Neuro-endocrine tumours

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

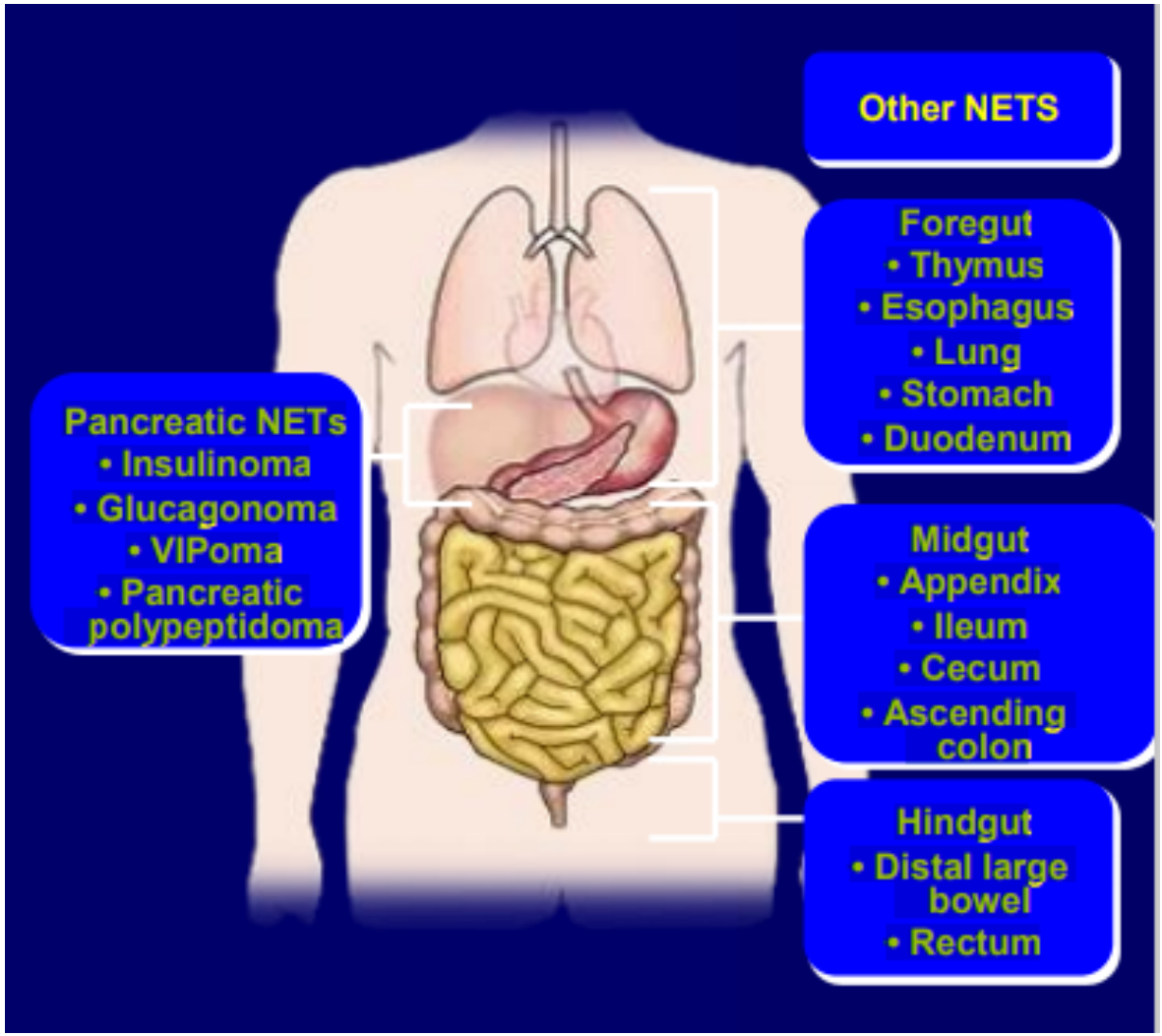
Overview of Neuroendocrine Tumors (NETs)

- NETs are sometimes called carcinoid tumors – Can be both symptomatic and asymptomatic

