UMC Utrecht

Neuroendocrine tumormetastases

Menno Vriens, endocrine surgeon
UMC Utrecht Cancer Center

1st Maastricht E-AHPBA Post-Graduate HPB Course

No disclosures

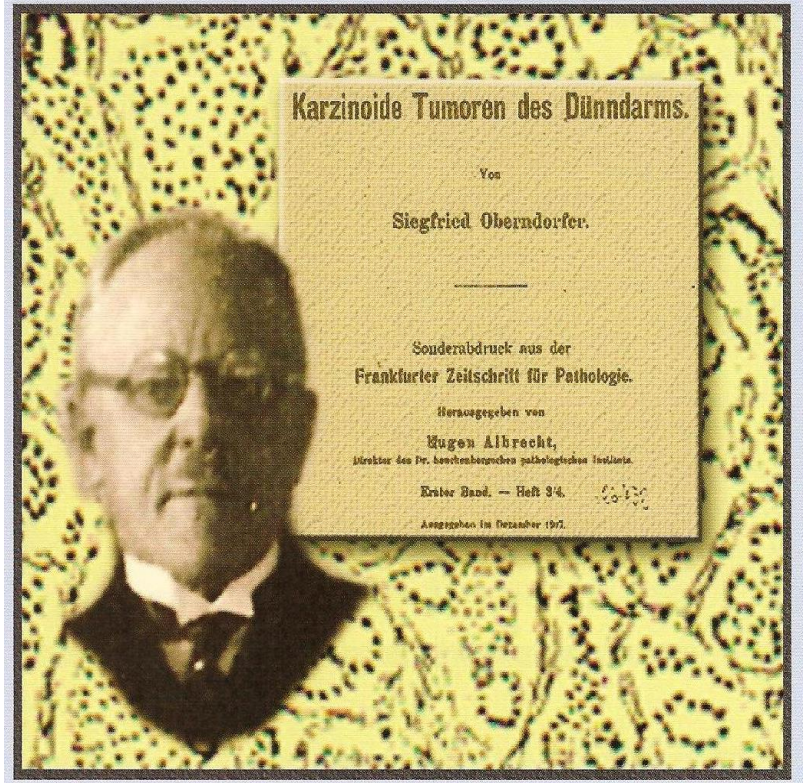
History

S.Oberdorfer (pathologist München) 1907

- benign tumor: carcinoid
- multiple/small intestines
- small as a pea
- harmless

1929 change of thoughts

- malignant characteristics
- ability to metastasize



Neuroendocrine tumors

Diversity!!

Serotonin production: carcinoid syndrome (diarea and flushes)

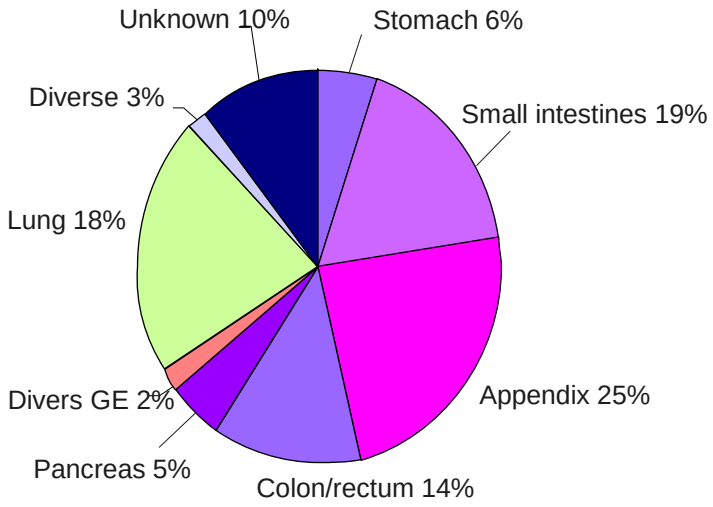
Different presentation of seemingly the same diagnosis:

- Primary tumor
- Location of metastases
- Functionality
- Histology

→ Individualized diagnosis and treatment

Neuroendocrine tumors

- can originate in all organs
- rare: 2-3 per 100.000 inhibitants; in NL ± 300-450/ year
- primary tumor often small, unknown
- at presentation already fully metastasized



Sporadic, but also familial

- Multiple endocrine neoplasia type 1 (MEN1)
- Von Hippel Lindau (VHL)

- Neurofibromatosis type 1 (NF1)
- Tubero-sclerose complex (TSC)

10% of all pNET are familial

Dreijerink et al. Front Horm Res. 2015;44:115-38

False diagnosis (N=115)

False diagnosis	Number of patients	Delay in months
Irritable bowel	52	64
Food allergy	13	168
Lactose intolerance	12	180
Psychiatric disorders	13	86
Depression	12	205
Menopause	8	66
Diversen	30	6-158

Toth Am J Surg 2004

Functional vs non-functional

Table 2 Nomenclature, incidence, location and malignancy of pancreatic NETs

Name	Hormone	Cell type	Incidence (M)	Pancreas (%)	Duodenum (%)	Malignant (%)
Insulinoma	Insulin	β islet cells	1/1.25	>99		5-11
Gastrinoma	Gastrin	G cells	1/2.5	21-65	6-35	60
Glucagonoma	Glucagon	α cells	<1/5	>99		>70
VIPoma	VIP	δ cells	<1/5	85-90	10-15	50
Somatostatinoma	Somatostatin	δ cells	<1/10	50	50	90
Nonfunctioning	Neuron-specific enolase, PP	F cells	1/5	>99		>50

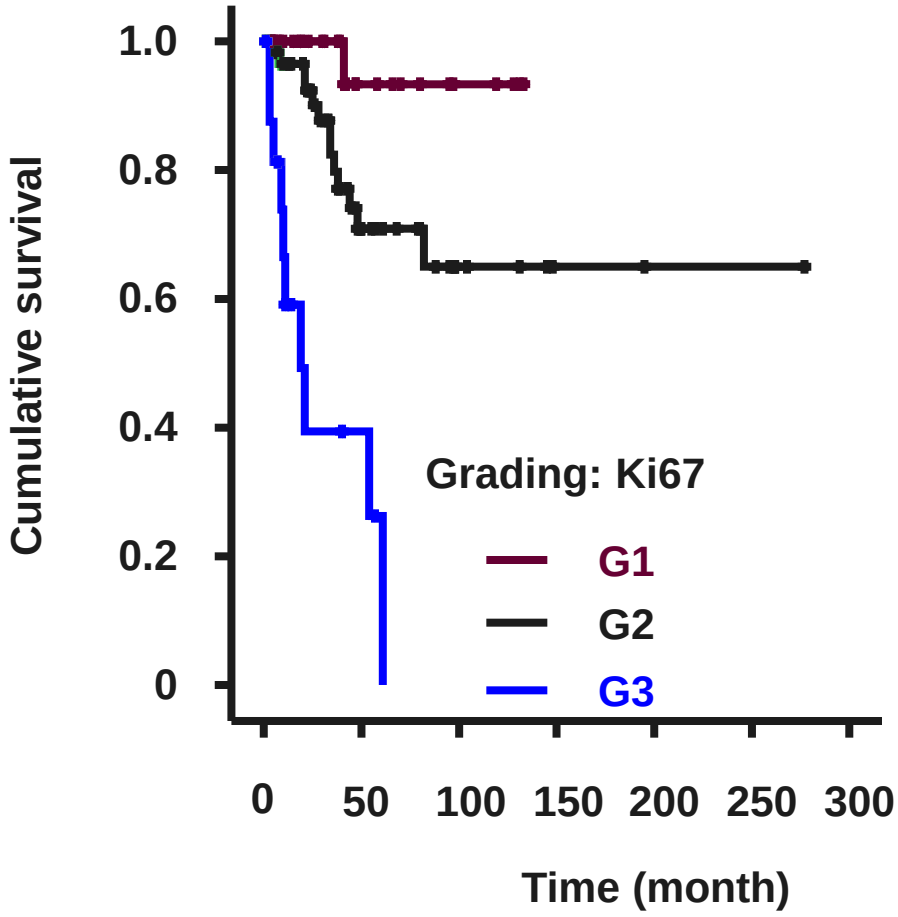
Norton *et al*. Surgery: basic science and clinical evidence; 2000,919-953. Reproduced with permission.

Histology of NETs

Grade	ENETS	WHO 2010	Differentiation	Ki-67 index (%)	Mitotic count (10 HPF)
Low grade	NET grade 1 (G1)	Neuroendocrine neoplasm grade 1	Well-differentiated	≤ 2	< 2
Intermediate grade	NET grade 2 (G2)	Neuroendocrine neoplasm grade 2	Well-differentiated	3 - 20	2 - 20
High grade	Neuroendocrine carcinoma grade 3 (G3)	Neuroendocrine carcinoma grade 3	Poorly differentiated	> 20	> 20

Prognosis based on NET grading

	Grading NET	
	Mitotic count (10 HPF)	Ki-67 index (%)
G1	< 2	≤ 2
G2	2–20	3–20
G3	> 20	> 20

