

1ª Reunión Multidisciplinar Gallega sobre Tumores Neuroendocrinos



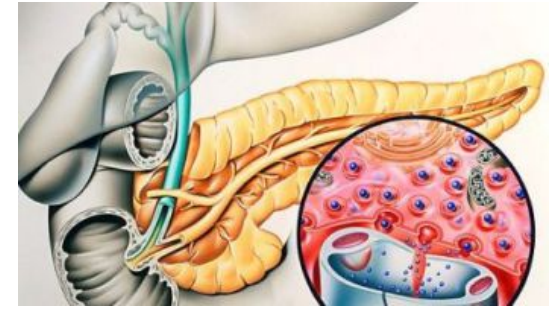
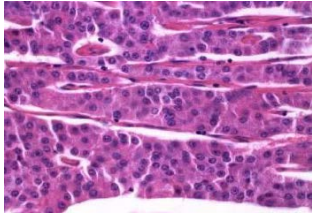
“Optimizando el manejo de los TNE”



Tumores neuroendocrinos pancreáticos G1-2



*Begoña Graña Suárez MD PhD
Servicio de Oncología Médica
Complejo Hospitalario Universitario A Coruña
begona.grana.suarez@sergas.es
18 de abril de 2017*



Tumores neuroendocrinos pancreáticos G1-2

- A. INTRODUCCIÓN:** *epidemiología, clasificación, estadificación, diagnóstico, retos, MEN-1, cáncer de páncreas funcional.*
- B. TRATAMIENTO** de los Tumores neuroendocrinos pancreáticos G1-2 P –NET (ENETS 2016)
- *objetivos del tratamiento*
 - *cirugía*
 - *análogos de la somatoestatina: lanreotide*
 - *terapia dirigida: everólimus y sunitinib*
 - *quimioterapia: estreptozocina y temodal*
 - *péptidos marcados con radionucleóticos: ^{177}Lu – dotatate*
 - *terapias locoregionales: radiofrecuencia y embolización*
- C. Caso clínico**
- D. CONCLUSIONES**

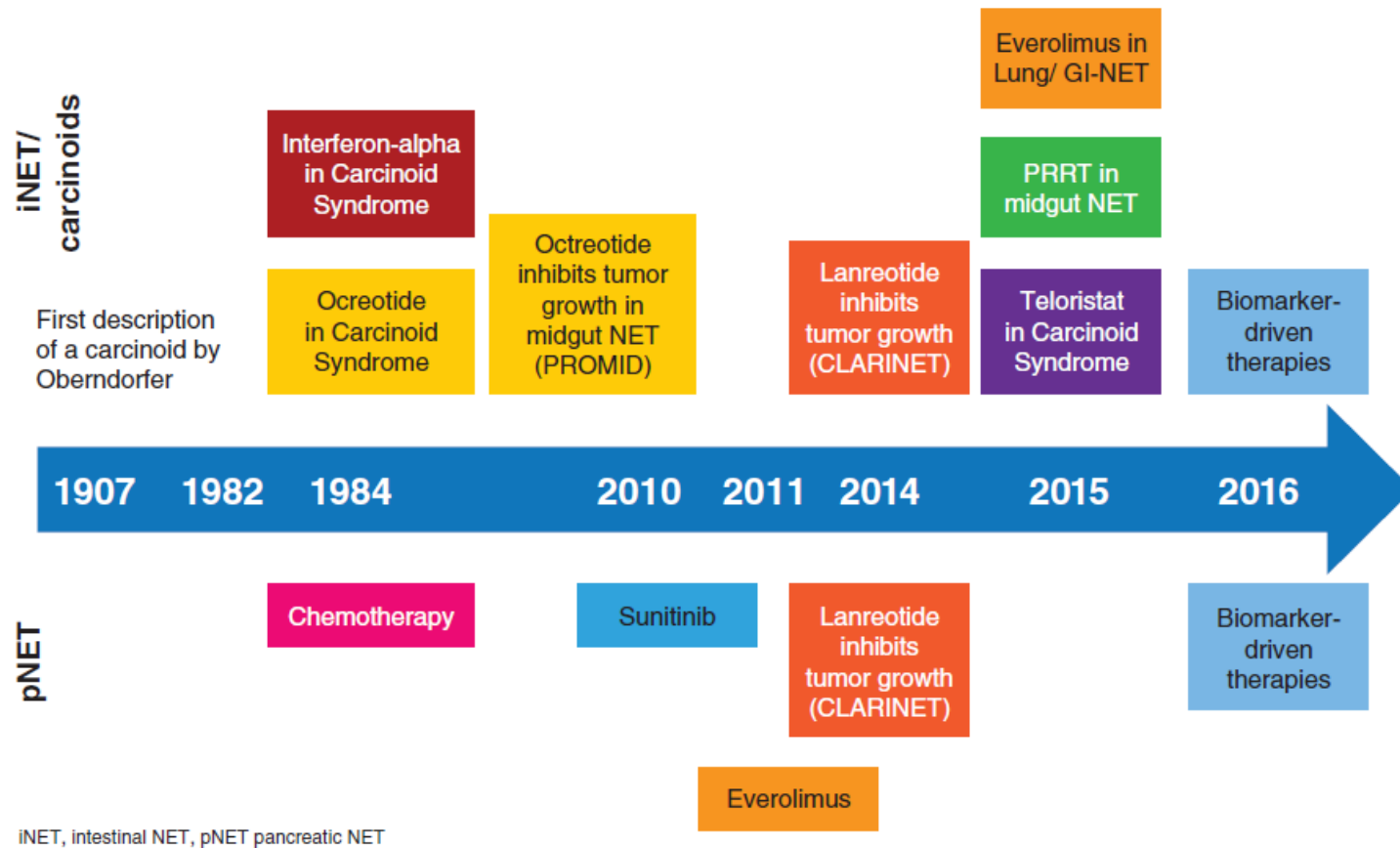


Figure 1
Evolution of therapies in neuroendocrine tumors.

Endocrine-Related Cancer
(2016) **23**, T135–T154

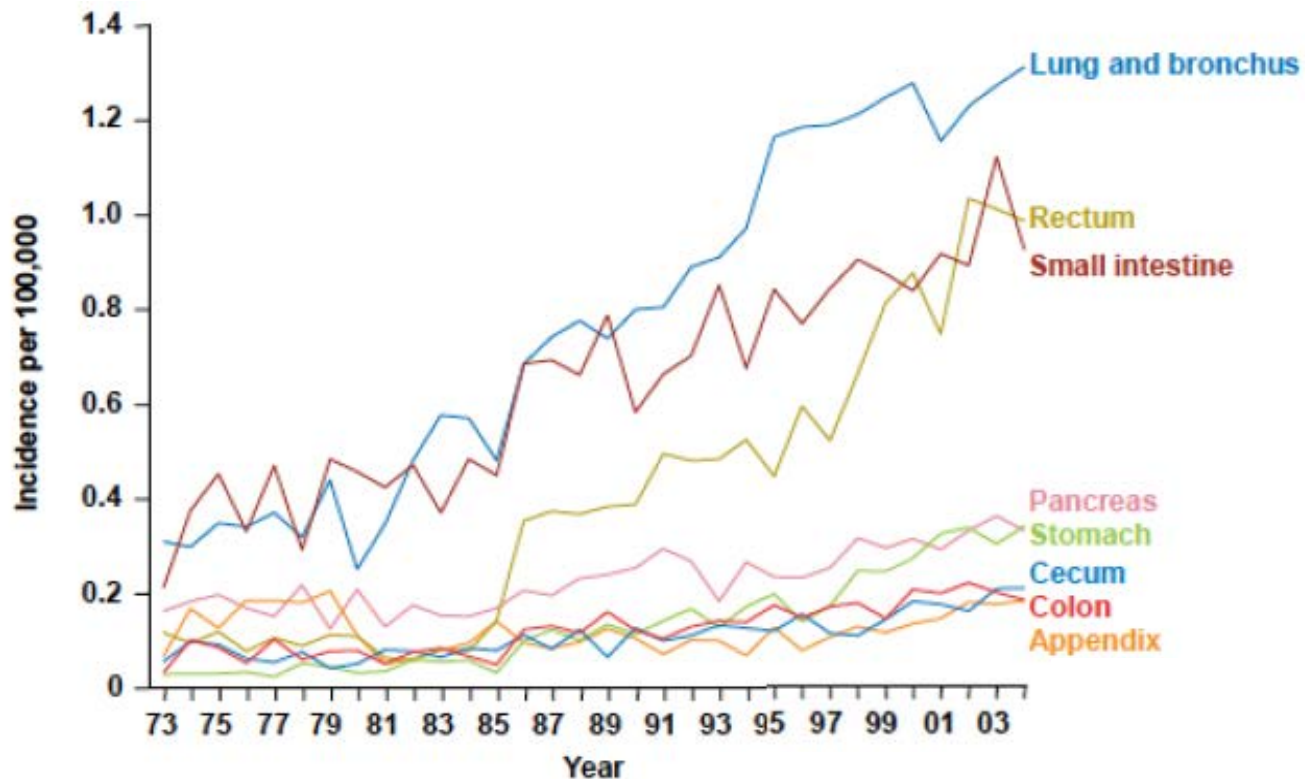
Incidence of NETs Increasing

- **Premise: All neuroendocrine neoplasms (NEN) have a malignant potential**

This premise has an influence on the incidence data

Initially, NET that were regarded as benign were not considered in the incidence data (eg, SEERS data)

NET now have to be included because they are known to have malignant potential



Localizaciones más frecuentes de los TNEs

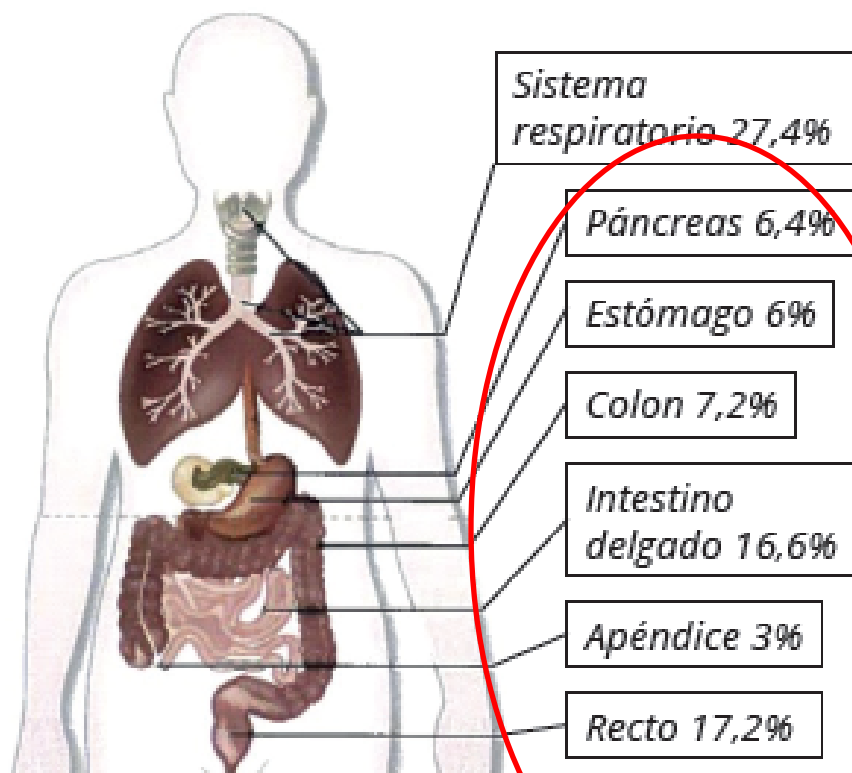


Imagen 1. Yao et al. JCO 2008, 26: 3063-72

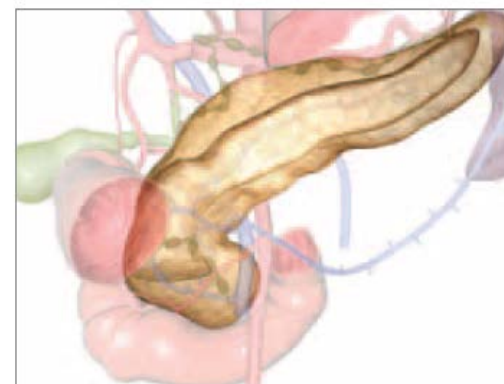
Prevalence of major pancreatic cancer types among all pancreatic cancers

Exocrine

- Pancreatic adenocarcinoma, 61%-70%³⁹⁻⁴¹
- Mucinous tumors, 6%-7%³⁹⁻⁴¹

Endocrine

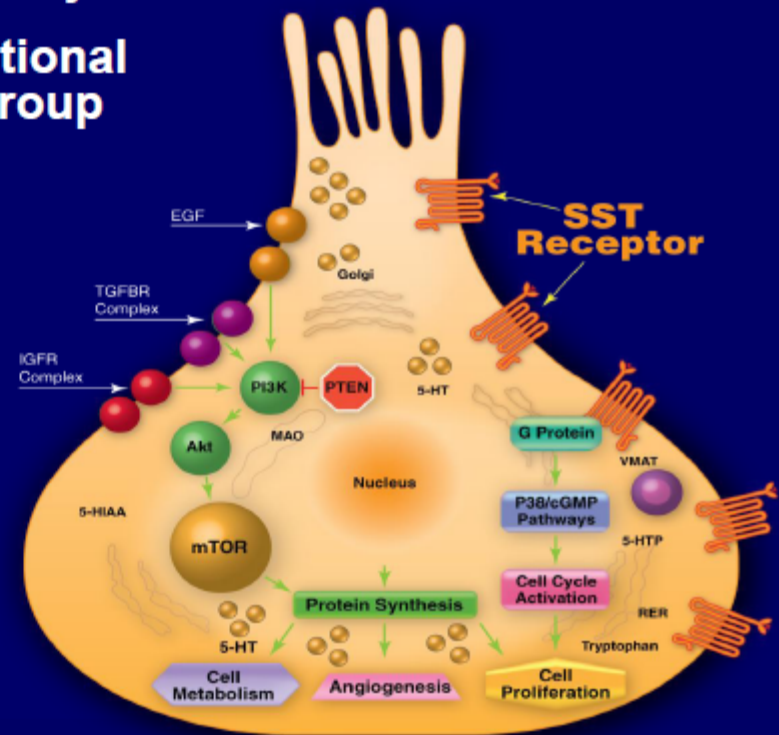
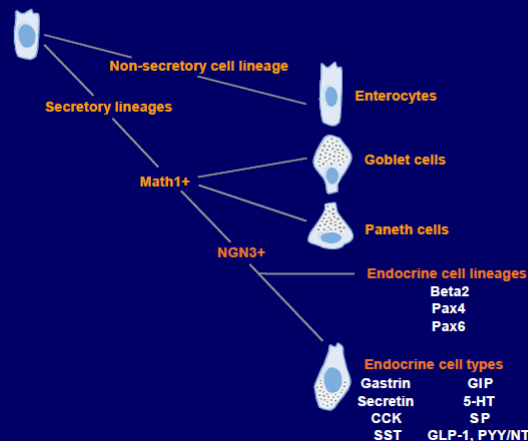
- Pancreatic NETs, 2%-4%³⁹⁻⁴¹



Neuroendocrine Tumors (NETs): A Diverse Group of Malignancies, a Clinical Challenge

- Neuroendocrine cells: migrated from the neural crest to the gut endoderm, from multipotent stem cells
- Tumors arising from enterochromaffin cells located in neuroendocrine tissue throughout the body
- NETs present with functional and nonfunctional symptoms and include a heterogeneous group of neoplasms^{1,2}

Cells of Origin



Clasificación de los TNE: evolución histórica

1897

•Identificación de las células enterocromafines



Kulchitsky 1856-1925

1907

•Introducción del concepto "carcinoide" (características benignas)

Siegfried Oberndorfer 1876-1944



1963

•Clasificación ~~embriológica~~ de los tumores carcinoides

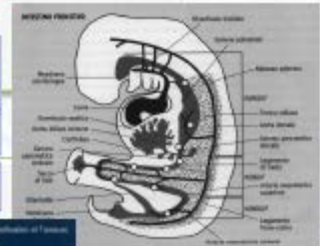
Williams E.D. e Sandler M.



Foregut

Midgut

Hindgut



1971

•Clasificación de patrones arquitecturales

Soga and Tazawa

2000

•Clasificación de la OMS



2010

•Clasificación ~~de la OMS~~

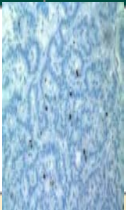
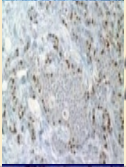
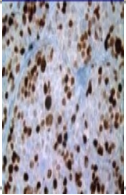


Clasificación histológica de los TNE: OMS (WHO)

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	Well-differentiated endocrine tumour (WDET) Well-differentiated endocrine carcinoma (WDEC) Poorly differentiated endocrine carcinoma/small-cell carcinoma (PDEC)	Neuroendocrine tumours Grade 1 Grade 2 Neuroendocrine carcinoma Grade 3
II. Mucocarcinoid III. Mixed forms carcinoid-adenocarcinoma	Mixed exocrine-endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)
IV. Pseudotumour lesions	Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions

Clasificación histológica de los TNE: OMS(WHO)

WHO 2010 Grading System for Pancreatic Neuroendocrine Neoplasms⁸

Grade		Criteria
Low grade NET G1		<2 mitoses/10 HPF AND/OR $\leq 2\%$ Ki-67 index
Intermediate grade NET G2		2-20 mitoses/10 HPF AND/OR 3%-20% Ki-67 index
High grade neuroendocrine carcinoma G3		>20 mitoses/10 HPF AND/OR >20% Ki-67 index

HPF, high-power field.

WHO Classification of Tumours of the Digestive System. 4th ed. Lyon, France: International Agency for Research on Cancer (IARC); 2010:13-14. *Mod Pathol*. 2010;23(6):824-833.

