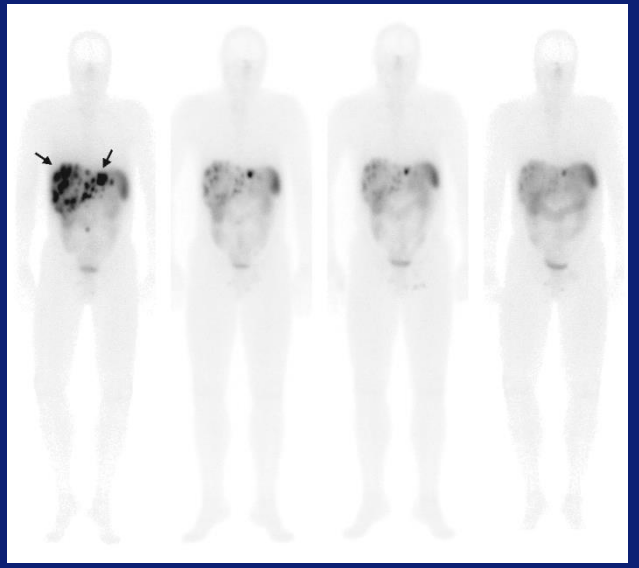
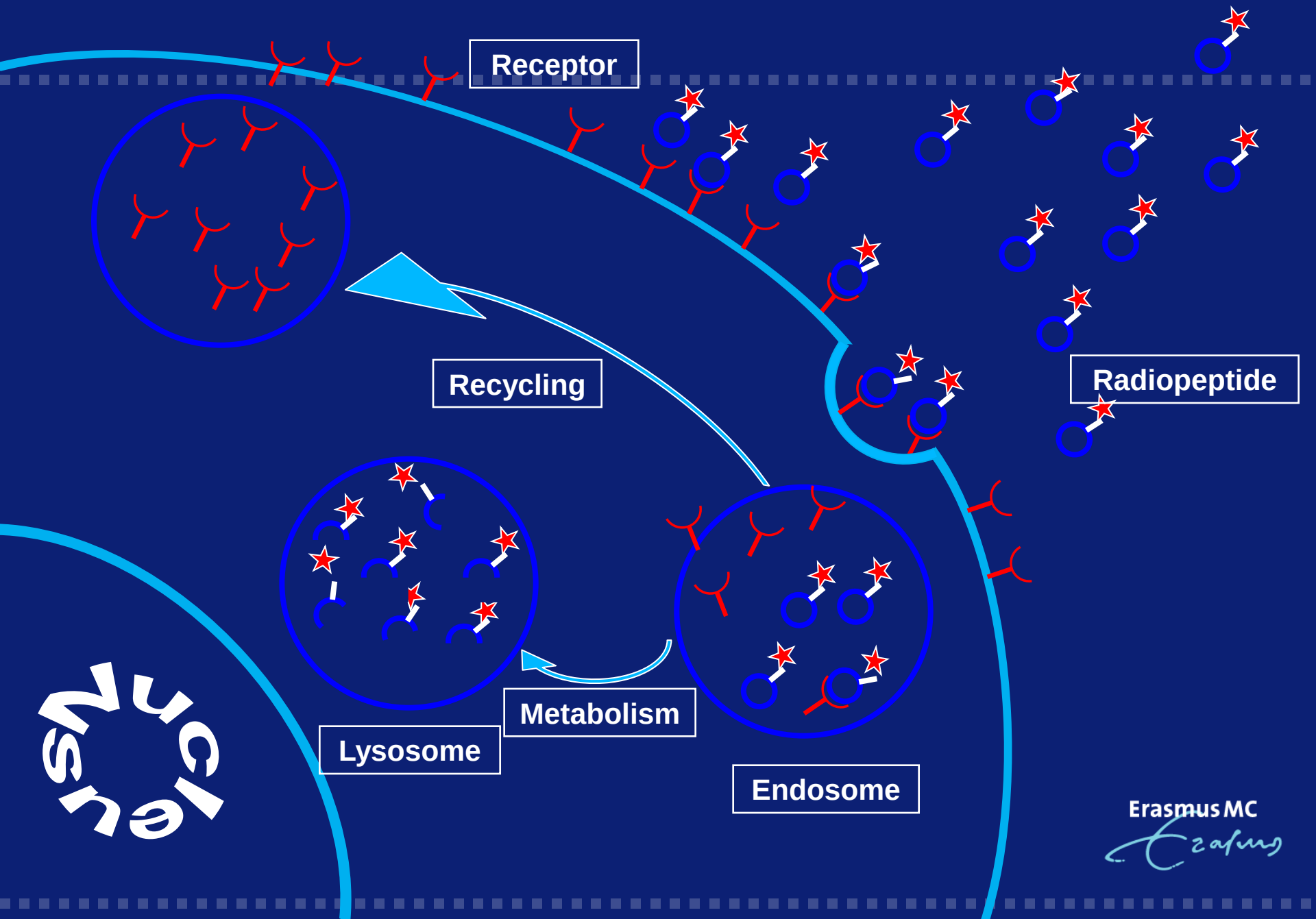
Erasmus MC
University Medical Center Rotterdam

PRRT: Status and future



Dik Kwekkeboom

PRRT: Mechanism of Action



[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy
Most important Inclusion Criteria

- Pathology proven, inoperable tumor
- Tumor uptake on octreoscan ≥ normal liver.
- No prior therapy with other radiolabelled somatostatin analogues.
- Hb ≥ 6 mmol/L; WBC ≥ $2*10^{9}$/L; Platelets ≥ $80*10^{9}$/L; serum creatinine ≤ 150 umol/L.
- Karnofsky Performance Status ≥ 50.
- Signed informed consent

