NeuroEndocrine Tumors

Diagnostic and therapeutic challenges: introduction

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Introduction to Neuroendocrine Tumours

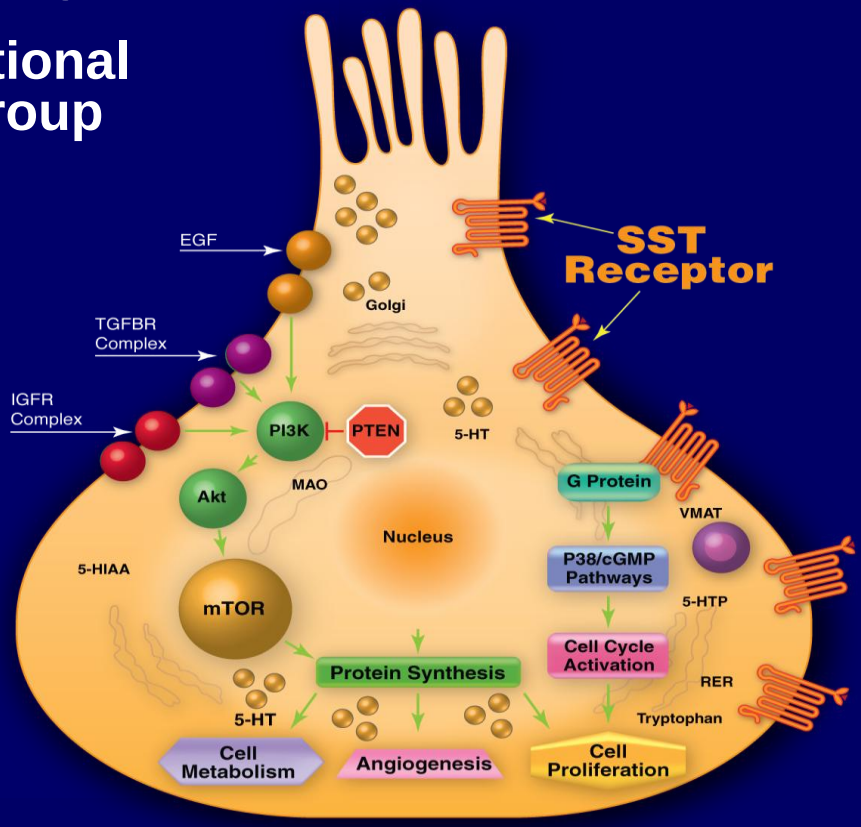
- Neuroendocrine tumours (NET) are relatively rare; this is associated with limited knowledge on disease management
- The natural history of NET is poorly understood
- At least 40 different entities are described arising in different organs; different terminologies have also caused confusion

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

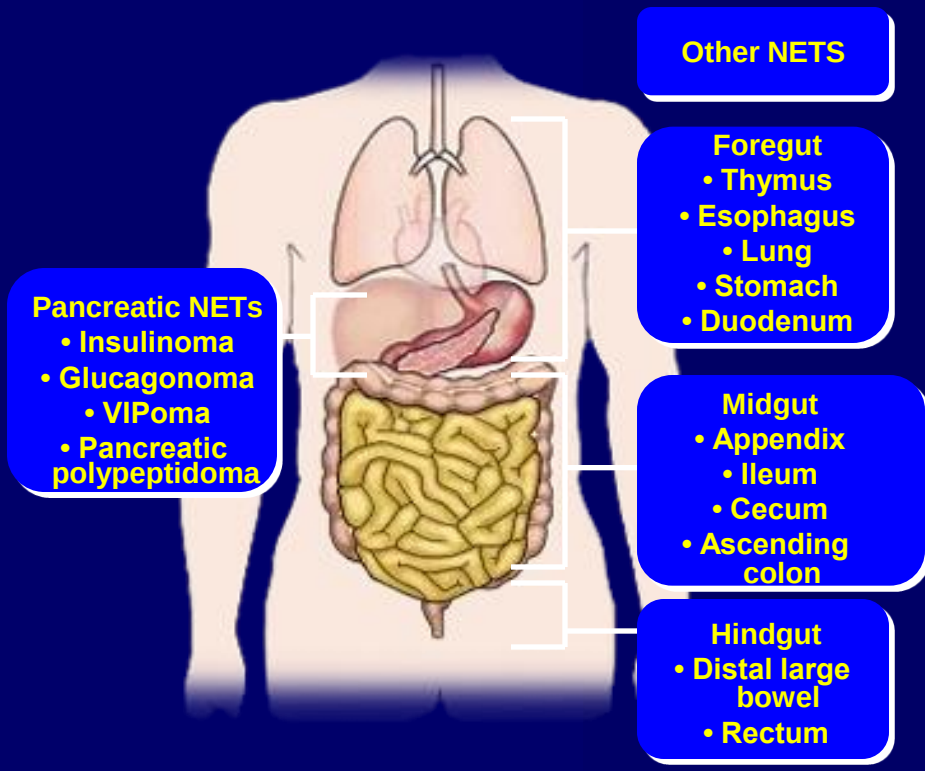
Neuroendocrine Tumors (NETs): A Diverse Group of Malignancies, a Clinical Challenge

- 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]
  - Multiple endocrine neoplasia (MEN)de, type 1 and type 2/medullary thyroid carcinoma
  - Gastroenteropancrtic neuroendocrine tumors (GEP-NETs)
  - Islet cell tumors
  - Pheochromocytoma/paraganglioma
  - Poorly differentiated/small cell/atypical lung carcinoid
  - Small cell carcinoma of the lung
  - Merkel cell carcinoma

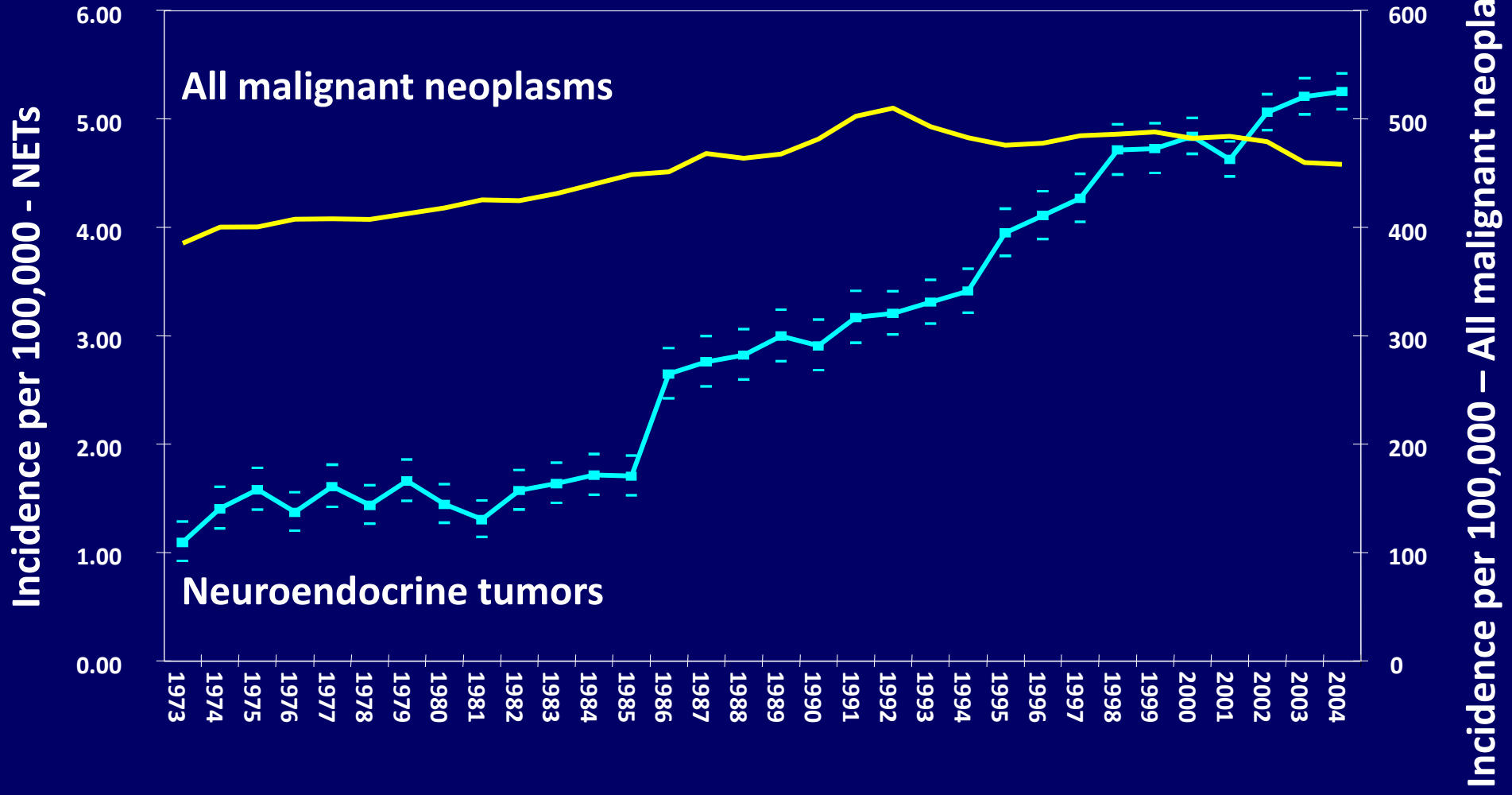


Overview of Neuroendocrine Tumors (NETs)

- NETs are sometimes called carcinoid tumors
  - Can be both symptomatic and asymptomatic
  - May be undetected for years without obvious signs or symptoms
- NETs are generally characterized by their ability to produce peptides that lead to their syndromes
- NETs are generally classified as foregut, midgut, or hindgut depending on their embryonic origin[3]
  - Foregut tumors develop in the respiratory tract, thymus, stomach, duodenum, and pancreas
  - Midgut tumors develop in the small bowel, appendix, and ascending colon
  - Hindgut tumors develop in the transverse colon, descending colon, or rectum

