

Clinical subgroups: focus on hormone liberation

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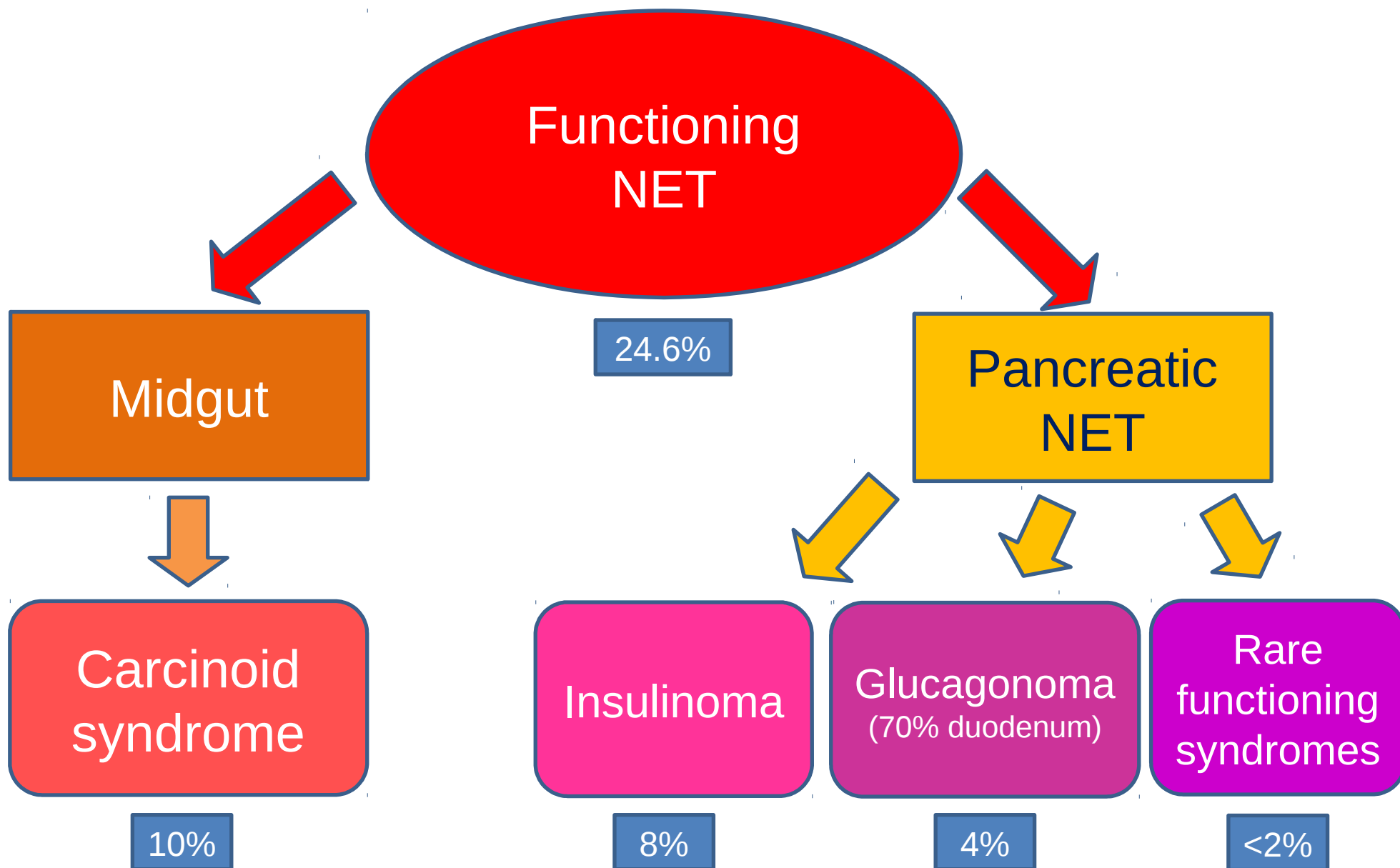
Two different diseases

Functioning
NET

Non
Functioning
NET

¿DIFFERENT BIOLOGY?

¿DIFFERENT PROGNOSIS?