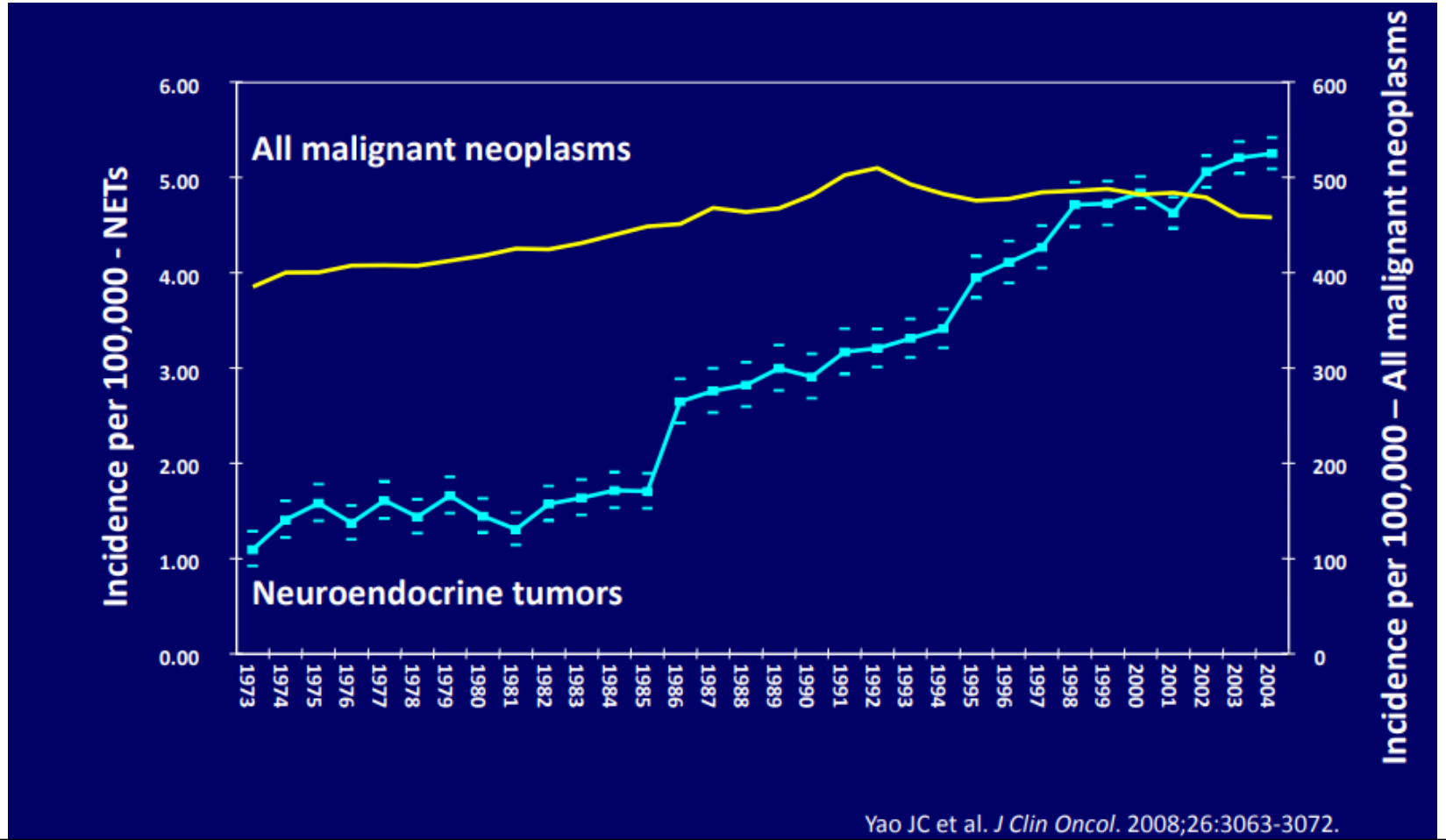
– May be undetected for years without obvious signs or symptoms

