

# NET wat anders



25 januari 2018

**Wouter Dercksen, internist-oncoloog  
Máxima Medisch Centrum**



máxima  
medisch centrum

## Disclosure belangen spreker

(potentiële) belangenverstrengeling	
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Bedrijfsnamen
<ul style="list-style-type: none"><li>● Sponsoring of onderzoeksgeld</li><li>● Honorarium of andere (financiële) vergoeding</li><li>● Aandeelhouder</li><li>● Andere relatie, namelijk ...</li></ul>	<ul style="list-style-type: none"><li>● Ipson, Novartis, Pfizer</li><li>●</li><li>●</li></ul>



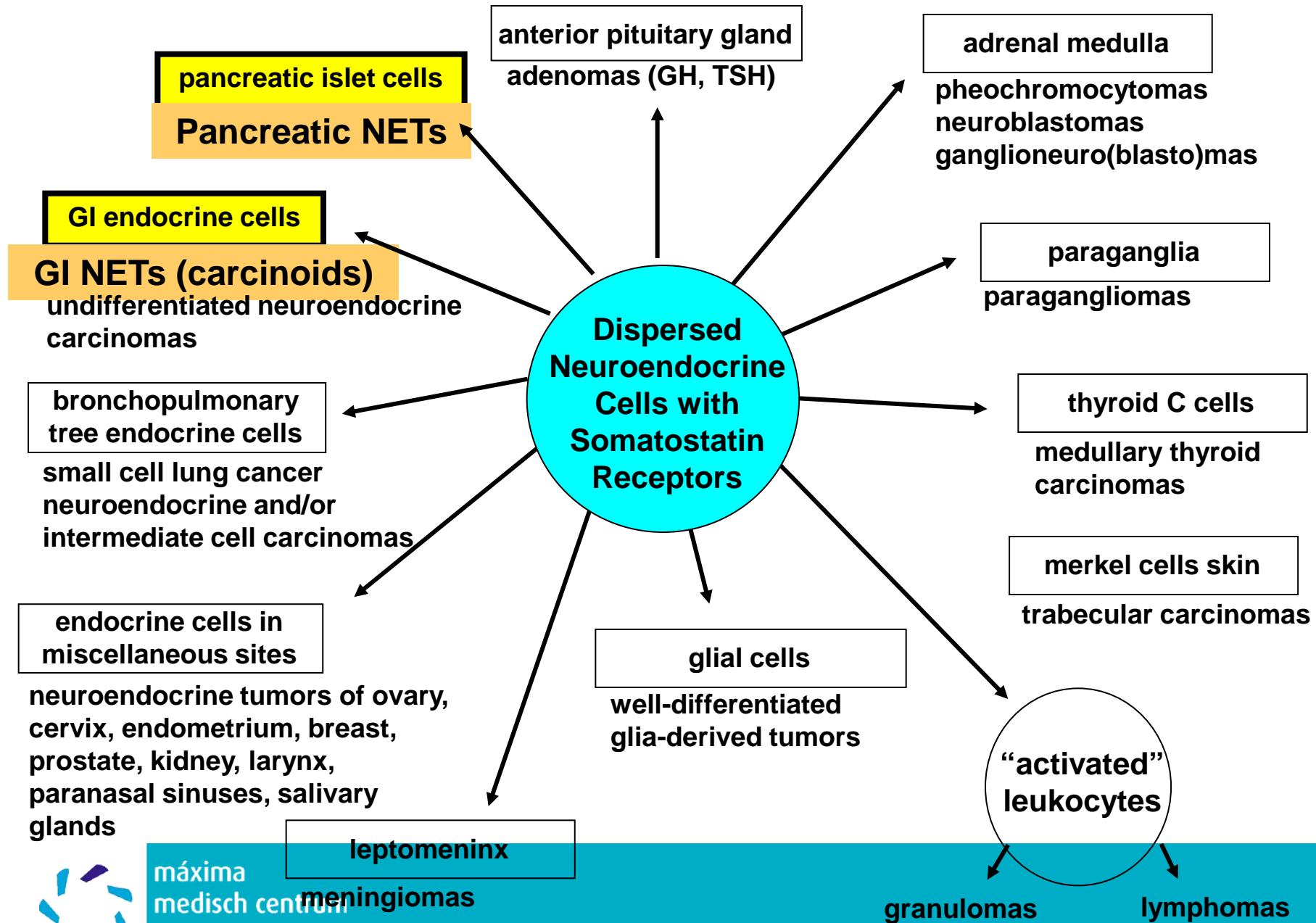
- **Introductie.**
- **Heterogeniteit:**
  - Locatie
  - Functioneel
  - Celnivo
  - Genetisch/moleculair
  - kliniek
- **Diagnostiek**
- **Pathologie/Gradering-Staging.**
- **Therapie (octreotide, TKI, PRRT).**



# Neuro-endocriene tumoren

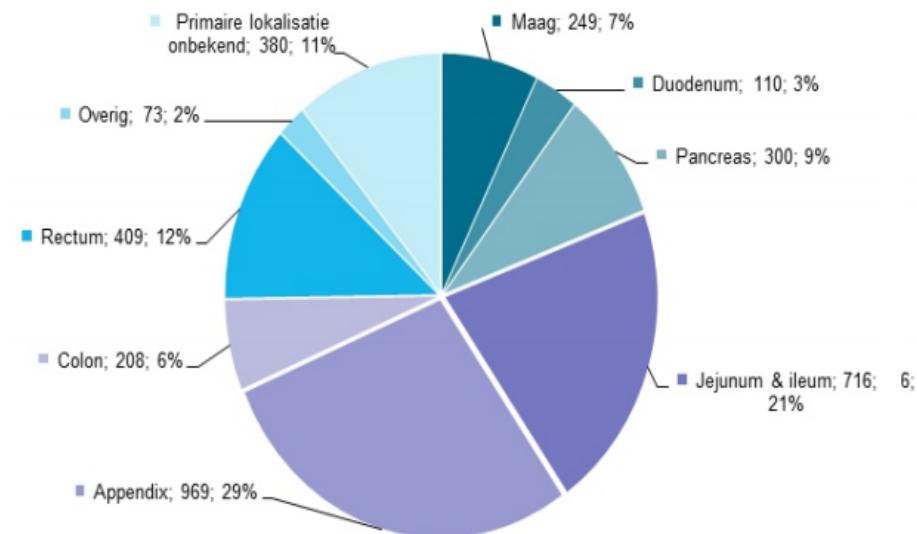
- Spectrum neuro-endocriene tumoren is groot
  - Niet één ziekte
  - Verschillen per locatie
    - Metastasering
    - Symptomatologie
  - Wel/geen hormoonproductie.
  - Therapie en follow up verschilt





# Diverse locaties NET

Breed spectrum van maligniteiten ontstaan in de neuro-endocriene cellen op vele plaatsen in het lichaam



Figuur 2. Incidentie van NET van de pancreas en tractus digestivus naar primaire lokalisatie (Nederland 2001-2010)



## NET Embryonale oorsprong

- Foregut
- Long
- Thymus
- Maag
- Duodenum

- Midgut
- Jejunum
- Ileum
- Appendix
- Colon ascendens

- Hindgut
- Colon transversum / descendens
- Sigmoid
- Rectum

- Bijkomende locaties
- Pancreas
- Urogenitaal
- Bijnier
- Paraganglia



# Functionele neuro-endocriene tumoren

• Tumor	• Hormoon	• Aantal per miljoen personen / jr.	Symptomen
• Gastrinoom	• Gastrine	• 0.5-1.5	• Peptische ulcera, >>diarree
• Insulinoom	• Insuline	• 1-2	• Hypoglycaemieën
• VIPoom	• VIP	• 0.05-0.2	• >>>Diarree, flushing
• Glucagonoom	• Glucagon	• 0.01-0.1	• Diabetes mellitus, rash, extreme cachexie
• Somatostatinoom	• Somatostatine	• 0.01-0.2	galstenen, steatorrhoe, diabetes mellitus
• GI-NET	• Serotonine Tachy-en bradykinines	• 20-50	• >>Diarree, flushing, hartklepziekte, darmobstructie
• Bronchial NET	• Serotonine Tachy-en bradykinines ACTH, GH	• 2-20	• >>Diarree, flushing, bronchusconstrictie, Cushing, acromegalie

# Symptomatologie NET

- Lokaal:

- buikklachten
- buikpijn
- darm obstructie



- Systemisch:

- Afgifte van mediatoren
- *in aanwezigheid van lever metastasen bij patiënten met dunne darm carcinoiden of long carcinoiden*



