

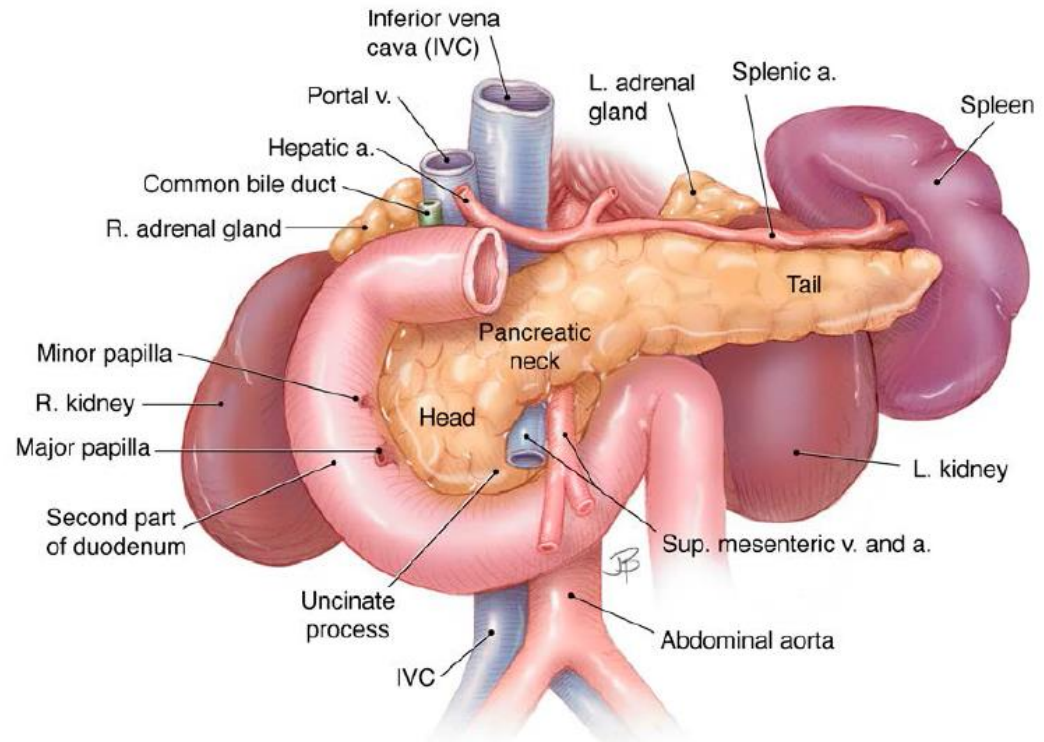
Prof Berrevoet, Dr Cesmeli, Prof Geboes,  
Prof Hindryckx, Dr Smeets

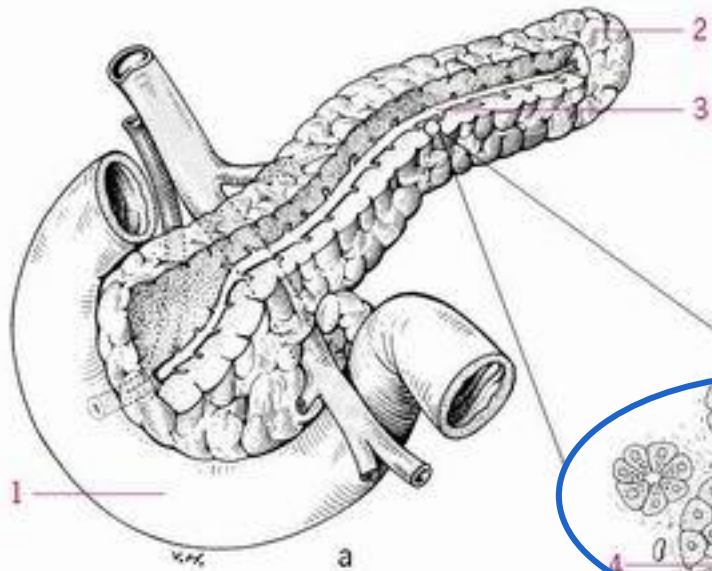
# DIAGNOSE, MEDICAMENTEUZE EN HEELKUNDIGE BEHANDELING VAN PATHOLOGIEEN VAN ENDOCRIENE ORGANEN:

## PANCREAS

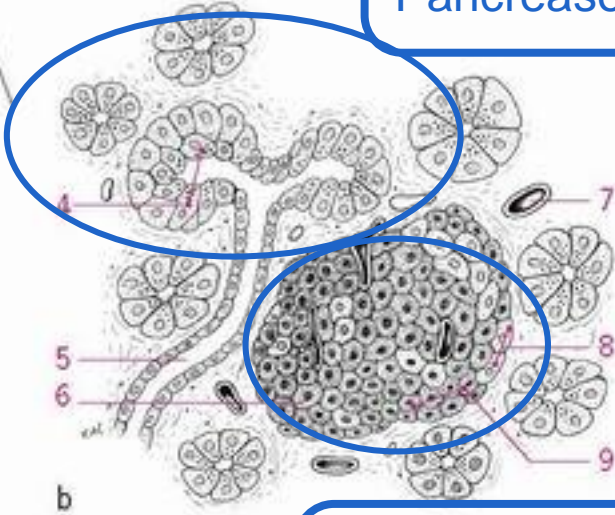


# Inleiding

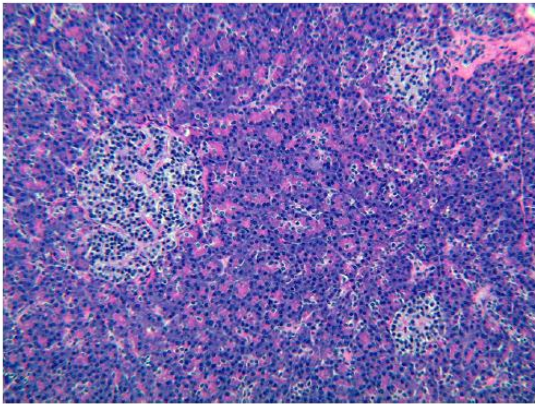


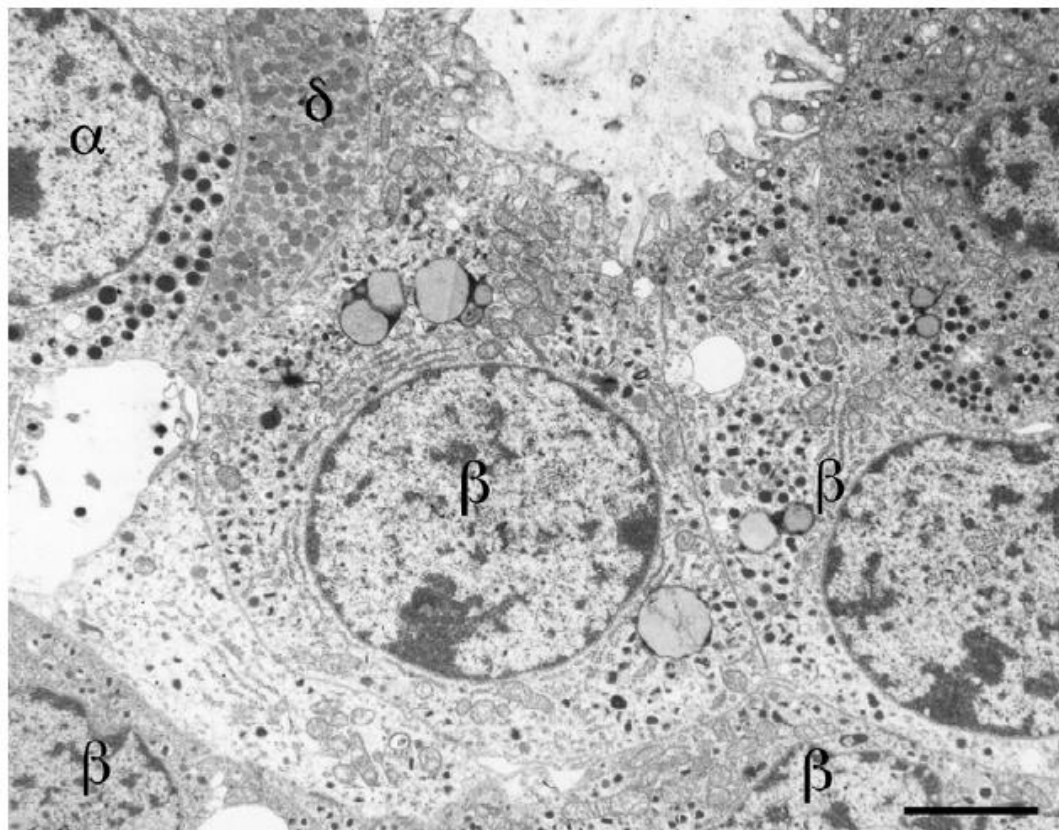
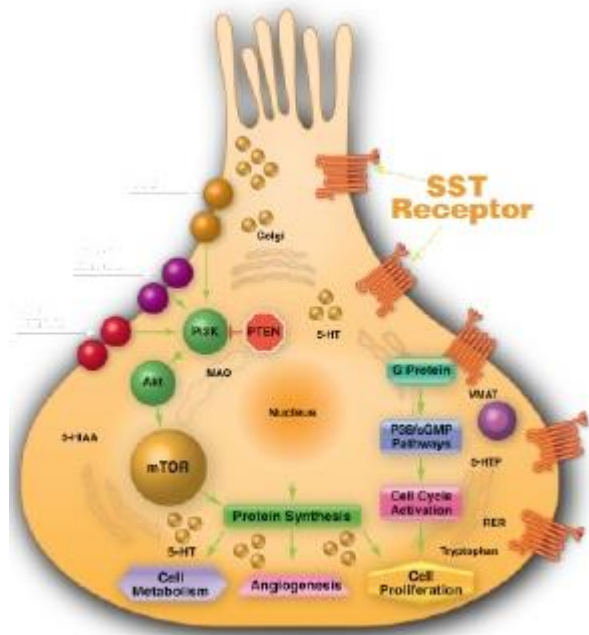