ESTADIFICACION de los TNE: AJCC vs. ENETS

PÁNCREAS

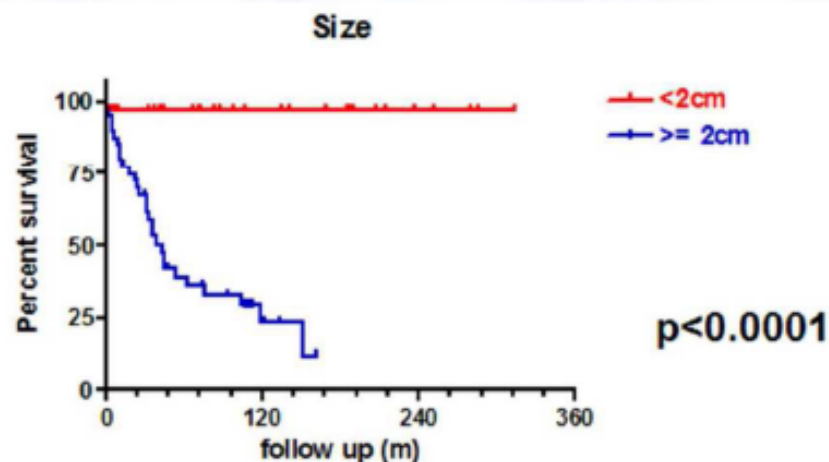
Estadio TNM

■ ENETS

■ Tamaño

■ AJCC/UICC

■ Criterios de resecabilidad



Schmitt et al AJSP 2007

	AJCC/UICC	ENETS
T1	Tumor limitado al páncreas, ≤2 cm en su dimensión mayor.	Tumor limitado al páncreas, ≤2 cm en su dimensión mayor.
T2	Tumor limitado al páncreas, >2 cm en su dimensión mayor	Tumor limitado al páncreas, más de 2 cm pero no más de 4 cm en su dimensión mayor.
T3	El tumor se extiende más allá del páncreas, pero no hay compromiso del tronco celiaco o la arteria mesentérica superior.	Tumor limitado al páncreas de más de 4 cm, o que invade el duodeno o la vía biliar.
T4	El tumor compromete el tronco celiaco o la arteria mesentérica (tumor primario irresecable).	El tumor invade órganos adyacentes (estómago, bazo, colon, gl. suprarrenal) o la pared de grandes vasos (tronco celiaco o arteria mesentérica superior)

DIAGNÓSTICO TNE

Systematic Approach to Diagnosing NETs

History and physical exam

- Characteristic symptoms (dry flushing, cramps, nocturnal diarrhea)
 - Present in 8% to 35% of metastatic NETs¹

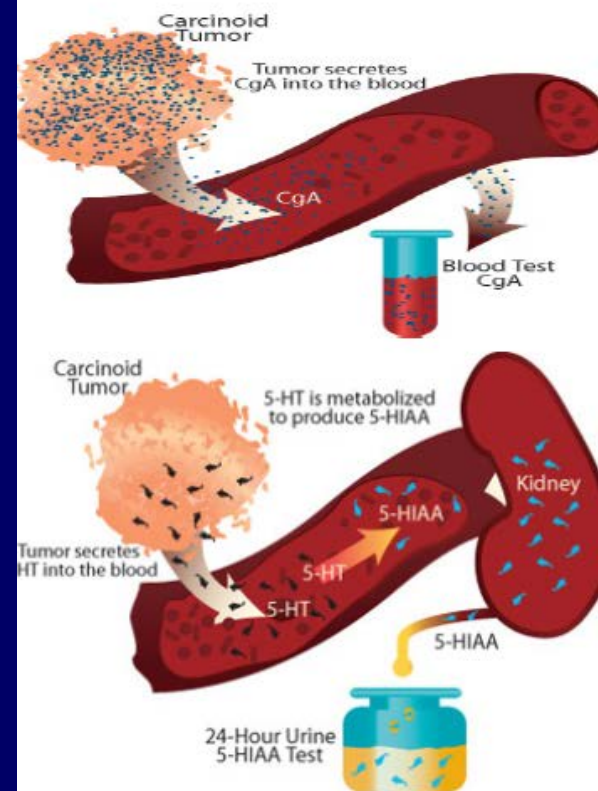
Biochemical markers

- Chromogranin A (CgA)
- Urinary 5-hydroxyindoleacetic acid [(5-HIAA) (with presence of carcinoid syndrome)]
- Synaptophysin on biopsies
- Other biomarkers, including glucagon, gastrin

Histologic diagnosis !!! (expertise)

Imaging

- Computerized tomography scan (CT)
- Endoscopic ultrasound (mainly pancreatic-NET and NET in duodenum)
- Magnetic Resonance Imaging (MRI)
- Somatostatin-receptor scintigraphy (Octreoscan™) or DOTA-TOC FDG/PET



FACTORES A TENER EN CUENTA EN LA TOMA DE DECISIONES

Classification of NET

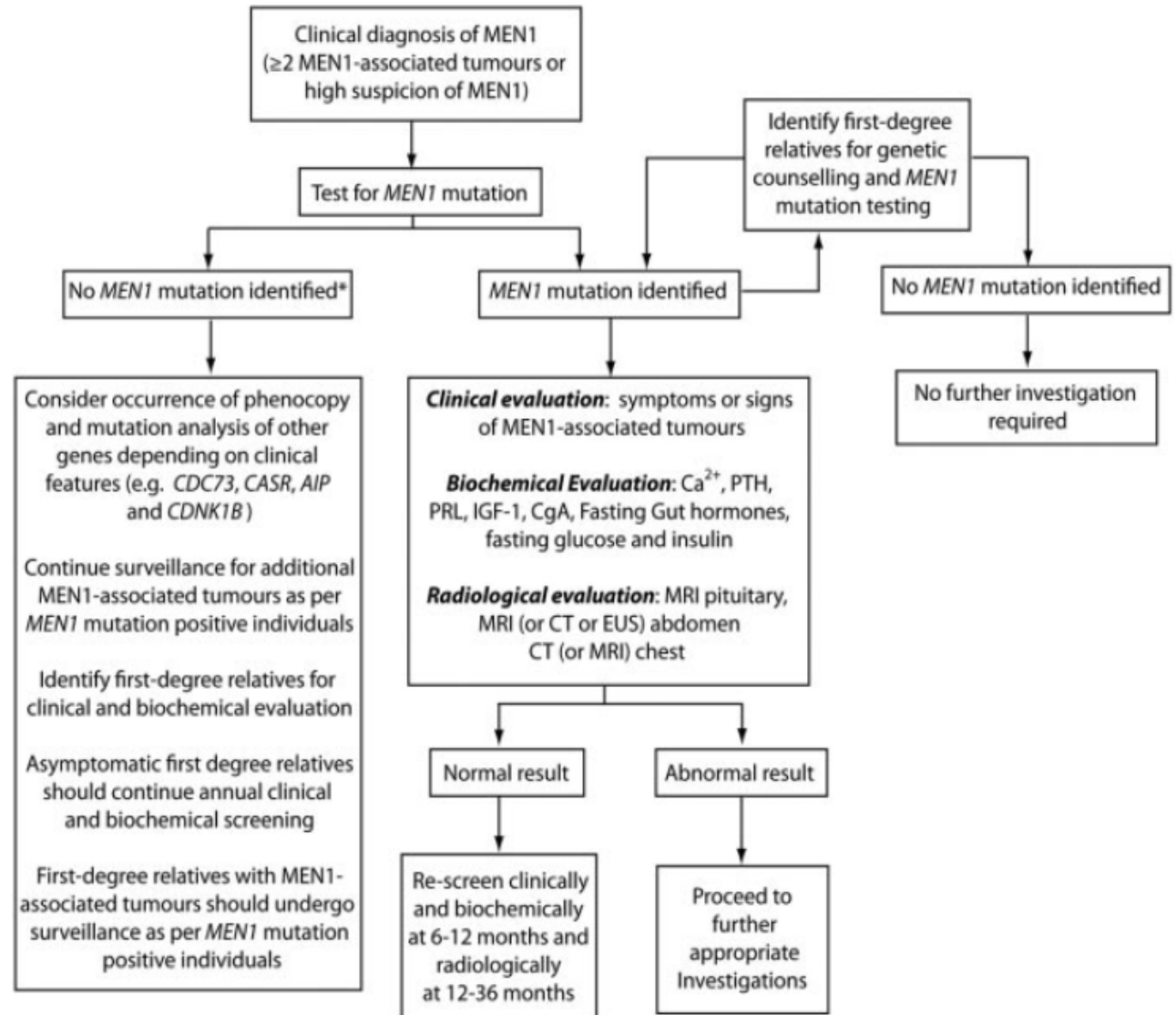
- **Functional versus non-functional**
- **Classification by site of origin**
 - nearly identical characteristics on routine histologic evaluation, but different responses to therapeutic agents
- **Classification by tumor stage: TNM**
 - AJCC
 - ENETS
- **Histologic classification**
 - well differentiated - poorly differentiated
 - tumors with a high grade (grade 3), a mitotic count >20 per 10 high powered fields, or a Ki-67 proliferation index of $>20\%$ represent highly aggressive malignancies
- **Molecular Classification**
 - MEN 1 & 2, Tuberous Sclerosis, Von Hippel Lindau disease



Diagnostic & therapeutic challenges in NET

- **Heterogeneous group of tumors**
- **Wide variety of clinical presentations**
- **Late presentation**
 - ✓ Over 60% of NETs are advanced at the time of diagnosis
 - ✓ The median survival for patients with advanced NET is 33 months
- **Different terminology and classifications**
- **Histologic diagnosis may be difficult**
- **Variety of therapeutic options/approaches**
 - ✓ Limited phase III evidence for chemotherapy and PRRT

SD.S DE CÁNCER HEREDITARIO Y TNE: MEN1



SD.S DE CÁNCER HEREDITARIO Y TNE: MEN1

Table 2. Frequency of Pancreatic NETs in Patients With Inherited Disorders^{6,17}

Inherited disorder	Frequency of pancreatic NETs (%)
MEN-1	80-100
VHL	10-17
von Recklinghausen disease (NF-1)	0-10
TSC	Uncommon

Table 3. Frequency of Pancreatic NETs in Patients With MEN-1^{6,17}

Type of pancreatic NET	Frequency in MEN-1 (%)
Nonfunctional	80-100, microscopic/asymptomatic 0-13, large/symptomatic
Gastrinoma	20-61 (mean 54)
Insulinoma	7-31 (mean 18)
Glucagonoma	1-6 (mean 3)
VIPoma	1-12 (mean 3)
Somatostatinoma	0-1



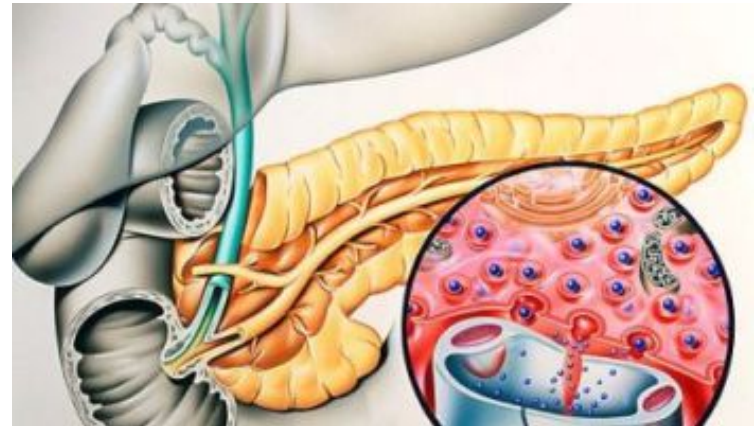
Table 1. Functional Pancreatic endocrine tumors [F-p-NET] syndromes

Name	Biologically active peptide(s) secreted	Incidence (new cases/10 ⁶ population/year)	Tumor location	Malignant, %	Associated with MEN-1, %	Main symptoms/signs
<i>A. Most common Functional Pancreatic Endocrine Tumor syndromes</i>						
Insulinoma	Insulin	1–32	Pancreas (>99%)	<10	4–5	Hypoglycemic symptoms (100%)
Zollinger-Ellison syndrome	Gastrin	0.5–21.5	Duodenum (70%) Pancreas (25%) Other sites (5%)	60–90	20–25	Pain (79–100%) Diarrhea (30–75%) Esophageal symptoms (31–56%)
<i>B. Established Rare functional Pancreatic Endocrine Tumor syndromes [RFTs] (>100 cases)</i>						
VIPoma (Verner-Morrison syndrome, pancreatic cholera, WDHA)	Vasoactive intestinal pPeptide	0.05–0.2	Pancreas (90%, adult) Other – (10%, neural, adrenal, periganglionic)	40–70	6	Diarrhea (90–100%) Hypokalemic (80–100%) Dehydration (83%)
Glucagonoma	Glucagon	0.01–0.1	Pancreas (100%)	<50–80	1–20	Rash (67–90%) Glucose intolerance (38–87%) Weight loss (66–96%)
Somatostatinoma	Somatostatin	Rare	Pancreas (55%) Duodenum/Jejunum (44%)	>70	45	Diabetes mellitus (63–90%) Cholelithiasis (65–90%) Diarrhea (35–90%)

B. Tratamiento de los Tumores neuroendocrinos pancreáticos G1-2 P –NET

¿ALTERNATIVAS TERAPEUTICAS?

¿¿SECUENCIA DE TRATAMIENTO ??



OBJETIVOS DEL TRATAMIENTO

**PROLONGAR LA
SUPERVIVENCIA**

**CONTROL DE
SÍNTOMAS**

**CONTROL
CRECIMIENTO
TUMORAL**

**EVITAR
COMPLICACIONES**

**MANTENER/MEJORA
R CALIDAD DE VIDA**

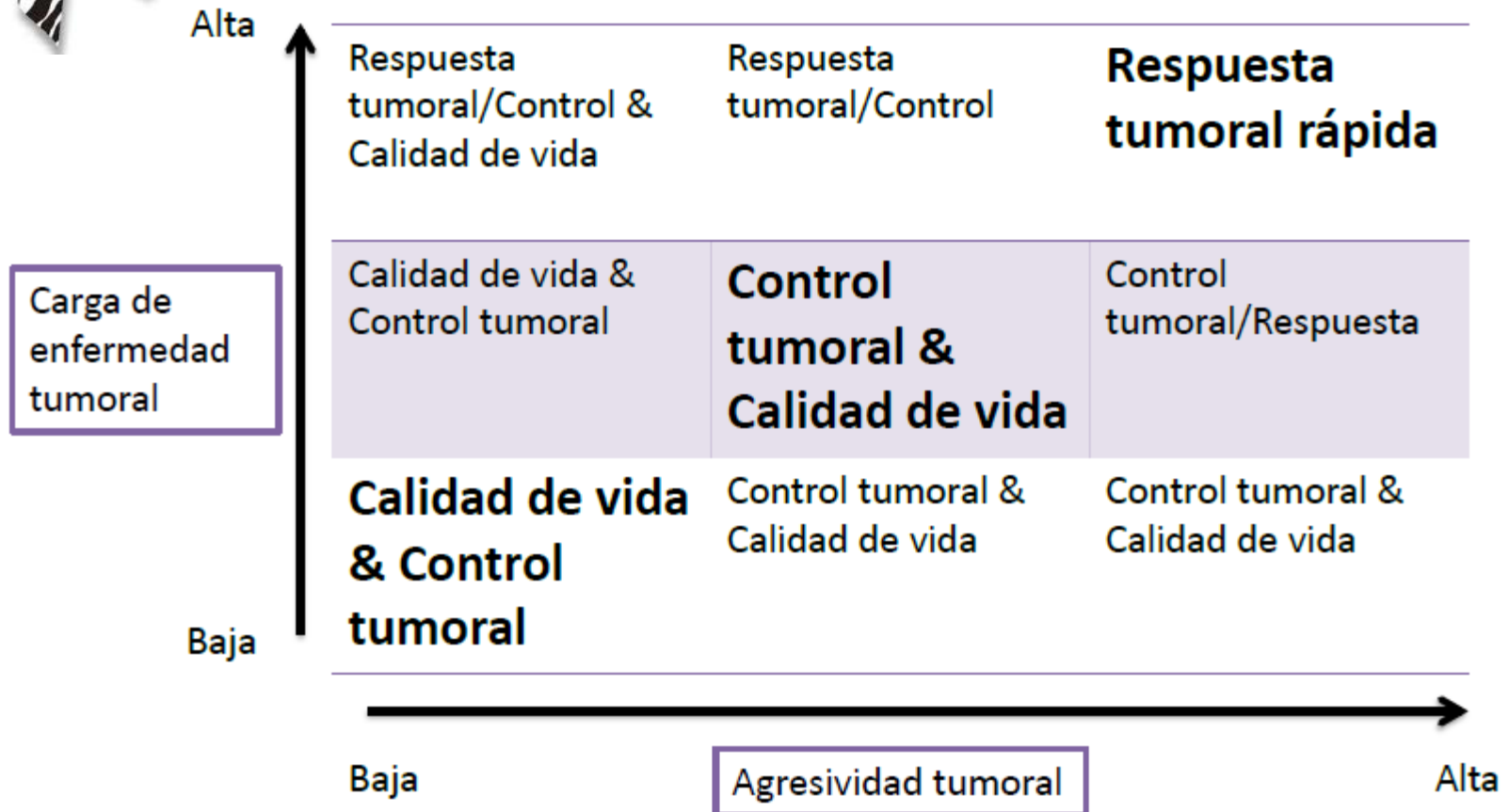
**VENTANA
OPORTUNIDAD
TERAPÉUTICA**

**ENTORNO
PERSONAL/SOCIAL/
LABORAL**





OBJETIVOS DEL TRATAMIENTO



Keys in decision making: patients



1. Age
2. Performance status
3. Comorbidities
4. Preferences



Less important due to:
Young
Good performance status



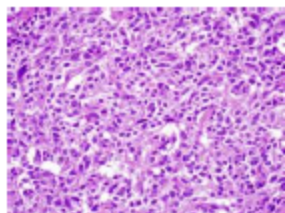
Keys in decision making: tumor



1. Age
2. Performance status
3. Comorbidities
4. Preferences



Less important due to:
Young
Good functionality



1. **Origin**
2. **Tumor Burden**
3. **Progression**
4. Histology, SSTR
5. Functionality
6. Resectability



Location or **molecular targets?**
Histology, burden or **evolution?**

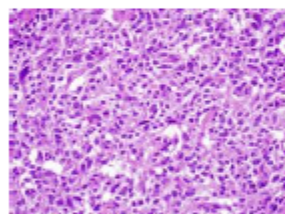
Keys in decision making: physician



1. Age
2. Performance status
3. Comorbidities
4. Preferences



Less important due to:
Young
Good functionality



1. **Origin**
2. Histology
3. Functionality
4. Resectability



Location or molecular targets?
Histology or evolution?