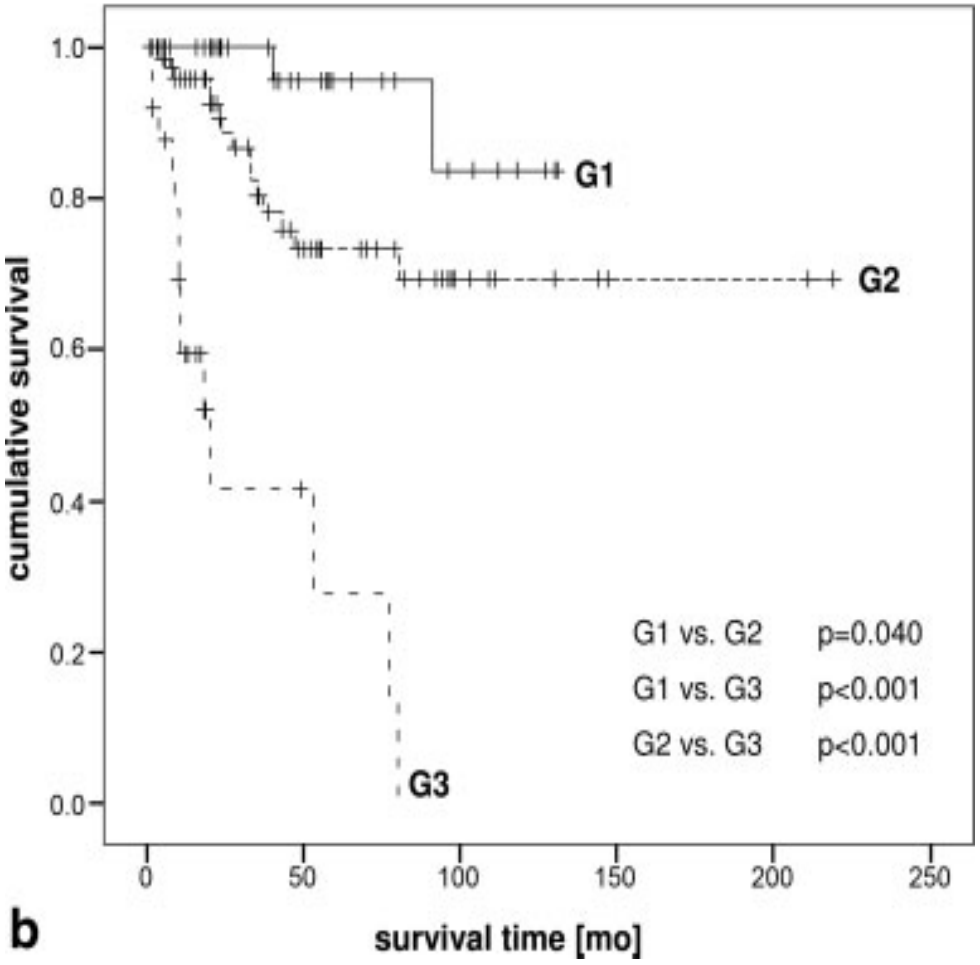


Rindi G, *et al*. Virchows Arch. 2006;449:395-401.

Pape UF, *et al*. Cancer. 2008;113:256-65.

Grade and overall survival

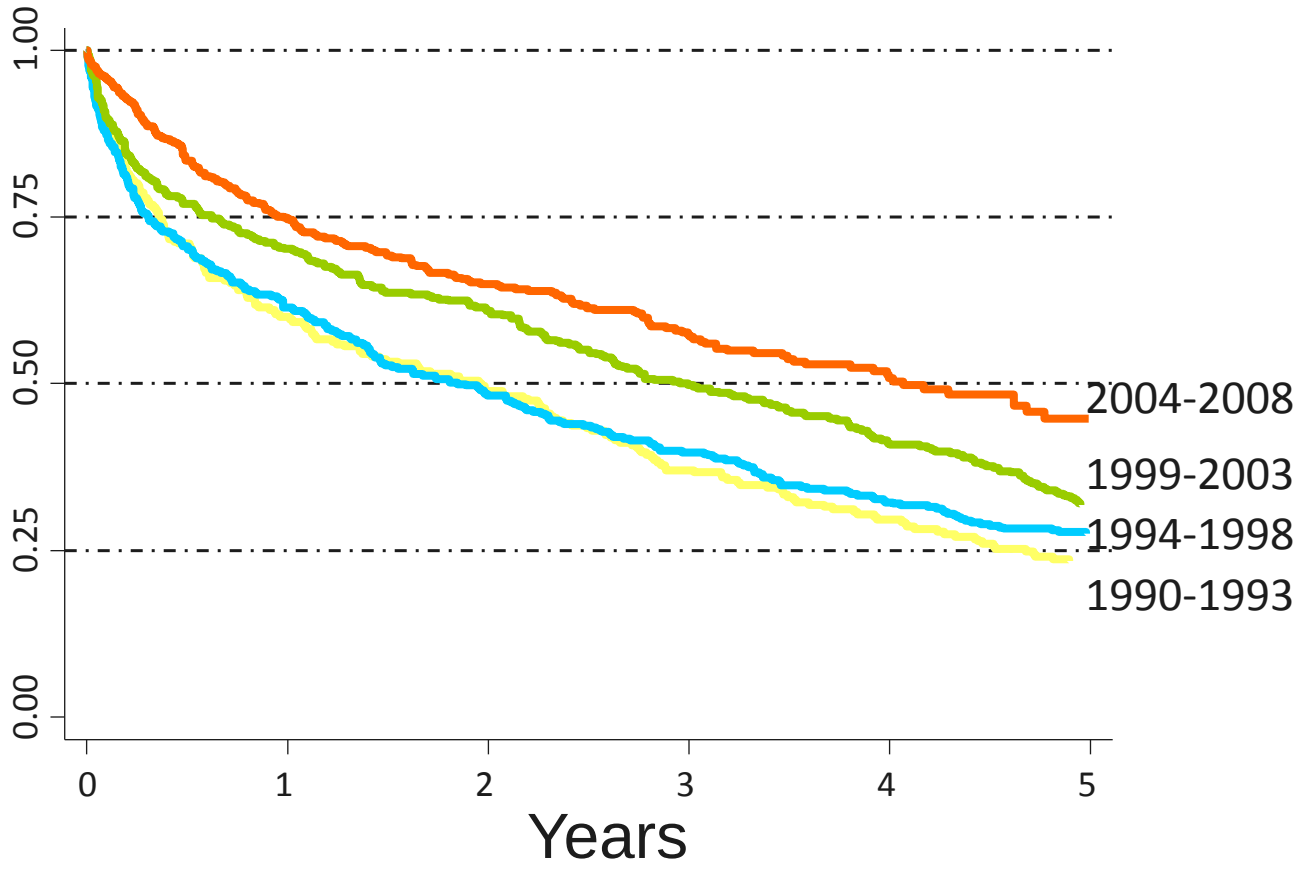
-n=202-



stomach (n=48), duodenum (n=23), pancreas (n=131).

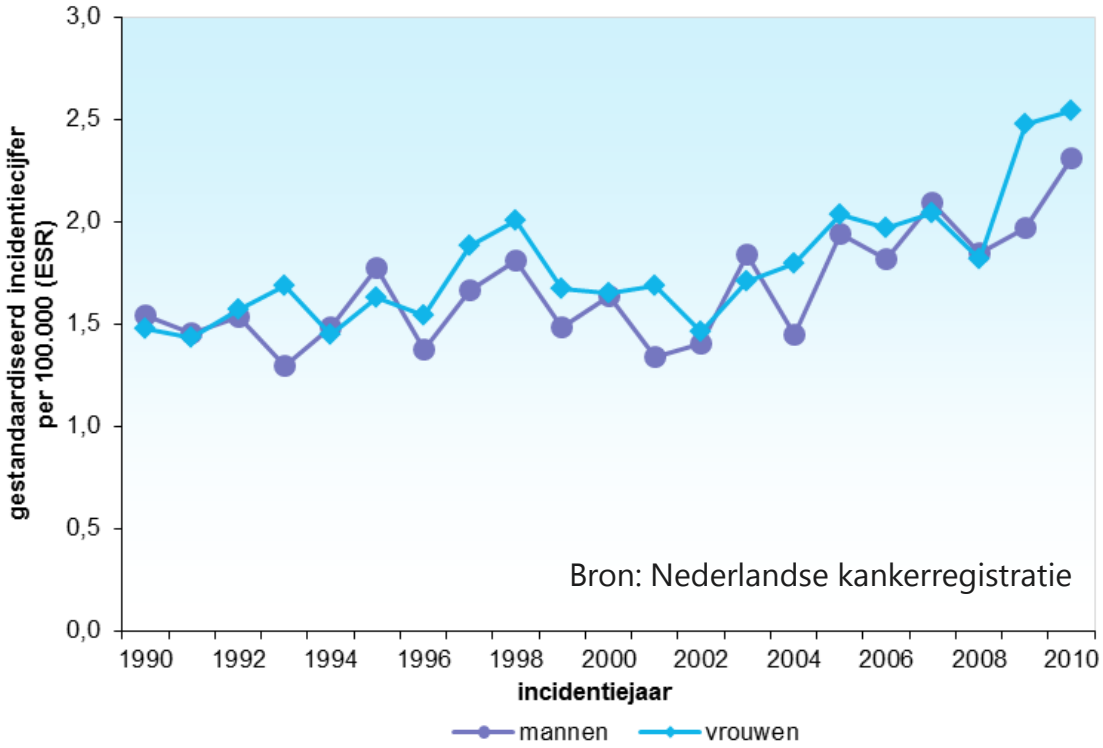
Pape, Cancer 2008;113:256–65.