Diarrea

Flushing

Carcinoid
Syndrome

Wheezing

Mesenteric
fibrosis

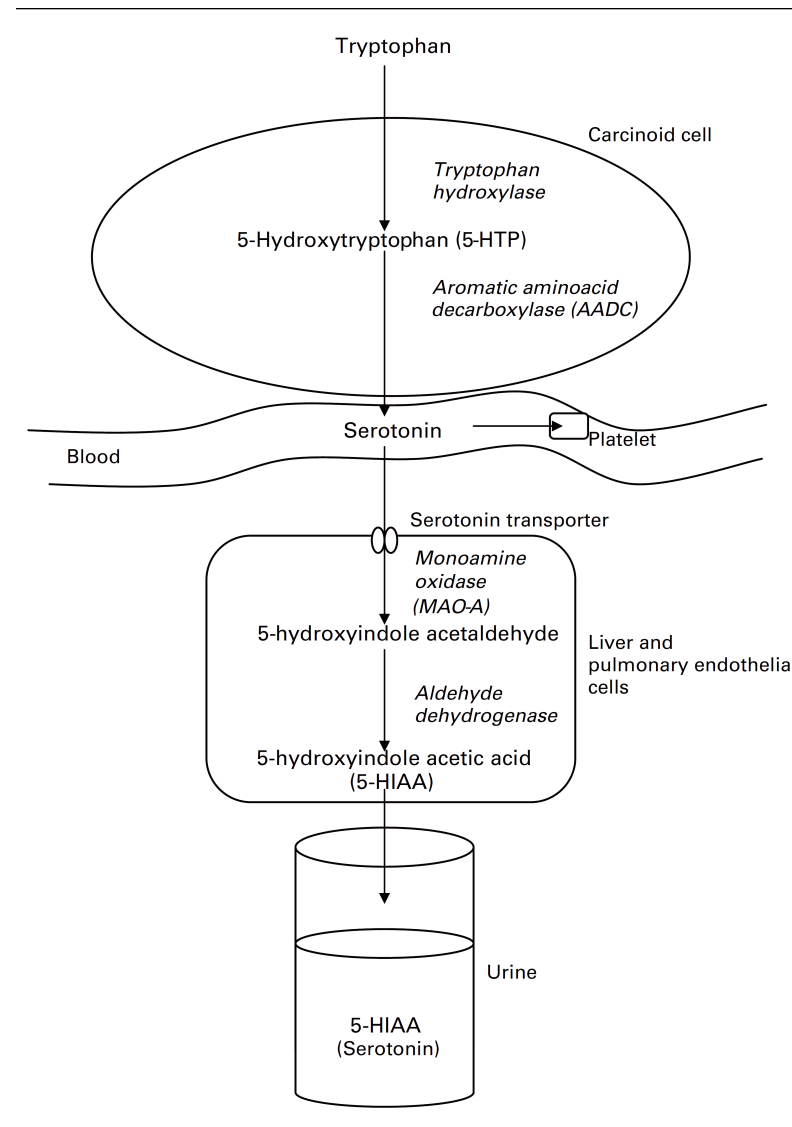
25-50%

Carcinoid
Heart Disease

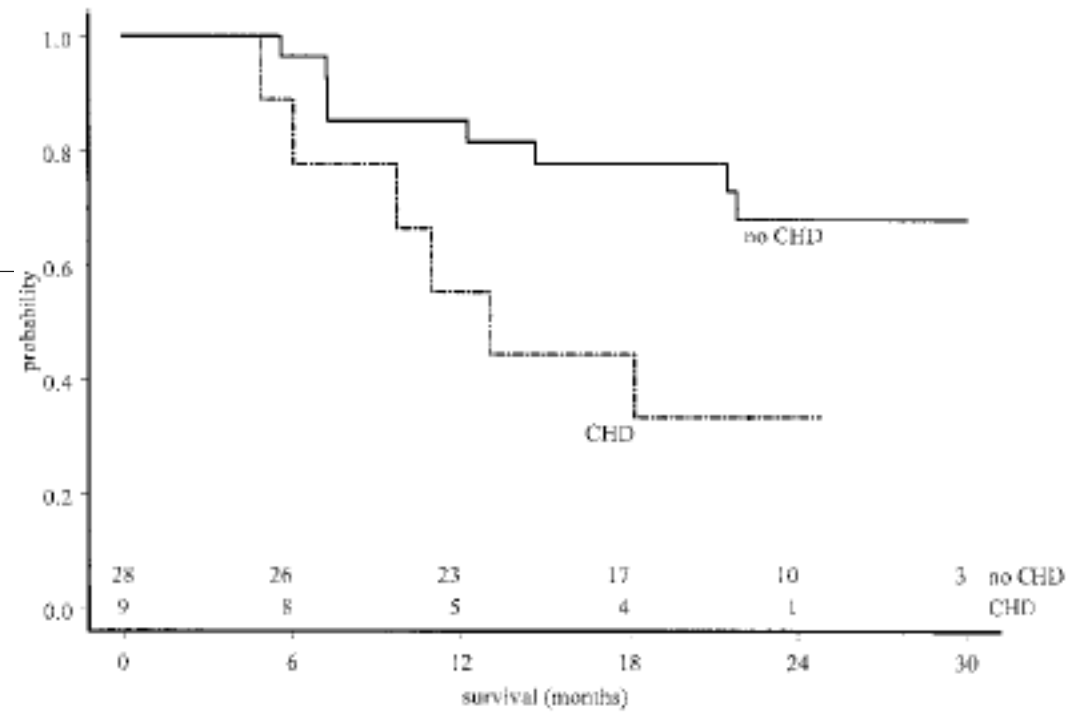
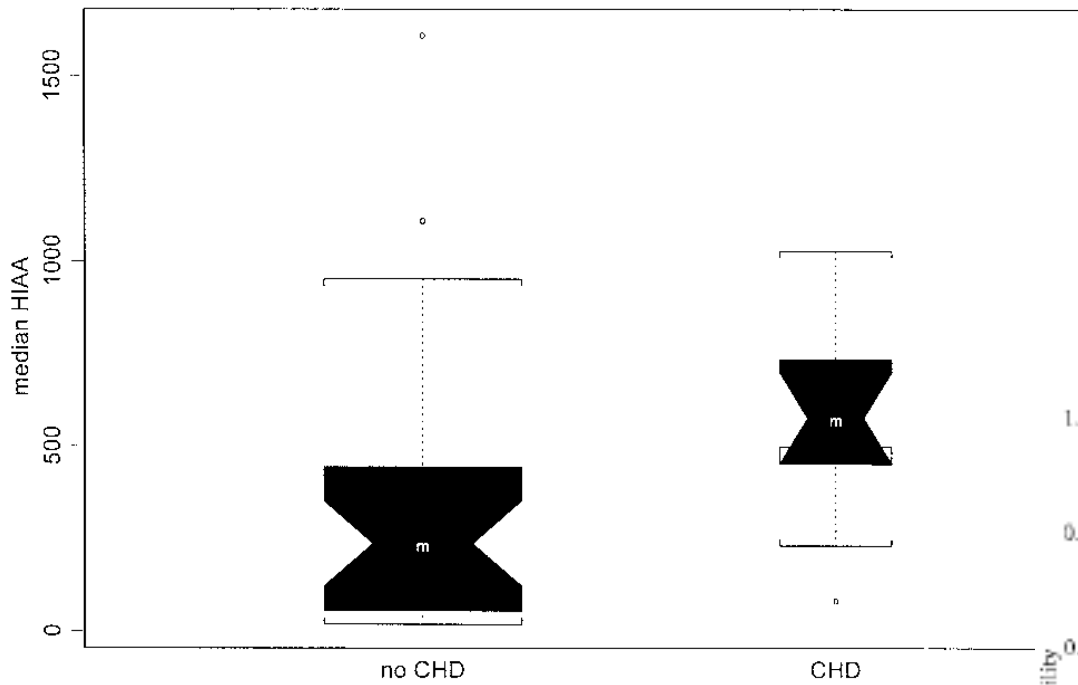
Insulinoma

Hypoglycemia

Carcinoid Syndrome



CARCINOID HEART DISEASE



CARCINOID HEART DISEASE

- 80 NETs with carcinoid syndrome
- Annual echocardiogram
 - Right CHD: 33% (26) // Left CHD: 8% (6)
 - CHD → 5HIAA = 384 ± 431 mg/24h
 - no CHD → 5HIAA = 43 ± 25 mg/24h
- After a median follow up of 26 months...
 - Right CHD: 53% (42) // Left CHD: 21% (17)
 - 20% new diagnosis
 - 20% progression of CHD
- >3 years with CS + \uparrow 5HIAA = CHD

CARCINOID HEART DISEASE

- What is the right time for valve replacement?
- Symptoms or right ventricular dysfunction
- Perioperative Mortality \approx 10-20%