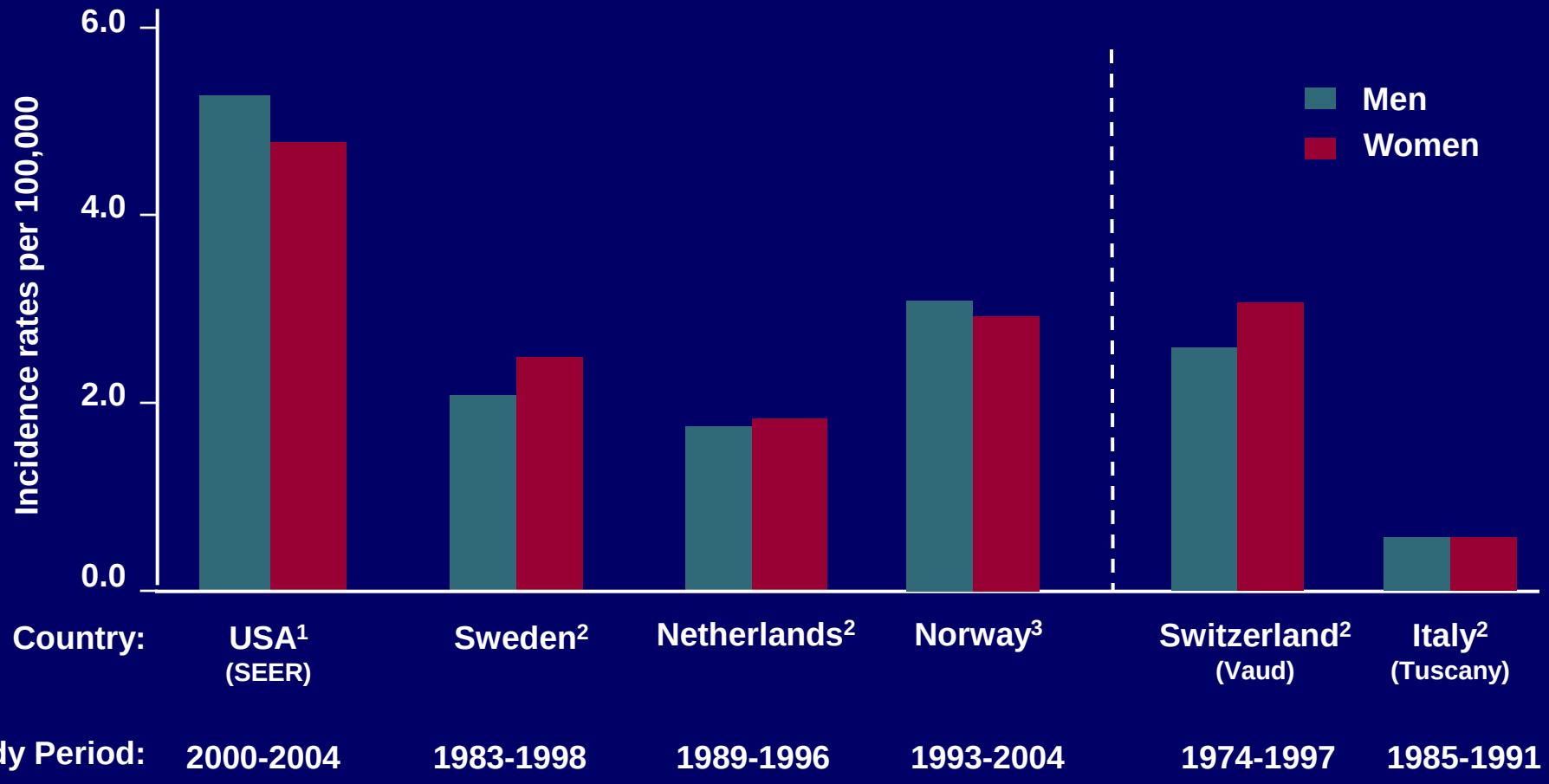


Incidence of NETs Increasing



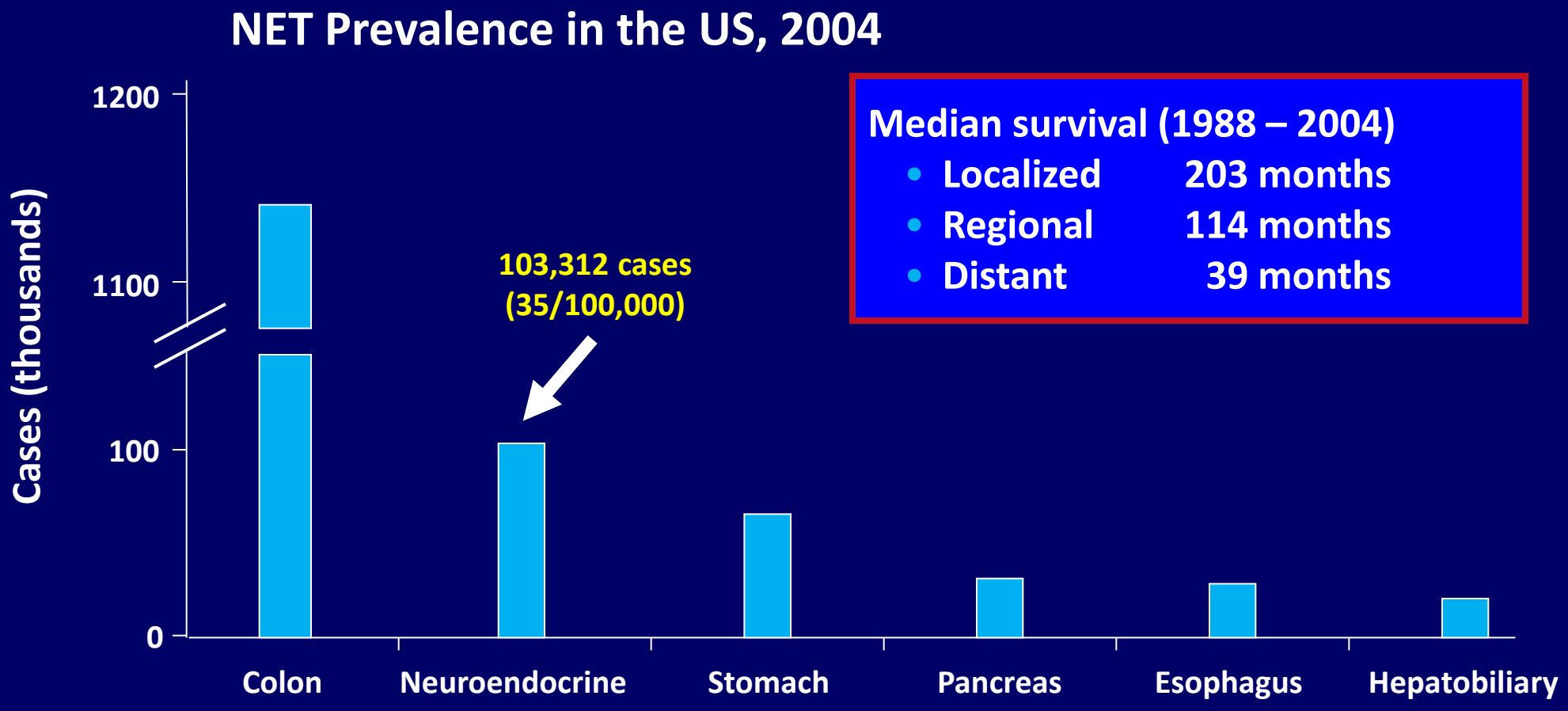
Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072.

US and European Incidence of NET



[1]Yao J, et al. *J Clin Oncol*. 2008;26:3063-3072. [2]Taal BG, et al. *Neuroendocrinology*. 2004;80(suppl 1):3-7.
[3]Hauso O, et al. *Cancer.* 2008;113:2655-2664.

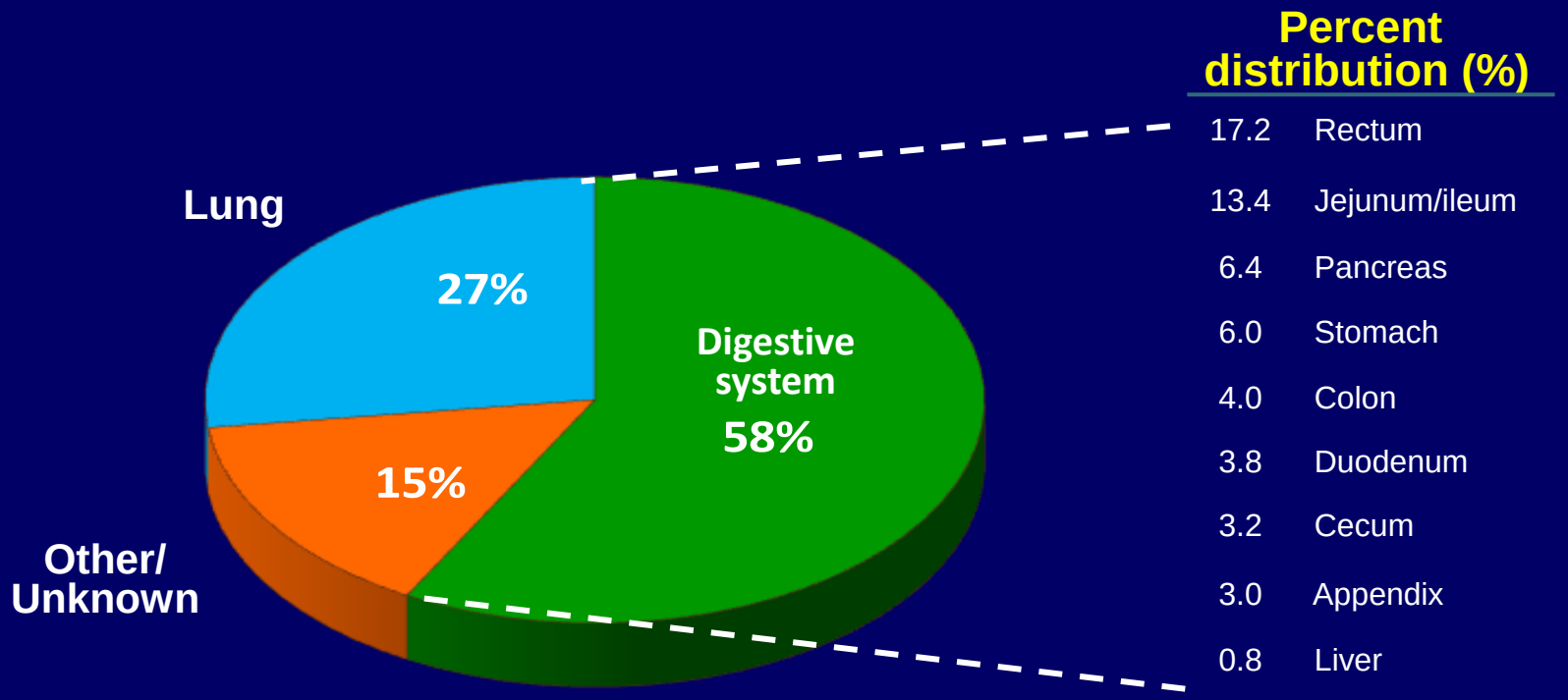
NETs Are Second Most Prevalent Gastrointestinal Tumor



29-year limited duration prevalence analysis based on SEER.
SEER: Surveillance, Epidemiology, and End Results.