Survival G1 NET-M1



IKA: 2010

Incidence NET is increasing

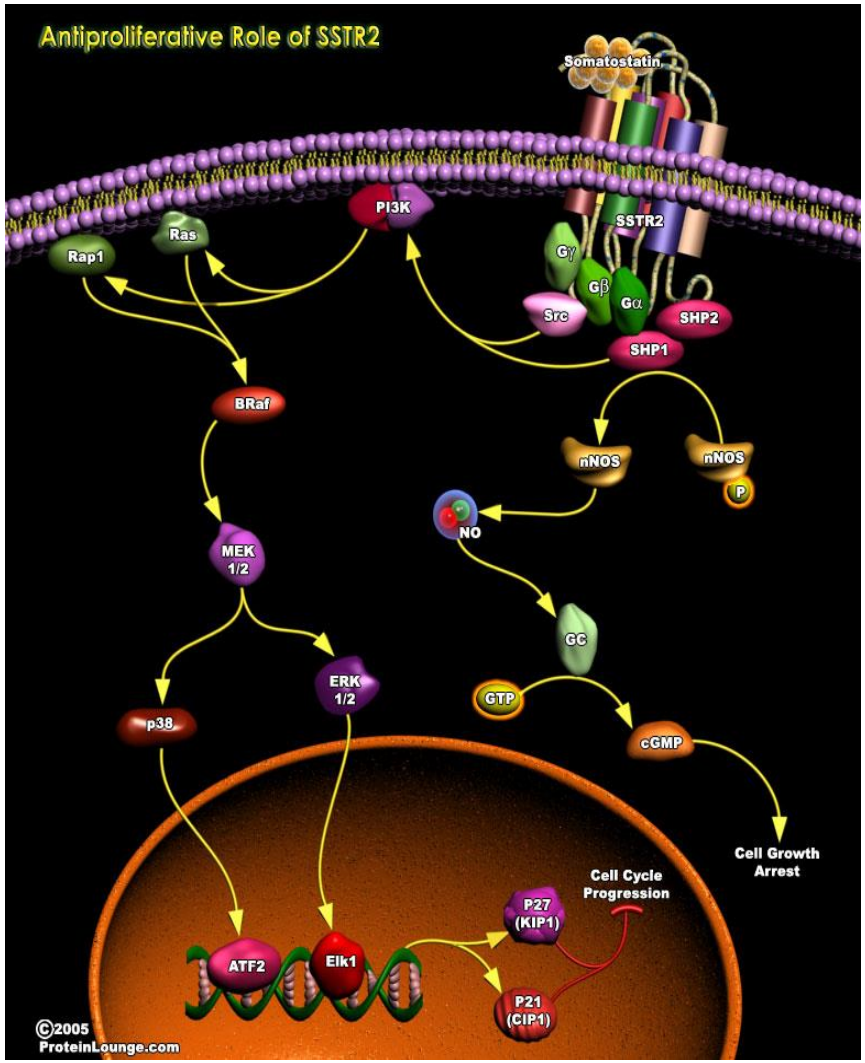


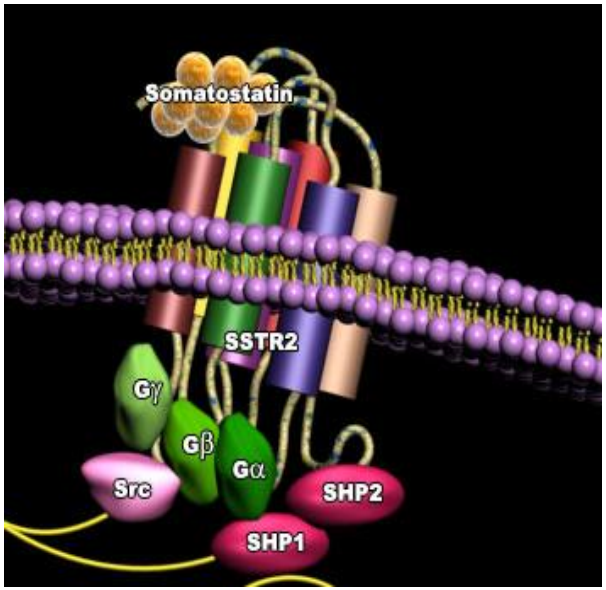
- Increase of incidence of grade 1 pancreas and rectum NET
- More awareness
- Improvement of diagnostics
- Use of diagnostics

Fraenkel et al. Endocr Relat Cancer 2014 6;21:R153-63

^{111}In-pentetreotidescan = Octreoscan

-somatostatin receptors-





5 Subtypes

NET: variation in expression of SSTR subtype

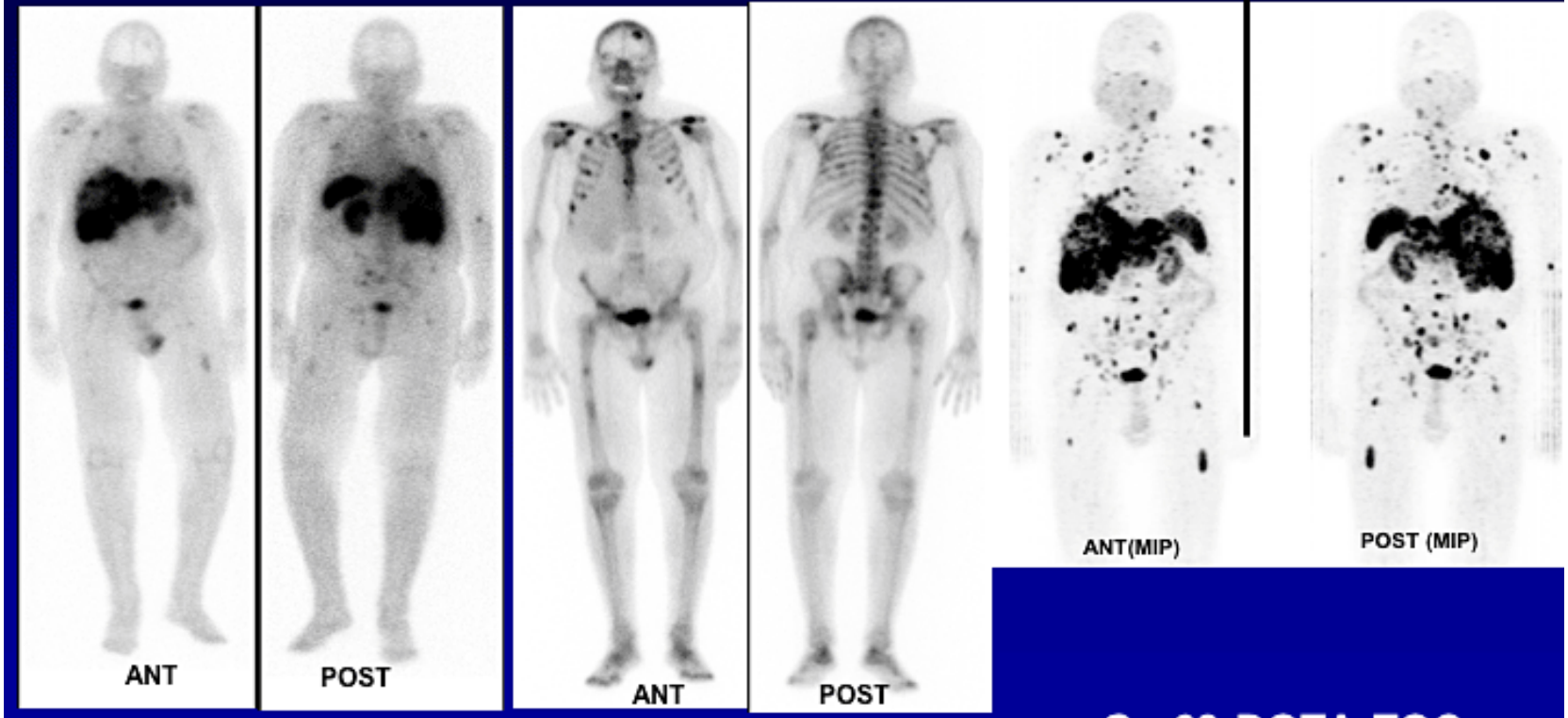
SST-R Subtype Expression in NET: in vitro

SST-R / Tumor	1	2	3	4	5
Gastrinoma	64-100	86-100	0-50	22-86	86-100
Insulinoma	60-100	75-100	0-100	20-96	0-100
NET functioneel	44-83	67-100	0-53	33-83	44-100
NET niet functioneel	22-77	67-100	0-50	11-70	22-80

NKI-AVL
Het Nederlands Kanker Instituut
Antoni van Leeuwenhoek Ziekenhuis

Sensitivity – OctreoScan vs. Ga-68 SMS PET

Metastasizing bronchus carcinoid



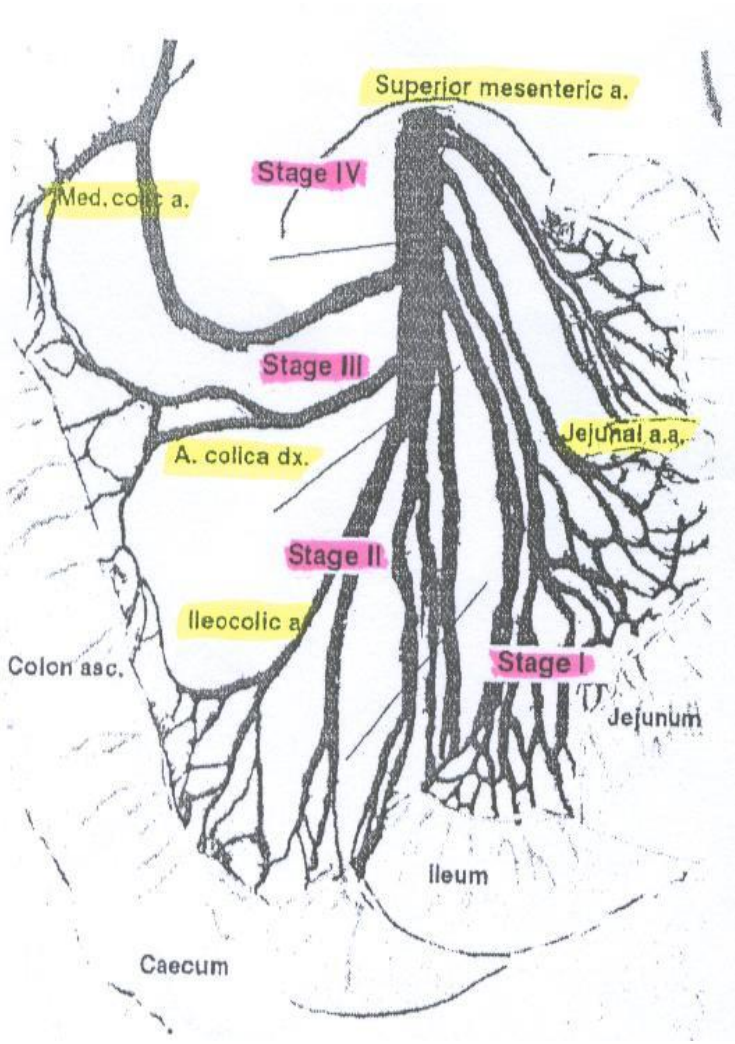
CT-scan abdomen (thorax)