GOALS FOR THERAPY

Tumor response

Control symptoms

Biochemical response

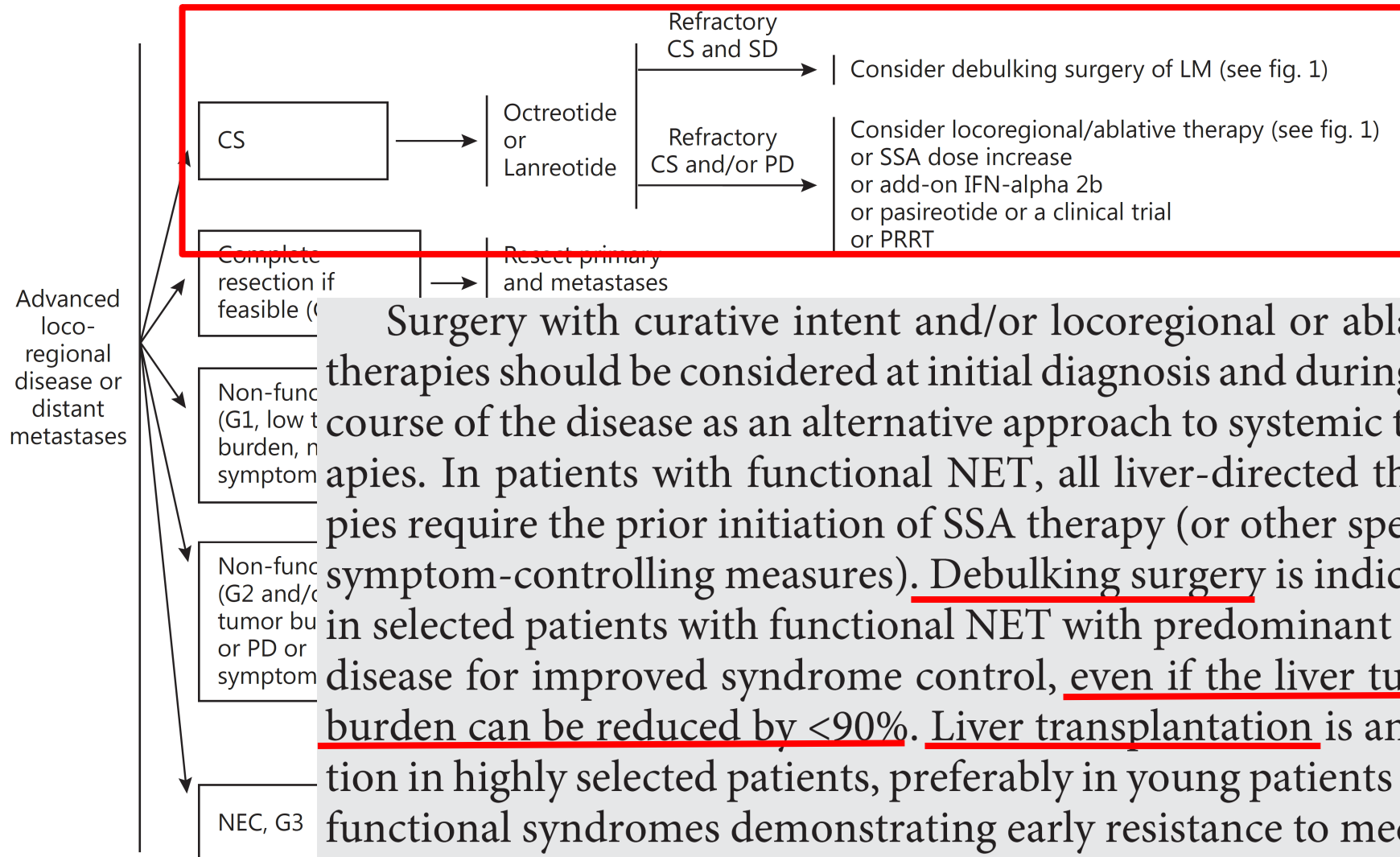
Progression
criteria

Best
antisecretory
treatment

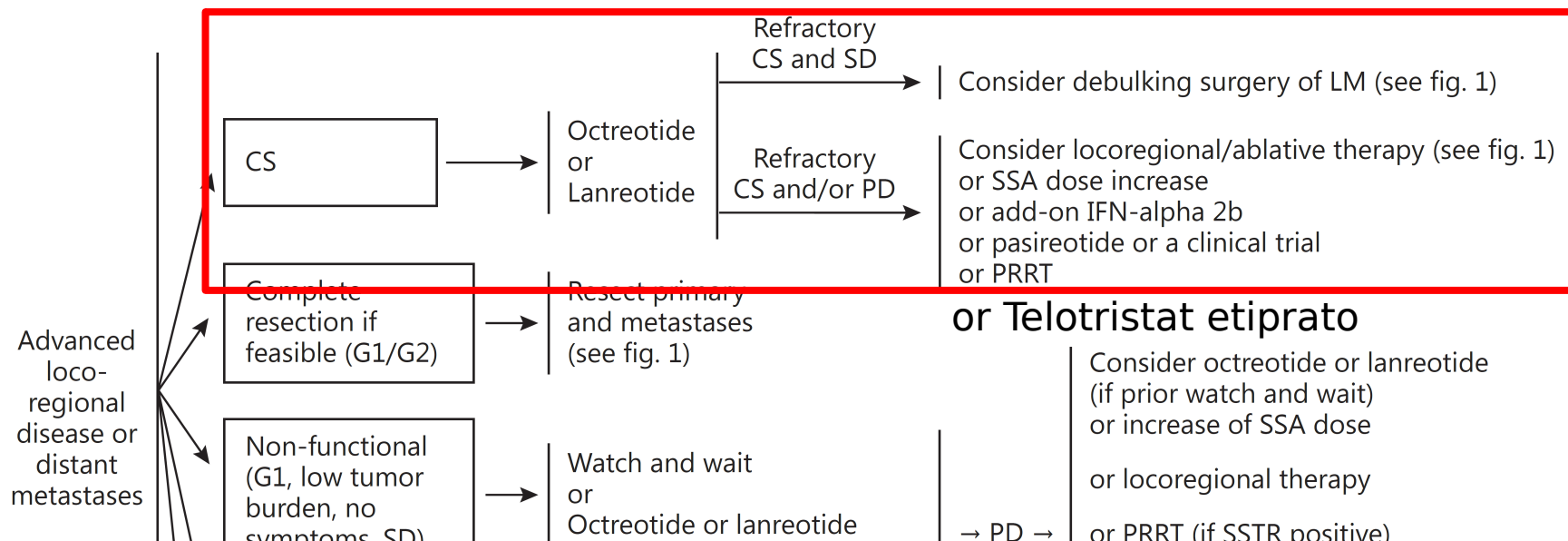


Best
antiproliferatory
treatment

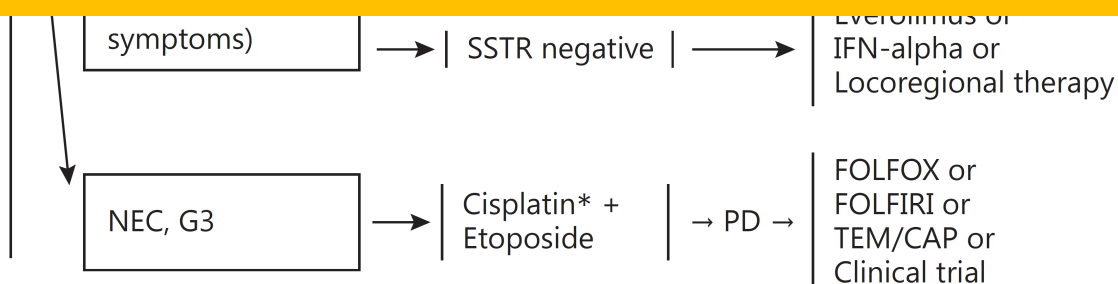
ENETS GUIDELINES: MIDGUT NEN



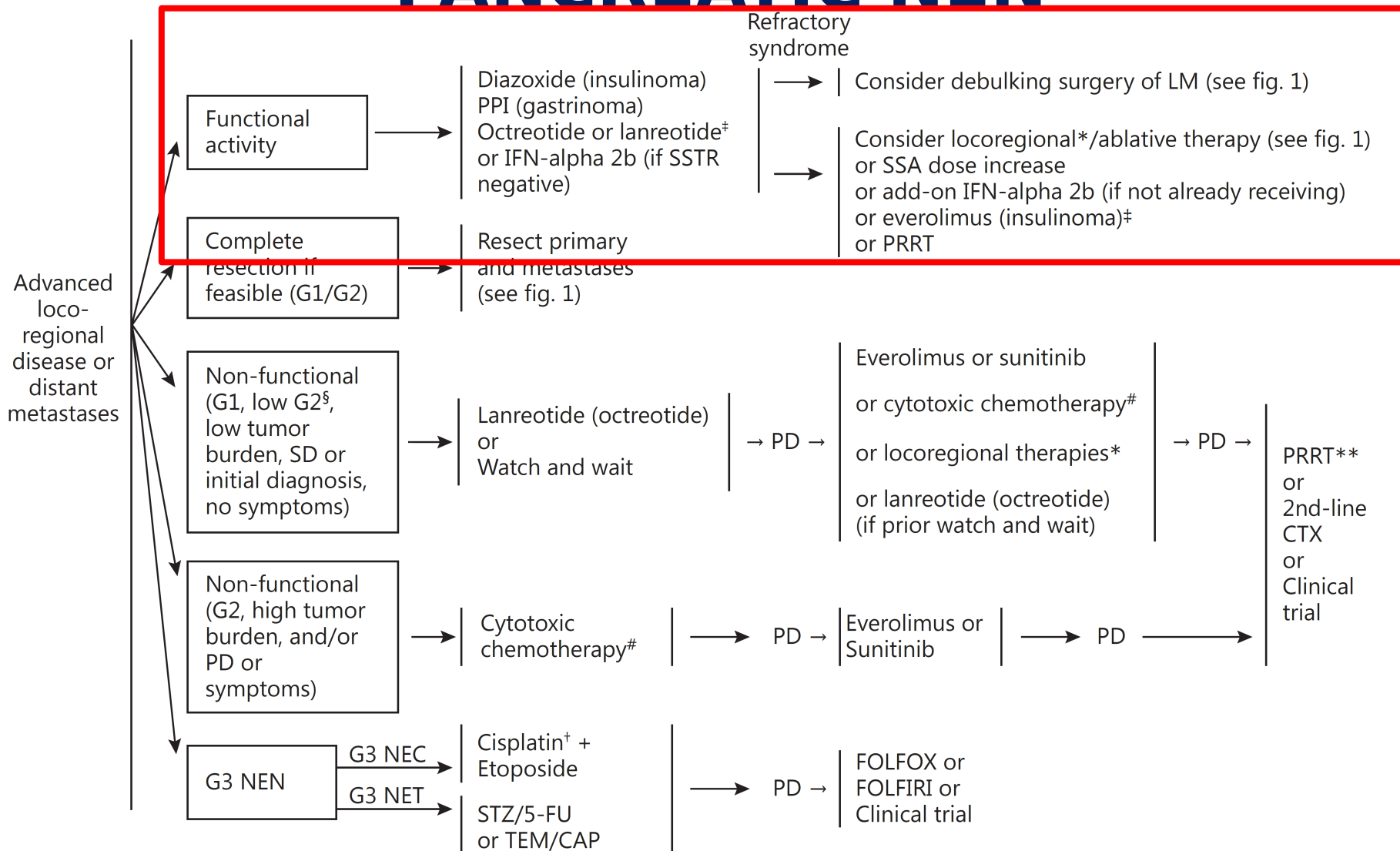
ENETS GUIDELINES: MIDGUT NEN



¿ACTIVE TREATMENT TO AVOID THE ONSET OF CHD?



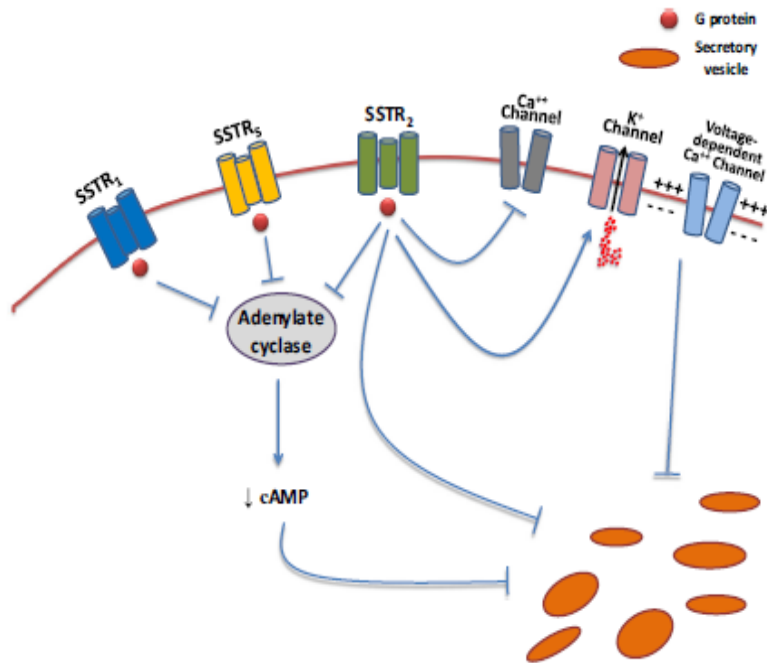
ENETS GUIDELINES: PANCREATIC NEN



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 pancreas midgut		atypical carcinoid and/or SSTR negative insulinoma or contraindication for CTX if SSTR negative
Sunitinib	+/-	G1/G2	pancreas		contraindication for CTX
PRRT	+/-	G1/G2	midgut	+ (required)	extended disease; extrahepatic disease, e.g. bone metastasis
Cisplatin ^S / etoposide	+/-	G3	any		all poorly differentiated NEC

SSAs: Antisecretory activity

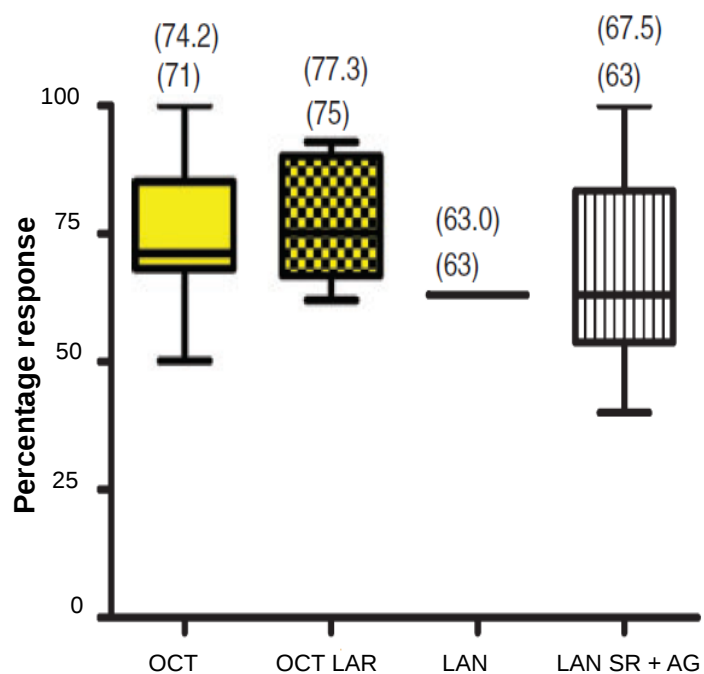


Cives M, et al. *Drugs* 2015; 75:847-58