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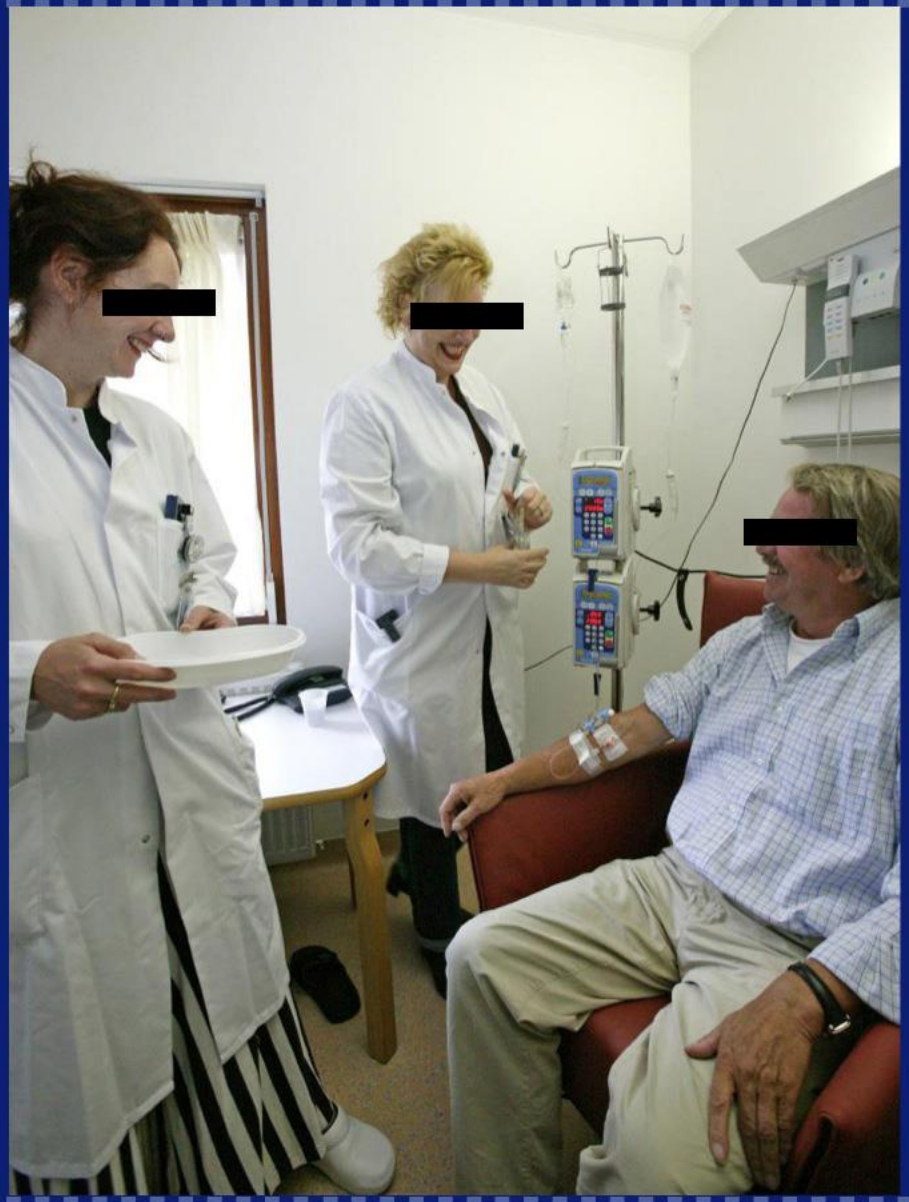
[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy in practice



- IV Aminoacids 4 h
- IV Granisetron 3mg
- IV ^{177}Lu-Octreotate 30 min
- Hospitalization 1 night

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[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: 504 patients treated according to protocol; Acute Toxicity

Side-effect	Present	Absent	Total
Nausea	450 25%	1322 75%	1772
Vomiting	170 10%	1602 90%	1772
Pain	173 10%	1599 90%	1772

Temporary Hairloss (no baldness; WHO grade 1): 62% of patients

Nausea/Vomiting WHO grade 1-2, duration <24h

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[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: 504 patients treated according to protocol; Subacute Toxicity

WHO Toxicity	Grade 3	Grade 4	Total
Hgb	0.4%	0.1%	0.4%
WBC	1.4%	0.1%	1.5%
PLT	1.9%	0.8%	2.6%

Percentages are treatment based

Any grade 3/4 toxicity: 3.6%

Any grade 3/4 toxicity patient based: 9.5%

Temporary Hairloss (no baldness; WHO grade 1): 62% of patients

Hormonal crises, need for special care ± 1 %

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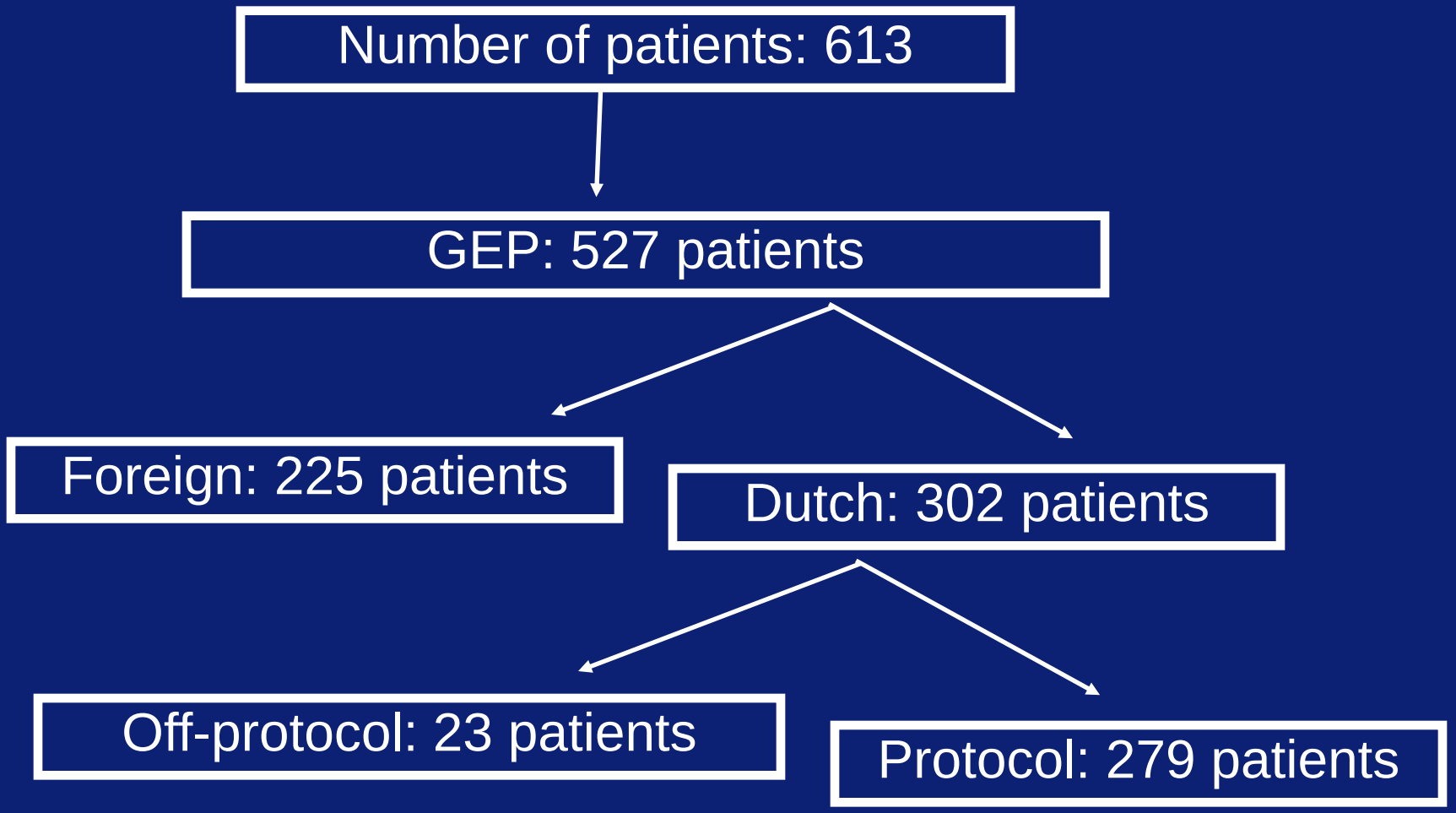
[^{177}Lu-DOTA^{0},Tyr^{3}]-Octreotate Therapy: Treatment update Patients treated 2000 - 2007 Update up to dec 2009



