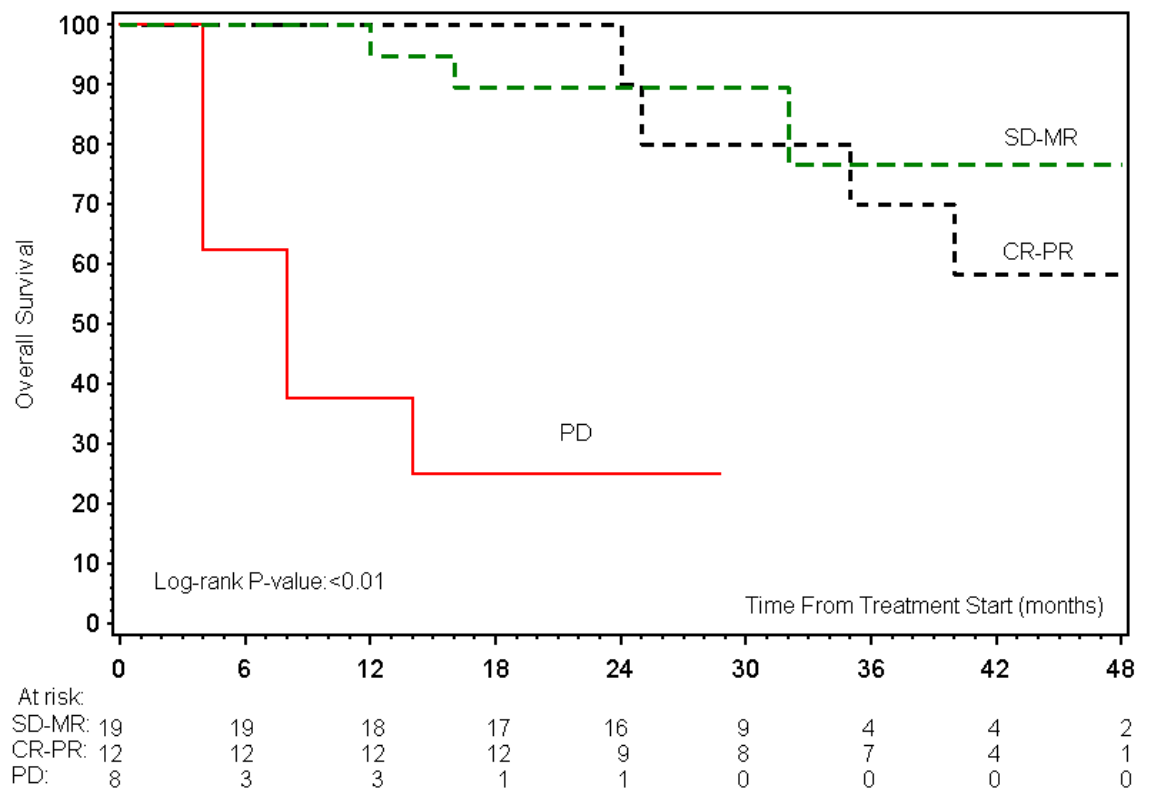
Survival benefit:

- **40-72 mo. from diagnosis**
- **12 – 21 mo. from therapy start**

Modified from Kwekkeboom DJ et al. JCO 2008

Survival in pts with progression at baseline

39 pts



From a prognostic point of view, stabilizations and objective responses showed the same survival probability

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Bodei et al. Eur J Nucl Med Mol Imaging 2011

Safety: organ dosimetry

Absorbed doses from radiopeptides

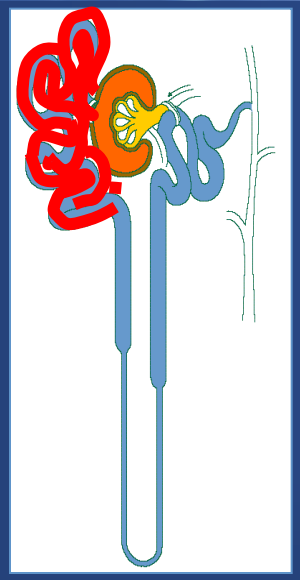
	Stabin 1997 [109], Kwekkeboom 2001 [50]	Kwekkeboom 2001 [50]	Cremonesi 1999 [47]	Forster 2001 [110]	Helisch 2004 [111]	Forrer 2004 [112]
Therapy	[^{111}In-DTPA^0, Tyr^3]-octreotide	[^{177}Lu-DOTA^0, Tyr^3]-octreotate	[^{90}Y-DOTA^0, Tyr^3]-octreotide	[^{90}Y-DOTA^0, Tyr^3]-octreotide	[^{90}Y-DOTA^0, Tyr^3]-octreotide	[^{90}Y-DOTA^0, Tyr^3]-octreotide
Dosimetry	[^{111}In-DTPA^0, Tyr^3]-octreotide	[^{177}Lu-DOTA^0, Tyr^3]-octreotate	[^{111}In-DOTA^0, Tyr^3]-octreotide	[^{86}Y-DOTA^0, Tyr^3]-octreotide	[^{86}Y-DOTA^0, Tyr^3]-octreotide	[^{111}In-DOTA^0, Tyr^3]-octreotide
Patients	16	5	30	3	8	5
Kidneys	0.52±0.24	1.65±0.47	3.9±1.9[b]	2.73±1.41		2.84±0.64
Kidneys + protection		0.88±0.19			1.71±0.89	
Liver	0.065±0.01	0.21±0.07	0.72±0.57	0.66±0.15	0.72±0.40	0.92±0.35
Spleen	0.34±0.16	2.15±0.39	7.62±6.30	2.32±1.97	2.19±1.11	6.57±5.25
Red marrow	0.03±0.01	0.07±0.004	0.03±0.01	0.49±0.002	0.06±0.02	0.17±0.02
Tumour (range)	0.72–6.8[a]	3.9–37.9	1.4–31	3.21–19.58	2.1–29.5	2.4–41.7

[a] From reference [50]
[b] Series enlarged from the original one, as in Bodei et al. [44]