1. Multidisciplinary team
2. Clinical trials
3. Diagnostic tools
4. Therapeutic tools



Reference centres
Experts

1. Tratamiento QUIRÚRGICO de los Tumores neuroendocrinos pancreáticos G1-2 P-NET

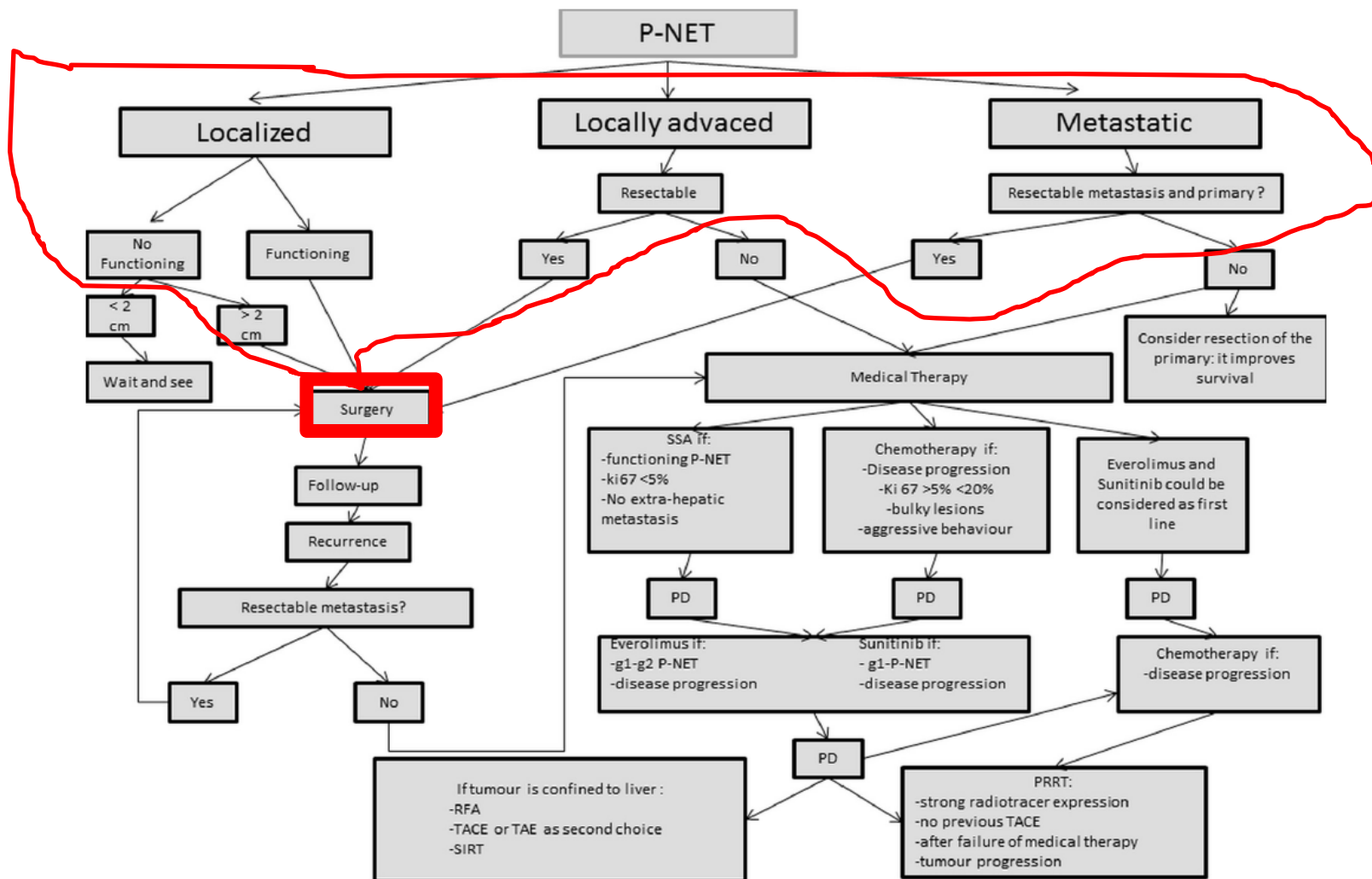
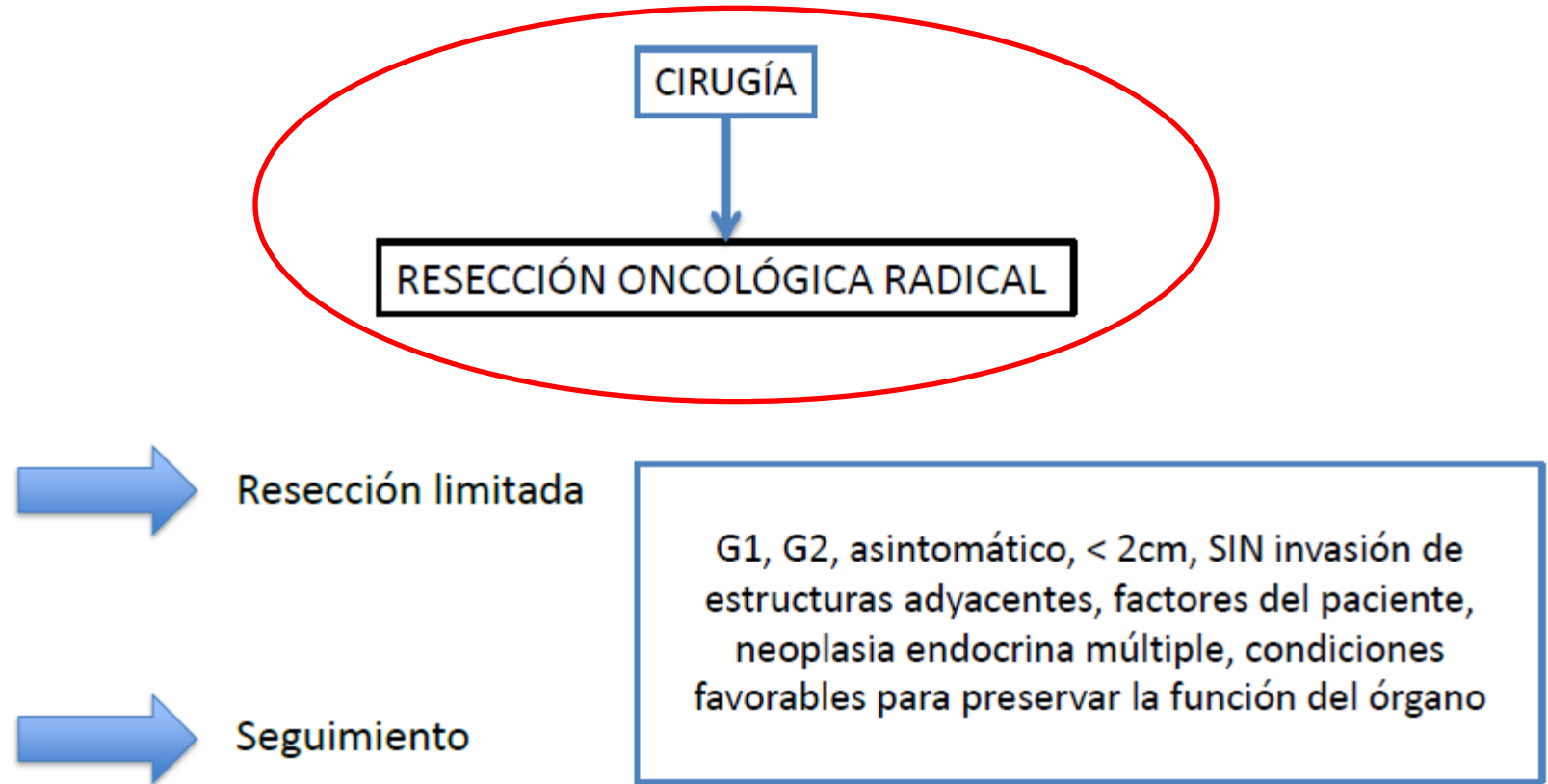


Fig. 1. Algorithm for treatment of pancreatic neuroendocrine tumors (P-NET).

1. Tratamiento QUIRÚRGICO de los Tumores neuroendocrinos pancreáticos G1-2 P-NET



No hay datos sobre el tratamiento adyuvante

Pancreaticoduodenectomy: biliary anastomosis can affect post-operative therapies

- Bilio-enteric anastomosis can lead to intestinal biliary reflux



Eckel F, et al. Digestion 2000

1. Tratamiento QUIRÚRGICO de los Tumores neuroendocrinos pancreáticos G1-2 P-NET

***Minimal consensus statement:** Surgery with curative intent and/or loco-regional or ablative therapies should be considered at initial diagnosis and in the course of the disease as an alternative approach to systemic therapies. In patients with functioning NET, all liver directed therapies require prior initiation of SSA therapy (or other specific symptom controlling measures). Debulking surgery is indicated in selected patients with functioning NET with predominant liver disease for improved syndrome control even if liver tumor burden can be reduced by less than 90%. Liver transplantation is an option in very highly selected patients, preferably in young patients with functional syndromes demonstrating early resistance to medical therapy.*

Neuroendocrinology (DOI:10.1159/000443167)



Tratamiento MÉDICO de los Tumores neuroendocrinos pancreáticos G1-2 P-NET

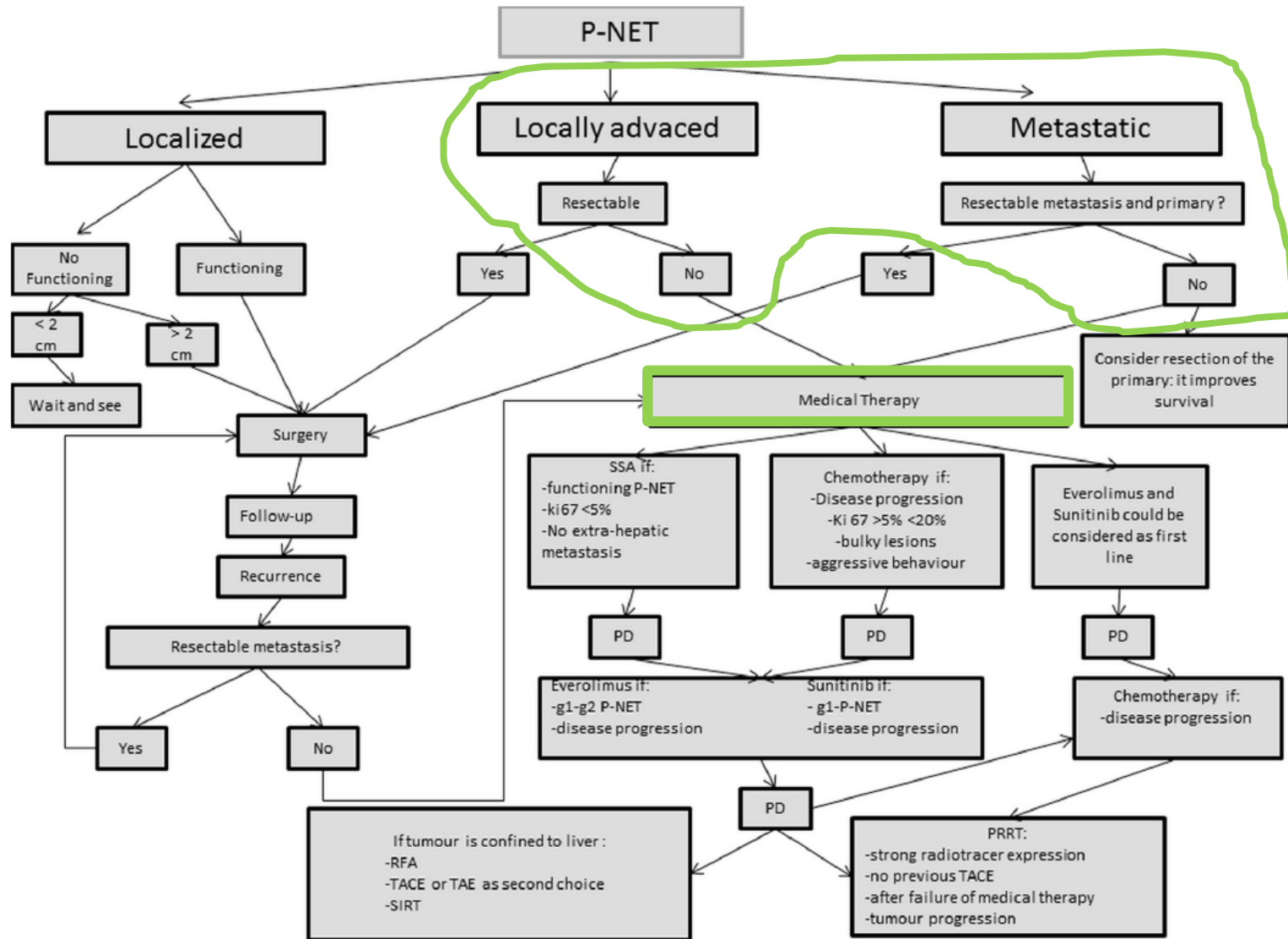
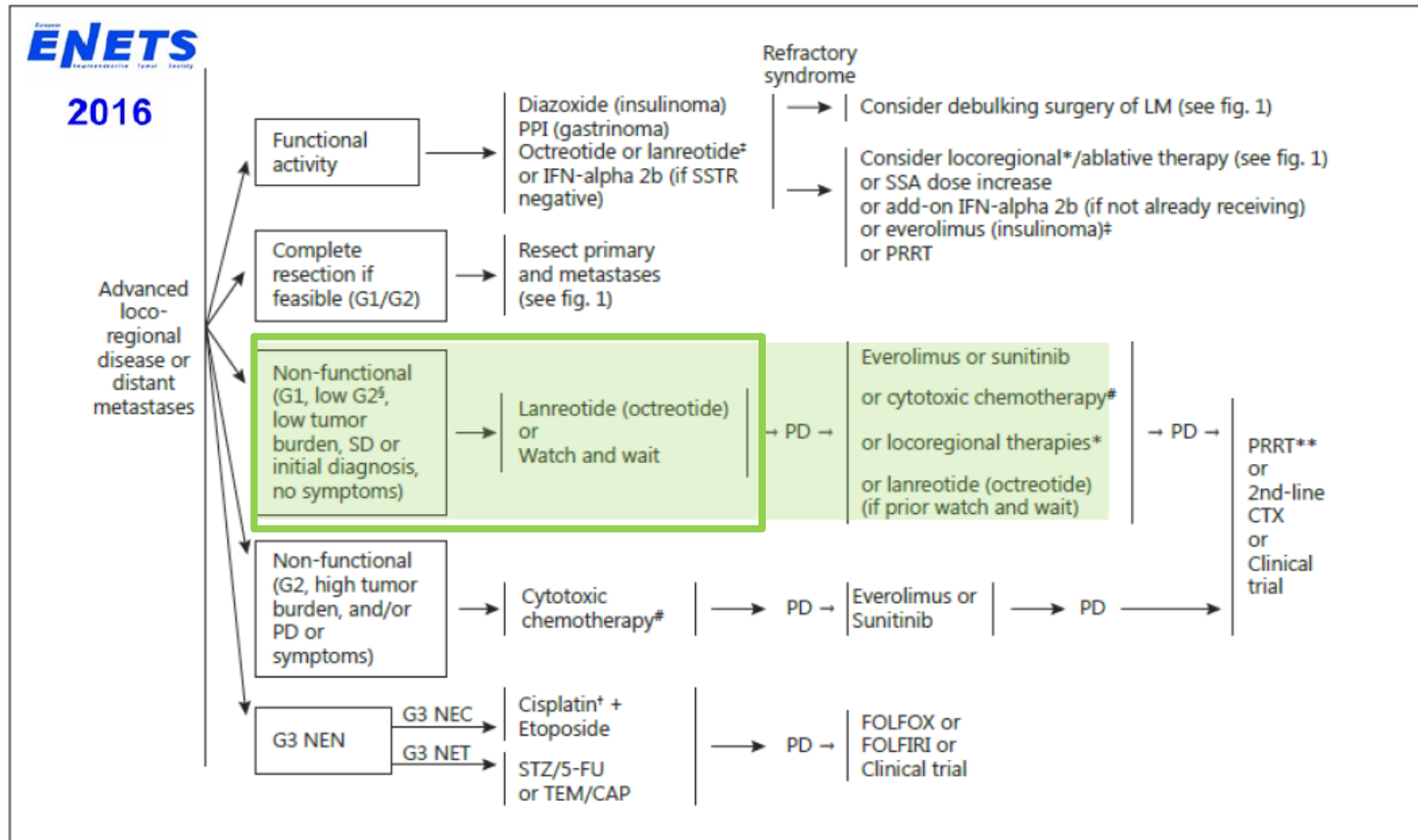


Fig. 1. Algorithm for treatment of pancreatic neuroendocrine tumors (P-NET).