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[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy 279 Patients / Serious Side-Effects

- **2** Renal insufficiencies
- **2** Leukemias (1 CML, 1 AML)
- **4** cases of MDS
- **1** pancytopenia > 6mo (2 bone marrow biopsies: No MDS)

- **9/279 = 3%**

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[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: 263 Dutch GEPNET patients 2000-2007 / 2010

Tumor	CR	PR	MR	SD	PD	Total
Midgut Carcinoid		37 27%	36 27%	41 30%	22 16%	136
NE Pancreas	3 5%	25 39%	10 16%	15 23%	11 17%	64
NE Unknown Origin		11 46%	3 13%	2 8%	8 33%	24
Gastrinoma/Insulinoma/ Vipoma		7 70%		1 10%	2 20%	10
Fore & Hindgut Carcinoid		13 45%	4 14%	9 31%	3 10%	29
Total	3 1%	93 35%	53 20%	68 26%	46 18%	263

- Best responses are listed

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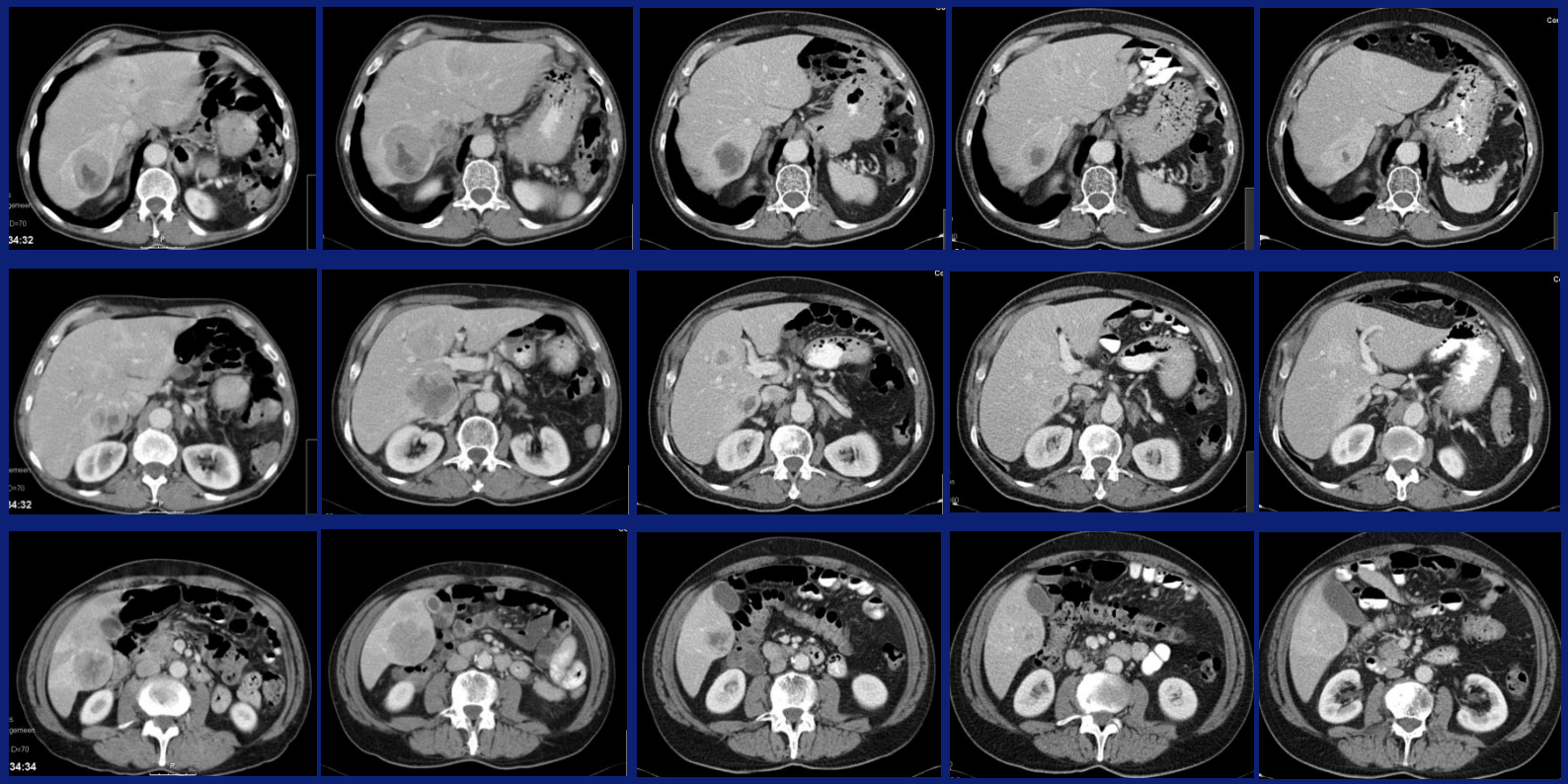
[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: Liver metastases from a Pancreatic NET



-3 mo | 0 mo; PD | 2 mo post Tx | 3 mo post | 6 mo post

Ongoing regression and change in appearance of liver metastases

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[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: Tumor Uptake and Response (MR, PR, CR)