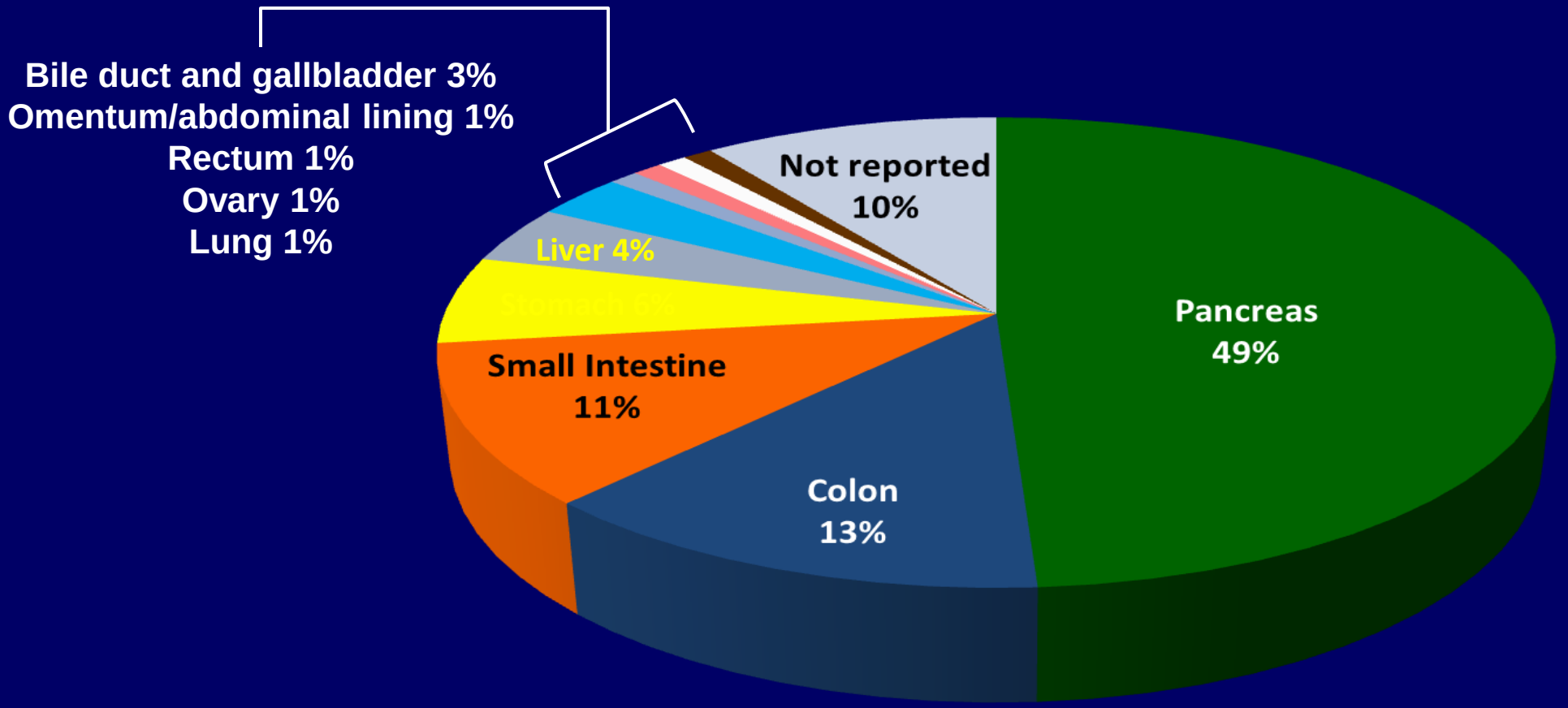
Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072.

The GI Tract Is the Most Common Primary Location of NET (US SEER Data)



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

The Pancreas Is the Most Common Primary Location of NET Breakdown (Middle East & Asia Pacific Region)



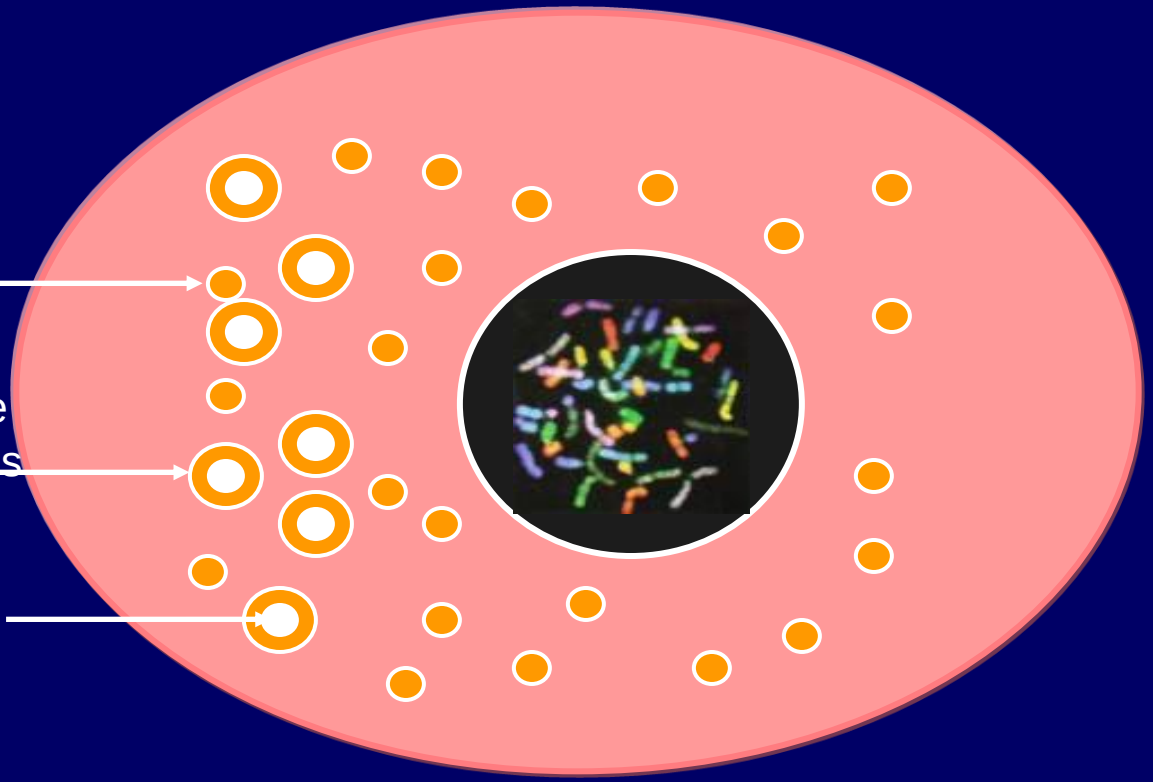
Hwang T, et al. Presented at: 8th Annual ENETS Conference; March 9-11, 2011; Lisbon, Portugal. Abstract C48.

Neuroendocrine Cells Are Peptide Hormone-Producing Cells that Share a Neural-Endocrine Phenotype

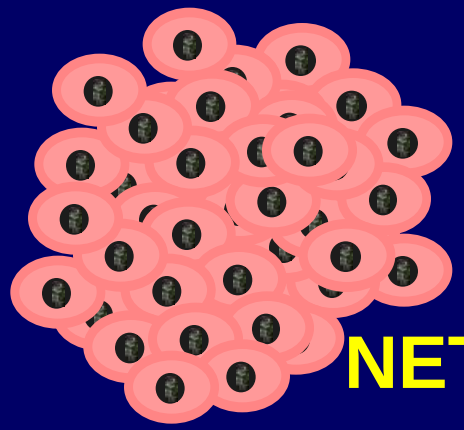
Synaptophysin
Small synaptic vesicles

Chromogranin A Membrane protein of neurosecretory granules

Peptide hormone
In neurosecretory granule



Secreted into the serum



NET

biomarkers

Klöppel G. et al. *International Collaboration on Neuroendocrine Tumours*. Vienna, Austria. 2011.

Cells of Origin

- Gastrointestinal neuroendocrine lineages arise from a common stem cell precursor in the base of the intestinal crypts or in the neck of the gastric glands

- Differentiate into diverse types of neuroendocrine cells under the influence of transcription factors Math1 and neurogenin 3 (NGN3)

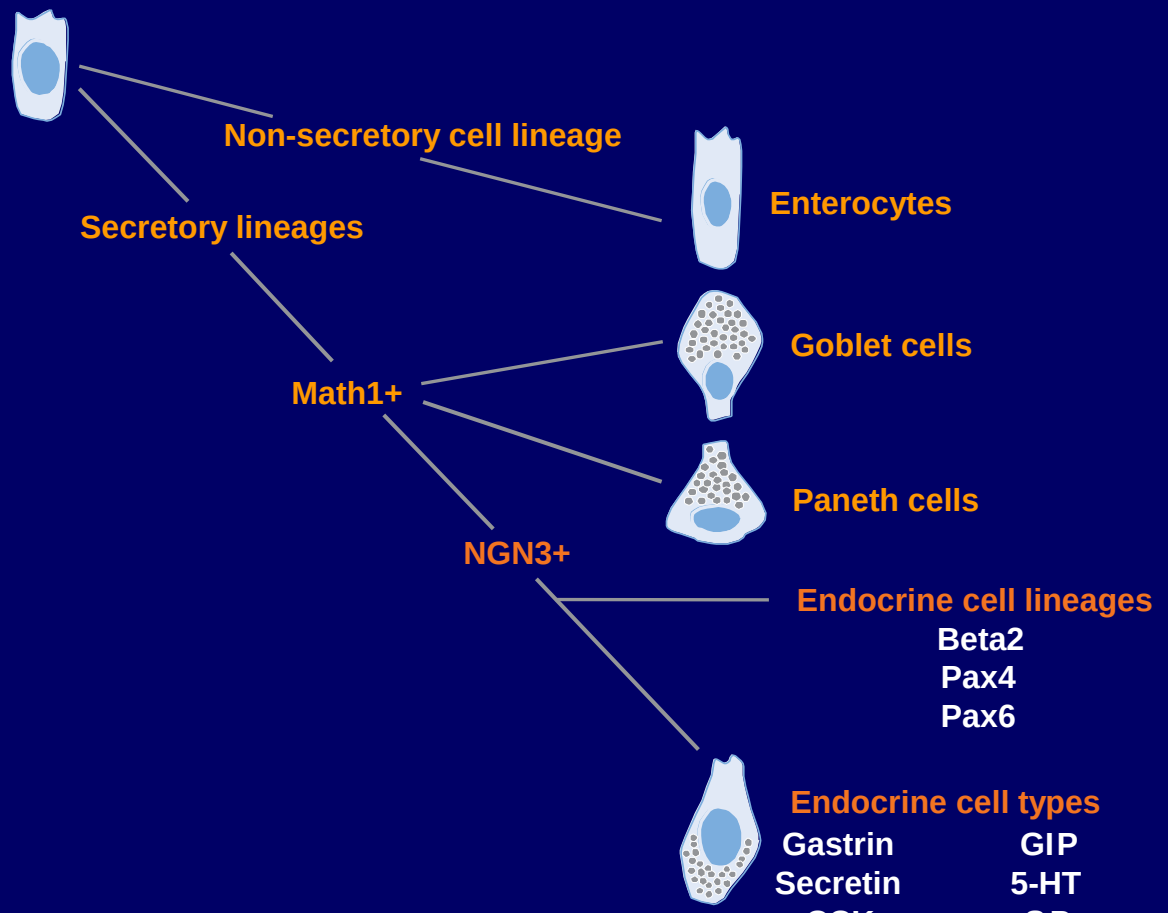


Image courtesy of IM Modlin.

