Management of Neuroendocrine Tumors

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Diagnostic Challenges in NET

- Heterogeneous group of tumours
- Wide variety of clinical presentations
- Late presentation
- Different terminology and classifications
- Histologic diagnosis may be difficult

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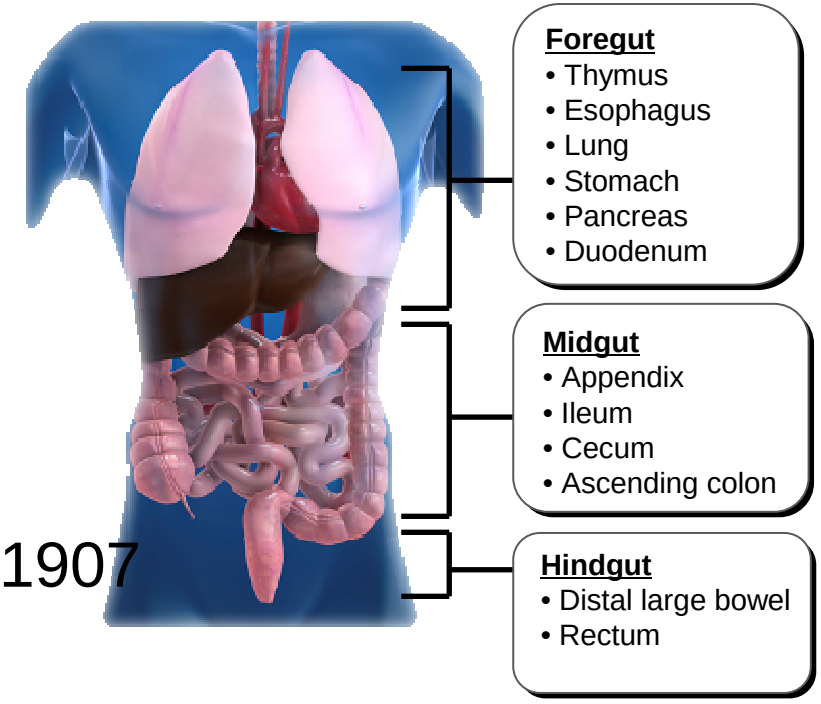
NET Vary by Primary Tumour Site

- Generally characterized by their ability to produce peptides that may lead to associated syndromes[1,2]
- Historically classified based on embryonic origin[3]
  - Foregut tumours
  - Midgut tumours
  - Hindgut tumours
- Today, primary tumour location is recommended for NET classification[4]
- “Karzinoide”, Oberndorfer 1907



[1]Modlin IM, et al. *Lancet Oncol*. 2008;9:61-72. [2]Modlin IM, et al. *Gastroenterology*. 2005;128:1717-1751.
[3]NCCN. In: *Practice Guidelines in Oncology*. V.1.2008. [4]Klimstra DS, et al. *Am J Surg Pathol*. 2010;34:300-313.

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Clinical syndromes associated with endocrine pancreatic tumors

- Functioning (70 → 30%)

insulinoma	1-3 per million (17%)	
gastrinoma	0.5-3 per million (15%)	
VIP-oma	0.05-0.2 per million (2%)	
glucagonoma	0.01-0.1 per million (1%)	
somatostatinoma		
ACTH-oma, GRF-oma	<10%	
calcitonin-, serotonin-		
PTH-rp producing		

- Non-functioning (30-70%) 0.2-2 per million

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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 tumour stage: TNM
  - AJCC
  - ENETS
- Histologic classification
  - Well differentiated, poorly differentiated
  - Tumours with a high grade (grade 3), a mitotic count >20 per10 high powered fields, or a Ki-67 proliferation index of >20% represent highly aggressive malignancies
- Molecular Classification
  - MEN 1 & 2, Tuberosis Sclerosis, Von Hippel Lindau disease

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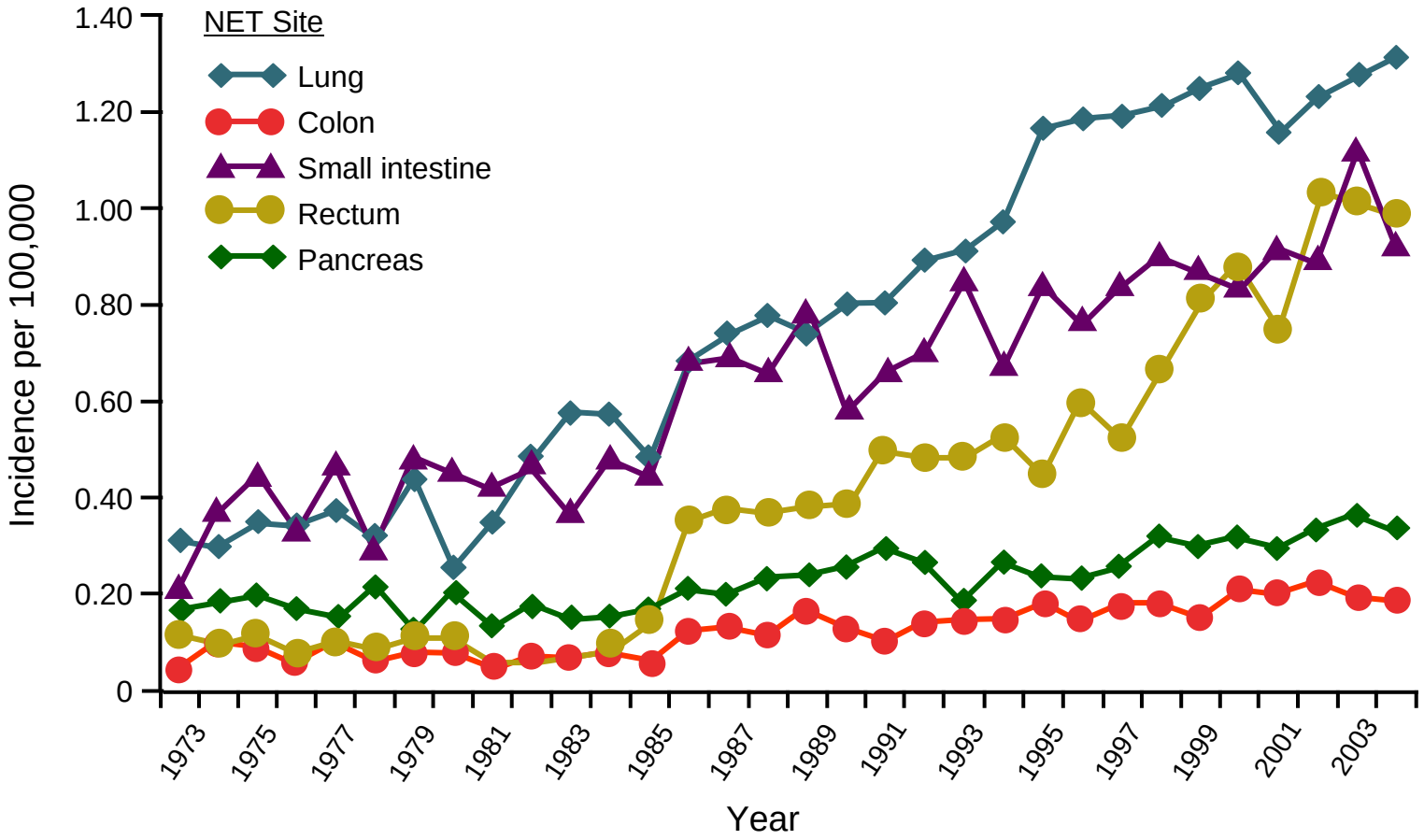
Incidence of NET is Increasing*



*Approximate 5-fold increase between 1975 and 2004
Approximate 7-fold increase also evident in Norwegian registry

SEER = Surveillance, Epidemiology, and End Results (for malignant NET)

Yao JC, et al. *J Clin Oncol*. 2008;26:3063-3072.

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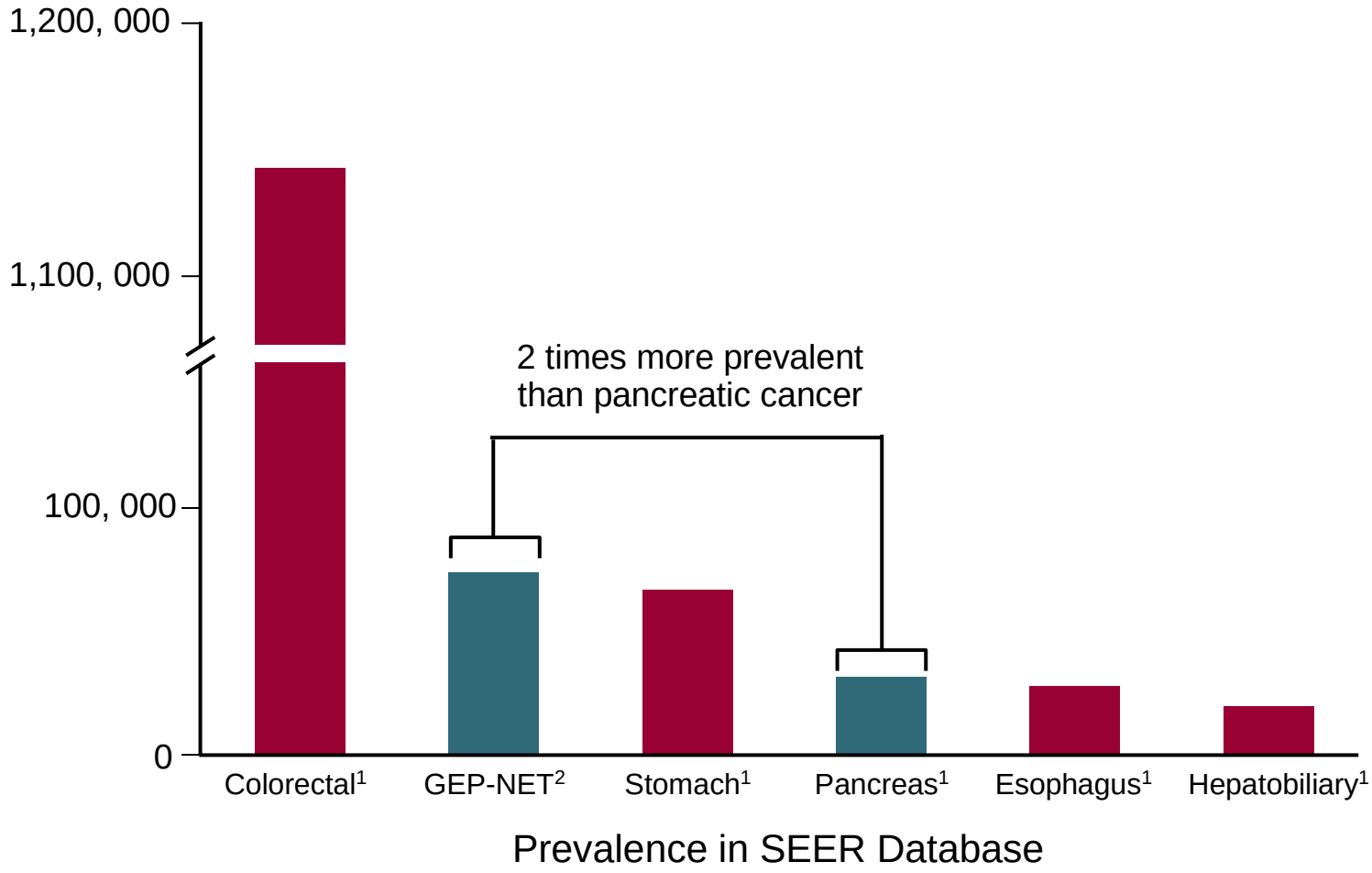
NET are the Second Most Prevalent Type of Gastrointestinal Malignancy



GEP = gastroenteropancreatic

[1]National Cancer Institute. SEER Cancer Statistics Review, 1975-2004. http://seer.cancer.gov/csr/1975_2004;
[2]Modlin IM, Lye KD, Kidd M. *Cancer*. 2003;97(4):934-959.