STUDY (year)	N	Treatment	Symptomatic response	Biochemical response
Kvols (1986)1	25	Octreotide sc	88%	72%
Di Bartolomeo (1996)2	16	Octreotide sc	73%	77%
Rubin (1999)3	93	Octreotide sc Octreotide LAR	58% 66%	NR NR
Tomassetti (1998)4	10	Lanreotide PR	90%	33%
Wymenga (1999)5	55	Lanreotide PR	38%	27%
O'Toole (2000)6	33	Octreotide sc Lanreotide PR	68% 54%	50% 58%
Ducreux (2000)7	38	Lanreotide PR	NR	41%
Khan (2011)8	69	Lanreotide autogel	94%	NR
Wolin (2015)9	110	Octreotide LAR Pasireotide LAR	46.2% 62.7%	NR

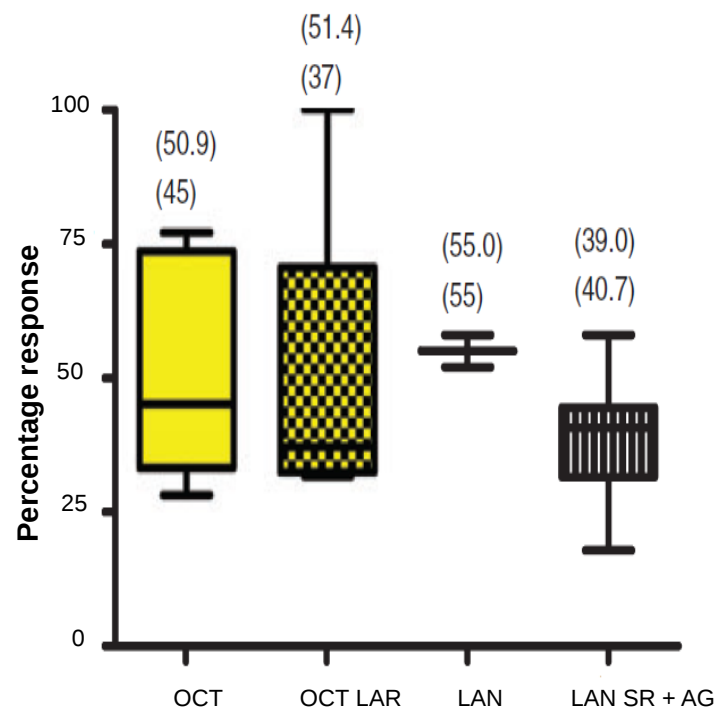
1. Kvols LK, et al. *N Engl J Med* 1986;315:663-6.
2. Di Bartolomeo M, et al. *Cancer* 1996;77:402-408.
3. Rubin J, et al. *J Clin Oncol* 1999;17:600-6064.
7. Tomassetti P, et al. *Am J Gastroenterol* 1998; 93:1468-71
9. Wymenga AN, et al. *J Clin Oncol* 1999;17:1111-16.
6. O'Toole D, et al. *Cancer* 2000;88:770-776;
7. Ducreux M, et al. *Am J Gastroenterol* 2000;95:3276-3281.
13. Khan M, et al. *Aliment Pharmacol Ther* 2011; 34:235-42.
14. Wolin E, et al. *Drug Des Develop Ther* 2015; 9: 5075-86.