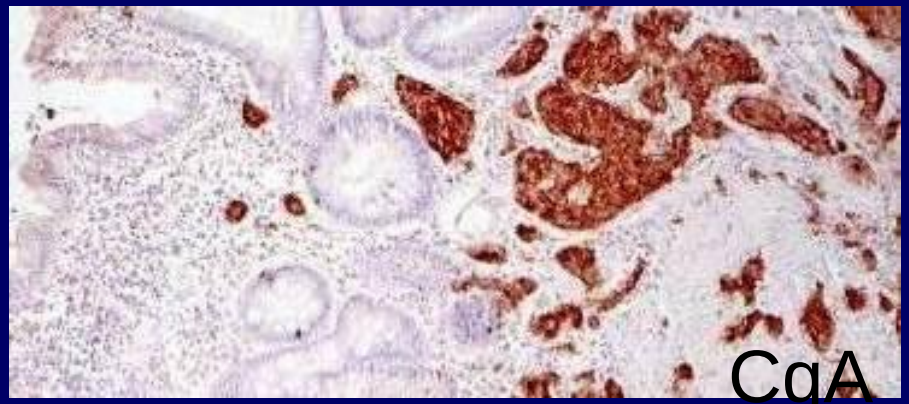
Role of CgA IHC in the Diagnosis of NET

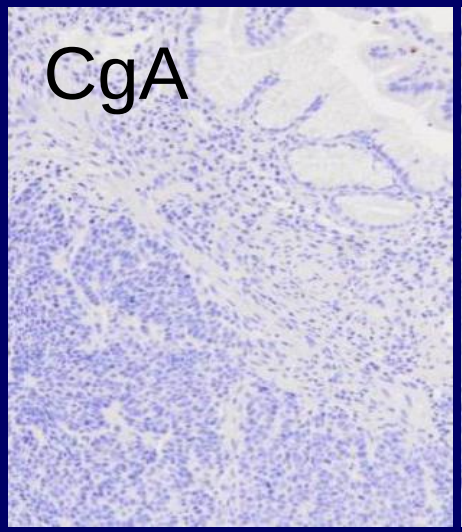
Benefits:

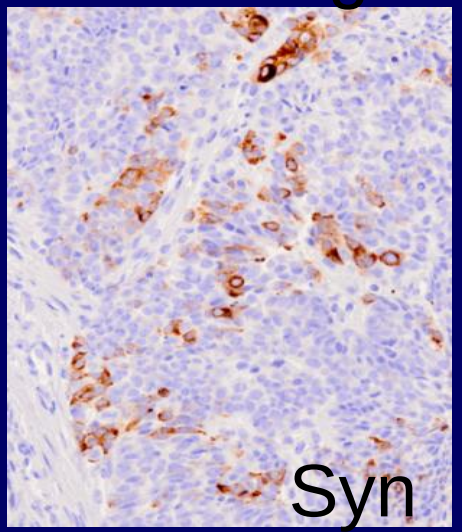
- Can be detected in the secretory granules of most NET both symptomatic and asymptomatic

Limitations:

- Many NET of the large bowel and some of the appendix primarily secrete CgB
- CgA may be negative in poorly differentiated NET







Taupenot L, Harper KL, O'Connor DT. *N Engl J Med*. 2003;348:1134-1149.

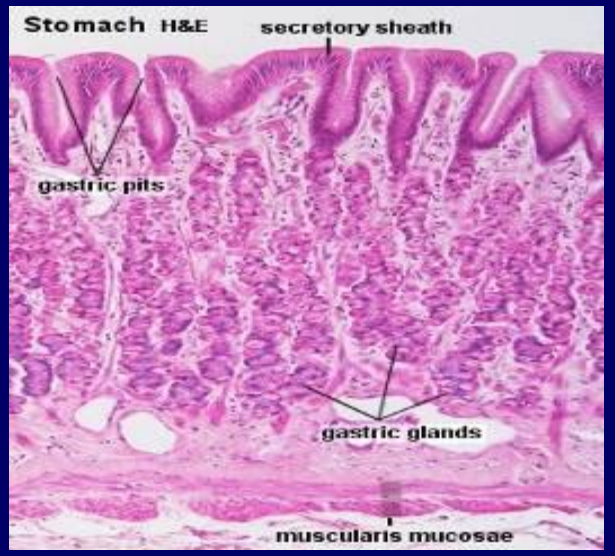
Role of Synaptophysin IHC in the Diagnosis of NET

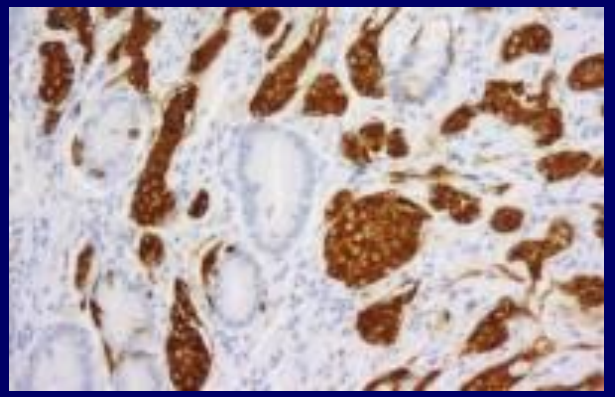
Benefits:

- Expressed independently of secretory granules
- Useful in identifying poorly granulated and poorly differentiated NET that may not exhibit CgA staining

Limitations:

- Expression is not limited to neuroendocrine cells

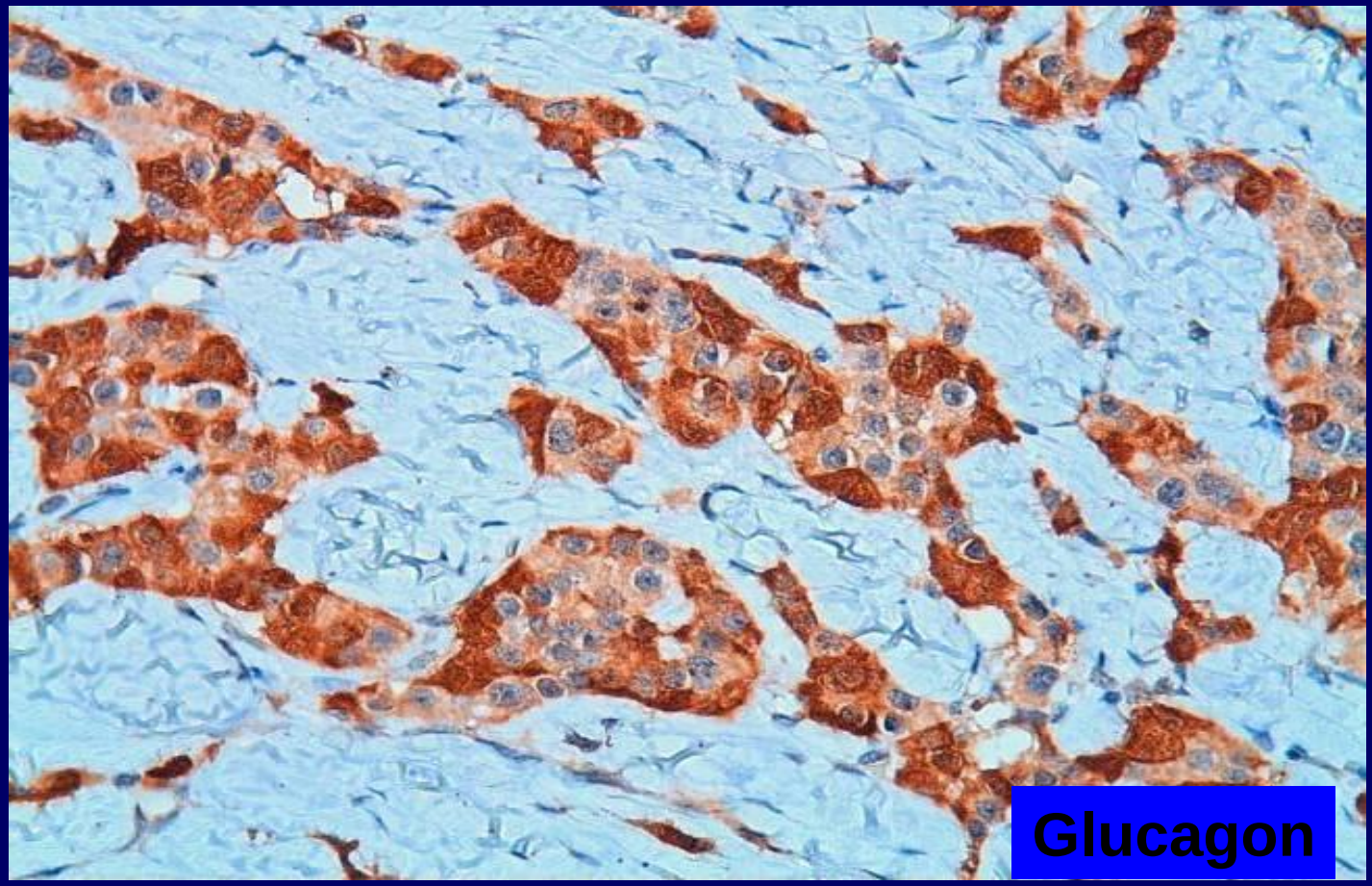




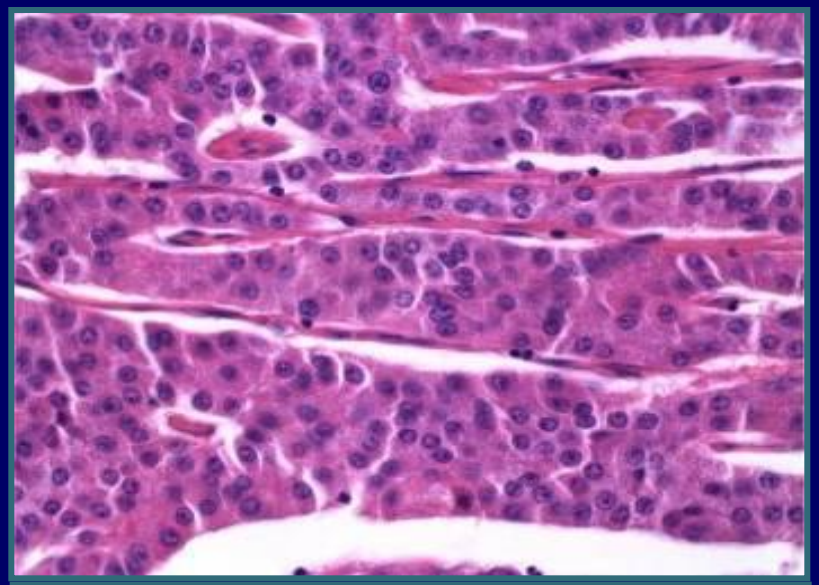
Chetty R et al. *Arch Pathol Lab Med* 2008;132:1285-1289.