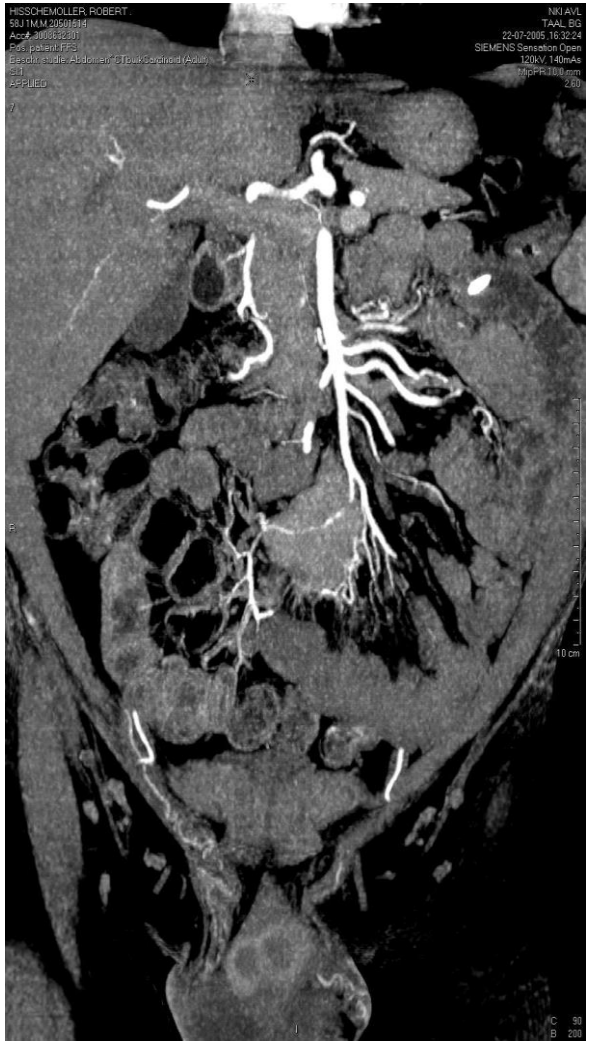
- Extension of met's:
  - Liver
  - Lung
  - Bones
- Localizing the primary tumor:
  - Small intestines
  - Lung
- :
  - Mesenteriale laesies

CT-abdomen: reconstruction

Mesenterial NETtumor: angio-CT scan

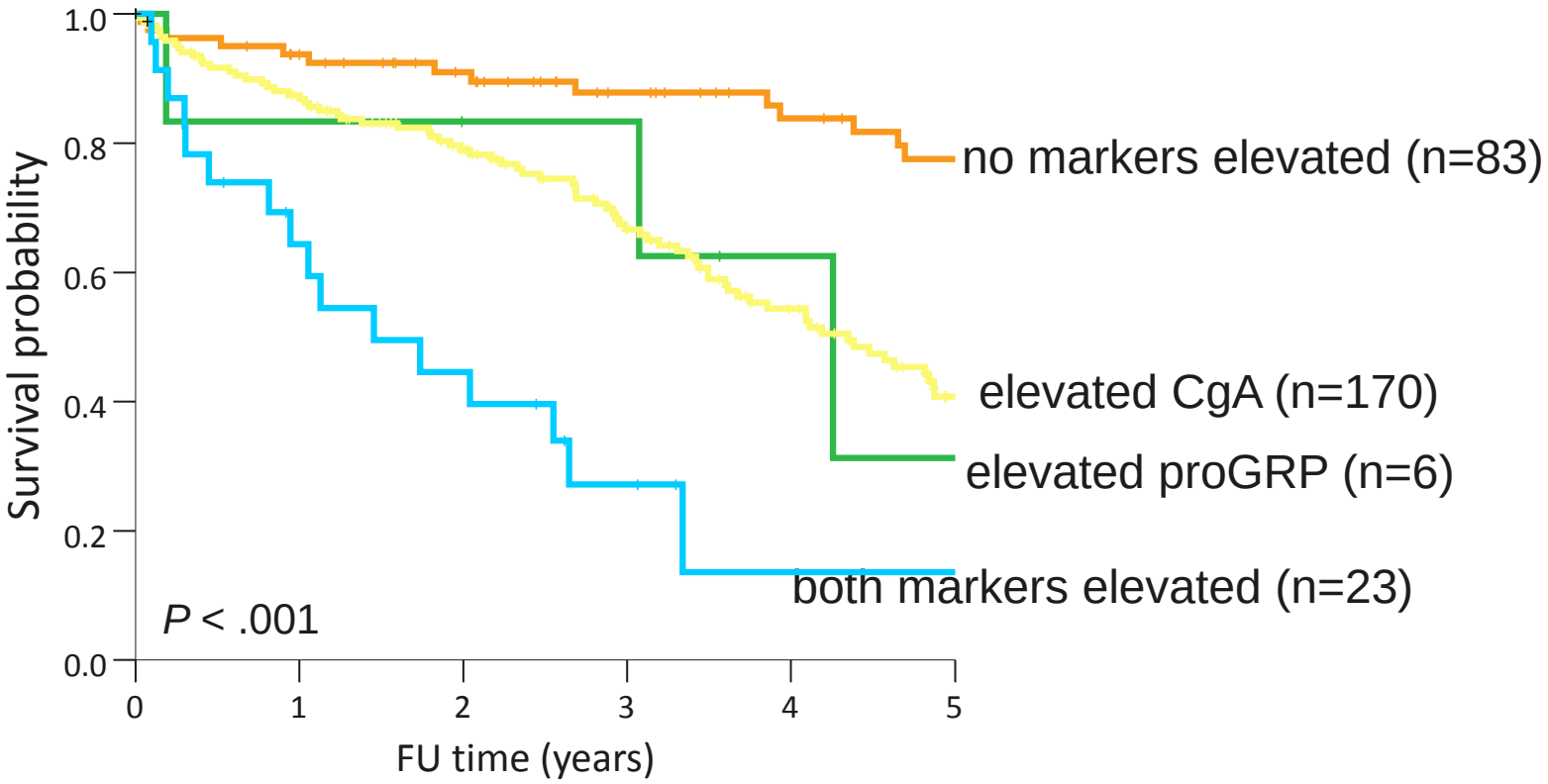
-vascular encasement-





Survival curve

-elevated markers-



Valuable as a FU marker, not as a diagnostic marker

Metastasized NETs (WHO grade 1 en 2)

- Primary resection, metastasectomy and/or debulking:
  -> curation or decrease of symptoms

- Producing NET: always SSA
- somatostatin analogue
- everolimus (mTOR inhibitor)
- sunitinib (tyrosin kinase inhibitor)
- PRRT
- streptozotocine + 5FU/doxorubicine
- Radioembolization
- alfa interferon

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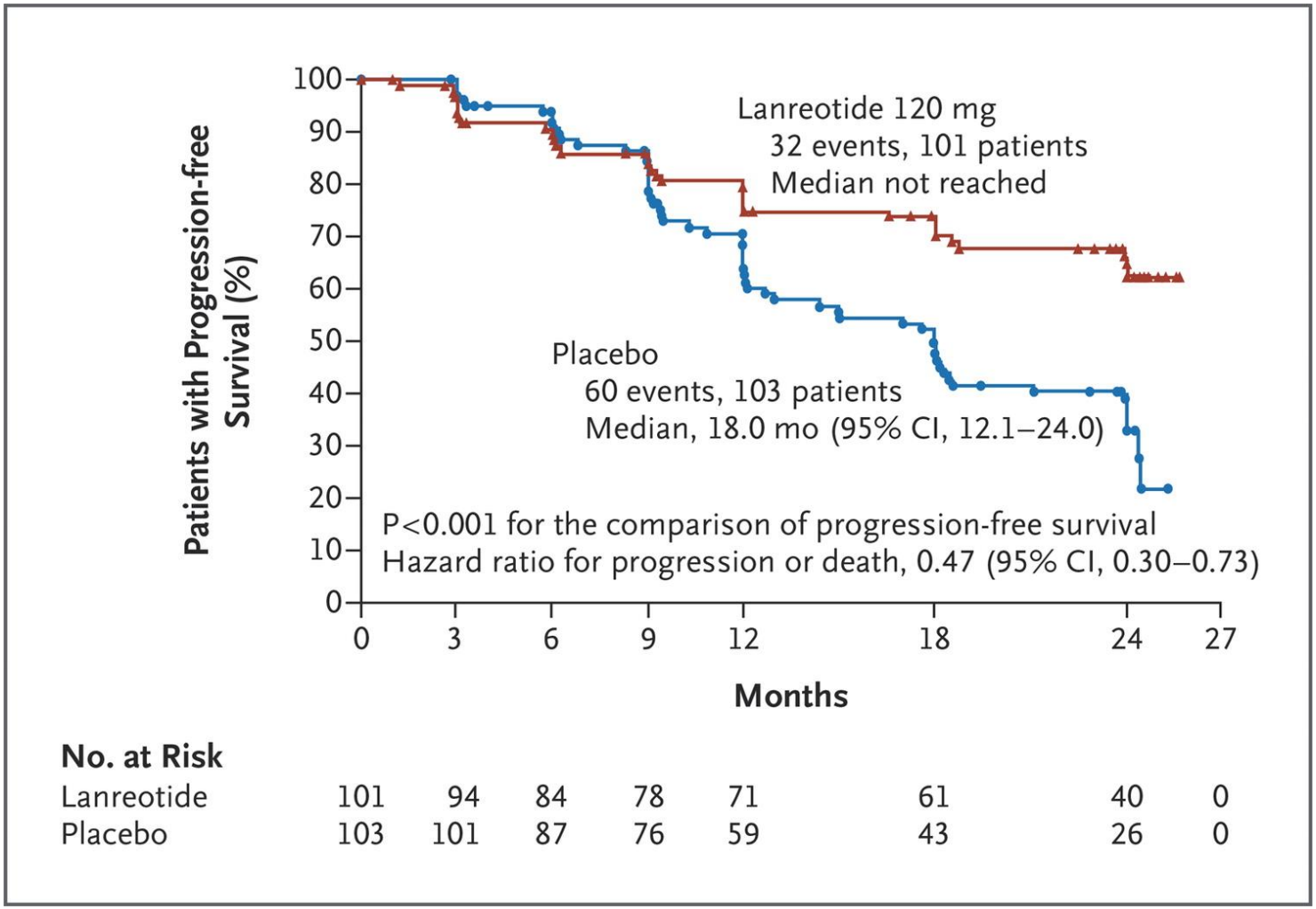
CLARINET: Progression-free Survival



Caplin ME et al. N Engl J Med 2014;371:224-233.