Symptomatic Response



Studies	n=11	n=7	n=1	n=7
Patients	n=261	n=122	n=30	n=185

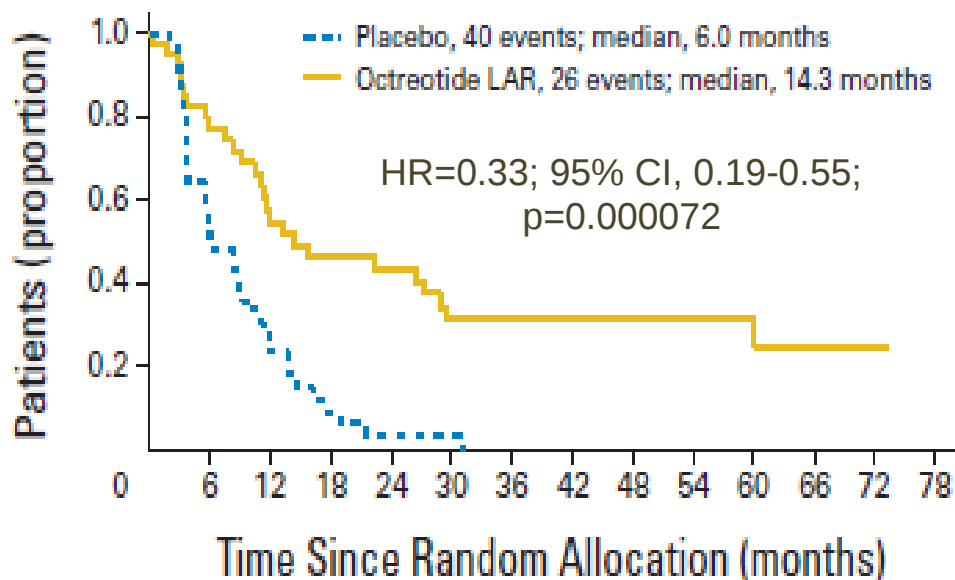
Biochemical Response (PR + CR)



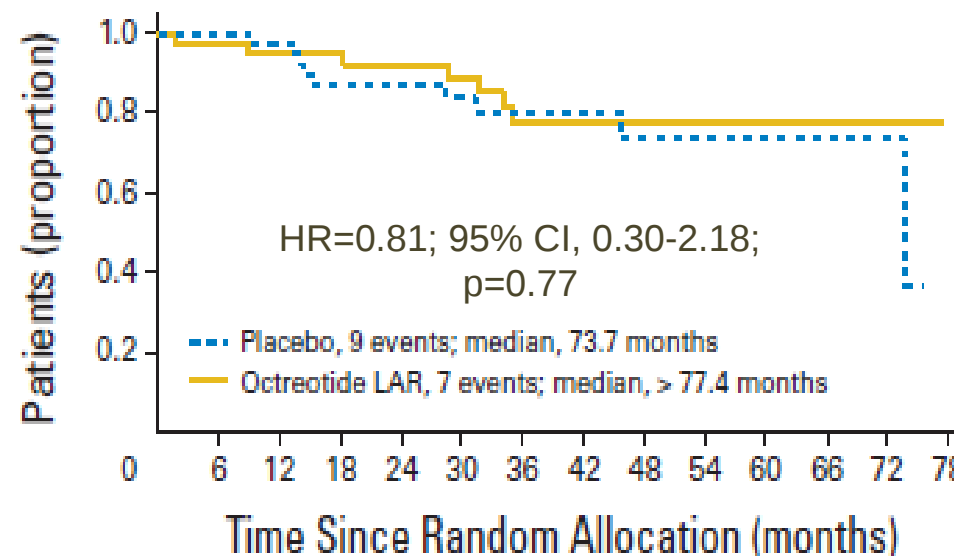
Studies	n=10	n=4	n=2	n=9
Patients	n=315	n=73	n=49	n=333

