Diagnosis and Systemic Approaches in the Treatment of Advanced Neuroendocrine Tumors

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Seattle Cancer Care Alliance

PNW Carcinoid/NET Support Group – Carinoid/NET Patient Education Day. October 25, 2014

Terminology

- NET = neuroendocrine tumor
- pNET = pancreatic neuroendocrine tumor
- GEP-NET = gastroenteropancreatic neuroendocrine tumor

Question 1

What statement is most accurate?

A. Incidence of NET is decreasing
B. Incidence of NET is increasing
C. Prevalence of NET is decreasing
D. Prevalence of NET is increasing
E. A and C
F. B and D

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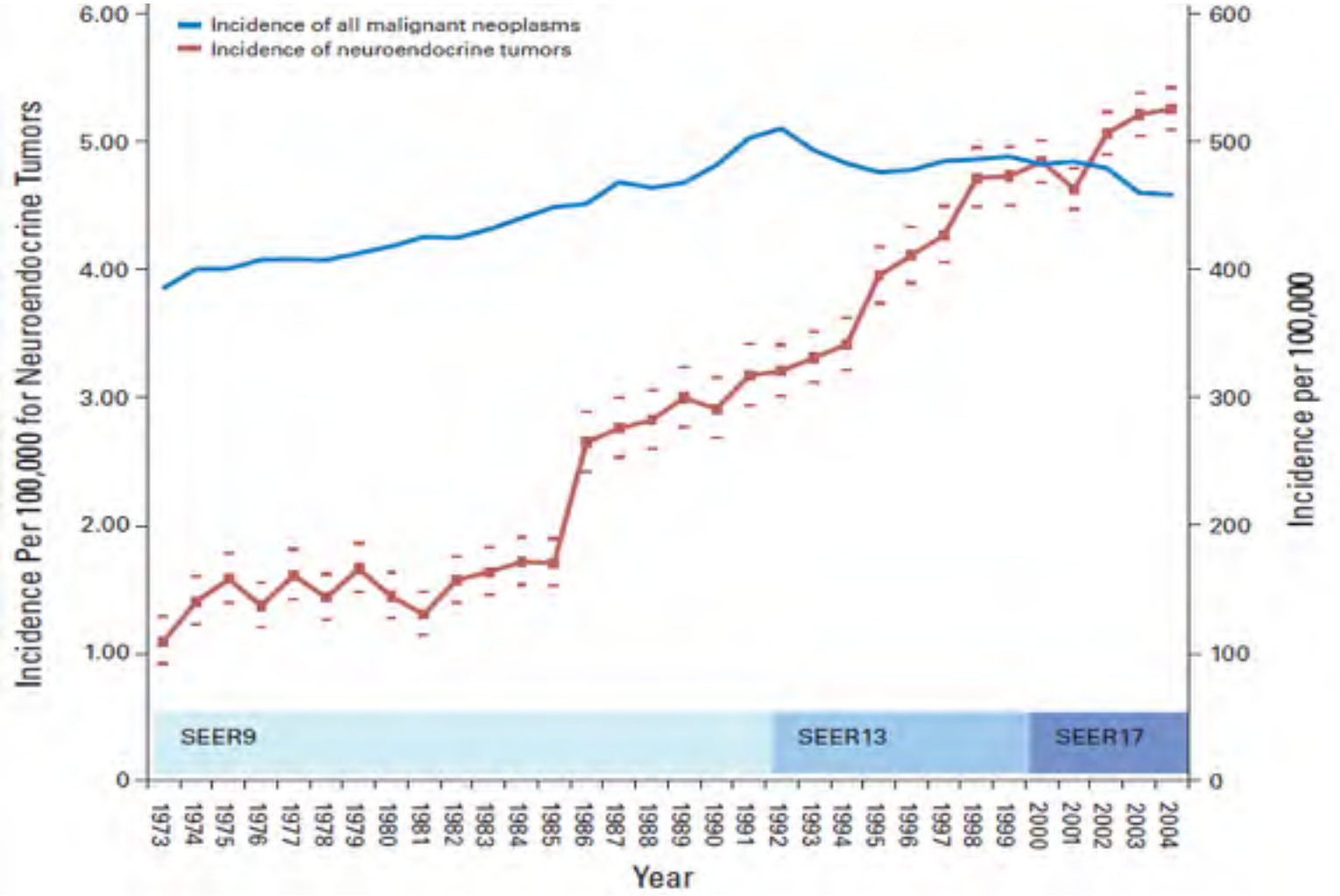
Rising Incidence in NETs: SEER Registry Data



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

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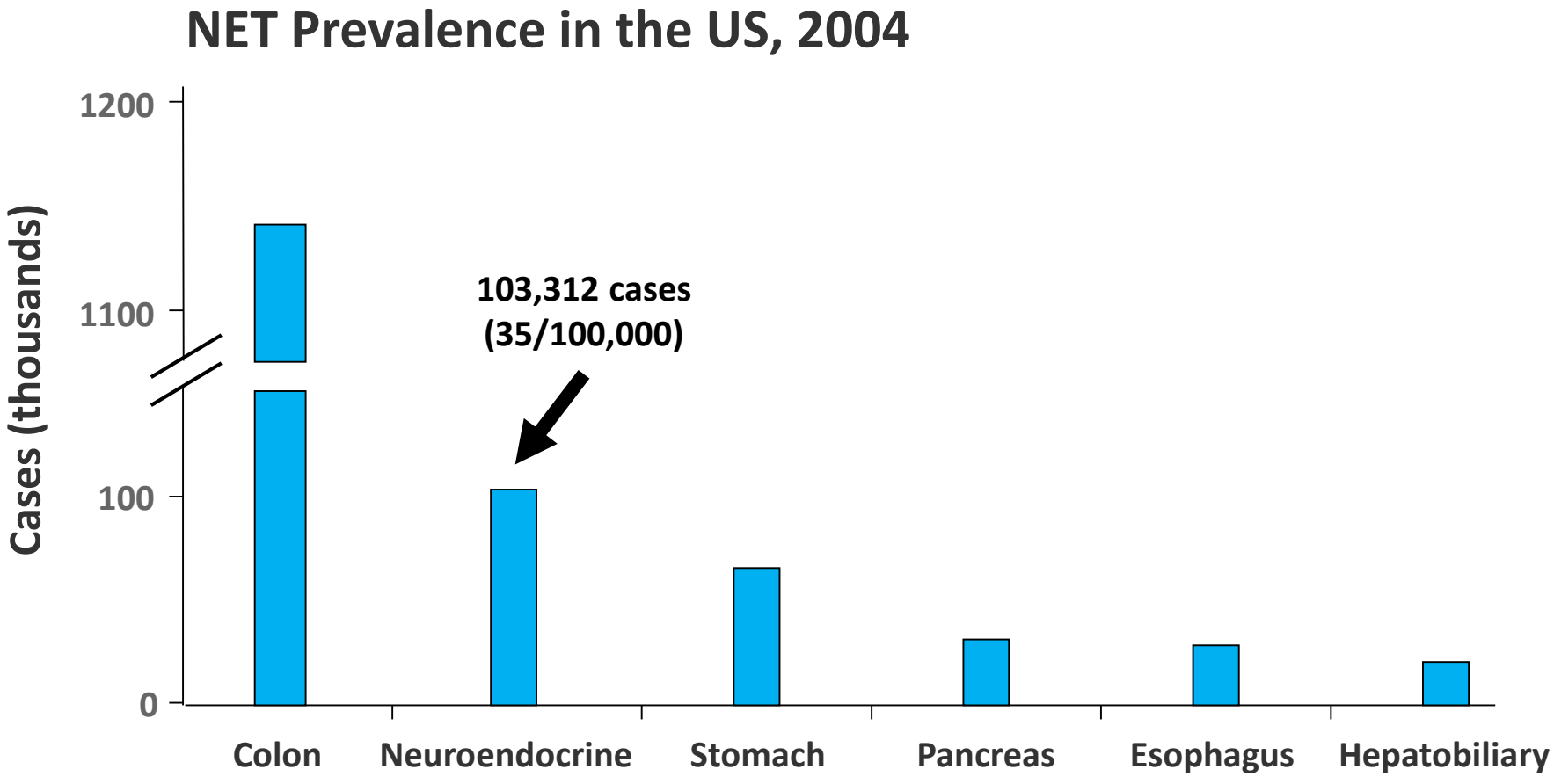
NETs Are Second Most Prevalent Gastrointestinal Tumor



29-year limited duration prevalence analysis based on SEER.
Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072.
SEER = Surveillance, Epidemiology, and End Results

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NETs - Overview

- NETs arise from enterochromaffin cells capable of producing a variety of hormones and peptides.

- NETs can be anatomically stratified:
  - Forgut (respiratory, stomach, duodenal, proximal jejunum, pancreas)
  - Midgut (distal jejunum, ileum, appendix, R-sided colon)
  - Hindgut (transverse & left colon, rectum)

- Biological heterogeneity– pathologic grading

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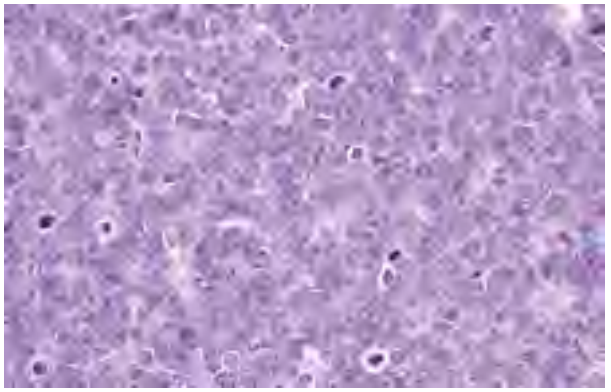
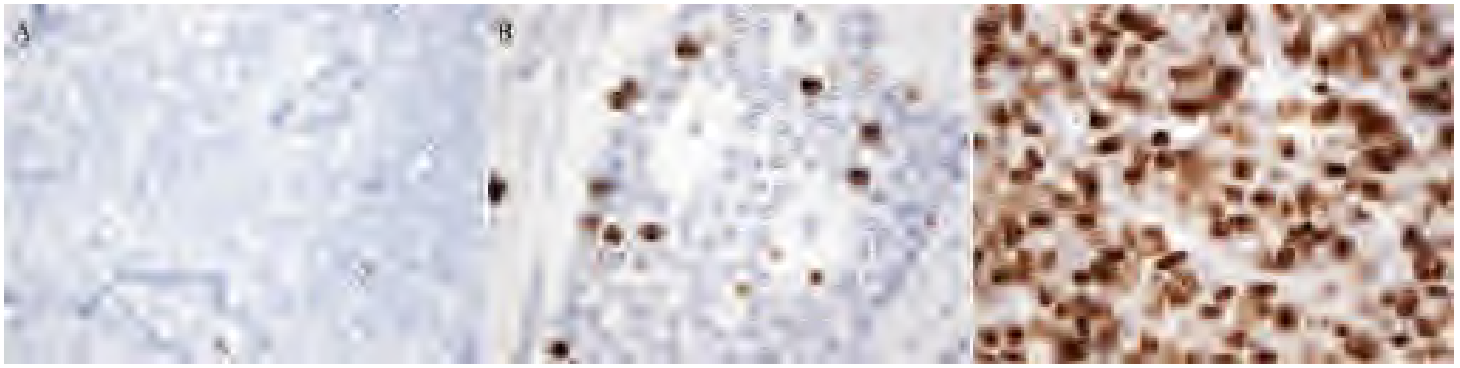
Grading Techniques – Ki67 and Mitotic Count

Mitotic count: 10 hpf ($2mm^2$), hard to distinguish mitoses



Ki67 Labeling Index: nuclear protein expressed at peak levels during mitoses. Eyeballing vs. manual counting of 2000 nuclei.



Khan et al. British Journal of Cancer. 2013; 108; 1838-1845.

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NETs – Pathologic Grading

Differentiation	Grade
Well-differentiated	Low grade
	Intermediate grade
Poorly differentiated	High grade

WHO grading system for GEP-NETs	
Low grade (G1)	< 2 mitoses / 10 hpf OR <3% Ki67 index
Intermediate grade (G2)	2-20 mitoses / 10 hpf OR 3-20% Ki67 index
High grade (G3)	>20% mitoses / 10 hpf OR >20% Ki67 index

Klimstra, D et al. *Pancreas*. 2010; 39:6, 707-12

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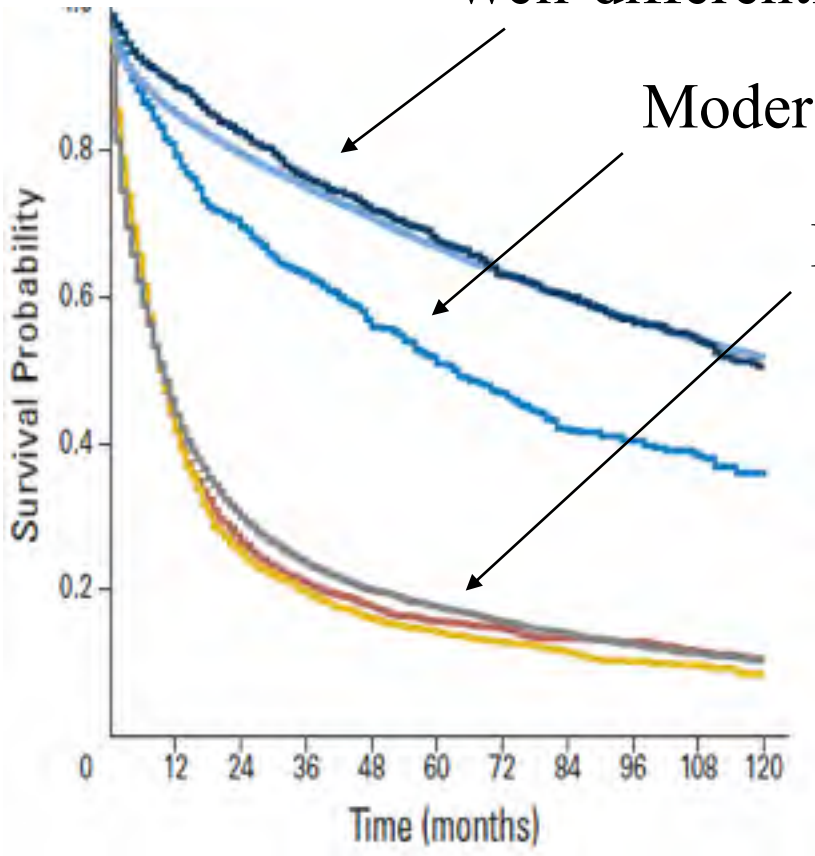
Prognosis According to Grade

Well-differentiated / Low grade

Moderately differentiated / Int grade

Poorly differentiated / High grade



	Median Survival	
	Months	95%CI
Carcinoid/islet cell: well-differentiated	124	101 to 147
Carcinoid/islet cell: unspecified grade	129	124 to 134
Carcinoid/islet cell: moderately differentiated	64	56 to 72
Neuroendocrine: poorly differentiated	10	9 to 11
Neuroendocrine: anaplastic	10	9 to 11
Neuroendocrine: unspecified grade	10	9 to 11

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

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Well-Differentiated NET Classification

Well-differentiated GEP-NETs

Carcinoid Tumor

- Without carcinoid syndrome (25-40%)
- With carcinoid syndrome (60-75%)

Pancreatic NETs (islet cell tumor)

- Non-functioning (50-75%)
- Functioning
  - Insulinoma
  - Gastrinoma
  - Glucagonoma
  - Somatostatinoma
  - VIPoma

Adapted from Kulke, M. *Hematol Oncol Clin N Am*. 2007; 21:3, 433-455
Feldman JM: Carcinoid tumors and syndrome. Semin Oncol 1987;14:237