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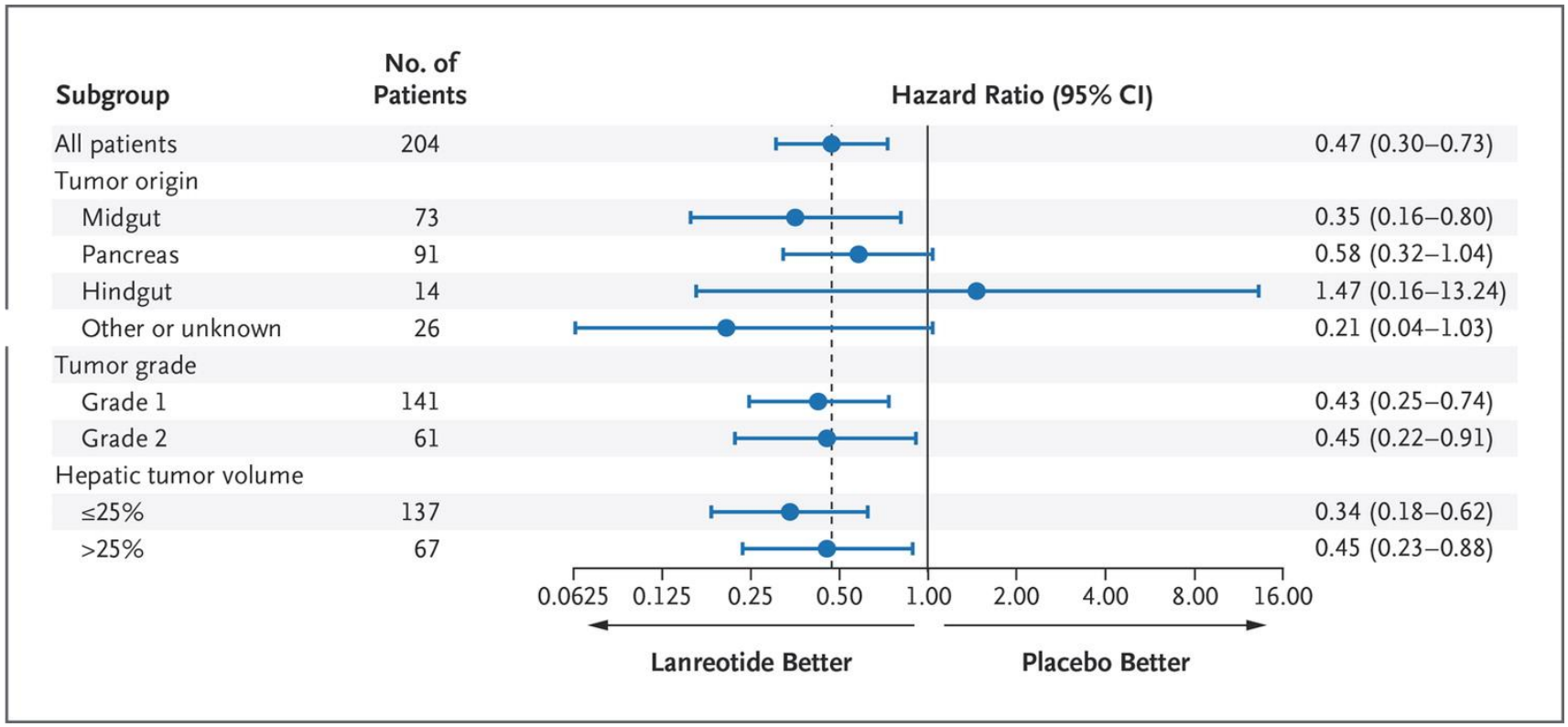

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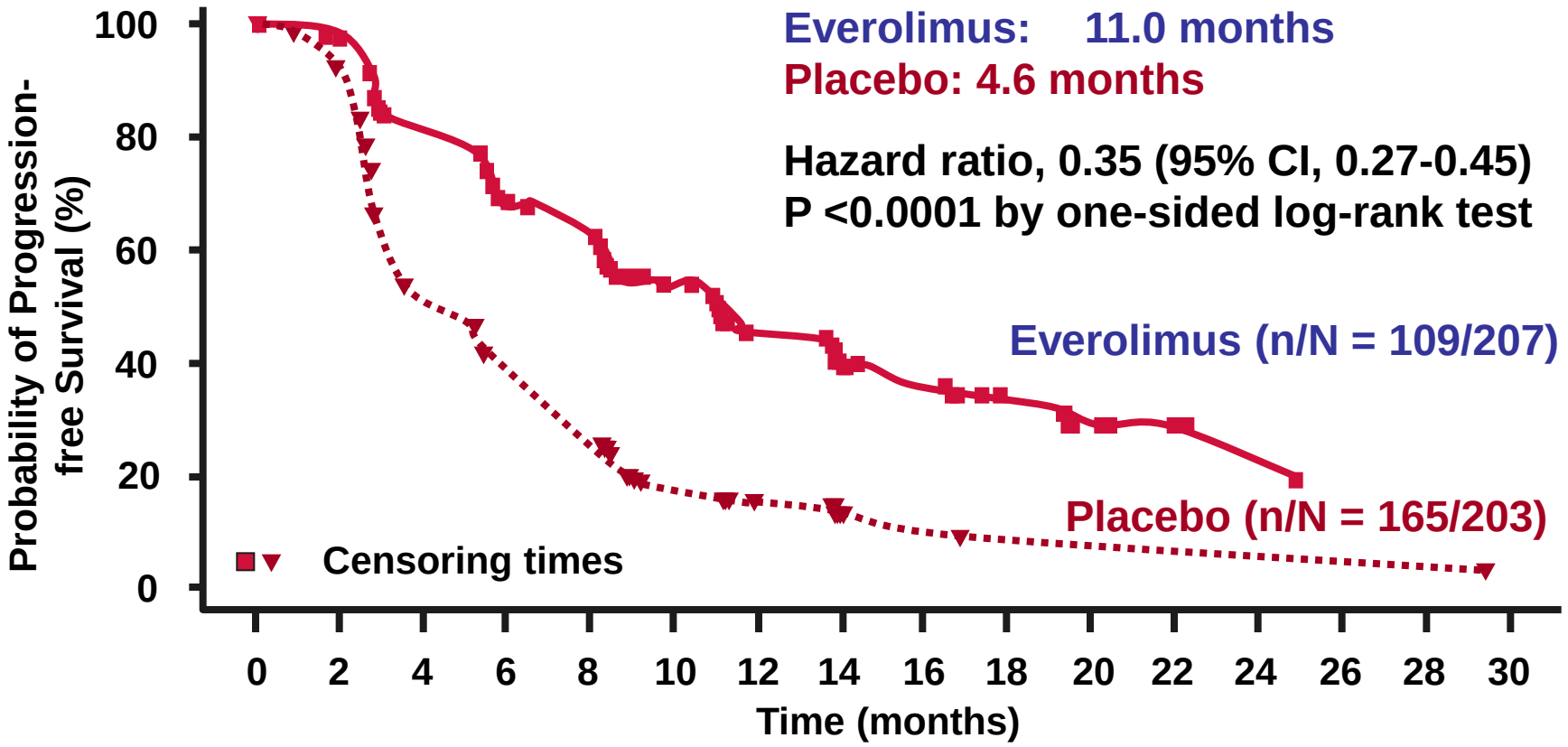
RADIANT-3: Progression-free Survival



Everolimus	207	189	153	126	114	80	49	36	28	21	10	6	2	0	0	0
Placebo	203	177	98	59	52	24	16	7	4	3	2	1	1	1	1	0

No. of patients still at risk

Yao JC, *et al*. N Engl J Med 2011; 364:514-523.

RADIANT-4 Study Design

ecco

Patients with well-differentiated (G1/G2), advanced, progressive, nonfunctional NET of lung or GI origin (N = 302)

- Absence of active or any history of carcinoid syndrome
- Pathologically confirmed advanced disease
- Enrolled within 6 months from radiologic progression

RANDOMIZE

2:1

Everolimus 10 mg/day
N = 205

Placebo
N = 97

Treated until PD, intolerable AE, or consent withdrawal

Endpoints:

- **Primary:** PFS (central)
- **Key Secondary:** OS
- **Secondary:** ORR, DCR, safety, HRQoL (FACT-G), WHO PS, NSE/CgA, PK

Stratified by:

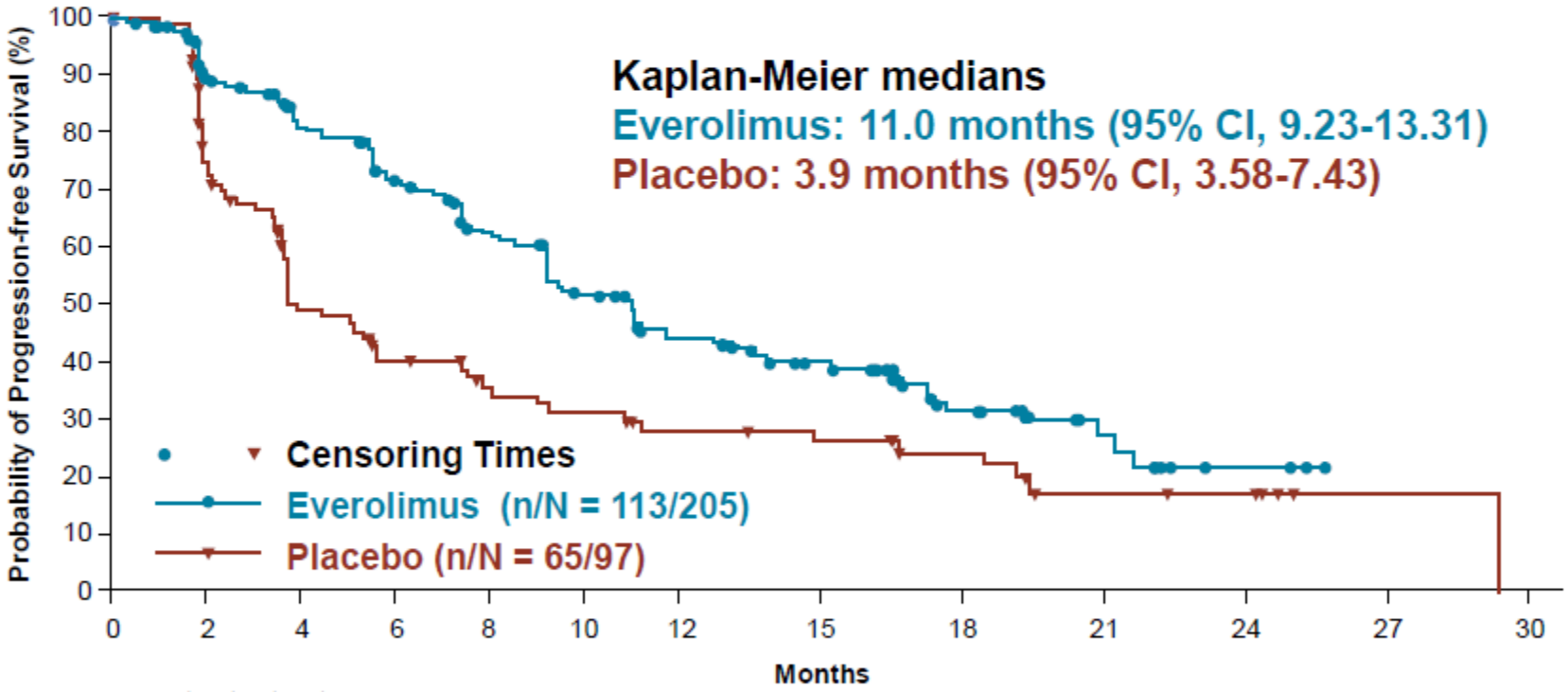
- Prior SSA treatment (yes vs. no)
- Tumor origin (stratum A vs. B)*
- WHO PS (0 vs. 1)