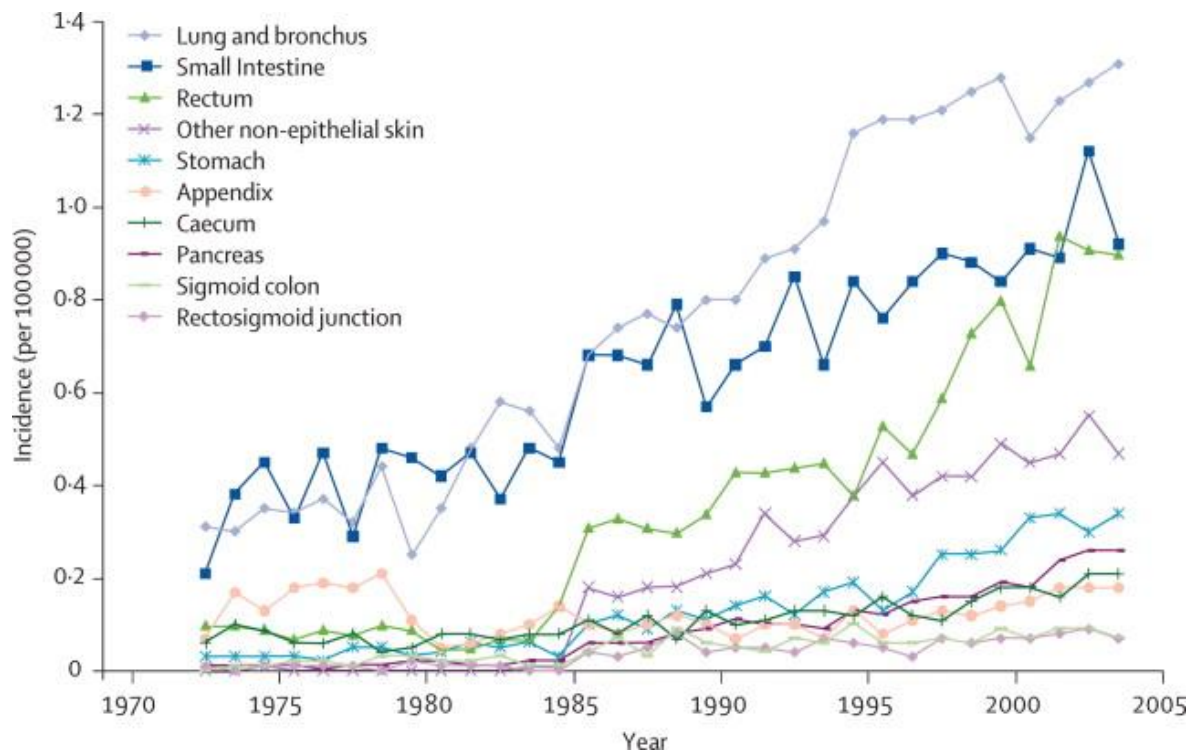
Exocriene pancreas:  
Acinaire en ductale cellen  
Pancreasenzymen → ducti



Endocriene pancreas:  
Hormonen → bloed





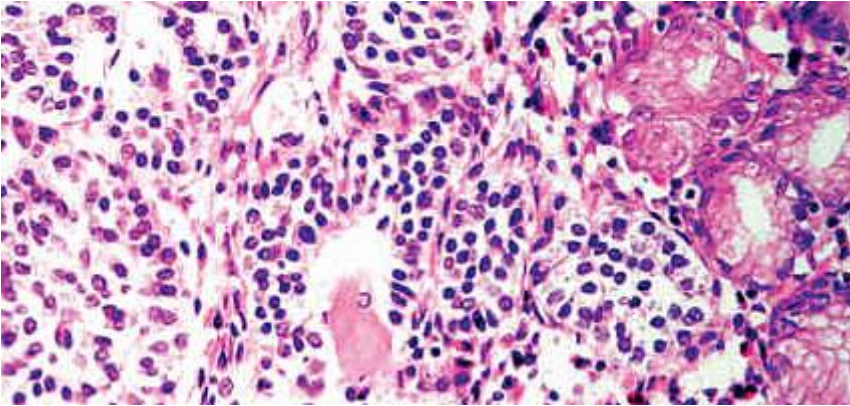


Modlin et al. Lancet Oncol, 2008

Tumor	Locatie	Hormoon	Syndroom
Carcinoid	Meestal extrapancreatisch: Midgut: 75-87% Foregut: 2-33% Hindgut: 1-8% Unknown: 2-15%	Serotonine	Flushing Diarree Dyspnoe Carcinoid heart disease
Insulinoom	Pancreas > 99%	Insuline	hypoglycemie, gewichtstoename
Gastrinoom			ulcera
VIPoom			hypokaliemie, acidose
Glucagonoom			h migrerend erytheem cachexie metabolische ziekte
Ppoom			erlies, diarree
Somatostatinoom			diabetes, galstenen
Corticotrofinoom			ndroom
PTHrPoom	Pancreas	Parathormone-related peptide	Nefrolithiase, nefrocalcinose, osteoporose
Calcitoninoom	Pancreas	Calcitonine	Diarree, warmteopwellingen
Somatotrofinoom	Pancreas 30% Long 54% Jejunum 7%		Acromegalie

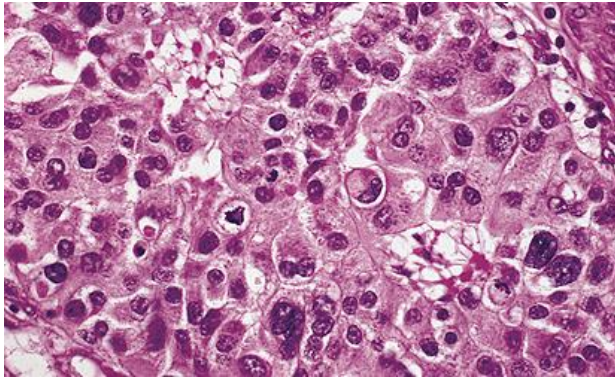
**FUNCTIONEEL  
VERSUS  
NIET FUNCTIONEEL**

## Goed gedifferentieerd

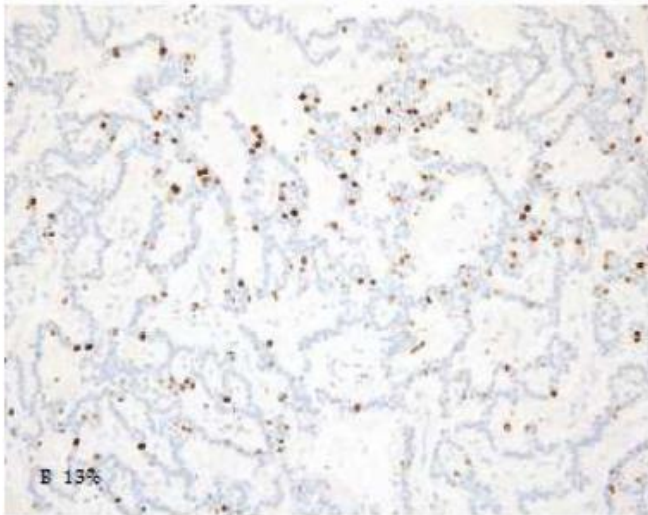
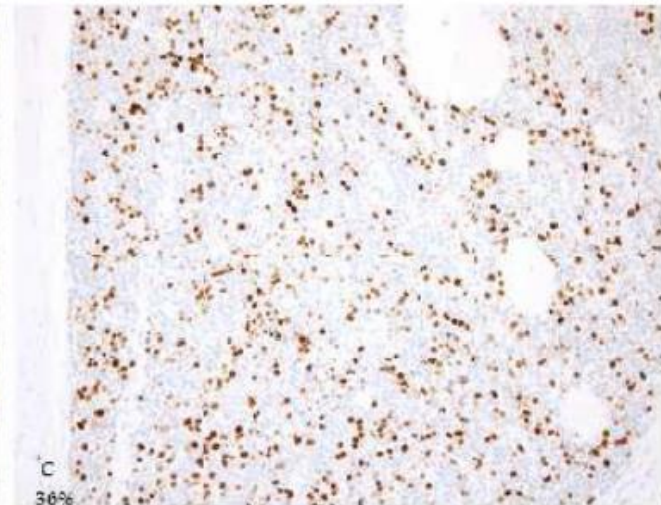
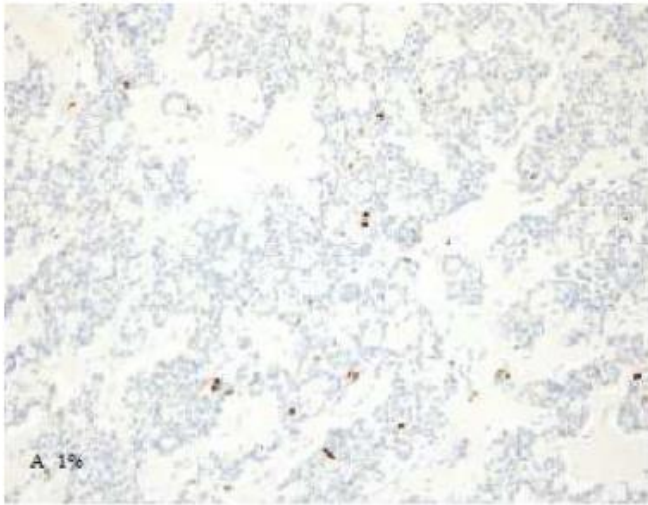


Weinig cel atypie  
Trabeculaire/glandulaire structuur  
Lage mitotische index  
Lage proliferatie index

## Slecht gedifferentieerd



Cellulaire atypie  
Solide groei – necrose  
Hoge mitotische index  
Hoge proliferatie



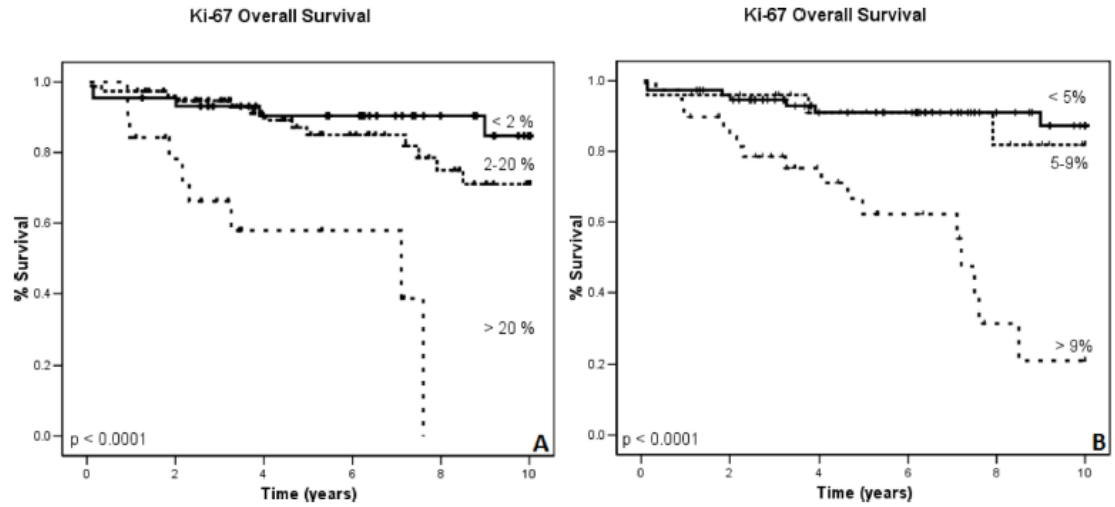
Ki-67 Immune Staining

A= 1%

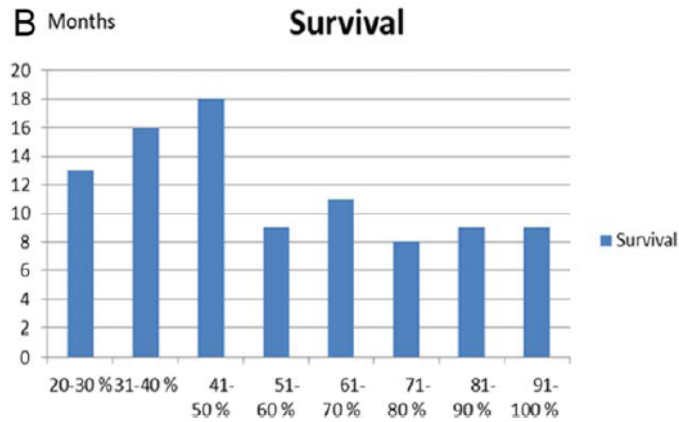
B= 13%

C= 36%





140 resected NET of the pancreas, Surgery 2012



Metastatic NET/NEC, Sorbye, Cancer 2014


**TABLE 1****Rustiger gedrag, rustigere behandeling****World Health Organization Classification 2017 for Pancreatic Neuroendocrine Neoplasms**

<b>Well differentiated NENs</b>	<b>Ki67index* </b>	<b>Mitotic index</b>
Neuroendocrine tumour (NET) G1	<3 %	<2/10 HPF
Neuroendocrine tumour (NET) G2	3-20 %	2-20/10 HPF
Neuroendocrine tumour (NET) G3	>20 %	>20/10 HPF
<b>Poorly differentiated NENs</b>		
Neuroendocrine carcinoma (NEC) G3	>20 %	>20/10 HPF
Small cell type		
Large cell type		

**Mixed neuroendocrine-nonneuroendocrine neoplasm (MiNEN)**

\* Ki67 index is based on at least 500 cells (not spots”); mitoses in 50 high power fields (HPF) (expressed per 10 HPF (2.0 mm<sup>2</sup>); the final grade based on whichever index (mitotic rate or Ki67) places the tumor in the highest grade category. For assessing Ki67, casual visual estimation (“eyeballing”) is not recommended; manual counting of printed images is suggested {25412850}.