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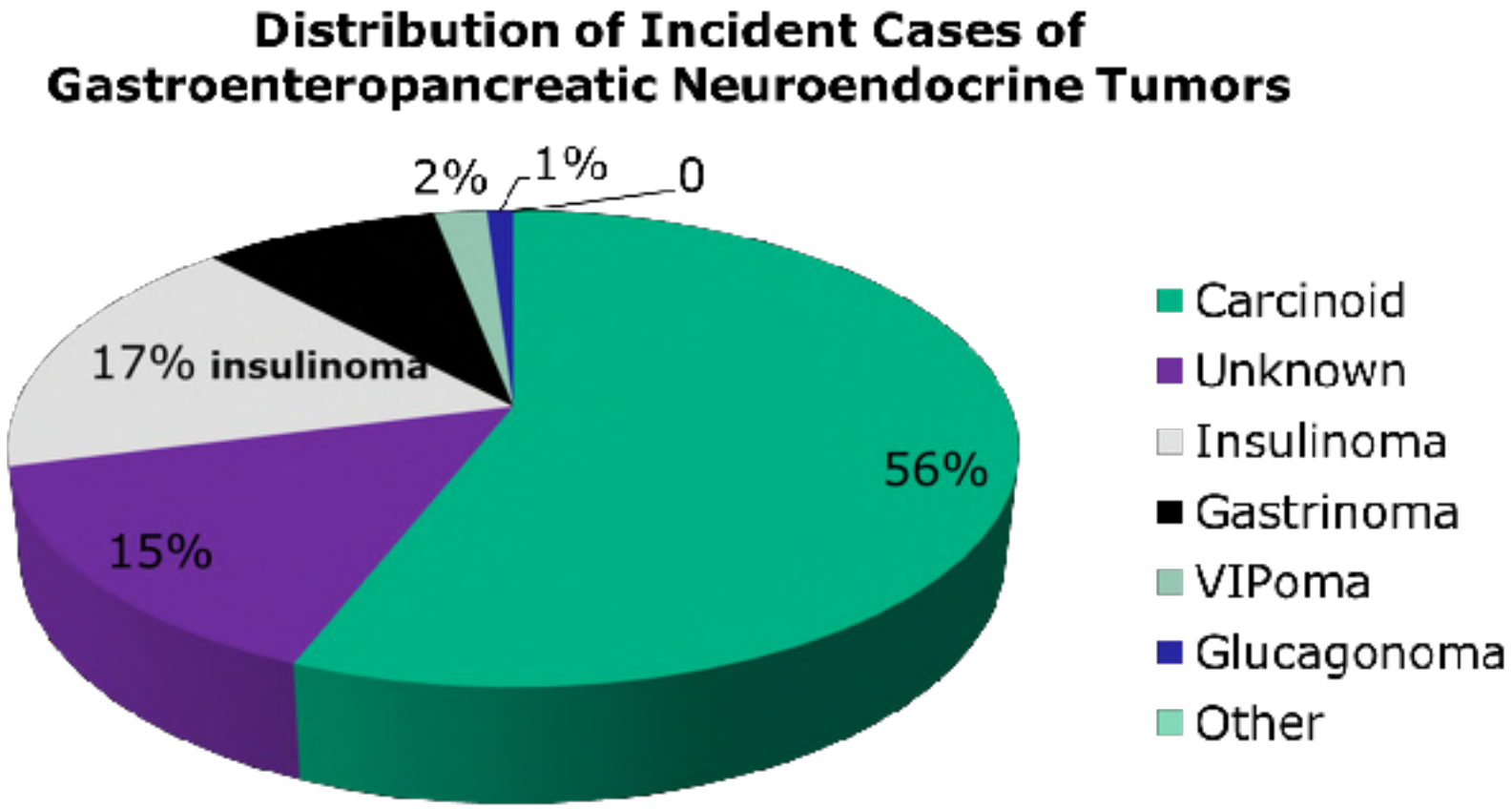
Distribution / Frequency of NETs



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GEP-NETs and Peptide and Hormone Production

Carcinoid Tumors	Pancreatic NETs
• Chromogranin • Serotonin, 5-hydroxytryptophan (not produced in hindgut carcinoids) • Histamine (gastric) • Kallikrein -> bradykinin • Prostaglandins • Substance P, Neurokinins • Insulin, ACTH, gastric, VIP, somatostatin (rarely in sufficient quantity to cause a clinical syndrome) • Others	• Chromogranin • Pancreatic polypeptide • Neuron specific enolase • Insulin • ACTH • Gastrin • VIP • Somatostatin • Glucagon • Others

Kulke, M. *Hematol Oncol Clin N Am*. 2007; 21:3, 433-455

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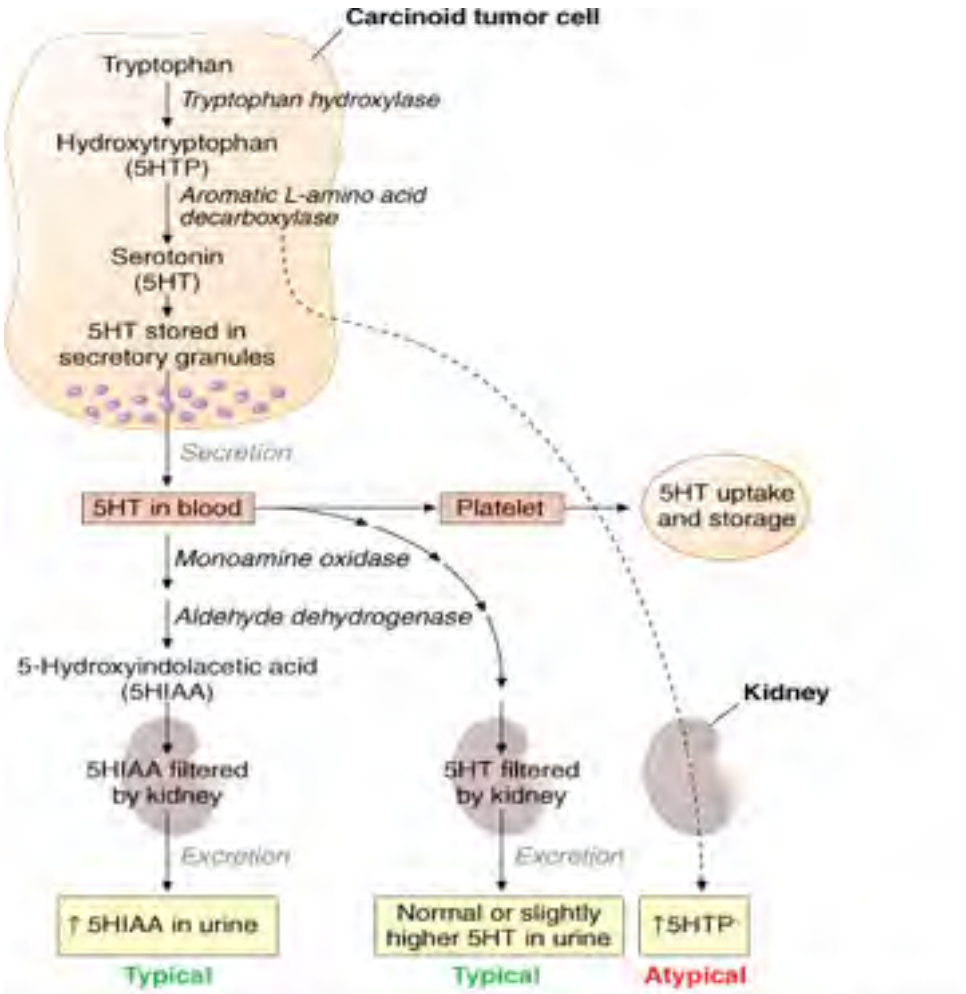
Carcinoid Syndrome: Altered Tryptophan Metabolism



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

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Question 2

Which of these individuals is LEAST likely to have symptoms of carcinoid syndrome?

A. 63 yo woman who is 3 months out from surgery to remove a rectal carcinoid
B. 54 yo male with a 5cm primary bronchial carcinoid
C. 39 yo woman with NET of unknown primary with extensive hepatic metastases
D. 47 yo woman with several tiny (all < 1cm) peritoneal metastases from a jejunal carcinoid
E. 60 yo woman with newly diagnosed ovarian carcinoid

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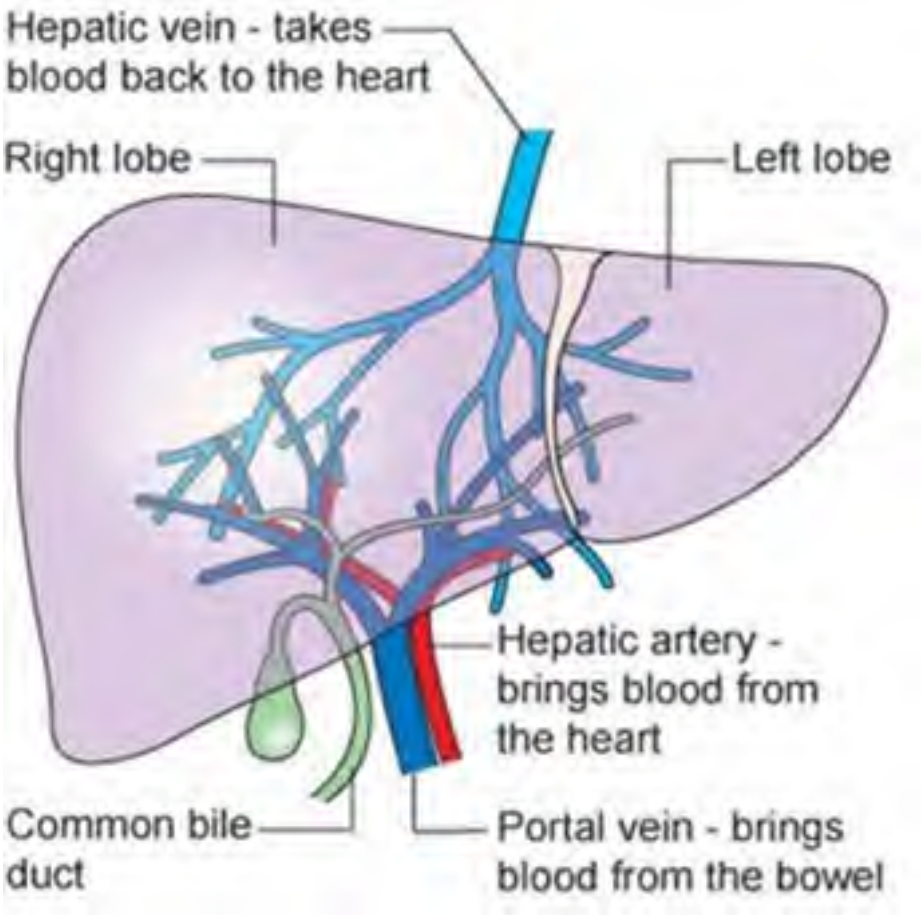
Portal Circulation



Exceptions:

- Ovarian carcinoid
- Peritoneal metastases
- Extensive retroperitoneal disease
- Bronchial carcinoids

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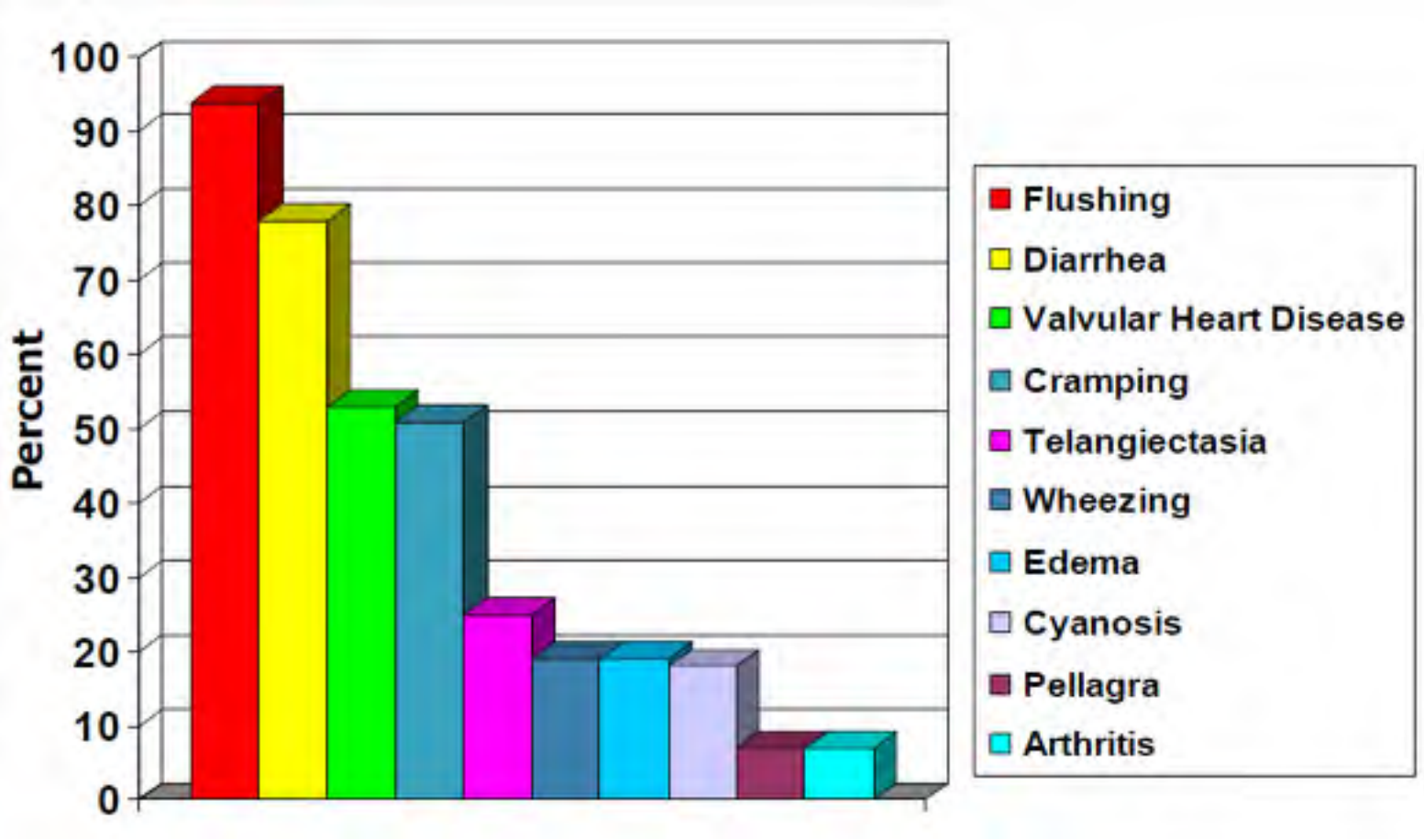
Carcinoid Syndrome Symptoms



Creutzfeldt, W. et al. World J Surgery. 1996; 20: 121-136.

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Diarrhea and Flushing in Carcinoid Syndrome

	Flushing	**Diarrhea**
Frequency	~ 90%	~ 80%
Characteristic Symptoms	• Dry flush • Several minutes to hours • Tachycardia • Venous telangictasias	• Increased small bowel colonic motility • Nocturnal, watery, nonbloody • Malabsorption • Urgency • Borborygmi
Triggers	EtOH Stress Infection Foods (spicy) Drugs	
Hormone	Kinins, prostaglandins	serotonin

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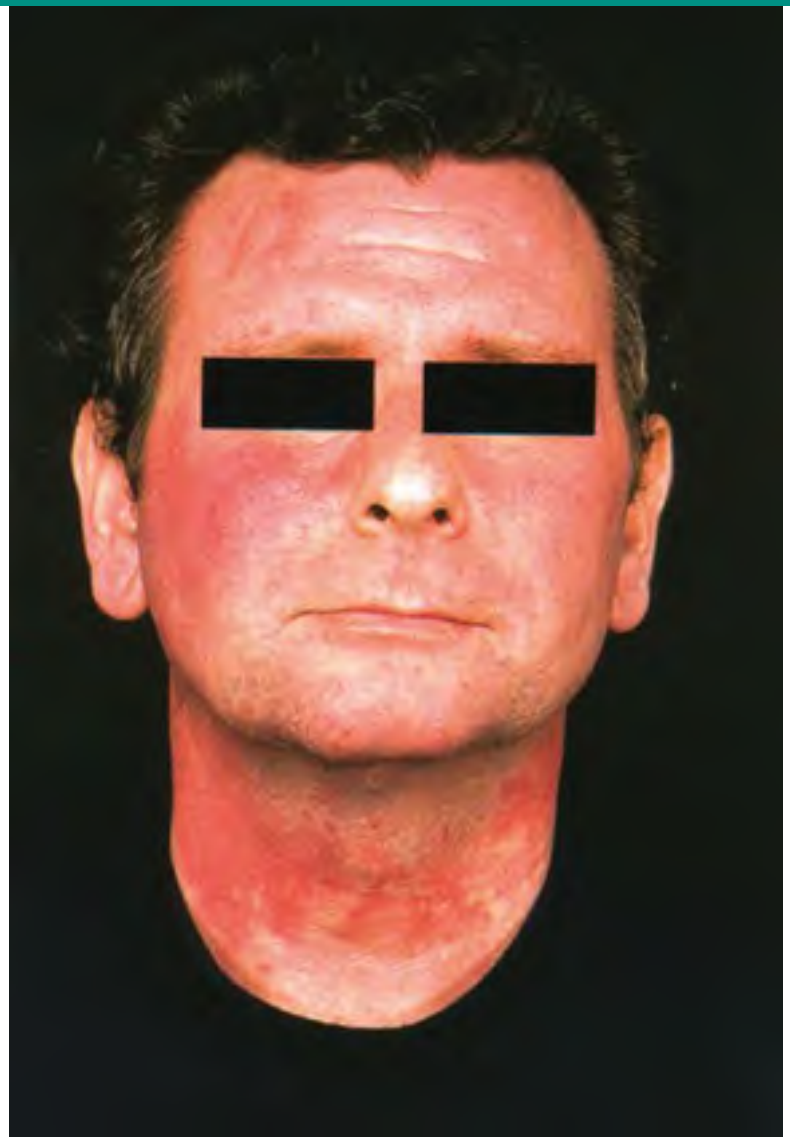
Flushing and Venous Telangiectasias