SSAs: Antiproliferatory activity

Time to tumour progression

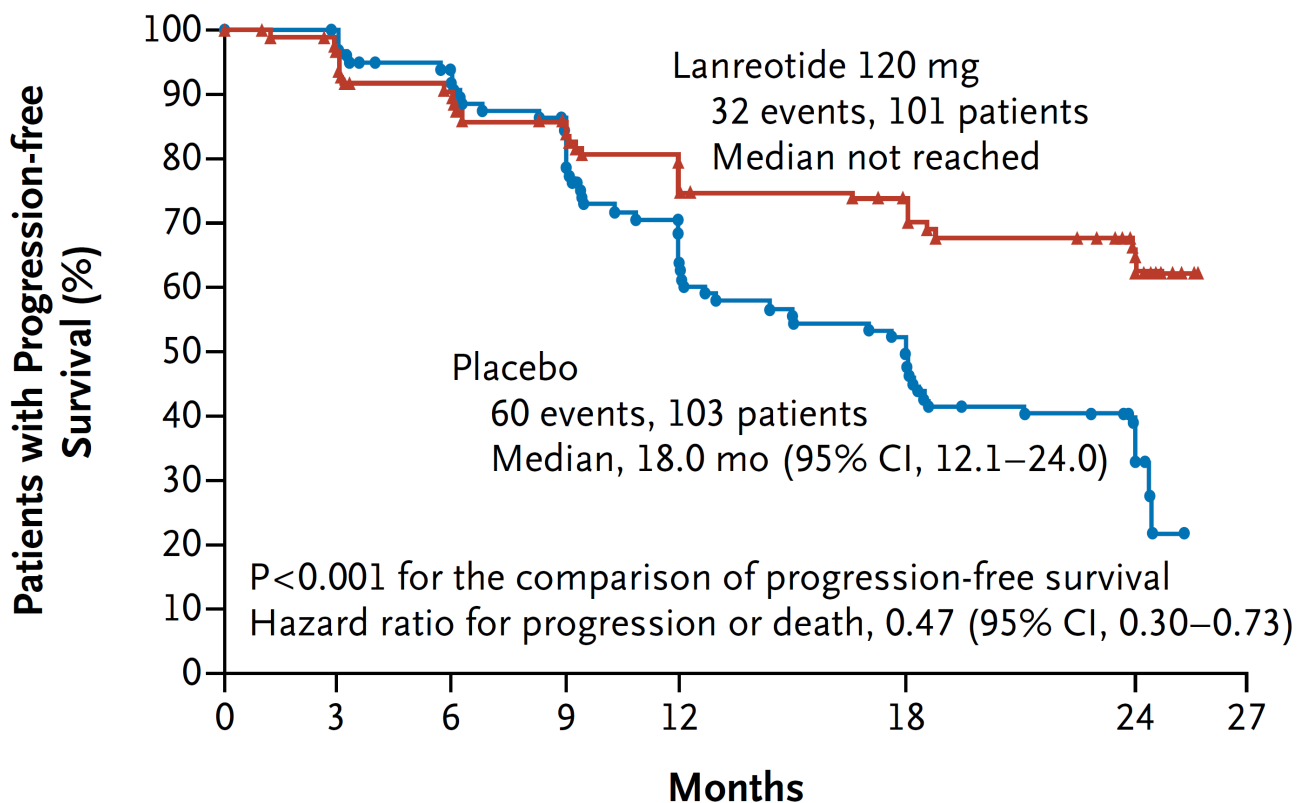


Overall survival

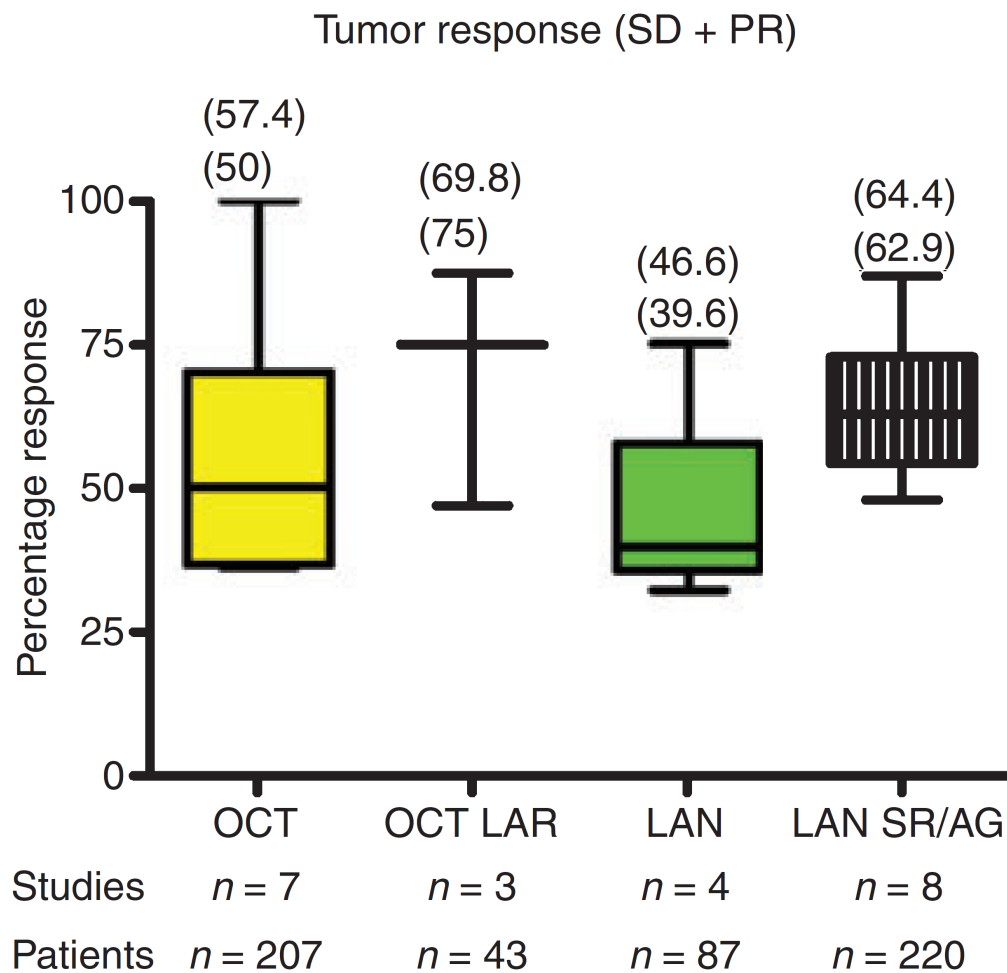


Factor	No. of Patients	Octreotide LAR	Placebo	HR	95% CI
Carcinoid syndrome	33	14.3	5.5	0.23	0.09 to 0.57

SSAs: Antiproliferatory activity

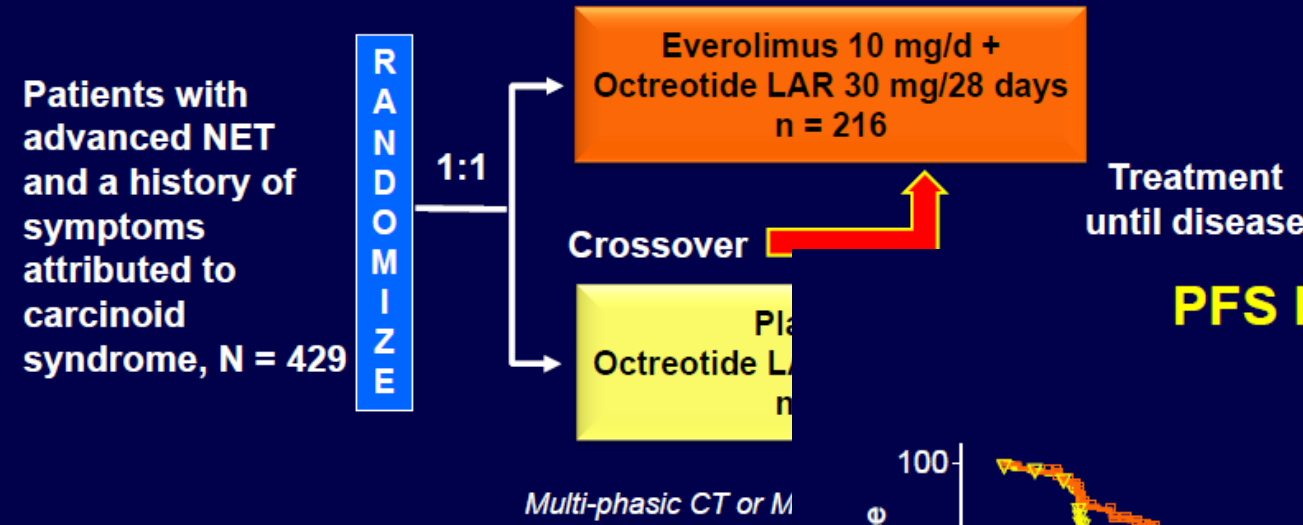


Non Functioning NET



RADIANT-2 Study Design

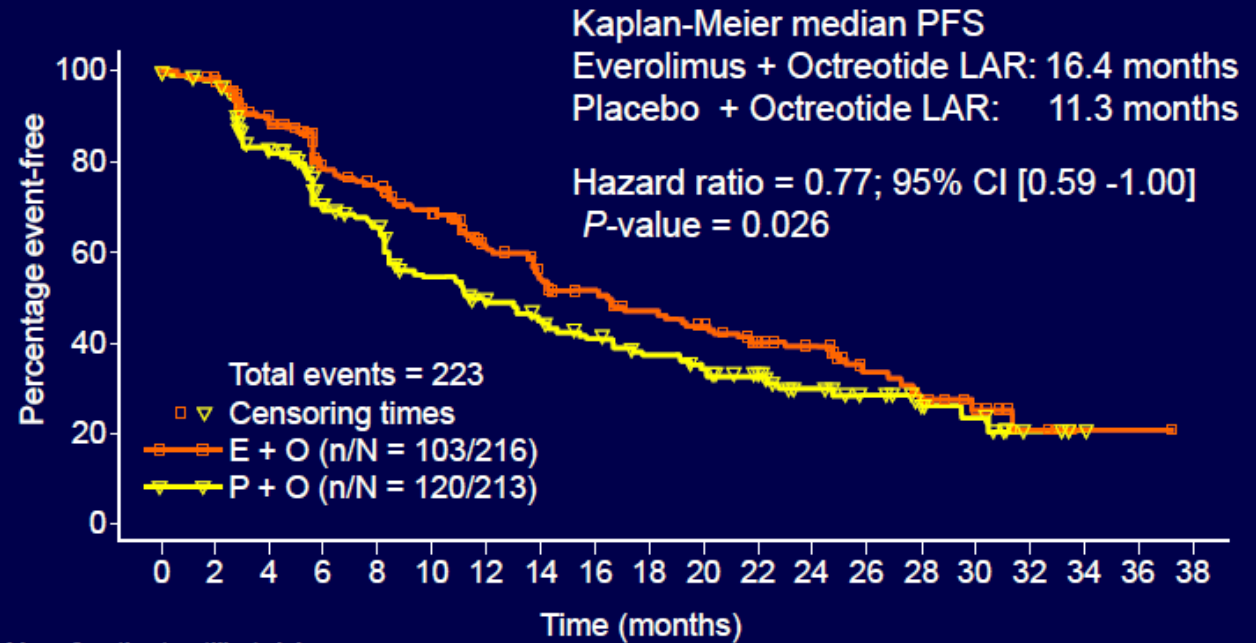
Phase III Double Blind Placebo Controlled Trial