**Slechte prognose, chemotherapie**



Diagnostiek:  
rol van echo-endoscopie en radiologie  
Dr. P. Hindryckx, Dr. E. Cesmeli, Dr. P. Smeets



# Behandeling van neuro-endocriene tumoren

## Prof. dr. K. Geboes

## Casus 1:

# Een patient met een functioneel beeld

Man, 58 jaar

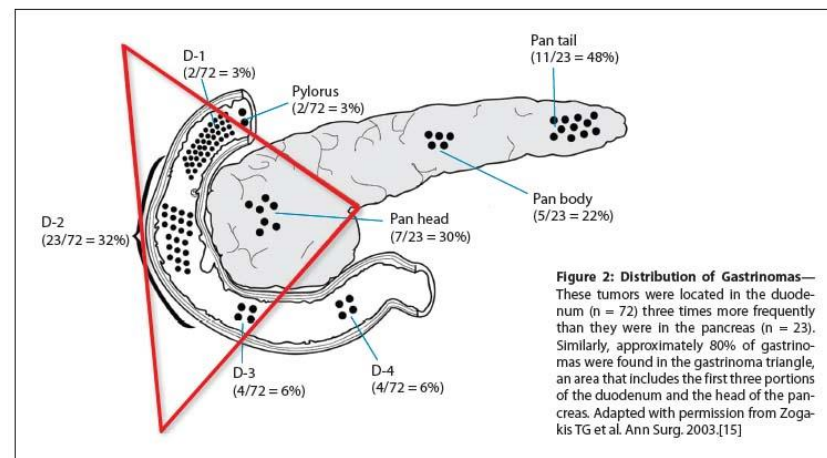
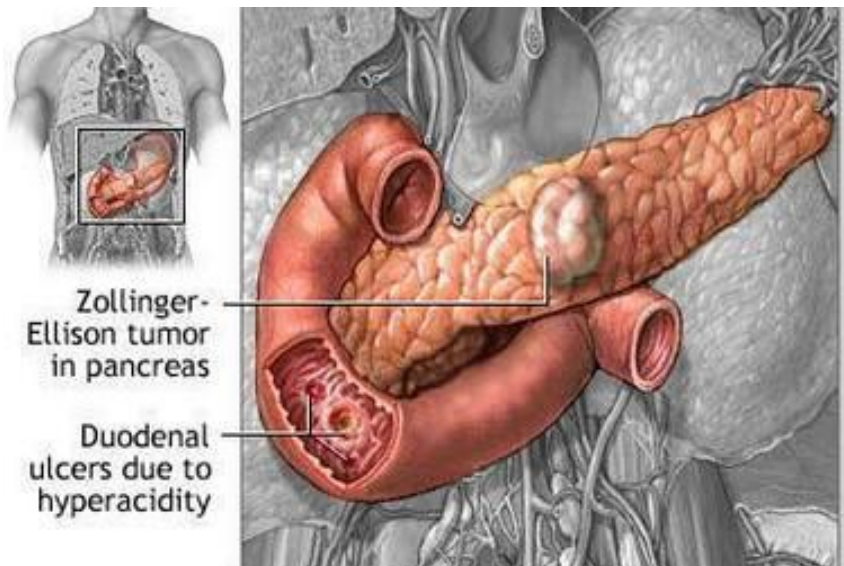
MVG:

2010: maagulcera

Klacht: diarree – ook 's nachts

Bij staken PPI: toename van klachten

Verhoogd gastrine: 727 ng/dl



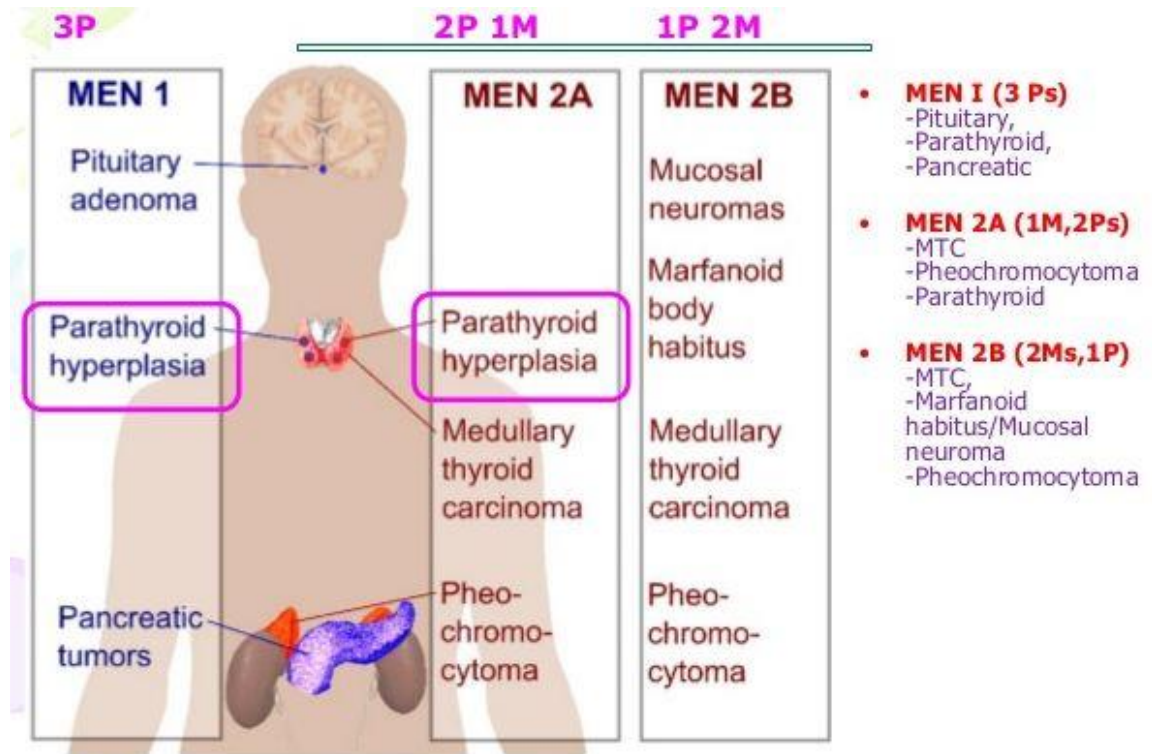
Zollinger-Ellison:  
Diarree < malabsorptie < duodenale ulcera

Ulcera < hyperaciditeit < gastrinoma

Behandelen functioneel beeld: hoge dosis PPI (80 – 120 mg)



# Heelkunde



- ▶ Lokalisatie neuro-endocriene tumor graad 1  
6/34 lymfeklieren bevatten tumor





- ▶ Medicamenteuze behandeling functioneel beeld

PPI bij Zollinger-Ellison

Diazoxide bij insulinoom

Somatostatine-analogen

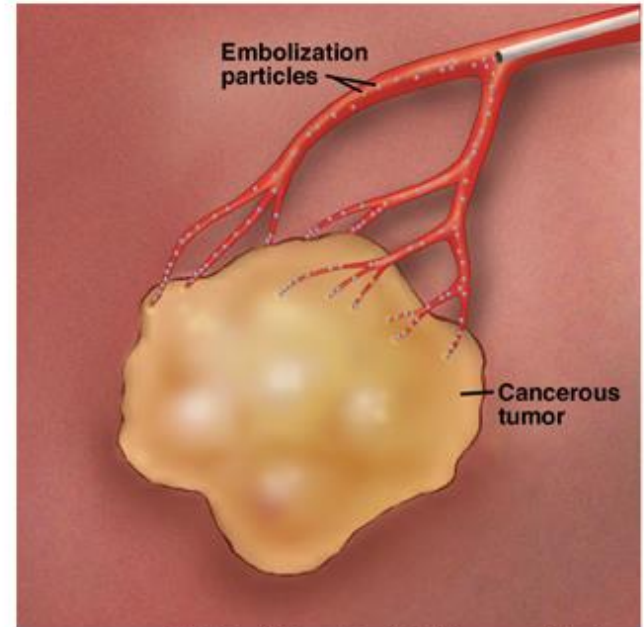
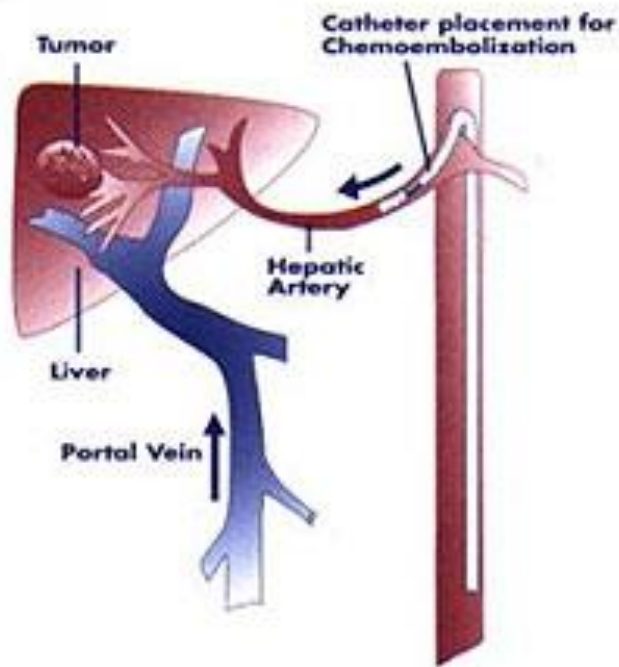
Everolimus/Afinitor bij gemetastaseerd insulinoom