Phase III trial-related evidence in NET

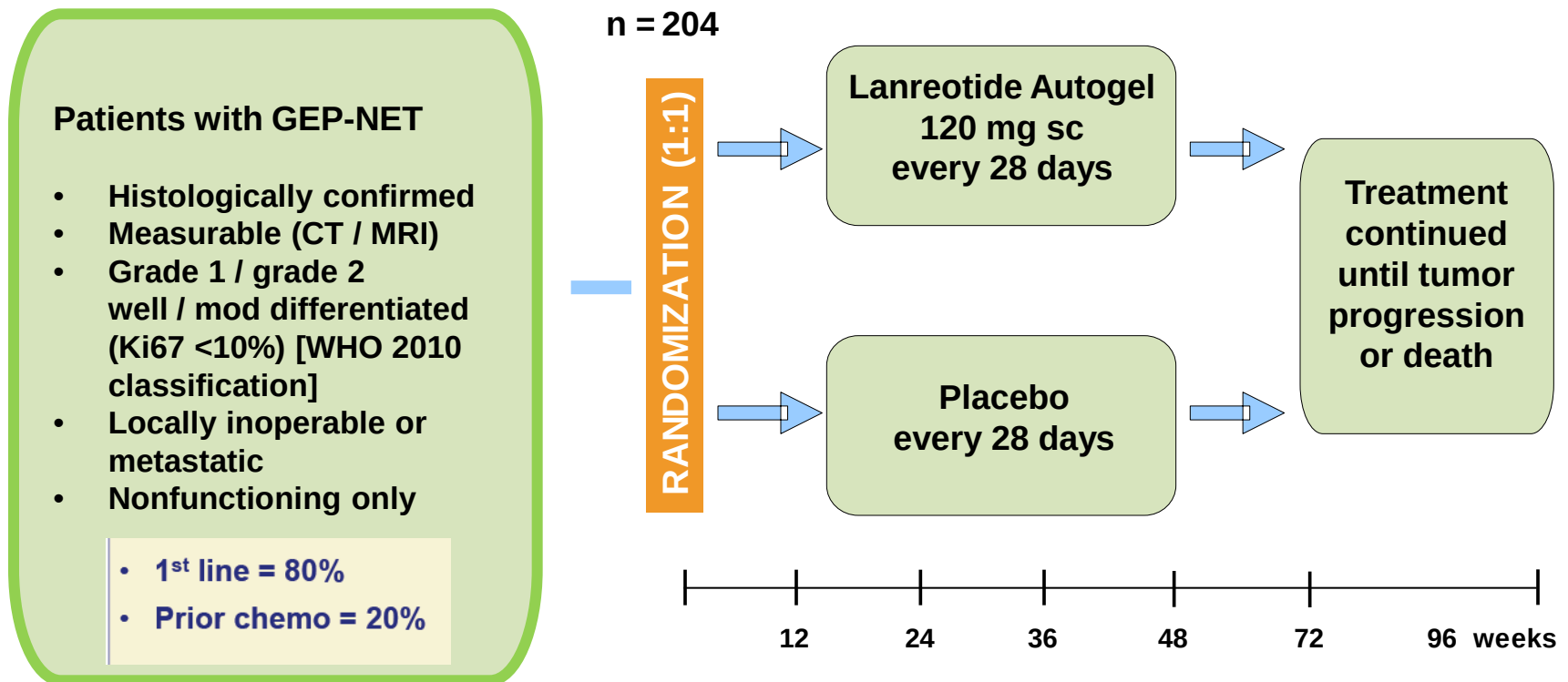
trial	Presented/published	therapy	outcome	setting
PROMID	Rinke, JCO 2009	OCT LAR vs. PLB	positive	Well-diff midgut
CLARINET	Caplin, NEJM 2014	LAN A vs. PLB	positive	Well-diff enteropancreatic <10% Ki-67
RADIANT-2	Pavel, Lancet 2012	EVE + OCT LAR vs. PLB + OCT LAR	negative	Carcinoid syndrome-related
RADIANT-3	Yao, NEJM 2011	EVE vs. PLB	positive	Well-diff pancreatic
A6181202	Raymond, NEJM 2011	SUN vs. PLB	positive	Well-diff pancreatic
RADIANT-4	Yao, Lancet 2015	EVE vs. PLB	positive	Non functioning well-diff GI and LUNG
TELESTAR	Kulke, JCO Oct 2016	Telotristat vs. PLB	positive	Carcinoid syndrome refractory to SSA
NETTER-1	Strosberg, ESMO 2015	PRRT+ OCT LAR vs. HD OCT LAR	positive	Midgut progressing on OCT LAR
SWOG	Yao, ASCO 2015	BEV + OCT LAR vs. IFN + OCT LAR	negative	Mixed population

2. Tratamiento de los P-NET G1-2 avanzados con análogos de la somatoestatina (SSA)



THE CLARINET STUDY

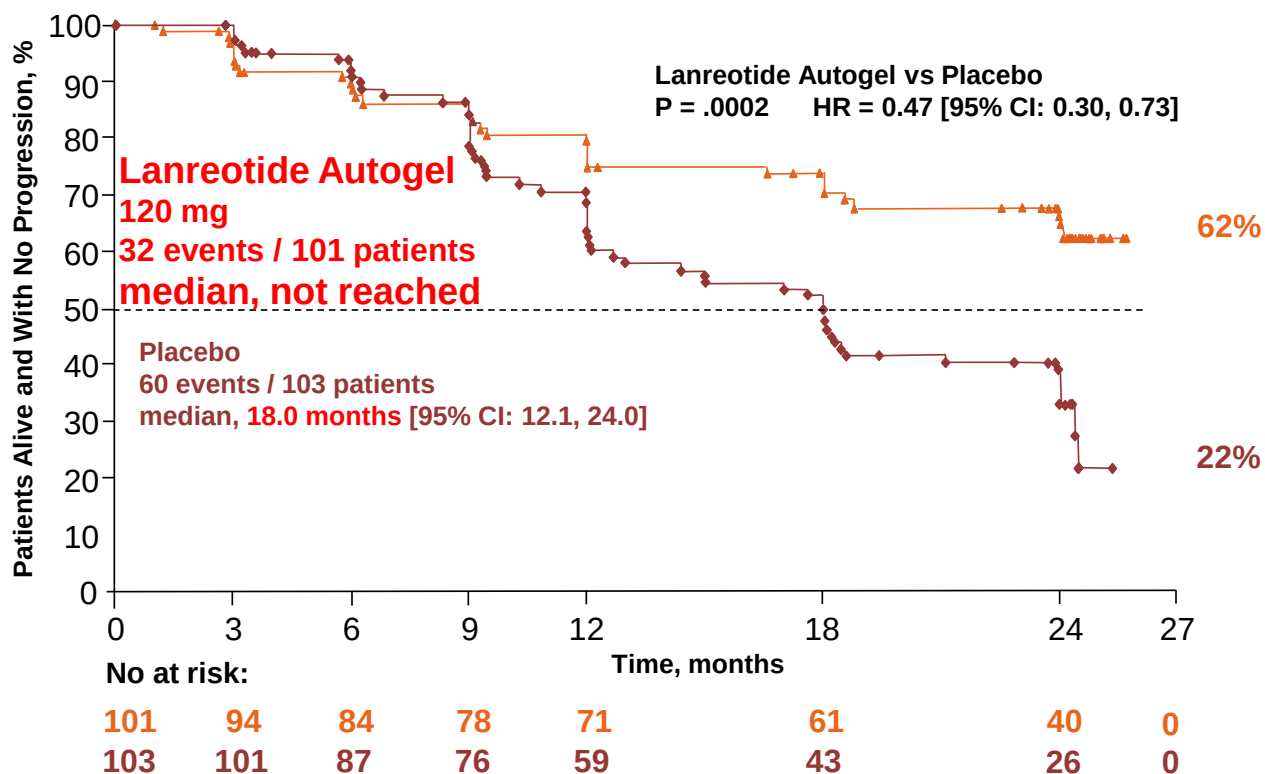
A randomized double-blind placebo-Controlled phase III study of Lanreotide Antiproliferative Response In enteropancreatic NET



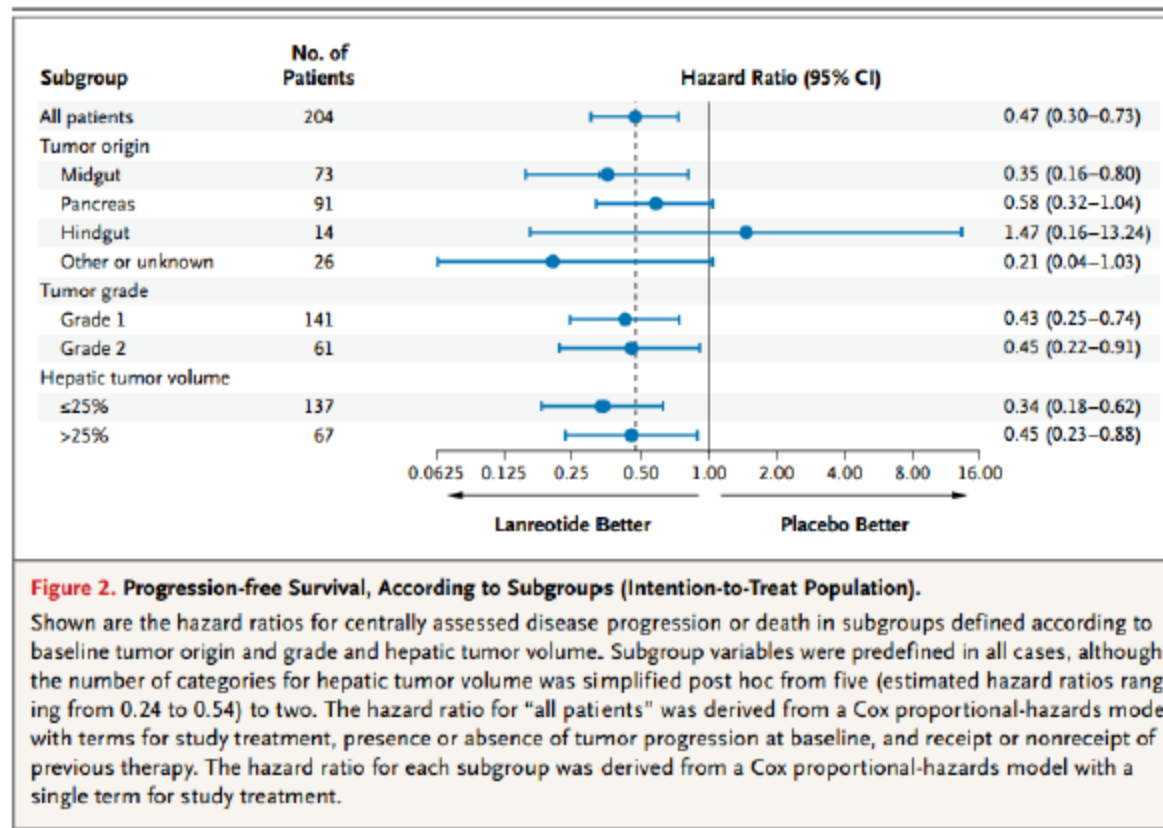
- **Primary endpoint: PFS**
- Secondary endpoints: Adverse events, pharmacokinetics, quality of life, CgA serum levels

CLARINET: LANREOTIDE PROLONG PFS IN ENTEROPANCREATIC NET

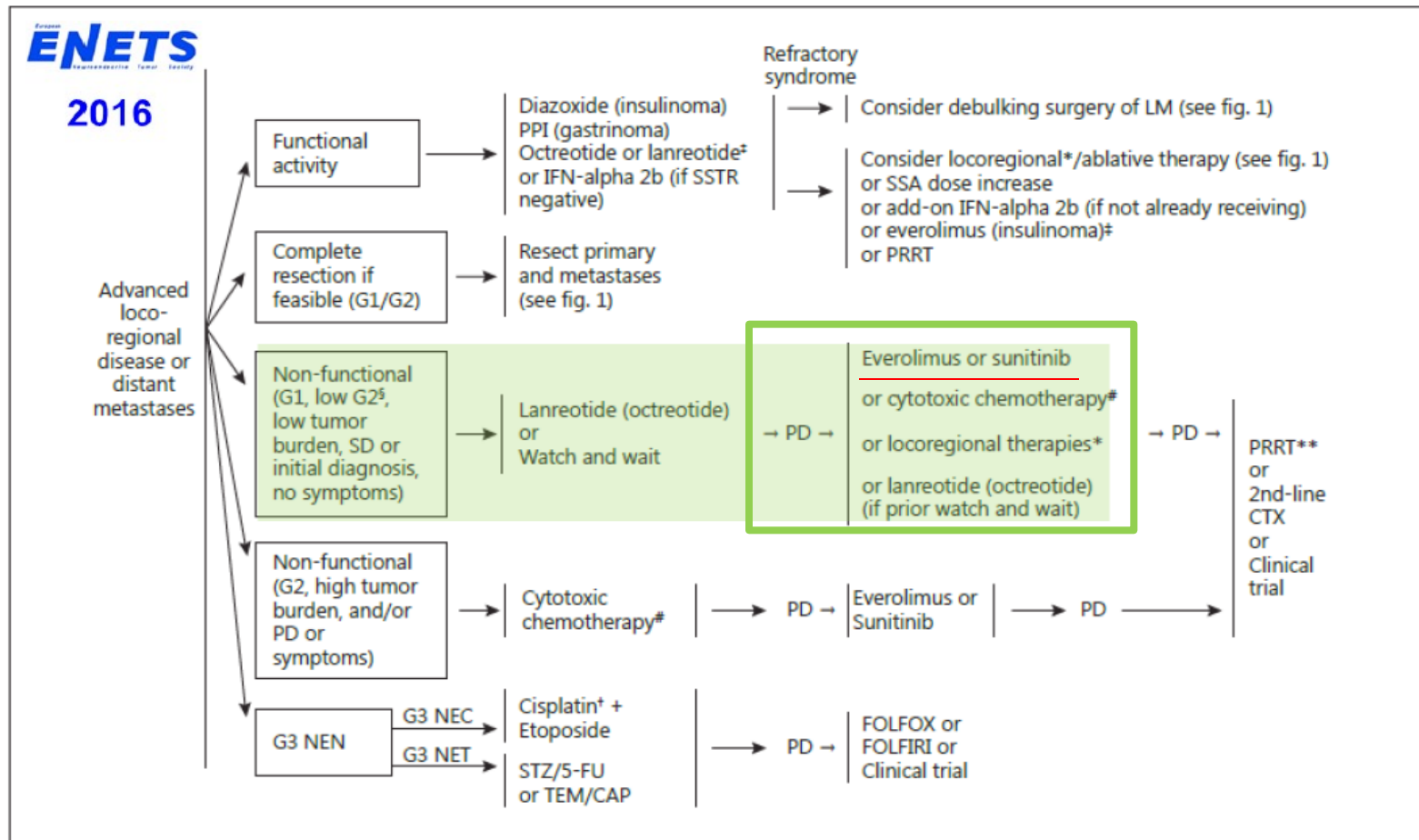
PFS (intention to treat population)



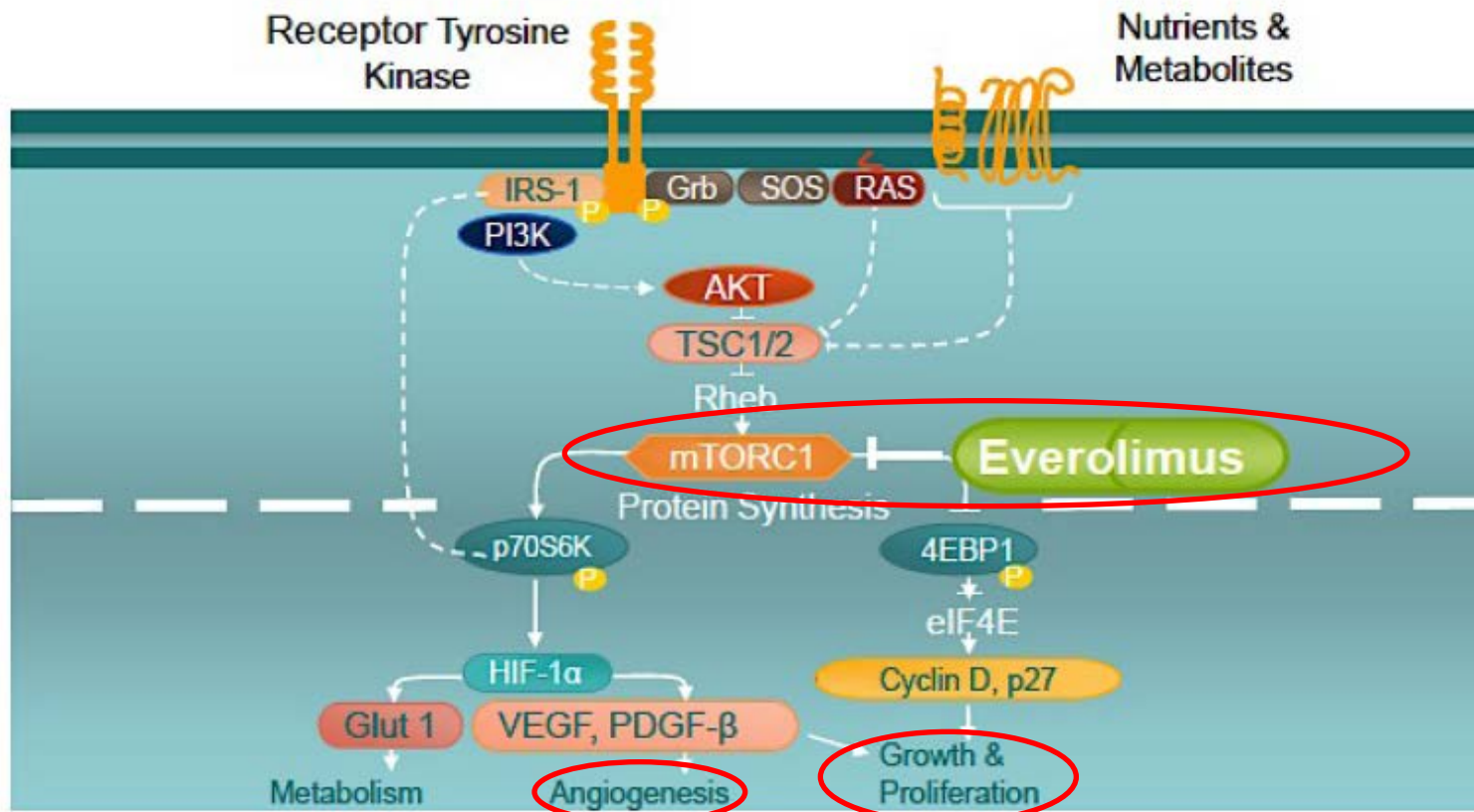
The CLARINET study showed benefit to be independent of the hepatic load, tumor grade (G1 vs. G2), and location.