- 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

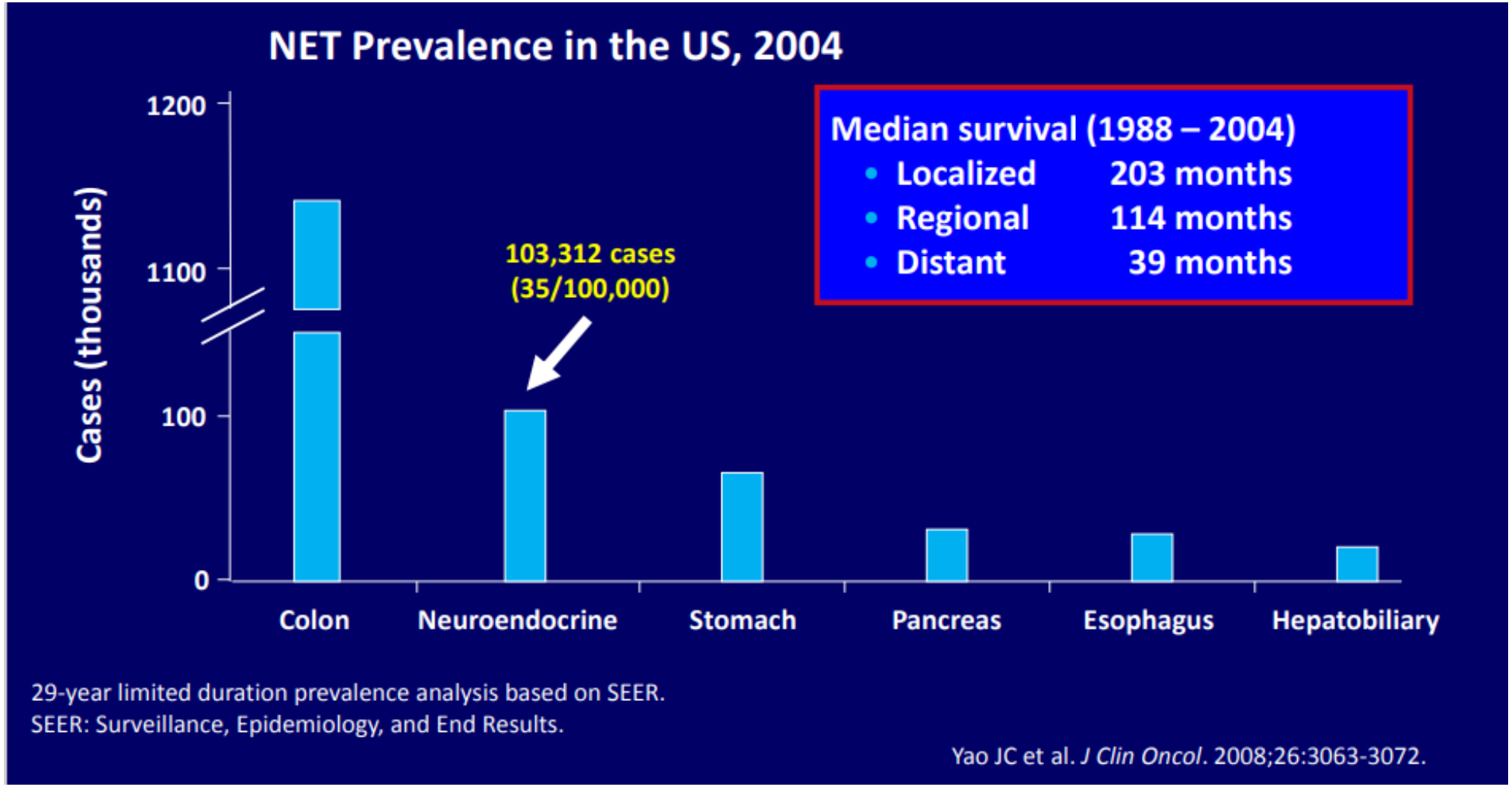

Other NETS
Foregut
• Thymus
• Esophagus
• Lung
• Stomach
• Duodenum
Pancreatic NETs
• Insulinoma
• Glucagonoma
• VIPoma
• Pancreatic polypeptidoma
Midgut
• Appendix
• Ileum
• Cecum
• Ascending colon
Hindgut
• Distal large bowel
• Rectum