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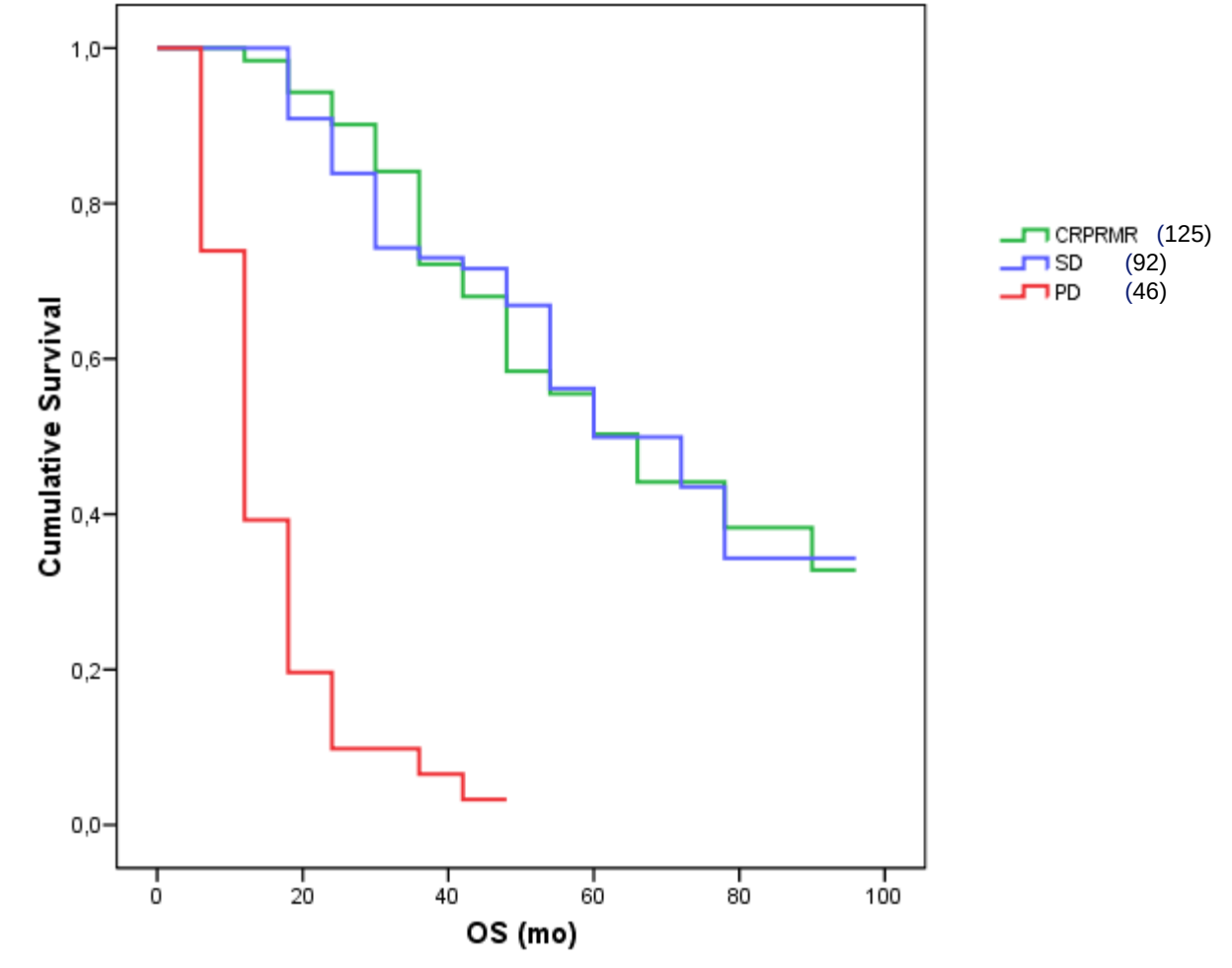
Overall Survival from treatment start: 263 Dutch GEPNET patients 2000-2007 / 2010



OS CR/PR/MR 60 mo, SD60 mo, PD 10 mo

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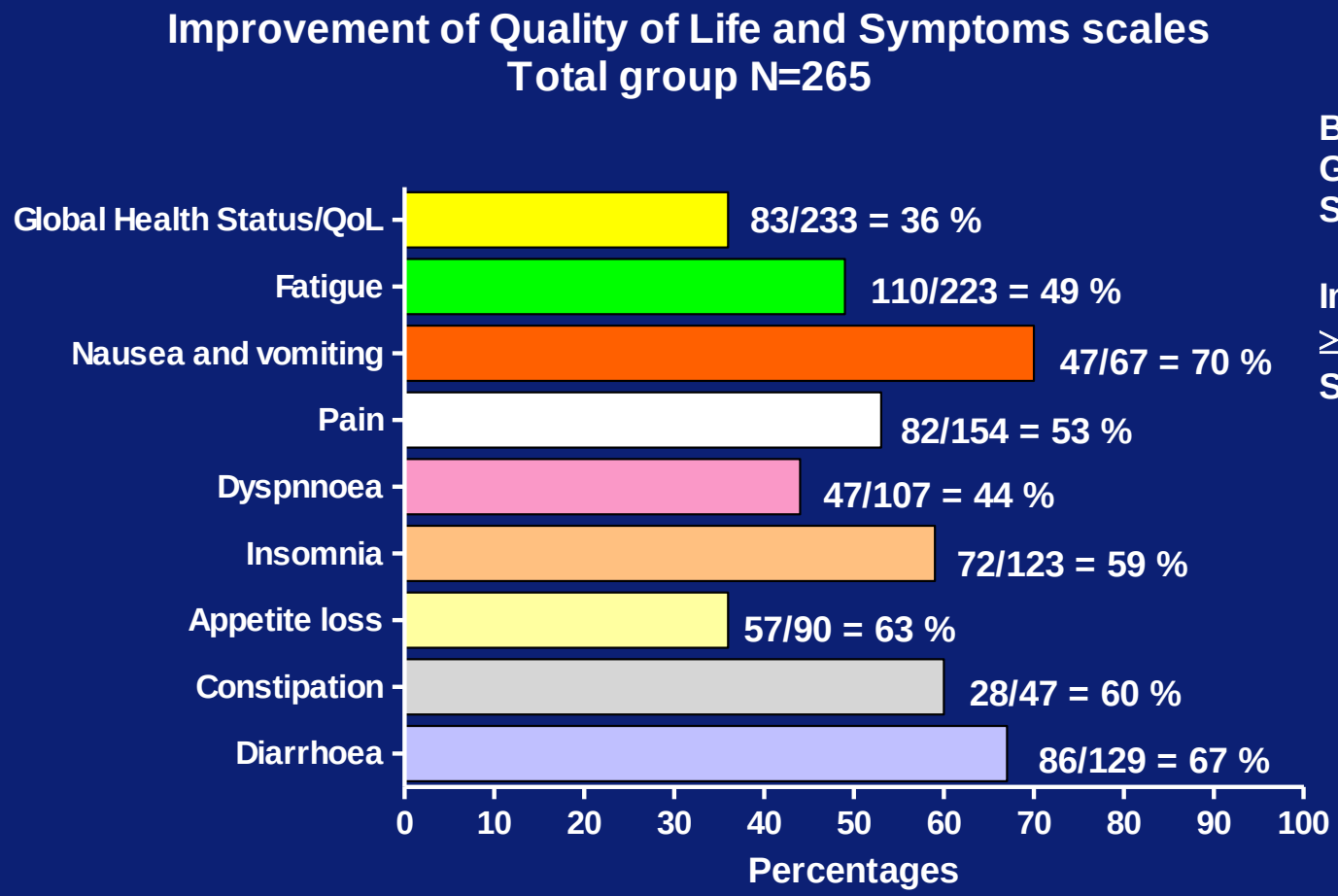
Evaluation after [^{177}Lu-DOTA^{0},Tyr^{3}]octreotate therapy of QoL and symptoms using QLQ scales in the total group