3. Tratamiento de los P-NET G1-2 avanzados con terapia dirigida



TERAPIA DIRIGIDA



RADIANT-3: STUDY DESIGN

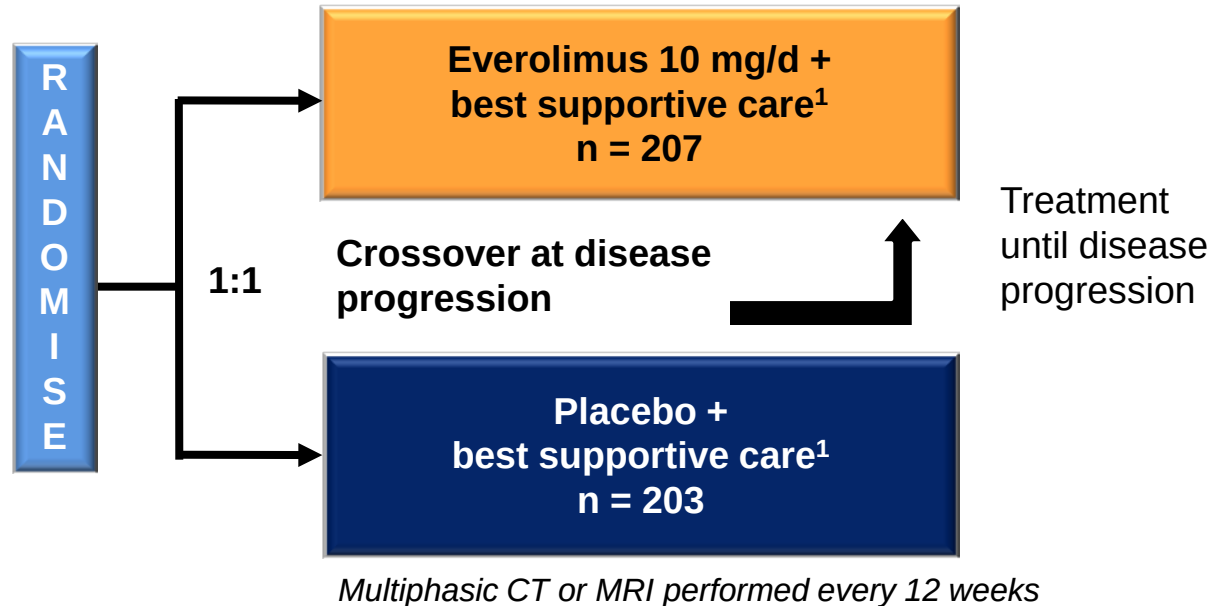
Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced pNET (N = 410)

- Advanced well or moderately differentiated
- Radiologic progression ≤ 12 months
- Prior antitumour therapy allowed, (50% 1st SSA/Chemo)
- WHO PS ≤ 2

Stratified by:

- WHO, PS
- Prior chemotherapy



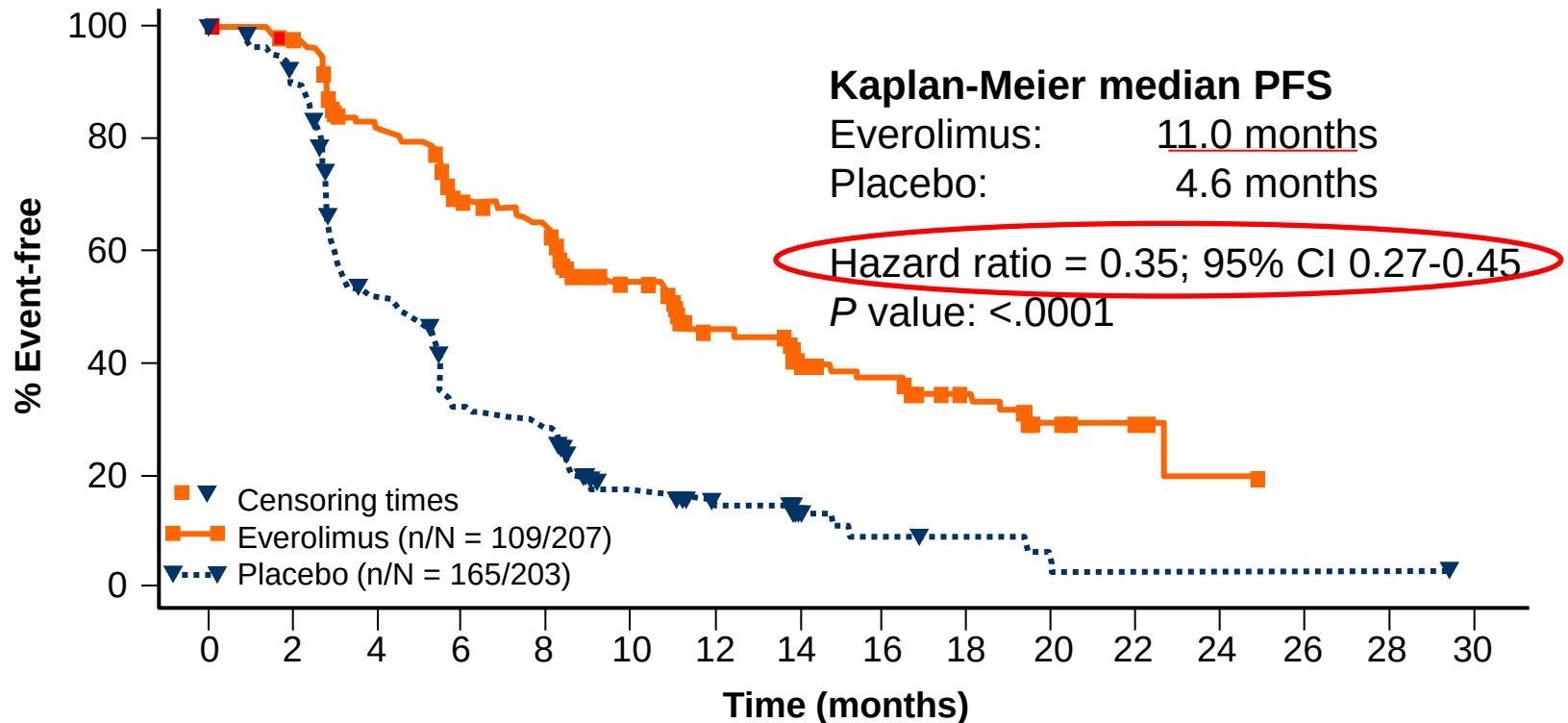
¹Concurrent somatostatin analogues allowed: 40% TREATED WITH CONCURRENT SSA

Primary Endpoint: Progression-free survival

Secondary Endpoints: OS, ORR, biomarkers, safety, pharmacokinetics (PK)

RADIANT-3

Progression Free Survival



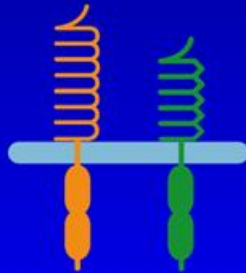
148 placebo patients crossed over to everolimus at the time of progression

P value obtained from stratified 1-sided log-rank test

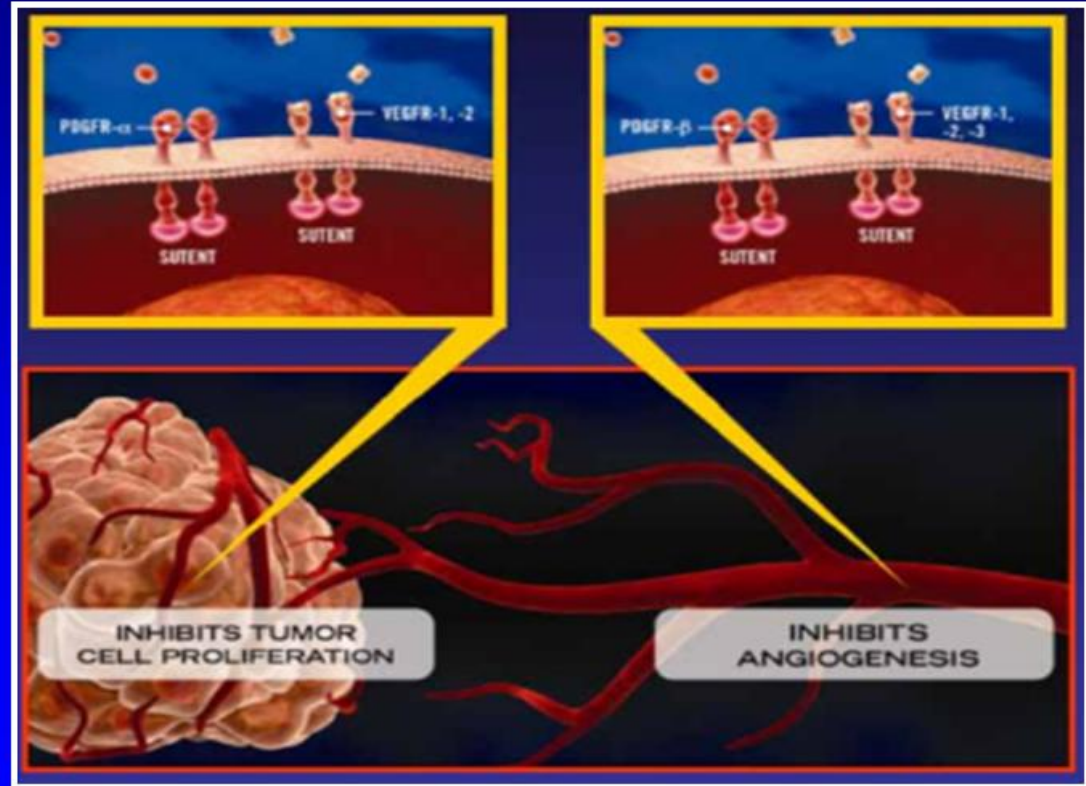
Hazard ratio is obtained from stratified unadjusted Cox model

Sutent/Sunitinib Inhibits Multiple Targets

Inhibits multiple signals



VEGFR-1	PDGFR- α
VEGFR-2	PDGFR- β
VEGFR-3	RET
	KIT
	FLT-3

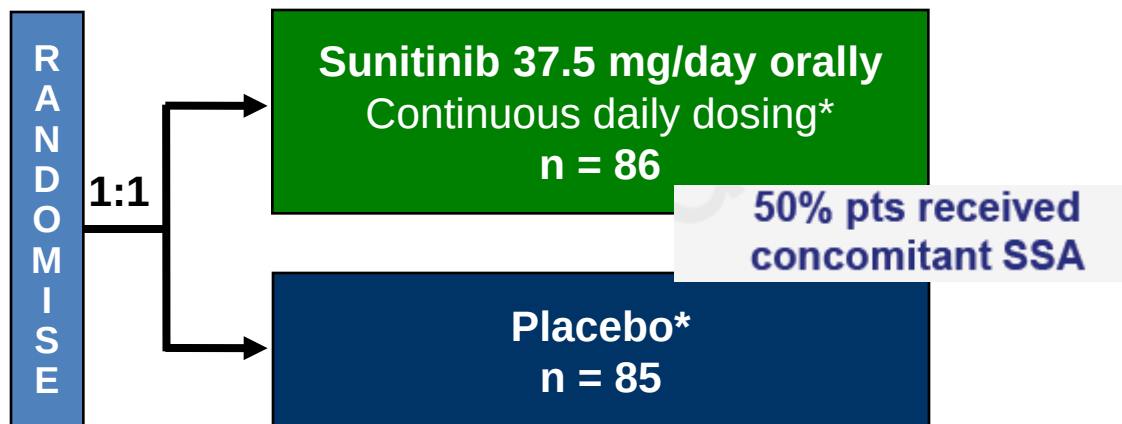


SUNITINIB VS PLACEBO IN ADVANCED PNET

- Phase III randomised, placebo-controlled, double-blind trial
- Trial terminated after unplanned early analysis due to treatment benefit

**Well differentiated
advanced pNET patients
(N = 171 enrolled / 340
planned)**

- Disease progression in past 12 mos 33% previous SSA
- Not amenable to curative treatment



Primary Endpoint:

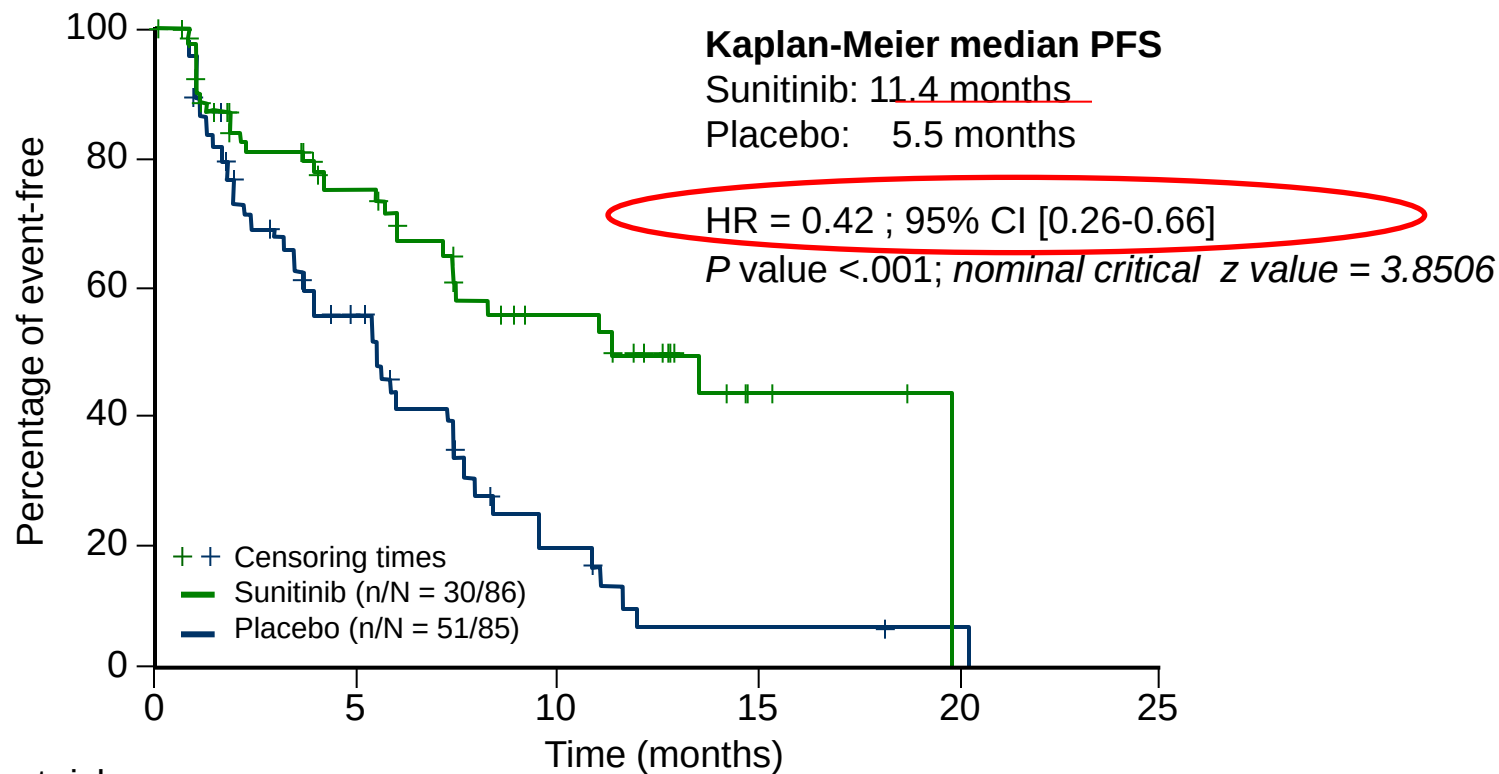
- PFS

Secondary Endpoints:

- OS
- ORR
- TTR
- Duration of response
- Safety
- Patient-reported outcomes

* With best supportive care Somatostatin analogues were permitted

SUNITINIB VS PLACEBO IN ADVANCED PNET



Number at risk:

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

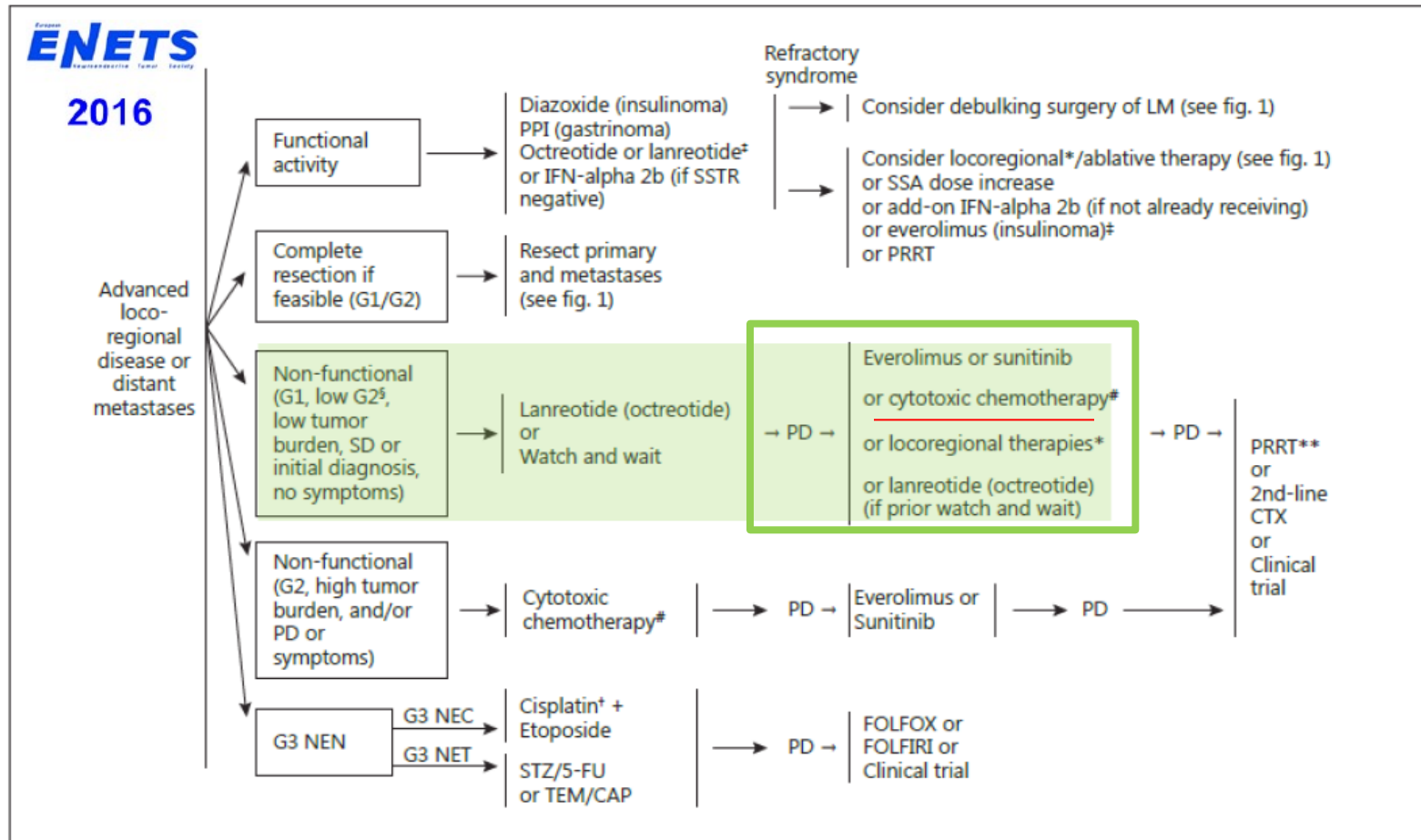
* Local review

Minimal consensus statement: Everolimus and sunitinib are approved antiproliferative therapies in progressive pancreatic NET, and represent one of the different treatment options next to SSA and systemic chemotherapy. They can be considered a first line therapy, especially if SSA is not an option, and if systemic chemotherapy is not clinically required, not feasible or not tolerated. Everolimus or sunitinib are generally recommended after failure of SSA or chemotherapy in pancreatic NET. In