*Based on prognostic level, grouped as: **Stratum A (better prognosis)** – appendix, caecum, jejunum, ileum, duodenum, and NET of unknown primary. **Stratum B (worse prognosis)** – lung, stomach, rectum, and colon except caecum.
Crossover to open label everolimus after progression in the placebo arm was not allowed prior to the primary analysis.

Primary Endpoint: PFS by Central Review

52% reduction in the relative risk of progression or death with everolimus vs placebo

HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001



No.of patients still at risk

Everolimus	205	168	145	124	101	81	65	52	26	10	3	0	0
Placebo	97	65	39	30	24	21	17	15	11	6	5	1	0

P-value is obtained from the stratified one-sided log-rank test; Hazard ratio is obtained from stratified Cox model.

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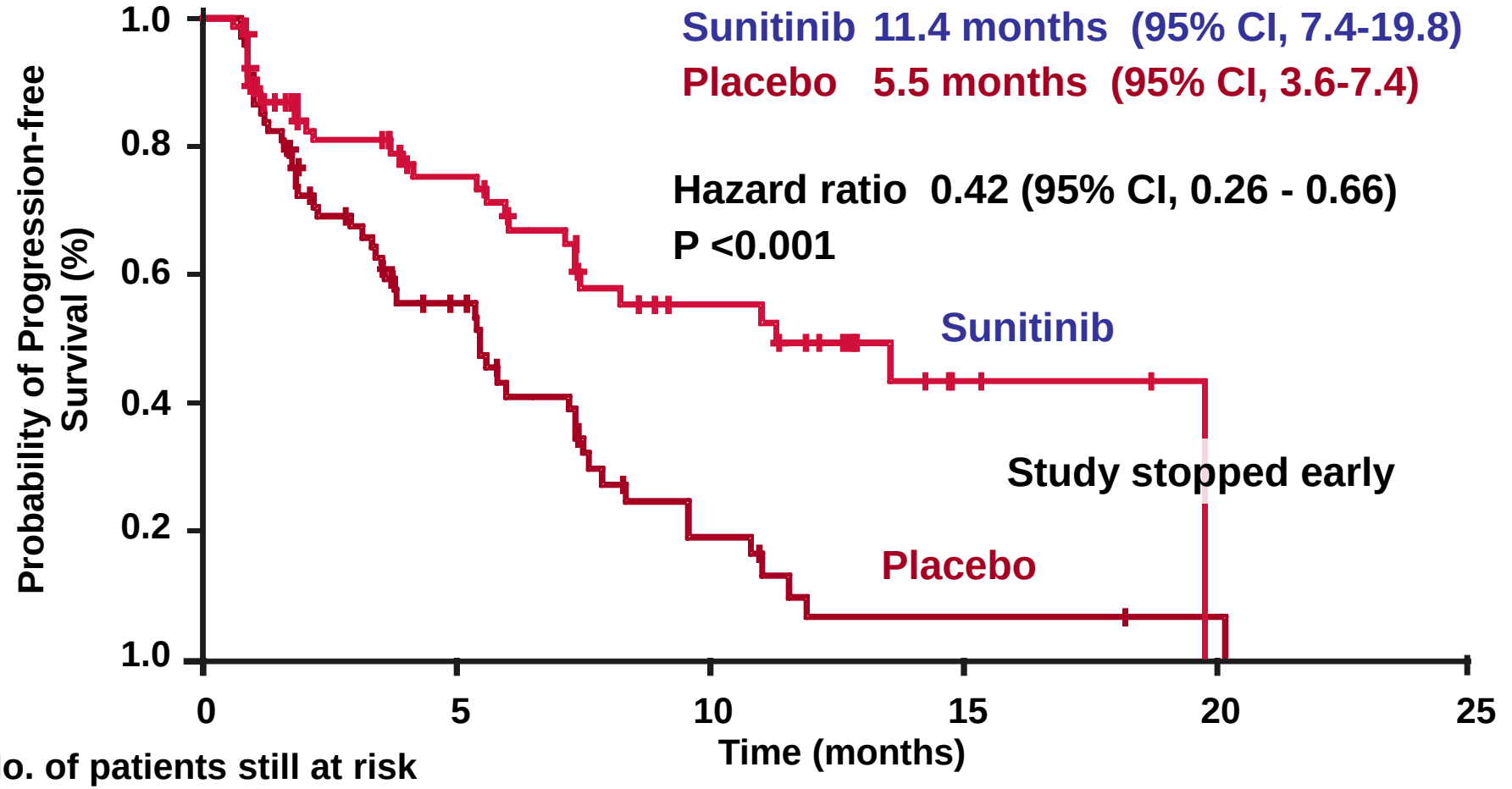
SUN III: Progression-free Survival



No. of patients still at risk

Sunitinib	86	39	19	4	0
Placebo	85	28	7	2	1

Raymond E, *et al*. N Engl J Med 2011; 364:501-513.

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- **Peptide receptor radionucliden therapy (PRRT)**
- streptozotocine + 5FU/doxorubicine
- Radioembolization
- alfa interferon

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

Anti-Tumor Effects at 3 Months Follow-up

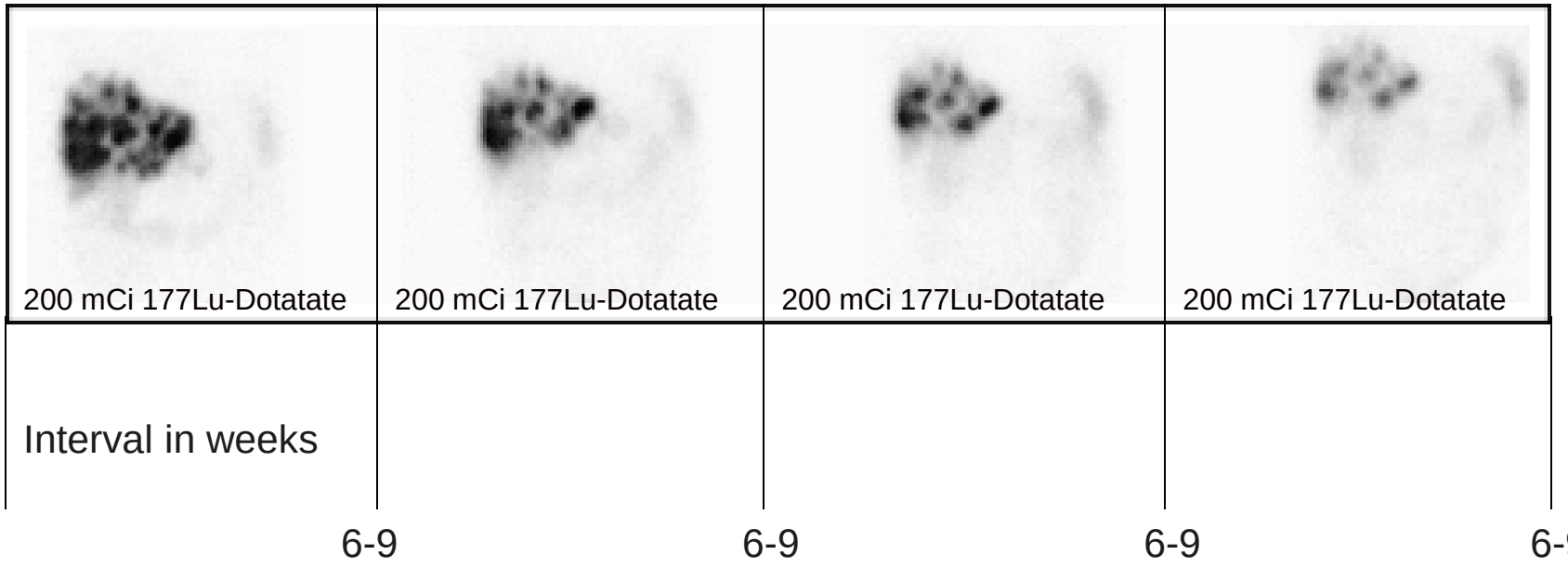
Tumor	CR	PR	MR	SD	PD	Total
Carcinoid	1 1%	41 22%	31 17%	78 42%	37 20%	188
NET Pancreas	4 6%	26 36%	13 18%	19 26%	10 14%	72
NET Unknown Origin		10 32%	3 10%	7 23%	11 36%	31
Gastrinoma / Insulinoma / VIPoma		9 47%	4 21%	3 16%	3 16%	19
Total	5 2%	86 28%	51 17%	107 35%	61 20%	310