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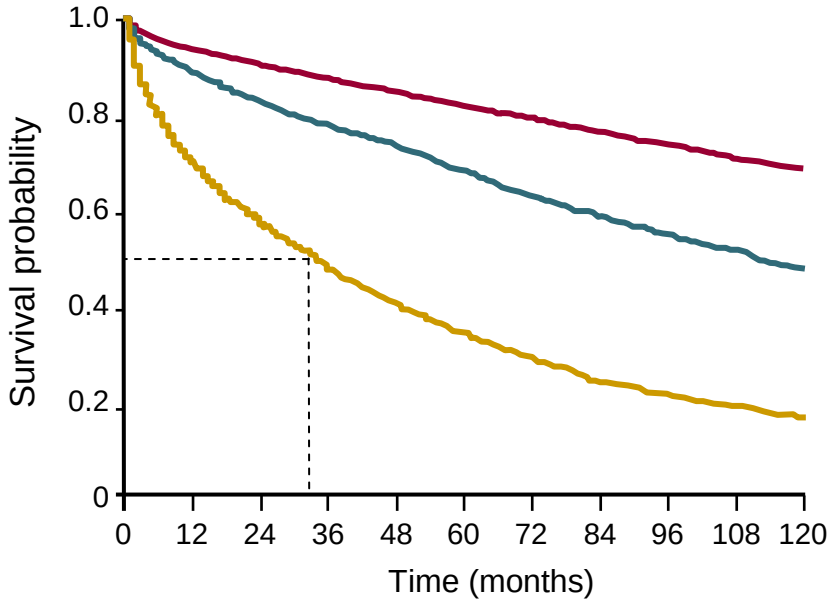
33-Month Median Survival for Patients with Metastatic NET

Tumours with well- and moderately differentiated histology[1]



Stage	Median survival	
	Month	95% CI
Localized	223	208-238
Regional	111	104-118
Distant	33	31-35

- SEER: 5-year survival, SI-NET: 54%; pNET 27%
- Survival rates are 3 times higher in specialized centres in Europe and US

CI = confidence interval

[1]Yao J, et al. *J Clin Oncol*. 2008;26:3063-3072; [2]Jemal A, et al. *CA Cancer J Clin.* 2010;60:277-300.

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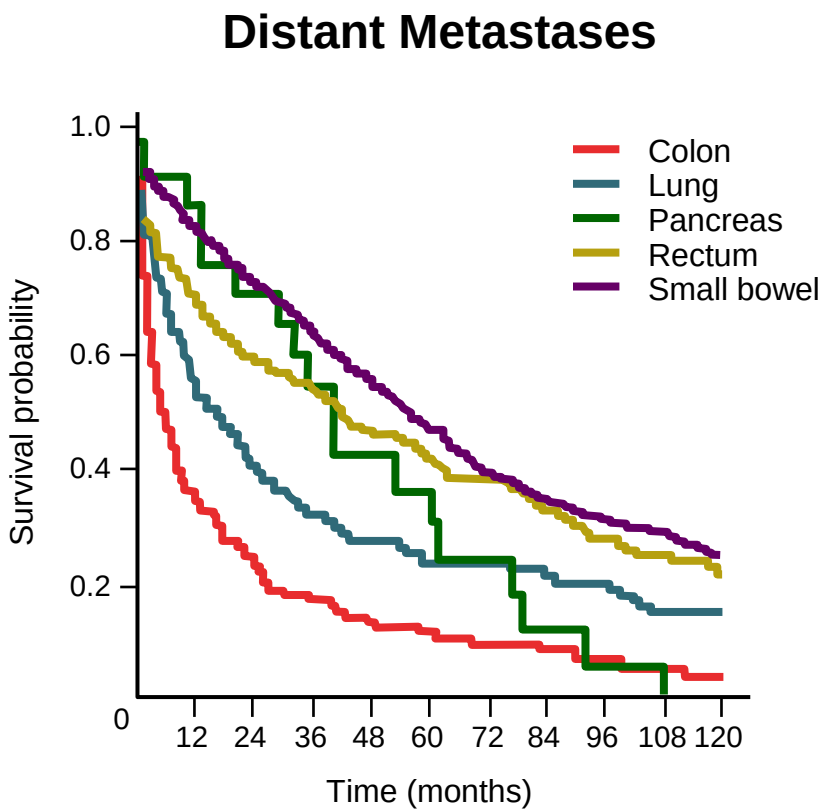
Correlation of Primary Tumour Site with Survival

Known prognostic factors include:

- Location of primary tumour
- Extent of disease
- Tumour stage
- Degree of differentiation/ proliferative index (PI)
- Tumour grade
- Patient age
- Performance status



Yao JC, et al. *J Clin Oncol*. 2008;26:3063-3072.

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WHO Classifications of Neuroendocrine Neoplasms of the GEP System

WHO 2000	WHO 2010
Well-differentiated endocrine tumour (WDET) Well-differentiated endocrine carcinoma (WDEC)	Neuroendocrine tumours Grade 1 Grade 2
Poorly differentiated endocrine carinoma/small-cell carcinoma (PDEC)	Neuroendocrine carcinoma Grade 3
Mixed exocrine-endocrine carcinoma (MEEC)	Mixed adenoneuroendocrine carcinoma (MANEC)
Tumour-like lesions (TLL)	Hyperplastic and preneoplastic lesions

Bosman FT, et al. *WHO Classification of Tumours of the Digestive System*. Lyon, France: IARC Press; 2010.

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ENETS/AJCC Grading System

ENET/AJCC		
Grade	**Mitotic count (10 HPF)***	**Ki-67 index (%)****
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

***10 HPF (high power field) = 2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density.
**** MIB1 antibody; % of 2,000 tumour cells in areas of highest nuclear labeling.

[1]Rindi G, et al. *Virchows Arch.* 2006;449:395-401. [2]Rindi G, et al. *Virchows Arch.* 2007;451:757-762.
[3]American Joint Committee On Cancer. AJCC Cancer Staging System. 7th ed.

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ENETS/AJCC TNM Staging Systems

ENET/AJCC Classification Criteria – GI NET			
Stage includes tumour location, size, lymph node involvement/distant metastasis			
Stage I	T1	N0	M0
Stage IIa	T2	N0	M0
Stage IIb	T3	N0	M0
Stage IIIa	T4	N0	M0
Stage IIIb	Any T	N1	M0
Stage IV	Any T	Any N	M1

ENETS = European Neuroendocrine Tumour Society
AJCC = American Joint Committee on Cancer

[1]Rindi G, et al. *Virchows Arch.* 2006;449:395-401. [2]Rindi G, et al. *Virchows Arch.* 2007;451:757-762.
[3]American Joint Committee On Cancer. AJCC Cancer Staging System. 7th ed.

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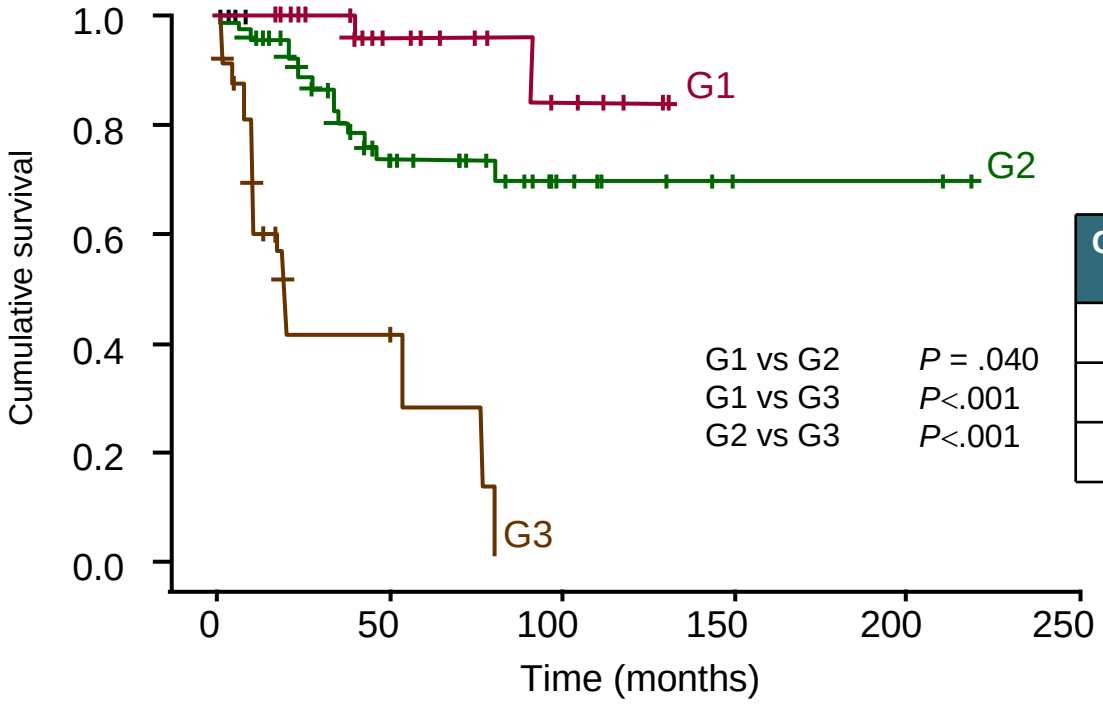
Correlation of Tumour Grade and Cumulative Survival (ENETS Grading Proposal)



Grade[1]	Mitotic count (10 HPF)[2]	Ki-67 index (%)[3]
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

[1]ENETS grading system.
[2]10 HPF = 2 mm^2 at least 40 fields (40 × magnification) evaluated in areas of highest mitotic density.
[3]Percentage of 2,000 tumour cells in areas of highest nuclear labeling with MIB1 antibody.

Pape UF, et al. *Cancer.* 2008;113:256-265.