- ▶ Chirurgie – ook overwogen in gemetastaseerde setting → debulking

- ▶ Peptide Receptor Radionuclide Therapie

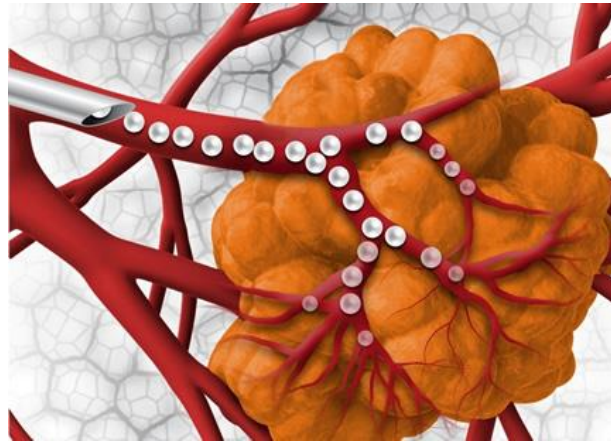
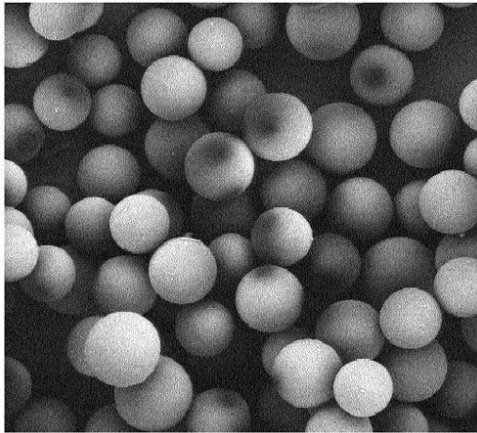
- ▶ Ablatie: radio-embolisatie, (chemo-) embolisatie

Cave: risico's post-Whipple

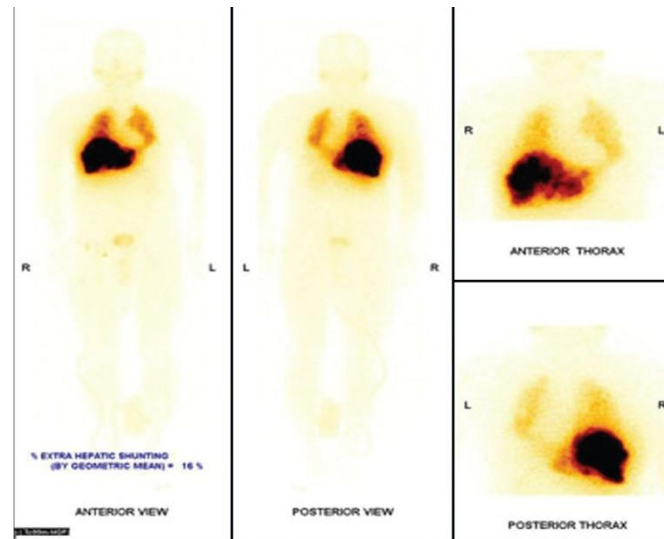


© Society of Interventional Radiology, www.SIRweb.org

(chemo-) embolisatie



# radio-embolisatie



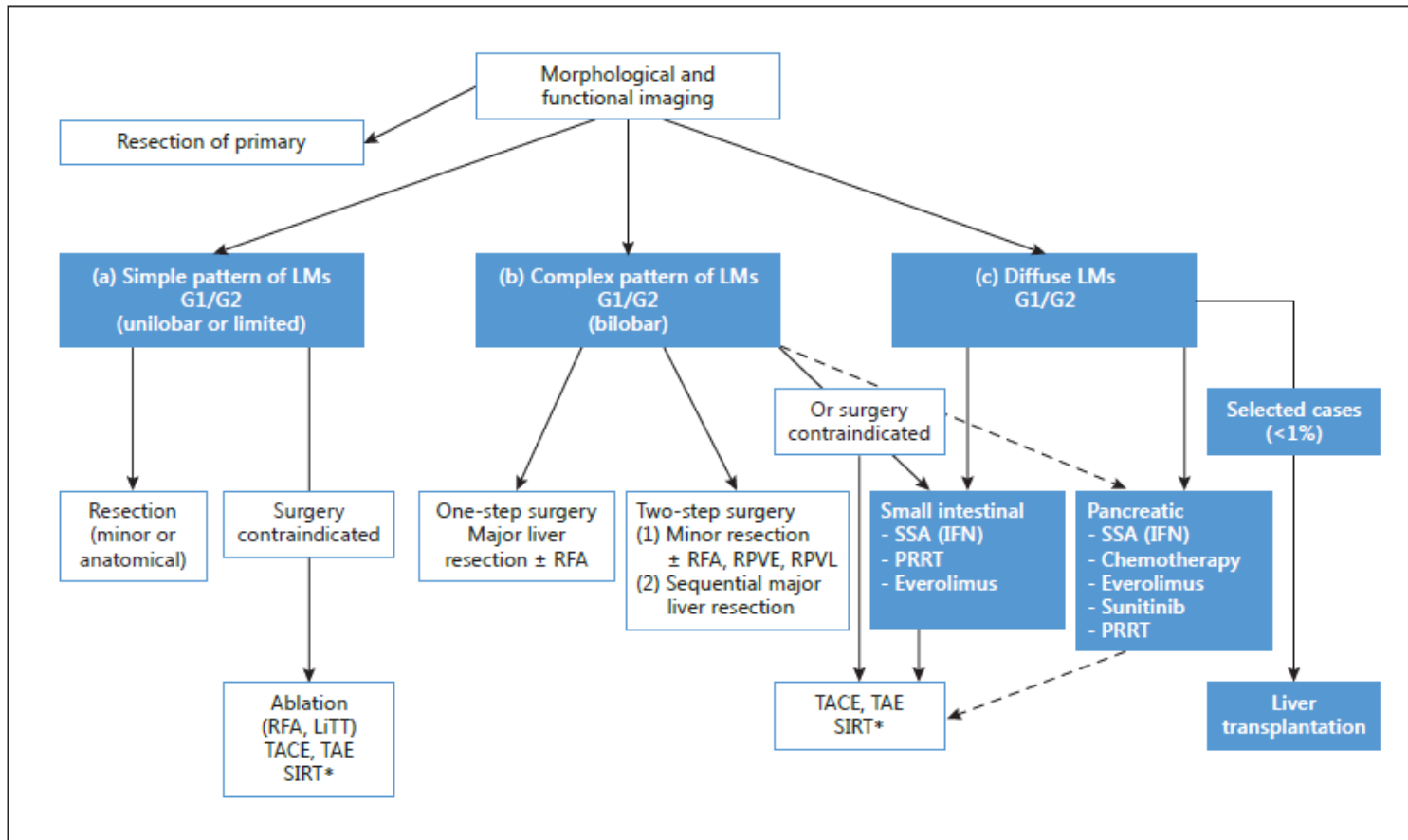
## Casus 2:

# Een patient met een gemetastaseerde NET

Vrouw, 56 jaar

2004: resectie van tumor in de staart van de pancreas + levermetastasen: goed gedifferentieerde NET pT3N1M1, ki 67 index 20%

November 2005: nieuwe leverletsels



**Fig. 1.** Management of liver metastases without extrahepatic disease in G1/G2 NEN. \* SIRT (selective internal radiation therapy) is still an investigational method. LiTT = Laser-induced thermotherapy; LMs = liver metastases; RFA = radiofrequency ablation; RPVE = right portal vein embolization; RPVL = right portal vein ligation; TACE = transarterial chemoembolization; TAE = transarterial embolization.

**Table 1.** Therapeutic options and conditions for preferential use as first-line therapy in advanced NEN

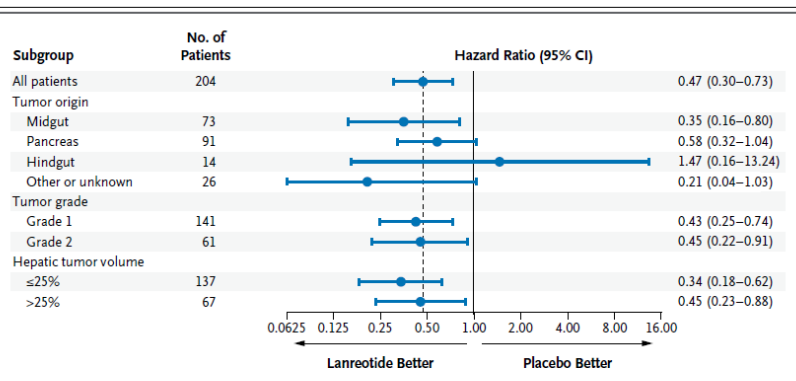
Drug	Functionality	Grading	Primary site	SSTR status	Special considerations
Octreotide	+/-	G1	midgut	+	low tumor burden
Lanreotide	+/-	G1/G2 (-10%)	midgut, pancreas	+	low and high (>25%) liver tumor burden
IFN-alpha 2b	+/-	G1/G2	midgut		if SSTR negative
STZ/5-FU	+/-	G1/G2	pancreas		progressive in short-term* or high tumor burden or symptomatic
TEM/CAP	+/-	G2	pancreas		progressive in short-term* or high tumor burden or symptomatic; if STZ is contraindicated or not available
Everolimus	+/-	G1/G2	lung		atypical carcinoid and/or SSTR negative
			pancreas		insulinoma or contraindication for CTX
			midgut		if SSTR negative
Sunitinib	+/-	G1/G2	pancreas		contraindication for CTX
PRRT	+/-	G1/G2	midgut	+ (required)	extended disease; extrahepatic disease, e.g. bone metastasis
Cisplatin <sup>§</sup> / etoposide	+/-	G3	any		all poorly differentiated NEC

CAP = Capecitabine; TEM = temozolomide. \* ≤6–12 months. § Cisplatin can be replaced by carboplatin.