**carcinoïd syndroom**

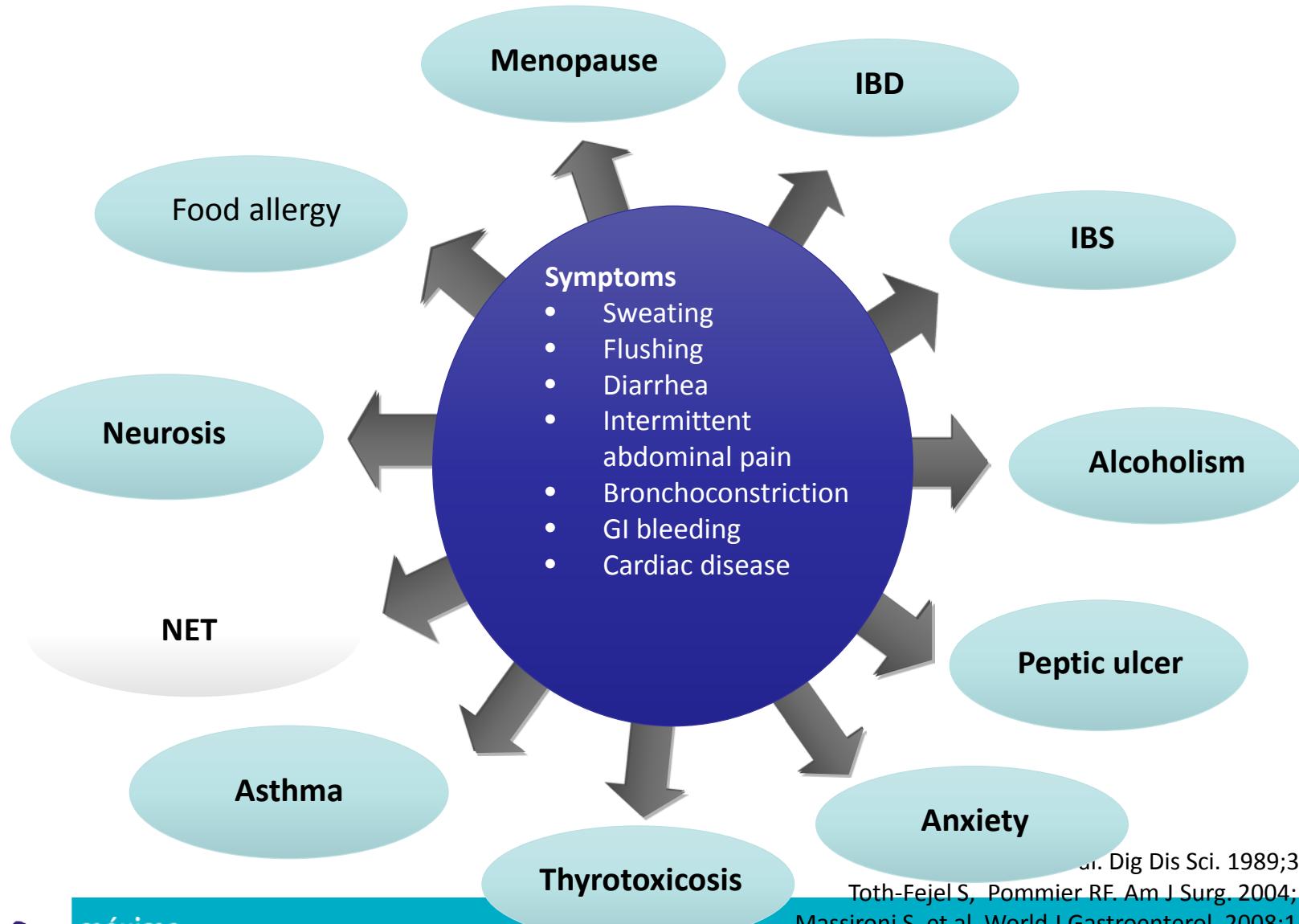
# Carcinoïd Syndroom

## Symptomatologie

- **Flushing, teleangiectasieën en pellagra dermatitis**
- **Diarree en buikkrampen**
- **Fibrose van het endocardium van het rechter hart, met o.a. als gevolg tricuspidalis en pulmonalis klep stenose en insufficiëntie**

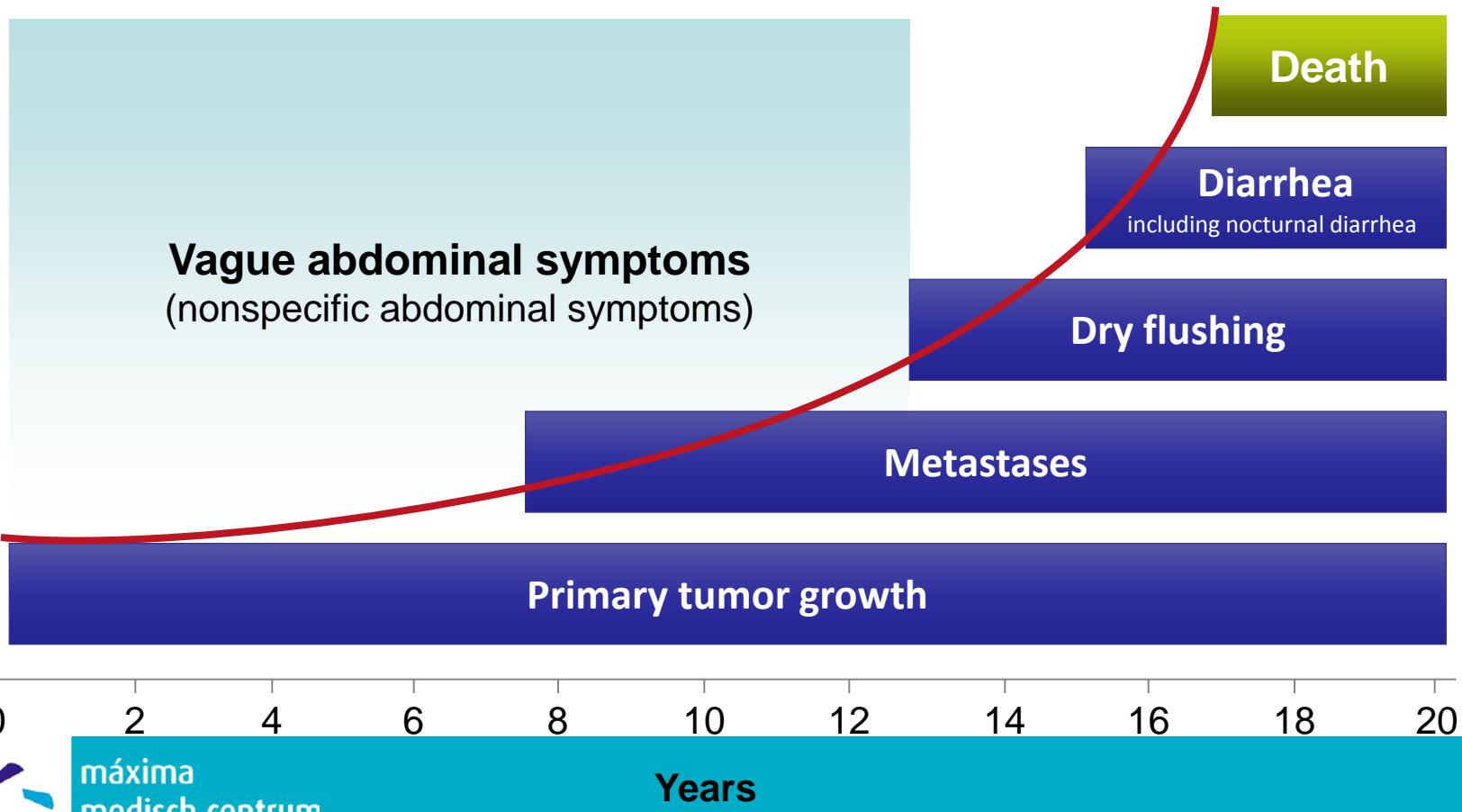


# Diverse presentaties



# Impact of delay in diagnosis

Incorrect diagnosis of irritable bowel —> correct diagnosis of NET



Vinik A, et al. Dig Dis Sci. 1989;34(3 Suppl):145-275.

Wiedenmann B, et al. Neuroendocrinology. 2004;80 Suppl 1:94-8.

# Diagnostiek NET

## ■ Laboratoriumonderzoek

- (Derivaten van) hormonale secretoire producten:
  - o.a. plasma serotonin, 5-HIAA excretie in the urine
- Chromogranin A, Neuron-specific enolase (NSE).