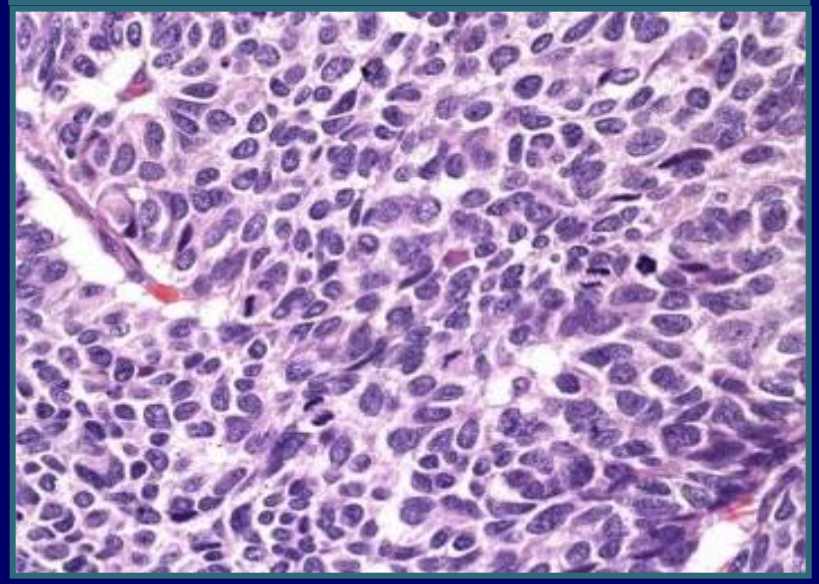
Immunohistochemical NE Markers

Definition of hormonal production



Neuroendocrine Tumours
WHO Classification 2010 of the Digestive System





Neuroendocrine tumour/ NET (Carcinoid)

Neuroendocrine carcinoma / NEC

Neuroendocrine Tumours
WHO Classification 2010 of the Digestive System

- **Working principles**
  - "Neuroendocrine" defines the peptide hormone-producing tumours and share neural-endocrine markers
  - The term "Neuroendocrine neoplasm" includes well- and poorly differentiated tumours
- **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

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

Neuroendocrine Tumours (NET):
A Stepwise Diagnostic Approach

1. NET vs nonNET → morphology & NE markers

2. NET vs NEC → structure + grade

3. Grade 1-2-3 → mitoses & Ki67

4. TNM Stage I-II-III-IV → size & invasion

Confusion Caused by the Term "Carcinoid"

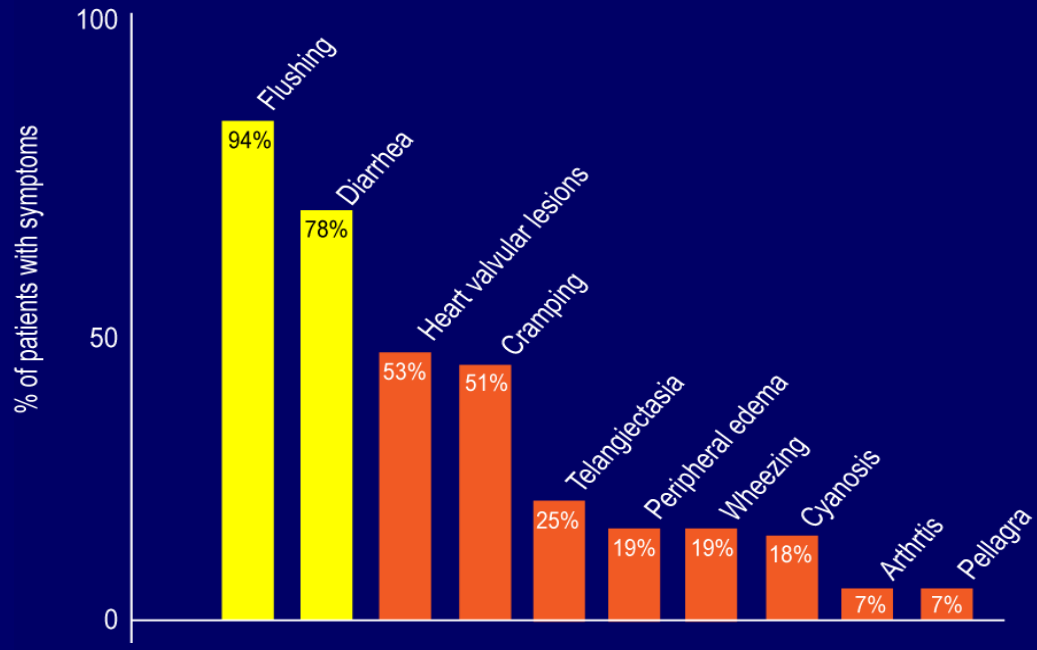
- Oberndorfer coined the term "karzinoide" in 1907[1]
  - This term implies that these tumours are benign; this is an unfortunate misnomer for the majority of NET
    - NET have malignant potential and metastasize, generally to the liver
  - Referring to any NET, the term "carcinoid" should only be used in reference to carcinoid syndrome
    - Symptoms of carcinoid syndrome include flushing, abdominal cramps, and diarrhea[2]
    - Most cases are associated with tumours of the intestines, which frequently metastasize to live[2]

[1]Klöppel G, et al. *Endocr Pathol.* 2007;18:141-144. [2]Bhattacharyya S, et al. *Nat Rev Clin Oncol*. 2009;6:429-433.

Carcinoid Syndrome

- Occurs in approximately 8% to 35% of patients with NETs and occurs mostly in cases of patients with hepatic metastases[1]
- Consequence of vasoactive peptides such as serotonin, histamine, or tachykinins released into the circulation[2,3]
- Manifested by episodic flushing, wheezing, diarrhea, and, potentially, the eventual development of carcinoid heart disease[2,3]

Percentage of patients with symptoms of carcinoid syndrome[4]



1. Rorstad O. *J Surg Oncol*. 2005; 89:151-60.

2. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. *Gastroenterology*. 2005;128:1717-1751.

3. Vinik A, Moattari AR. *Dig Dis Sci*. 1989;34(3 Suppl):14S-27S.

4. Creutzfeldt W. *World J Surg*. 1996;20:126-131.

WHO Classifications of Neuroendocrine Neoplasms of the GEP System

WHO 1980	WHO 2000	WHO 2010
I. Carcinoid	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
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

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

Staging of NET According to Tumour-Node-Metastasis (TNM)

- The European Neuroendocrine Tumour Society (ENETS) and American Joint Committee on Cancer (AJCC) have developed TNM staging systems
- Staging systems are developed for the following tumour locations:
  - Gastric, duodenum/ampulla/proximal jejunum, pancreas[1]
  - Lower jejunum and ileum, appendix, and colon and rectum[2]

[1]Rindi G, et al. *Virchows Arch*. 2006;449:395-401; [2]Rindi G, et al. *Virchows Arch*. 2007;451:757-762.

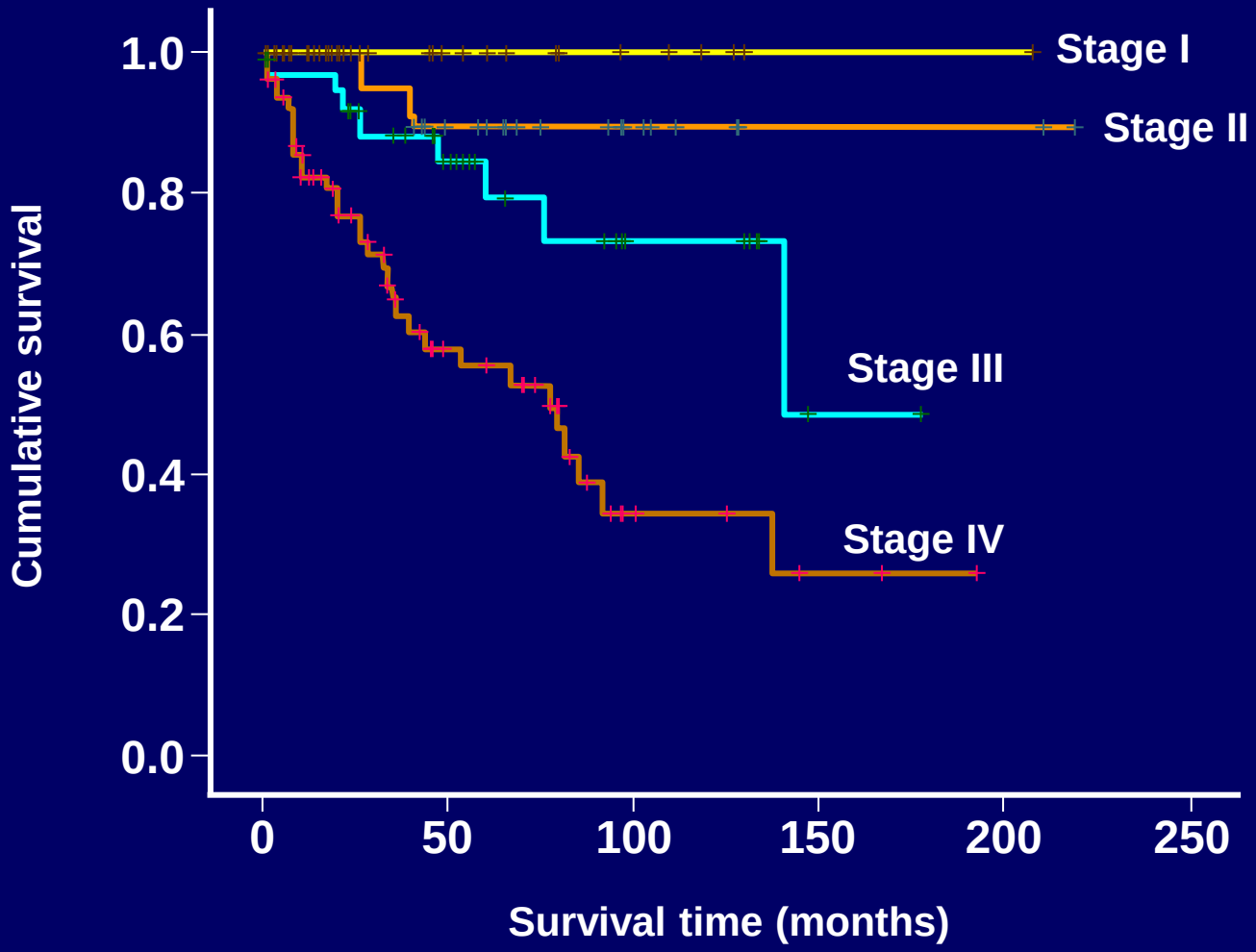
ENETS/AJCC TNM Staging Systems

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.