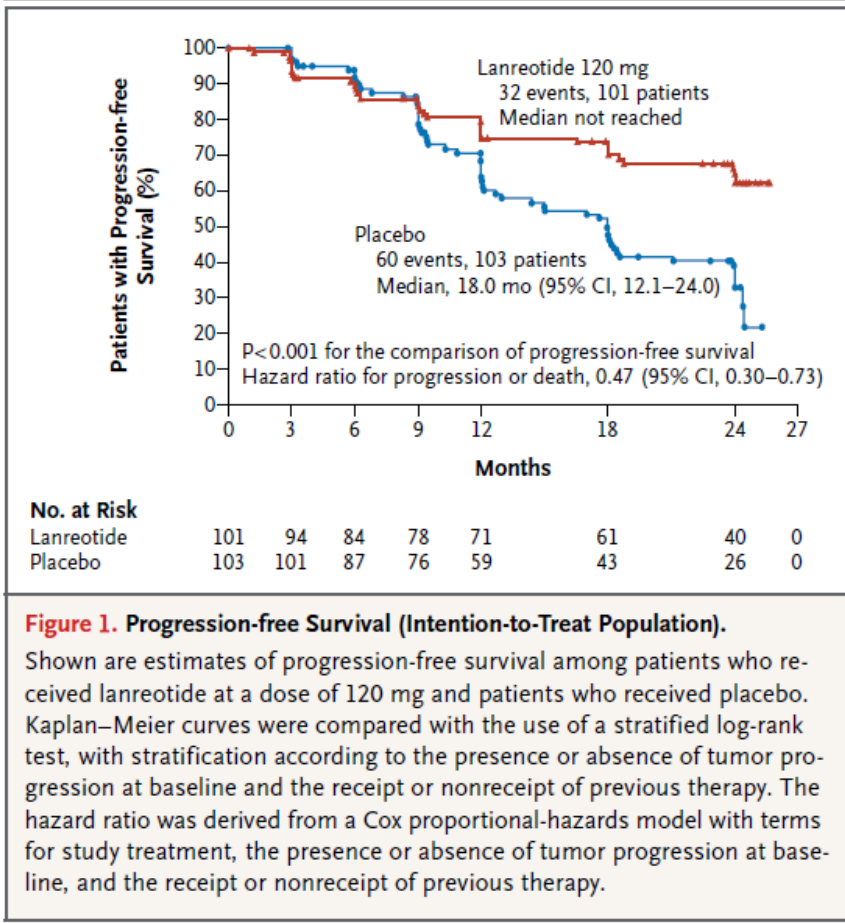
ORIGINAL ARTICLE

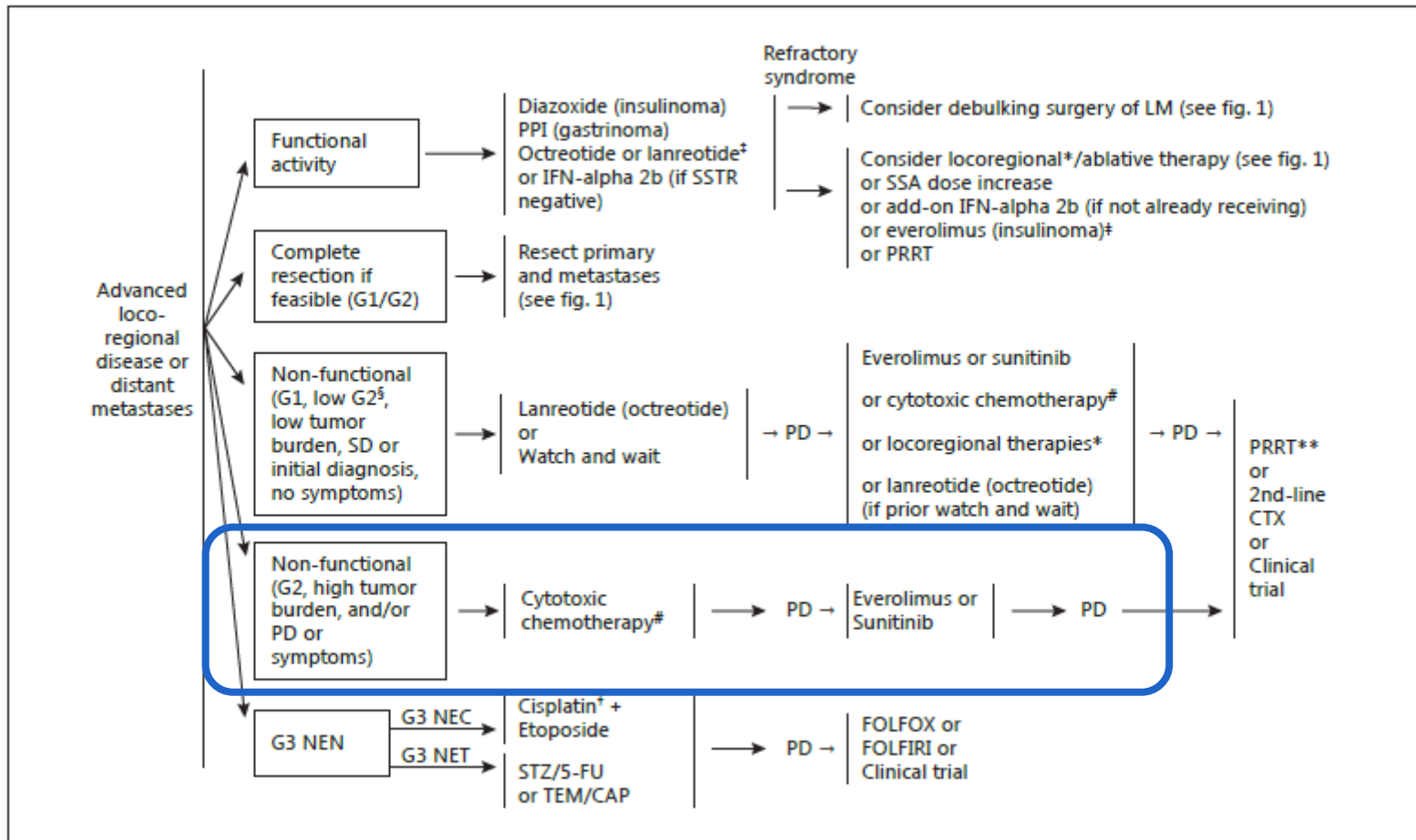
# Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D., Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D., Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaime Capdevila, M.D., Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc., Séverine Martinez, B.Sc., Joëlle Blumberg, M.D., and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators\*



**Figure 2. Progression-free Survival, According to Subgroups (Intention-to-Treat Population).** Shown are the hazard ratios for centrally assessed disease progression or death in subgroups defined according to baseline tumor origin and grade and hepatic tumor volume. Subgroup variables were predefined in all cases, although the number of categories for hepatic tumor volume was simplified post hoc from five (estimated hazard ratios ranging from 0.24 to 0.54) to two. The hazard ratio for “all patients” was derived from a Cox proportional-hazards model with terms for study treatment, presence or absence of tumor progression at baseline, and receipt or nonreceipt of previous therapy. The hazard ratio for each subgroup was derived from a Cox proportional-hazards model with a single term for study treatment.







- ▶ Streptozotocine-5FU: complete remissie

2008: herval

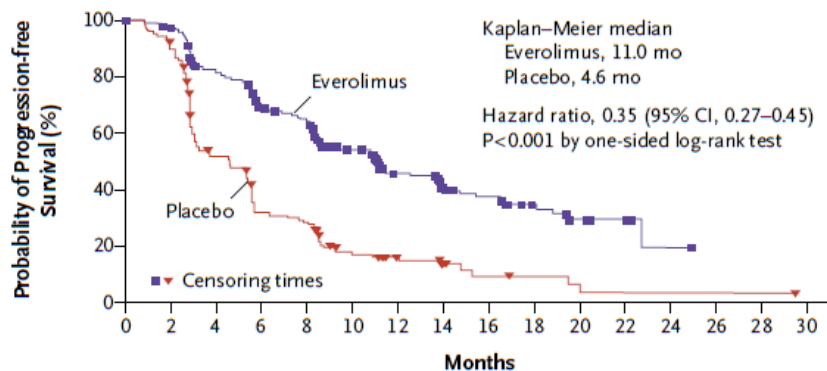
- ▶ Afinitor (everolimus) 10mg



## Everolimus for Advanced Pancreatic Neuroendocrine Tumors

James C. Yao, M.D., Manisha H. Shah, M.D., Tetsuhide Ito, M.D., Ph.D., Catherine Lombard Bohas, M.D., Edward M. Wolin, M.D., Eric Van Cutsem, M.D., Ph.D., Timothy J. Hobday, M.D., Takuji Okusaka, M.D., Jaume Capdevila, M.D., Elisabeth G.E. de Vries, M.D., Ph.D., Paola Tomassetti, M.D., Marianne E. Pavel, M.D., Sakina Hoosen, M.D., Tomas Haas, Ph.D., Jeremie Lincy, M.Sc., David Lebwohl, M.D., and Kjell Öberg, M.D., Ph.D., for the RAD001 in Advanced Neuroendocrine Tumors, Third Trial (RADIANT-3) Study Group





### A Progression-free Survival, Local Assessment



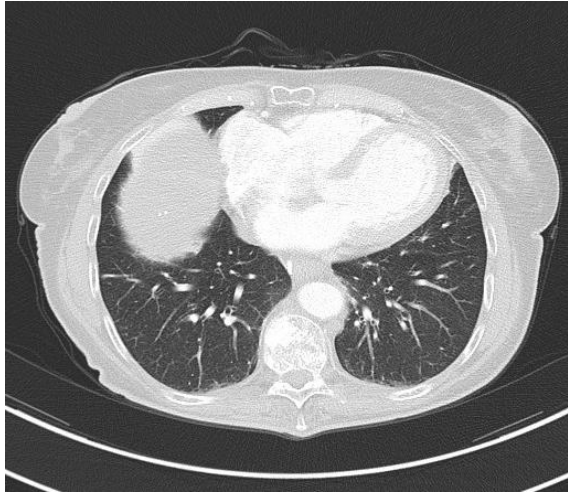
### METHODS

We randomly assigned 410 patients who had advanced, low-grade or intermediate-grade pancreatic neuroendocrine tumors with radiologic progression within the previous 12 months to receive everolimus, at a dose of 10 mg once daily (207 patients),

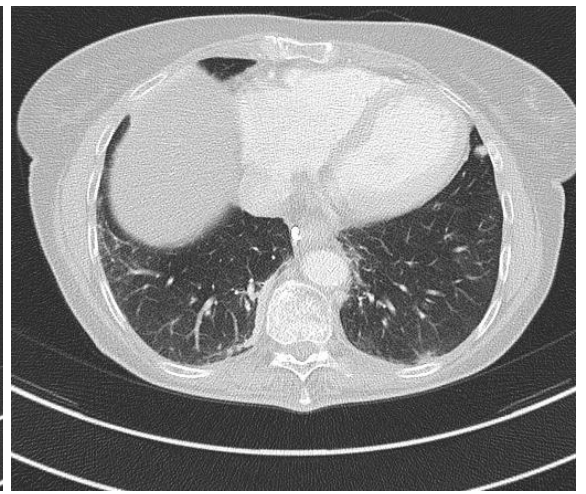
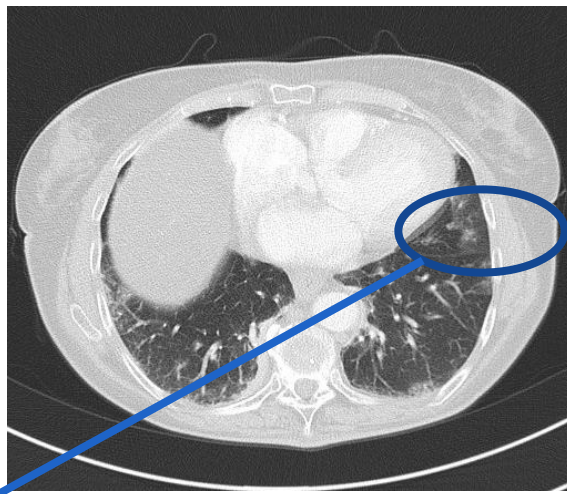


CLINICAL PRESENTATION AND GRADING OF STOMATITIS <sup>1</sup>				
	GRADE 1	GRADE 2	GRADE 3	GRADE 4
Presentation: clinical exam	Erythema of the mucosa	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes, bleeding with minor trauma	Tissue necrosis, significant spontaneous bleeding, life-threatening consequences
Presentation: functional/symptomatic	Minimal symptoms, normal diet	Symptomatic but can eat and swallow, modified diet	Symptomatic and unable to adequately aliment or hydrate orally	Symptoms associated with life-threatening consequences
Identification				
	Reprinted with permission from ELSEVIER, A261. <sup>1</sup>	Reprinted with permission from ELSEVIER, A261. <sup>1</sup>	Photo courtesy of Mark Schubert, MSD. Reprinted with permission. <sup>10</sup>	Photo courtesy of Mark Schubert, MSD. Reprinted with permission. <sup>10</sup>