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Carcinoid Crisis

Etiology
Massive release of serotonin, histamine, kallikreins, or catecholamines
Symptoms
Profound flushing Hemodynamic instability Bronchoconstriction Confusion/stupor
Triggers
Anesthesia, Infection, Stress, Tumor manipulation, Embolization,
Treatment
Extra caution in patients with large hepatic tumor bulk, high 5HIAA, carcinoid heart disease IV octreotide (100-500 micrograms) f/b infusion, if necessary Avoid catecholamines for hypotension

Koopmans, KP et al. *J Nuc Med*. 2005; 46(7): 1240-43

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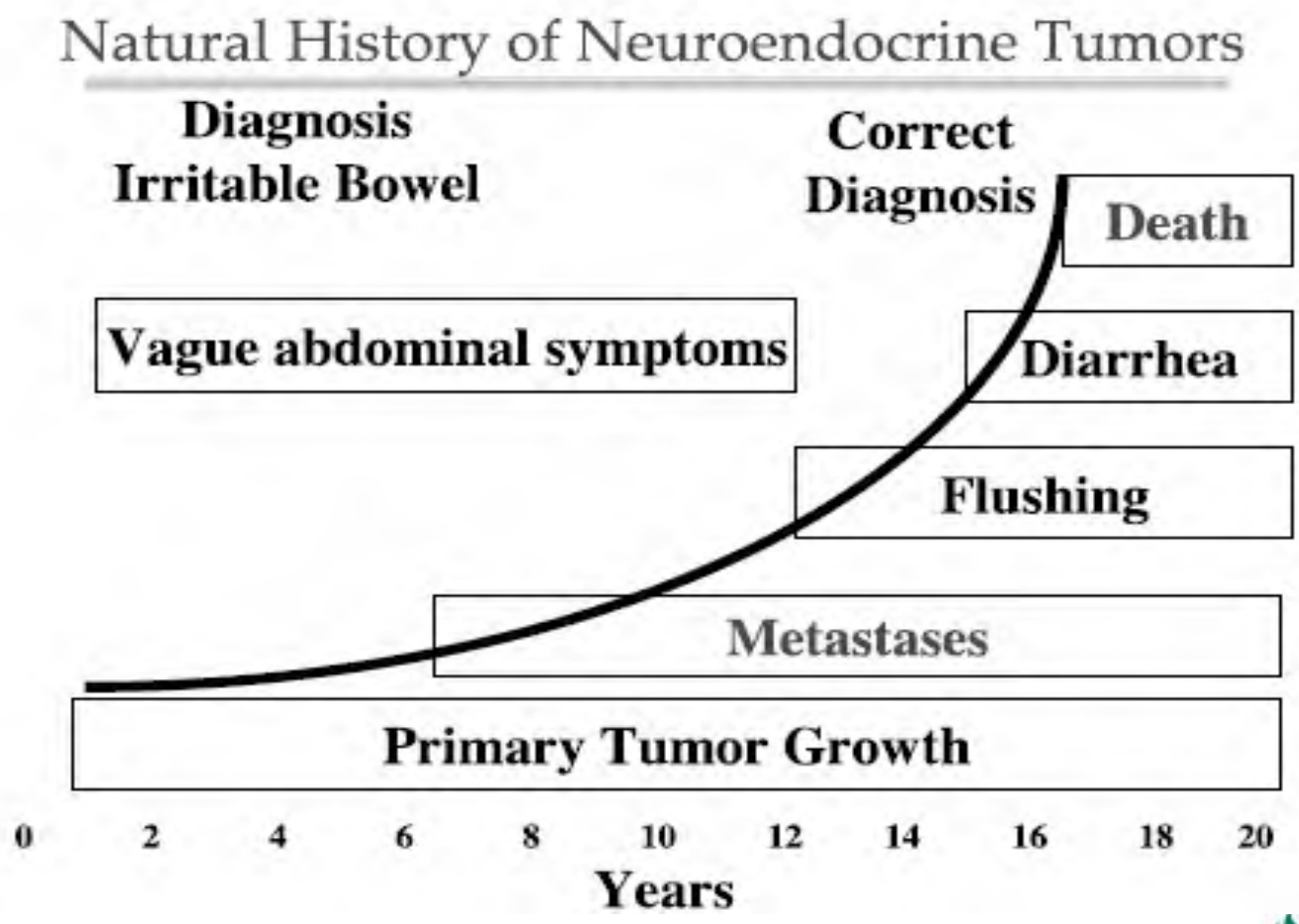
Delayed Diagnosis of Carcinoid Syndrome



Vinik A, et al. *Pancreas*. 2009; 38:8, 876-89

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Diagnosis of NET – Lab Evaluation

General NET Markers
Chromogranin-A: should be tested in same lab; trend Neuron specific enolase (NSE)
Carcinoid Syndrome
24 hour urine 5HIAA: (Usually > 100mg/d in patients with carcinoid syndrome (normal 2-8 mg/d) Serum serotonin: more variable than 5HIAA; no significant added value to 5HIAA BNP: sensitive and specific marker for carcinoid heart disease
Functioning Pancreatic NETs
Insulinoma: insulin, c-peptide, proinsulin, 72 hour fast Gastrinoma: gastrin (>1000 pg/mL is diagnostic); secretin stimulation test VIPoma: VIP level (serum VIP > 75 pg/mL) Glucagonoma: glucagon level (>500pg/mL)

Bhattacharyya S, et al. *Am J Cardiology*, 2008; 102(7): 938-42
Kulke, M. *Hematol Oncol Clin N Am*. 2007; 21:3, 433-455

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Use of Endoscopy in Diagnosis of NETs

- Standard endoscopy helpful in diagnosis of gastric, duodenal, hindgut NETs
- Endoscopic ultrasound (EUS) can be very useful in detecting small pancreatic lesions which are difficult to detect by conventional imaging
- EUS can be used as screening modality for patients at high risk of pancreatic NET (MEN1, VHL)

Vinik A, et al. *Pancreas*. 2010; 39:6, 713-34

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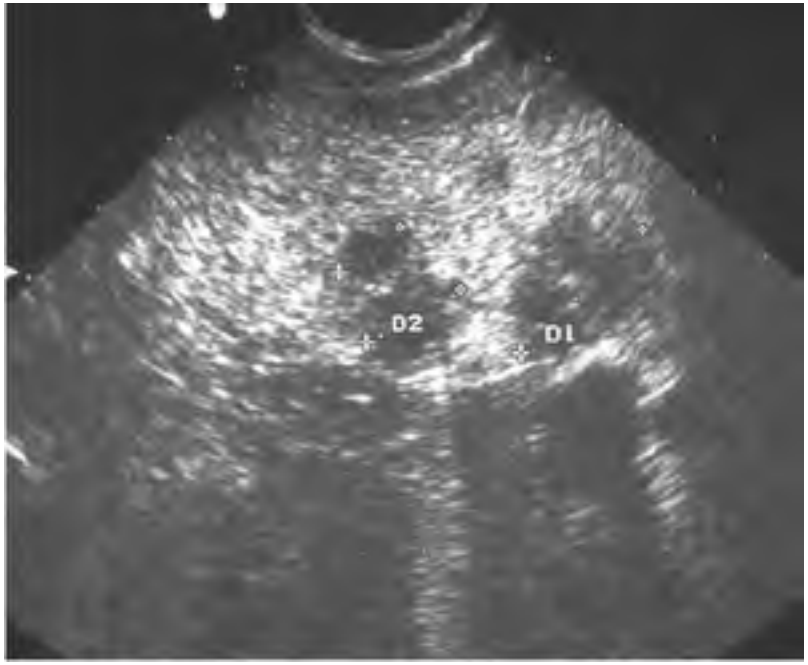
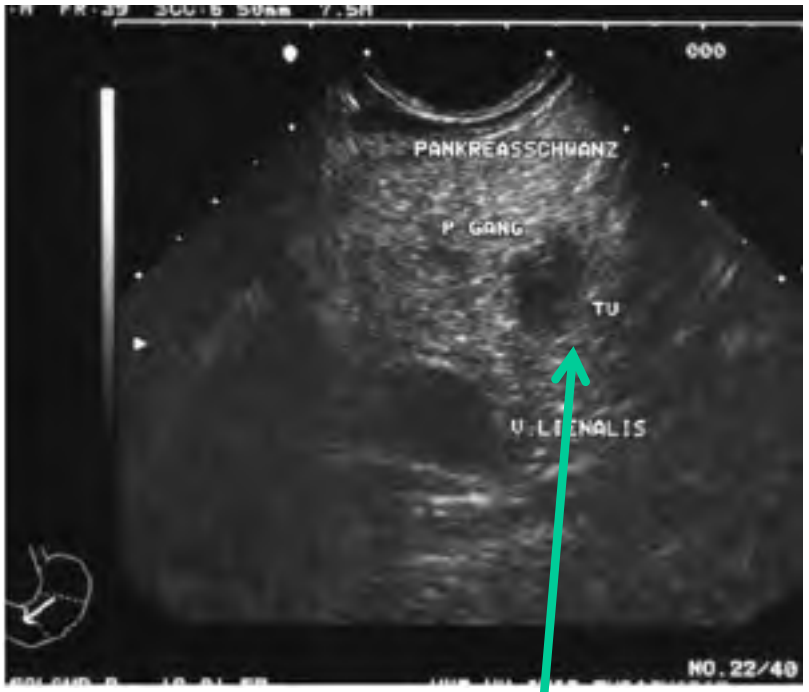
Endoscopic ultrasound



Multiple insulinomas measuring up to 15mm in diameter in neck of pancreas



Gastrinoma in tail of pancreas

Fritscher-Ravens. *J Pancreas*, 2004; 5(4):273-281.

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Cross-sectional Imaging

- CT/MRI typically to assess for metastatic disease
- NETs are vascular tumors which enhance in arterial phase and generally washout in delayed portal venous phase
  - Multiphase CT with thin cuts
  - Oral contrast to detect small bowel tumors
  - Dynamic contrast-enhanced MRI – high signal on T2 weighted images
  - CT enterography might help to better identify small bowel tumors

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Somatostatin Receptor Scintigraphy

- Indium-111 radiolabeled octreotide can be used to image tumors expressing somatostatin (SST) receptors 2 and 5
  - 80-90% of NETs express SST2 receptor
  - 50-60% of NETs express SST5 receptor
- Can be used 4 wks post octreotide LAR therapy dose
- Anachronistic in light of improved CT / MR quality?

Feldman: *Sleisenger and Fordtran's Gastrointestinal and Liver Disease*, 9th ed.
Reidy-Lagunes D, et al. *J Clin Oncol*. 2011; 29(3):e74-5

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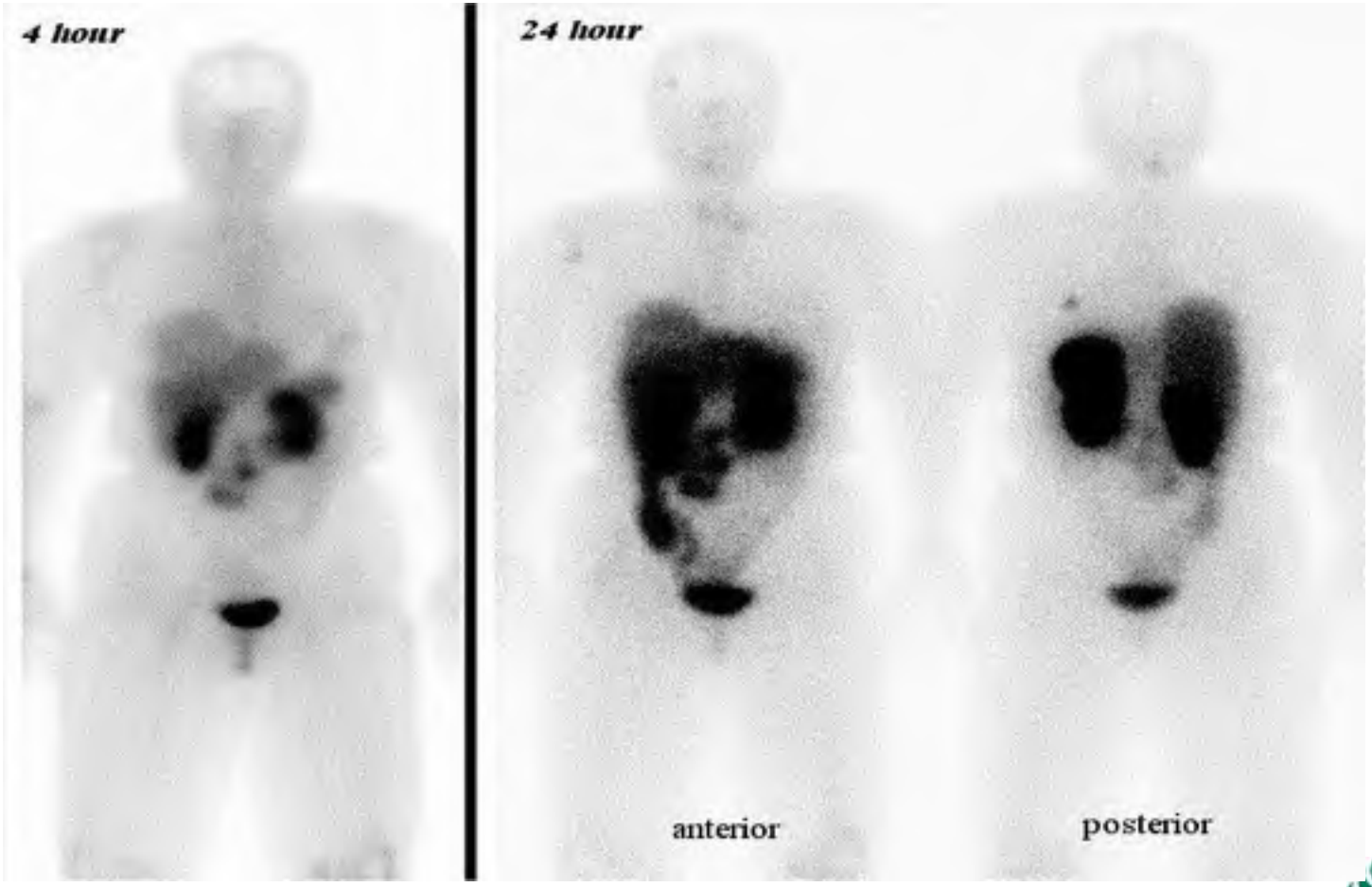
Somatostatin Receptor Scintigraphy