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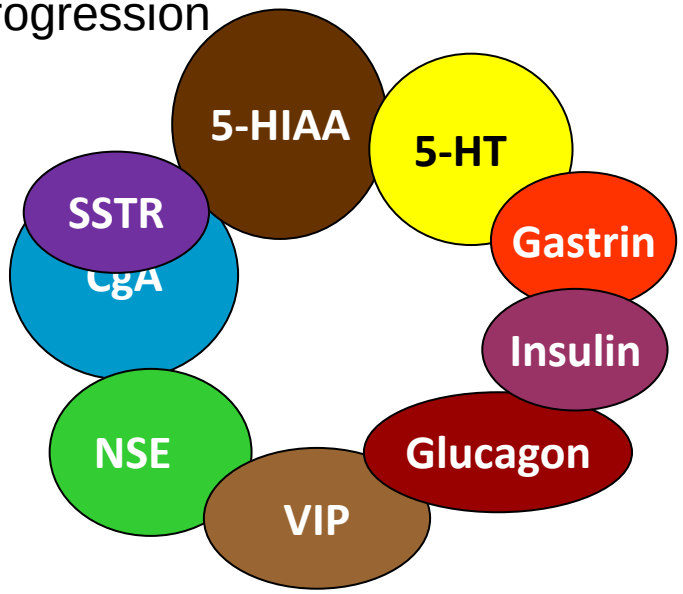
Biomarkers in NET

- CgA is the best available biomarker for diagnosis of NET
  - Elevated CgA may correlate with tumour progression
  - CgA is elevated 80% to 100% of the time
- NSE is also expressed in NET
  - Not as commonly used as CgA
  - Also elevated in pNET and poorly differentiated NEC
- 5-HIAA reflects serotonin levels
  - Elevated serotonin levels over time lead to comorbidities such as cardiac disease
- Specific markers for different syndromes
- New biomarkers in NET are needed to provide better diagnostic and prognostic information



CgA = Chromogranin A; 5-HIAA = 5-hydroxy-3-indoleacetic acid, 5-HT = serotonin, NSE = neuron-specific enolase, VIP = vasoactive intestinal peptide; SSTR = somatostatin receptor

Vinik A, et al. *Pancreas*. 2009;38:876-889.

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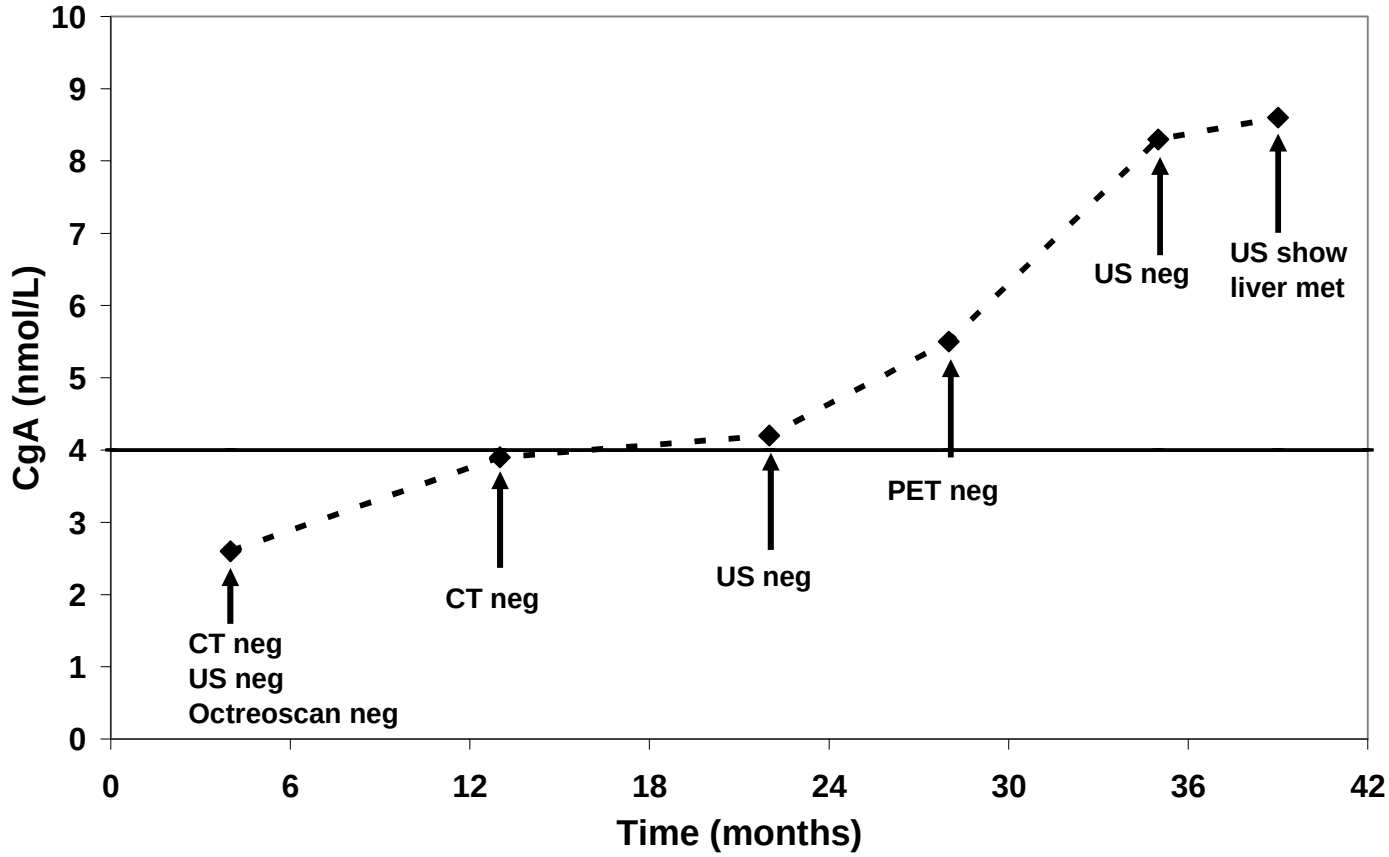
CgA raised for a median of 30 mo before recurrence was confirmed by imaging



Welin, et al, 2009: P-CgA first marker to indicate recurrence

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Radiological Techniques

CT/MRI/US – diagnosis and follow-up	60-95% of metastases 50-70% of primary tumours
Endoscopic ultrasonography	75-90%
Intraoperative ultrasonography	>90%
Rarely angiography	

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Functional techniques

- OctreoScan® (somatostatin receptor scintigraphy [SRS])
- Metaiodobenzylguanidine (MIBG)-scintigraphy
- Positron emission tomography (PET) (^{11}C-5-HTP, ^{18}F-DOPA, ^{68}Ga-DOTA-octreotide, ^{68}Ga-exendin 4)
- For staging and localization

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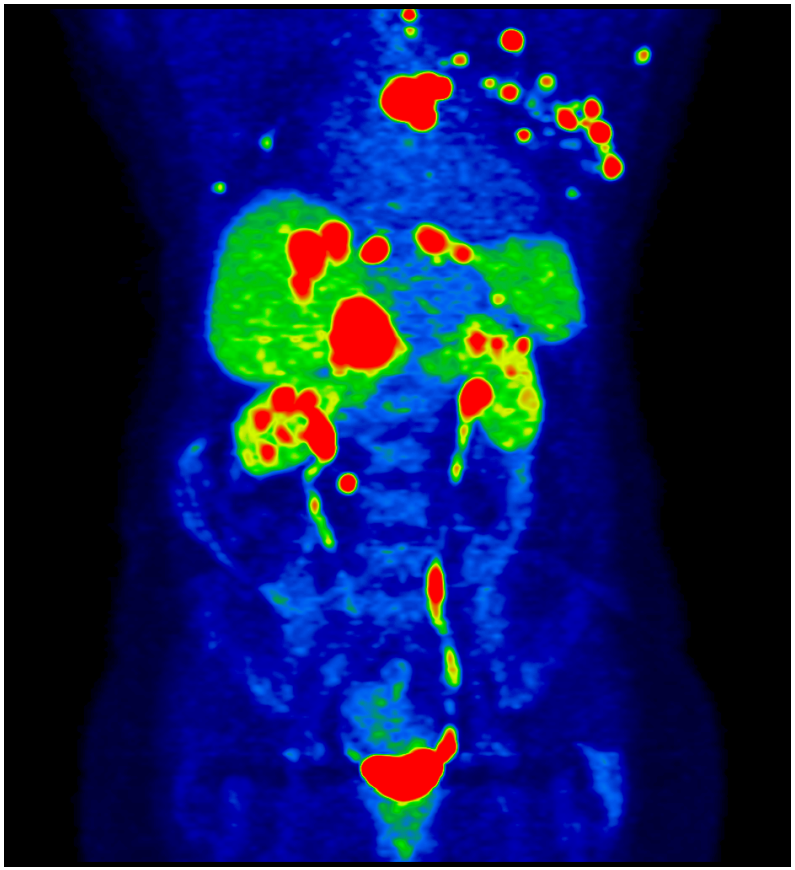
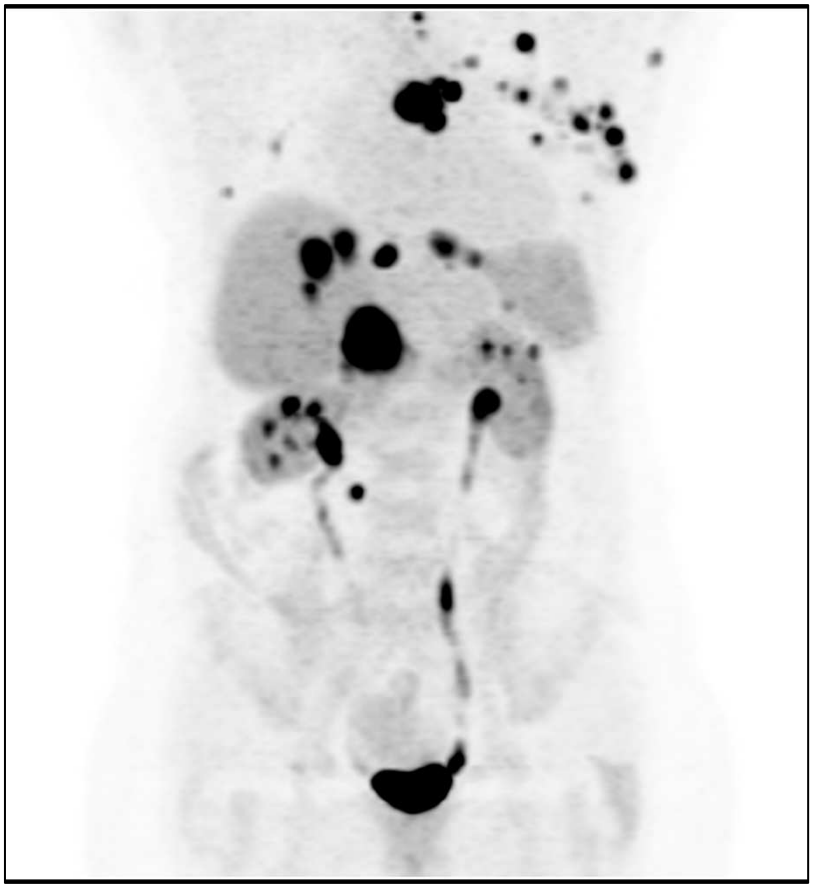
PET/CT with ^{11}C-5-HTP improves morphological accuracy