Primary endpoint:
• PFS (RECIST)

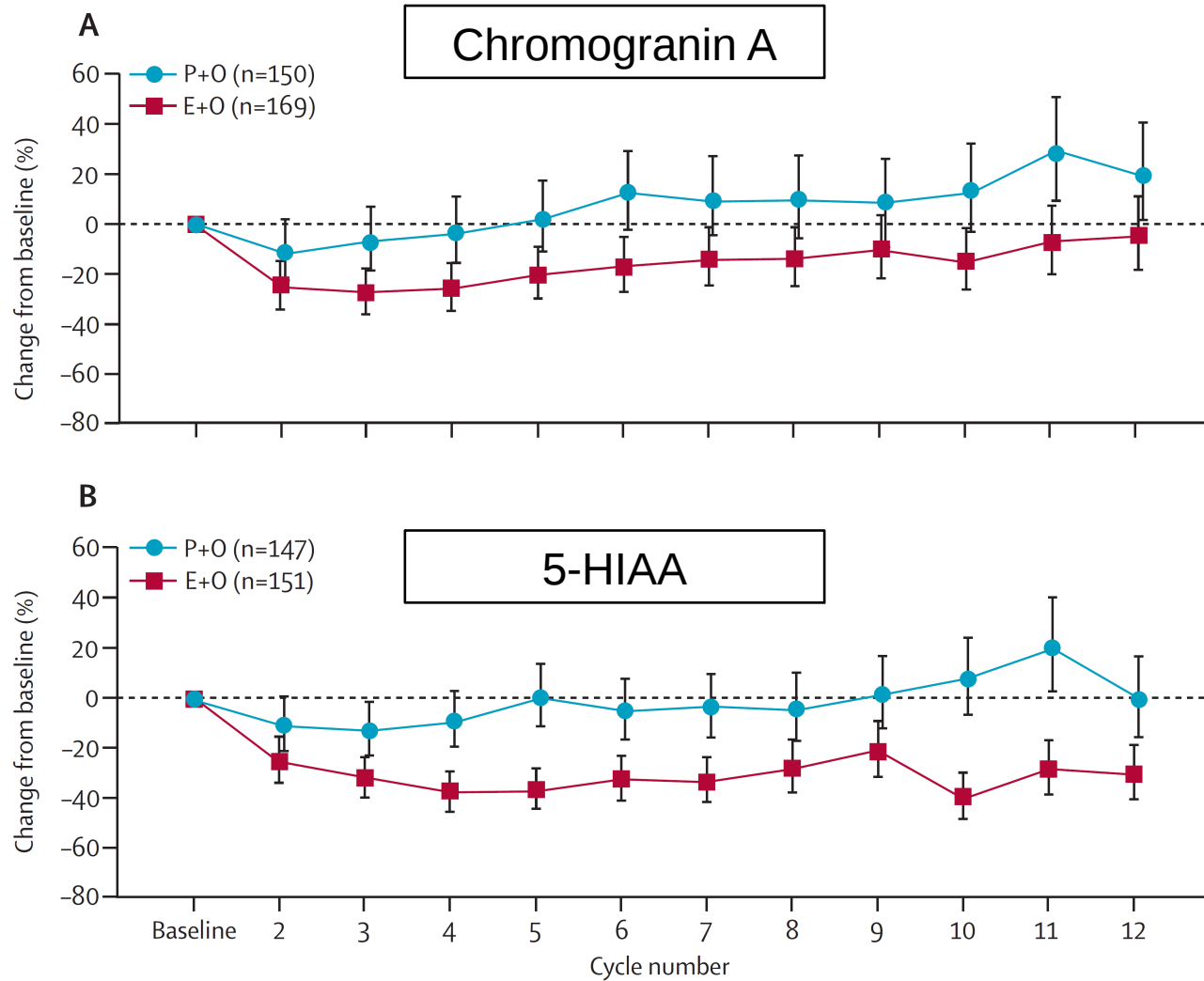
Secondary endpoint:
• Tumour response

PFS by Central Review*

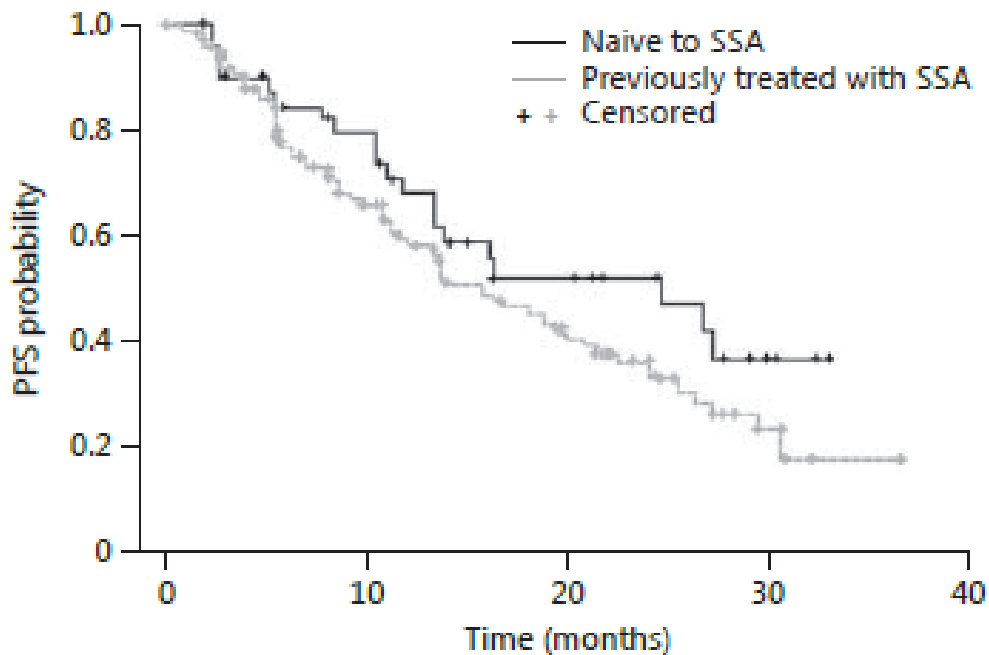


No. of patients still at risk

E + O	216	202	167	129	120	102	81	69	63	56	50	42	33	22	17	11	4	1	1	0
P + O	213	202	155	117	106	84	72	65	57	50	42	35	24	18	11	9	3	1	0	0



	n	Median PFS (95% CI), months	
		everolimus plus octreotide LAR	placebo plus octreotide LAR
<i>Overall population</i>			
Central radiological review	429	16.4 (13.7-21.2) HR 0.77 (95% CI, 0.59-1.00), p = 0.026	11.3 (8.4-14.3)
Previous SSA use	339	14.3 (12.0-20.1) HR 0.81 (95% CI, 0.60-1.09), p = 0.077	11.1 (8.4-14.6)
No previous SSA use	90	25.2 (12.0-NR) HR 0.63 (95% CI, 0.35-1.11), p = 0.054	13.6 (8.2-22.7)
<i>Small intestine NET</i>			
Central radiological review	224	18.6 (13.6-25.9) HR 0.77 (95% CI, 0.53-1.13), p = 0.184 ^a	14.0 (9.4-19.8)
Previous SSA use	190	17.1 (11.2-24.8) HR 0.82 (95% CI, 0.55-1.24), p = 0.178 ^a	11.1 (8.3-19.3)
No previous SSA use	34	NR (13.7-NR) HR 0.48 (95% CI, 0.16-1.40), p = 0.084 ^a	22.7 (11.1-30.4)