Brans B, Bodei L et al. EJNMMI 2007

Safety: renal toxicity

Center (reference)	Ligand	No. of patients	Toxicity			
			Grade 3 or 4 hematologic*			
			Platelets	Hb	WBC	Other†
Rotterdam (*2*)	[^{111}In-DTPA^{0}]octreotide	50	10	15	2	3 AML or MDS
New Orleans (*3*)	[^{111}In-DTPA^{0}]octreotide	27	7	11	7	3 liver, 1 renal
Milan (*10*)	[^{90}Y-DOTA^{0}, Tyr^{3}]octreotide	40	7	3	7	
Basel (*4*)	[^{90}Y-DOTA^{0}, Tyr^{3}]octreotide	29	3	7	0	4 renal‡
Basel (*6*)	[^{90}Y-DOTA^{0}, Tyr^{3}]octreotide	39	0	3	0	1 renal
Rotterdam (*11*)	[^{90}Y-DOTA^{0}, Tyr^{3}]octreotide	60	12	8	13	1 MDS, 1 liver, 1 renal
Rotterdam (*18*)	[^{177}Lu-DOTA^{0}, Tyr^{3}]octreotate	200	3	1	2	1 MDS, 1 renal

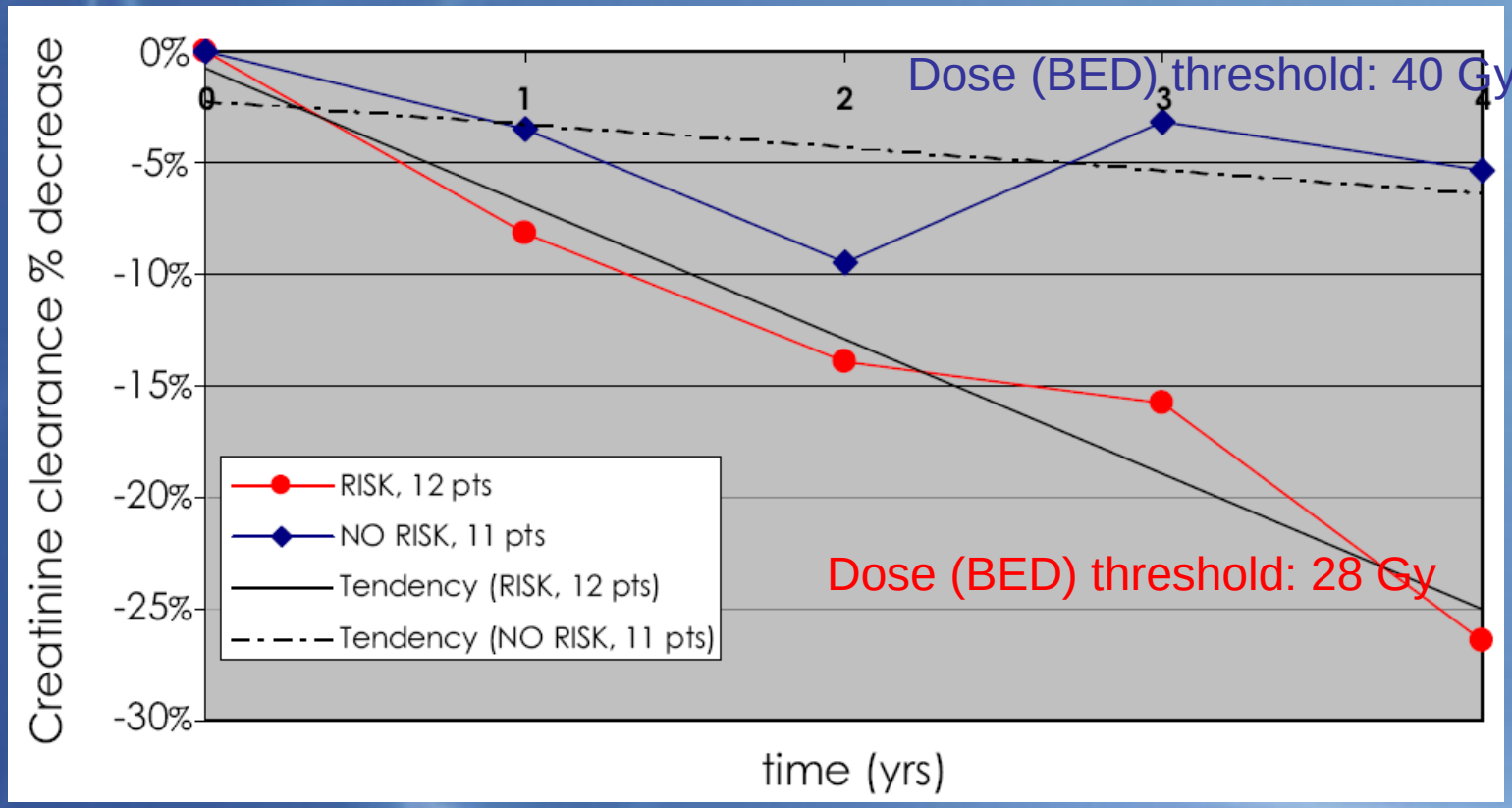


arginine **lisine**

dose reduction: 27-50%*

*de Jong JNM 2002

Dose thresholds according to risk factors (hypertension, diabetes)