Incidence of NETs Increasing

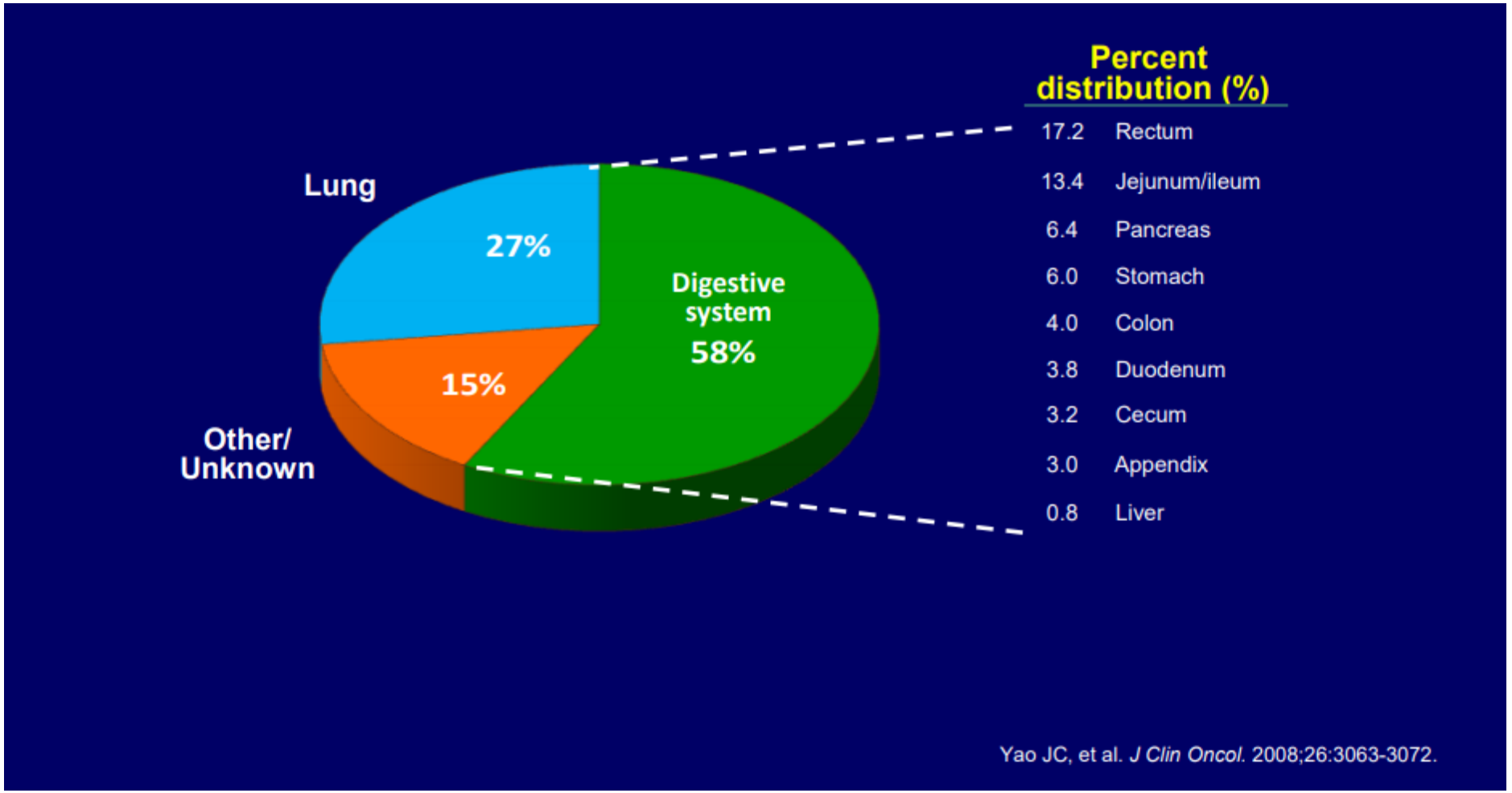


Yao JC et al. *J Clin Oncol*. 2008;26:3063-3072.

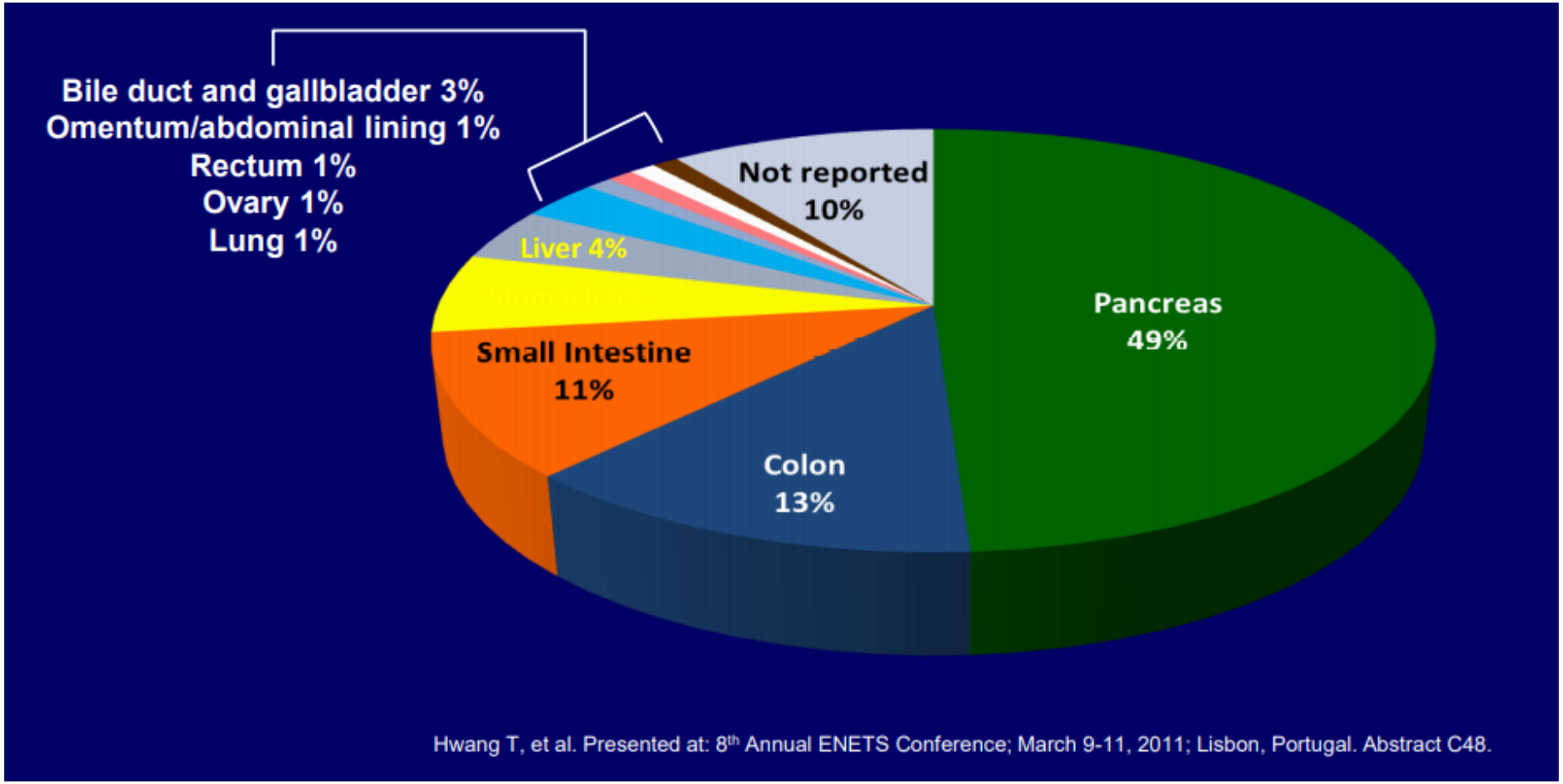
NETs Are Second Most Prevalent Gastrointestinal Tumour