Örlefors et al. JCEM 2005

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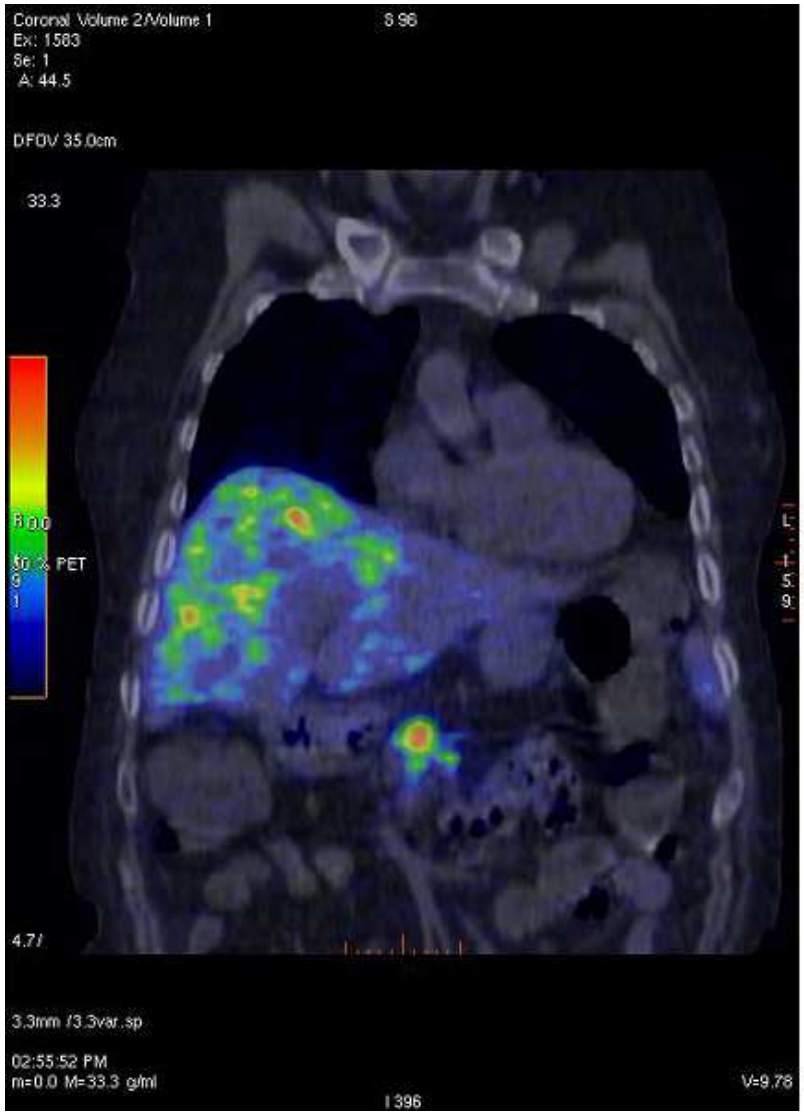
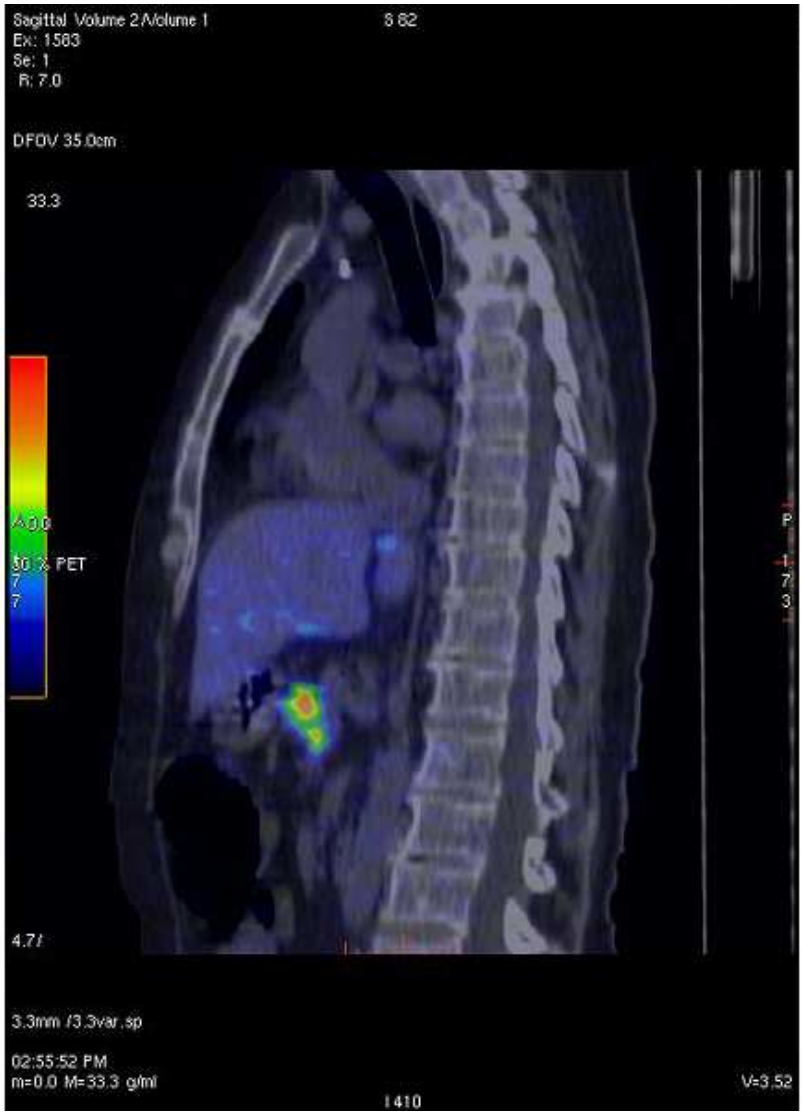
Hofmann et al, Eur J Nucl Med 2001: Biokinetics and imaging with somatostatin PET radioligand ^{68}Ga-DOTATOC: preliminary data

PET/CT with ^{68}Ga-DOTA-octreotide





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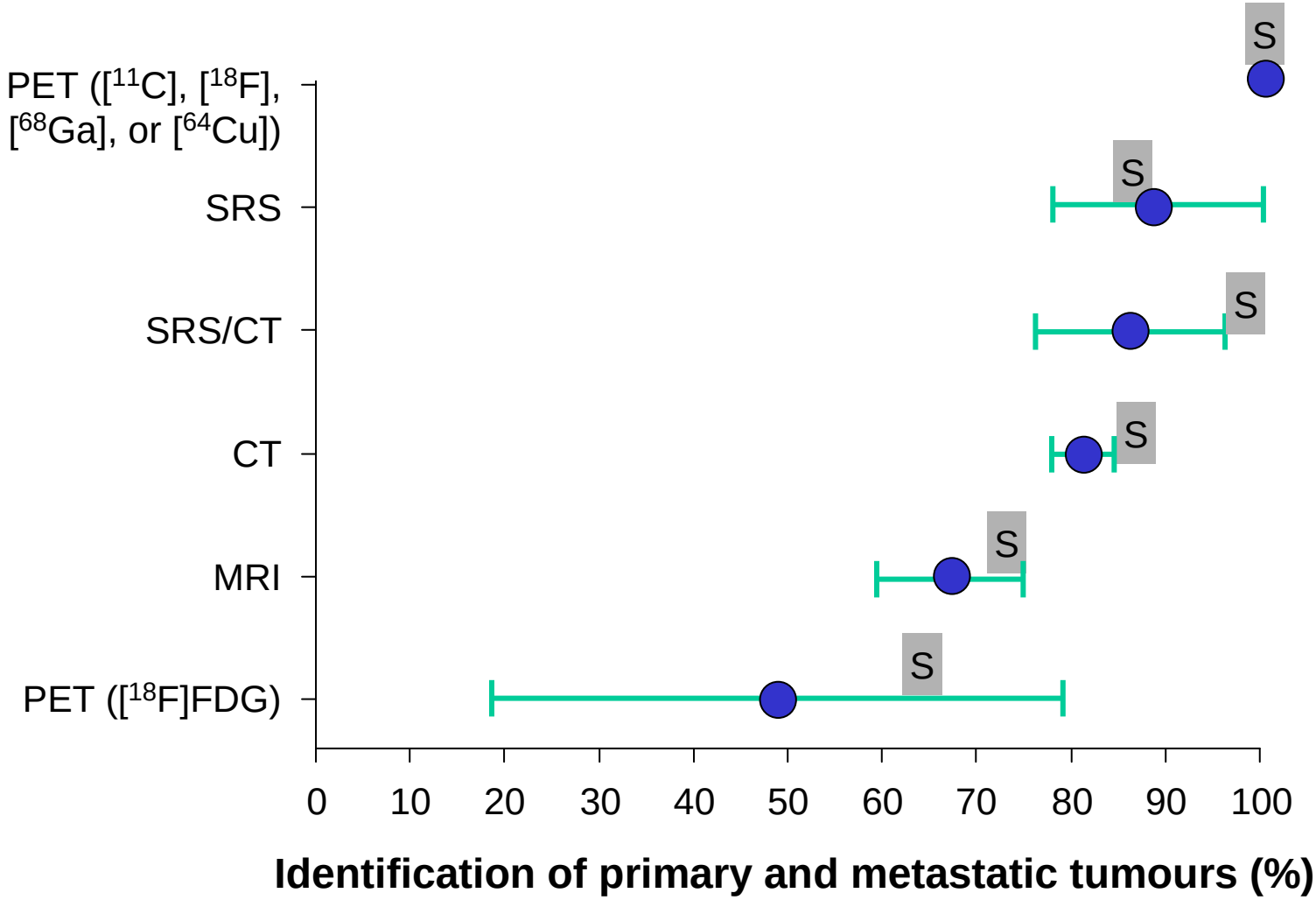
Methods for identification of primary and metastatic GEP NET



S = calculated sensitivity.

Modlin IM, et al. Lancet Oncol. 2008;9:61-72.

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Current Challenges in Treating Patients with Advanced NET

- More than half of NET patients are diagnosed with advanced disease
- Advanced NET are incurable and most patients will succumb to the disease
- There is a need for new therapeutic options for patients with advanced NET

[1]Moertel, et al. *N Engl J Med.* 1980;303:1189-1194. [2].oertel, et al. *N Engl J Med*. 1992;326:519-523.
[3]Cheng, et al. *Cancer.* 1999;86:944-948. [4]McCollum, et al. *J Clin Oncol* 2004;27(5):485-488.