Dartmouth Hitchcock Medical Center – case presentations

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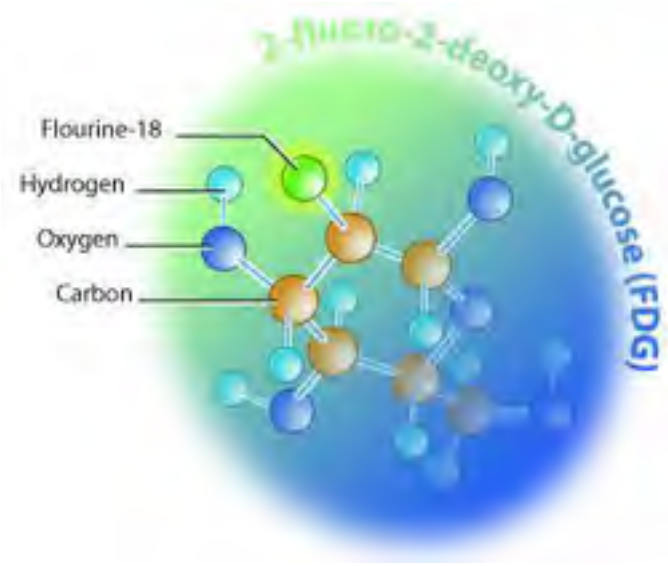
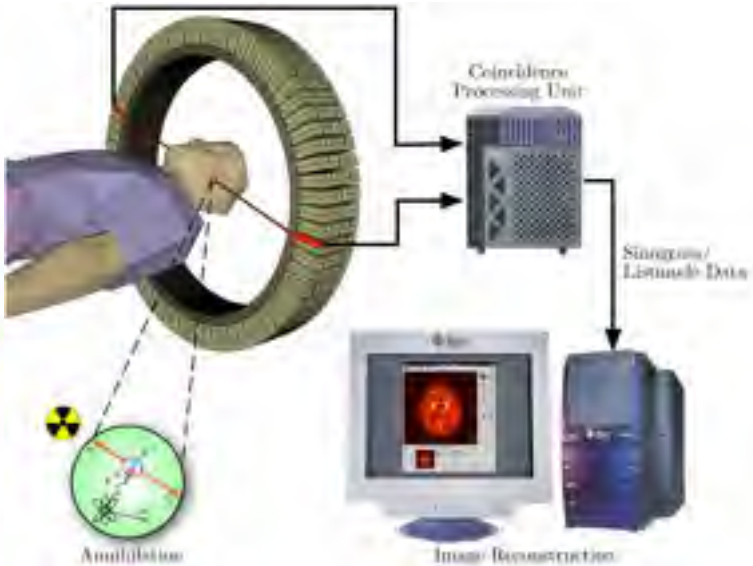
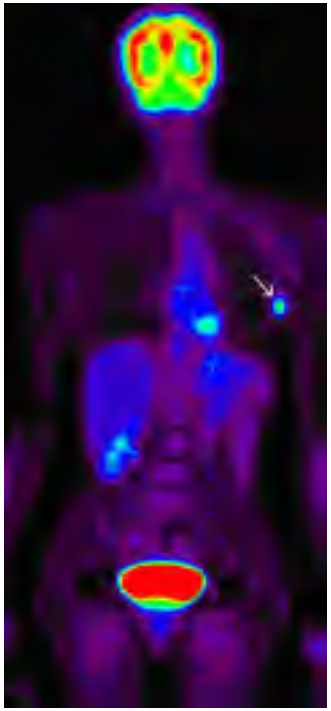
PET/CT Imaging in NETs







- Good for many solid tumors – aggressive cancers
- Not great for NET imaging

Dept of Radiology, University of Michigan Medical School

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Functional PET Imaging

- Several PET tracers for functional imaging:
  - ^{18}F-DOPA (18-F-dihydroxy-phenyl-alanine)
  - C-5-HTP (C-5-hydroxytryptophan)
  - 68-Ga-DOTATOC (68-Ga-DOTA-D-Phe^{1}-Tyr^{1}-Octreotide)
- Combined with high resolution PET-CT imaging

Koopmans KP, et al. *J Clin Oncol*. 2008; 26(9): 1489-95

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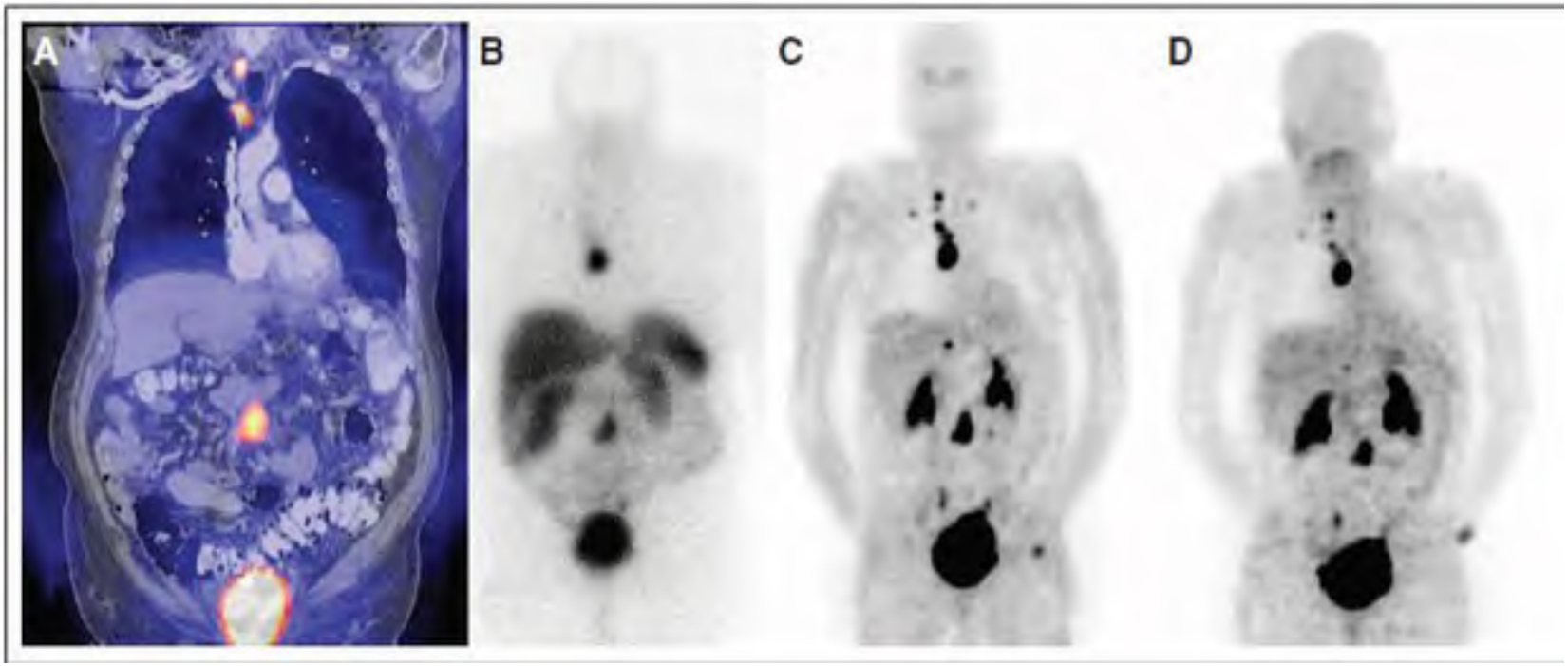
Functional PET Imaging



A. ^{18}F-DOPA PET; B. Somatostatin receptor scintigraphy; C. ^{18}F-DOPA PET; D. C-5-HTP PET

Koopmans KP, et al. *J Clin Oncol*. 2008; 26(9): 1489-95

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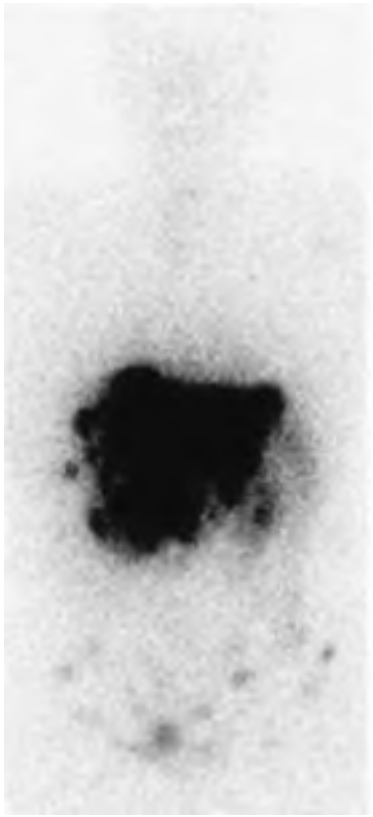
Functional PET Imaging

68-Ga-DOTATOC PET



111-In-DTPAOC SPECT

Buchmann I., et al. Eur J Nucl Med Mol Imaging. 2007; 34: 1617-1626

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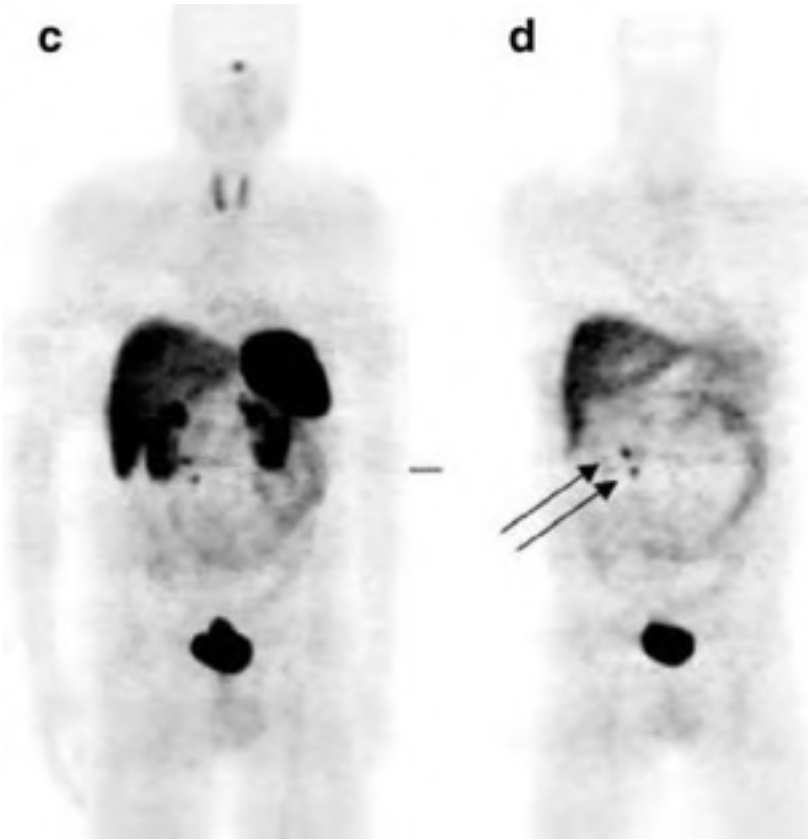
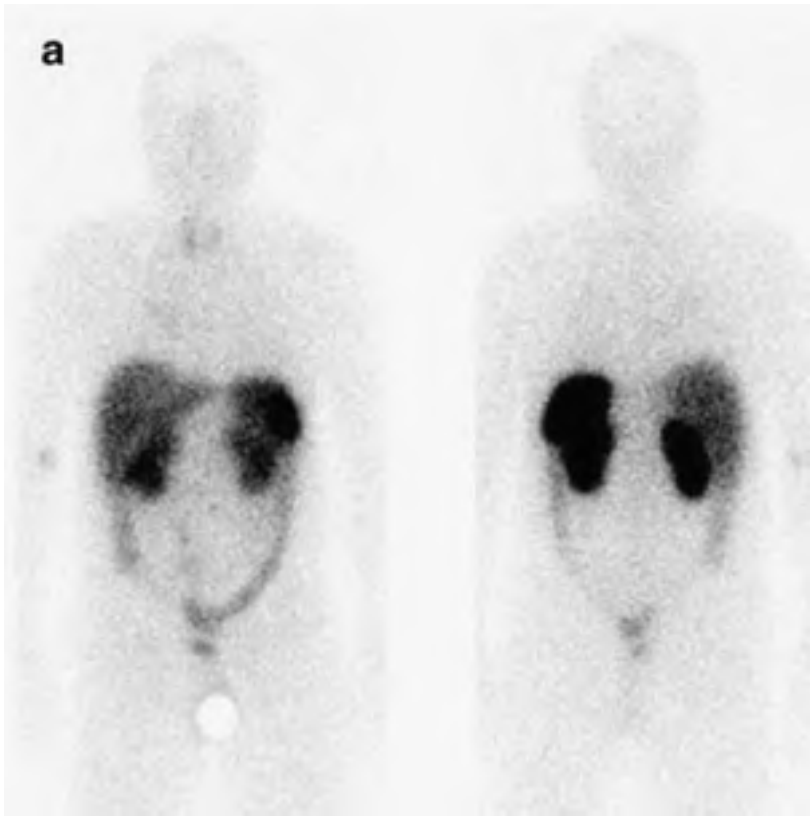
Functional PET Imaging



68-Ga-DOTATOC PET



111-In-DTPAOC SPECT

Buchmann I., et al. Eur J Nucl Med Mol Imaging. 2007; 34: 1617-1626

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Question 3

What are the major goals of therapy in individuals with metastatic NET?

A. Control symptoms of hormone hypersecretion
B. Delay disease progression / improve survival
C. Prevention of bowel obstruction
D. Maintain high quality of life
E. All of the above

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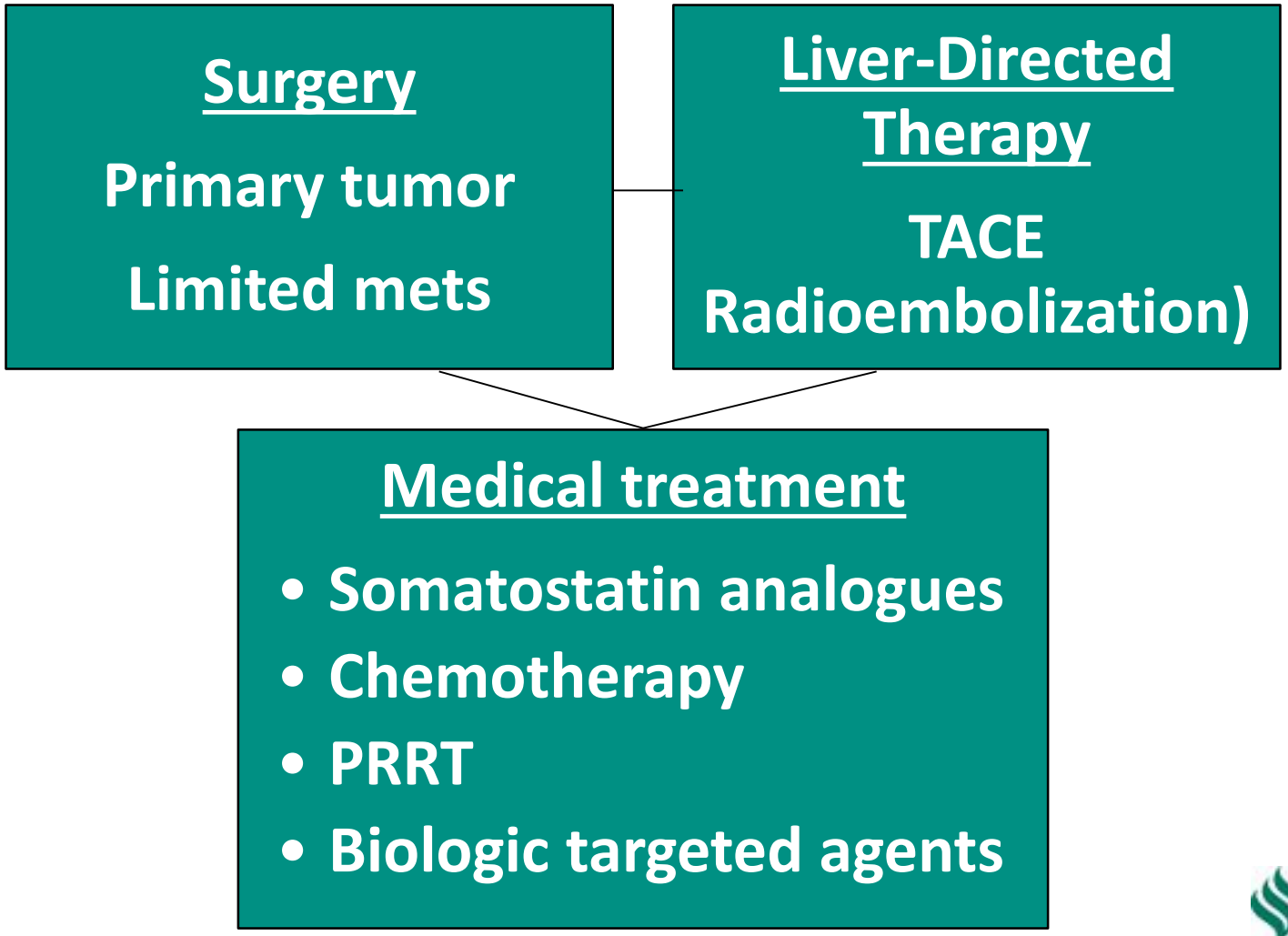
Advanced GEP-NETs: Treatment Approaches