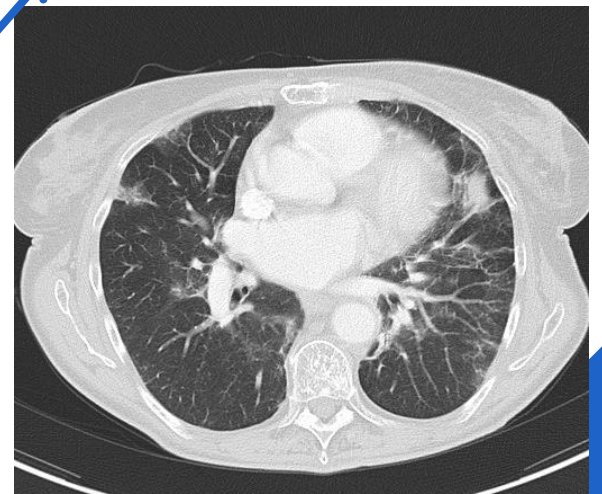
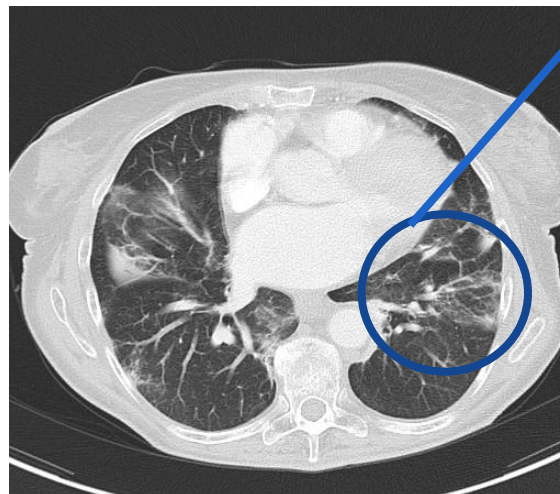
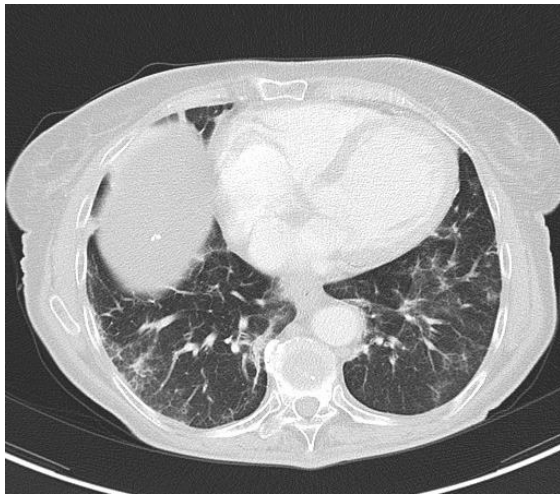
Severity <sup>a</sup>	AFINITOR dose adjustment and management recommendations <sup>1</sup>
<b>Grade 1</b>	<ul style="list-style-type: none"> <li>• If toxicity is tolerable, no dose adjustment required</li> <li>• Initiate appropriate medical therapy and monitor</li> </ul>
<b>Grade 2</b>	<ul style="list-style-type: none"> <li>• If toxicity is tolerable, no dose adjustment required</li> <li>• Initiate appropriate medical therapy and monitor</li> <li>• If toxicity becomes intolerable, temporary dose interruption until recovery to grade <math>\leq 1</math>. Reinitiate AFINITOR at the same dose</li> <li>• If toxicity recurs at grade 2, interrupt AFINITOR until recovery to grade <math>\leq 1</math>. Reinitiate AFINITOR at a lower dose</li> </ul>
<b>Grade 3</b>	<ul style="list-style-type: none"> <li>• Temporary dose interruption until recovery to grade <math>\leq 1</math></li> <li>• Initiate appropriate medical therapy and monitor</li> <li>• Consider reinitiating AFINITOR at a lower dose. If toxicity recurs at grade 3, consider discontinuation</li> </ul>
<b>Grade 4</b>	<ul style="list-style-type: none"> <li>• Discontinue AFINITOR and treat with appropriate medical therapy</li> </ul>

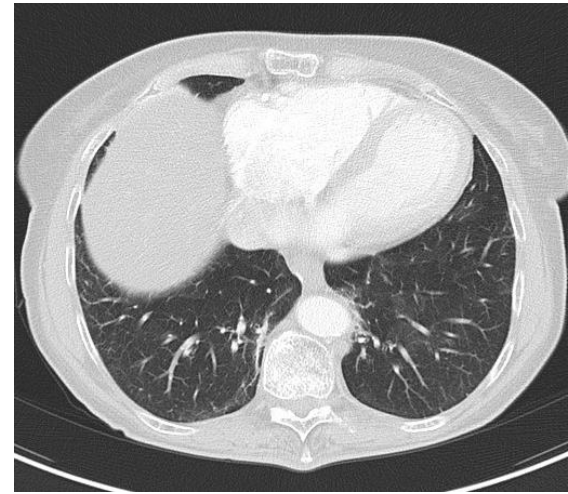
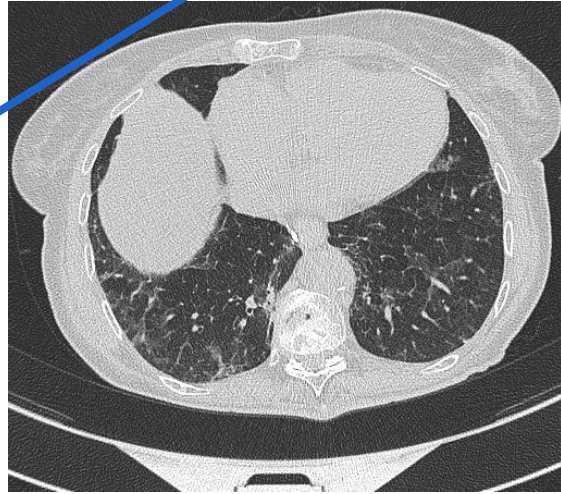
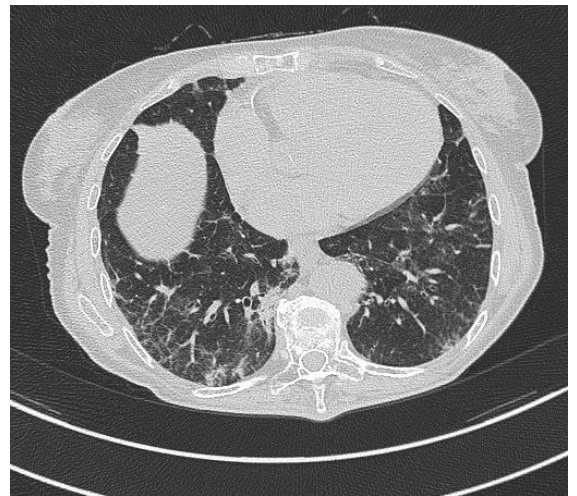
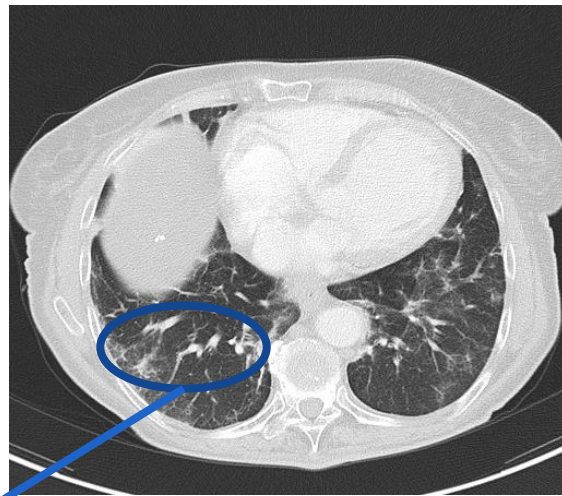
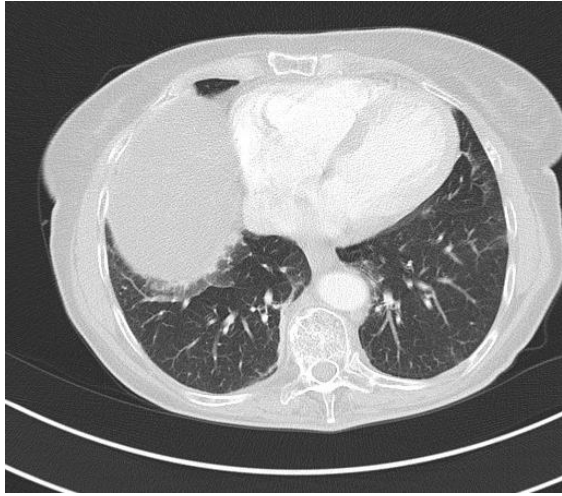


Stop & herstart

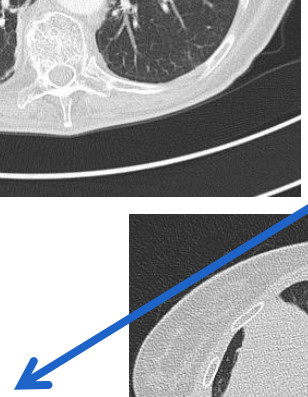


Stop & herstart 5mg/d





Stop & herstart  
5mg/2d



erythemateuze maculaire dermatitis na een episode van oedeem



R/ topische corticosteroid crème



**Strong CYP3A4/PgP inhibitors (avoid)**

Antibiotics	Antidepressants	Antifungals	Anti-HIV agents
Clarithromycin Telithromycin	Nefazodone	Itraconazole Ketoconazole Voriconazole	Atazanavir Indinavir Nelfinavir Ritonavir Saquinavir

**Moderate CYP3A4/PgP inhibitors  
(coadminister with caution and reduce dose of AFINITOR)**

Antibiotics	Antiemetics	Antifungals	Anti-HIV agents	Calcium channel blockers
Erythromycin	Aprepitant	Fluconazole	Amprenavir Fosamprenavir	Diltiazem Verapamil

**Strong CYP3A4/PgP inducers (avoid)**  
If coadministration is required, consider increasing the AFINITOR dose

Anticonvulsants	Antituberculosis agents
Carbamazepine Phenobarbital Phenytoin	Rifabutin Rifampin Rifapentine



Eind 2009: progressie

- ▶ Sutent 37,5 mg continu





# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

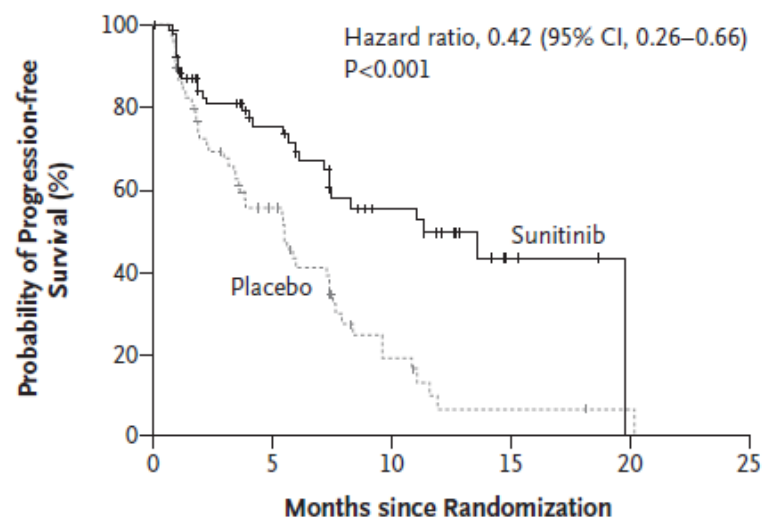
FEBRUARY 10, 2011

VOL. 364 NO. 6

## Sunitinib Malate for the Treatment of Pancreatic Neuroendocrine Tumors

Eric Raymond, M.D., Ph.D., Laetitia Dahan, M.D., Ph.D., Jean-Luc Raoul, M.D., Ph.D., Yung-Jue Bang, M.D., Ivan Borbath, M.D., Ph.D., Catherine Lombard-Bohas, M.D., Juan Valle, M.D., Peter Metrakos, M.D., C.M., Denis Smith, M.D., Aaron Vinik, M.D., Ph.D., Jen-Shi Chen, M.D., Dieter Hörsch, M.D., Pascal Hammel, M.D., Ph.D., Bertram Wiedenmann, M.D., Ph.D., Eric Van Cutsem, M.D., Ph.D., Shem Patyna, Ph.D., Dongrui Ray Lu, M.Sc., Carolyn Blanckmeister, Ph.D., Richard Chao, M.D., and Philippe Ruszniewski, M.D.