Before therapy:
GHS /QoL < 100
Symptom scales > 0

Improvement after therapy:
≥ + 10 in GHS/QoL
Symptom scales ≤ -10

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PRRT in GEPNET Patients: Tumor Response

Center	Ligand	Patients	CR+PR
Rotterdam (Valkema 2002)	[^{111}In-DTPA^{0}]octreotide	26	0%
New Orleans (Anthony 2002)	[^{111}In-DTPA^{0}]octreotide	26	8%
Milan (Bodei 2003)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	21	29%
Basel (Waldherr 2001/2)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	74	24%
Basel (Waldherr 2002)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	33	33%
Multicenter (Valkema 2006)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	9%
Multicenter (Bushnell 2010)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	90	4%
Copenhagen (Pfeifer 2011)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	53	23%
Warsaw (Cwikla 2010)	[^{90}Y-DOTA^{0},Tyr^{3}]octreotide	58	23%
Rotterdam (Kwekkeboom 2008)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	310	29%
Gothenburg (Sward 2010)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	26	38%
Lund (Garkavij 2010)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	12	17%
Milan (Bodei 2011)	[^{177}Lu-DOTA^{0},Tyr^{3}]octreotate	42	31%

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PRRT in GEPNET Patients: Survival Data

Center	Ligand	Patients	Liver Mets	PFS (mo)	OS (mo)
Multicenter (Valkema 2006)	^{90}Y-DOTATOC	58	-	29	37
Multicenter (Bushnell 2010)	^{90}Y-DOTATOC	90	72%	16	27
Copenhagen (Pfeifer 2011)	^{90}Y-DOTATOC	53	87%	29	-
Warsaw (Cwikla 2010)	^{90}Y-DOTATOC	58	85%	17	22
Rotterdam (Kwekkeboom 2008)	^{177}Lu-octreotate	310	89%	33	46

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PRRT: Adverse events

- ^{90}Y-DOTATOC: Renal insufficiency in 1-3.5% (3 studies); MDS in 2% of patients (1 study).
- ^{90}Y-DOTATOC: Renal insufficiency in 9% in 1 study; not all had amino acid protection; poor baseline kidney function not excluded.
- ^{177}Lu-DOTA-Octreotate: Renal insufficiency in 0.5%; MDS in 1% in 1 study.
- ^{177}Lu-DOTA-Octreotate update in 279 Dutch patients (long follow-up): 2 renal insufficiencies; 2 Leukemias (1 CML, 1 AML); 4 MDS; 1 pancytopenia > 6mo (2 bone marrow biopsies: no MDS). 9/279 = 3%

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PRRT and established therapies

- Except for Sandostatin LAR in midgut carcinoids no proof of efficacy with prospective randomised trials for any treatment.
- Streptozotocin + Doxorubicin, Everolimus, and Sunitinib were proven effective with randomised trials in Pancreatic NETs.
- Many other studies are RETROspective.
- Available retrospective data favour PRRT in terms of PFS.

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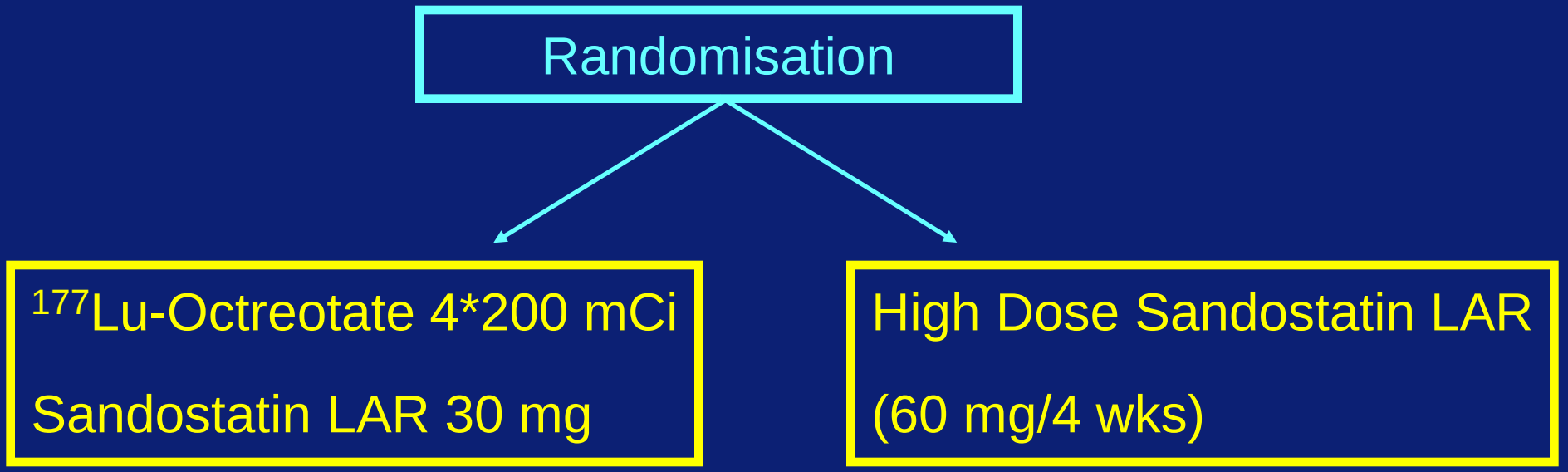
[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: Randomised Registration Trial

Prospective randomised trial started 2012



- Midgut carcinoid patients, progressive under Sandostatin LAR
- Primary endpoint: PFS

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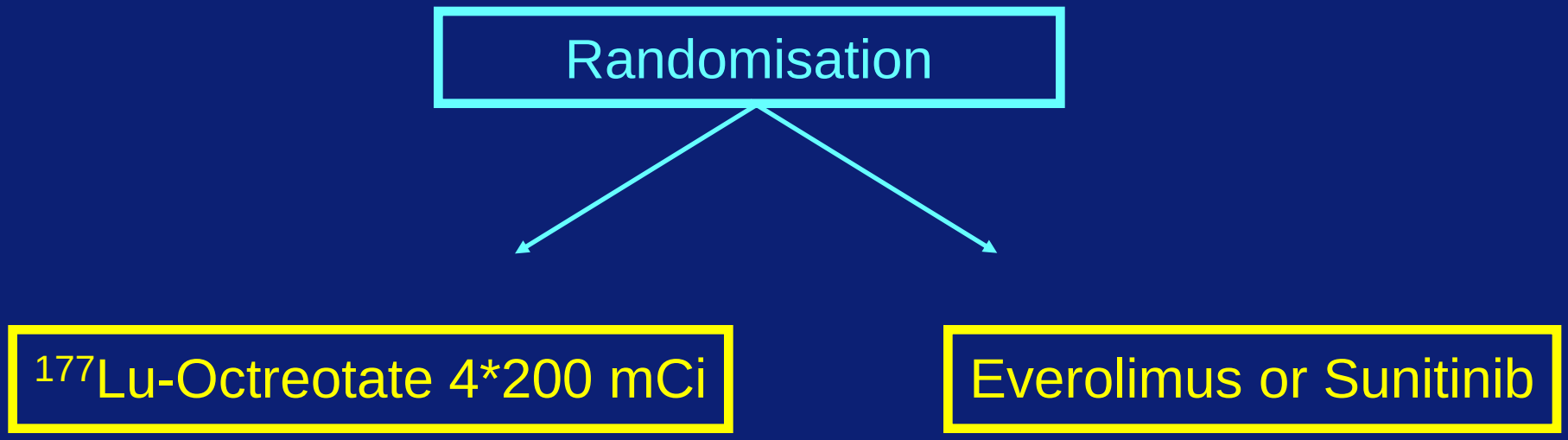
[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: Expected Next Randomised Trial