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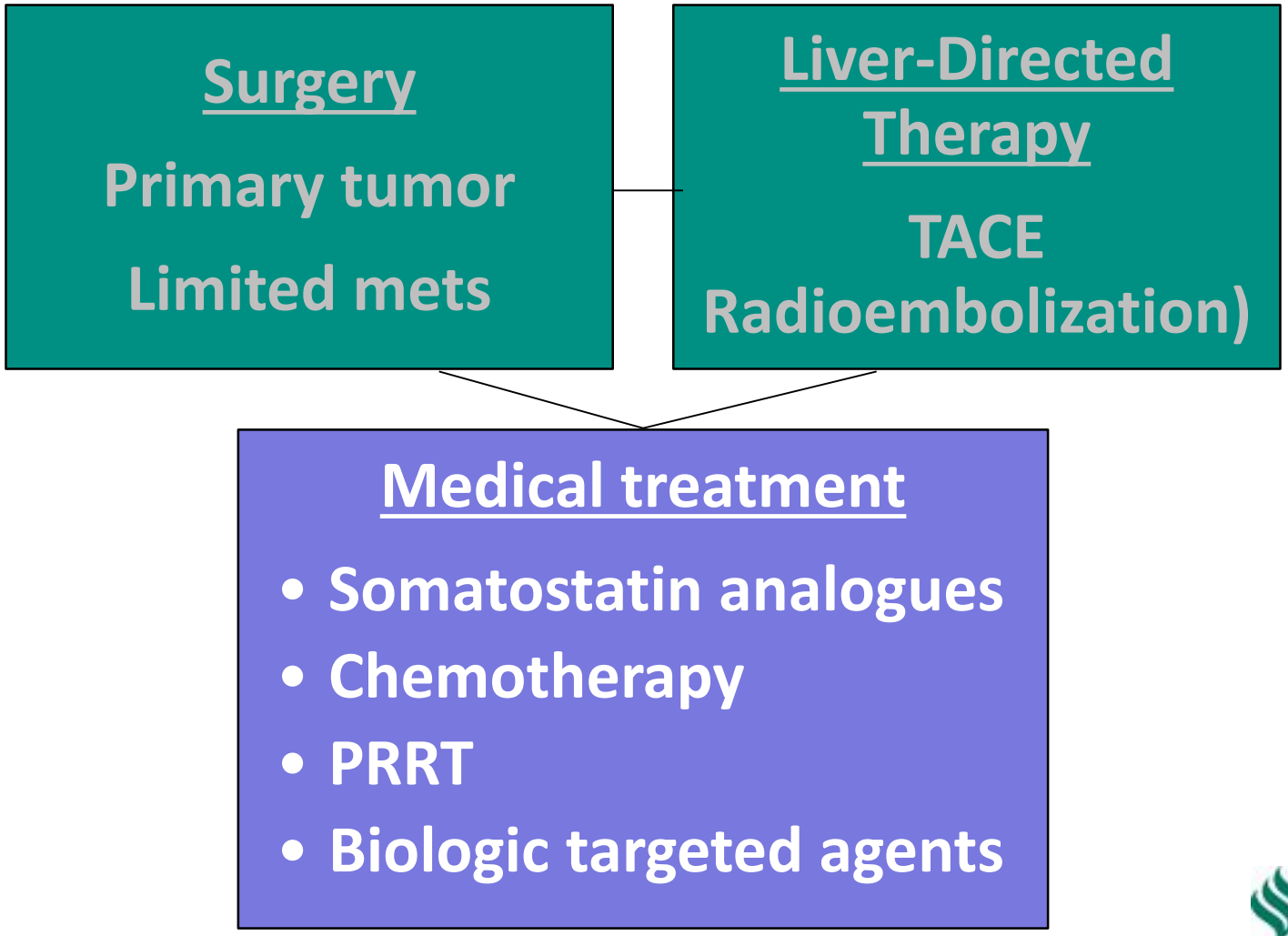
Advanced GEP-NETs: Treatment Approaches



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Backbone of NET Therapy: Somatostatin Analog Treatment

- Important role in the control of symptoms related to functional NETs
- Anti-proliferative effect (PROMID, CLARINET)
- Well-tolerated

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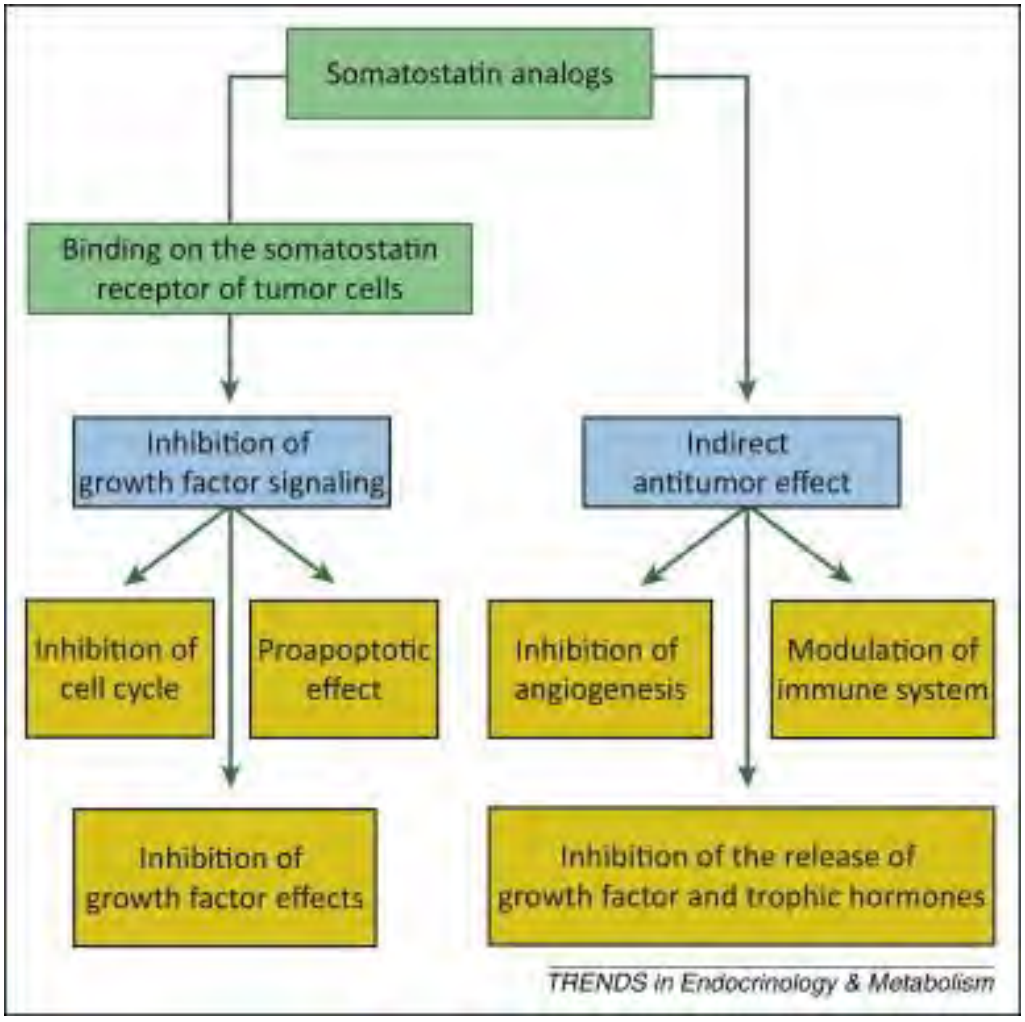
Somatostatin Analogues – Antiproliferative Effect Schematic



Chalabi, M et al. Trends in Endocrinology and Metabolism. 25:3, 115-127

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PROMID Study: Octreotide LAR

VOLUME 27 · NUMBER 28 · OCTOBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Placebo-Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors: A Report From the PROMID Study Group

Anja Rinke, Hans-Helge Müller, Carmen Schade-Brittinger, Klaus-Jochen Klose, Peter Barth, Matthias Wied, Christina Mayer, Behnaz Aminossadati, Ulrich-Frank Pape, Michael Bläker, Jan Harder, Christian Arnold, Thomas Gress, and Rudolf Arnold

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PROMID Study

Study Design
•Randomized, double-blind, placebo-controlled •Randomization dynamically balanced: age, Ki67, mets, functionality
Inclusion/Exclusion
•Well differentiated NET •Midgut origin •No somatostatin analogue use for ≥ 4 weeks
Enrollment
90 patients randomized (Recruitment terminated early) •*Octreotide LAR* 30mg q28d (n=42) versus •*Placebo* (n=43)

Rinke A, et al. *J Clin Oncol*. 2009; 27(28): 4656-63

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PROMID Study: Patient Characteristics

Characteristic	Octreotide (n=42)	Placebo (n=43)	p-value
Median age	63.5	61	0.54
Male	20 (47.6%)	23 (53.5%)	0.67
Median time since diagnosis	7.5 months	3.3 months	0.10
Karnofsky >80%	35 (83.3%)	338 (88.4%)	0.55
Carcinoid syndrome	17 (40.5%)	16 (37.2%)	0.83
Resection of primary tumor	29 (69.1%)	27 (62.8%)	0.65
Ki-67 up to 2%	41 (98%)	40 (93%)	0.62
Octreoscan Positive Negative	 32 (76.2%) 4 (9.5%)	 31 (72.1%) 6 (14%)	0.88
Liver involvement <25% 25-50% >50%	 35 (83.3%) 5 (11.9%) 2 (4.8%)	 34 (79%) 4 (9.3%) 5 (11.6%)	0.77
Chromogranin-A Elevated Not elevated	 26 (61.9%) 15 (35.7%)	 30 (69.8%) 12 (27.9%)	0.74

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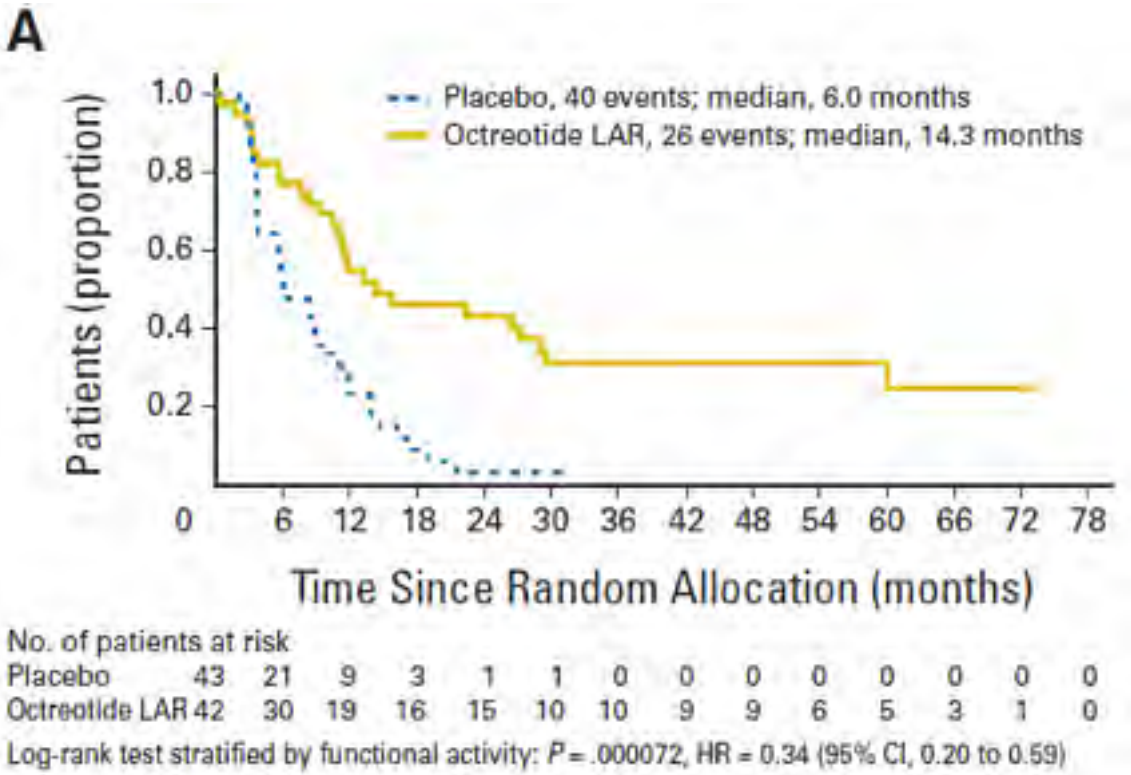
PROMID – primary endpoint

- Time to tumor progression 14.3 mo vs. 6 mo (HR 0.34, 95% CI 0.20, 0.59; p=0.00072



Rinke A, et al. *J Clin Oncol*. 2009; 27(28): 4656-63

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PROMID - Conclusions

- Long-acting octreotide delayed tumor progression in patients with *midgut* NETs who had minimal prior exposure to somatostatin analog
- No statistically significant difference in overall survival
- Should be considered as an option for disease stabilization regardless of functionality or uptake on octreoscan
- Optimal timing of treatment initiation remains unclear
- Well-tolerated

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Somatostatin Analogues: Octreotide vs. Lanreotide

	SSTR1	SSTR2	SSTR3	SSTR4	SSTR5
Octreotide	1140	0.56	34	7030	7
Lanreotide	2330	0.75	107	2100	5.2
Pasireotide	9.3	1	1.5	>100	0.16

Receptor subtype affinity (IC50, nM)

Baldelli, R. et al. Frontiers in Endocrinology. Feb 2014.

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CLARINET Study: Lanreotide

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., Jaume 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*

Caplin M et al. NEJM. 2014, 371 (3): 224-233

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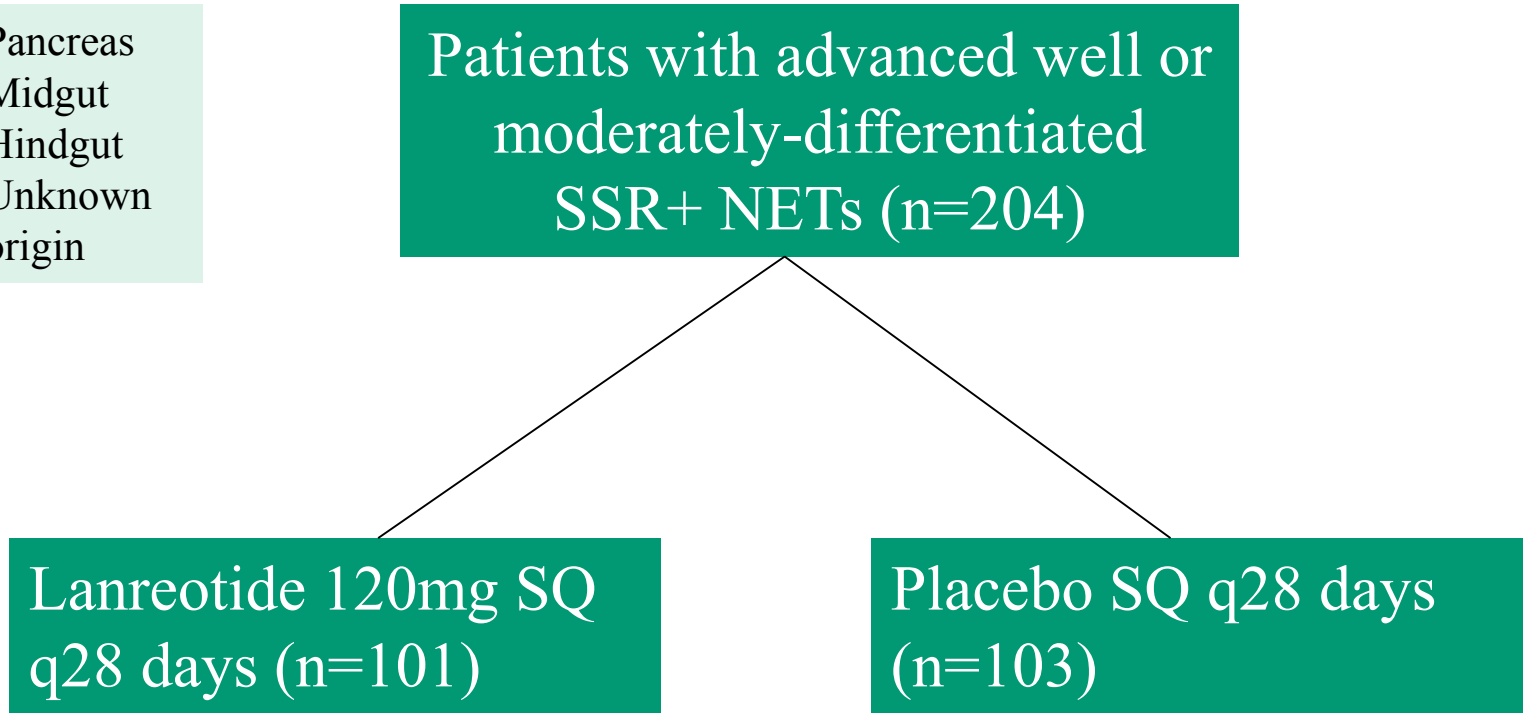
CLARINET Study: Lanreotide