### A Progression-free Survival



#### No. at Risk

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

### METHODS

We conducted a multinational, randomized, double-blind, placebo-controlled phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic neuroendocrine tumors. All patients had Response Evaluation Criteria in Solid Tumors—

➔ **Februari 2010:**

- ➔ Hypothyroidie (Grade 2) en diarree (Grade 2)
- ➔ R/Thyroid hormoon

➔ **Maart 2010:**

- ➔ Handvoet huidreactie (Grade 2)
- ➔ Sunitinib onderbroken gedurende een week





Huidtoxiciteit	Symptomen	Behandeling	Dosisaanpassing	Doorverwijzing dermatoloog
<b>Graad 1</b>	Minimale huidveranderingen of dermatitis (bv. erytheem, oedeem, of hyperkeratose) zonder pijn.	<ul style="list-style-type: none"> <li>- Xerial crème 10%-40%-50% / 2 x daags</li> <li>- Optioneel Salicylzuur 5%-10% (in vaseline) thv hyperkeratose/ 2 x daags</li> <li>- Diprosone crème thv erytheem/ 1 x daags</li> <li>- Lokale koeling</li> </ul>	Geen dosisaanpassing	Neen
<b>Graad 2</b>	Huidveranderingen (bv. schilfering, blaasjes, bloeding, oedeem, of hyperkeratose) met pijn; beperking IADL	<ul style="list-style-type: none"> <li>- Xerial crème 10%-40%-50% / 2 x daags</li> <li>- Salicylzuur 5%-10% (in vaseline) thv hyperkeratose/ 2 x daags</li> <li>- Diprosone crème thv erytheem/ 2 x daags</li> <li>- Systemische pijnbehandeling</li> </ul>	<p><u>Bij eerste optreden:</u>            Verminder dosis 1 trap en herevalueer na 7 dagen;            - Indien geen verbetering, behandeling tijdelijk onderbreken            - Ingeval respons, gereduceerde dosis herstarten en opdrijven naar initiële dosis wanneer toxiciteit onder controle is (= min 1 week stabiel)</p> <p><u>Tweede of derde optreden:</u>            Zie eerste optreden. Terug opdrijven naar initiële dosis dient worden overwogen.</p> <p><u>Vierde optreden:</u>            Stop behandeling definitief</p>	Aangewezen
<b>Graad 3</b>	Ernstige huidverandering (bv. schilfering, blaasjes, bloeding, oedeem, of hyperkeratose) met pijn; beperking ADL	<ul style="list-style-type: none"> <li>- Xerial crème 10%-40%-50% / 2 x daags (niet thv ulceratie)</li> <li>- Salicylzuur 5%-10% (in vaseline) thv hyperkeratose/ 2 x daags (niet thv ulceratie)</li> <li>- Diprosone crème thv erytheem/ 2 x daags</li> <li>- Lokaal antisepticum thv ulceraties (antiseptisch bad)</li> <li>- Systemische pijnbehandeling</li> </ul>	<p><u>Bij eerste optreden:</u>            Onderbreek behandeling en herstart wanneer huidtoxiciteit is verminderd tot graad 0 of 1, in dosis 1 trap lager gaan. Dosis 1 trap opdrijven wanneer toxiciteit onder controle blijft (= min 1 week stabiel).</p> <p><u>Tweede optreden:</u>            Zie eerste optreden. Terug opdrijven naar initiële dosis dient worden overwogen.</p> <p><u>Derde optreden:</u>            Stop behandeling definitief</p>	Ja

Xerial = ureumcrème  
 → Verzachten hoornlaag





➔ Mei 2010:

- ➔ Hypertensie (Grade 2) en diarree (Grade 2)
- ➔ Medicamenteuze behandeling hypertensie

➔ Augustus 2010:

- ➔ Onderbreking behandeling omwille van handvoet huidreactie (grade 3) en diarree
- ➔ Sunitinib herstart aan 25 mg/d

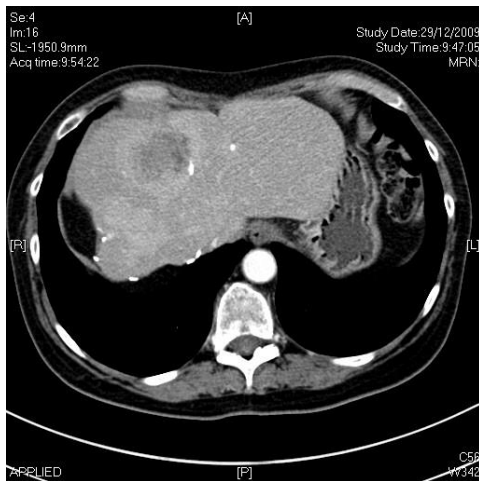


➔ Juli 2011:

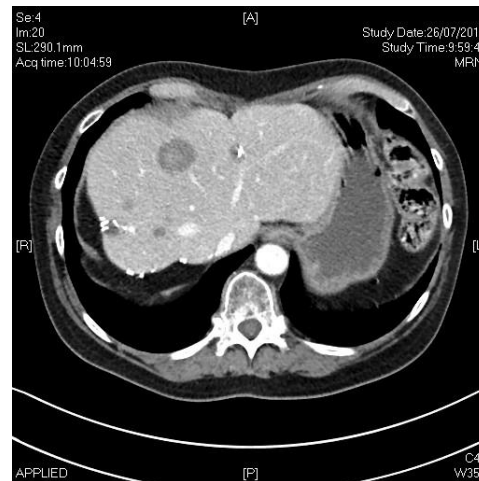
Onderbreking behandeling < ernst nevenwerkingen

➔ Oktober 2011:

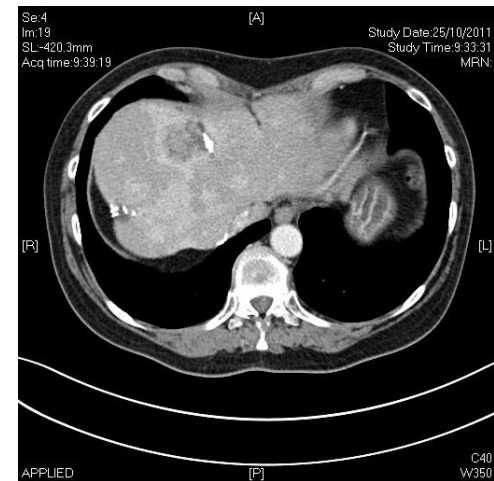
- ➔ Geen behandeling
- ➔ Alle nevenwerkingen verdwenen
- ➔ Geen antihypertensiva meer



December 2009



Juli 2011



Oktober 2011

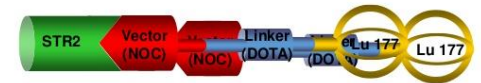
Herstart sutent, maar snel recidief nevenwerkingen.

Voorstel tot behandeling met PRRT – aanvaard  
maart 2012



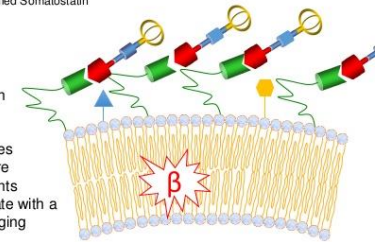


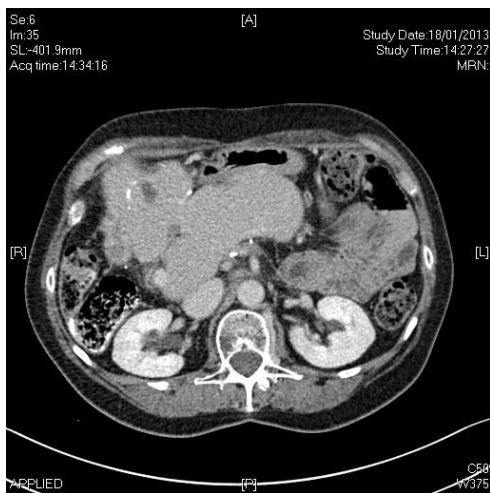
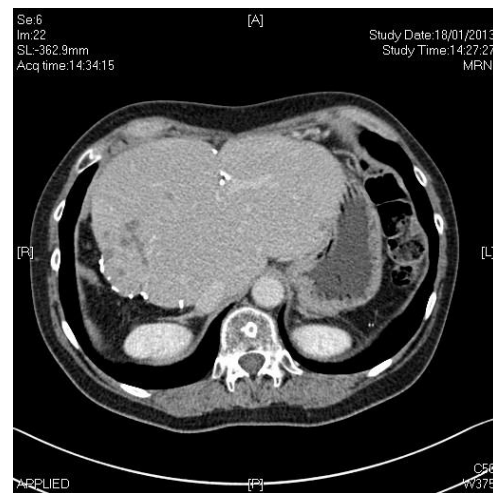
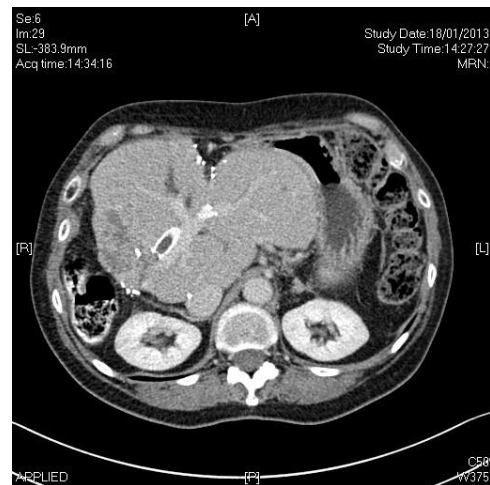
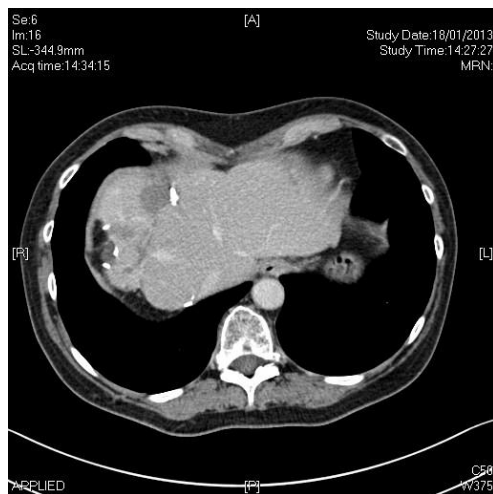
## Peptide Receptor Radionuclide Therapy (PRRT) <sup>177</sup>Lu-DOTA,Tyr3]octreotate