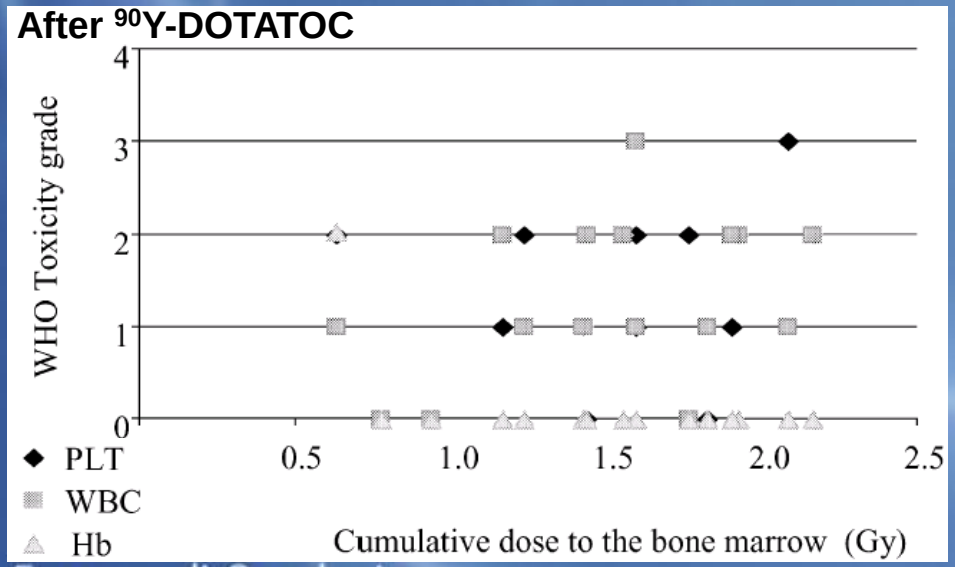


Bodei L. et al. Eur J Nucl Med Mol Imaging 2008

Safety: bone marrow

Center (reference)	Ligand	No. of patients	Toxicity: Grade 3 or 4 hematologic* Platelets	Hb	WBC	Other†
Rotterdam (2)	[^{111}In-DTPA^0]octreotide	50	10	15	2	3 AML or MDS
New Orleans (3)	[^{111}In-DTPA^0]octreotide	27	7	11	7	3 liver, 1 renal
Milan (10)	[^{90}Y-DOTA^0, Tyr^3]octreotide	40	7	3	7	
Basel (4)	[^{90}Y-DOTA^0, Tyr^3]octreotide	29	3	7	0	4 renal‡
Basel (6)	[^{90}Y-DOTA^0, Tyr^3]octreotide	39	0	3	0	1 renal
Rotterdam (11)	[^{90}Y-DOTA^0, Tyr^3]octreotide	60	12	8	13	1 MDS, 1 liver, 1 renal
Rotterdam (18)	[^{177}Lu-DOTA^0, Tyr^3]octreotate	200	9.5% after at least one cycle			1 MDS, 1 renal

Kwekkeboom DJ et al, J Nucl Med 2005
Kwekkeboom DJ et al. Endocrine Rel Cancer 2010



Bodei L et al, Eur J Nucl Med 2004

When to plan PRRT

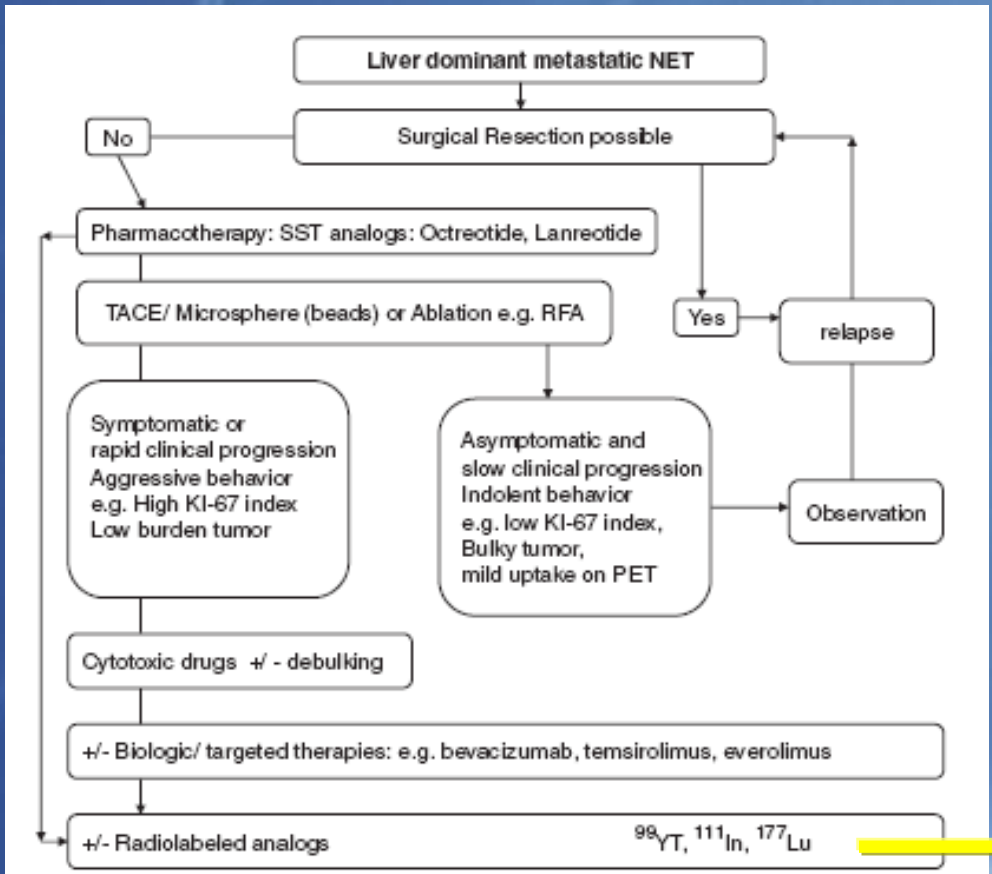


FIGURE 5. Suggested treatment algorithm for liver dominant metastatic NETs.

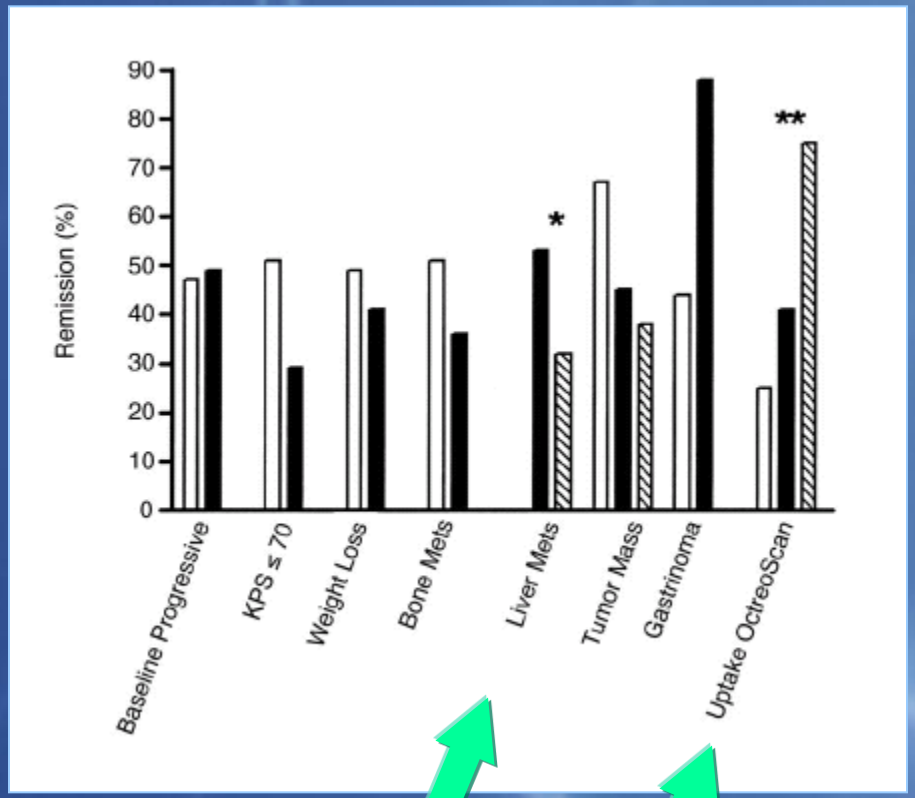
last resource..?