- Pancreas
- Midgut
- Hindgut
- Unknown origin



Primary Endpoint = PFS

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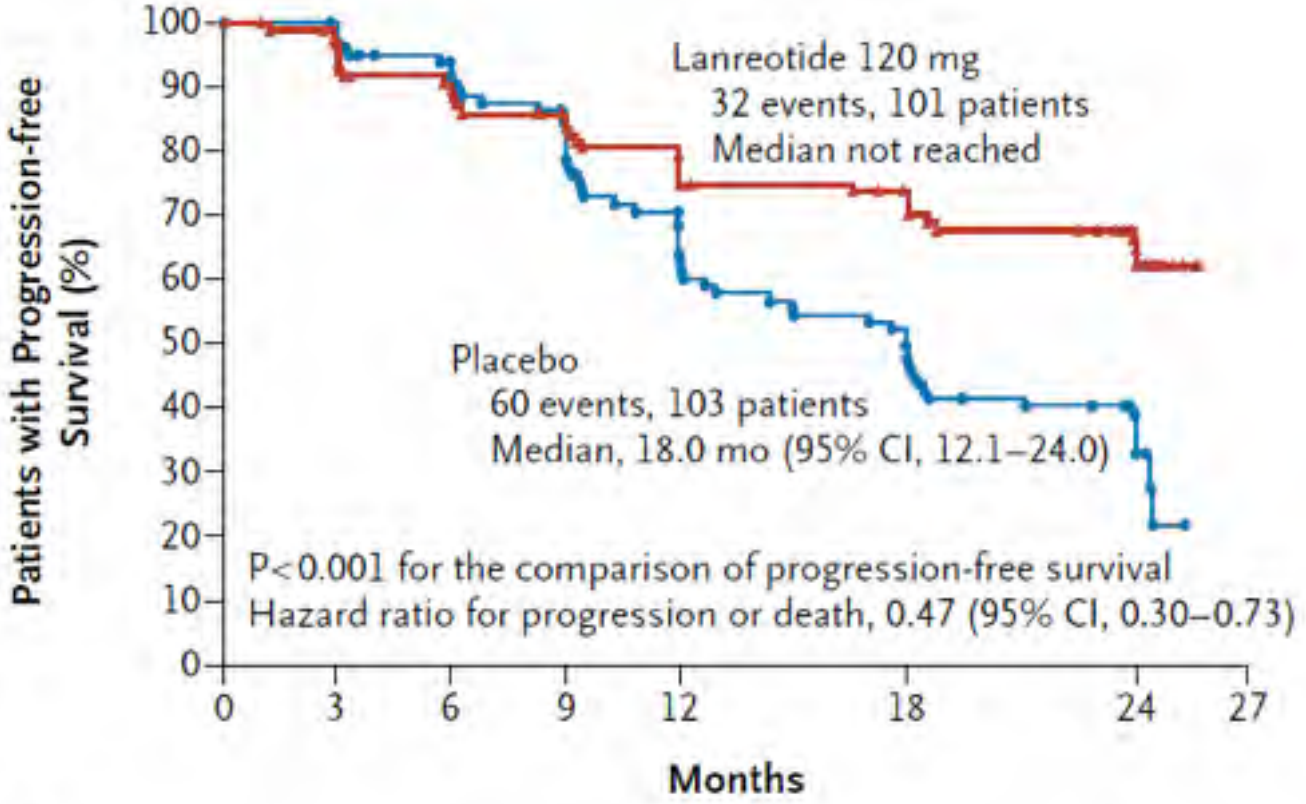
CLARINET Study: Lanreotide

Table 1. Baseline Demographic and Disease Characteristics of the Patients (Intention-to-Treat Population).*

Variable	Lanreotide (N=101)	Placebo (N=103)
Male sex — no. (%)	53 (52)	54 (52)
Age — yr	63.3±9.8	62.2±11.1
Time since diagnosis — mo		
Mean	32.6±46.1	34.4±41.4
Median	13.2	16.5
Prior treatment for neuroendocrine tumor — no. (%)	16 (16)	16 (16)
Primary tumor resected — no. (%)	40 (40)	39 (38)
Origin of neuroendocrine tumor — no. (%)†		
Pancreas	42 (42)	49 (48)
Midgut	33 (33)	40 (39)
Hindgut	11 (11)	3 (3)
Unknown or other	15 (15)	11 (11)
Tumor progression — no. (%)	4 (4)	5 (5)
Tumor grade — no. (%)‡		
1: Ki-67 0–2%	69 (68)	72 (70)
2: Ki-67 3–10%	32 (32)	29 (28)
Data missing	0	2 (2)

CLARINET Study: Lanreotide



No. at Risk								
Lanreotide	101	94	84	78	71	61	40	0
Placebo	103	101	87	76	59	43	26	0

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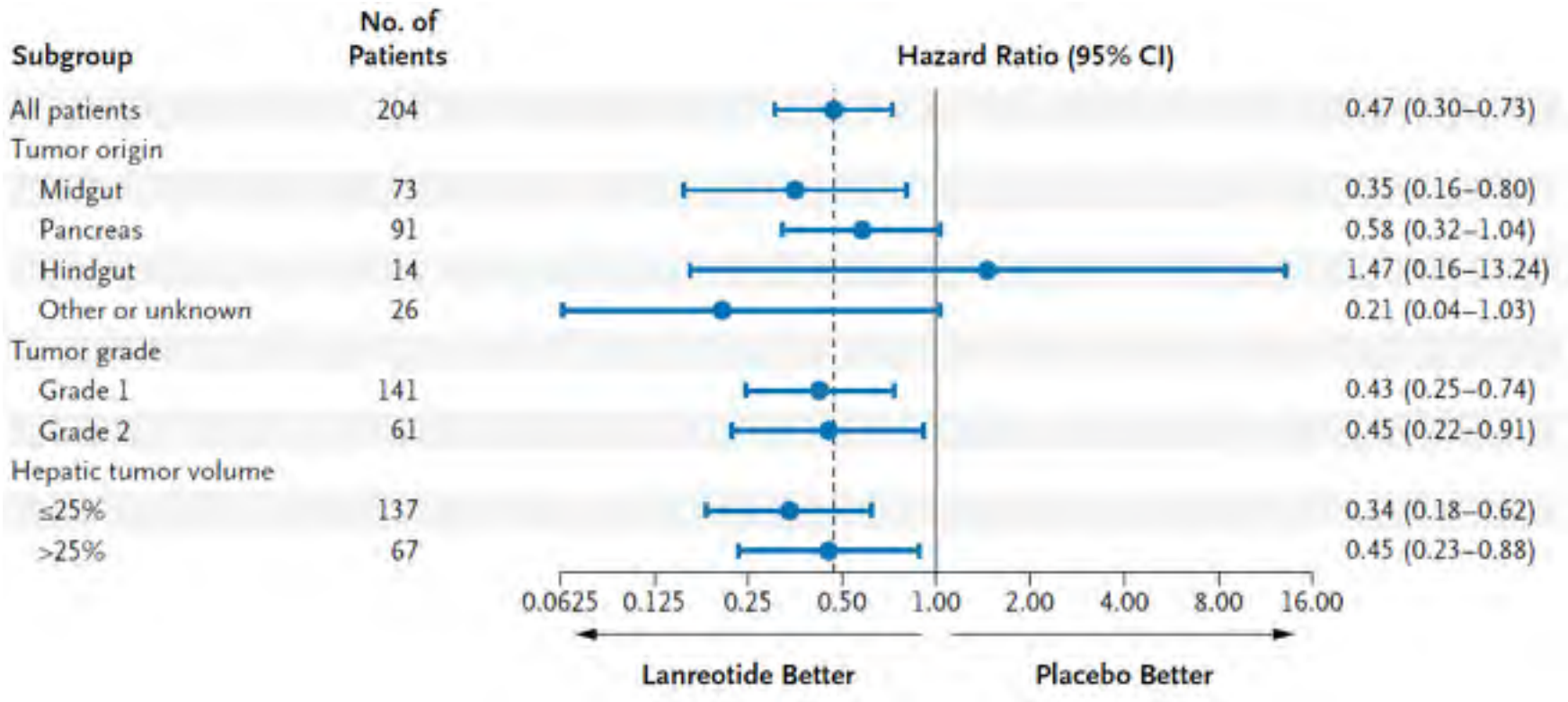
CLARINET Study: Lanreotide



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Question 4

What is a better initial treatment option for delaying disease progression in advanced midgut NET?

A. Octreotide LAR 30mg monthly
B. Lanreotide 120mg SQ monthly
C. Both are equivalent

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PROMID vs CLARINET

PROMID	CLARINET
N=85 (did not complete accrual)	N=204
Midgut NETs	GEP-NETs (including pNET)
Well-differentiated	Well or moderately differentiated
Ki67 ≤ 2% = 98%	Ki67 ≤ 2% = 70% Ki67 3-10% = 30%
~ 5 months since dx	~ 14 months since dx
PFS 6 months (placebo) 14.3 months (Octreotide LAR)	PFS 18 months (placebo) Not reached (lanreotide)
WHO bidimensional response	Unidimensional RECIST v1.1
Either positive or negative on SST receptor scintigraphy	Positive on SST receptor scintigraphy
Octreotide LAR FDA approved	Lanreotide under FDA priority review

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Cytotoxic Chemotherapy in NET

- Pancreatic NETs more responsive to cytotoxic chemotherapy: streptozocin and temozolamide-containing regimens.
- Cytotoxic chemotherapy plays little to no role in carcinoid tumors.
- Various agents have been investigated alone and in combination
  - 5-fluorouracil, Capecitabine
  - Streptozocin
  - Doxorubicin
  - Dacarbazine
  - Temozolamide
  - Cisplatin/carboplatin
  - Etoposide

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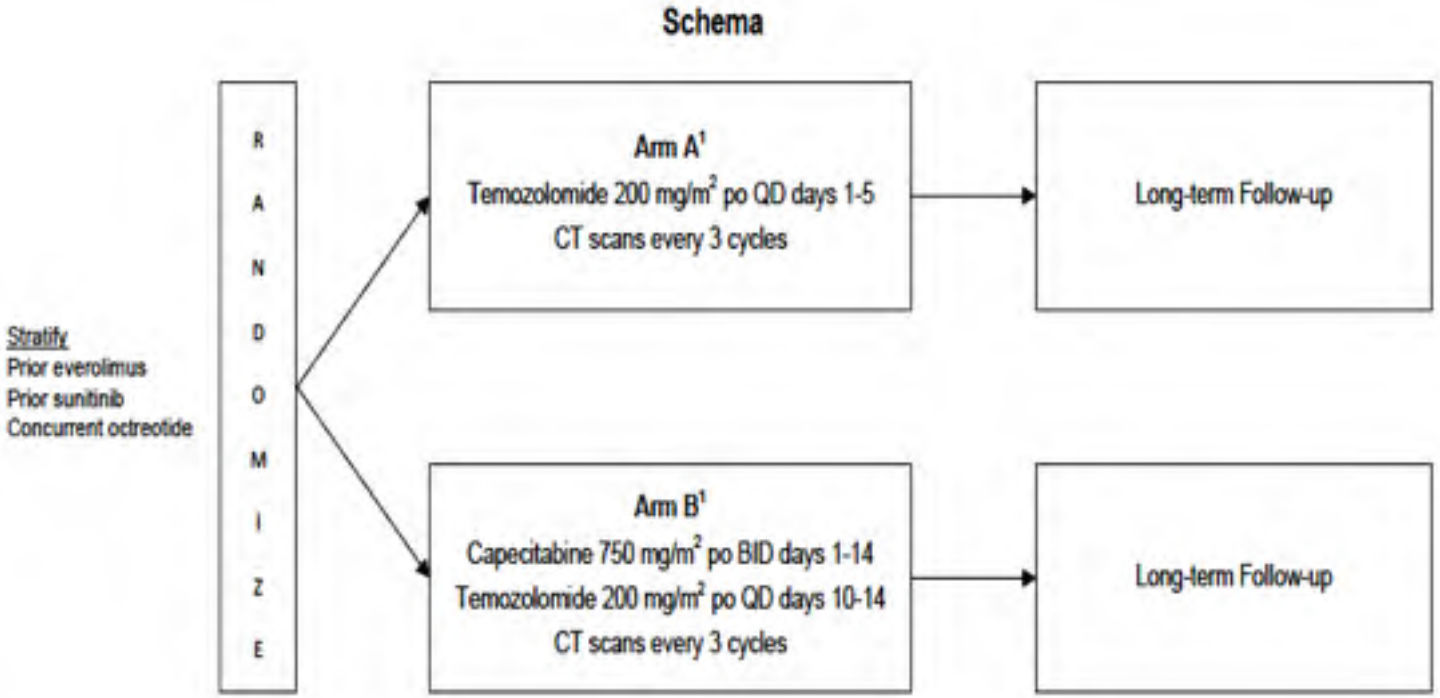
Pancreatic NETs – Cytotoxic Chemotherapy

Study	Design/Tx	# Pts	Population	Findings
Streptozocin-based combinations				
Moertel, NEJM, 1992	Multicenter, randomized: streptozocin + FU (S+F) vs. streptozocin + doxorubicin (S+D) vs. chlorozotocin alone (C)	105	Advanced islet cell tumors	(S+D) vs. (S+F): RR 69% vs. 45% PFS 20 mo vs. 6.9 mo, p=0.001 OS 2.2 yr vs. 1.4 yr, p=0.004
Kouvaraki JCO, 2004	Retrospective: 5-FU, doxorubicin,streptozocin	84 pts	Metastatic/ locally advanced pNET	RR 39% Median PFS 17 mo; Median OS 37 mo
Turner Br J Ca, 2010	Observational: 5-FU, cisplatin, streptozocin	82 pts	Progressive (radiographic or symptomatic) NETs	RR: 66% Median OS 31.5 mo
Temozolamide-based combinations				
Ramanathan Ann Onc, 2001	Phase II (ECOG 6282): Dacarbazine	55 pts	Islet cell tumor– symptomatic or radiographic progression	RR 34% Median survival 19.3 mo
Kulke JCO, 2006	Phase II: temozolamide + thalidomide	30 pts	Metastatic NETs (pancreatic and non-pancreatic)	RR: 25% 2-year survival rate 61%
Strosberg, Cancer, 2011	Retrospective: temozolamide + capecitabine	30 pts	Low or intermediate grade pancreatic NET	RR: 70% Median PFS 18 mo; 2-year OS 92%

ECOG 2211 – Activated April 2013



Accrual = 145

Cycle = 28 days

All doses are based on actual body weight.