- Pancreatic NET patients, metastatic, inoperable disease, baseline progressive
- Primary endpoint: PFS

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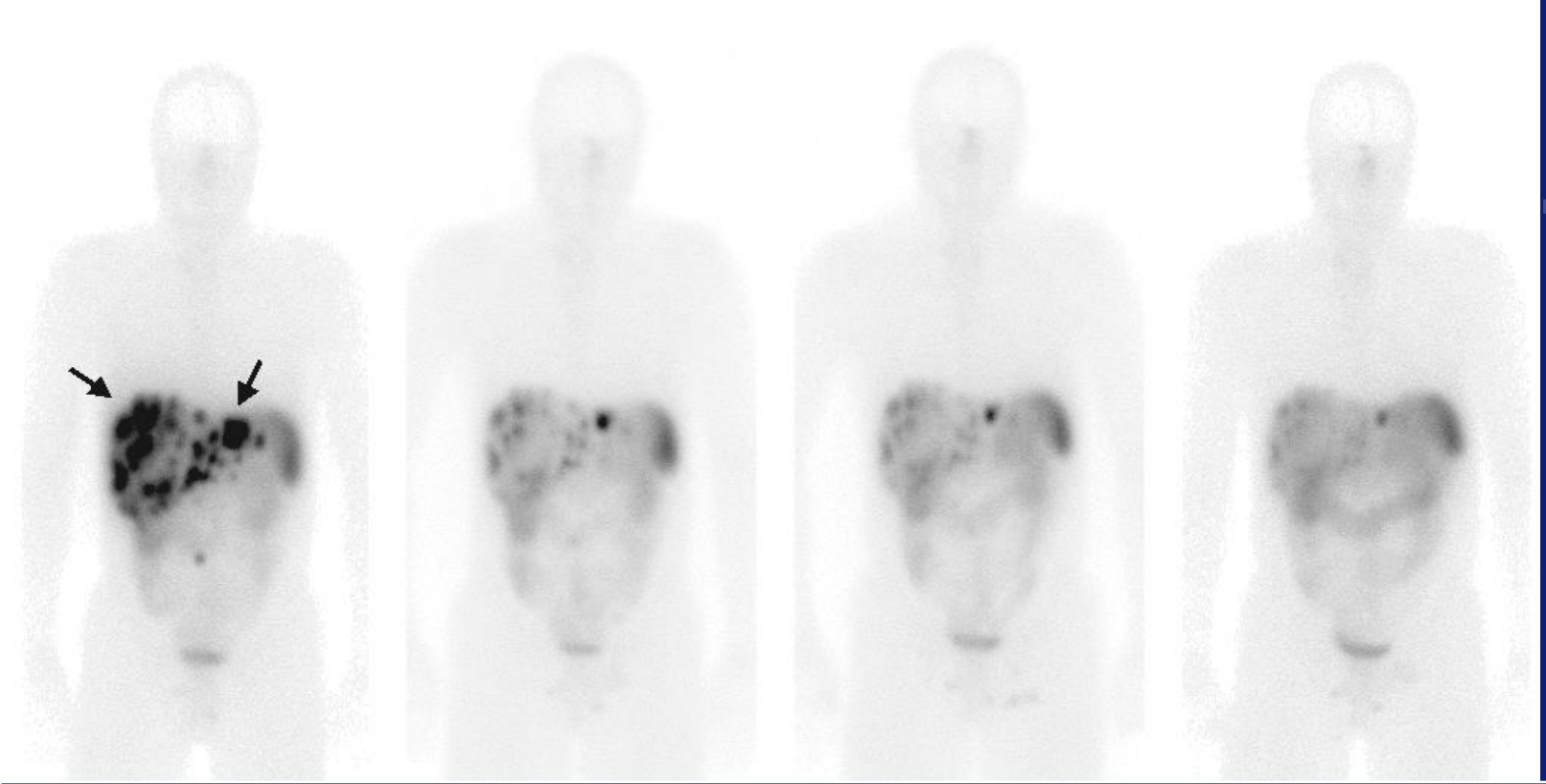

Additional treatment cycles with ^{177}Lu-octreotate in patients with gastroenteropancreatic neuroendocrine tumours who developed progressive disease after an initial tumour response

Martijn van Essen, Eric P Krenning, Boen L Kam, Dik J Kwekkeboom

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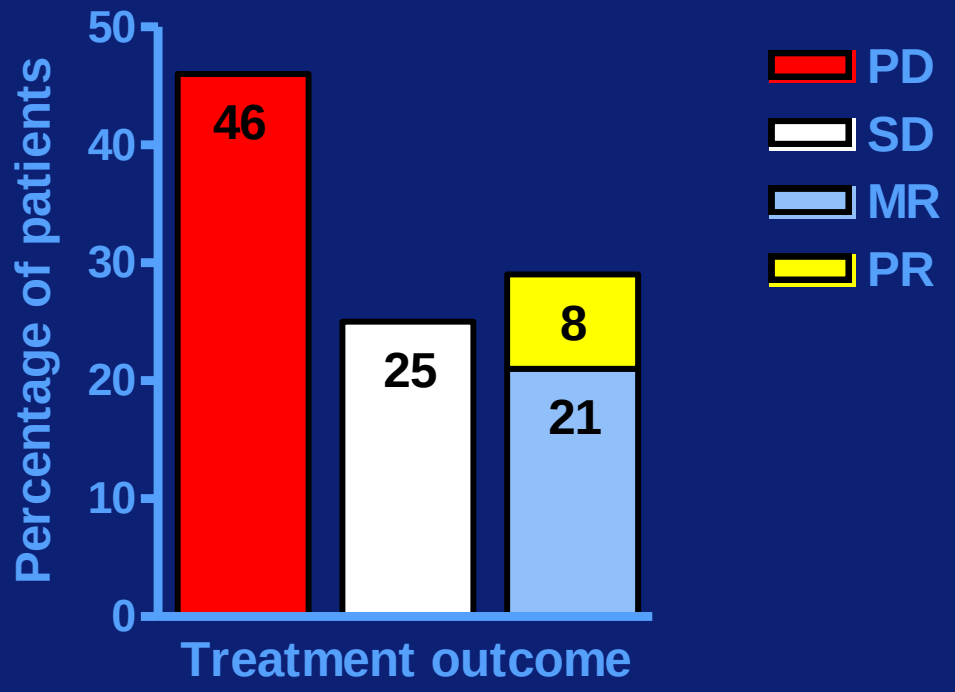
Additional treatment with ^{177}Lu-octreotate after relapse