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Therapeutic Options for Patients with Advanced NET

Surgery
- curative or ablative

Debulking
- radiofrequency ablation (RFA)
- embolisation/chemo-/radio

Medical therapy
- chemotherapy
- biological treatment:
  - somatostatin analogs
  - alpha interferon
  - m-TOR inhibitors
  - VEGF-R inhibitors
  - other TKI's

Irradiation
- external (bone, brain metastases)
- tumour targeted, radioactive treatment (^{90}Y-DOTATOC, ^{177}Lu-DOTATE)

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Chemotherapy for NET

- Streptozotocin, a chemotherapeutic agent, approved in some countries (US, France) for pancreatic NET (pNET), however, it is not effective in the treatment of GI-NET

- Most recent reports of outcome with STZ/Dox or STZ/5-FU describe PR (WHO, RECIST) of 36-39% with median duration of 9.3, PFS 18 months, SD 50%; first-line in G2

- Toxicity; gastro-intestinal (grade 1-2), renal (mainly grades 1-2, grade 3: 8%, grade 4: 0%) with appropriate monitoring and dose adjustments

Kouvaraki, J Clin Oncol, 2004

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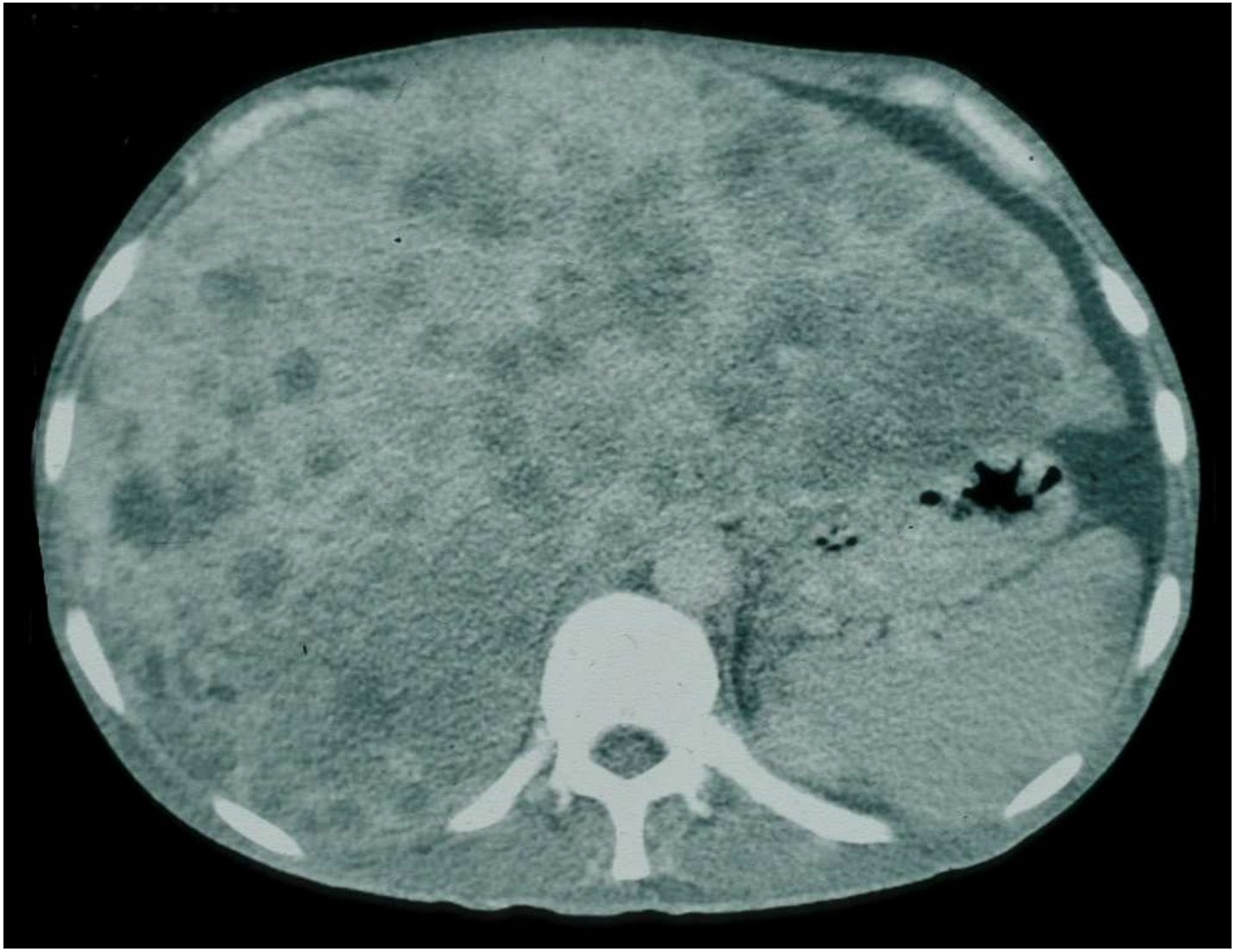

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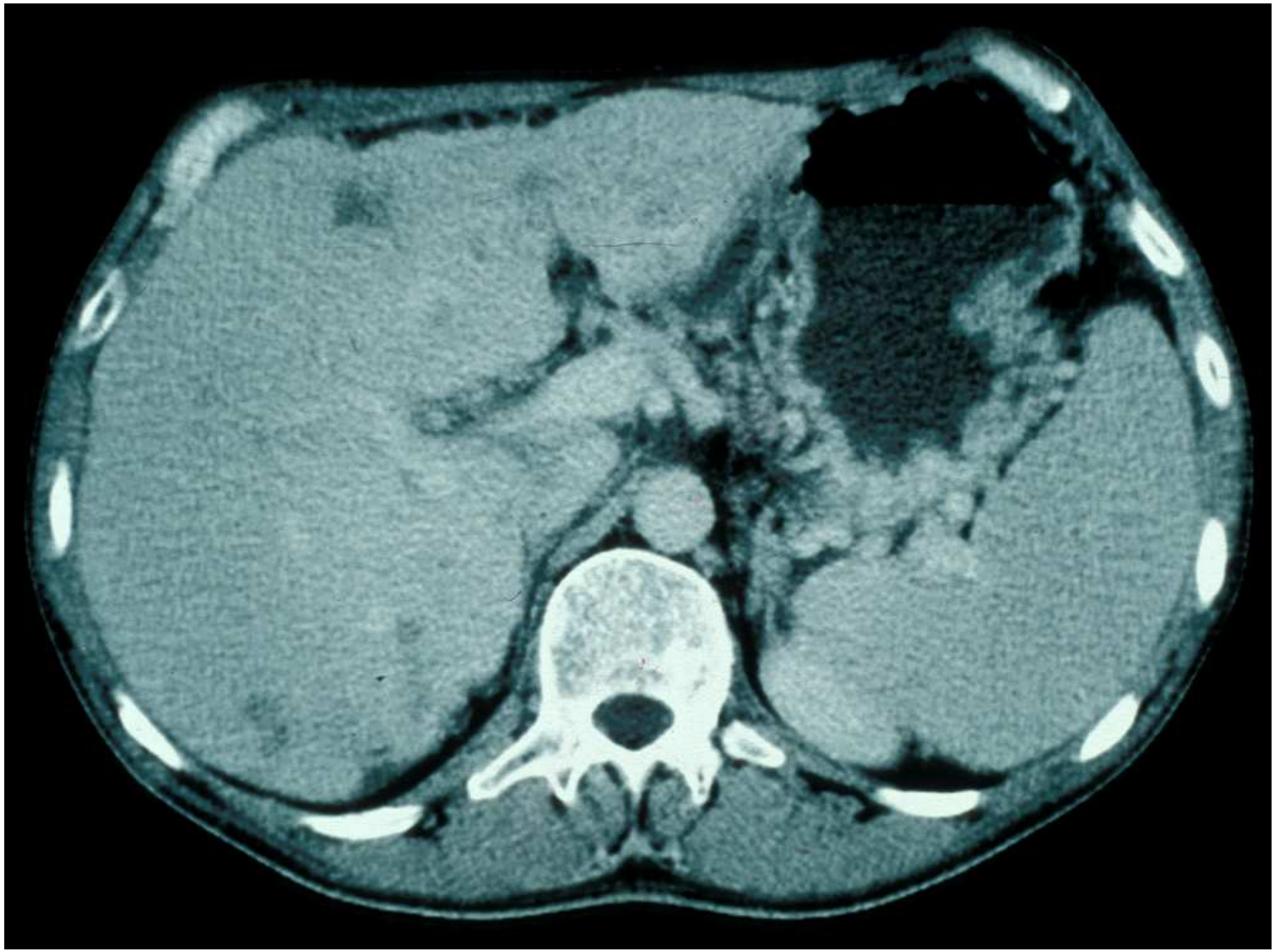

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Chemotherapy: Temozolomide

Ekeblad; Clin Cancer Res 2007

- 36 patients (35 foregut: 12 EPT, 12 bronchial 7 thymus)
- median 2.4 prior antitumour medical therapies
- RR 14% (40% in low MGMT)
- TTP 7 months

Kulke; ASCO 2006 abstract 4044

- + bevacizumab
- 34 patients (18 EPT, 16 carcinoids)
- 12 prior chemo
- EPT 24% PR, carcinoids 0%
- PFS 8.6 months

Kulke; Clin Cancer Res 2009

- correlation MGMT-deficiency and response

Strosberg; Cancer 2011

- + capecitabine
- 30 patients with EPT
- first line
- PR 21/30 (70%)

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Biotherapy in NET: Interferon Studies

- 27 studies, 679 patients
- 3 randomised trials
- biochemical responses 50%, symptomatic 60%, tumour response 10%
- side-effects constitute a problem; mainly given in combination with somatostatin analogs in low-proliferative tumours