CR = complete response, PR = partial response, MR = minor response,
PD = progressive disease

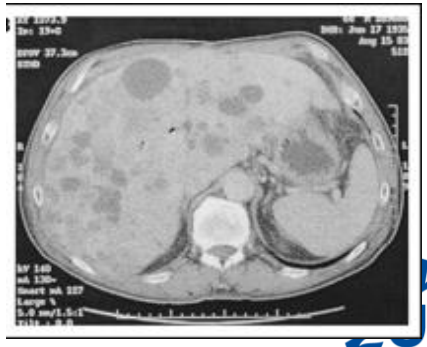
Erasmus MC
Universitair Medisch Centrum Rotterdam

Kwekkeboom DJ, *et al*. J Clin Oncol. 2008;26:2124-2130

^{177}Lu-DOTA,Tyr^{3}-octreotate



Partial remission of a GEP-NET with massive hepatic metastases with ^{177}Lu-Dotatate



Courtesy Marion de Jong / Dik Kwekkeboom

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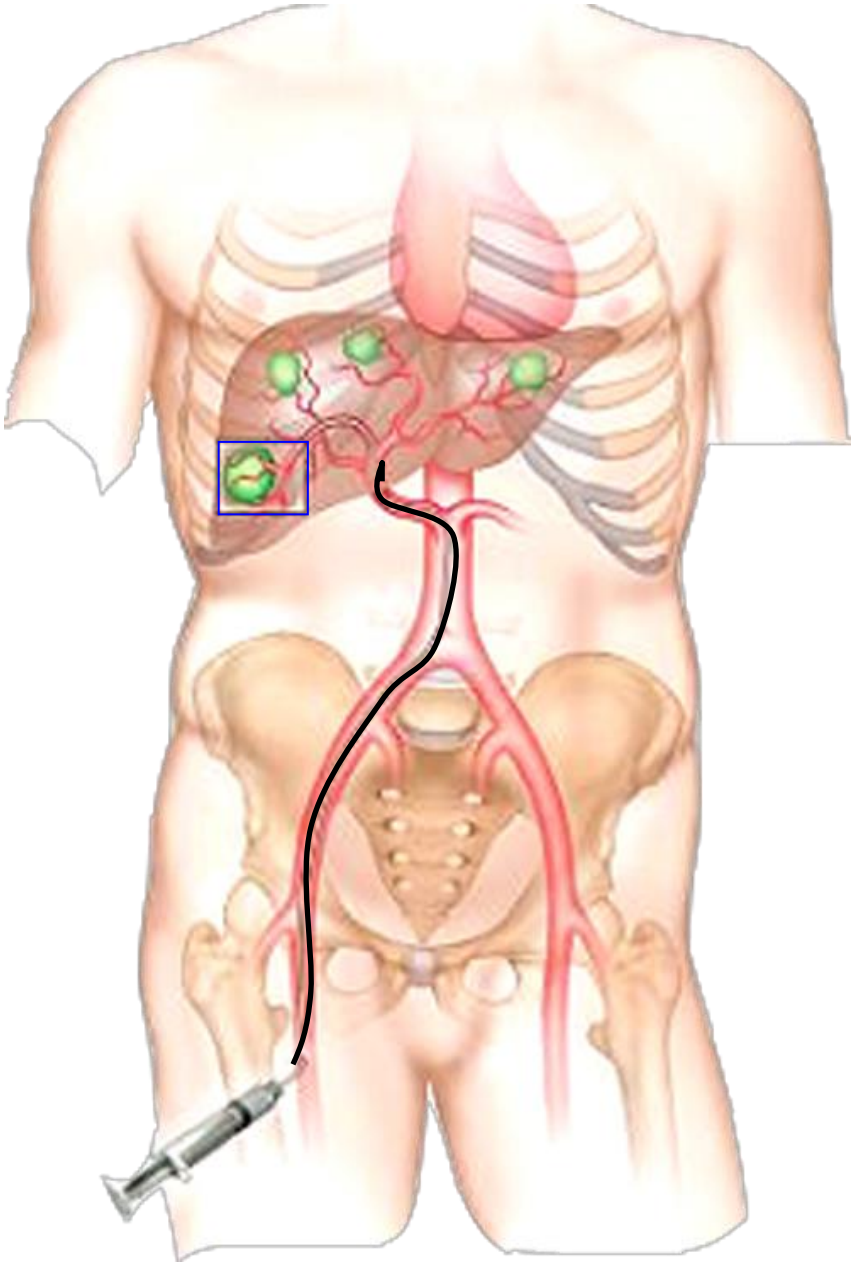
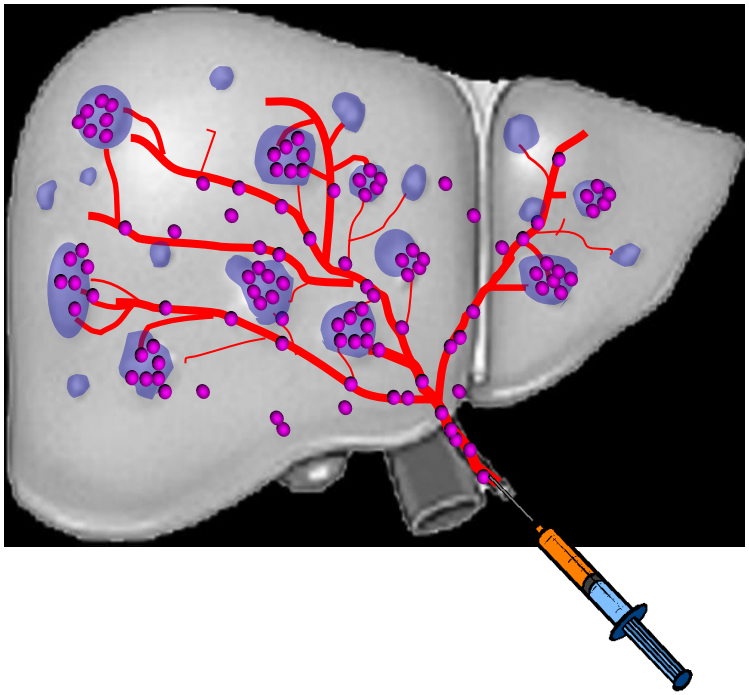
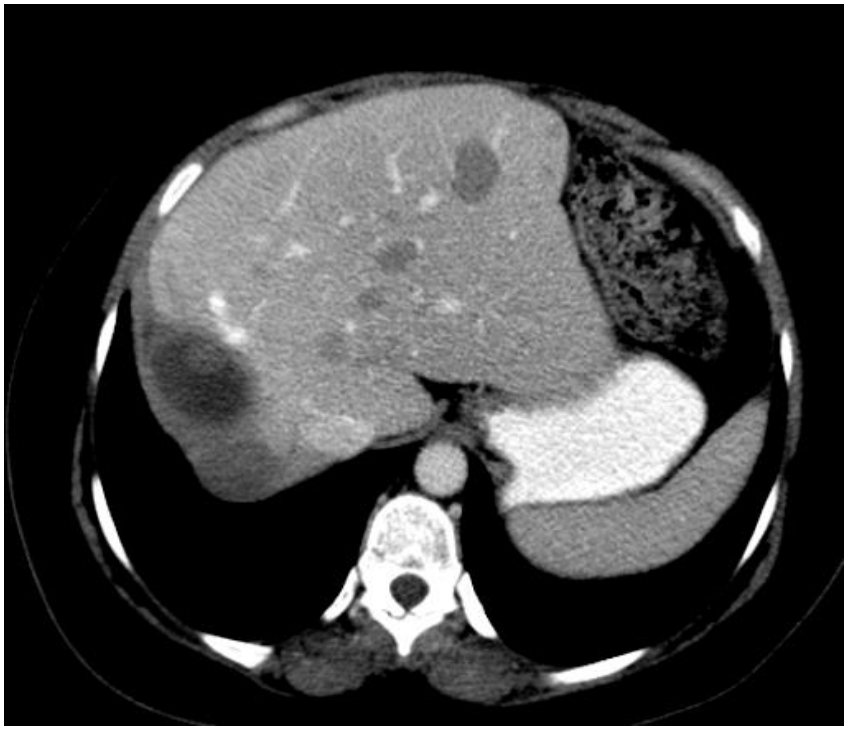




Preferential arterial supply of hypervascular NET liver metastasis

Oorspronkelijke figuren van “www.sirtex.com” en animatie van “www.nordion.com”

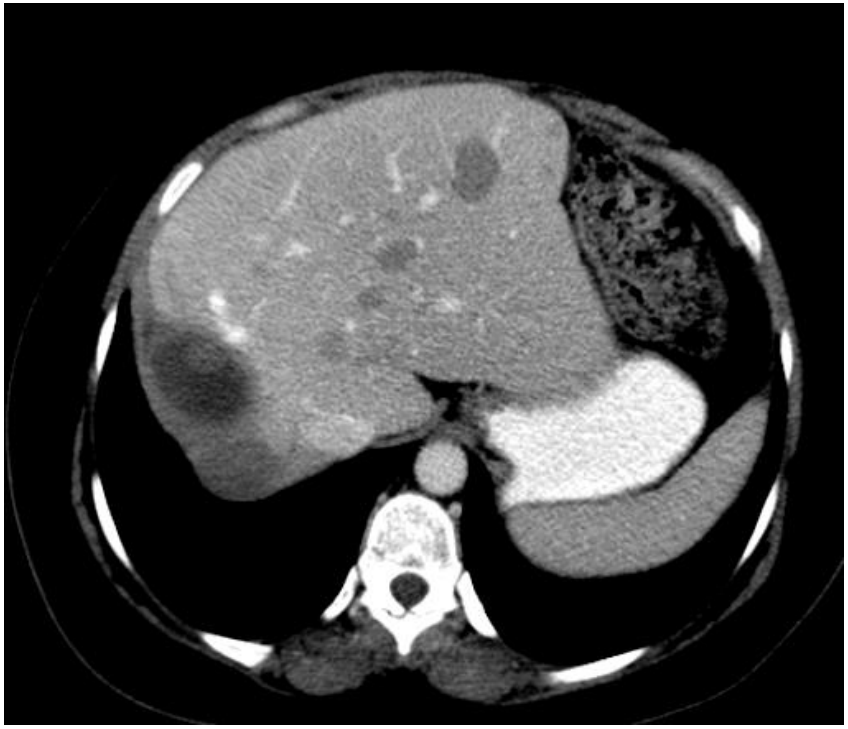
Partial response after yttrium-90 radioembolization