The GI Tract Is the Most Common Primary Location of NET



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



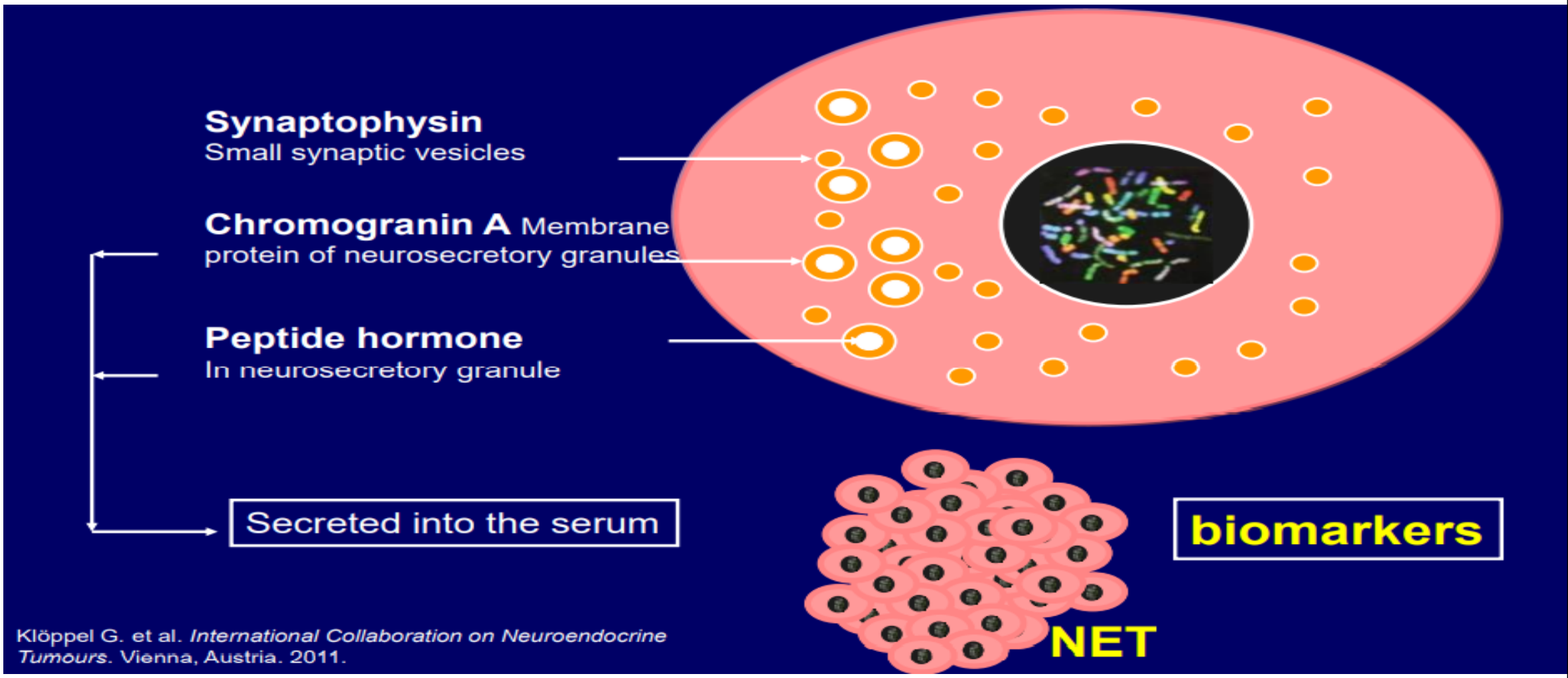
Cells of Origin

- 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)

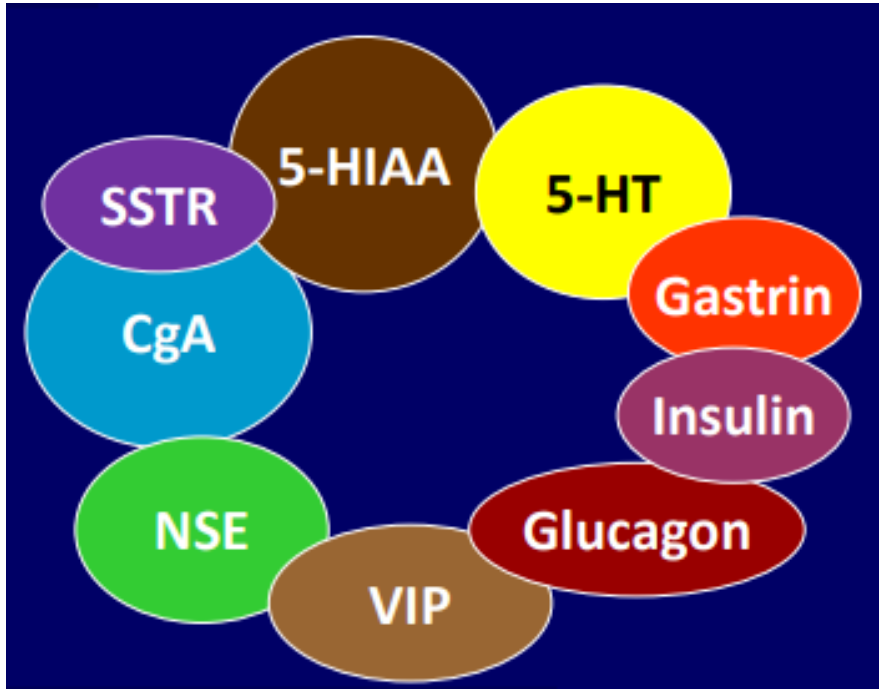
- **NET originates from APUD (Amine Precursor Uptake and Decarboxylation) cells.**
- **APUD cells constitute the diffuse endocrine system of the body.**