Anti-tumour effects:

- Renewed tumour regression
  - 7 / 24 patients (29%)
    - 2 partial remissions
    - 5 minor responses
- Stable disease
  - 6 / 24 patients (25%)
- Progressive disease
  - 11 / 24 patients (46%)



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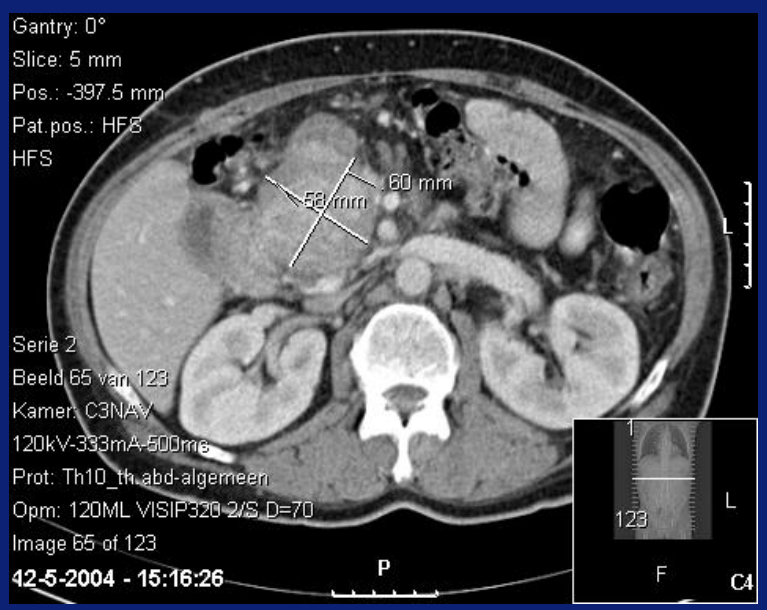
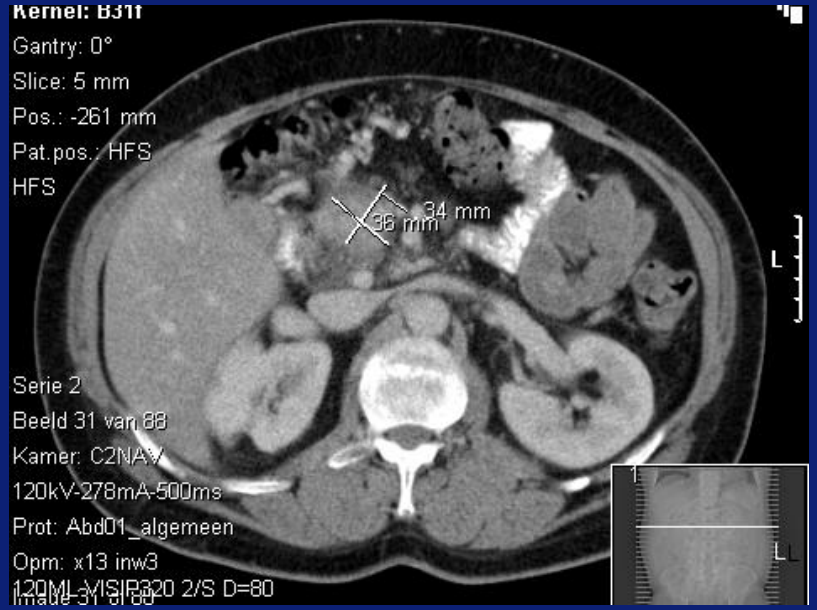
Neoadjuvant Treatment of Nonfunctioning Pancreatic Neuroendocrine Tumors with [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate

E.I. van Vliet,[1] C.H.J. van Eijck,[2] R.R. de Krijger,[3] E.J. Nieveen van Dijkum,[4] J.J.M. Teunissen,[1] B.L.R. Kam,[1] W.W. de Herder,[5] R.A. Feelders,[5] B.A. Bonsing,[6] E.P. Krenning,[1] D.J. Kwekkeboom[1]

[1]Department of Nuclear Medicine, [2]Department of Surgery, [3]Department of Pathology, [5]Department of Internal Medicine, Erasmus MC, University Medical Center, Rotterdam, the Netherlands, [4]Department of Surgery, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands, [6]Department of Surgery, Leiden University Medical Center, Leiden, the Netherlands.

[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy: Inoperable Tumor of the Head of the Pancreas





- Initially inoperable tumor. CT before (May 2004) and 3 months after the last treatment (March 2005). Identical scaling. PR.
- Increase in bodyweight: 14 kg.
- CT at 6 months identical. Successful Whipple procedure plus reconstruction portal vein July 2005. Resection edges and lymphnodes free of tumor. Discharge August 2005.