## ■ Orgaanspecifiek onderzoek (scopie)

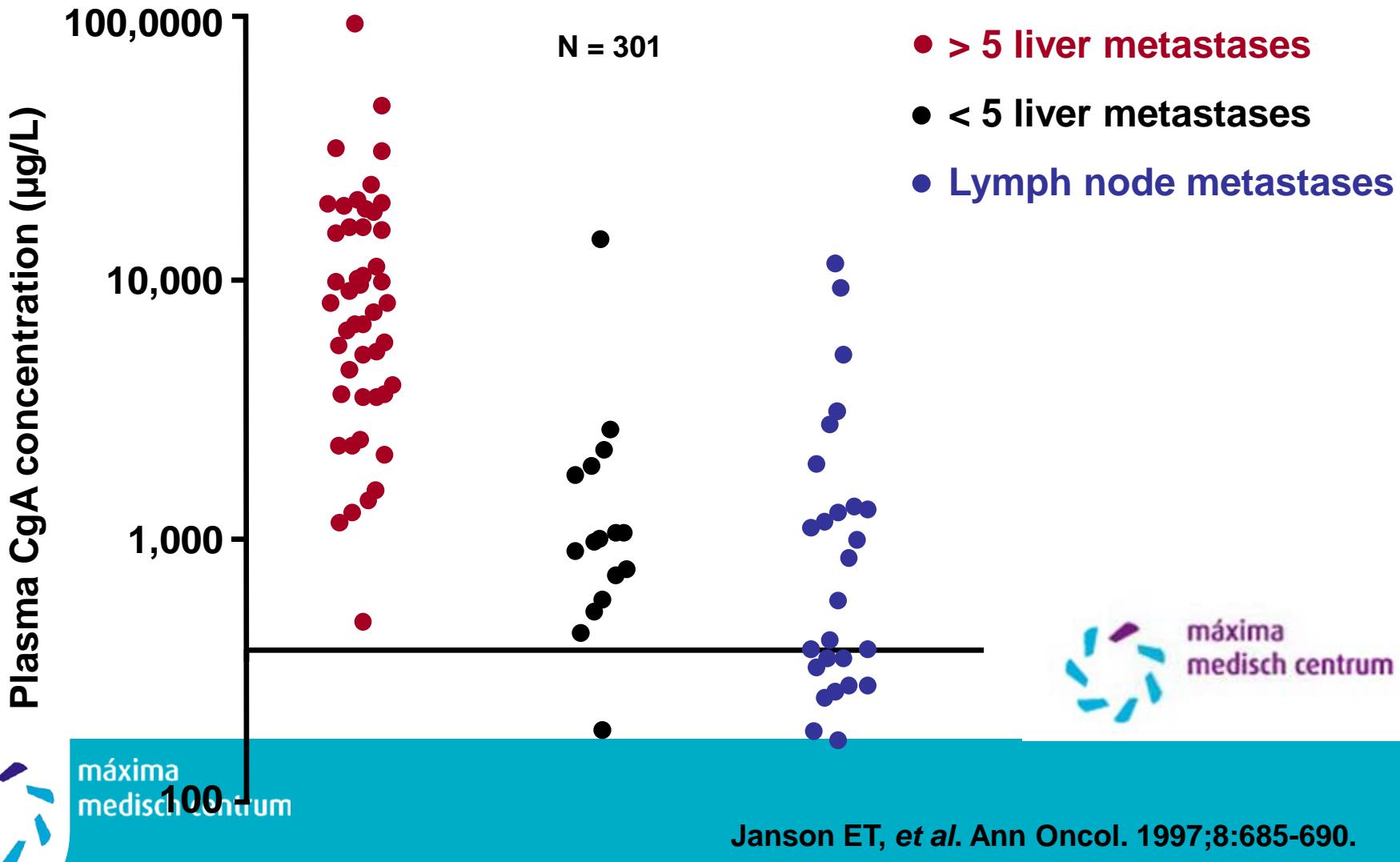
## ■ Radiologisch onderzoek

## ■ Nucleair onderzoek

## ■ Pathologisch onderzoek

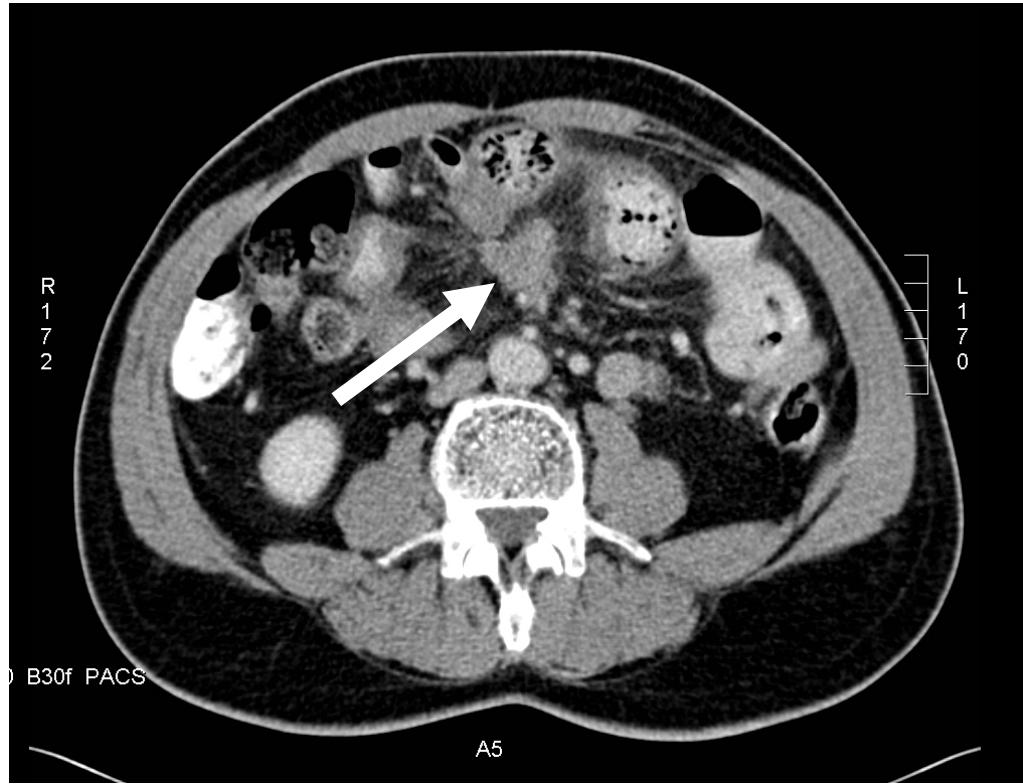


# Plasma Chromogranin A (CgA) is Elevated in Patients with Metastatic GEP NETs



# Neuro-endocrine tumoren

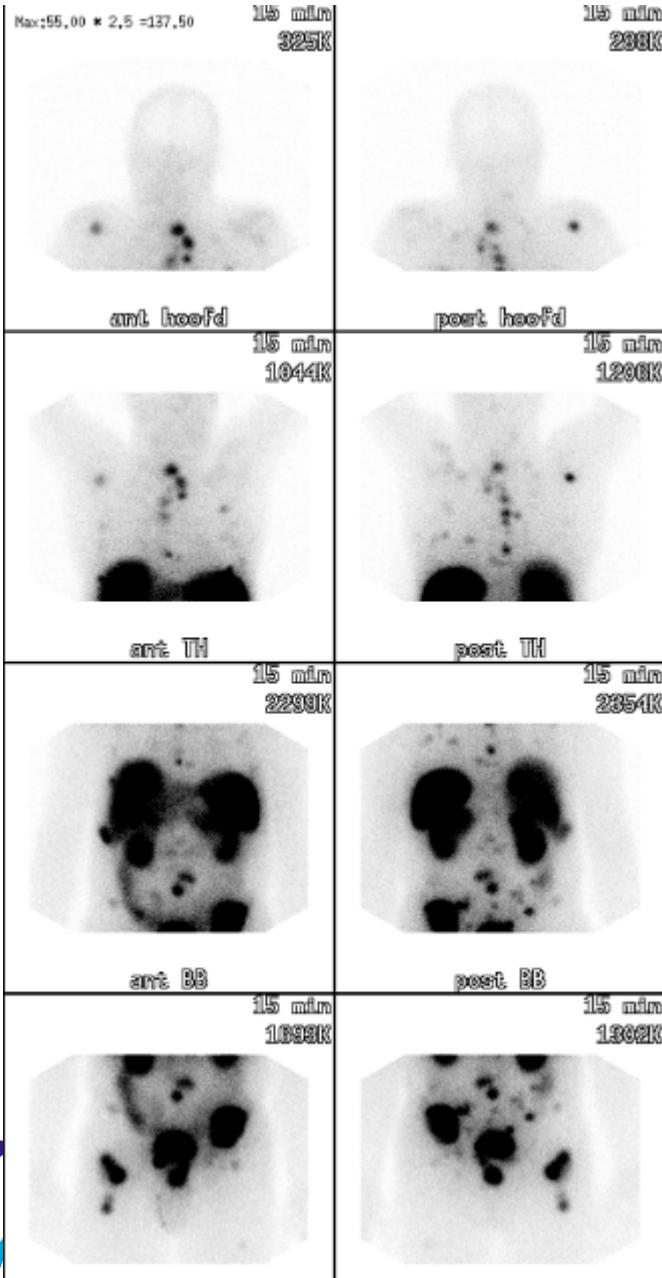
## Desmoplastische reactie



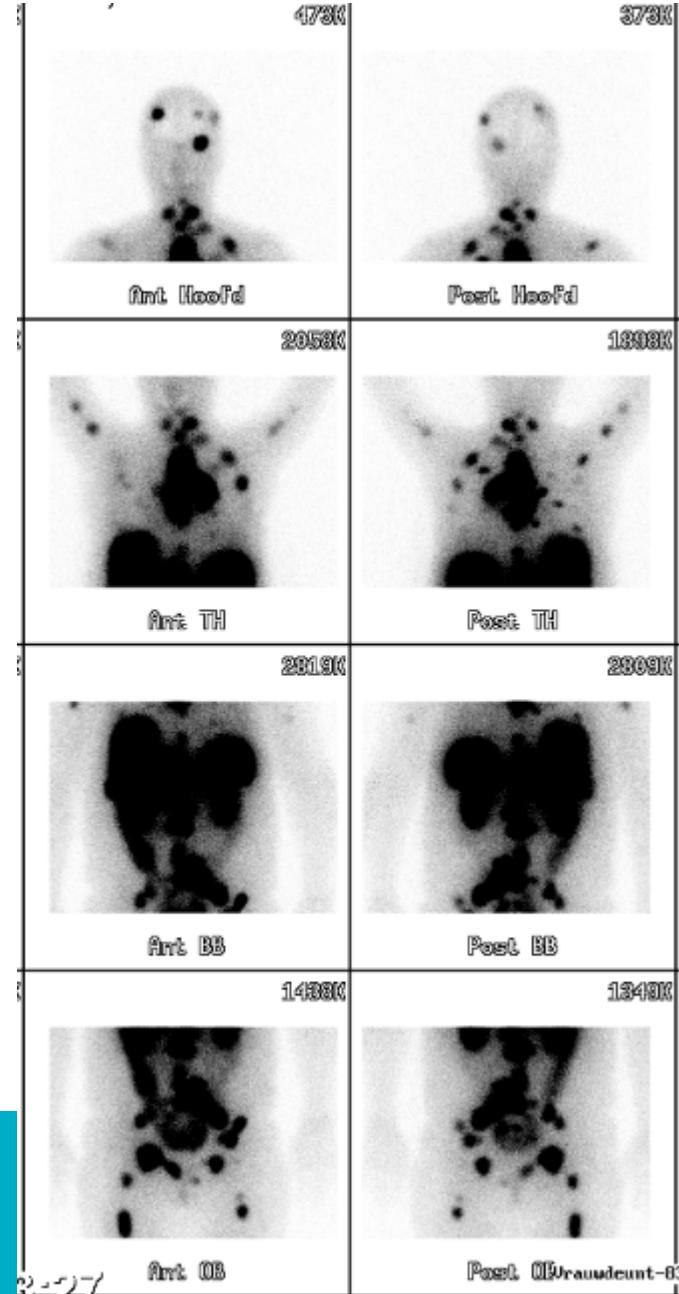
máxima  
medisch centrum

# $^{111}\text{In}$ -pentetreotide Scintigrafie

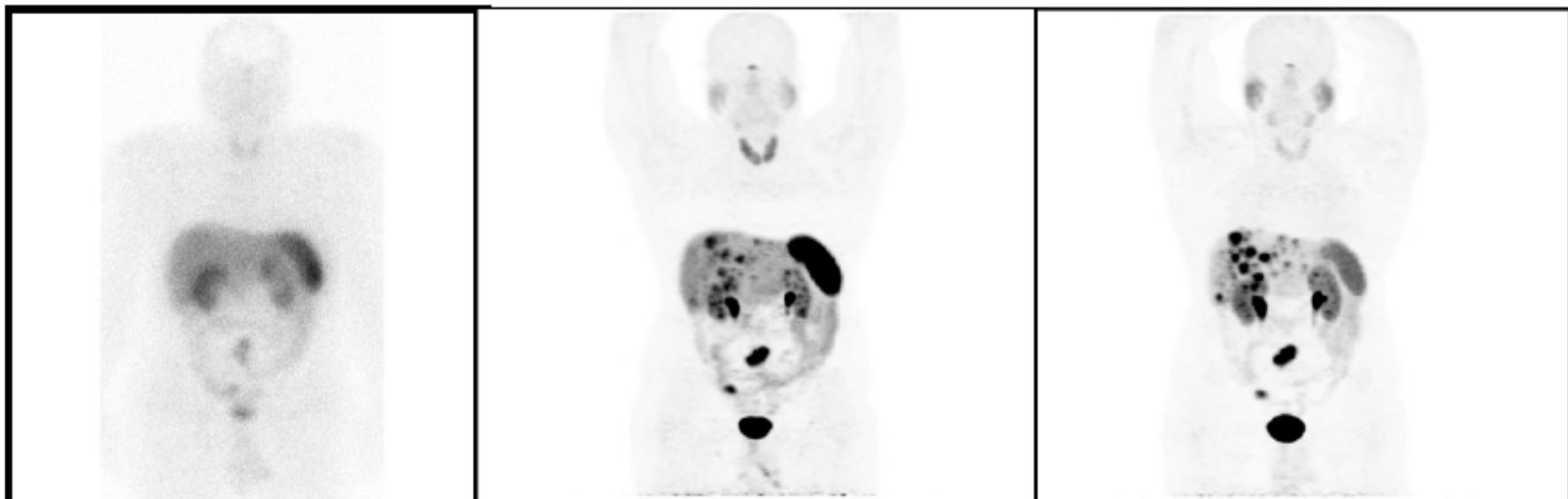
## Gemetastaseerd Rectum Carcinoïd



## Gemetastaseerd Thymus Carcinoïd



# 20 years after $^{111}\text{In}$ -Octreotide: Prospects in molecular imaging of GEP-NET with antagonists



$^{111}\text{In}$ -Octreotide  
Past

$^{68}\text{Ga}$ -DOTA-TOC  
Present

$^{68}\text{Ga}$ -OPS202\*  
Future?