Modified Somatostatin

- ✦ Higher affinity for somatostatin receptors
- ✦ Gamma emission allow post-therapeutic biodistribution studies
- ✦ PR, MR and SD responses are reported in the majority of patients
- ✦ Tumor regression was correlate with a high uptake on Octreoscan imaging







## Casus 3:

# Een patient met een gemetastaseerde NEC

Man, 72 jaar

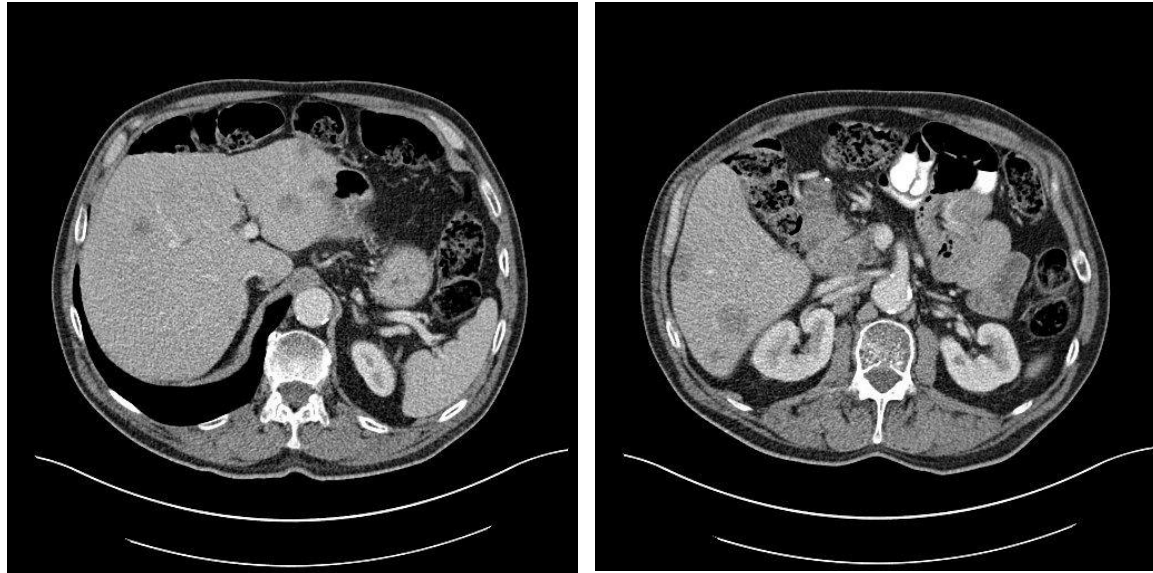
MVG

Hypertensie

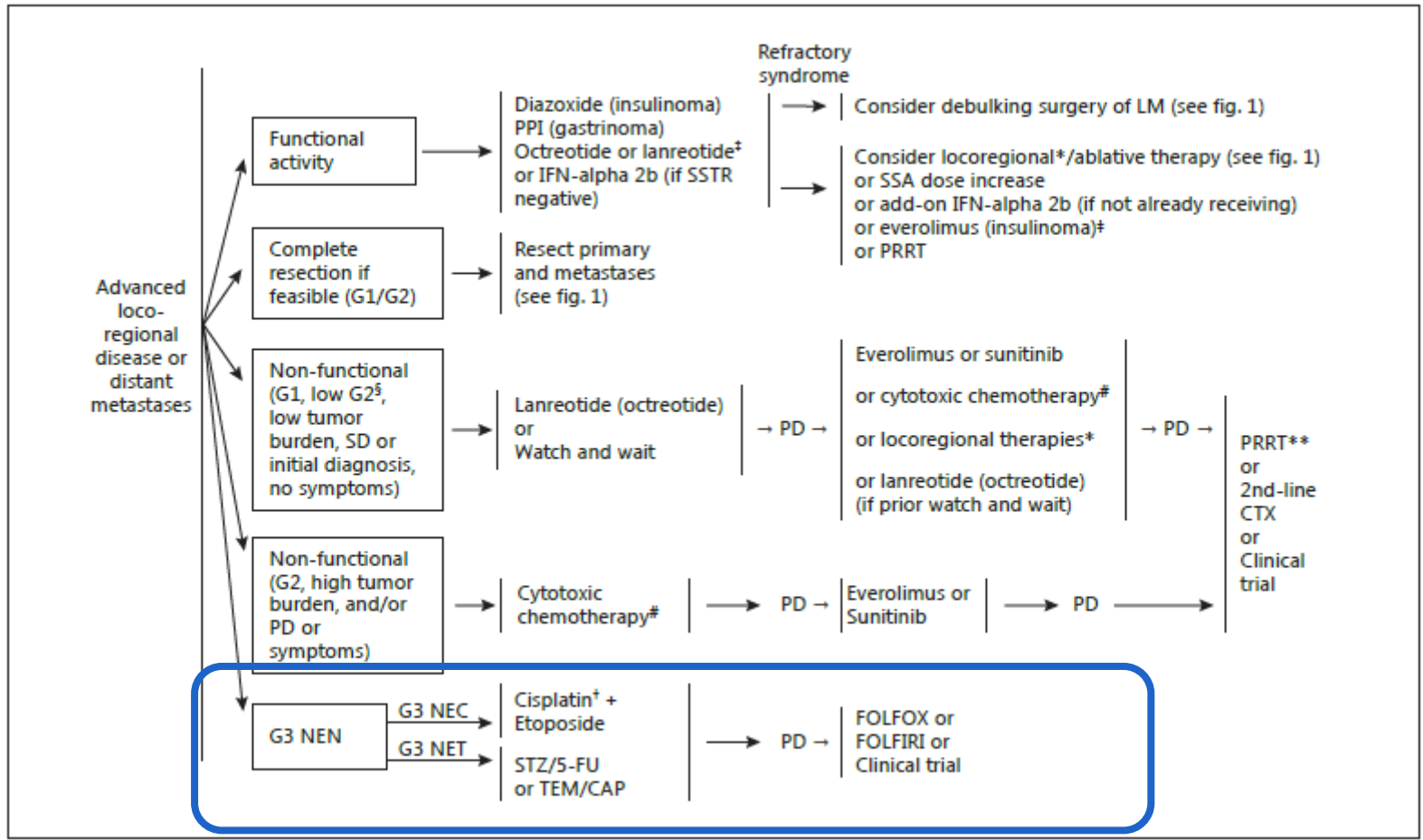
8/2011: Pijnloze icterus

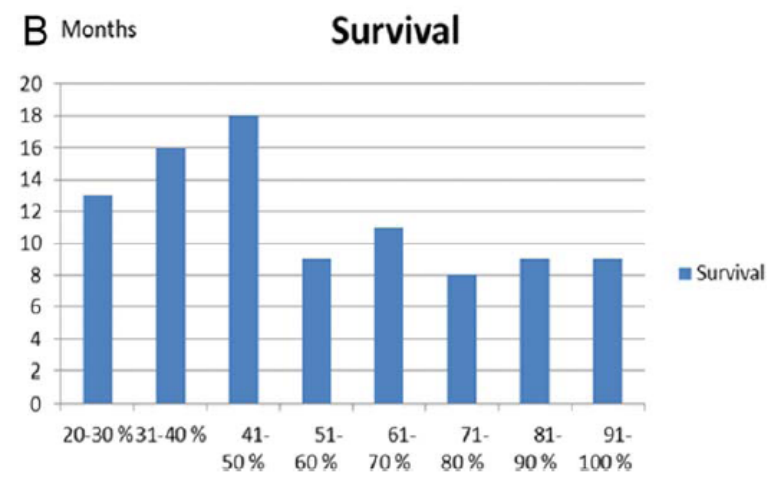
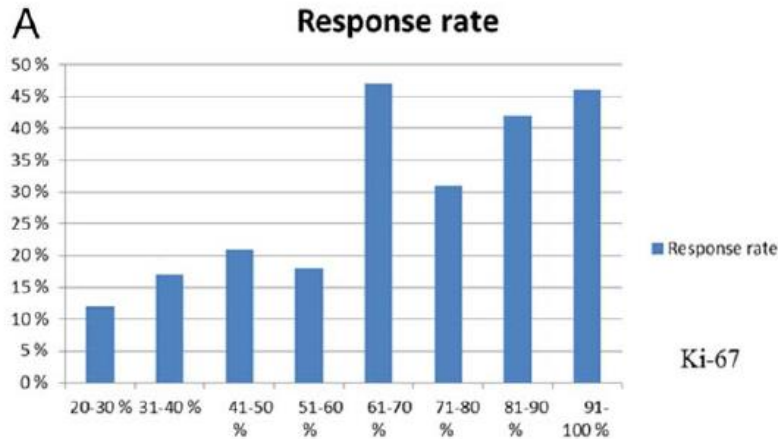
Plan: resectie, want geen letsels op afstand

Peroperatief metastasen: bypass  
Nieuwe beeldvorming postoperatief



Biopsie: weinig gedifferentieerd grootcellig neuro-endocrien  
carcinoom, ki 67 index 80%



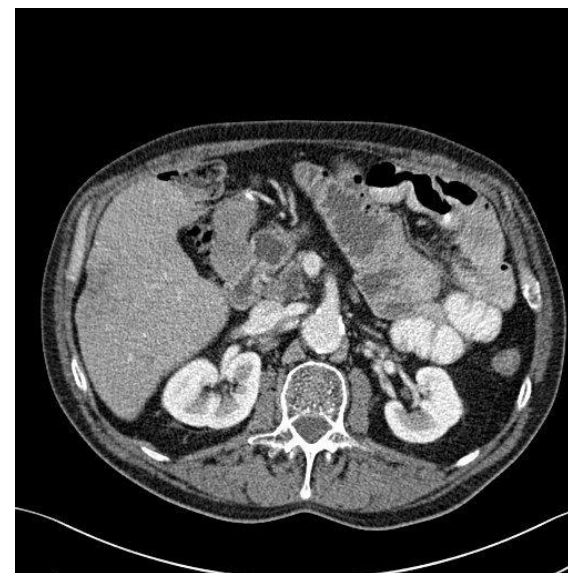


**Figure 3.** Response rates (A) and survival (B) are illustrated after platinum-based chemotherapy among patients with advanced gastroenteropancreatic neuroendocrine carcinoma according to the Ki-67 index (in 10% percentiles). Adapted from: Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol.* 2013;24:152-160.<sup>16</sup>

Cisplatinum-etoposide

Goede respons

Overlijden 11/2012





# Heelkunde van de pancreas en nazorg

## Prof. dr. F. Berrevoet



PROF BERREVOET, DR CESMELI, PROF GEBOES, PROF HINDRYCKX,  
DR SMEETS

AFDELINGEN ABDOMINALE EN HEPATOBILIAIRE HEELKUNDE,  
GASTROENTEROLOGIE EN RADIOLOGIE

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Universitair Ziekenhuis Gent  
C. Heymanslaan 10 | B 9000 Gent  
T +32 (0)9 332 21 11  
E info@uzgent.be

[www.uzgent.be](http://www.uzgent.be)

Volg ons op