Khasraw M et al. J Clin Gastroenterol 2009

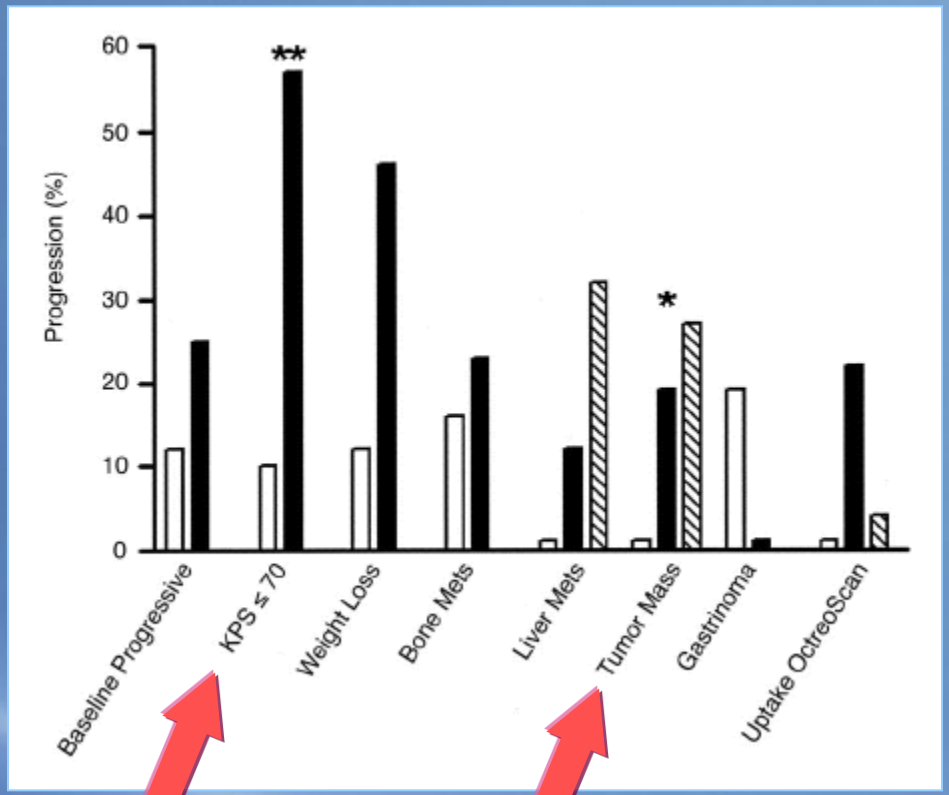
Tumor shrinkage: predictive factors

(177Lu-octreotate)

Response



Progression

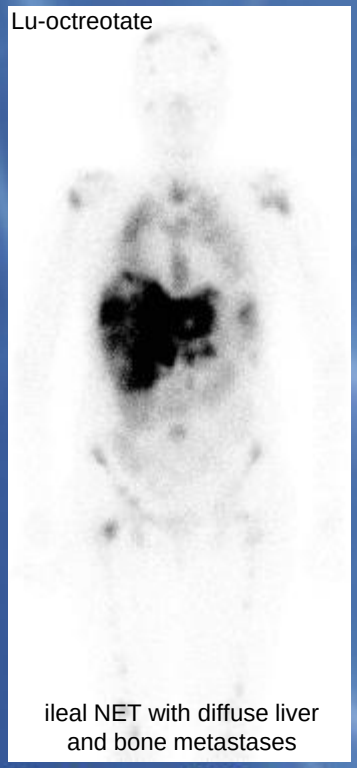


Kwekkeboom DJ et al, J Clin Oncol 2005

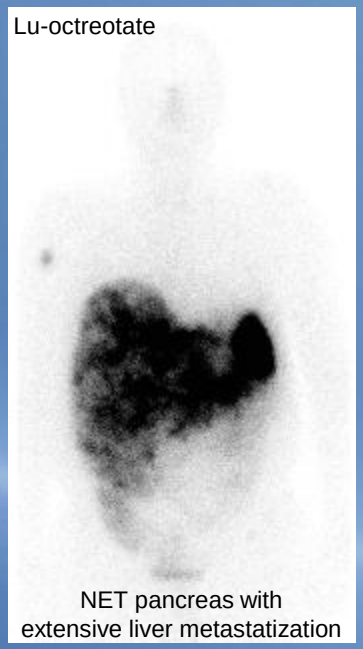
Factors negatively impacting on survival

- extensive liver involvement
- Karnofsky performance status <70%
- weight loss
- bone metastases
- functional activity of pancreatic NEC