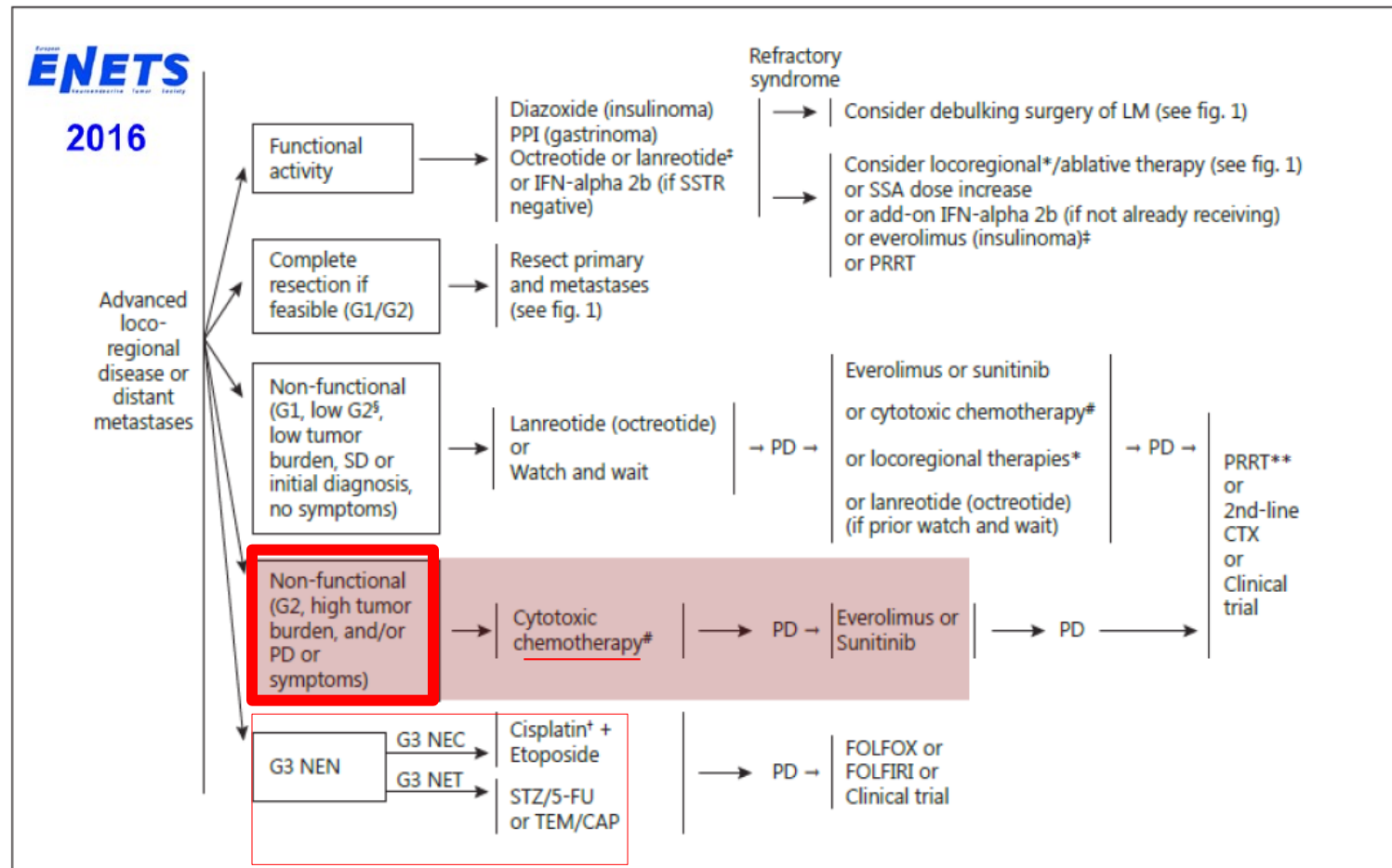
Neuroendocrinology (DOI:10.1159/000443167)

Adverse Events	SSA (N=42) (PROMID)	Everolimus (N=202) (RADIANT-4)	Eve + SSA (N=215) (RADIANT-2)	Sunitinib (N=107)(phase II)
Fatigue	19%	31%/3%	31%/7%	64%/24.3%
Diarrhea	11.9%	31%/7%	27%/6%	61%/4.7%
Nausea		17%/1%	20%/0.5%	51%/5.6%
Vomiting			11%/0.5%	25%/6.5%
Stomatitis		63%/9%	62%/7%	32%/1.9%
Rash		27%/1%	37%/1%	26%/0.9%
Decreased weight			15%/0.5%	
Decreased appetite		16%/1%	13%/0%	25%/2.8%
Hyperglycaemia		10%/3%	12%/5%	
Pulmonary events		16%/1%	12%/2%	
Anemia	14.2%	16%/4%	15%/1%	42%/2.8%
Leucopenia				39%/14%
Thrombocytopenia				30%/8.4%
Infections		29%/7%	20%/5%	
cholelithiasis	11.9%			
Skin/Hair color changes				32%/0%
Hand-Foot Syndrome				15%/1.9%
Hypertension				5.6%/10.3%
Periorbital edema				15.9%/0%
Cardiac Failure				0%/0.9%

4. Tratamiento de los P-NET G1-2 avanzados con quimioterapia



4. Tratamiento de los P-NET G1-2 avanzados con QUIMIOTERAPIA



4. Tratamiento de los P-NET G1-2 avanzados con QUIMIOTERAPIA

Chemotherapy in gastro-entero-pancreatic tumours (GEP-NETS).

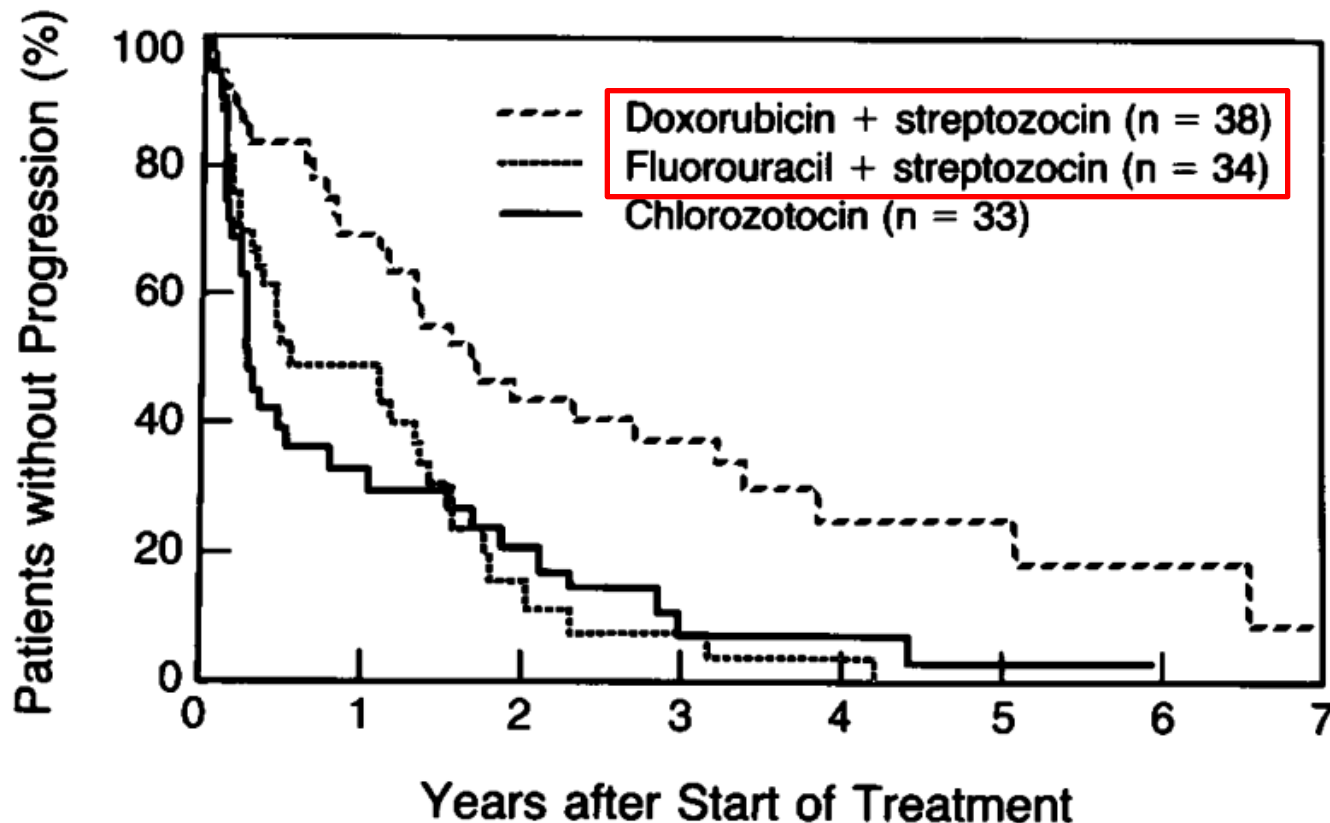
First author and year of the study	Type of study	Experimental drugs	Patients included	PFS (months)	Type of response with experimental drug (%) (RECIST) or RR (%)	OS (months)
Moertel et al. (1980)	Randomized, phase II	Streptozocin alone or streptozocin plus fluorouracil.	84 Advanced pNETs		RR = 63% vs. 36% in STZ alone arm	
Moertel et al. (1992)	Randomized, phase II	Streptozocin plus doxorubicin versus STZ plus 5-FU vs. chlorozotocin alone	105 Advanced pNETs	20 vs. 6.9 vs. 6.9	CR = 33% vs. 12% RR = 69% vs. 45% vs. 30%	26 vs. 17 vs. 18
Kouvaraki et al. (2004)	Retrospective study	Bolus of fluorouracil, doxorubicin and streptozocin	84 Advanced pNETs	36	RR = 39%	18
Ramanathan et al. (2001a,b)	Phase II	Dacarbazine	50 Advanced pancreatic islet cell tumors, having progressive symptoms or evidence of rapidly advancing disease.	Unknown Unknown	Between 8% and 15% in carcinoid tumors and 33% in pancreatic islet cell tumor.	19.3
Strosberg et al. (2011)	Retrospective single-center,	Capecitabine and temozolomide	30 Chemo-naïve pancreatic G1 and G2 NET patients	18	RP = 70%	92 (2 years)
Chan et al. (2012)	Phase II trial	Temozolomide in combination with bevacizumab	15 pNETs	14.3	RR = 33%	
Kulke et al. (2006)	Multicenter, phase 2 trial	Temozolomide in combination with thalidomide	29 Patients with advanced pNETs or carcinoid tumors.	Not reached	RR = 25%	Not reached
Ekeblad et al. (2007a,b)	Prospective study	Temozolomide	36 Patients with advanced NETs	TTP= 7	PR = 14% SD = 53%	Unknown
Koumariou et al. (2012)	Prospective study	Combination treatment with metronomic temozolomide, bevacizumab and long-acting octreotide	15 Advanced NETs	TTP= 36 weeks	CR = 7% PR = 57% SD = 21%	Unknown
Brizzi et al. (2009)	Phase II trial	Continuous 5-fluorouracil infusion plus long acting octreotide	29 Metastatic or locally advanced well-differentiated NETs.	TTP= 22,6	RP = 24.1% SD= 69.0%	Not reached
Turner et al. (2010)	Retrospective study	5-fluorouracil, cisplatin and streptozocin	79 Patients with locally advanced or metastatic NETs	TTP= 9.1	RR = 33%	31.5
Cassier et al. (2009)	Retrospective study	Gemcitabine and oxaliplatin	20 Patients with metastatic well-differentiated NETs after other chemotherapy regimen failure	7	RP = 17%	23.4
Bajetta et al. (2007)	Retrospective study	Capecitabine and oxaliplatin (XELOX)	27 Advanced well-differentiated NETs after SSAs progression	Unknown	RR: 78%	Unknown
Chan et al. (2012)	Prospective study	Temozolomide and Bevacizumab	34 Patients with locally advanced and metastatic pNETs or carcinoid tumors.	11	RR = 15%	33.3
Walter et al. (2010)	Retrospective study	5-fluorouracil, dacarbazine, and epirubicin	39 Patients with advanced well-differentiated NETs	11	RR: 44%	21
Bajetta et al. (1998)	Retrospective study	5-Fluorouracil, dacarbazine, and epirubicin	30 GEP-NETs	Unknown	RR = 30%	Unknown

4. Tratamiento de los P-NET G1-2 avanzados con QUIMIOTERAPIA

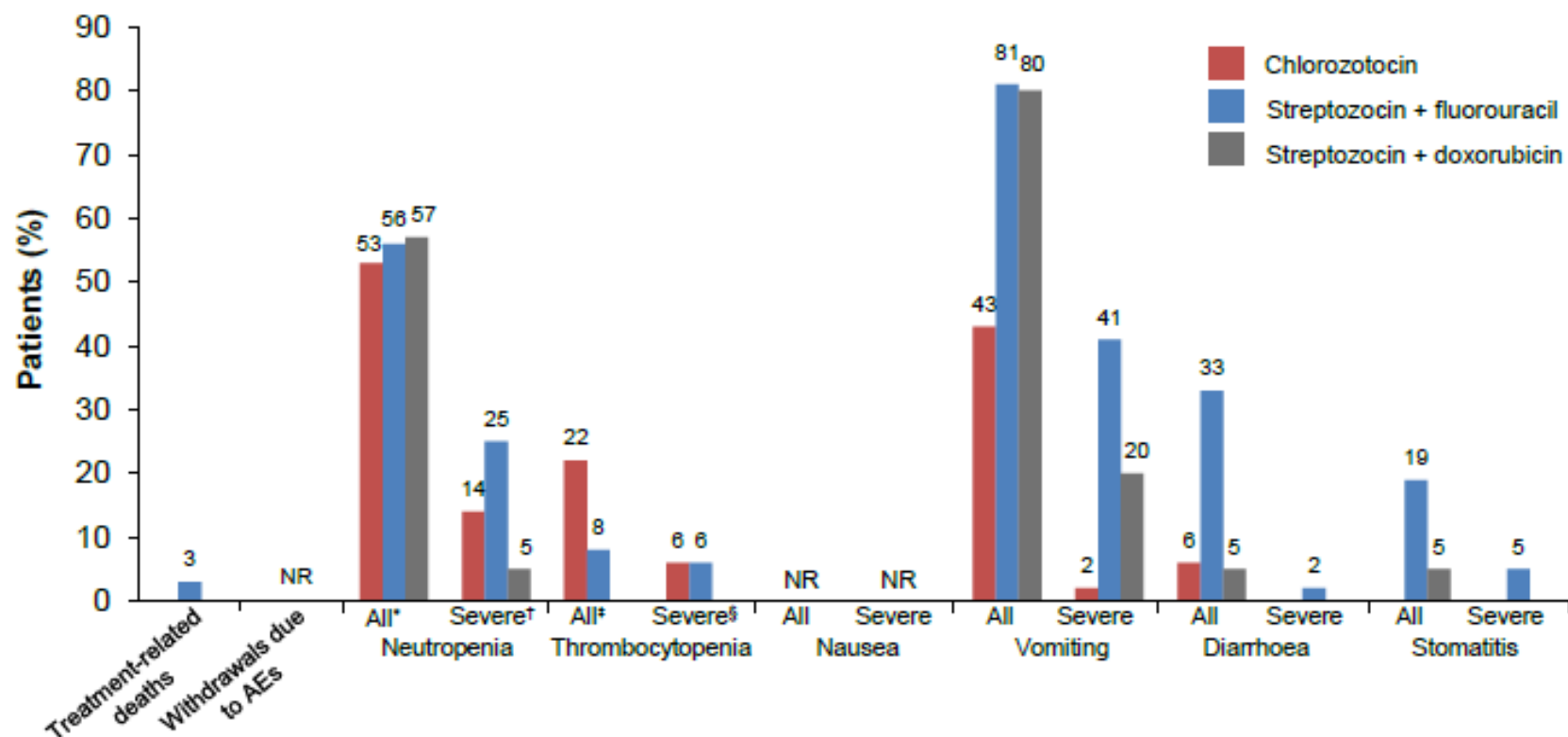
Estreptozocina

Compuestos derivado de la metilnitrosourea. Ejerce efecto citotóxico mediante la metilación del ADN (alquilante).