\*Not approved in any market

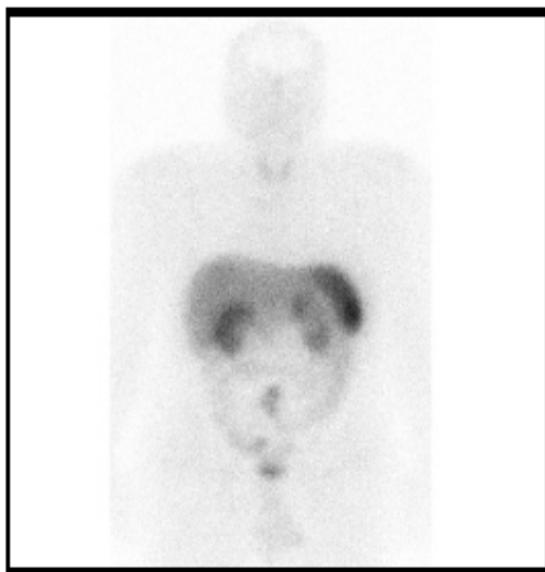


máxima  
medisch centrum

# From SPECT to PET

Duration  
24 to 48h

FDA approval: 1994



Radiation  
Exposure  
12mSv

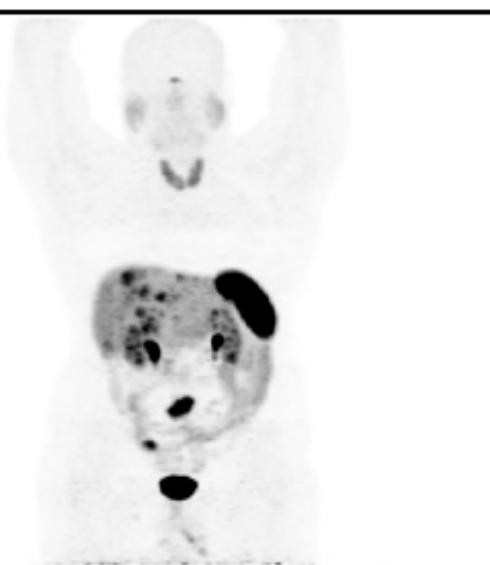
Resolution  
>1cm

Sensitivity  
52 – 86%

Cost  
± Euro 1855

$^{111}\text{In}$ -DTPA-Octreotide  
 $^{99\text{m}}\text{Tc}$ -HYNIC-Octreotide

FDA approval: 2/06/2016  
( $^{68}\text{Ga}$ -DOTA-TATE only)



$^{68}\text{Ga}$ -DOTA-TOC  
 $^{68}\text{Ga}$ -DOTA-TATE  
 $^{68}\text{Ga}$ -DOTA-NOC

Duration  
<2h

Radiation  
Exposure  
4mSv

Resolution  
≈ 5mm

Sensitivity  
>90%

Cost  
± Euro 1400

M. Gabriel et al. J Nucl Med, 2007;48:508-18; I. Buchmann et al. Eur J Nucl Med Mol Imaging, 2007;34:1617-26; E. Etchebehere et al. J Nucl Med, 2014;55:1-7



máxima  
medisch centrum

# Classificatie neuro-endocriene tumoren

## ► Primaire locatie:

- Dunne darm NETs, dike darm NETs, appendix NETs, pancreas NETs, maag NETs, long NETs. 15% van onbekende origine

## ► Embryogene origine (foregut, midgut, hindgut).

## ► Pathologische classificatie



### Foregut (40-45%)

- Lungs
- Thymus
- Stomach
- Pancreas
- First part of duodenum

### Midgut (20-25%)

- Second part of duodenum
- Jejunum
- Ileum
- Right colon

### Hindgut (20-25%)

- Transverse, left, sigmoid colon
- Rectum

### Pancreatic NETs (6-8%)

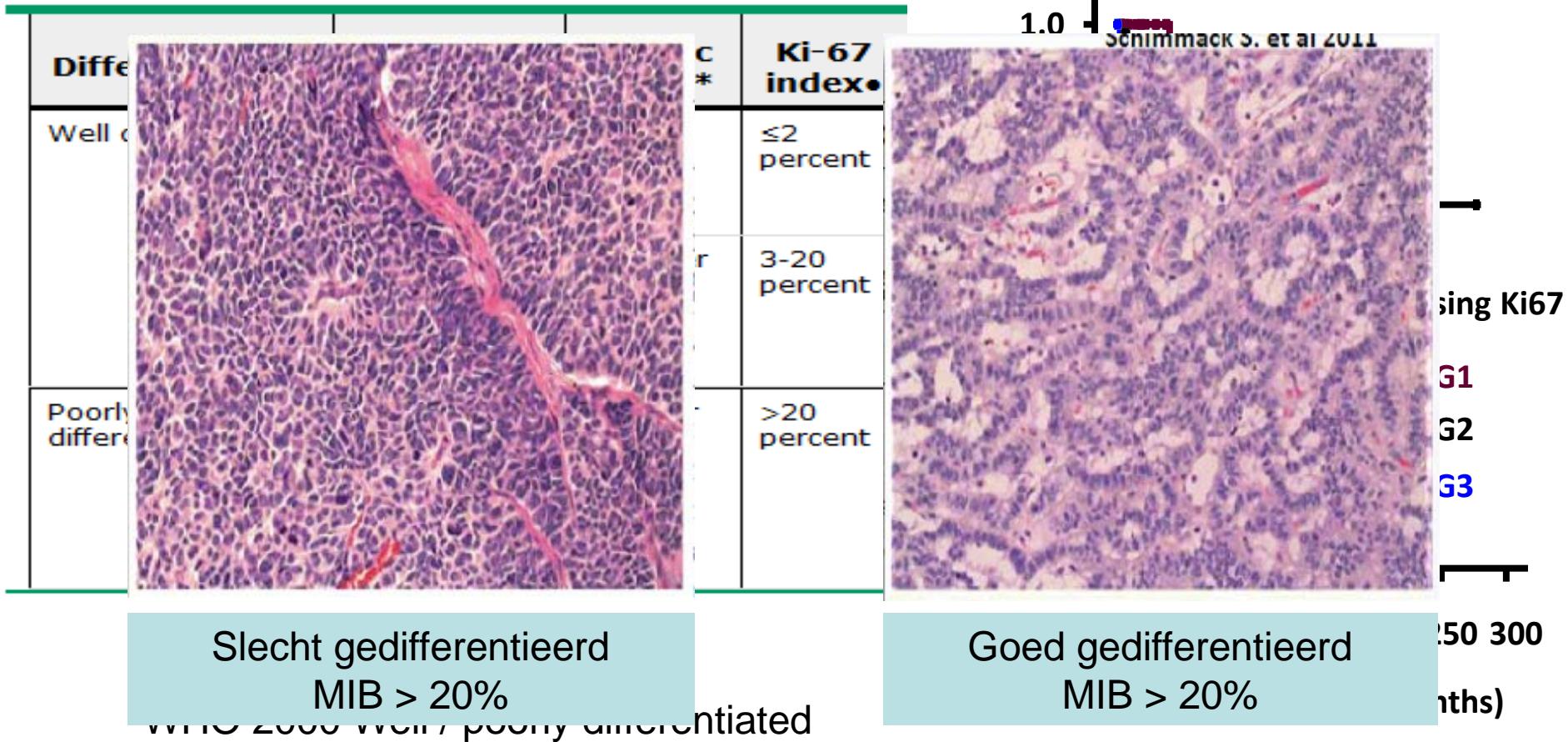
- Gastrinoma
- Insulinoma
- Glucagonoma
- Somatostatinoma
- VIPoma
- Pancreatic polypeptidoma
- Non-functioning tumours

\* Includes GEP-NETs as well as non GEP-NETs. Non-GEP-NETs represent ~40% of all NETs with bronchopulmonary NETs being the most frequent (~70% of all non GEP-NETs)

Unknown primary in 10-15% of cases



# WHO-gradering 2010



Slecht gedifferentieerd  
MIB > 20%

WHO 2010 very poorly differentiated

Goed gedifferentieerd  
MIB > 20%

250 300  
months)

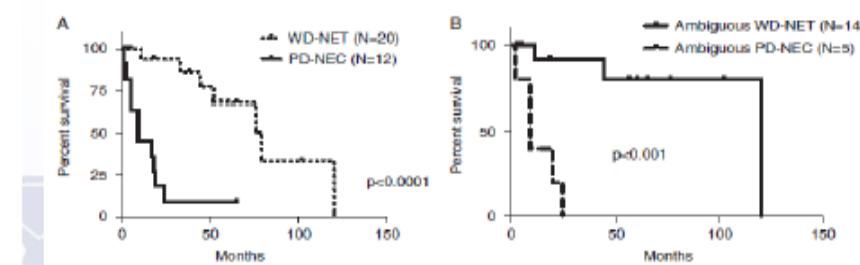


máxima  
medisch centrum

TABLE 2. Classification of High-grade Pancreatic Neuroendocrine Neoplasms by Secondary Evidence