Kwekkeboom DJ. J Clin Oncol 2008

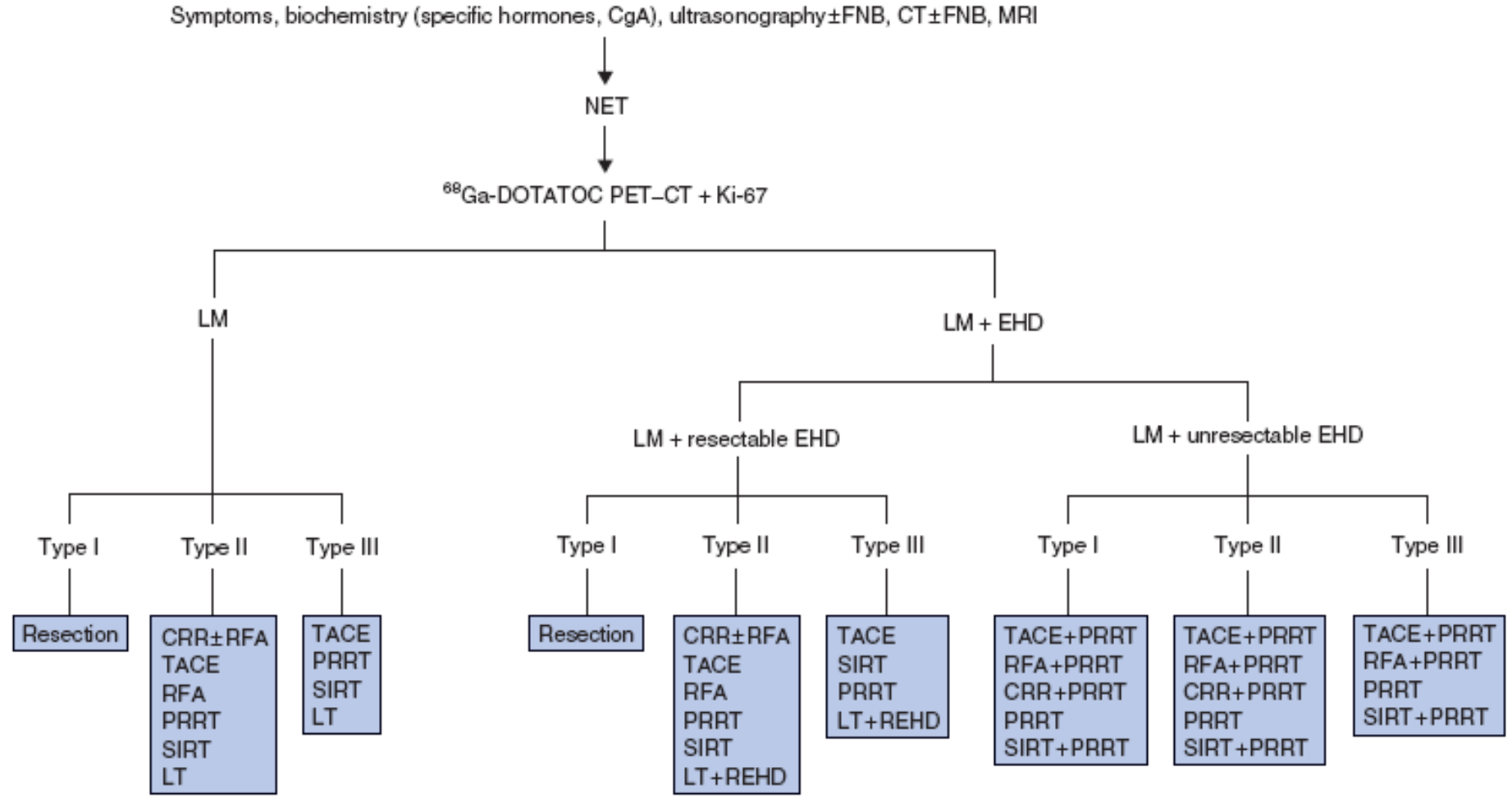


ileal NET with diffuse liver and bone metastases



NET pancreas with extensive liver metastatization

Algorithm for liver mets



Frilling A et al. B J Surgery 2009

When should PRRT be proposed..?

…within NET tumor board

Unresectable/ metastatic
WHO G1-G2; functioning/non functioning

sst_2 +

SSA ± IFNα
± molecular
targeted agents

"early" PD
or bulky

if possible…

cytoreduction
(surgery on ≥90% of the disease, TACE, RFA, PEI radioembolization, HIFU)

PRRT
(syndrome ctrl, growth ctrl, eradication)

usually…

PRRT
(syndrome ctrl, growth ctrl, cytoreduction)

if possible…

salvage…

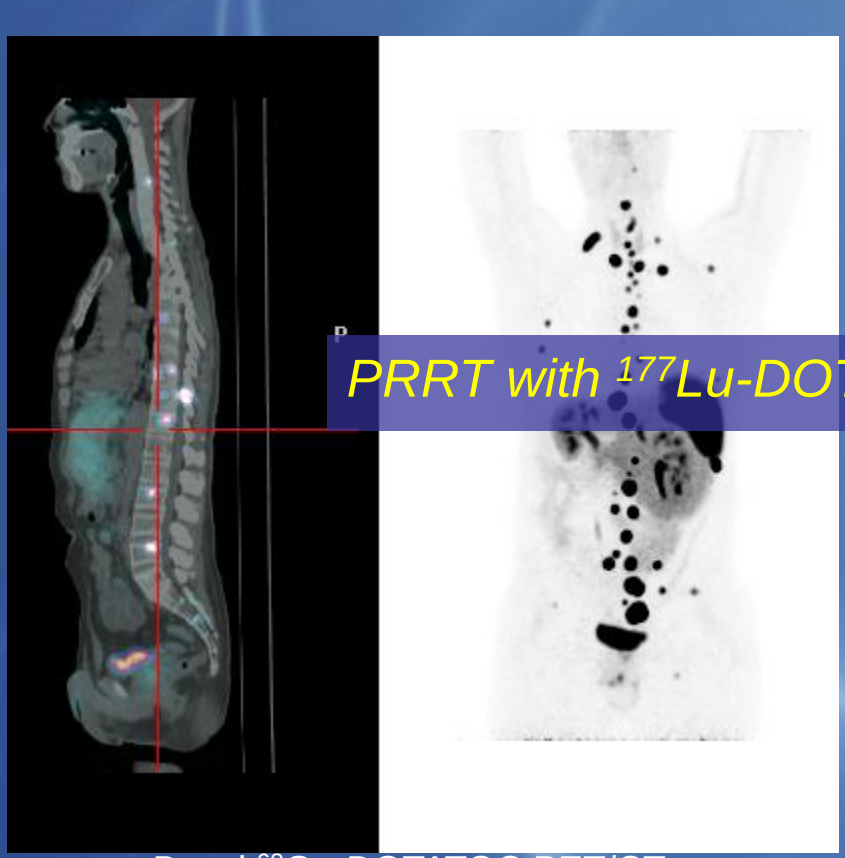
cytoreduction
(surgery, TACE, RFA, PEI radioembolization, HIFU)