- Tratamiento del carcinoma metastásico de células de los islotes del páncreas. (**E: extrajero y off label**).
- Tratamiento de tumor carcinoide metastático en adultos (**E: extranjero y off label**).



EVENTOS ADVERSOS ASOCIADOS A QUIMIOTERAPIA



4. Tratamiento de los P-NET G1-2 avanzados con QUIMIOTERAPIA

Regimen alternativo:
TEMOZOLOMIDA+ CAPECITABINA (ORAL)

RETROSPECTIVE STUDY

mPFS: 18 months

RR: 70% (15% monoterapia)

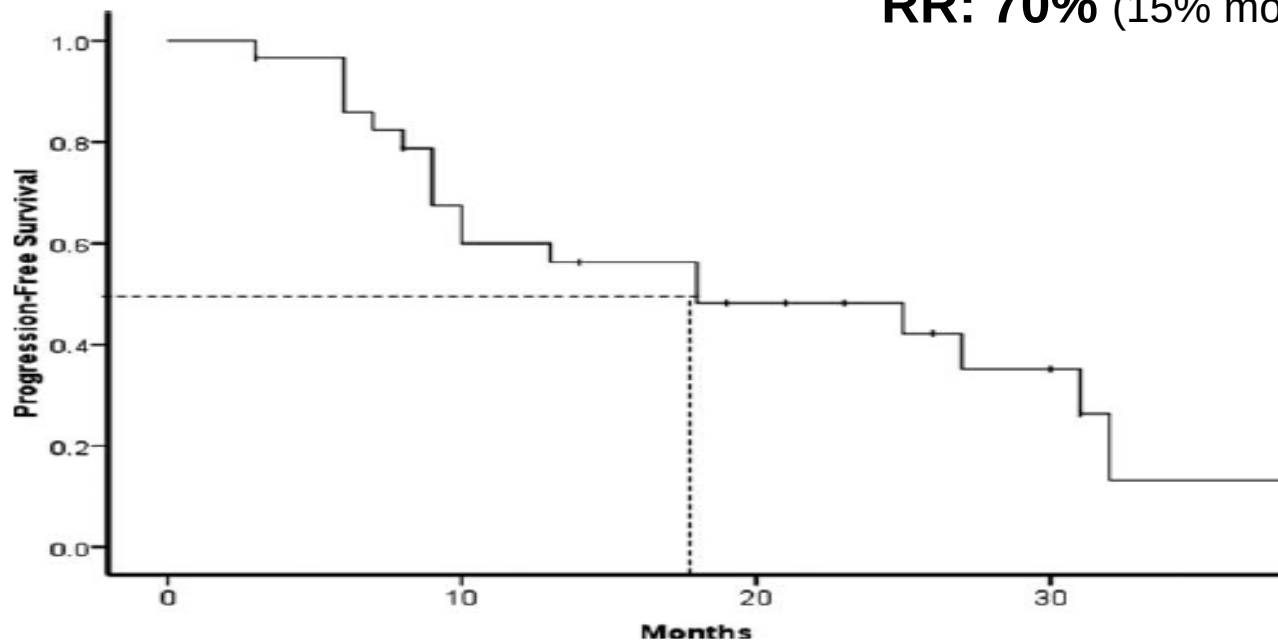


Figure 4. Progression-free survival.

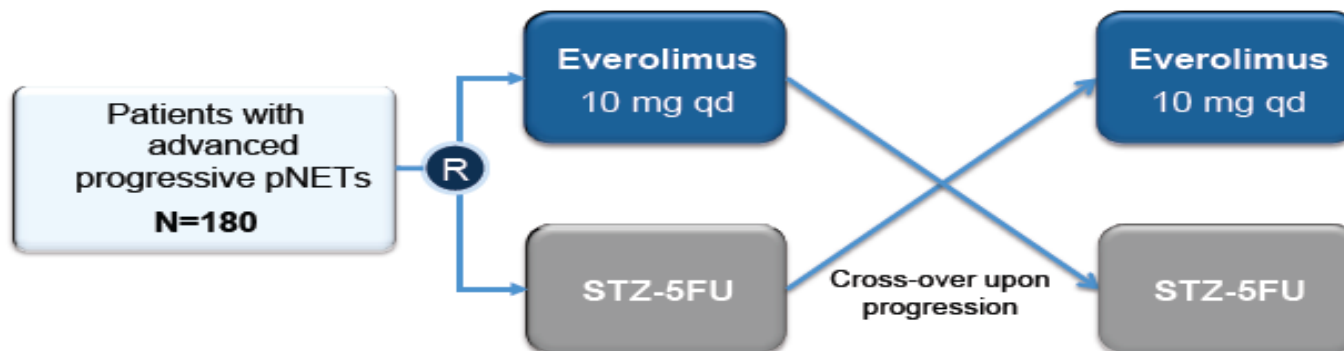
4. Tratamiento de los P-NET G1-2 avanzados con QUIMIOTERAPIA

factors that favour chemotherapy

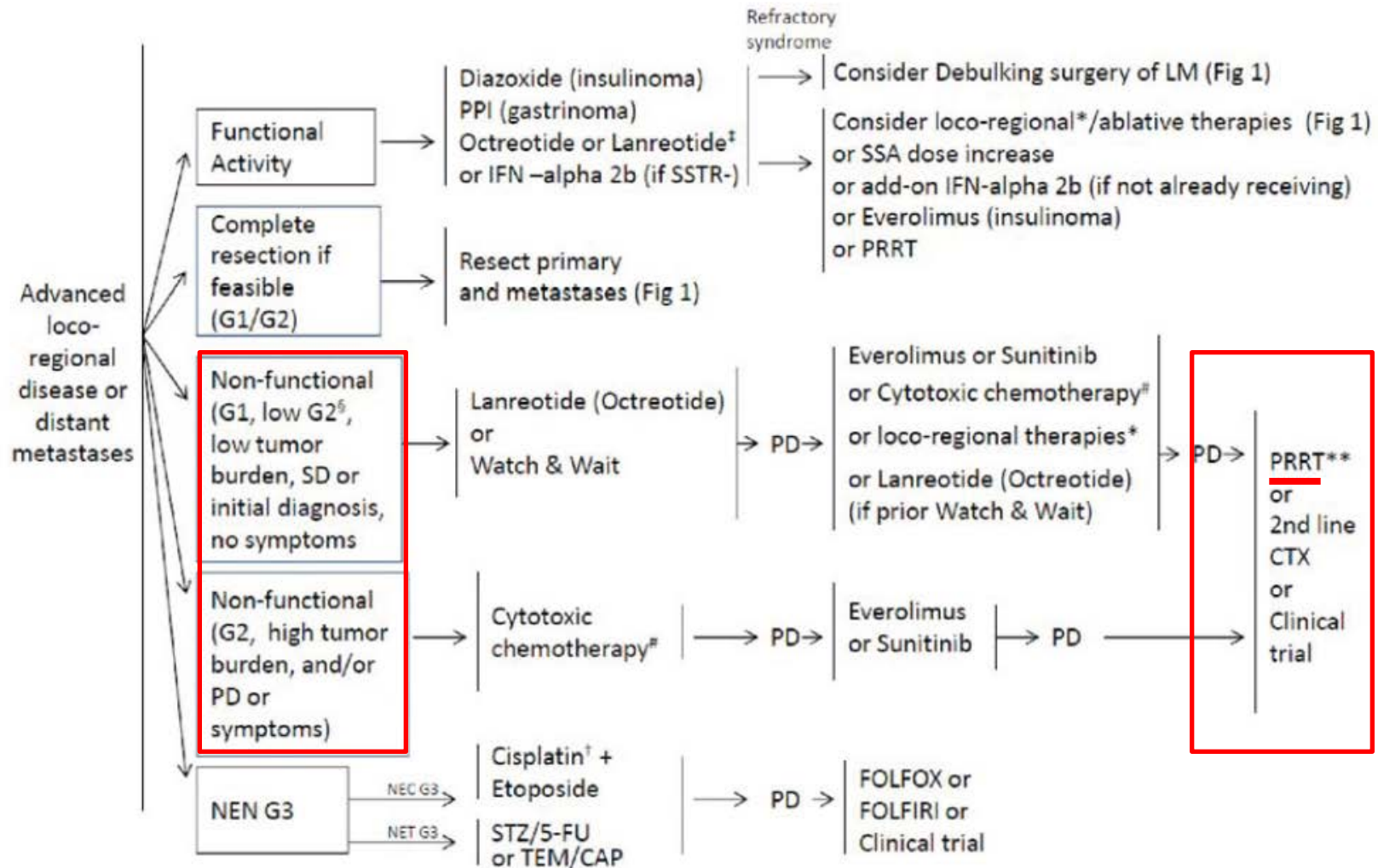
- Bulky disease;
- Symptomatic patient;
- Rapid tumor progression in $\leq 6-12$ months;
- Patients with a possible chance of achieving a response to allow for surgery (neoadjuvant option)

Neuroendocrinology (DOI:10.1159/000443167)

Randomized, open label study comparing efficacy of everolimus followed by chemotherapy with STZ-5FU or the reverse sequence, chemotherapy with STZ-5FU followed by everolimus, in advanced progressive pNETs



5. Tratamiento de los P-NET G1-2 avanzados con RADIONÚCLIDOS



5. Tratamiento de los P-NET G1-2 avanzados con RADIONÚCLIDOS



Infusión



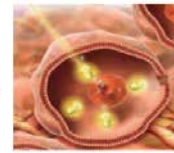
Concentración en el nicho del tumor neuroendocrino (NET)



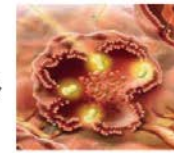
El radiopéptido se une a los receptores de somatostatina del tipo 2 (sstr2) sobreexpresados



El radiopéptido se internaliza en la célula tumoral



El radiopéptido emite radiación en la célula tumoral



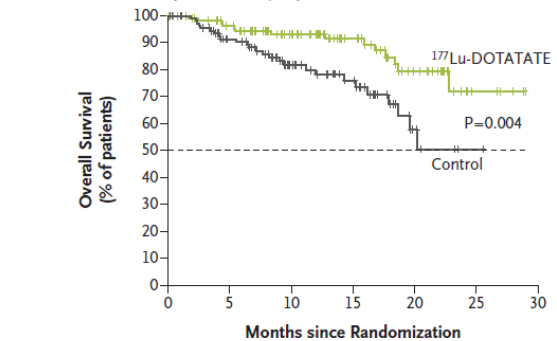
La radiación induce ruptura de ADN de la célula tumoral



Denominación del estudio	ERASMUS	NETTER-1
Tipo	Fase I/II	Fase III
Localización	Rotterdam (Holanda)	Multicéntrico (UE, EE. UU.)
Número de pacientes	615	230
Tipo de paciente	TNE gastroenteropancreático y bronquial	TNE de intestino medio inoperable, metastásico
Estudio con comparador	No	Sí, brazo control con tratamiento con análogos de somatostatina a altas dosis

Consenso de manejo de PRRT en el tratamiento de TNEs

B Overall Survival (Interim Analysis)

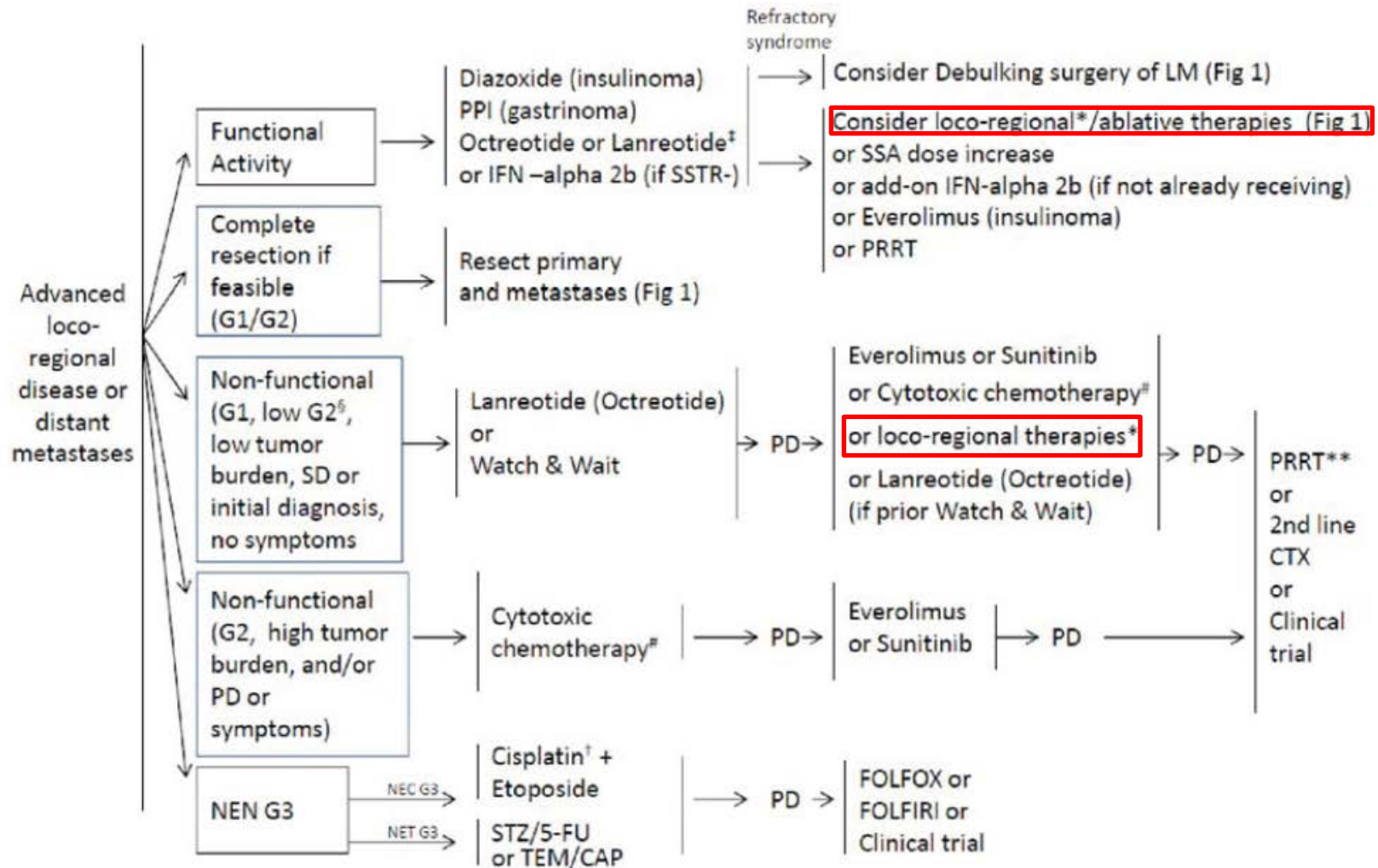


No. at Risk	116	108	96	79	64	47	31	21	8	3	0
¹⁷⁷ Lu-DOTATATE											
Control group	113	103	83	64	41	32	17	5	1	0	0

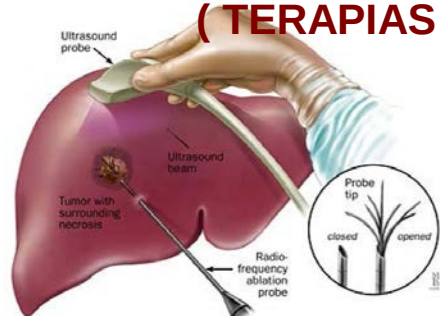
N Engl J Med 2017;376:125-35.

Minimal consensus statement: PRRT is recommended after failure of medical therapy. Data from the prospective trial in midgut NET support its role as a second-line therapy option in intestinal NET if the general requirements for PRRT are fulfilled and as an alternative option to everolimus. The optimal sequencing with targeted drugs and/or chemotherapy needs to be defined in pancreatic NET when data from prospective randomized trials in pancreatic NET become available.

6. Tratamiento de los P-NET G1-2 avanzados con TERAPIAS LOCOREGIONALES



6. Tratamiento de los P-NET G1-2 avanzados con TERAPIAS LOCOREGIONALES (TERAPIAS ABLATIVAS: RADIOFRECUENCIA /crioterapia/microondas)



“No hay Ensayos Randomizados...”

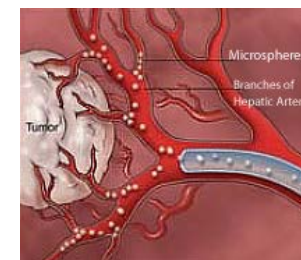
Table. Demographics and Outcomes following RF Ablation for NETs (14,15,29–34)

Study, Country of Origin	No. of Pts.	Mean Age (y)	Sex (M/F)	NET Only	Symptoms (%)	Concomitant Resection	Technique	Follow-up (mo)	Morbidity (%)	Procedural Mortality	5-y Survival (%)	Survival after RF (mo)	Local Recurrence (per Lesion)
Akyildiz et al (29), U.S.	89	56	54/35	Yes	44 (n = 39)	No	119 Laparoscopic	30	6.0	1	5-y OS 57	DFS 15, OS 72	7.90%
Gillams et al (30), U.K.	25	56	13/12	Yes	56 (n = 14)	Yes (1/25)	65 Percutaneous, 1 open	21	12	1	NR	OS 29	NR
Amersi et al (31), U.S.	25	NR	NR	No	NR	No	NR	NR	NR	NR	NR	OS 48.3	20% of > 3 cm
Henn et al (34), U.S.	7	56	1/6	Yes	100 (n = 7)	No	7 Percutaneous	22.9*	57	0	NR	NR	NR
Wessels and Schell (32), U.S.	3	39.6	1/2	Yes	100 (n = 3)	No	2 Open, 1 laparoscopic	6	NR	0	NR	NR	NR
Elias et al (14), France	16	48	7/9	Yes	31 (n = 5)	Yes (13/16)	197 Open	27	62.5	0	3-y OS 84	NR	NR
Elvin et al (15), Sweden	42	61.2	19/23	Yes	NR	Yes (23/42)	84 Percutaneous, 25 open	NR	NR	NR	NR	NR	NR
Taner et al (33), U.S.	94	53.7	41/53	Yes	62 (n = 59)	Yes (all 94)	94 Open	58*	1.06	0	5-y OS 80, SFS 16	SFS 24	4.25%

Yang TX, et al. *Surgical Oncology* 2012

6. Tratamiento de los P-NET G1-2 avanzados con TERAPIAS LOCOREGIONALES (EMBOLIZACIÓN/ QUIMIOEMBOLIZACIÓN/radioembolización)

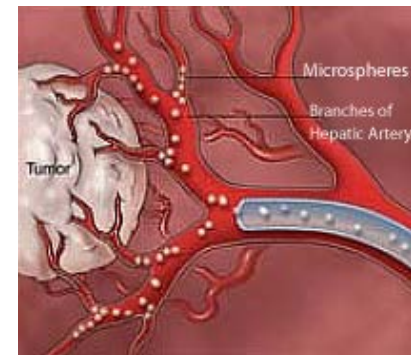
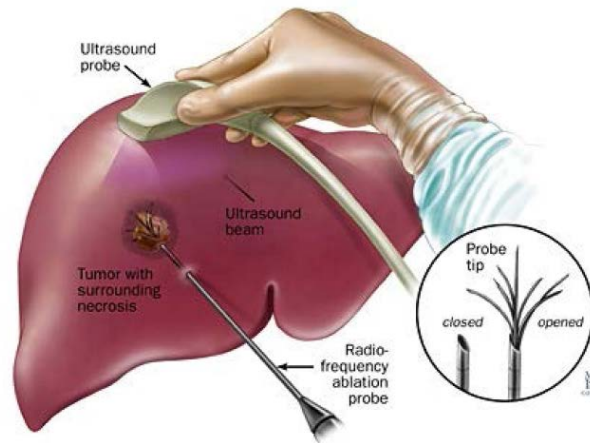
“No hay Ensayos Randomizados...”