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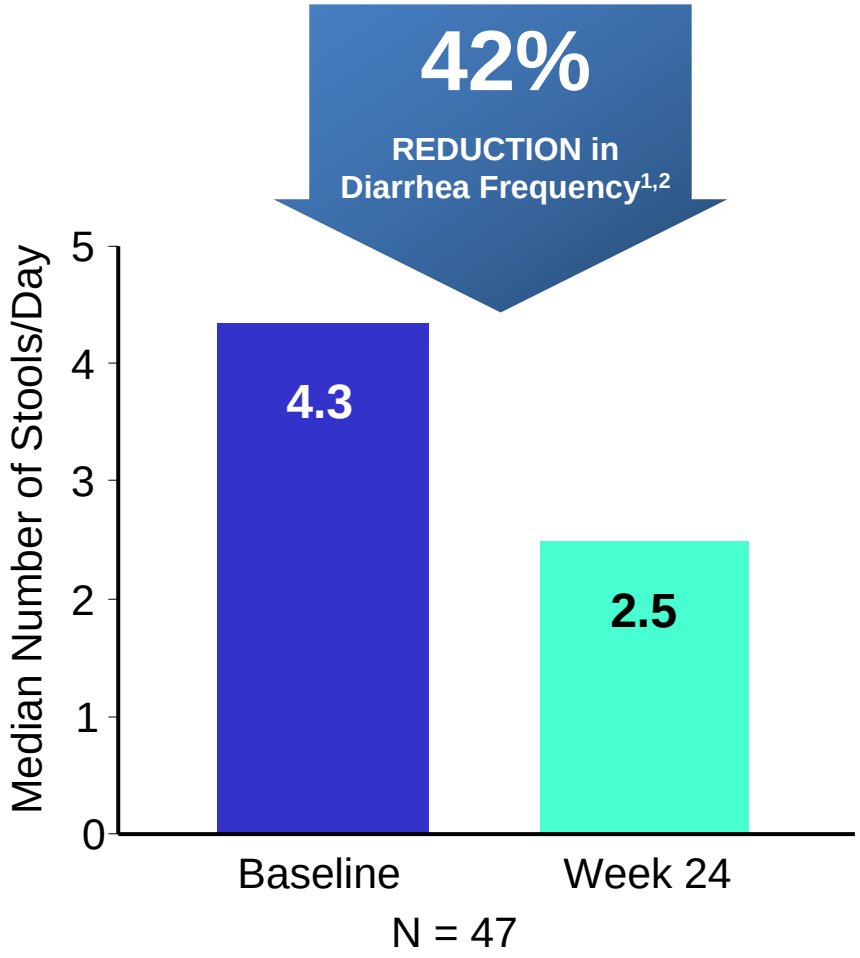
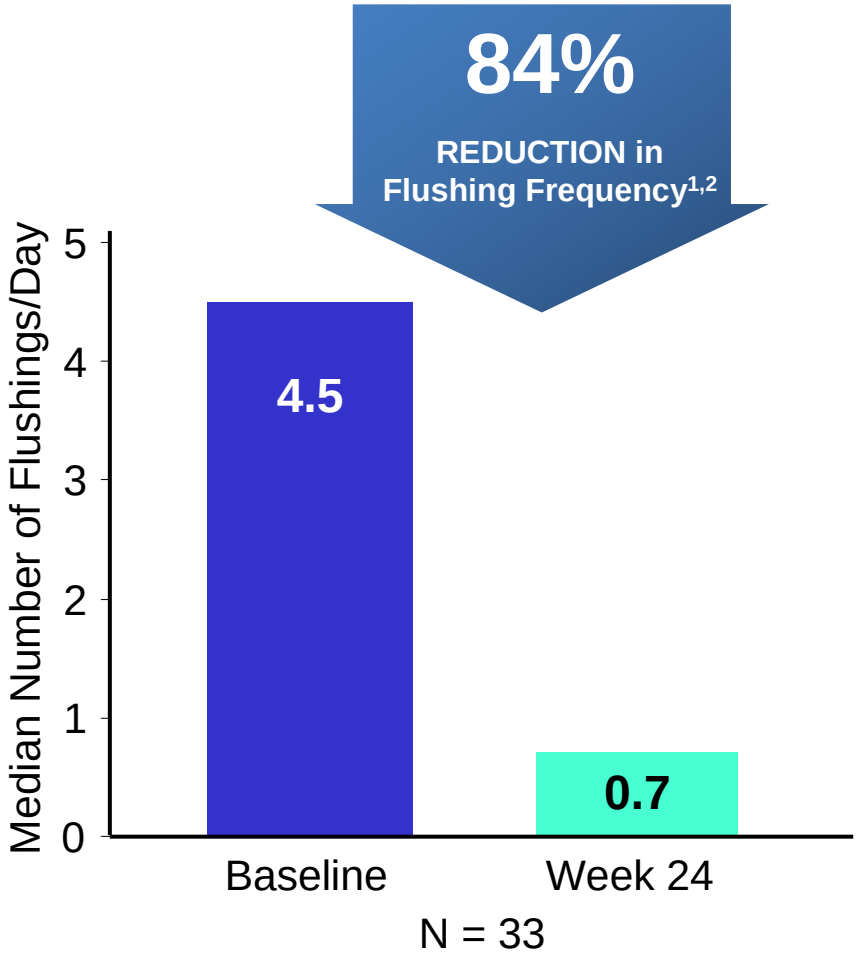
Octreotide LAR Provides Effective Symptom Relief





[1]Rubin J, et al. *J Clin Oncol*.1999;17:600-606. [2]Anthony L, et al. *Curr Med Res Opin.* 2009;25:2989-2999.

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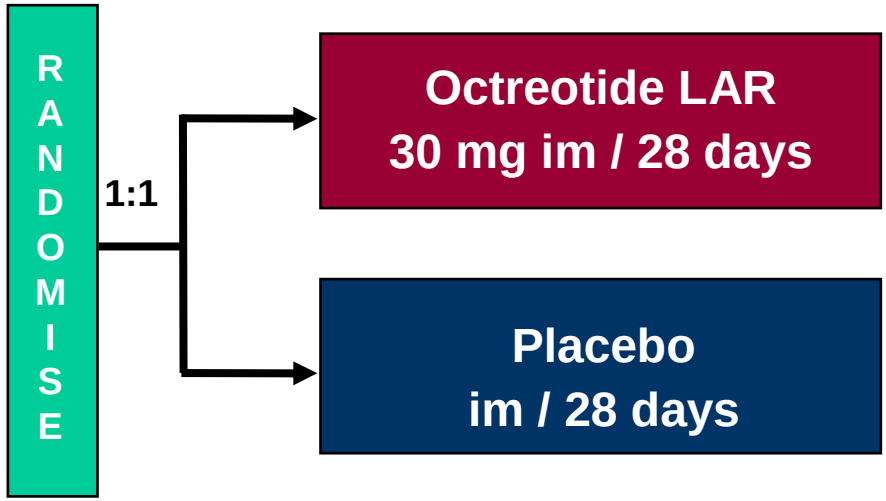
PROMID: Phase III Randomised, Double-Blind, Placebo-Controlled Study

Patients:

- Well-differentiated midgut NETs
- Treatment naïve
- Locally inoperable or metastasised

  N = 85



Treatment until CT/MRI-documented tumour progression or death

Primary endpoint:

- Median time to tumour progression

Secondary endpoints:

- Objective tumour response rate
- Symptom control
- Overall survival

im = intramuscular; CT = computed tomography; MRI = magnetic resonance imaging

Rinke A, et al. *J Clin Oncol*. 2009;27(28):4656-4663.

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Patient Characteristics

	Octreotide LAR n = 42	Placebo n = 43
Median age, years (range)	63.5 (38-79)	61.0 (39-82)
Sex male (%) female (%)	47.6 52.4	53.5 46.5
Time since diagnosis, months (range)	7.5 (0.8-271.2)	3.3 (0.8-109.4)
Karnofsky score ≤80 (%) >80 (%)	16.7 83.3	11.6 88.4
Carcinoid syndrome* (%)	40.5	37.2
Resection of primary (%)	69.1	62.8
Hepatic tumour load 0% 0% - 10% 10% - 25% 25% - 50% >50%	 16.7 59.5 7.1 11.9 4.8	 11.6 62.8 4.7 9.3 11.6
Octreoscan positive (%)	76.2	72.1
Ki-67 up to 2% (%)	97.6	93.0
CgA elevated (%)	61.9	69.8

* Not requiring octreotide for symptom control

Rinke A, et al. *J Clin Oncol*. 2009;27(28):4656-4663.

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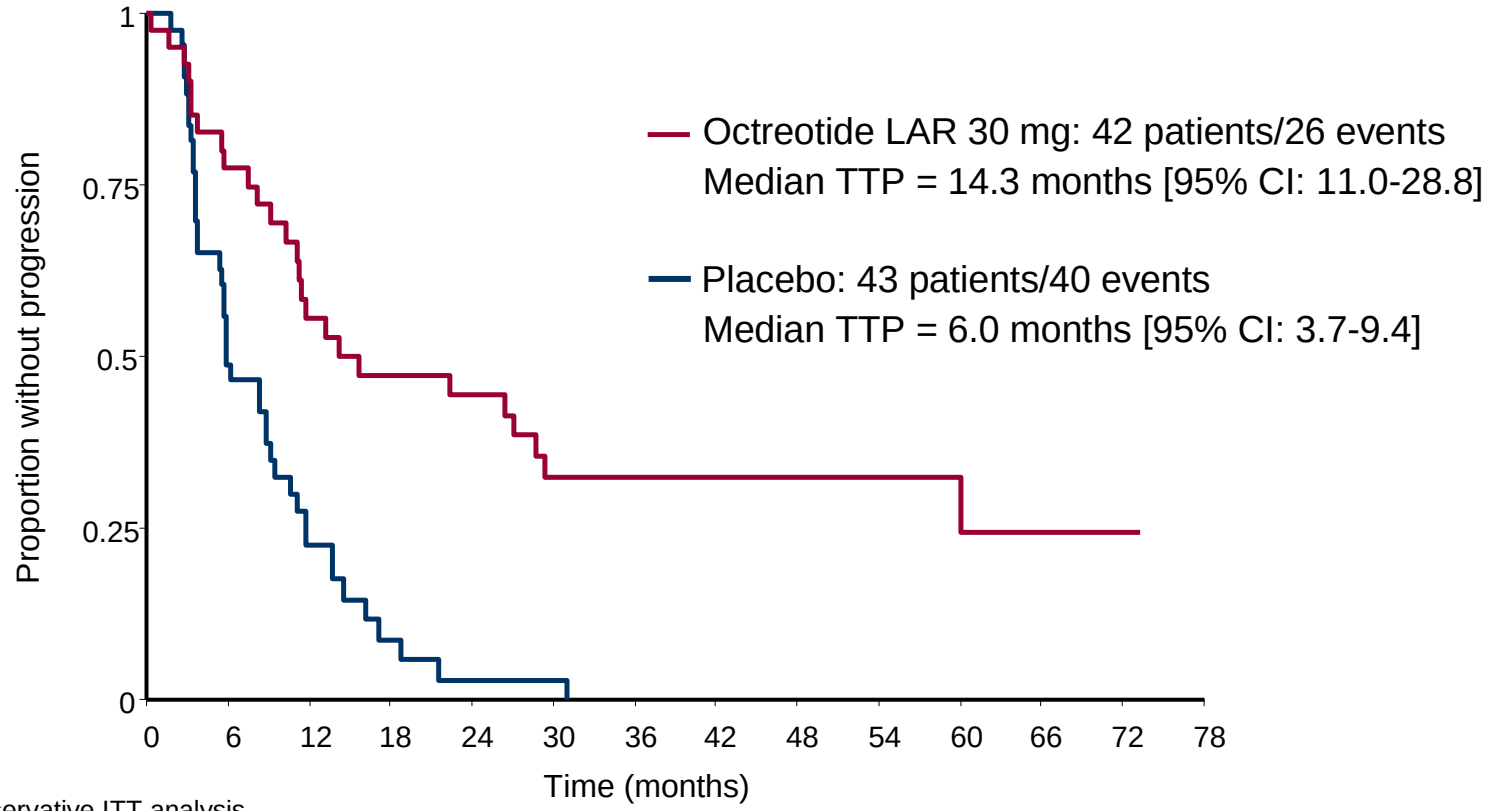
Octreotide LAR 30 mg Significantly Prolongs Time to Tumour Progression

66% reduction in the risk of tumour progression
HR = 0.34; 95% CI: 0.20-0.59; *P* = .000072



Based on the conservative ITT analysis
TTP = time to progression

Rinke A, et al. *J Clin Oncol*. 2009;27(28):4656-4663.