1. Treatment will continue for up to 13 cycles (approximately 1 year).

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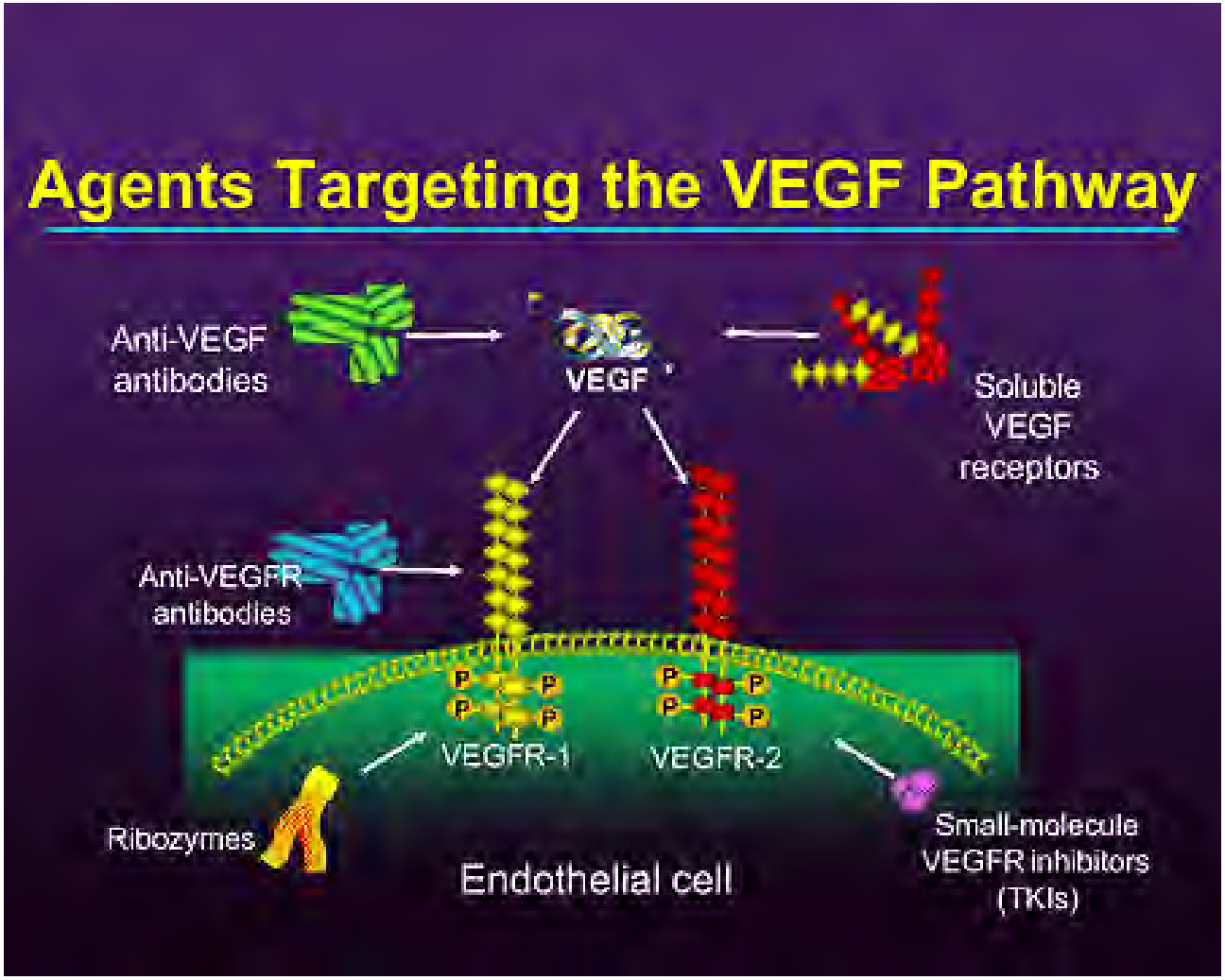
VEGF Pathway in NET



Herbst, R Medscape Multispecialty

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Advanced NETs - Sunitinib

Study Design
•Phase II
Inclusion/Exclusion
•Unresectable, well differentiated NET •Pancreatic NET and carcinoid
Enrollment / Patient Characteristics
•107 patients treated (41 carcinoid, 66 pancreatic) •Sunitinib administered in 6-wk cycles: 50mg daily x 4 weeks followed by 2 weeks rest •Nearly all patients had prior surgery •Close to half had received previous systemic therapy (43.9% carcinoid, 60.6% pancreatic)

Kulke, M et al. *J Clin Oncol*, 2008: 26;20, 3403-10

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Advanced NETs - Sunitinib

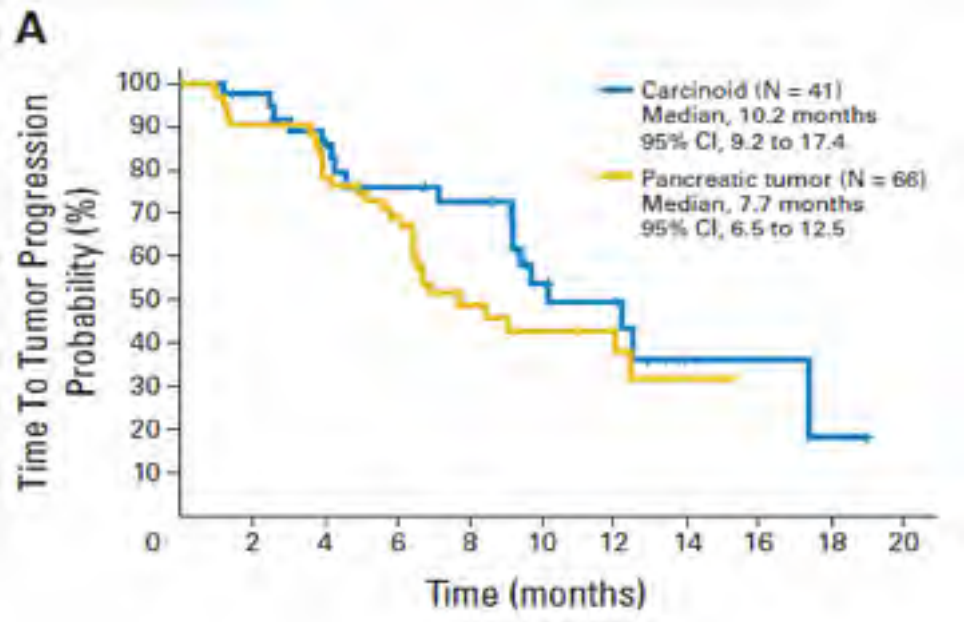
Results

-overall response 16.2% (pancreatic) vs. 2.4% (carcinoid)

-majority of patients had stable disease

-time to progression 10.2 months (carcinoid) and 7.7 months (pancreatic)

-grade 3-4 adverse events: fatigue (24%) , hypertension (10.3%)



Kulke, M et al. J Clin Oncol, 2008: 26;20, 3403-10

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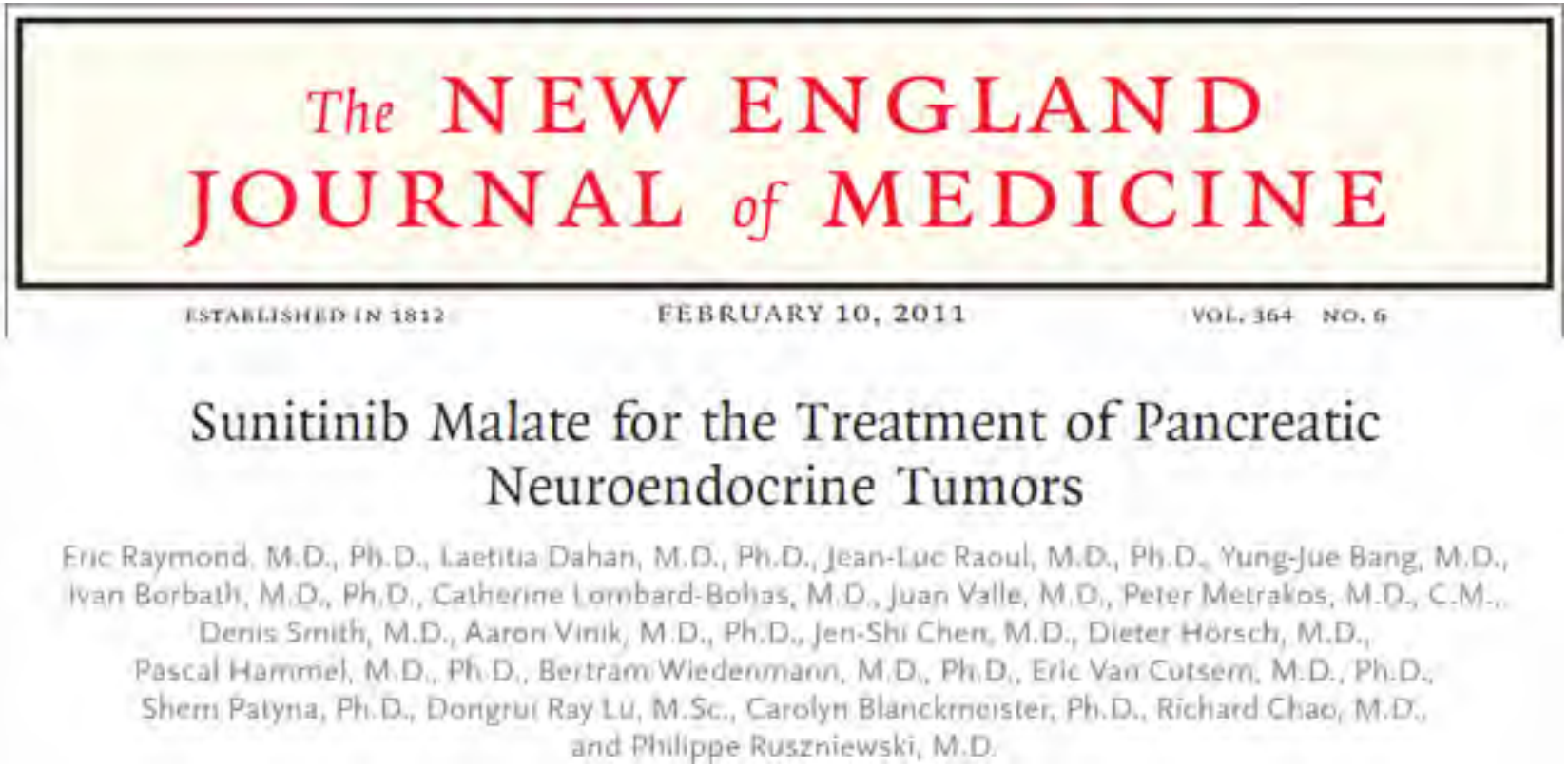
Pancreatic NETs: Sunitinib



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.

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Pancreatic NET – Sunitinib vs. Placebo

Study Design
•Randomized, double-blind, placebo-controlled
Inclusion/Exclusion
•Well-differentiated, unresectable, pancreatic NETs •Documented progression in the previous 12 months •Poorly differentiated tumors excluded
Enrollment
•171 patients enrolled •Continuous administration of 37.5mg daily sunitinib vs. placebo

Raymond, E et al. NEJM. 2011; 364(6): 501-13

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Pancreatic NETs: Sunitinib – Patient Characteristics

Characteristic	Sunitinib (n=86)	Placebo (n=5)
Median age	56	57
Male sex	42 (49%)	40 (47%)
ECOG PS 0 1 2	 53 (62%) 33 (38%) 0	 41 (48%) 43 (51%) 1 (1%)
Median time since diagnosis	2.4 years	3.2 years
Nonfunctioning tumor	42 (49%)	44 (52%)
Ki-67 index ≤2% >2%-5% >5%-10% >10%	 7 (19%) 16 (44%) 5 (14%) 8 (22%)	 6 (17%) 14 (39%) 10 (28%) 6 (17%)
Any previous chemotherapy	57 (66%)	61 (72%)

Raymond, E et al. NEJM. 2011; 364(6): 501-13

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Results: Sunitinib vs. Placebo PNET

Study terminated early due to increased deaths, shorter PFS, and adverse events in placebo group: 171 enrolled out of a planned 340

	PFS*	**RR**	**Median OS**	**Survival at 6 months**
Suntinib (n=86)	11.4 months	9.3%	Not reached	92.6%
Placebo (n=85)	5.5 months	0%	Not reached	85.2%
P-value	<0.001	0.007	--	--

On May 20, 2011: sunitinib FDA approved for treatment of well-differentiated, progressive pNET – unresectable, locally advanced, metastatic

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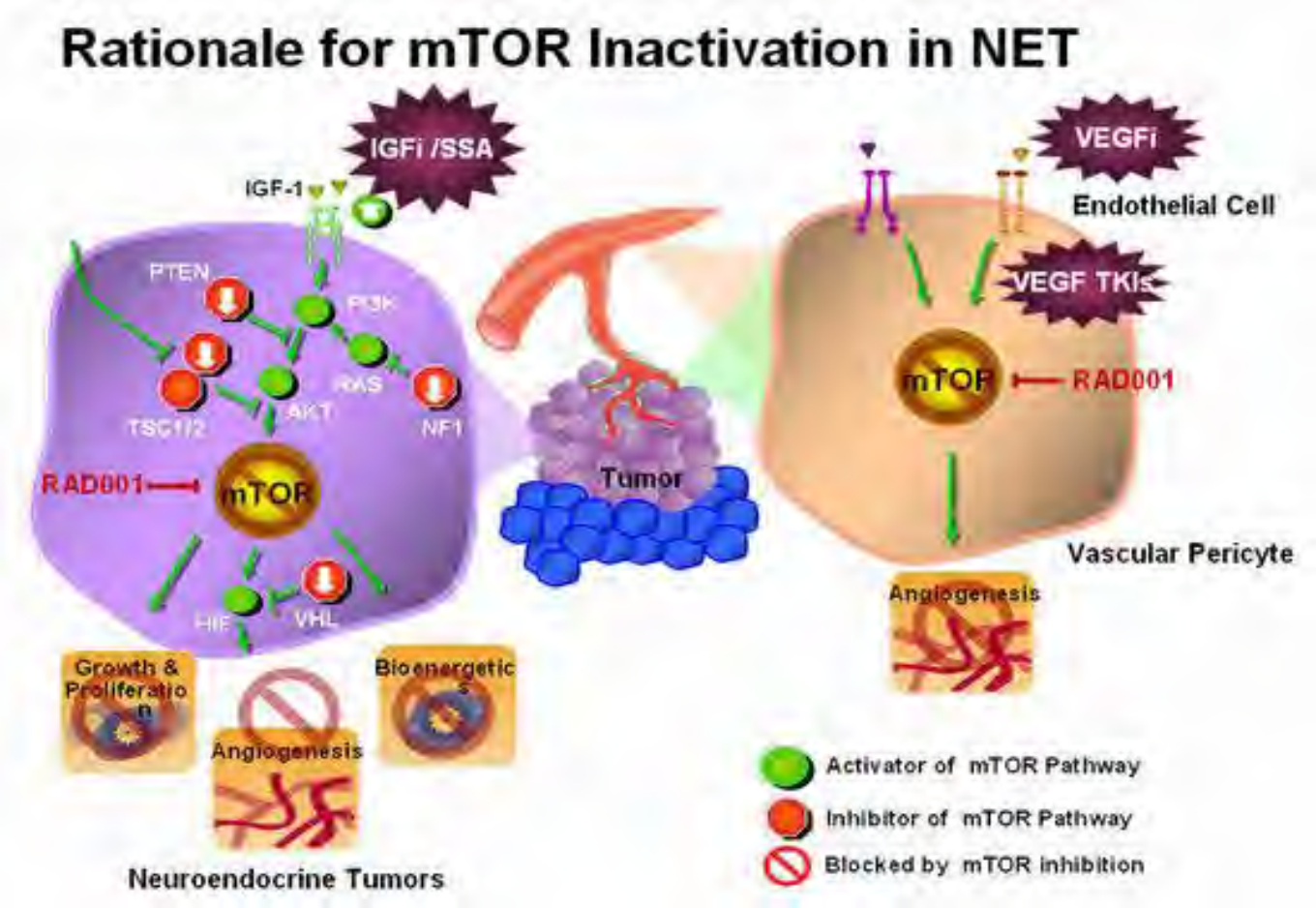
Metastatic NETs: mTOR pathway and RADIANT studies



Melmed: Williams Textbook of Endocrinology, 12th ed.; Chapter 44

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Everolimus in pNET: Radiant 1

Study Design
•Phase II study •Nonrandomized stratification by ongoing octreotide therapy at study entry •Stratum 1 (Everolimus 10mg qd) *vs*. Stratum 2 (Octreotide LAR q28d + Everolimus 10mg qd)
Inclusion/Exclusion
•Well to moderately differentiated pancreatic NET •Advanced (unresectable or metastatic) disease •Progressive disease documented by RECIST during or after cytotoxic chemotherapy •No chemotx within 3 weeks, no TACE within 6 months of enrollment
Enrollment / Patient characteristics
160 patients enrolled (115 Stratum 1, 45 Stratum 2) Median age 55 Majority nonfunctional tumors

Yao, J. *J Clin Oncol*. 2010; 28(1): 69-76

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RADIANT-1: Results

Stratum 1: Everolimus **(n = 115)**

Central radiology	ITT, n (%)
PR	11 (9.6)
SD	78 (67.8)
Clinical benefit (PR + SD)	89 (77.4)
PD	16 (13.9)
Unknown	10 (8.7)

Stratum 2: Everolimus + Octreotide LAR **(n = 45)**

Central radiology	ITT, n (%)
PR	2 (4.4)
SD	36 (80.0)
Clinical benefit (PR + SD)	38 (84.4)
PD	0 (0.0)
Unknown	7 (15.6)