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



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

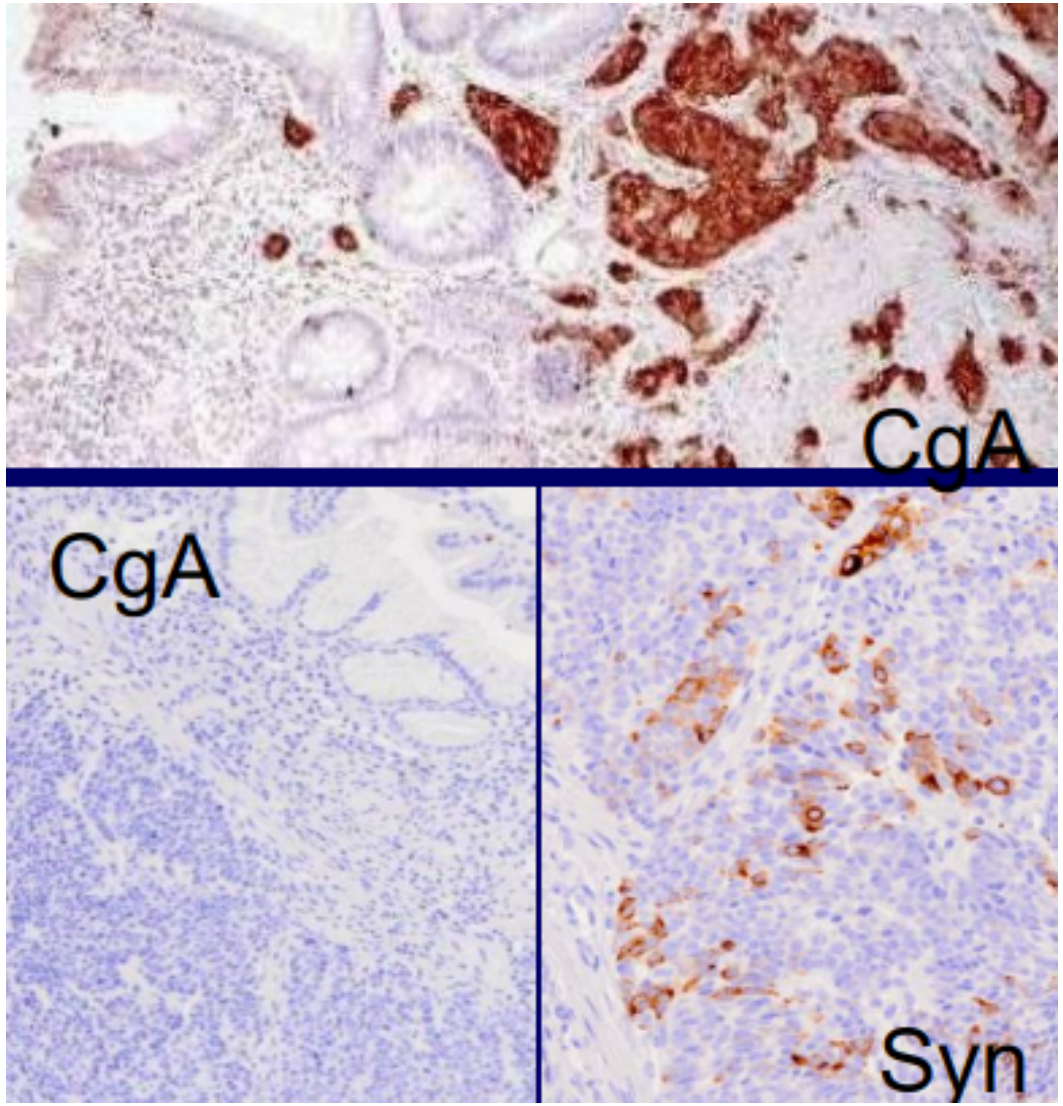
Role of CgA IHC in the Diagnosis of NET

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



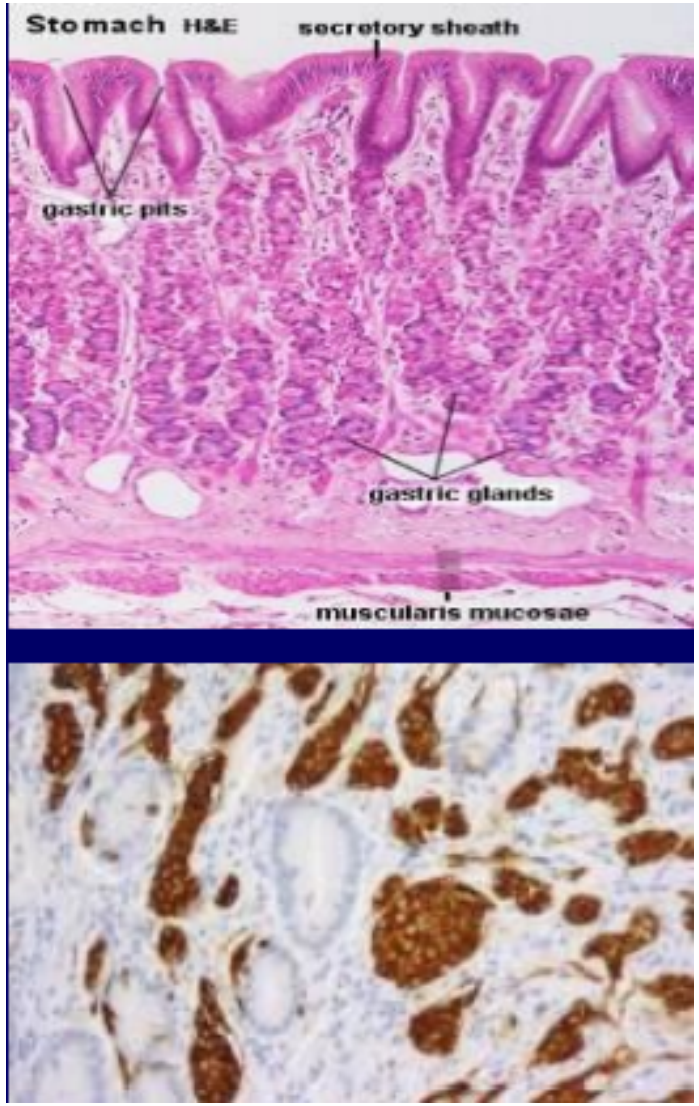
Role of Synaptophysin IHC in the Diagnosis of NET

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



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

NET vs non NET : morphology & NE markers