Initial Consensus	IHC Abnormalities	Ki67%	Other Histologic Components	Confirmed Classification
WD-NET		50	G1/G2 WD-NET	WD-NET
WD-NET	DAXX	70	G1/G2 WD-NET	WD-NET
WD-NET	ATRX	50	G1/G2 WD-NET	WD-NET
WD-NET		40	G1/G2 WD-NET	WD-NET
WD-NET	DAXX	35	G1/G2 WD-NET	WD-NET
WD-NET		32	G1/G2 WD-NET	WD-NET
Ambiguous		35	G1/G2 WD-NET	WD-NET
Ambiguous		65	G1/G2 WD-NET	WD-NET
Ambiguous	DAXX	50	G1/G2 WD-NET	WD-NET
Ambiguous	ATRX	35	G1/G2 WD-NET	WD-NET
Ambiguous	DAXX	30	G1/G2 WD-NET	WD-NET
Ambiguous		60	G1/G2 WD-NET	WD-NET
Ambiguous	ATRX	40		WD-NET
Ambiguous	DAXX	80	G1/G2 WD-NET	WD-NET
Ambiguous	DAXX	49	G1/G2 WD-NET	WD-NET
Ambiguous		38	G1/G2 WD-NET	WD-NET
Ambiguous		60	G1/G2 WD-NET	WD-NET
Ambiguous		50	G1/G2 WD-NET	WD-NET
Ambiguous		70	G1/G2 WD-NET	WD-NET
Ambiguous	p53/Rb	88		PD-NEC
Ambiguous	p53/SMAD4	38	Ductal adenocarcinoma	PD-NEC
Ambiguous	p53/Rb	70		PD-NEC
Ambiguous	p53/Rb	85		PD-NEC
Ambiguous	p53	60		PD-NEC
Ambiguous		70	Undetermined	
PD-NEC-LCC	DAXX	66	G1/G2 WD-NEI	WD-NEI
PD-NEC-LCC	Rb	44		PD-NEC
PD-NEC-LCC		26	Ductal adenocarcinoma	PD-NEC
PD-NEC-SCC	p53	80	Ductal adenocarcinoma	PD-NEC
PD-NEC-SCC	Rb	90		PD-NEC
PD-NEC-SCC	p53/Rb	94	Ductal adenocarcinoma	PD-NEC
PD-NEC	Rb	84		PD-NEC
PD-NEC	p53	88		PD-NEC

- Mean Ki-67:  
WT-NET (46%, 30-80%) vs.  
PD-NEC (72%, 26-93%)
- Median disease specific survival:  
WD-NET (n=20) vs. PD-NEC  
(n=12) 75 vs. 11 months



Tang L et al. Am J Surg Pathol, 2016, 40:1192-1202

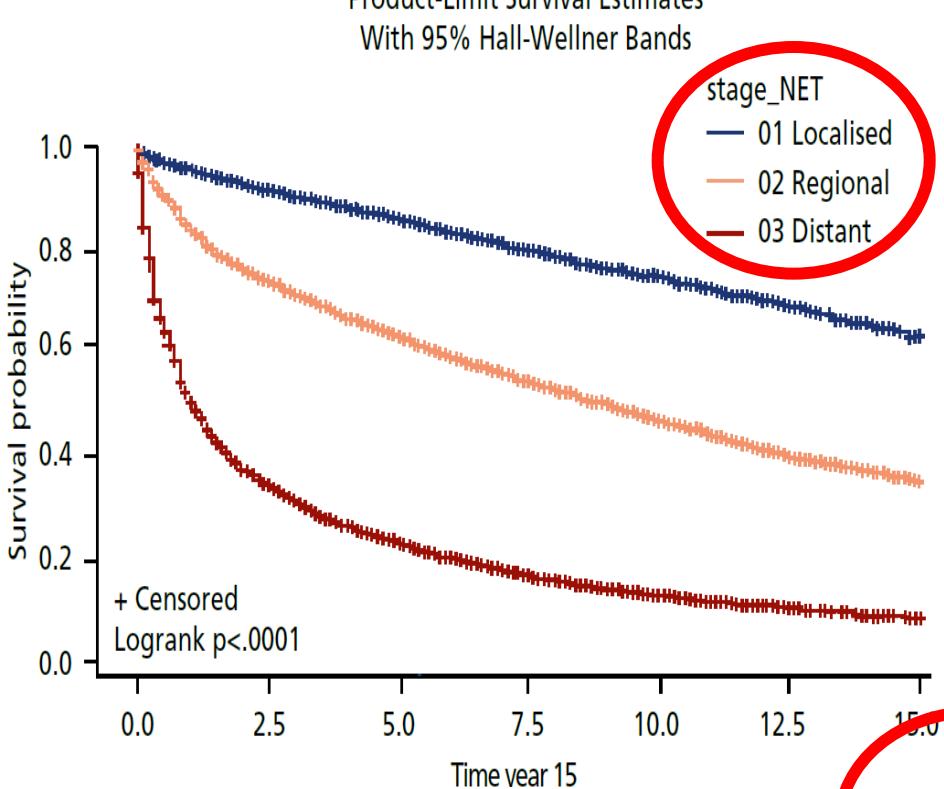


# Spectrum van NET op MDO

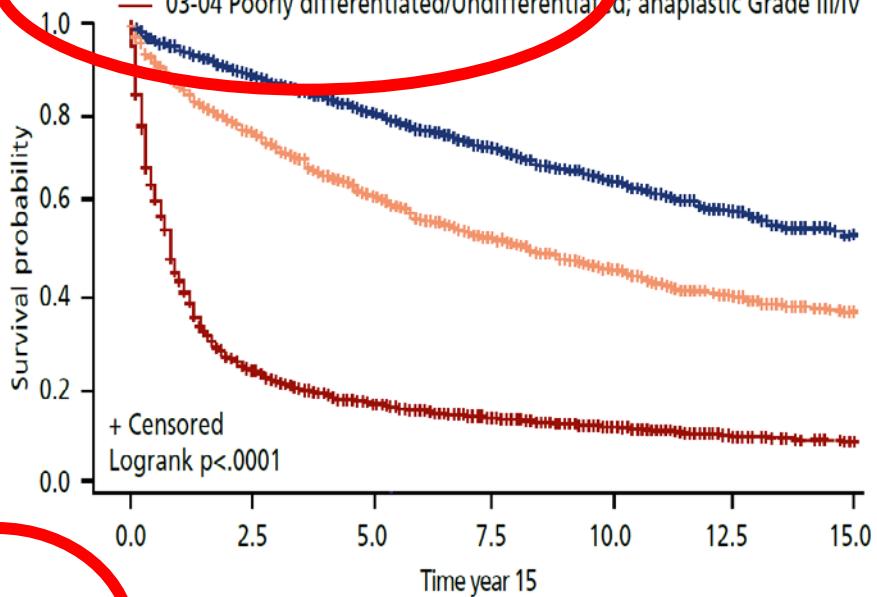
- Diverse presentaties
  - Hormoon gerelateerde symptomen/syndromen, tumorexpansie, leeftijd, co-morbiditeit
- Diverse localisaties
- Diverse specialismen
  - Oncoloog, MDL-arts, chirurg, longarts, endocrinoloog, radioloog, nucleair geneeskundige, patholoog, evt cardiololoog.
- Radicaal verwijderd
- Locaal / regionaal / metastasen
- Follow-up



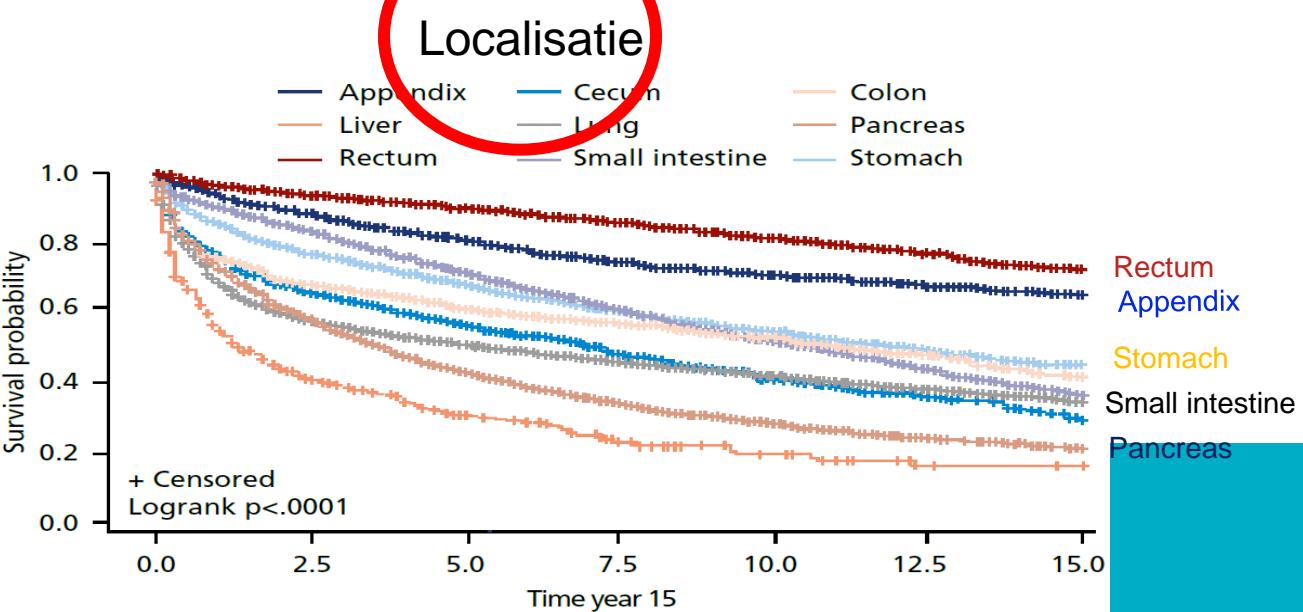
Product-Limit Survival Estimates  
With 95% Hall-Wellner Bands