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[177Lu-DOTA0, Tyr3] Octreotate

310 patients

Dose 600-800 m Ci (22.2 to 29.6 GBq)

PR	30%
MR	16%
SD	35%
PD	20%

- higher remission rates –
  higher uptake on Octreoscan grade 3-4
- Performance status KPS >70

Median time to progression: 40 mo

Serious adverse events:

MDS (3 patients), acute leukemia, liver toxicity (2 patients)

- higher response rates but shorter duration in EPT

Kwekkeboom et al, JCO, 2008

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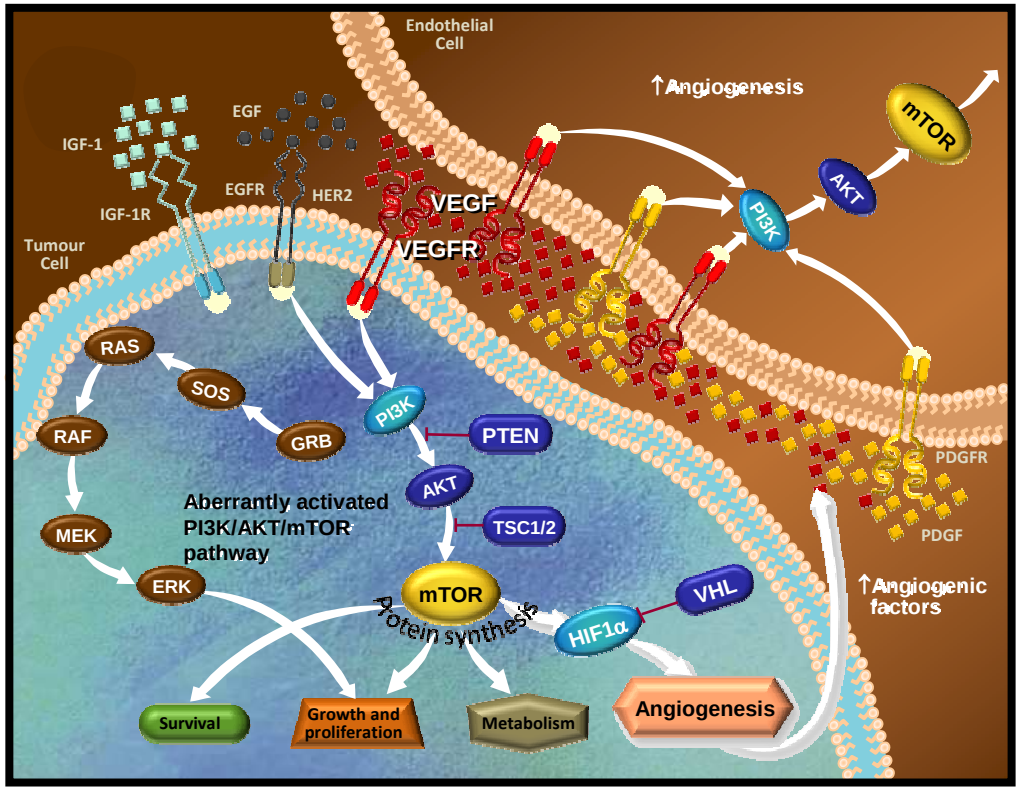
Rationale for the Use of Angiogenesis Inhibitors in NET

- NET are highly vascularised and express VEGF and VEGF-R[1]
- Angiogenesis inhibitors that target VEGF have been shown to have clinical activity in NET[3]



[1]Yao JC, et al. *J Clin Oncol.* 2008;26(8)1316-1323. [2]Phan AT, et al. *J Clin Oncol*. 2006;24(18s suppl):abstract 4091.
[3]Eriksson B. *Curr Opin Oncol*. 2010;22(4):381-386.

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New Antiangiogenic Agents

- VEGF antibodies
  - Bevacizumab
- Inhibition of PDGF + VEGF receptors
  - Sunitinib, sorafenib, vandetanib
- Inhibition of mTOR which regulates HIF-1 impacting the transcription of VEGF-A
  - Everolimus
- ("Old": IFN-α, somatostatin analogs)

PDGF = platelet-derived growth factor; HIF = hypoxia inducible factor

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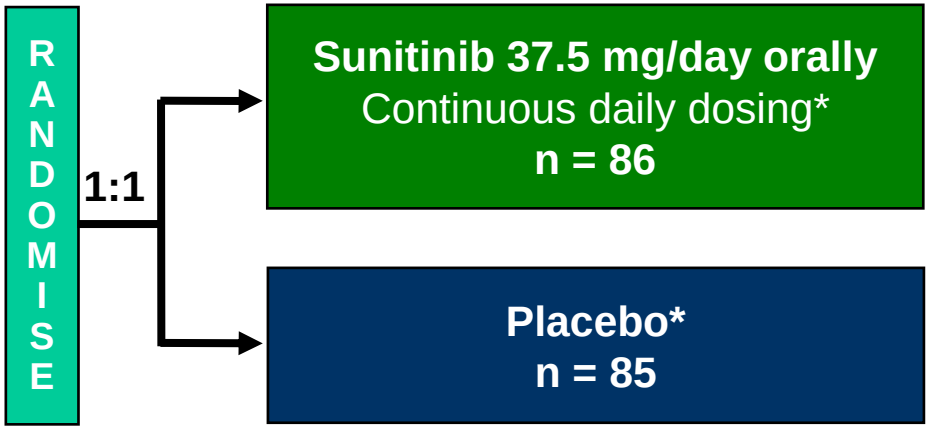
Sunitinib vs Placebo in Advanced pNET

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

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

- Disease progression in past 12 mo
- Not amenable to curative treatment



Primary Endpoint:
• PFS
Statistical significance required nominal critical z value ≥3.8809

Secondary Endpoints:
• OS
• ORR
• TTR
• Duration of response
• Safety
• Patient-reported outcomes

* With best supportive care
Somatostatin analogues were permitted

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

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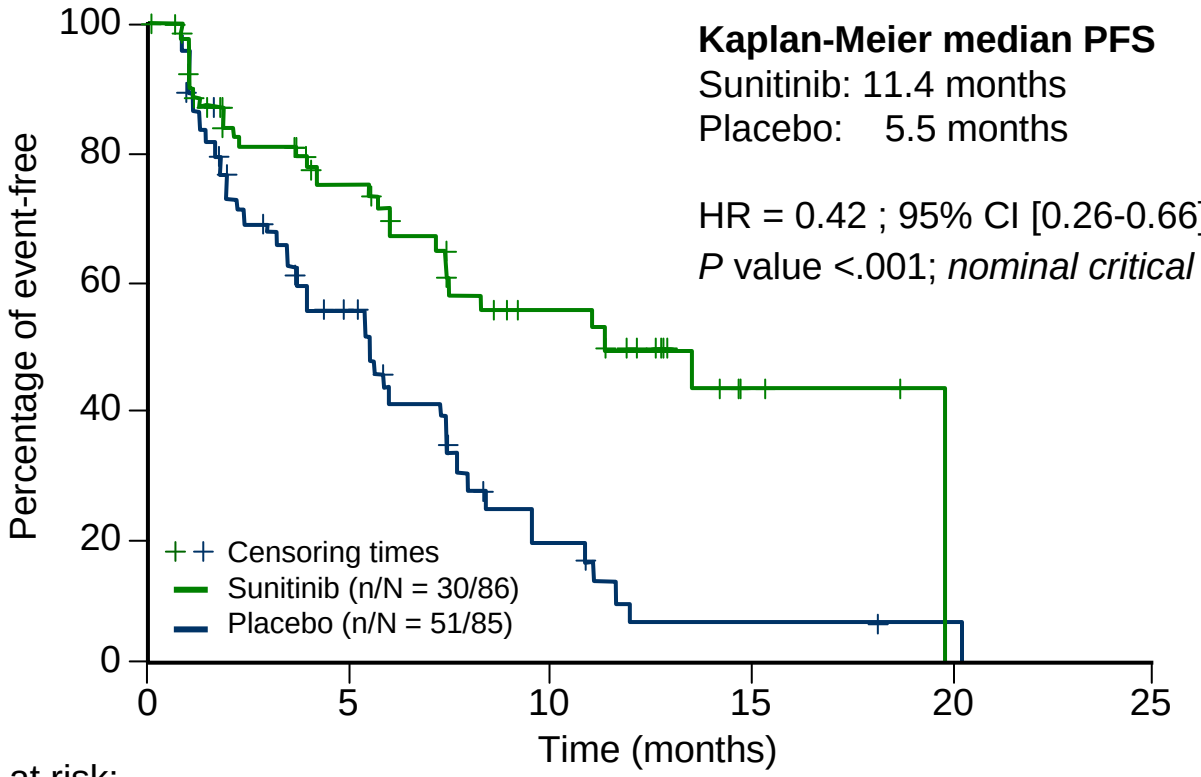
Progression-Free Survival*



Kaplan-Meier median PFS
Sunitinib: 11.4 months
Placebo: 5.5 months

HR = 0.42 ; 95% CI [0.26-0.66]
P value <.001; *nominal critical z value = 3.8506*

Number at risk:

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

* Local review

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

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Adverse Events: Sunitinib

- Most frequently reported all-grade AEs with sunitinib were diarrhea (59%), nausea (45%), asthenia (34%), vomiting (34%), and fatigue (33%)
- Grade 3/4 AEs (≥ 5%) in the sunitinib arm included neutropenia (12%), hypertension (10%), leukopenia (6%), PPE* (6%), asthenia (5%), diarrhea (5%), fatigue (5%), and abdominal pain (5%)

* Palmar-plantar erythro-dysesthesia

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

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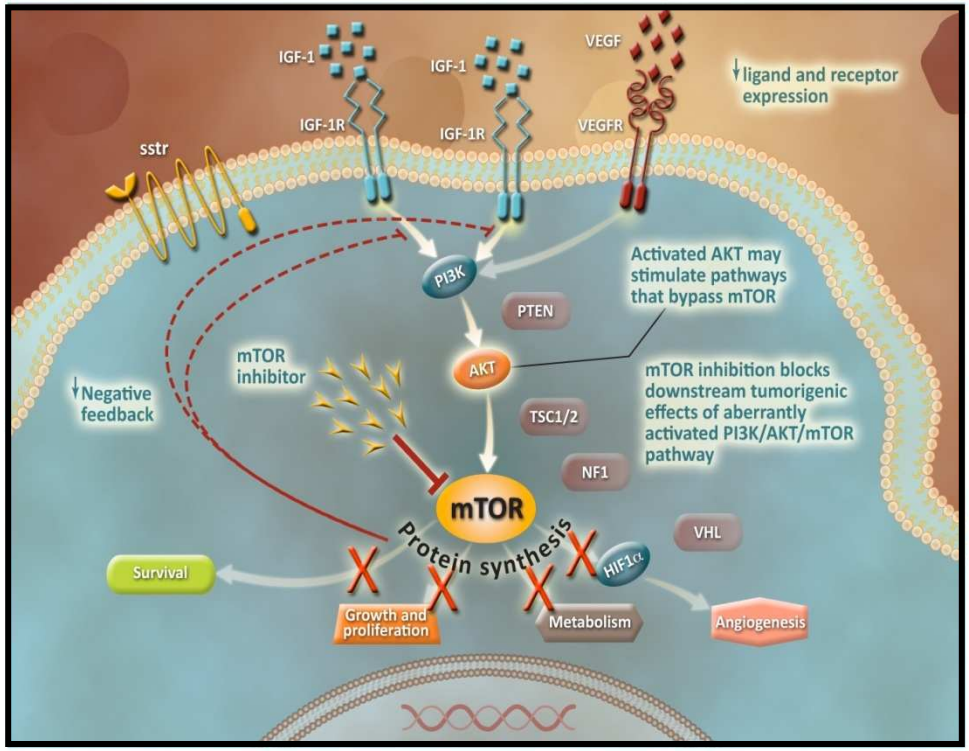
Rationale for mTOR Inhibition in NET

- mTOR is a central regulator of growth, proliferation, cellular metabolism, and angiogenesis[1-3]
- mTOR pathway activation is observed with genetic cancer syndromes associated with pNET[4]
  - TSC2, NF1, VHL
- Everolimus has demonstrated antitumour activity in pNET in phase II and phase III studies[5-7]



TSC2 = tuberous sclerosis 2; NF1 = neurofibromatosis type I; VHL = von Hippel-Lindau disease

[1]O'Reilly T, et al. *Transl Oncol*. 2010;3(2):65-79. [2]Meric-Bernstam F, et al. *J Clin Oncol*. 2009;27:2278-2287. [3]Faivre S, et al. *Nat Rev Drug Disc*. 2006;5:671-688. [4]Yao JC, et al. Pancreatic Endocrine Tumours. In: DeVita VT, Lawrence TS, Rosenberg SA, eds. *Cancer: Principles & Practice of Oncology.* 8th Edition. Philadelphia, PA: Lippincott Williams & Wilkins; 2008:1702-1721. [5]Yao JC, et al. *J Clin Oncol.* 2008;26:4311-4318. [6]Yao JC, et al. *J Clin Oncol*. 2010;28:69-76. [7]Yao J, et al. *NEJM* 2011; 364:514-23.