Yao, J. *J Clin Oncol*. 2010; 28(1): 69-76

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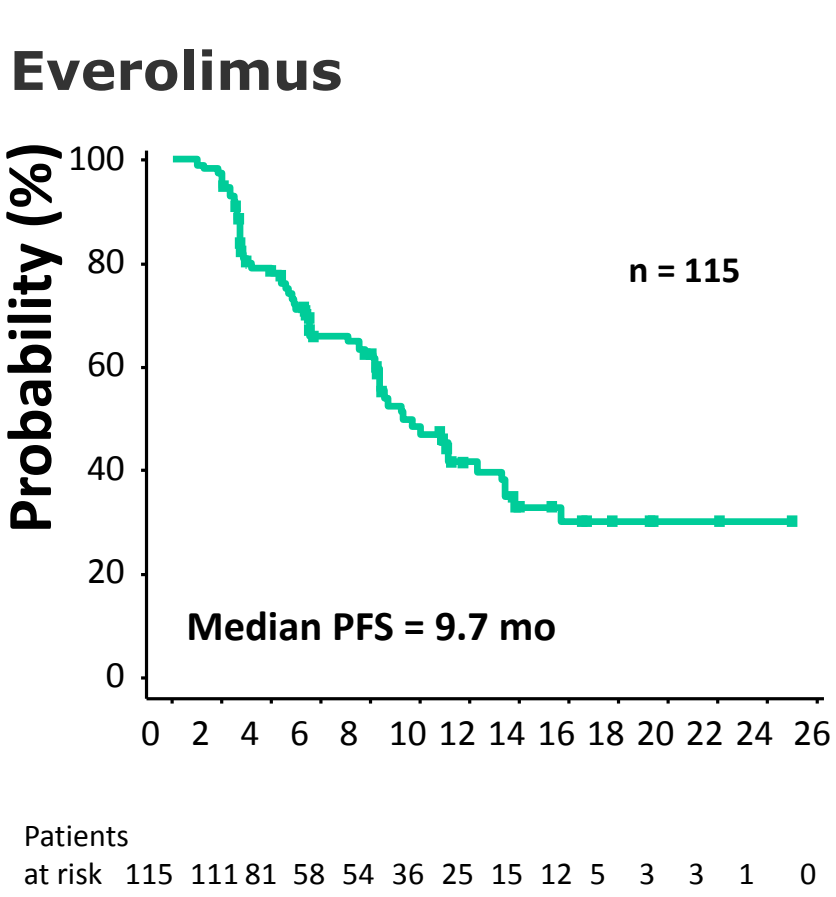
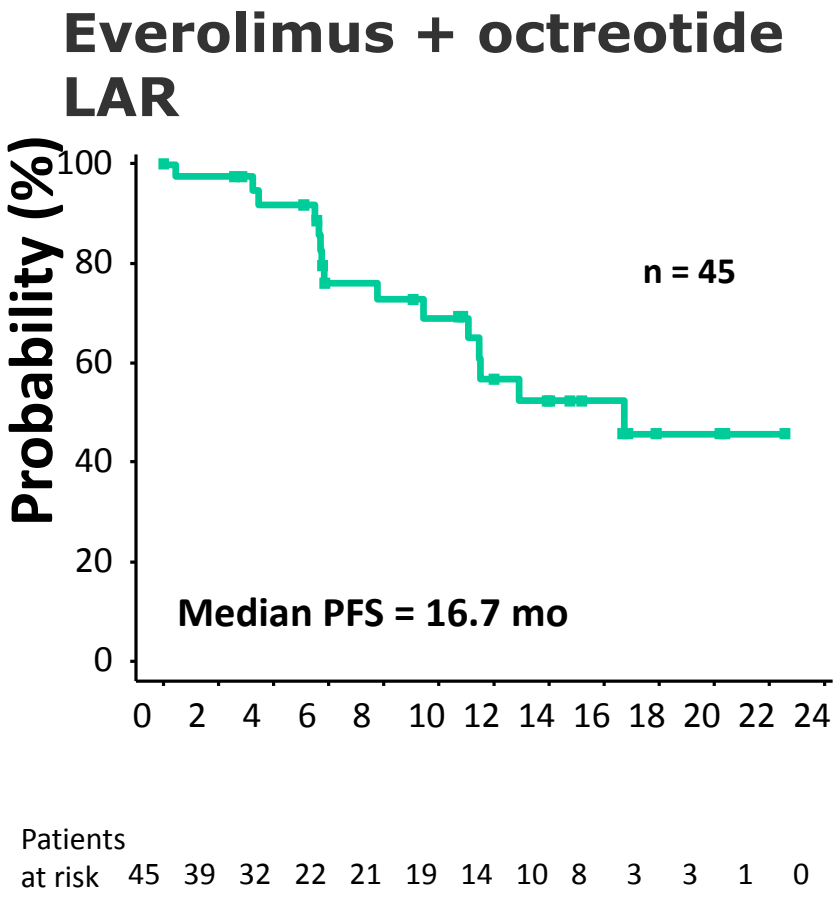
RADIANT-1 PFS by Central Review





Yao, J. *J Clin Oncol*. 2010; 28(1): 69-76

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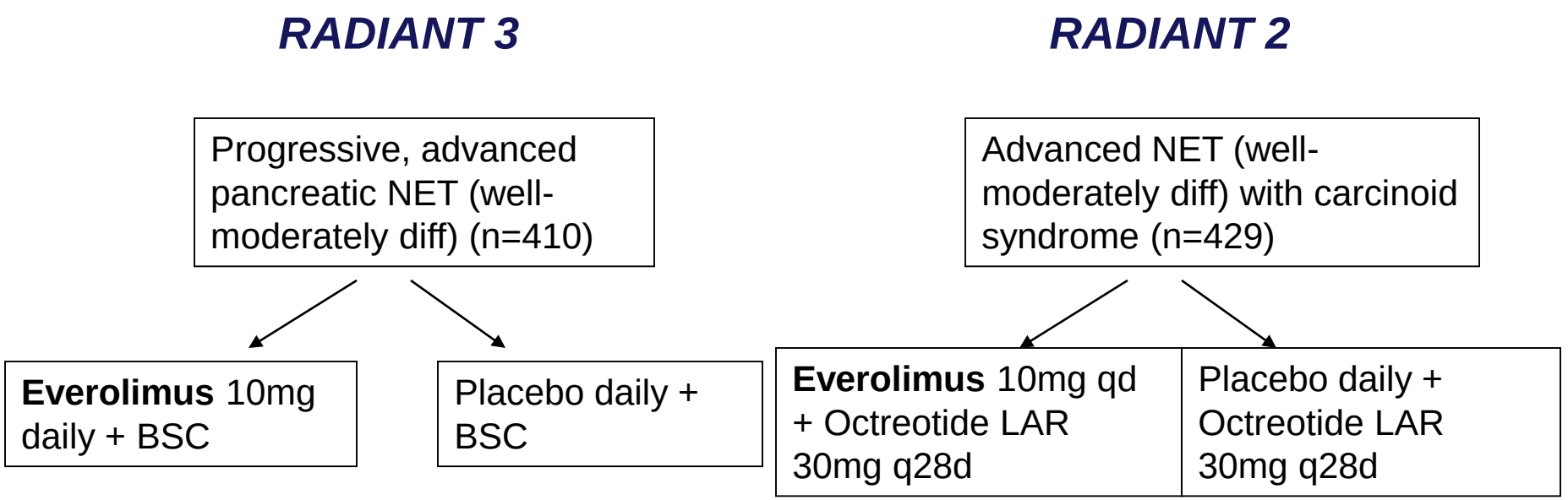
Everolimus in NETs: Radiant 2 & Radiant 3



Primary endpoint = PFS
Crossover allowed on both studies

Yao, J et al. NEJM. 2011; 364(6): 514-23
Yao, J et al. Lancet. 2011; Dec, 278(9808): 2005-12

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Everolimus in PNET: Radiant 3 Results

	PFS*	SD	OS	Toxicity – All grades	Toxicity – Grades 3-4
Everolimus + BSC (n=207)	11.0 mo	73%	44.0 mo (35.6-51.8)	Stomatitis 64% Rash 49% Diarrhea 34% Fatigue 31%	Stomatitis 7% Anemia 6%
Placebo + BSC (n=203)	4.6 mo	51%	37.7 mo (29.1-45.8)	Stomatitis 17% Rash 10% Diarrhea 10% Fatigue 14%	Stomatitis 0% Anemia 0%
P value	P<0.001		HR 0.94, p=0.30		

Yao, J et al. NEJM. 2011; 364(6): 514-23
Yao, J et al. ESMO 2014 abstract

85% crossover from placebo arm

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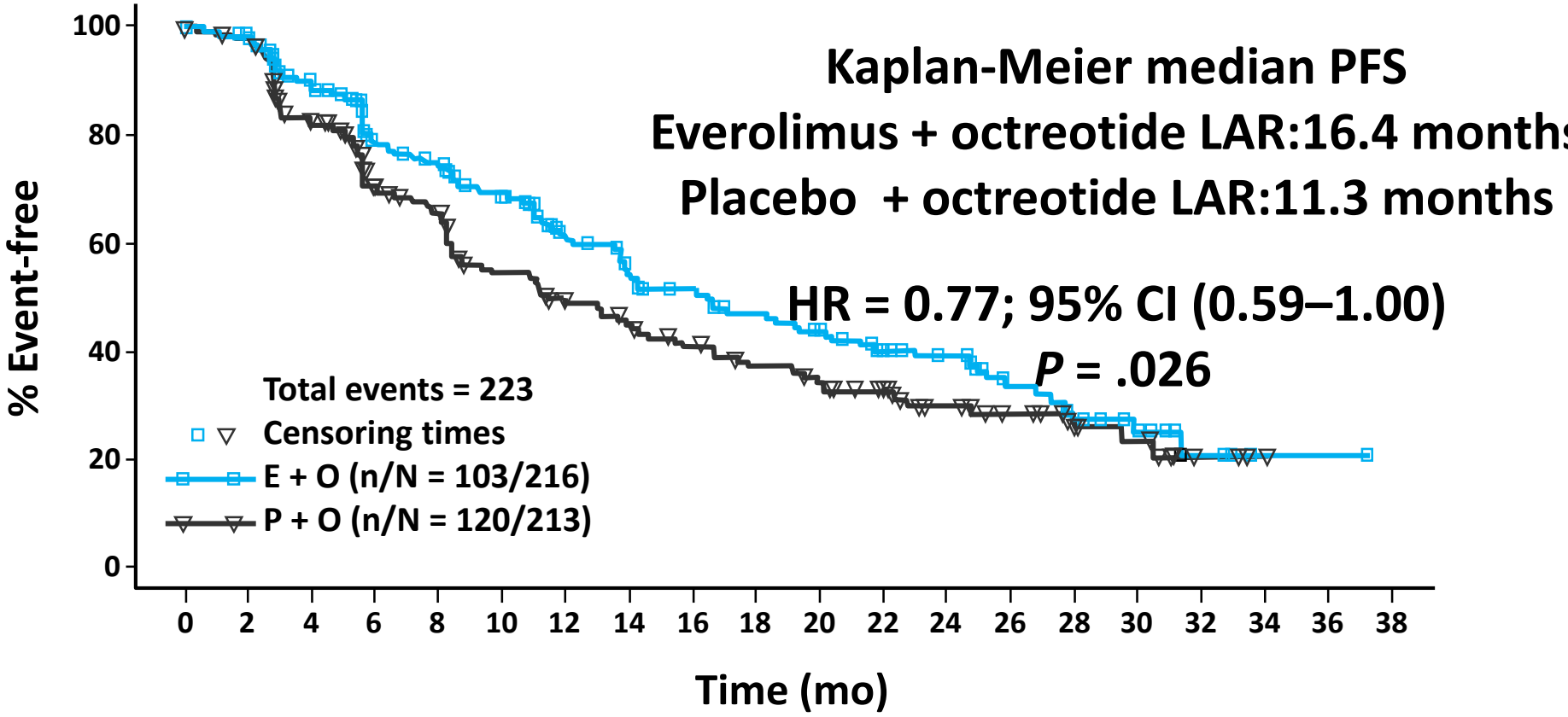
RADIANT-2: PFS by Central Review*



*Independent adjudicated central review committee; *P* value obtained from one-sided log-rank test; HR obtained from unadjusted Cox model.

E + O: everolimus + octreotide LAR; HR: hazard ratio; P + O: placebo + octreotide LAR.

Pavel M, et al. ESMO 2010; Abstract LBA 8.
Yao, J et al. ASCO 2011 GI Cancer Symposium abstract

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PNET: Sunitinib vs. Everolimus

	PFS*	RR
Suntinib (n=86)	11.4 months	9.3%
Placebo (n=85)	5.5 months	0%
Everolimus + BSC (n=207)	11.0 months	5%
Placebo + BSC (n=203)	4.6 months	2%

For progressive advanced PNET, choice of treatment may depend on patient-related factors and concern about particular toxicities.

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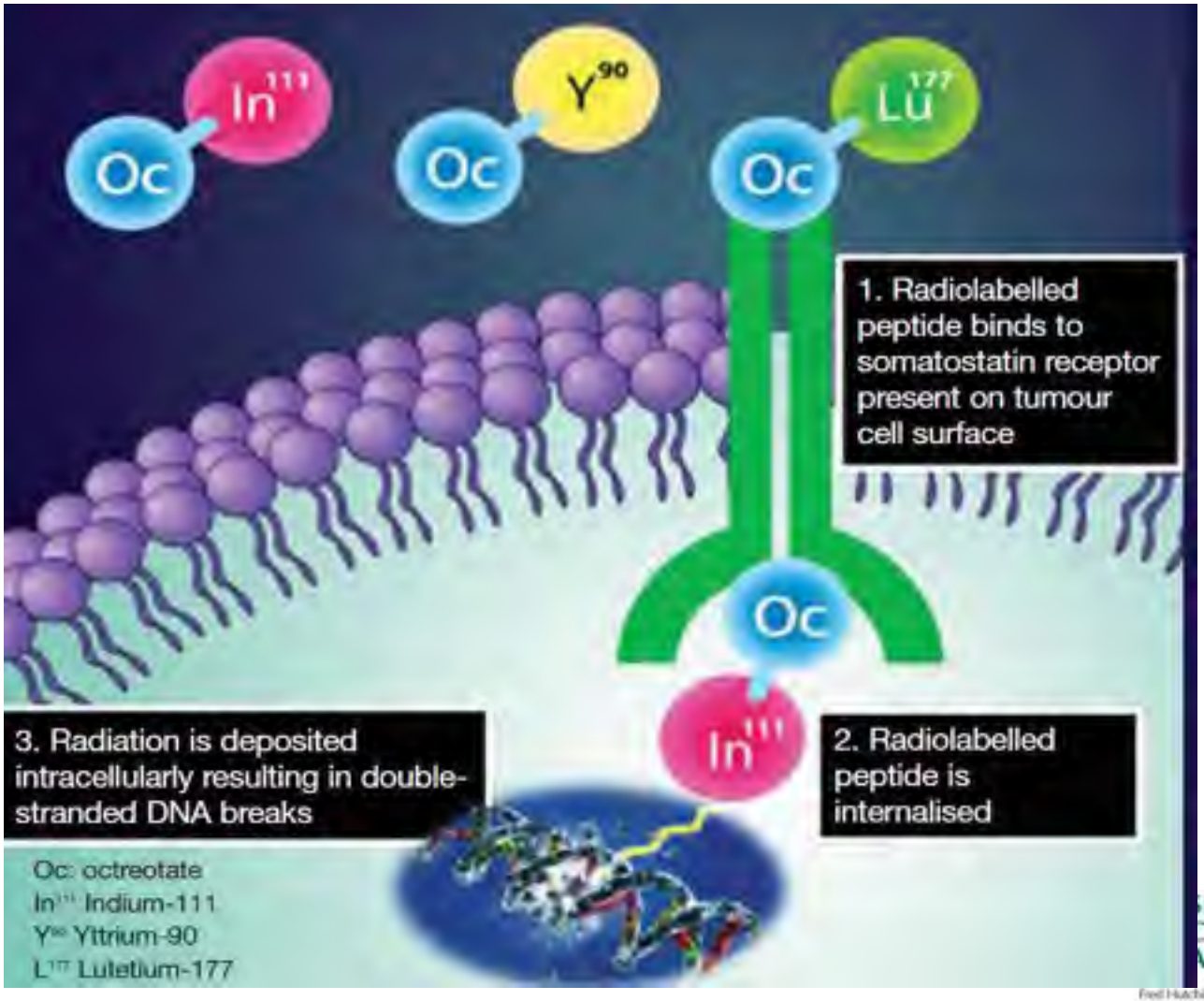
Peptide Receptor Radionuclide Therapy (PRRT): General Principles



AustralianDoctor Educatiton
'How to Treat' , March 2012

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177Lu-DOTATATE

VOLUME 26 · NUMBER 13 · MAY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Hepatic toxicity
Hematologic toxicity

Treatment With the Radiolabeled Somatostatin Analog [^{177}Lu-DOTA^{0},Tyr^{3}]Octreotate: Toxicity, Efficacy, and Survival

Dik J. Kwekkeboom, Wouter W. de Herder, Boen L. Kam, Casper H. van Eijck, Martijn van Essen, Peter P. Kooij, Richard A. Feelders, Maarten O. van Aken, and Eric P. Krenning

	CR	PR	SD
Carcinoid (n=188)	1 (1%)	41 (22%)	78 (42%)
Nonfunc pNET (n=72)	4 (6%)	26 (36%)	19 (26%)
Total(310)	5 (2%)	86 (28%)	107 (35%)

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Summary

- Recognition of carcinoid syndrome symptoms
- Somatostatin analogues and proliferative effects
- Targeted therapies (everolimus and sunitinib) have shown benefit in pNET
- PRRT is an emerging therapeutic option

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Thank you for your attention!

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