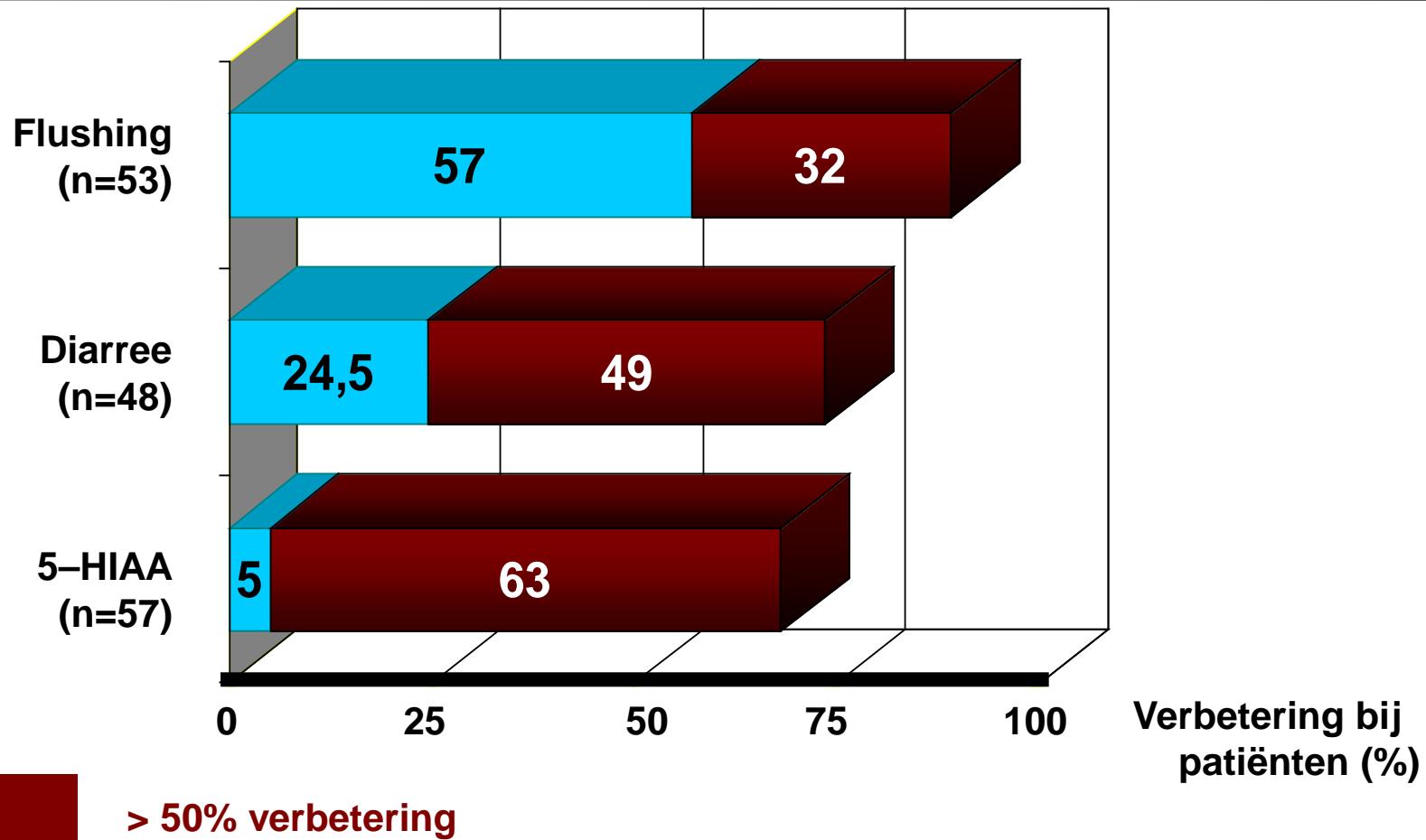
Product-Limit Survival Estimates  
With 95% Hall-Wellner Bands



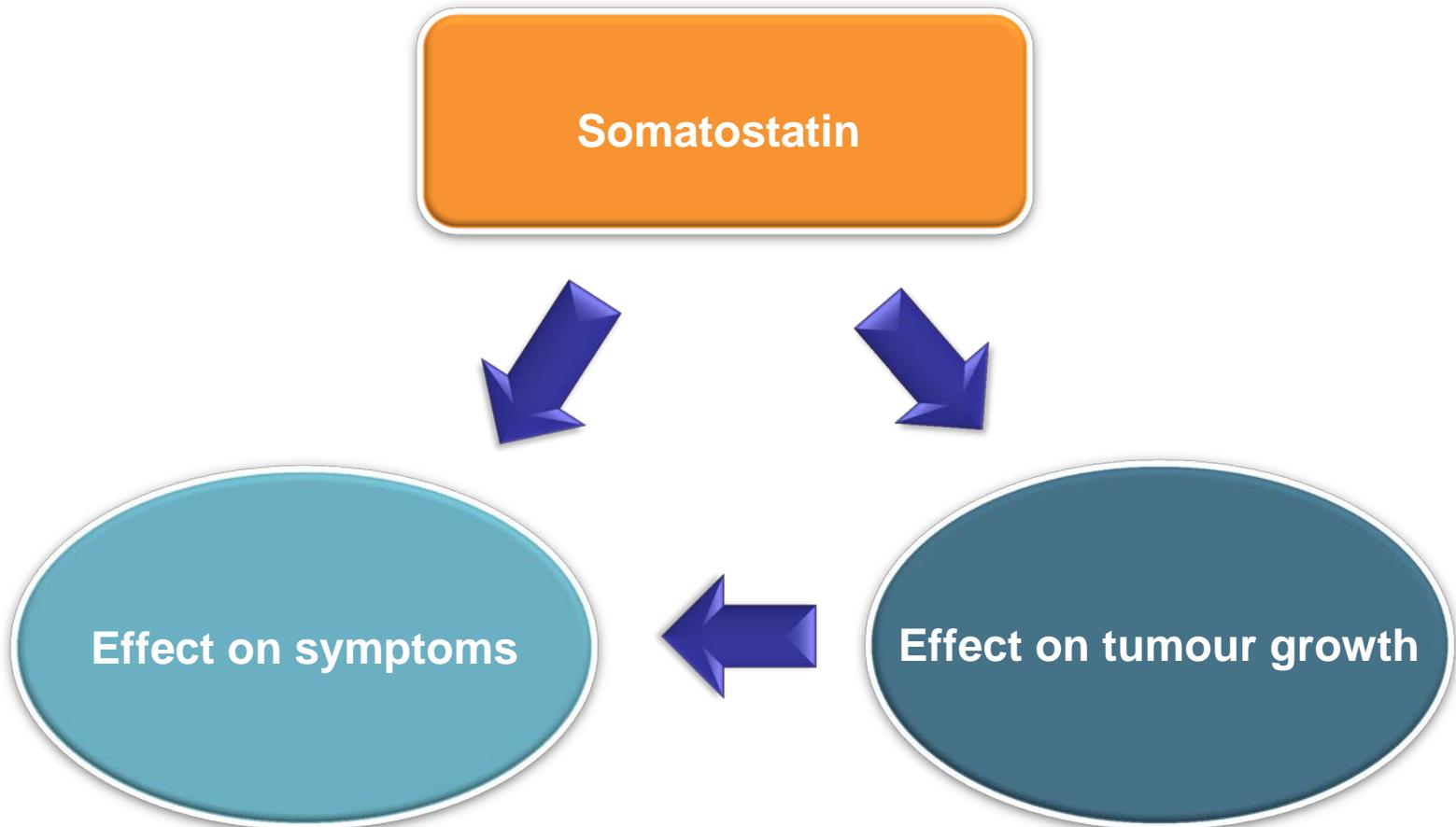
Localisatie



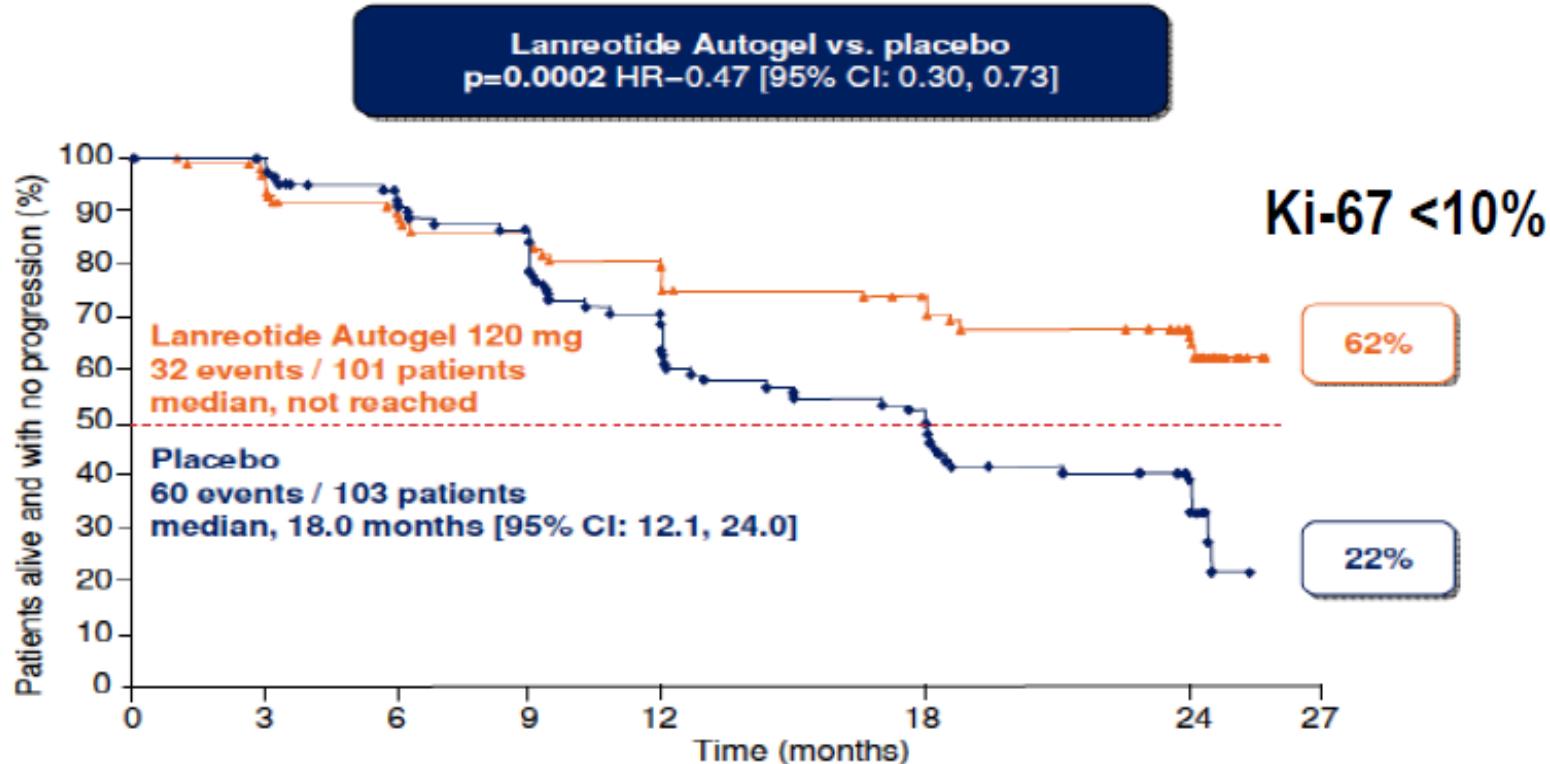
# Somatostatine Analoog Behandeling van het Carcinoïd Syndroom



# Importance of somatostatin receptors in NETs



# CLARINET: Evaluation of the Antiproliferative Effect of Lanreotide Autogel 120 mg q4w in G1-2 GEP-NETs



P-value derived from stratified log-rank test; HR derived from Cox proportional hazard model.  
HR, hazard ratio; ITT, intention-to-treat.