Correlation of Tumour Stage and Cumulative Survival (ENETS TNM Staging Proposal)



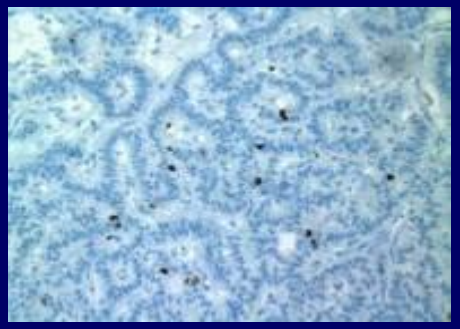
I vs II	*P* = .227
I vs III	*P* = .048
I vs IV	*P*<.001
II vs III	*P* = .171
II vs IV	*P*<.001
III vs IV	*P* = .004

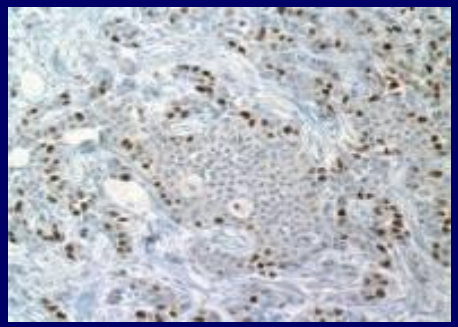
202 cases: gastric (48), duodenal (23), pancreatic (131)

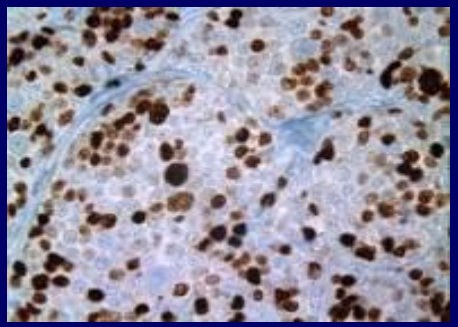
Pape UF, et al. *Cancer.* 2008;113:256-265.

Grading of GEP-NET According to ENETS/WHO/AJCC

Grade	G1	G2	G3
Ki67 index (%)**	≤2	3–20	>20
MI (mitotic count)*	<2	2-20	>20



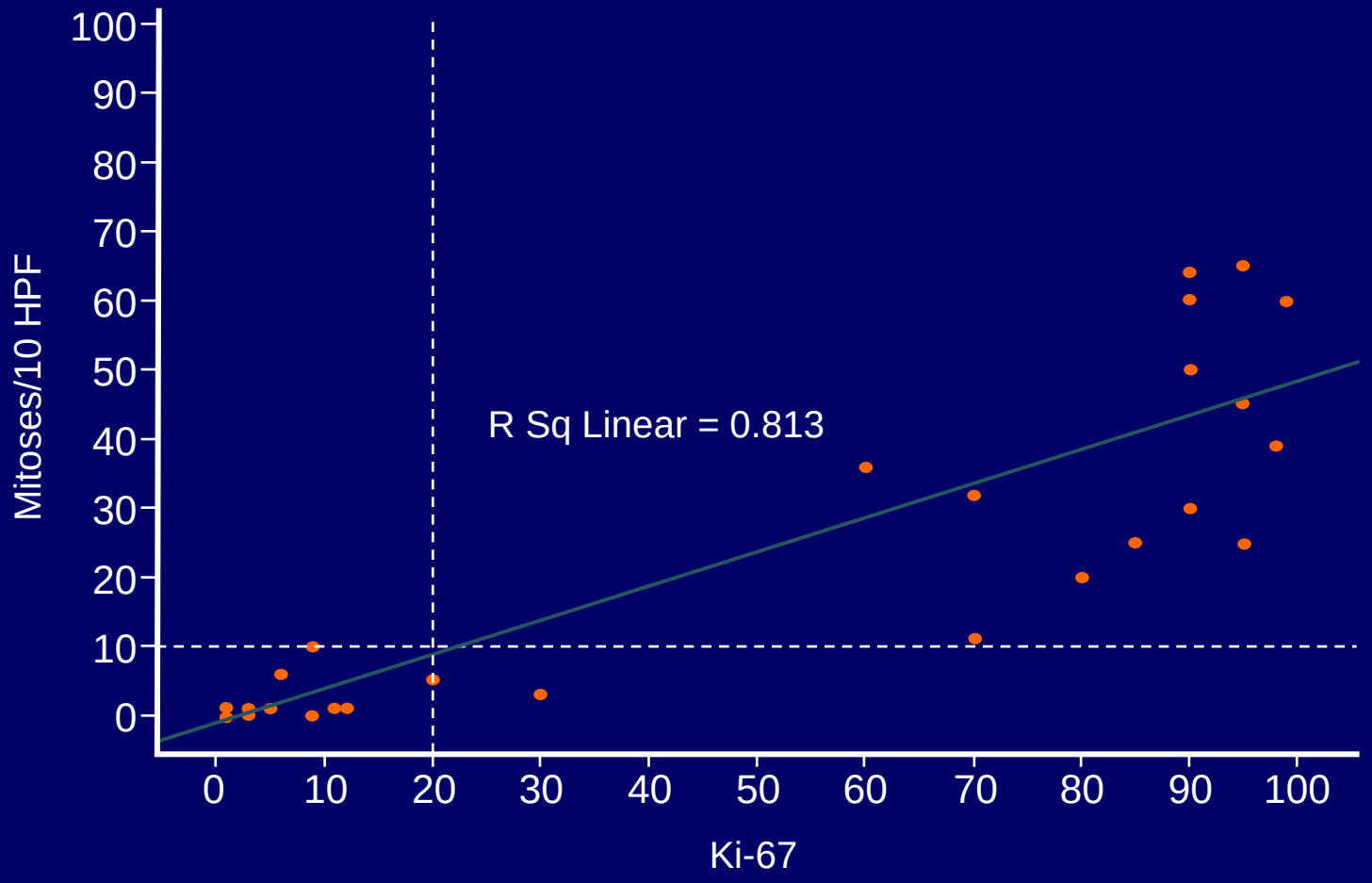




*10 HPF (high power field) = 2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density.
** MIB1 antibody; % of 2,000 tumour cells in areas of highest nuclear labeling.

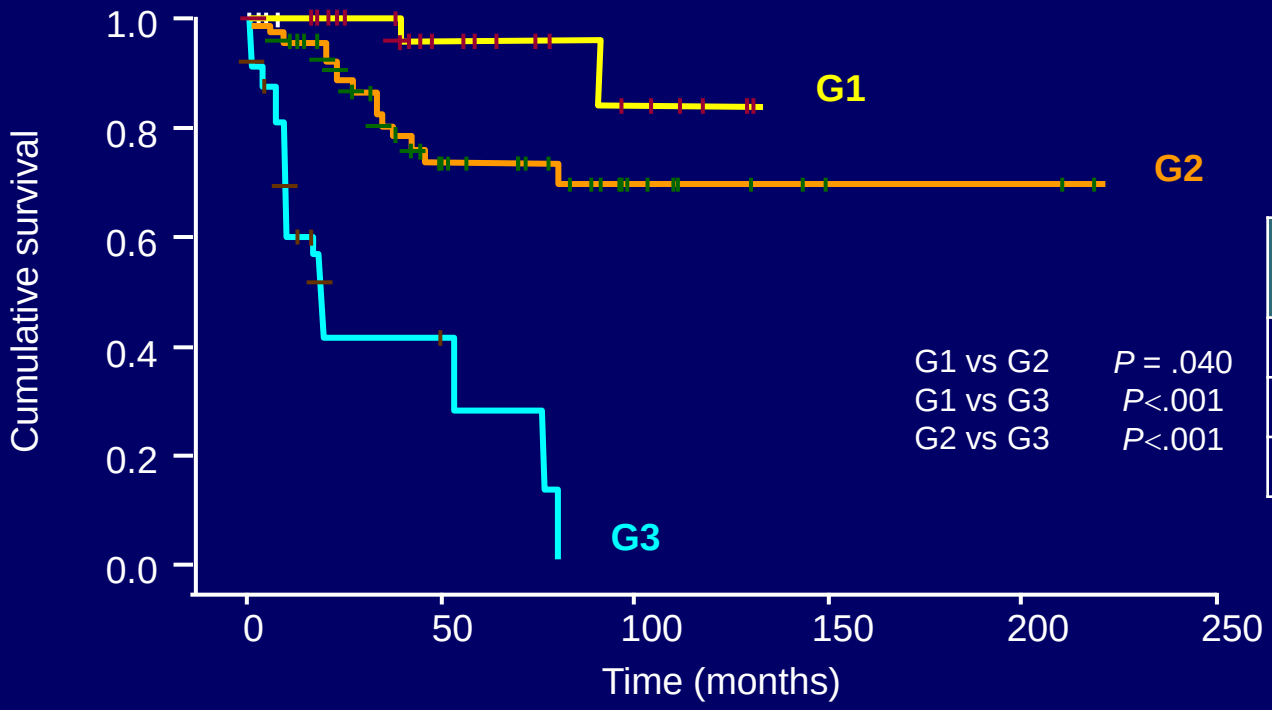
1. Rindi G, et al. *Virchows Archiv.* 2006;449:395-401. 2. Rindi G, et al. *Virchows Archiv.* 2007;451:757-762.

Metastatic GEP-NET: Correlation Between Mitotic Count and Ki-67 Index



Strosberg J, et al. *Human Pathology*. 2009;40:1262-1268.