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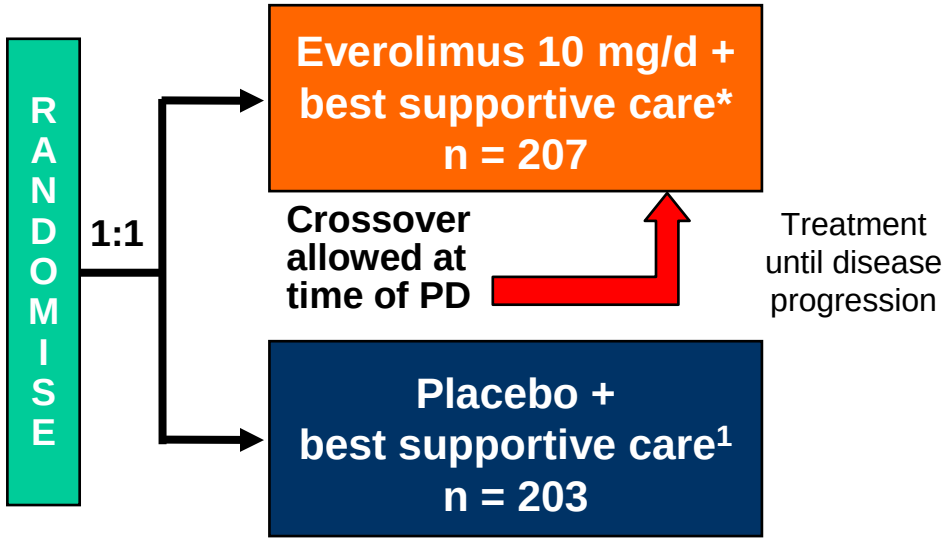
RADIANT-3 Study Design: Phase III Double-Blind, Placebo-Controlled Trial

Patients with progressive advanced pNET, N=410

- Advanced low- or intermediate-grade pNET
- Radiologic progression ≤12 months
- Prior antitumor therapy allowed
- WHO PS ≤2

Stratified by:

- WHO PS
- Prior chemotherapy



Multiphasic CT or MRI performed every 12 weeks

<u>Primary Endpoint</u>:

- PFS

Statistical boundary ≤.025

<u>Secondary Endpoints</u>:

- OS
- ORR
- Biomarkers
- Safety
- PK

Randomisation: August 2007-May 2009

* Concurrent somatostatin analogues allowed

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

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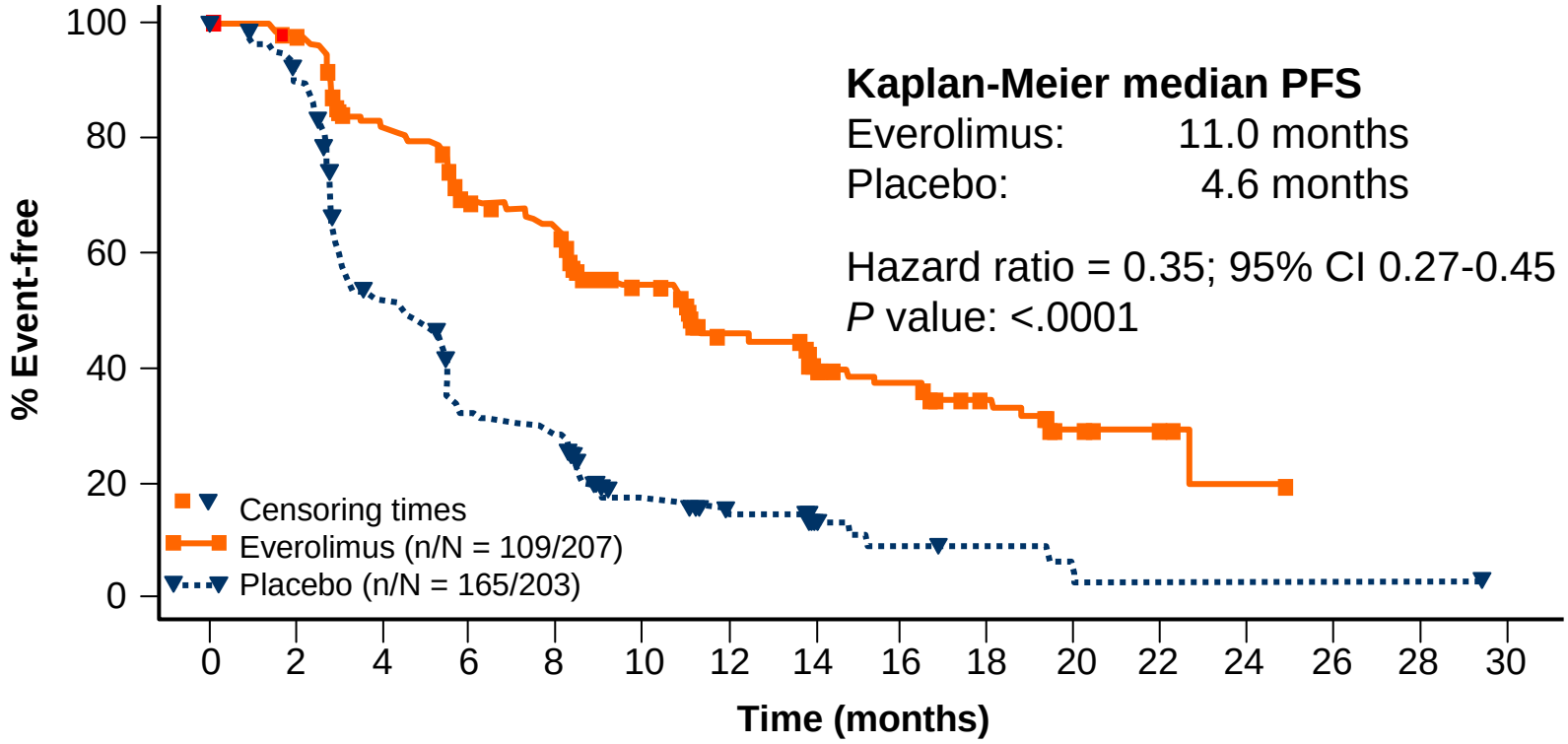
Progression-Free Survival



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

[1]Yao J, et al. *N Engl J Med.* 2011;364:514-523. 2. Yao JC, et al. 35th ESMO Congress; October 8-12, 2010; Milan, Italy; Abstract LBA9.

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Adverse Events: Everolimus

- Most frequently reported all-grade treatment-related AEs with everolimus were stomatitis (64%), rash (49%), diarrhea (34%), fatigue (31%), and infections (23%)
- Grade 3/4 AEs (≥ 5%) in the everolimus arm included stomatitis (7%), anemia (6%), and hyperglycemia (5%)

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

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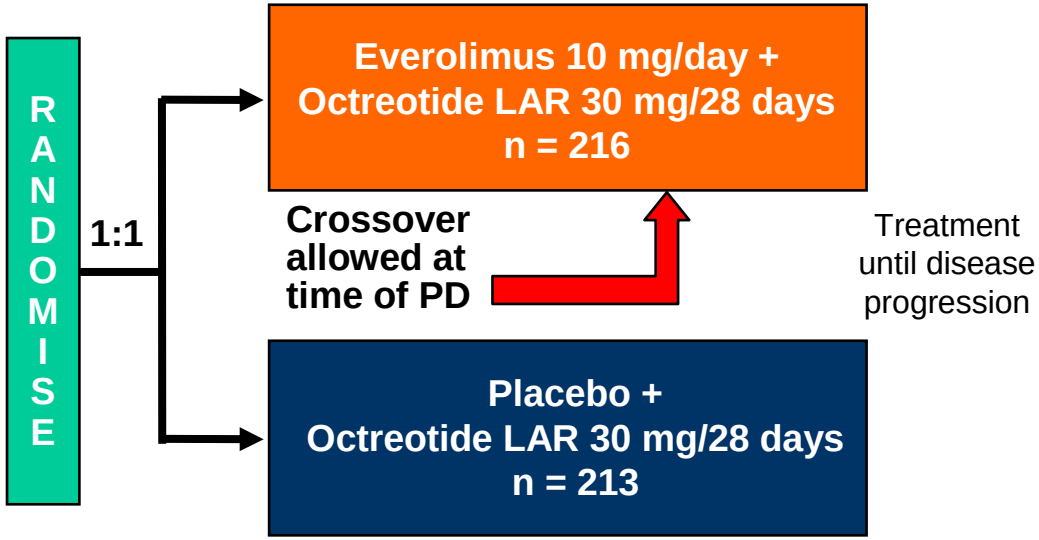
RADIANT-2 Study Design: Phase III, Double-Blind, Placebo-Controlled Trial

Patients with advanced NET and a history of secretory symptoms (N = 429)

- Advanced low- or intermediate-grade NET
- Radiologic progression ≤12 months
- History of secretory symptoms (flushing, diarrhea)
- Prior antitumour therapy allowed
- WHO PS ≤2



Multiphasic CT or MRI performed every 12 weeks

<u>Primary Endpoint</u>:

• PFS

Statistical boundary = .0246

<u>Secondary Endpoints</u>:

- OS
- ORR
- Biomarkers
- Safety
- PK

Enrollment January 2007-March 2008

PD = progressive disease; ORR = overall response rate; PK = pharmacokinetics

Yao JC, et al. Gastrointestinal Cancers Symposium; January 20-22, 2011; San Francisco, CA. Abstract 159.

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Requirements for improved therapeutic outcome in NET

- Applied classification and grading, possibly refined (Rindi et al. 2012; Ki-67 >5%)
- Elucidation of molecular genetics and cell biology
- Identification of serum markers for early diagnosis and follow-up; age at diagnosis
- Improved molecular imaging (PET) for therapy evaluation
- Markers that serve as predictors of response (SST, MGMT, PTEN? hLMHI?
- Individualize treatment
- Establishment of Centres of Excellence with multidisciplinary specialized clinical teams for NET

PET = positron emission tomography.

NET Treatment Algorithm