Presentation Presidential Session of the 17th ECCO – 38th ESMO – 32nd ESTRO European Cancer Congress, 28 September 2013,  
abstract E17-7103 , Amsterdam- EJC, vol 49 (3), 2013

Caplin, *N Engl J Med* 2014; 371:224-233.



máxima  
medisch centrum

# Clinical Trial Landscape in NET

## Phase III clinical trials

Intestine

Pancreas

Lung

PROMID

Octreotide vs placebo

CLARINET

Lanreotide vs placebo

NETTER-1

RADIANT-3

Everolimus vs placebo

PRRT vs Octreotide LAR

Sunitinib

Sunitinib vs placebo

RADIANT-4

RADIANT-4

Everolimus vs placebo

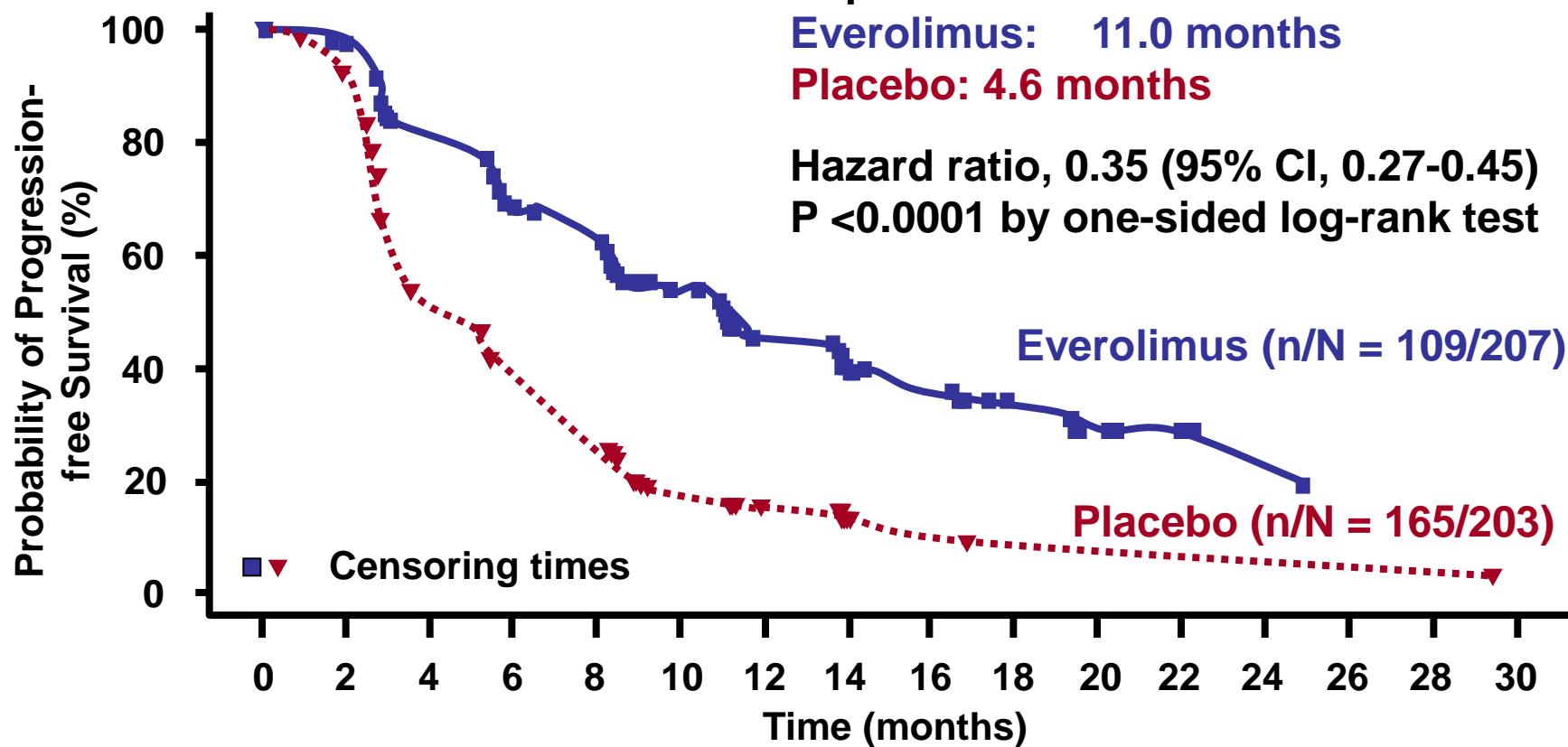
Everolimus vs placebo



máxima  
medisch centrum



# RADIANT-3: Progression-free Survival Local Assessment

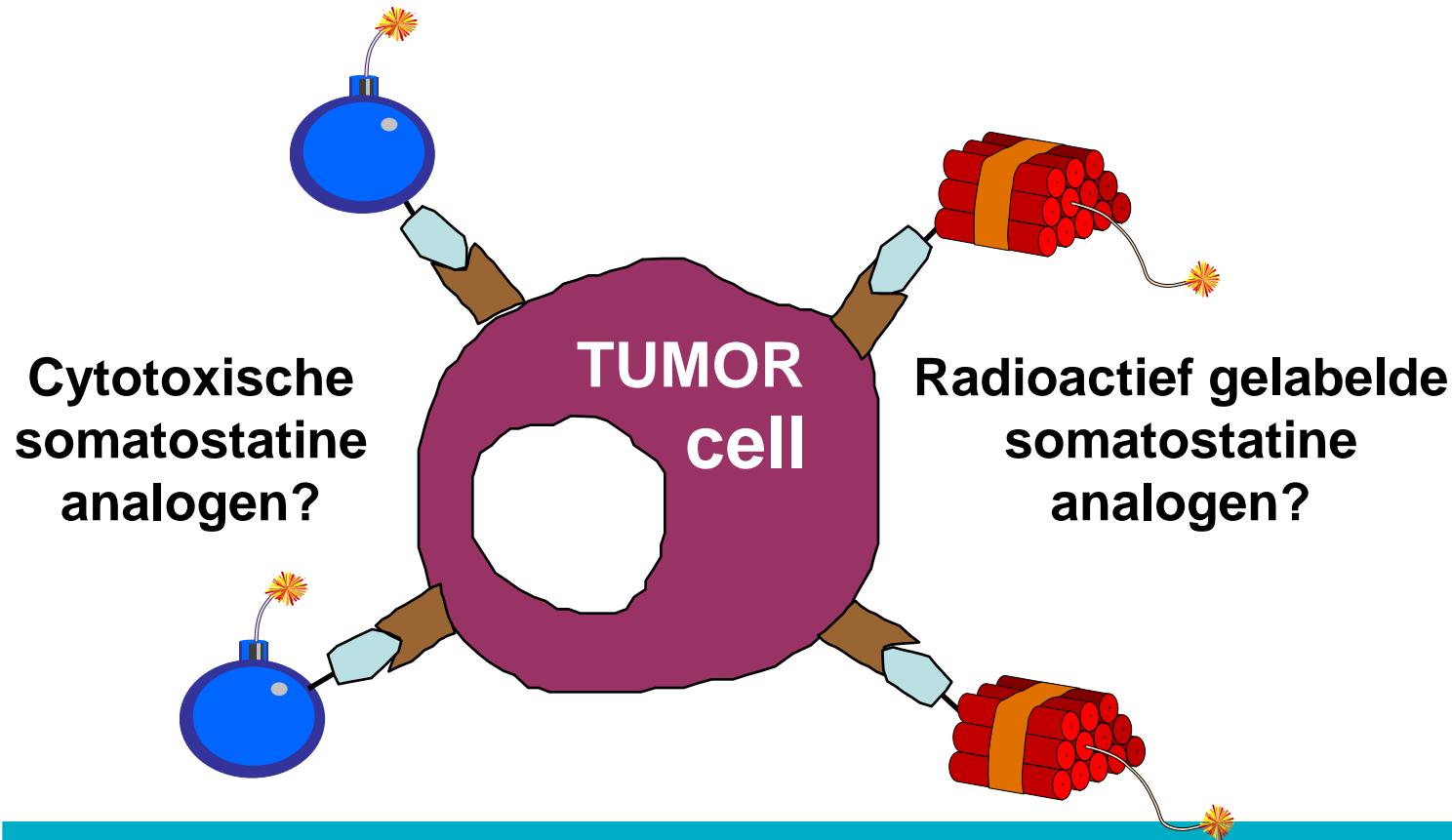


Everolimus	207	189	153	126	114	80	49	36	28	21	10	6	2	0	0	0
Placebo	203	177	98	59	52	24	16	7	4	3	2	1	1	1	0	0
No. of patients still at risk	máxima medisch centrum															