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

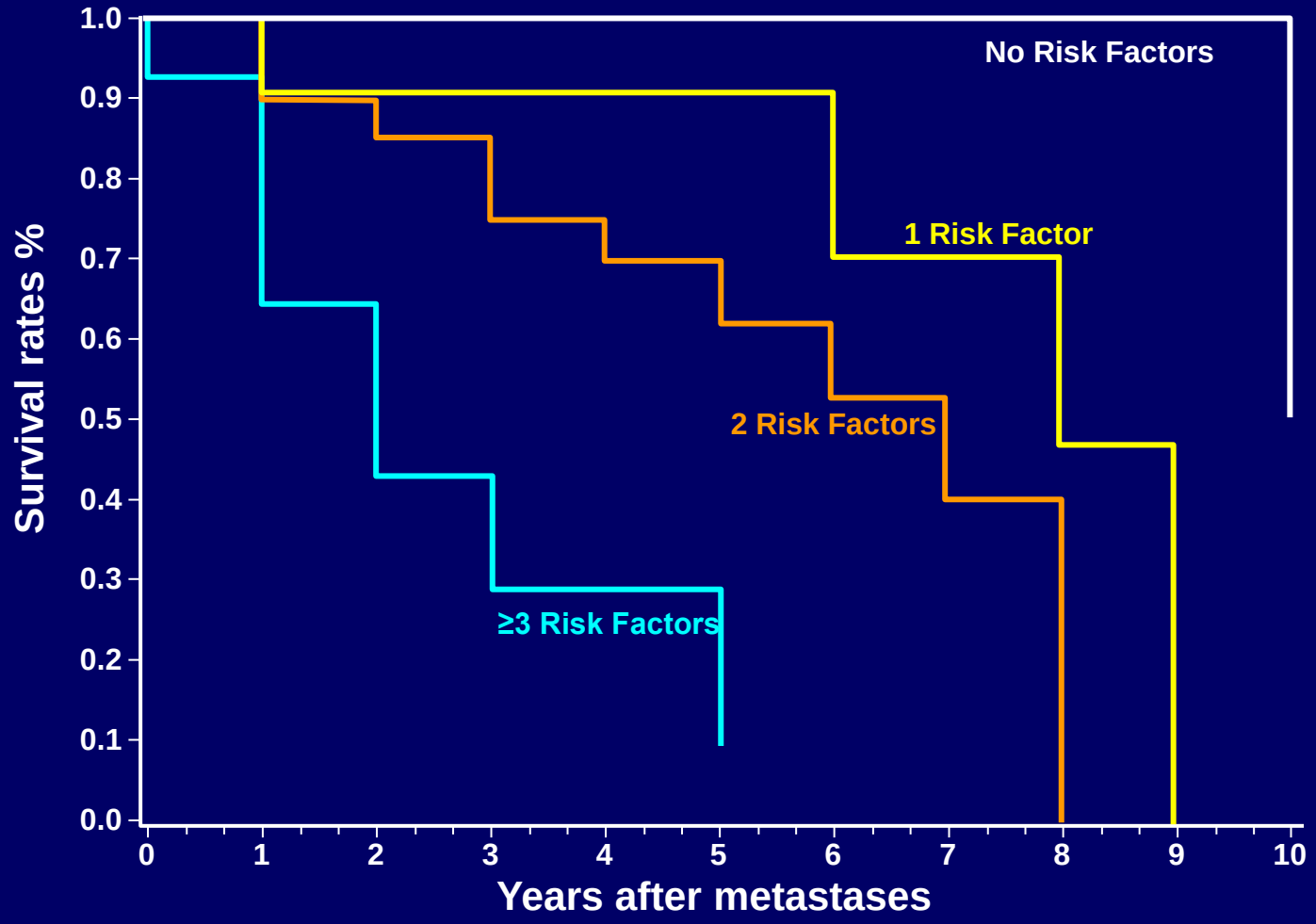


Grade[1]	Mitotic count (10 HPF)[2]	Ki-67 index (%)[3]
G1	<2	≤2
G2	2-20	3-20
G3	>20	>20

[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.

Metastatic Well-Differentiated Neuroendocrine Neoplasms: Prognosis



MV = mean variance

Prognostic factors (MV analysis):

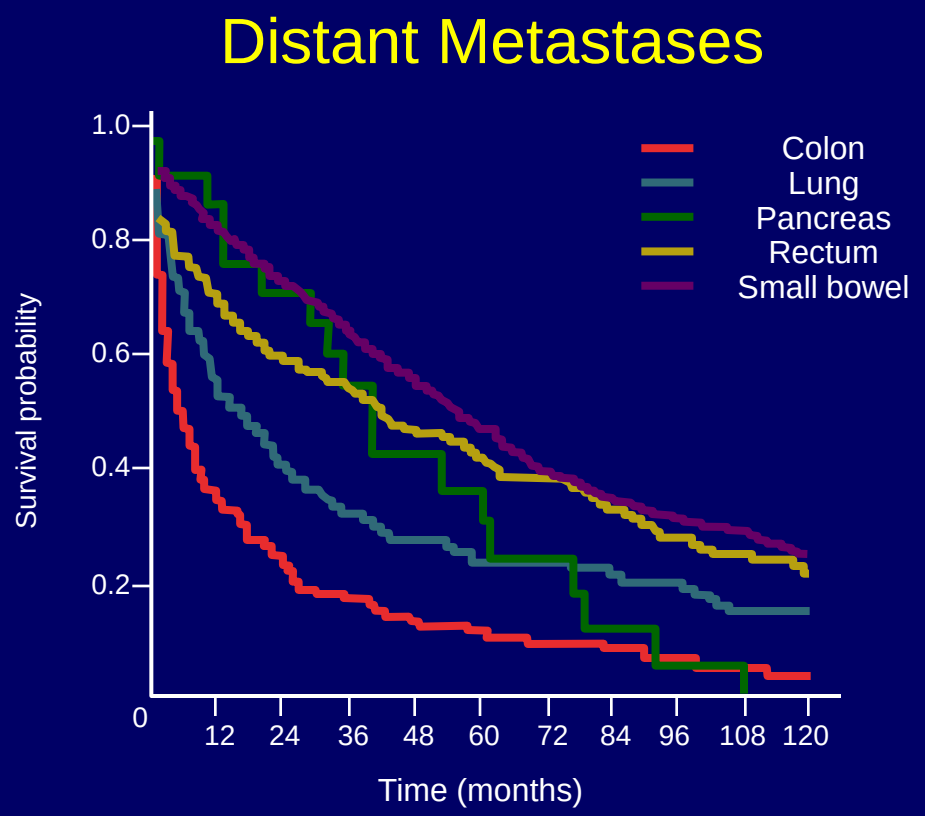
- Age >65 years
- Number of liver metastases (>10)
- Tumour progression (100% if Ki67 >10%)
- Primary not removed

Durante C, et al. *Endocr Rel Cancer.* 2009;16:585-597.

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**

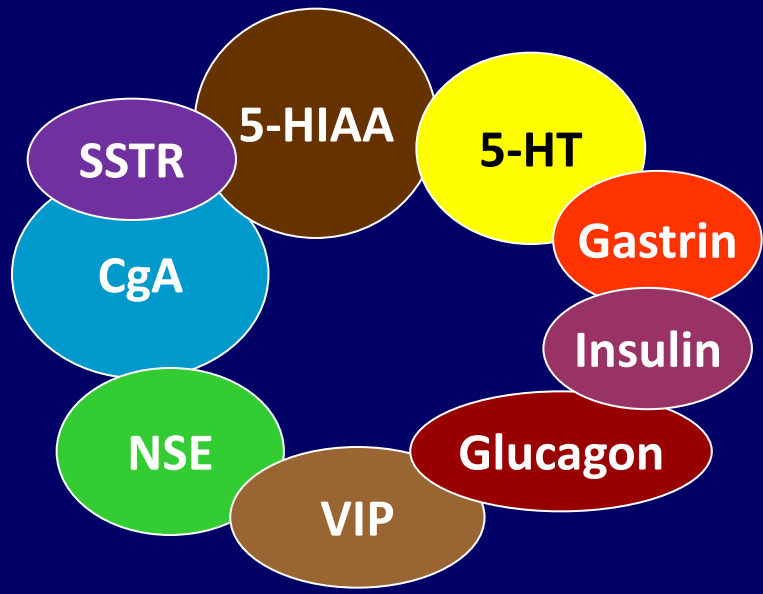


65% of patients with advanced NET will not be alive in 5 years

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

Biomarkers in NET

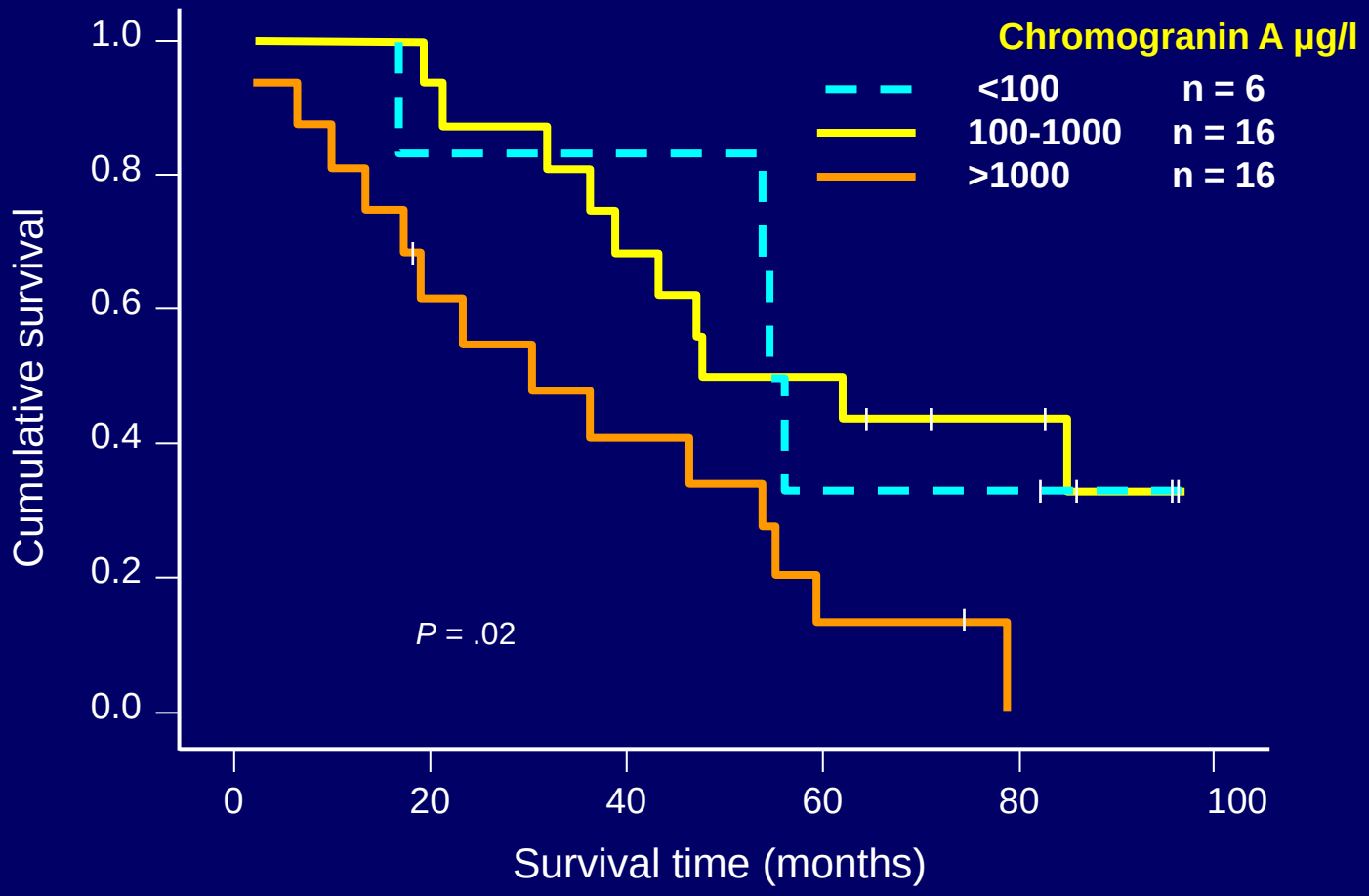
- CgA is the best available biomarker for diagnosis of NET
  - Elevated CgA may correlate with tumour progression
  - CgA is elevated 80% to 100% of the time
- NSE is also expressed in NET
  - Not as commonly used as CgA
  - Also elevated in pNET and poorly differentiated NEC
- 5-HIAA reflects serotonin levels
  - Elevated serotonin levels over time lead to comorbidities such as cardiac disease
- Other biomarkers are available, however, few have achieved widespread acceptance
- 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.