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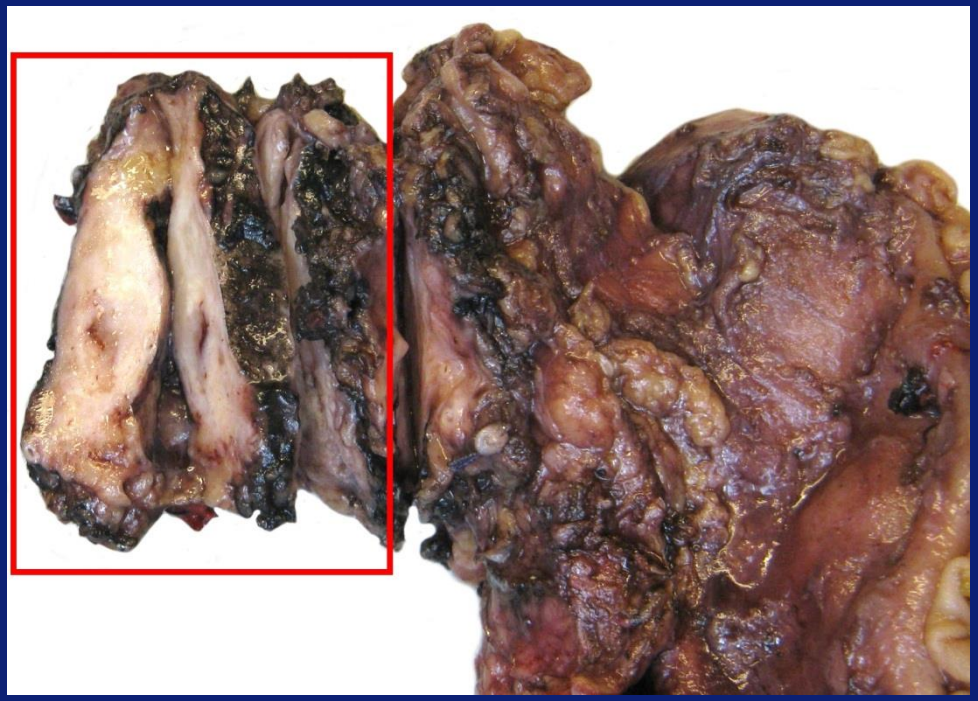
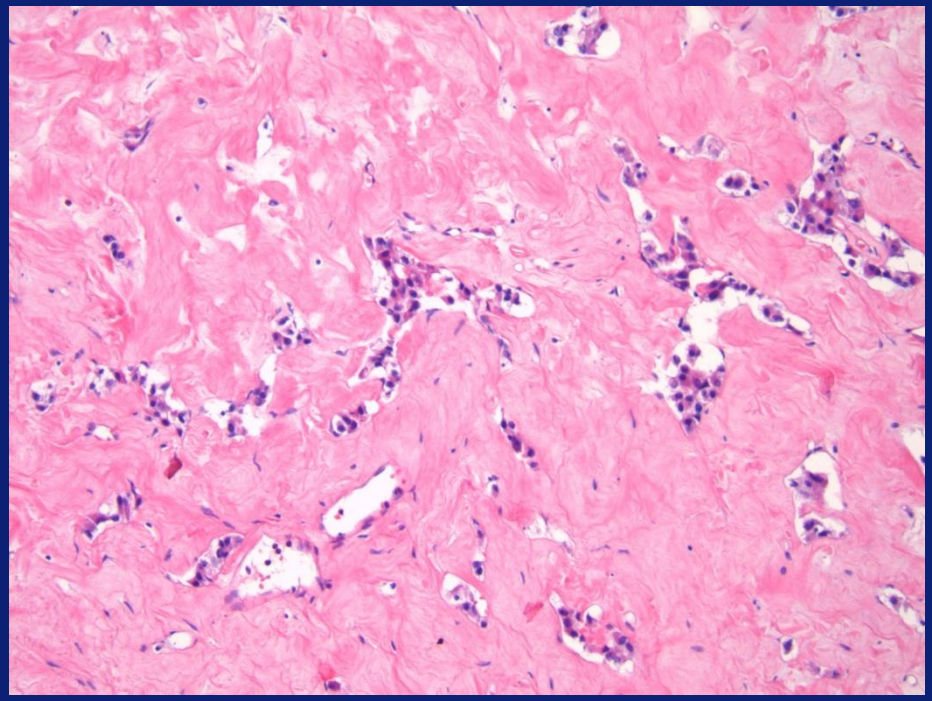
Pathology





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Conclusions

- Successful surgery after ^{177}Lu-octreotate in an encouraging rate of 9/29 neoadjuvant treated patients (31%)
- Surgery after ^{177}Lu-octreotate seems to be associated with improved PFS
- Surgery after ^{177}Lu-octreotate could be safely performed in all patients
- Prospective study on the neoadjuvant use of ^{177}Lu-octreotate in patients with nonfunctioning pancreatic NETs should be initiated, in which predefined criteria of tumor resectability should be incorporated

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PRRT: variants

- Combined ^{90}Y- and ^{177}Lu DOTATOC/TATE: 3 retrospective human studies reporting better PFS (No RCT)
- Intraarterial PRRT: Better response rate livermetastases several studies (No RCT)
- Chemosensitisation (Capecitabine): RCT ongoing
- Neoadjuvant PRRT pNETs: several case reports (No RCT)
- Adjuvant PRRT: No Studies

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Combinations of ^{177}Lu- and ^{90}Y-labeled [DOTA^{0},Tyr^{3}]Octreotide/Octreotate Therapy

RANDOMISED, PROSPECTIVE TRIALS ARE NEEDED

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PRRT combined with other Treatments

- Combination of PRRT and other treatments promising?

YES

BUT:

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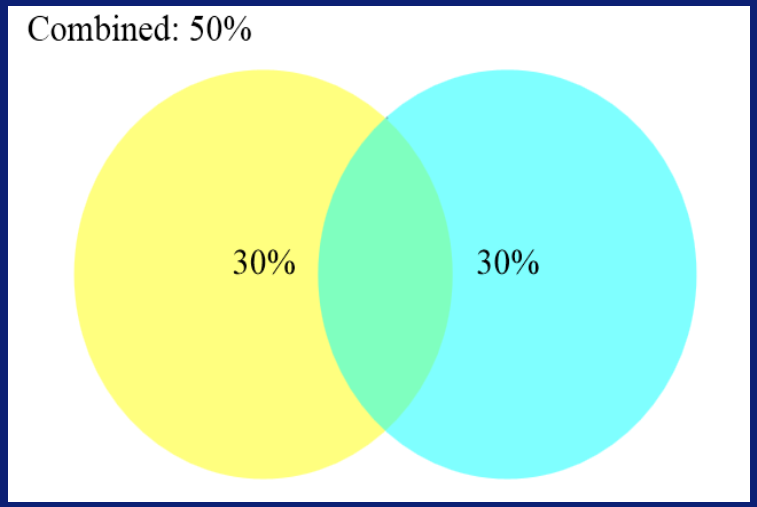
PRRT combined with other Treatments Considerations

- Combination of PRRT and other treatments:
- Objective Response Rate is not indicative of success, because a percentage of patients that does not respond to one therapy will respond to the alternative.



- PFS is the outcome parameter to be used

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PRRT combined with other Treatments Considerations

- The question is whether combination within a short timeframe gives better PFS than use the treatments sequentially when there is (renewed) tumor progression
- The control arm for the combination should not be one of the components (PRRT or the treatment with which it is combined) but sequential treatment when there is (renewed) tumor progression

- PRRT+Tx ⟶ PFS1
- PRRT ⟶ PD ⟶ TX ⟶ PFS2

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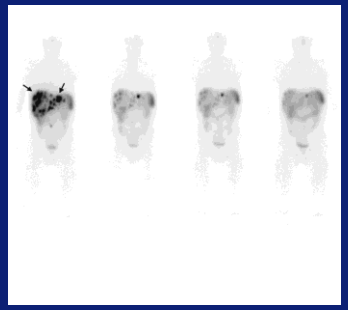
[^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate Therapy Conclusions

- PRRT holds great promise
- High tumor response rate
- Limited side-effects
- Good quality of life
- Long progression free period
- Variants, (neo)adjuvant use
- Randomised prospective trial started in carcinoids
- Trial in Pancreatic NETs expected to follow soon



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