NET vs NEC : structure + grade

Grade 1-2-3 : mitoses & Ki67

TNM Stage I-II-III-IV : size & invasion

Confusion Caused by the Term "Carcinoid"

Oberndorfer coined the term "karzinoide" in 1971

– 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

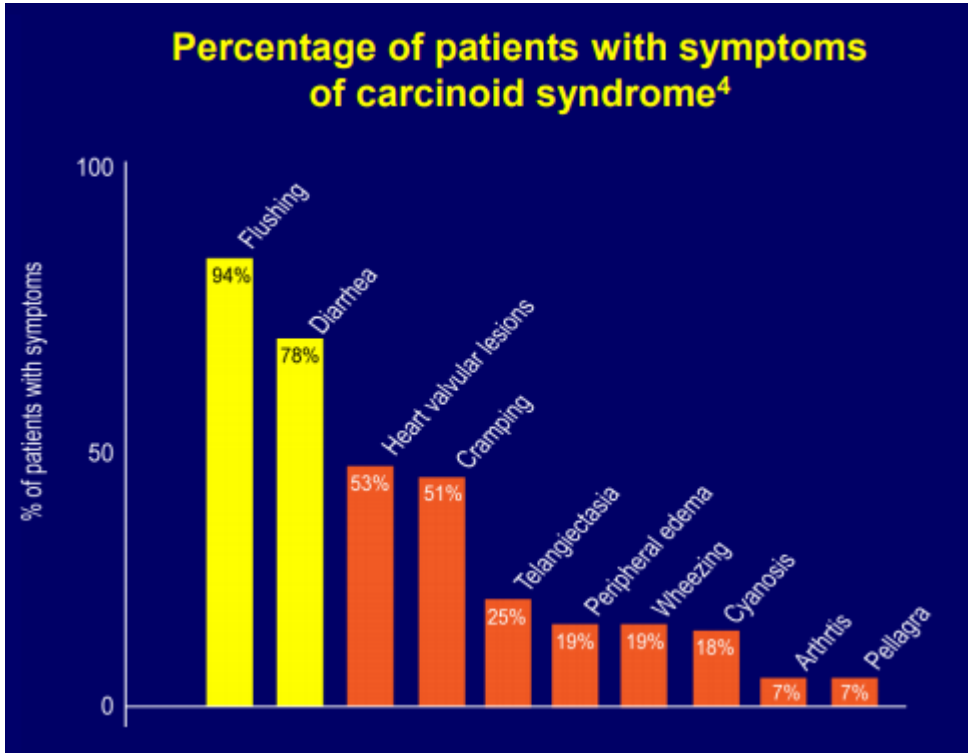
- Symptoms of carcinoid syndrome include flushing, abdominal cramps, and diarrhea
- Most cases are associated with tumours of the intestines, which frequently metastasize to the liver.