Correlation of Baseline CgA Levels with Survival



Korse C, et al. *Neuroendocrinology*. 2009;89:296-301.

CgA and NSE: Prognostic Biomarkers

	Nonelevated CgA	Elevated CgA	Nonelevated NSE	Elevated NSE
Everolimus, n	**121**	**84**	**155**	**48**
Median PFS, mos	11.2	8.5	13.86	8.11
HR (95% CI)*	1.2 (0.82, 1.76)		2.03 (1.33, 3.09)	
P value†	.173		<.001	
Placebo, n	**97**	**103**	**138**	**56**
Median PFS, mos	4.9	4.3	5.36	2.83
HR (95% CI)*	1.33 (0.98, 1.82)		2.01 (1.43, 2.84)	
P value†	.035		<.001	

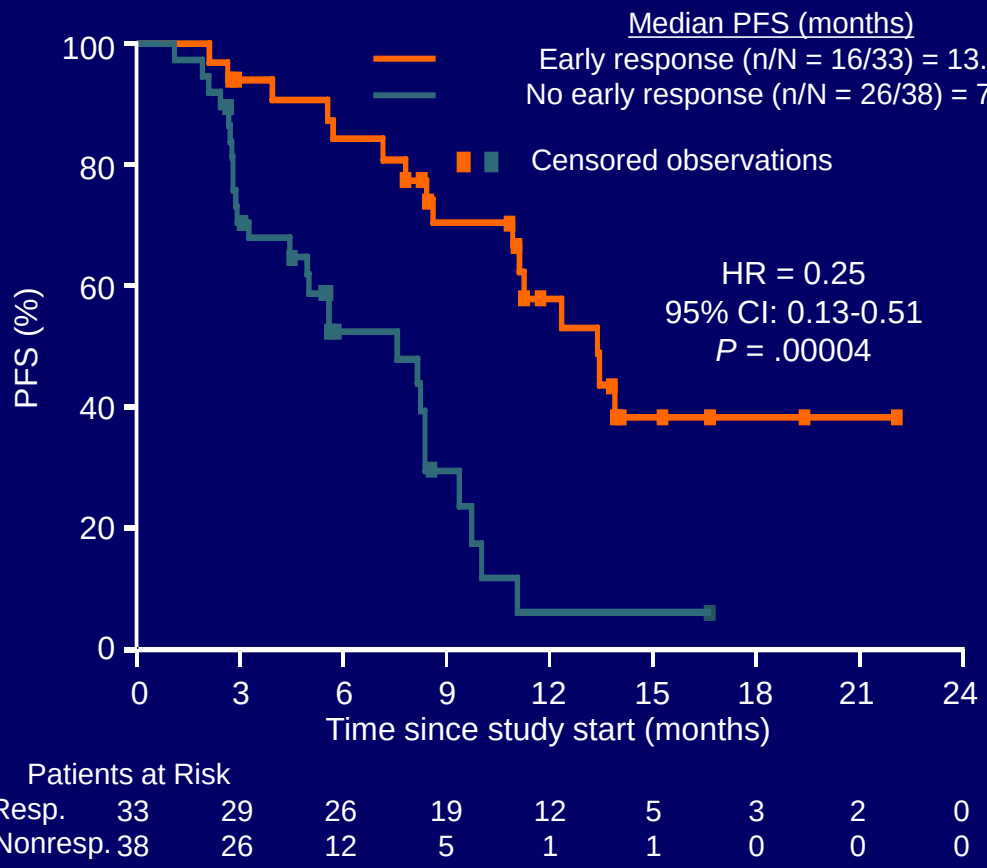
- Elevated baseline CgA were associated with shorter PFS in patients who received everolimus or placebo, suggesting that these biomarkers are predictive for outcome
- Everolimus improved PFS vs placebo regardless of patients' baseline CgA levels

PFS = progression-free survival
* Obtained from unstratified Cox model.
† Obtained from unstratified 1-sided log-rank test.

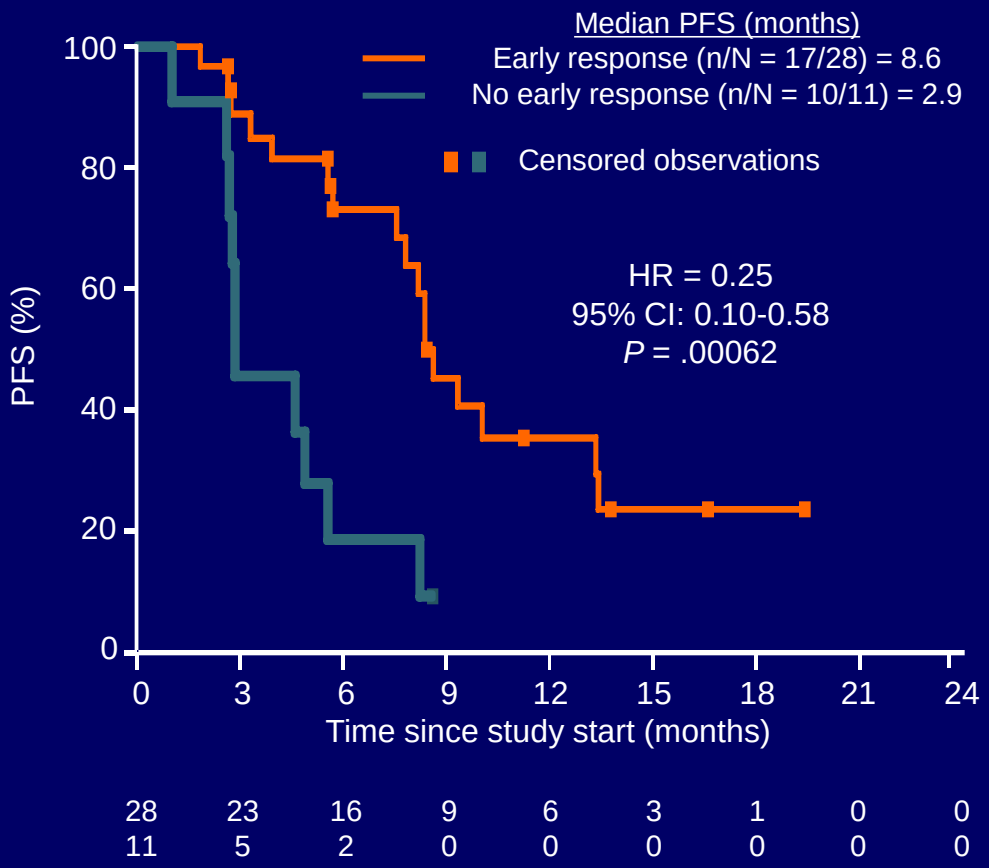
Öberg K, et al. Presented at: 8th Annual ENETS Conference; March 9-11, 2011; Lisbon, Portugal. Abstract C81.

CgA and NSE: Predictive Biomarkers*

CgA



NSE



***Data from RADIANT-1 clinical trial.**
An early CgA or NSE response was defined as normalization or ≥30% decrease at week 4.

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

Pathology Report of NET

- ✓ Define **location** and **tumour type**
- ✓ Define differentiation **grade** (including Ki-67 proliferative index)
- ✓ Describe the presence of **additional histologic features** (multicentric disease, non-ischemic tumour necrosis, vascular or perineural invasion)
- ✓ Assess the **TNM stage**
- ✓ Define the **resection margins**
- ✓ Define the **hormonal** production, if any

- ✓ ***Upon request***, assess prognostic or **predictive factors** useful for target therapy (e.g. somatostatin receptors, mTor pathway molecules, other target enzymes, …)

See also: Klimstra D, et al. *Am J Surg Pathol.* 2010;34:300-313.

Systematic Approach to Diagnosing NETs

History and physical exam

- Characteristic symptoms (dry flushing, cramps, nocturnal diarrhea)
  - Present in 8% to 35% of metastatic NETs[1]

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

Nomenclature – Summary

Neuroendocrine tumours originate from a wide variety of different cell types that can secrete their own peptide hormone

Site = Pancreas vs intestine

- **Organ of origin should be determined**
- **Nomenclature could be simplified by using location of origin**

Classification = Give a name to the disease

- **WHO classification is based on morphology and clinical pathological information (and is independent from presence and type of hormone secretion)**

Staging = Measure the extent of the disease

- **TNM staging for ENETS and AJCC is same for GI NET but differ for pNET (ENETS has proved preliminary clinical effectiveness while AJCC needs confirmation)**

Grading = Measure the pace of NET growth

- **Mitosis count or Ki67 with cut-off at 5% and 20% discern prognosis between diseases**

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 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

Collaboration for optimal patient management

Multidisciplinary patient management

Clinical research team

Basic research team

Expertise/ network

patient

European ENETS Neuroendocrine Tumor Society

ENETS Centers of Excellence

University hospitals Leuven

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