Cytoreduction *before* PRRT

Kwekkeboom DJ et al Endocr Rel Cancer 2010

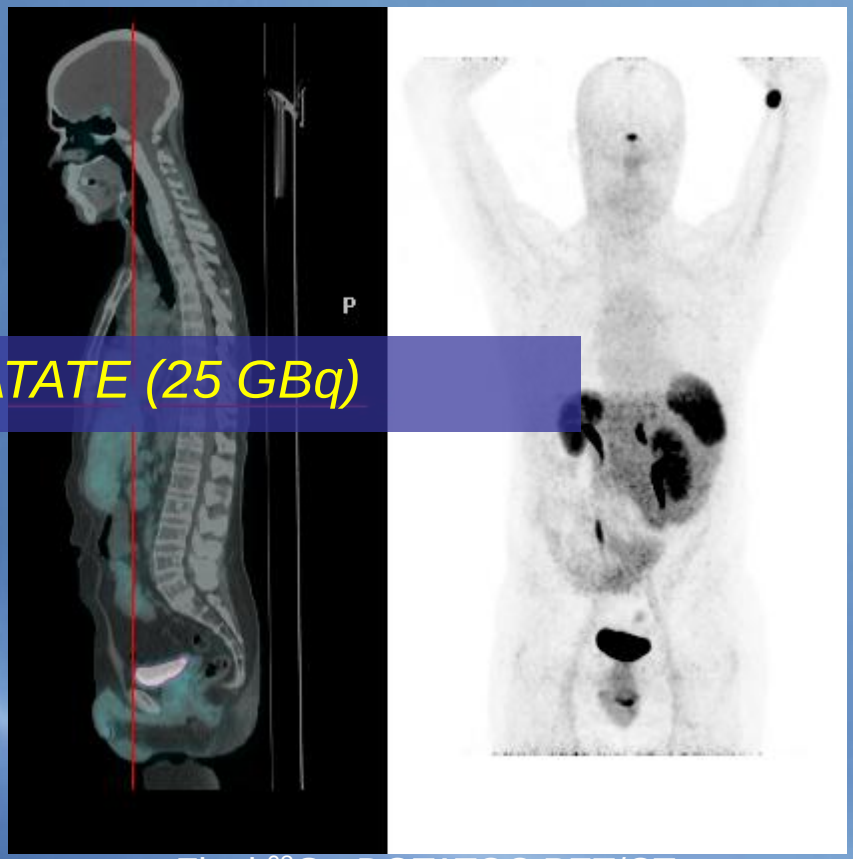
FOLLOW UP: bone marrow mets from a pancreatic NET G2

Resection of a 16-cm liver met involving the right lobe



Basal ^{68}Ga-DOTATOC PET/CT

PRRT with ^{177}Lu-DOTATATE (25 GBq)



Final ^{68}Ga-DOTATOC PET/CT

Cytoreduction *after* PRRT

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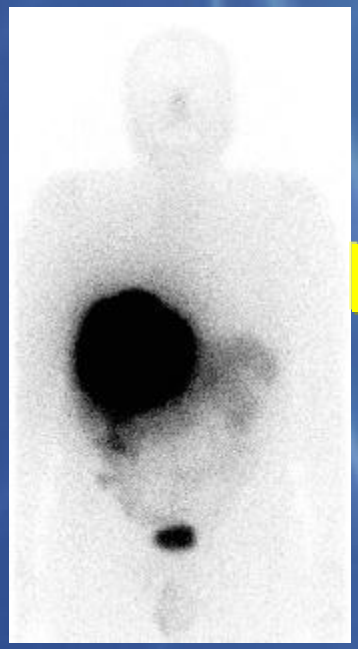
Kwekkeboom DJ et al Endocr Rel Cancer 2010

Rectal NET with a synchronous inoperable liver met

- Rectosigmoid resection
- Capecitabine (500 bid) + SSA → **PD**
- **Negative ^{18}FDG PET**

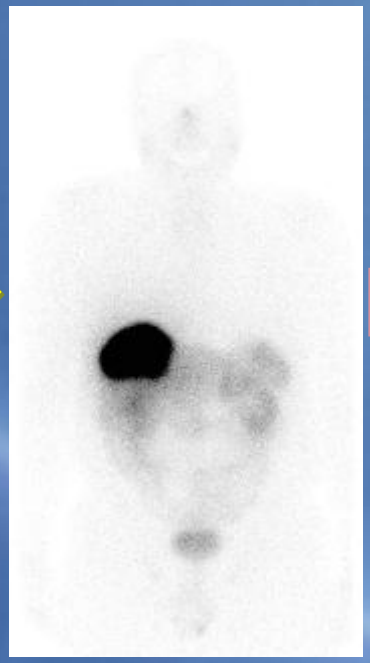
Start PRRT with ^{177}Lu-octreotate



basal ^{177}Lu-octreotate

CT ⌀ 21.5 cm

772 mCi

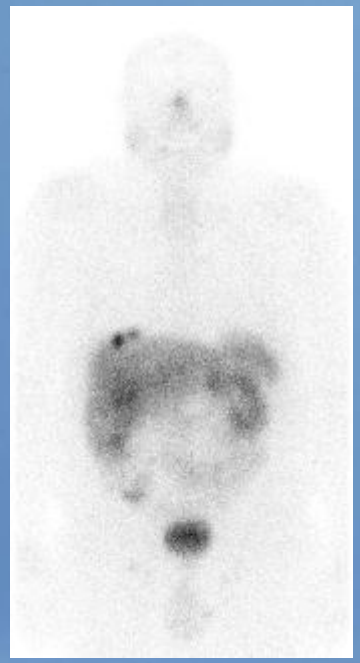


final ^{177}Lu-octreotate

CT ⌀ 12.5 cm

3 TAE

"Neo-adjuvant" PRRT (2^{nd} course)