¿More aggressive systemic treatment?
Secuential systemic treatment vs frontline

Sunitinib: SUN-1111

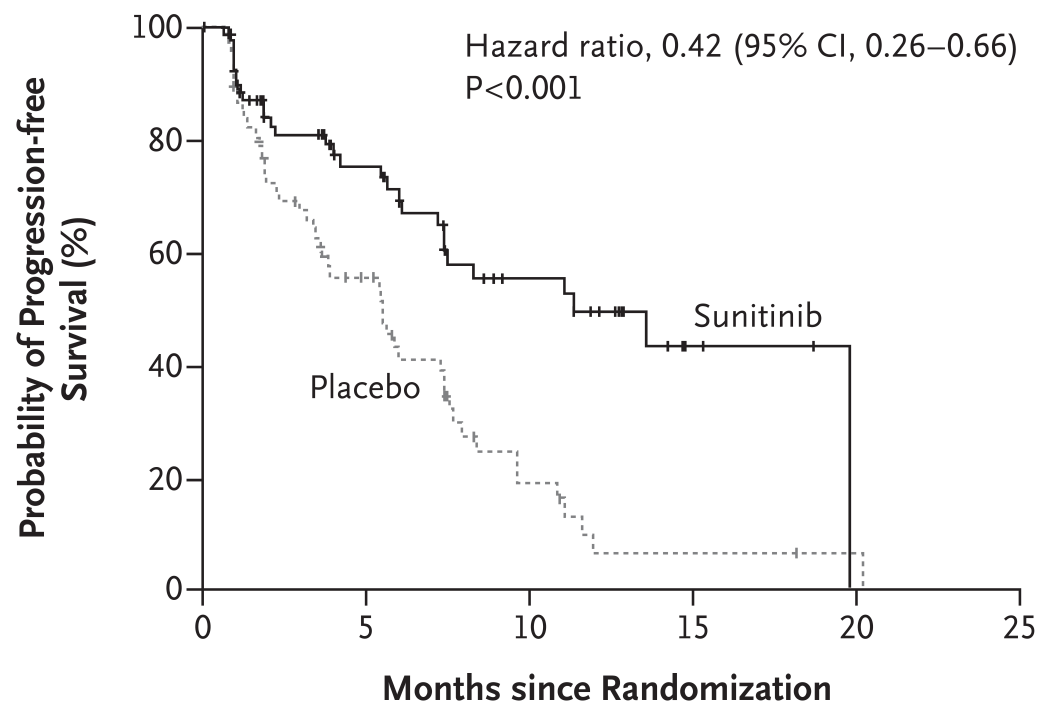
Tumor functionality — no. (%)§**

Nonfunctioning	42 (49)	44 (52)
Functioning		
Gastrinoma	9 (10)	10 (12)
Glucagonoma	3 (3)	2 (2)
Insulinoma	2 (2)	2 (2)
Vasoactive intestinal peptide–secreting tumor	0	2 (2)
Somatostatinoma	1 (1)	0
Other, multisecretory, or unknown	10 (12)	5 (6)
Not specified	19 (22)	20 (24)

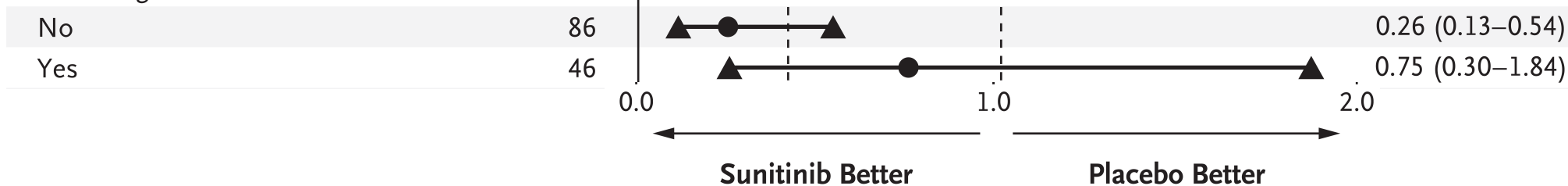
26%

Sunitinib: SUN-1111

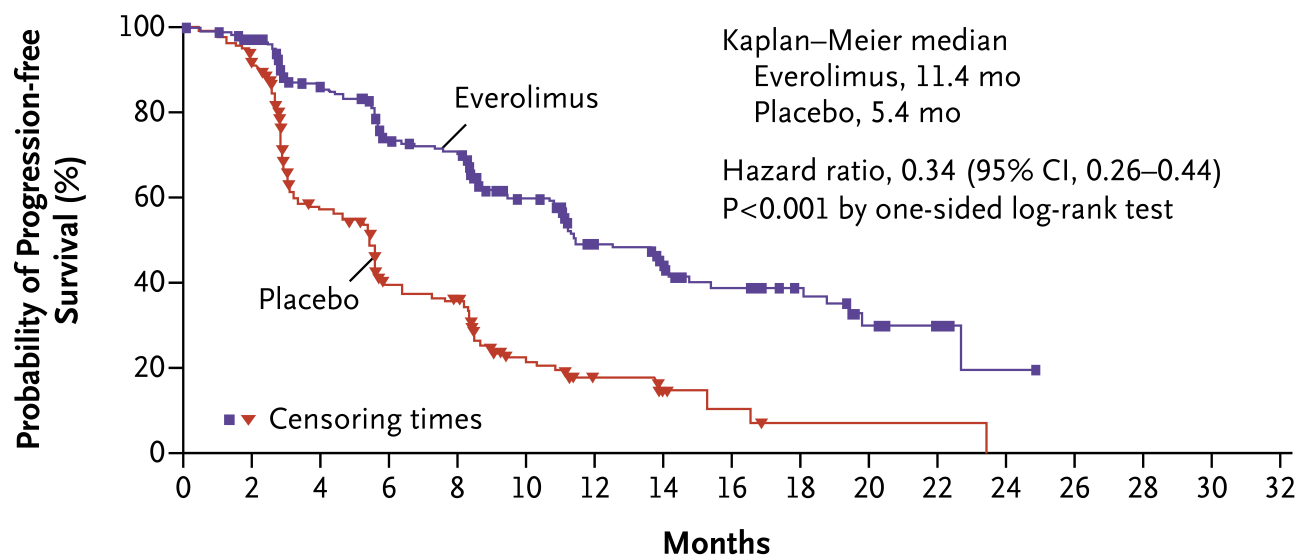
Progression-free Survival



Functioning tumor



Everolimus: RADIANT-3



Insulinoma
Gastrinoma
VIPOMA
Somatostatinoma

26%

CONCLUSSIONS

- Treat functioning NETs requires a more aggressive approach than non functioning NETs
- Surgical management include debulking (<90%) and liver transplantation
- Select the best antisecretory therapy + the best antiproliferative treatment
- Control 5-HIAA to avoid Carcinoid Heart Disease
- Combination treatment frontline is an option in selected patients