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

# Targeted Somatostatine Analogen?

PRRT = Peptide Receptor Radionuclide Therapie

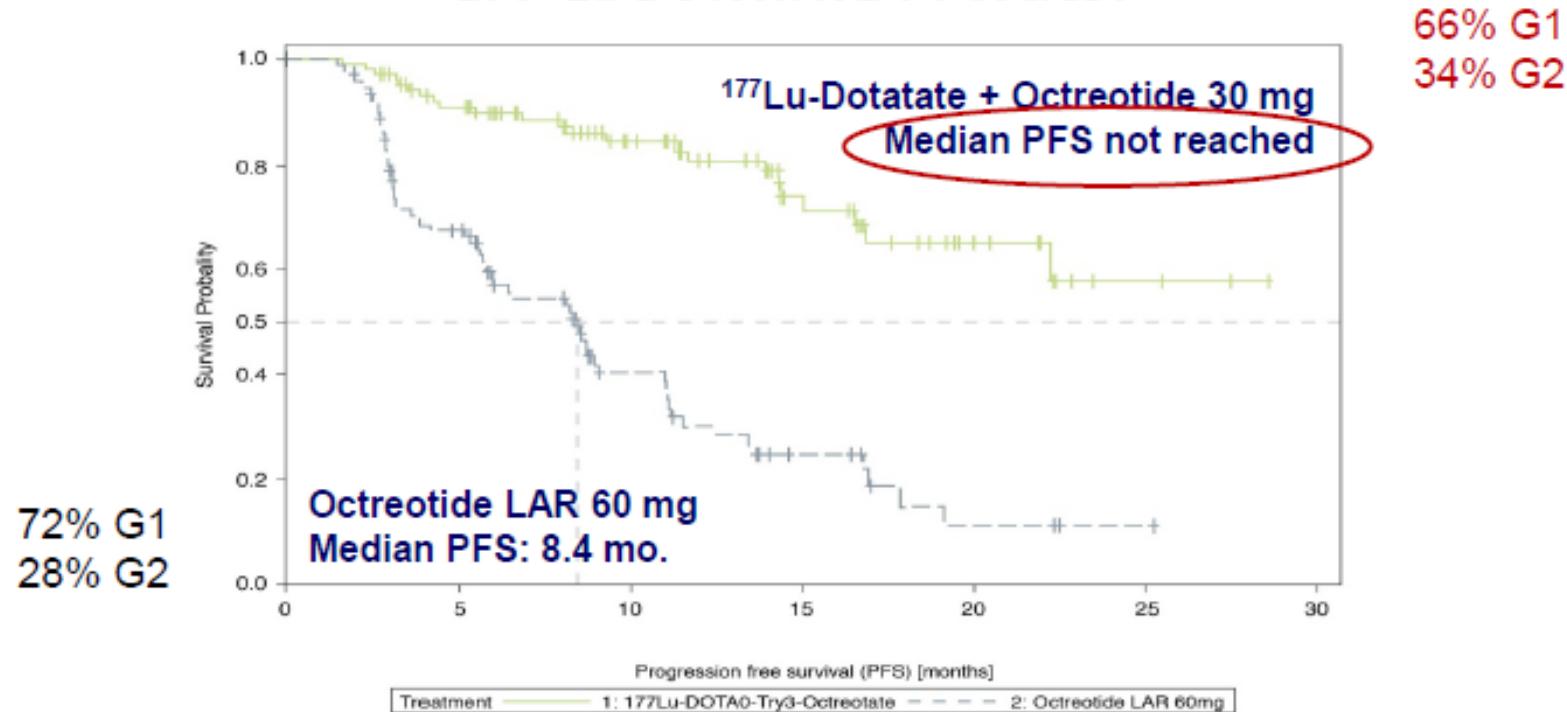


# NETTER-1 Trial

## Peptide Receptor Radiotherapy (PRRT)

### Progressive Midgut NET after failure of SSA

177-Lu DOTATATE (4 cycles)



ORR 19% vs. 3% PRRT vs Octreotide high dose

Strosberg et al ESMO 2015



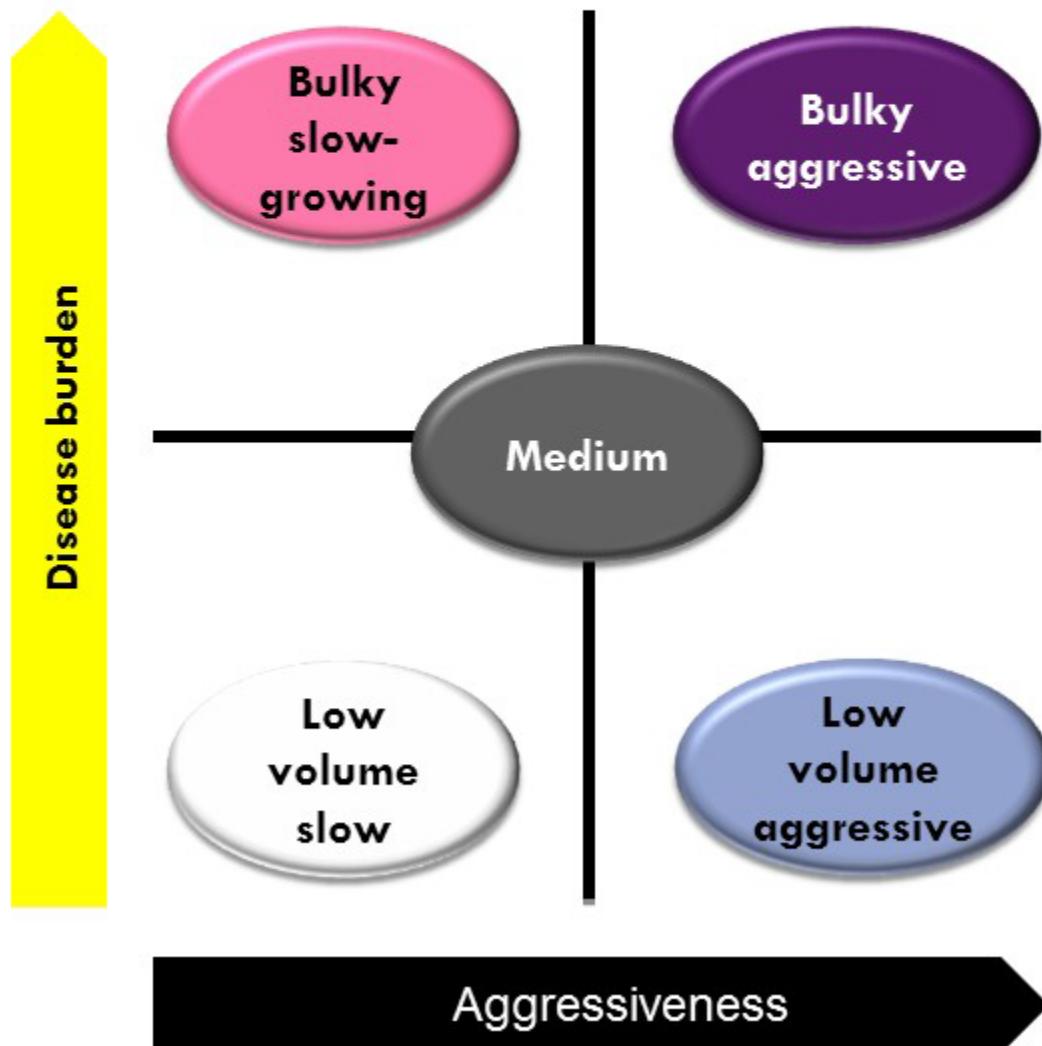
máxima  
medisch centrum

# Behandelopties

- Wait and see
- Locale behandeling voor primaire tumor en metastasen:
  - Resectie
  - RFA
  - Cryoablatie
  - TACE
  - SIRT
- Systeemtherapie:
  - Octreotide
  - Everolimus
  - Sunitinib
  - PRRT
  - chemotherapie (CAPTEM, platinum/etoposide, STZ-5FU)



# Current Management of Grade 1&2 P-NETs



## Available options:

- Observation.
- Somatostatin analogs.
- Everolimus.
- Sunitinib.
- Streptozocin-based chemotherapy.
- Temozolomide-based chemotherapy.
- PRRT with  $^{177}\text{Lu}$ -SSA.
- Liver directed therapy.

Courtesy J. Yao

## *NET in onze regio*

- Samenhang
- Belang patiënten
- Soncos ea argumenten
- NET-centrum Máxima - MUMC



máxima  
medisch centrum

# Overleg NET-centrum Máxima - MUMC

- Pre-operatief (voorkeur)
  - DOTA-scan
  - CT meerfasen
  - ea beeldvorming
  - Specifiek lab: (CgA, NSE, 5HIAA, op indicatie)
- Post-operatief
  - Revisie pathologie
  - Advies voor follow up
  - Advies therapie



# Na het MDO

- Bevestiging/bijstellen diagnose
  - Therapie advies
  - Advies voor beleid in follow up
- 
- In verwijzend centrum
  - In NET-centrum Máxima - MUMC
  - Elders op indicatie



# Conclusie, waarom centraliseren NET?

- Spectrum neuro-endocriene tumoren is groot
  - Niet één ziekte
  - Verschillen per tumorlocatie
  - Therapie en follow up verschilt
- Databestand, wijzer van te worden



# NET-centrum Máxima

- Medisch oncologen
  - Wouter Dercksen, Lieke Simkens/Art Vreugdenhil
- Endocrinologen
  - Harm Haak, Pleun Wouters/Ronald Erdtsieck
- VSO/casemanager
  - Simone Bruurmijn, Irma Behr
- Chirurgen
  - oa Ignace de Hingh, Micha Luyer CZE, pancreas
  - oa Wouter Leclercq, Rudi Roumen, Gerrit Slooter MMC lever
- Maag-darm-leverartsen
  - oa Martijn ter Borg
- Pathologen
- Radiologen



Drug	Functioneel	graad	Primaire lokalisatie	SSTR status	Speciale overwegingen
Octreotide	+/-	G1	midgut	+	Lage tumorload
Lanreotide	+/-	G1/G2 (MIB<10%)	midgut pancreas	+	Lage en hoge (>25%) tumorload in lever
IFN-alpha 2b	+/-	G1/G2	midgut		Als SSTR status negatief
STZ-5FU	+/-	G1/G2	pancreas		Progressief in korte termijn* of hoge tumorload of symptomatisch
CAP/TEM	+/-	G2	pancreas		Progressief in korte termijn* of hoge tumorload of symptomatisch. Als STZ gecontra-indiceerd of niet beschikbaar
Everolimus	+/-	G1/G2	long pancreas Midgut		
Sunitinib	+/-	G1/G2	pancreas		Contra-indicatie CTX
PRRT	+/-	G1/G2	midgut	+ (benodigd)	Hoge tumorload, extrahepatische ziekte
Cisplatin#/etoposide	+/-	G3	elke		Alle slecht gedifferentieerde NEC

CAP =capecitabine TEM =temozolomide \* <6-12 maanden # cisplatin evt vervangen door carboplatin