^{177}Lu-octreotate: 2^{nd} course, 1^{st} cycle

CT ⌀ 7.5 cm

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Re-cycling

van Essen M et al J Nucl Med 2010

Re-treatment

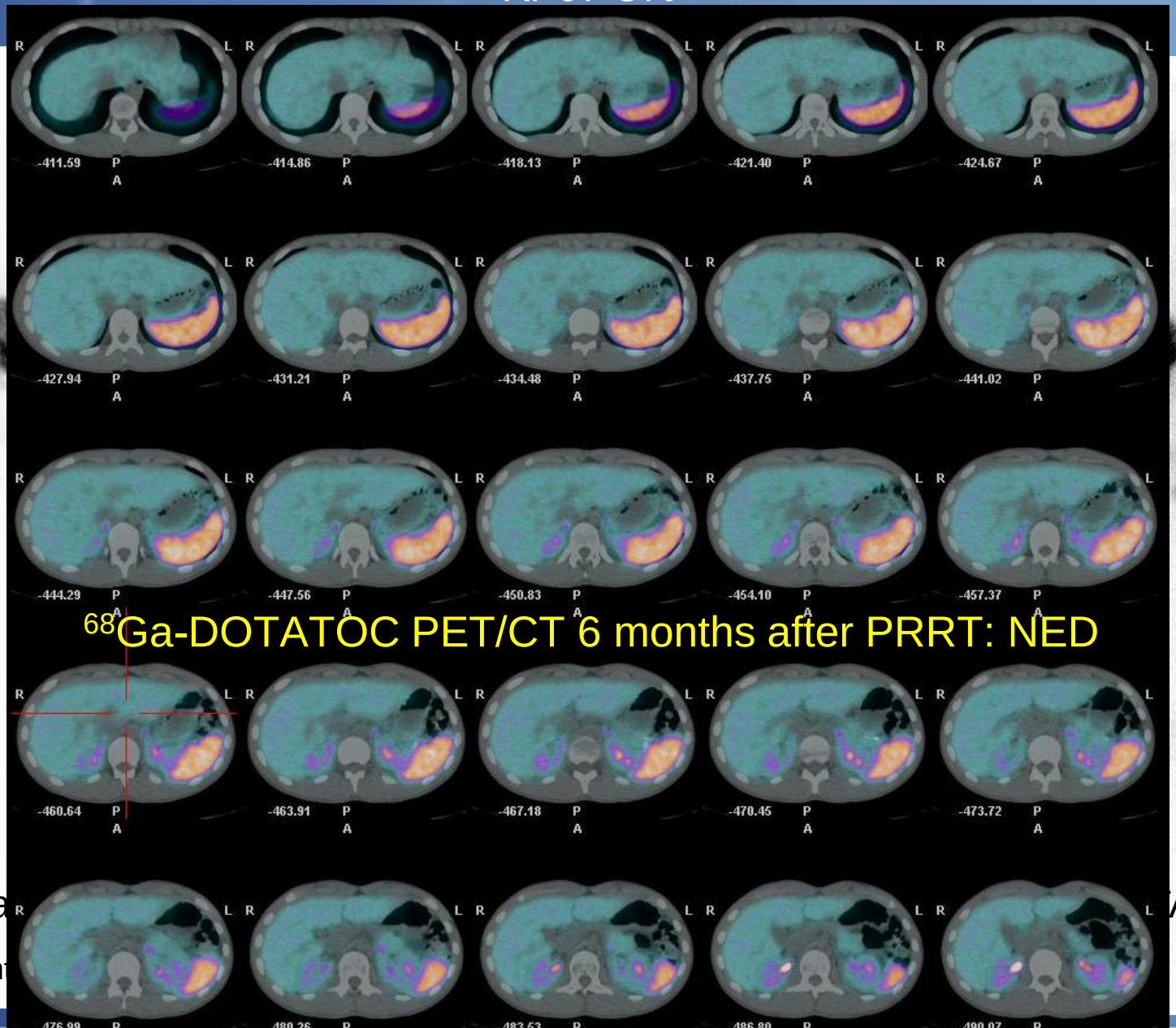
TABLE 4. Therapy Outcome

Outcome	Radiologic evaluation	Clinical evaluation
PD	15 (45%)	17 (52%)
SD	10 (30%)*	8 (24%)
MR	6 (18%)	6 (18%)
PR	2 (6%)	2 (6%)

van Essen M et al. J Nucl Med 2010

Diffuse liver and bone mets from a pancreatic NET G2

Ki-67 8%

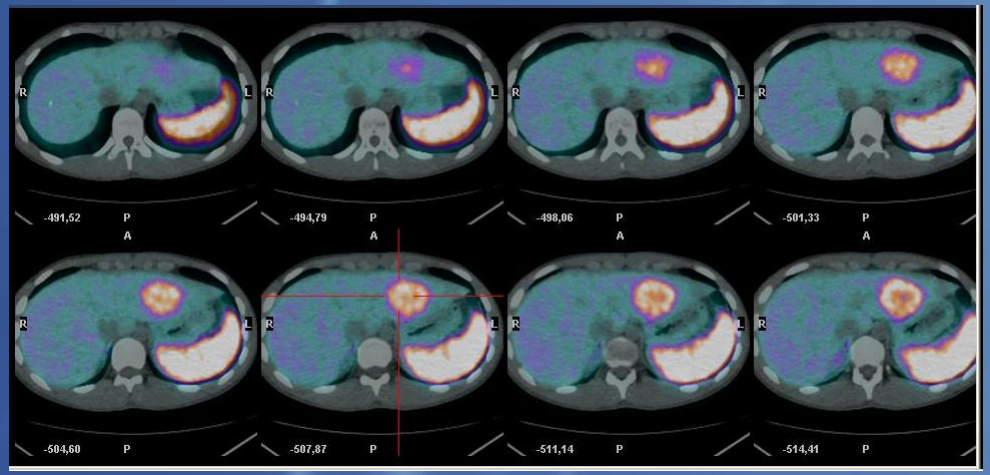


^{68}Ga-DOTATOC PET/CT 6 months after PRRT: NED

basa ATE

Ant Post

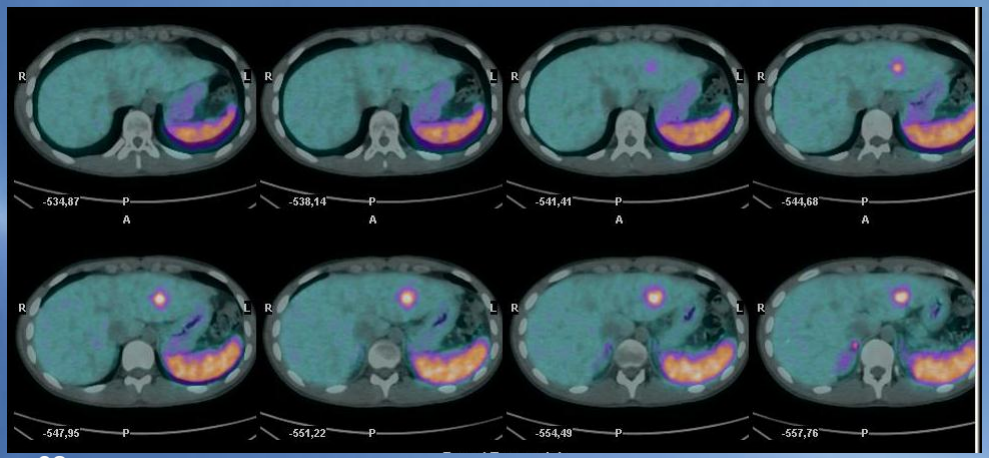
TTP 31 months…



^{68}Ga-DOTATOC PET/CT, fused transaxial slices
16 months after PRRT end

New PRRT with
^{177}Lu-DOTATATE
(14.5 GBq)