Study	Patients, n	Device used	Toxicity	Radiological response (RECIST 1.0)	Survival times and rates
Dong & Carr ⁷	123	TACE	Abdominal pain (44%), diarrhoea (30%), weight loss (22%)	62%	Mean: 3.3 years 3-, 5- and 10-year survival: 59%, 36% and 20%, respectively
de Baere <i>et al.</i> ⁶	20	TACE with doxorubicin eluting beads	Nausea (61%), fever (36%)	80%	Not reported
Vogl <i>et al.</i> ¹⁶	48	TACE with mitomycin C	Nausea and vomiting (27.8%), abdominal pain (11.1%)	11.1%	Median: 38.7 months 5 years: 11.11%
		TACE with mitomycin C + gemcitabine	Nausea and vomiting (16.7%), abdominal pain (10%)	23.3%	Median: 57.1 months 5 years: 46.67%
Loewe <i>et al.</i> ¹¹	23	Bland embolization	Not reported	73%	Median: 69 months 1- and 5-year survival: 95.7% and 65.4%, respectively
Eriksson <i>et al.</i> ⁸	41	Bland embolization	Post-embolization syndrome (all), nausea (33%), fever (n = 7), median hospitalization: 12 days	50%	Median: 80 months 5 years: 60%
Pitt <i>et al.</i> ¹³	100	Bland (n = 51) versus TACE (n = 49)	Bland: 7/51, (3 liver abscesses, 1 groin hematoma, 2 ileus, 1 hypotension) TACE: none	N/A	Median from diagnosis: TACE, 50.1 months; bland, 39.1 months 1-, 2- and 5-year survival: TACE, 69%, 52%, 19%, respectively; bland, 19%, 70%, 13%, respectively
Ruutinen <i>et al.</i> ¹⁵	67	Bland (n = 23) versus TACE (n = 44)	Grade 3 or worse toxicity in 25% of TACE and 22% of bland patients TACE (≥Grade 3): pain (3); nausea (1); GET/ALP (4); AST (1), and infection (1) Bland (≥Grade 3): GET/ALP (3); AST (1), and cardiac (1)	TACE: 22% Bland: 38%	1-, 3- and 5-year survival: TACE, 86%, 67%, 50%, respectively; bland, 68%, 46%, 33%, respectively
Gupta <i>et al.</i> ¹⁰	49	TACE (n = 27) versus bland (n = 42)	Serious adverse events in 19 patients (8.5%), hepatorenal syndrome (7), sepsis (6), transient myelosuppression (1), anasarca (1), cortical blindness (1), necrotizing cholecystitis (1), hepatic abscess (2) Overall complications: TACE, 20%; bland, 12%	TACE: 50% Bland: 25%	Median survival for carcinoid tumours: TACE, 33.8 months; bland, 33.2 months; islet tumours: TACE, 31.5 months; bland, 18.2 months
Maire <i>et al.</i> ¹²	26	TACE (n = 12) versus bland (n = 14)	TACE: post-embolization syndrome (10), carcinoid crisis (2), acute liver failure (1), neutropoenia (2) Bland: post-embolization syndrome (10), carcinoid crisis (0), acute liver failure (2), neutropoenia (0)	TACE: 100% Bland: 92%	2-year survival: TACE, 80%; bland, 100% Median PFS: TACE, 19.2 months; bland, 23.6 months

6. Tratamiento de los P-NET G1-2 avanzados con TERAPIAS LOCOREGIONALES

Minimal consensus statement: Surgery with curative intent and/or loco-regional or ablative therapies should be considered at initial diagnosis and in the course of the disease as an alternative approach to systemic therapies. In patients with functioning NET, all liver directed therapies require prior initiation of SSA therapy (or other specific symptom controlling measures). Debulking surgery is indicated in selected patients with functioning NET with predominant liver disease for improved syndrome control even if liver tumor burden can be reduced by less than 90%. Liver transplantation is an option in very highly selected patients, preferably in young patients with functional syndromes demonstrating early resistance to medical therapy.



All tumors will eventually become refractory several months after starting therapy



Tumor “escape” mechanisms are not well understood but may include:

- *The internalization and suppression of SSTR2*
- *Mutations or truncated SSTRs*
- *Activation of parallel pathways (IGF-1R, PI3K/Akt/mTOR, etc...)*
- *... or presumably other unknown mechanisms*

INTENTANDO RESPONDER A LAS PREGUNTAS:
¿ALTERNATIVAS TERAPEUTICAS?
¿¿SECUENCIA DE TRATAMIENTO ??



C. CASO PARA INTENTAR RESPONDER A LAS PREGUNTAS:
¿ALTERNATIVAS TERAPEUTICAS? ¿SECUENCIA DE TRATAMIENTO ??

- ❖ **Female 52 y.o.**
- ❖ **Performance status = 0 (ECOG)**
- ❖ **Asymptomatic**
- ❖ **No comorbidity**
- ❖ **No familial history**



Routine abdominal US → liver focal lesions

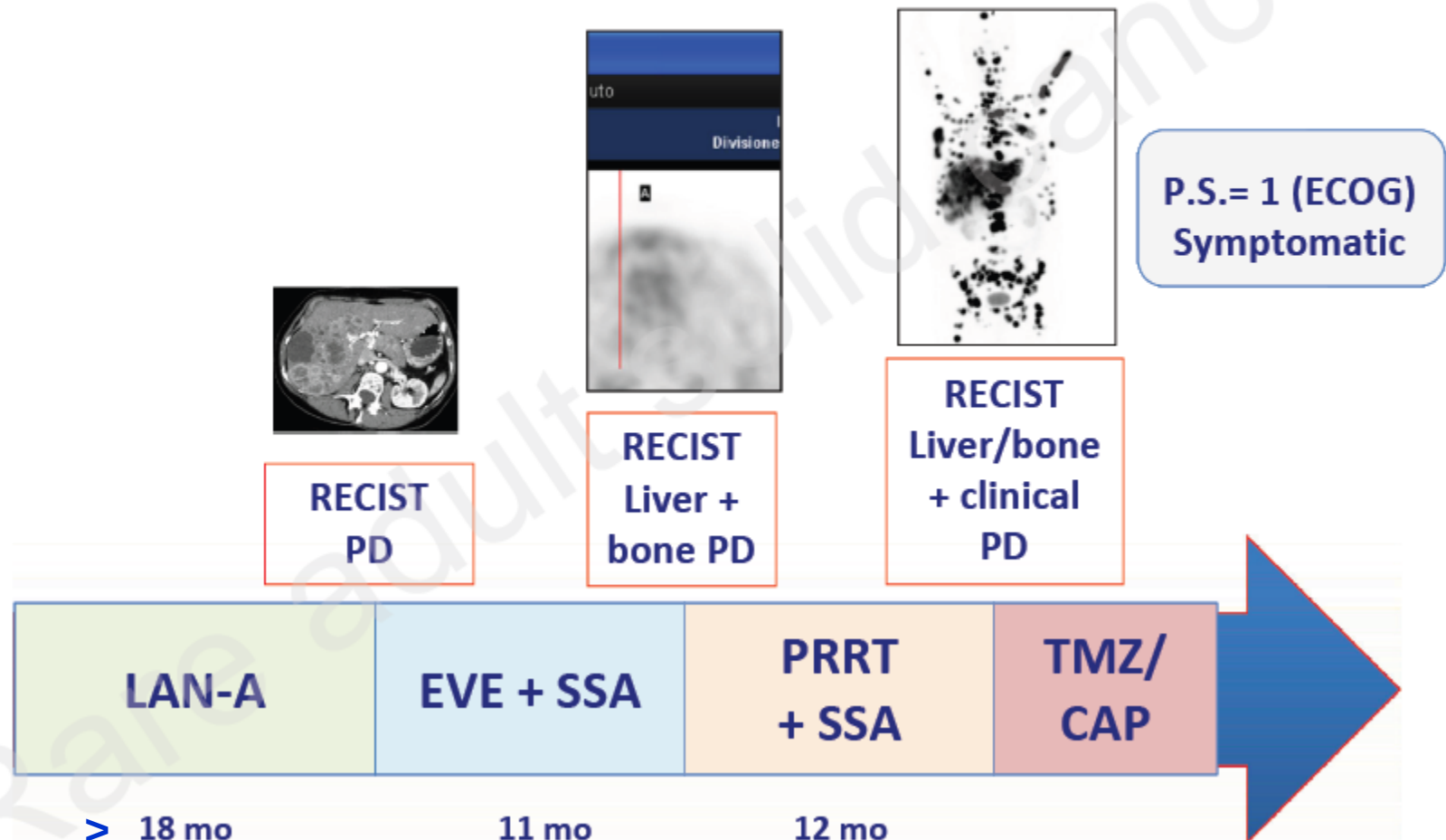
US-guided liver biopsy:
"well-diff. NET"
Ki-67 = 5%

Abdominal CT-scan

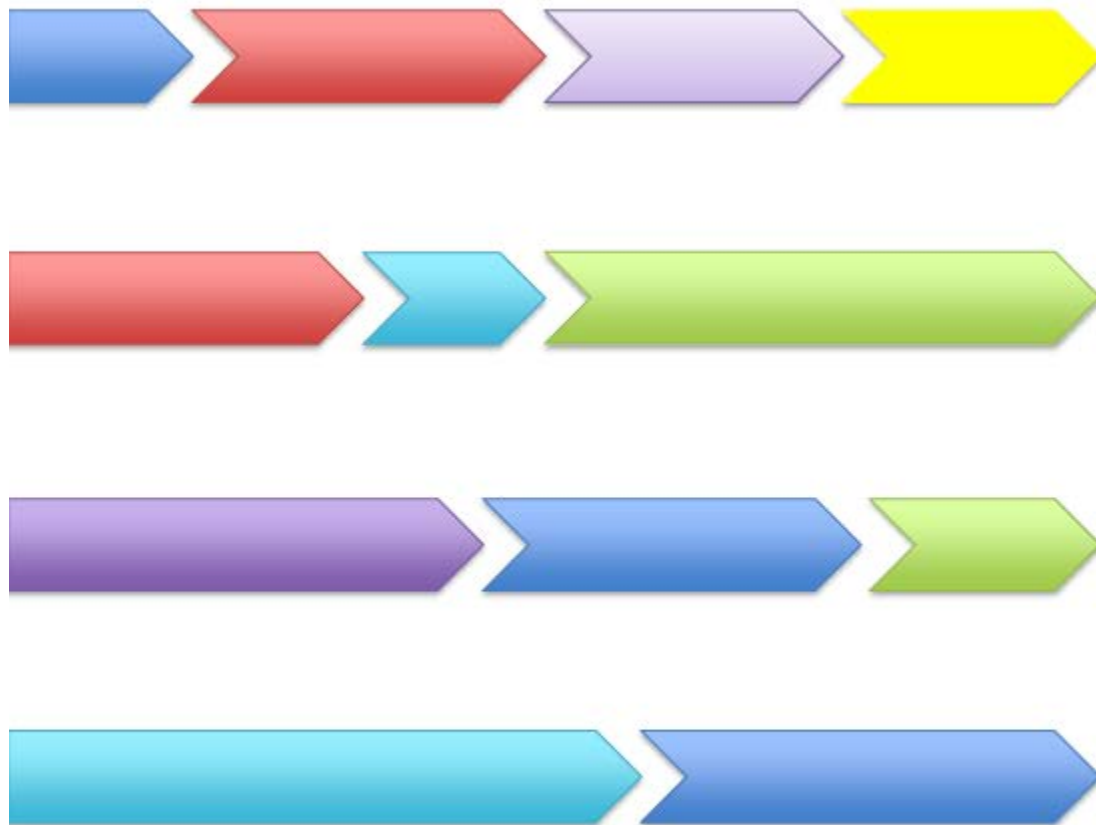


Primary tumor: pancreatic
body/tail

Non-functioning G2 pNET (body/tail), SSTR-2 ++, with synchronous liver metastases: clinical history



IDENTIFICAR LA MEJOR SECUENCIA DE TRATAMIENTO PARA CADA PACIENTE



↑ de Sobrevida sin Progresar en 1ª Línea + 2ª Línea + 3ª Línea +..... = ↑Sobrevida Global

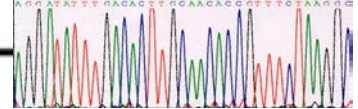


ISSN 0025-7757 (Print); 2012; 140; 1; 20-91



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Artículo especial

Abordaje multidisciplinar en el diagnóstico y tratamiento de pacientes con tumores endocrinos

Multidisciplinary approach in the diagnosis and therapy of patients with endocrine tumors

Juan J. Díez^{a,b,*}, Enrique Grande^c, Teresa Alonso^c y Pedro Iglesias^a

^a Servicio de Endocrinología, Hospital Universitario Ramón y Cajal, Madrid, España

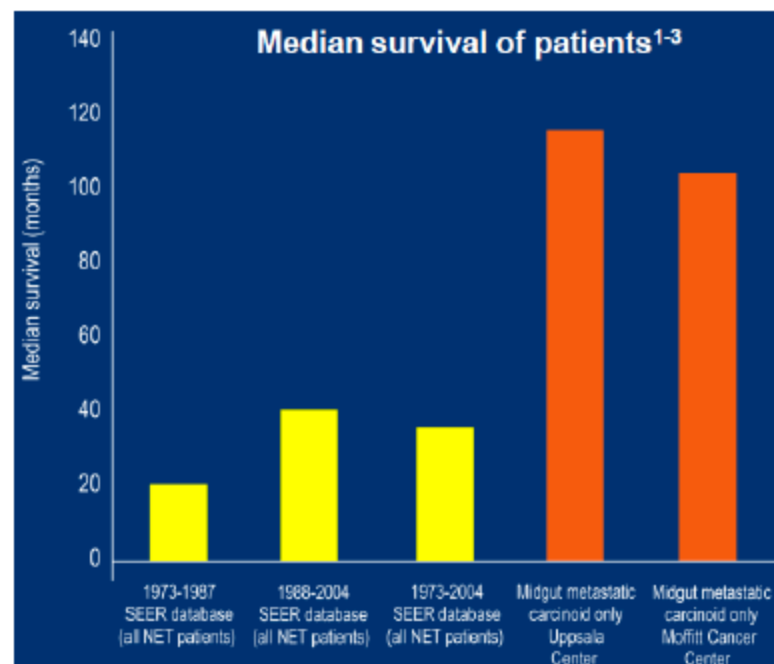
^b Departamento de Medicina, Universidad de Alcalá de Henares, Alcalá de Henares, Madrid, España

^c Servicio de Oncología Médica, Hospital Universitario Ramón y Cajal, Madrid, España



A four-bed room in the new hospital

La mediana de Supervivencia de los pacientes con TNEs metastásicos tratados en “centros de excelencia” es 3 veces superior que los datos arrojados en la base SEER



Yao JC, et al. J Clin Oncol. 2008;26:3063-3072
Öberg K. Oral presentations at ENETS, CCNETS, and NANETS, 2008
Strosberg J. Poster presented at ASCO GI 2008.



MENSAJES PARA CASA:



- **Realizar un diagnóstico clínico y patológico adecuado:** clasificación (grado/diferenciación) , estadificación, factores pronosticos, historia familiar, ¿ funcionante?¿ no funcionante? ¿ tumor localizado, localmente avanzado, metastático?
- **Manejo multidisciplinar.**
- Los nuevos tratamientos han modificado la historia natural de la enfermedad por lo que se debe Identificar “ a priori” la mejor **secuencia de tratamientos para cada paciente para aumentar la supervivencia global** teniendo en cuenta toxicidades secundarias e impacto en calidad de vida.
- Participar en **ensayos clínicos** siempre que sea posible

If you want to go fast, go alone.
If you want to go far,

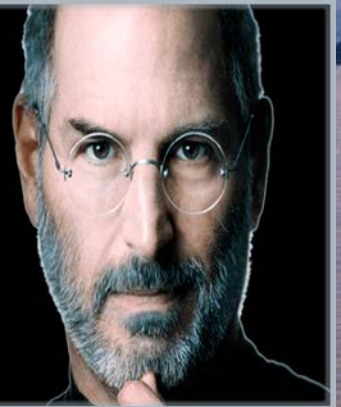
GO TOGETHER.

African Proverb

"Los **grandes éxitos** no son
hechas por **una persona**.
Son hechas por **un equipo**
de personas"

Steve Jobs

Co-fundador de Apple Inc.



SYMPHONY OF LOVE
Photo by Nisha Gill