Prior to treatment

1.5 months post treatment

Partial response after yttrium-90 radioembolization



Prior to treatment

3 months post treatment

First prospective trial combining PRRT and liver directed therapy

Erasmus MC
Universitair Medisch Centrum Rotterdam

HEPAR+

^{177}Lu

^{166}Ho

^{177}Lu-DOTA,Tyr^{3}-octreotate

4 cycles of 200 mCi

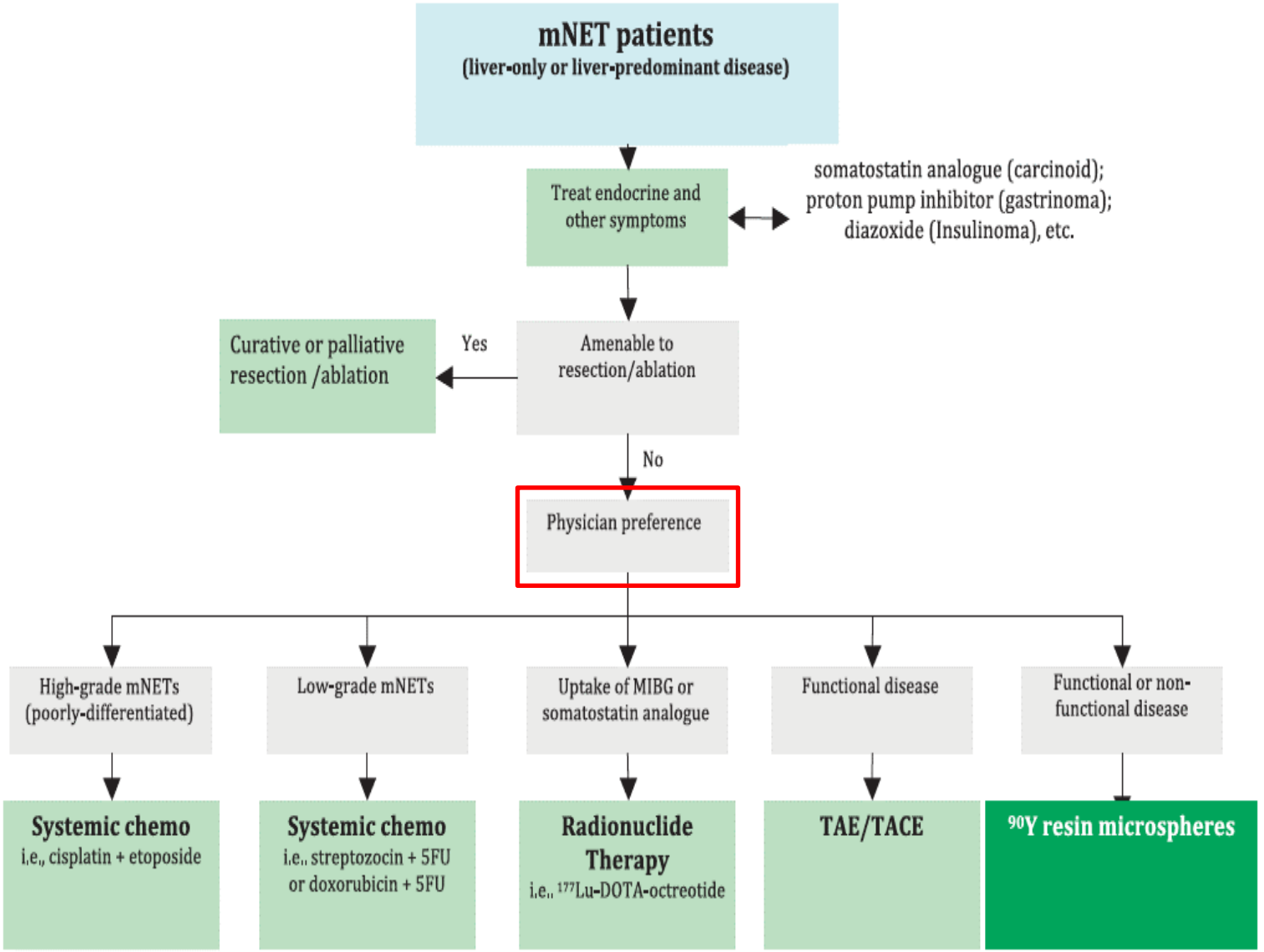
3 months later

^{166}Holmium-radioembolization

Endpoints

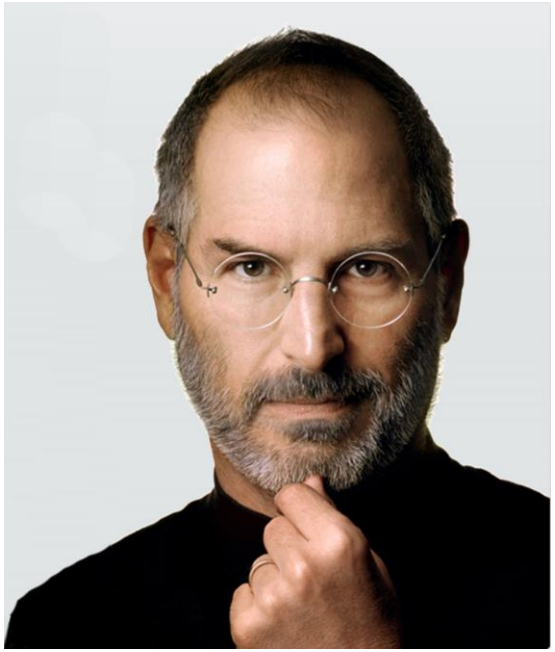
Toxicity, safety and efficacy

Hepatic mNET treatment algorithm



Kennedy et al. 2012

Even…….. a livertransplantation can be an option!



The (near) future

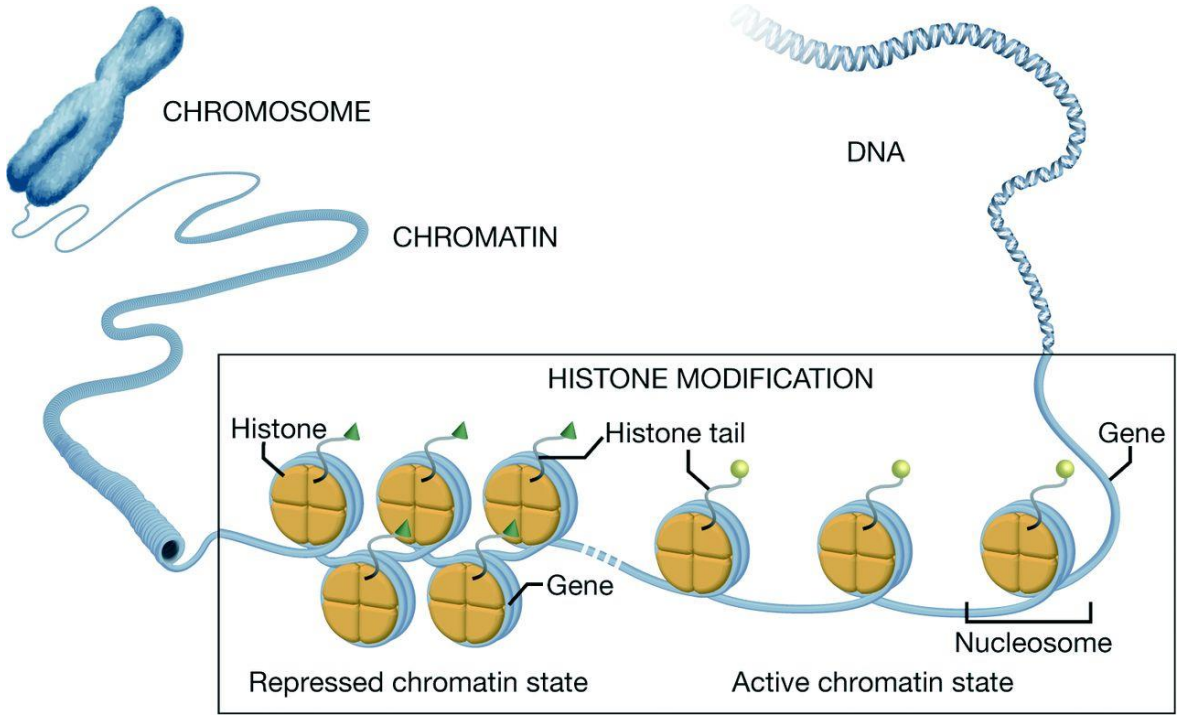
'Exome sequencing': rare DNA mutations

Identified mutations involved in epigenetic modifications (reversible changes in gene function)

44% pNET mutations in *MEN1* gen

***MEN1* gen** involved in reversible histone modifications

Treatment potential



C.R.C. Pieterman et al. Endocr Relat Cancer 2014;21:R121-R142

Hubrecht Institute

- Developmental Biology & Stem Cell Research
- Creating organoids of pNETS
- Both sporadic, familial, and metastized disease
- Aiming for targeted therapy

In conclusion

- In metastasized NETS surgery remains the most important treatment
- Large variety of other treatments for metastasized disease
- Treatment in Centers of Excellence

European ENETS Neuroendocrine Tumor Society

September 29 - October 1, 2016

Utrecht THE NETHERLANDS

WorldMEN 2016 Utrecht

15th International Workshop
on Multiple Endocrine Neoplasia
and other rare endocrine tumors

Radioembolization (contra-)indications

Main indications

Confirmed metastatic malignancy, dominant liver metastases without surgical options

Life expectancy of at least 3 months, WHO performance 0-2

Main contra-indications

Radiation- or chemotherapy, surgery within the last 4 weeks

Serum bilirubin >1.5 x ULN, serum creatinine >185 µmol/L, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) >5 x ULN, leukocytes <2.0 10^9/L, platelet count <50 10^9/L

Child pugh C