Partial response



^{68}Ga-DOTATOC PET/CT, fused transaxial slices
After PRRT re-cycling

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Areas of improvement

1- PRRT in variable Ki67/MI (G1/G2): to be studied

2- PRRT + SSA / vs SSA: to be studied

3- Therapy combinations: capecit

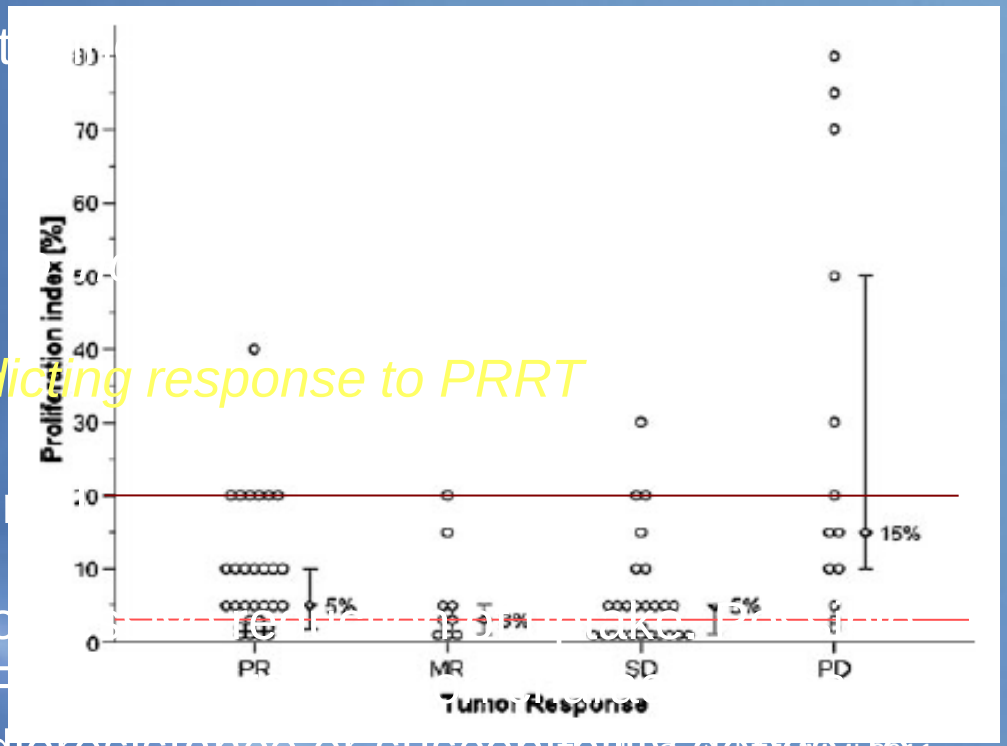
4- *Timing…*

5- *Definition of therapy schedule*

6- *The role of ^{18}FDG PET in predicting response to PRRT*

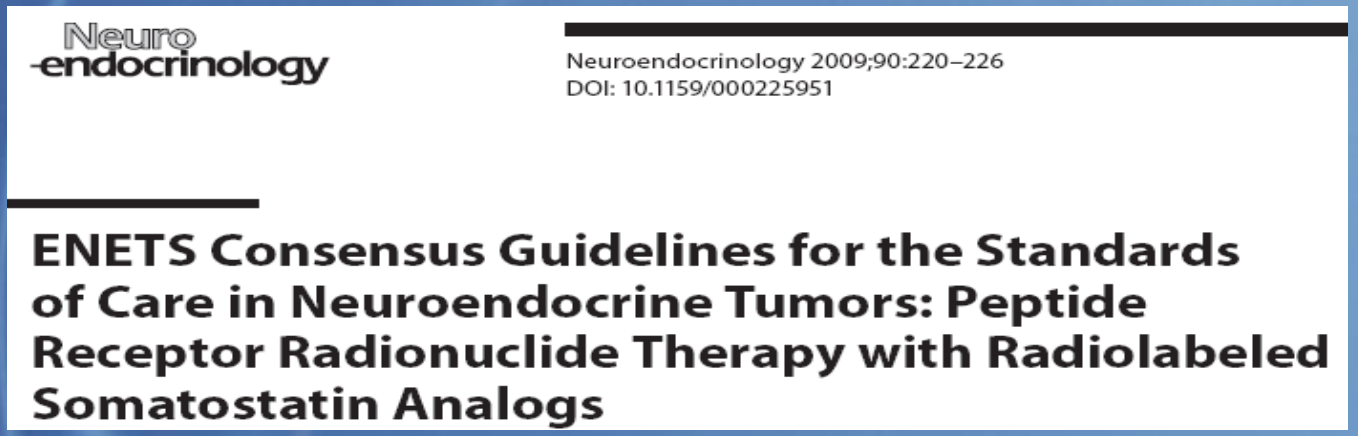
7- PRRT in G3 tumors: experimen

8- Early markers of response: pro
measurement of hypoxia (^{18}F
(^{18}FLT), SSTR mutations, radioresistance or susceptibility genes, to
individualize treatments



Ezziddin et al EJNMMI 2011

PRRT: regulatory issues



- Permission for PRRT in several European countries is based on national legislation and production according to GMP regulations

- ^{177}Lu-DOTATATE and ^{90}Y-DOTATOC have been granted orphan drug status by EMA and US FDA

CONCLUSIONS

- PRRT with ^{90}Y-DOTATOC or ^{177}Lu-DOTATATE is oncologically active and is likely to have an impact on survival parameters

- PRRT has an acceptable toxicity (kidney and bone marrow) and is reasonably "safe" for renal function (adequately selecting pts according to risk factors)

➔ *Now we need…*

– *Prospective phase III randomized trials*

- ***PRRT vs "cold" SSA***
- *PRRT vs everolimus*
- *PRRT vs sunitinib*
- *^{90}Y-octreotide vs ^{177}Lu-octreotate*

Thank you for your attention!