Klöppel G, et al. Endocr Pathol. 2007;18:141-144.

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 metastases1
- Consequence of vasoactive peptides such as serotonin, histamine, or tachykinins released into the circulation2,3
- Manifested by episodic flushing, wheezing, diarrhea, and, potentially, the eventual development of carcinoid heart disease2,3



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
  - Lower jejunum and ileum, appendix, and colon and rectum

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

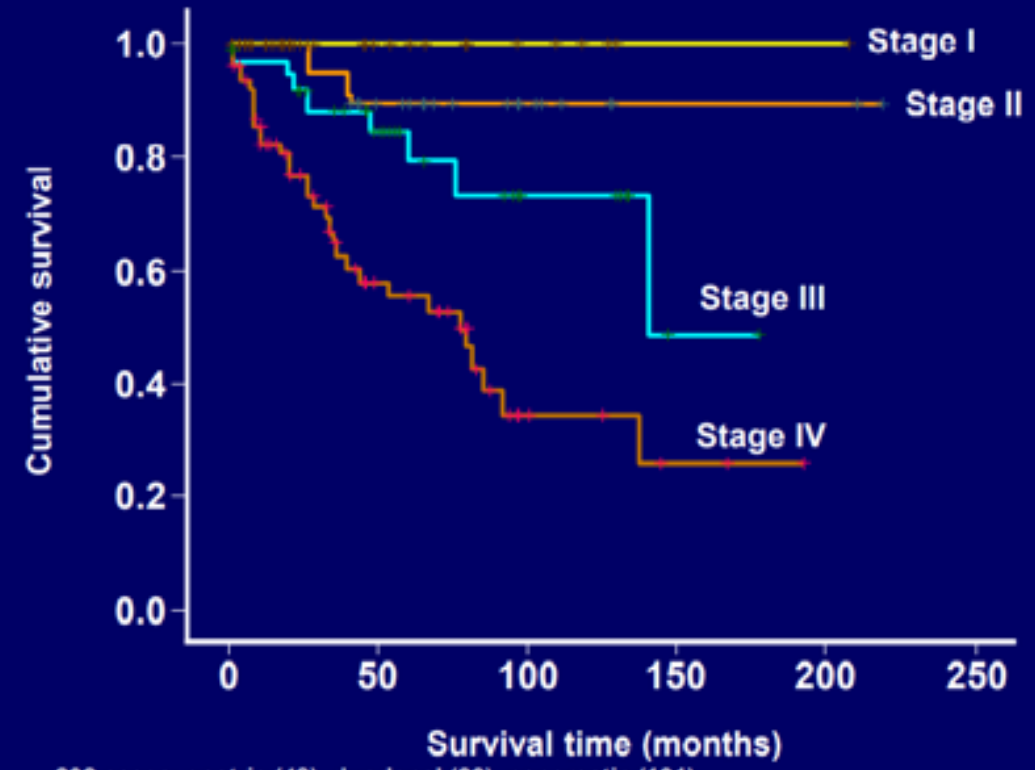
ENETS/AJCC TNM Staging Systems

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)



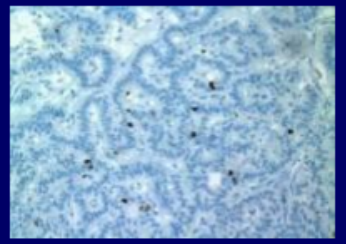
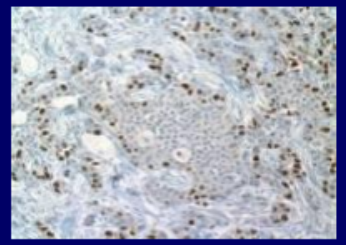
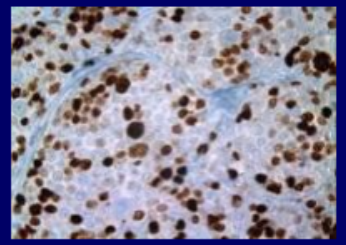
I vs II	*P* = .227
I vs III	*P* = .048
I vs IV	*P*<.001
II vs III	*P* = .171
II vs IV	*P*<.001
III vs IV	*P* = .004

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.

Systematic Approach to Diagnosing NETs

History and physical exam

Characteristic symptoms (dry flushing, cramps, nocturnal diarrhea)

– Present in 8% to 35% of metastastic NETs1

Biochemical markers

– Chromogranin A (CgA)

– Urinary 5-hydroxyindoleacetic acid [(5-HIAA) (with presence of carcinoid syndrome]

– Synaptophysin on biopsies

– Other biomarkers, including glucagon, gastrin

Histologic diagnosis !!! (expertise)

Imaging

– Computerized tomography scan (CT)

– Endoscopic ultrasound (mainly pancreatic-NET and NET in duodenum)

– Magnetic Resonance Imaging (MRI)

– Somatostatin-receptor scintigraphy (Octreoscan™) or DOTA-TOC FDG/PET

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

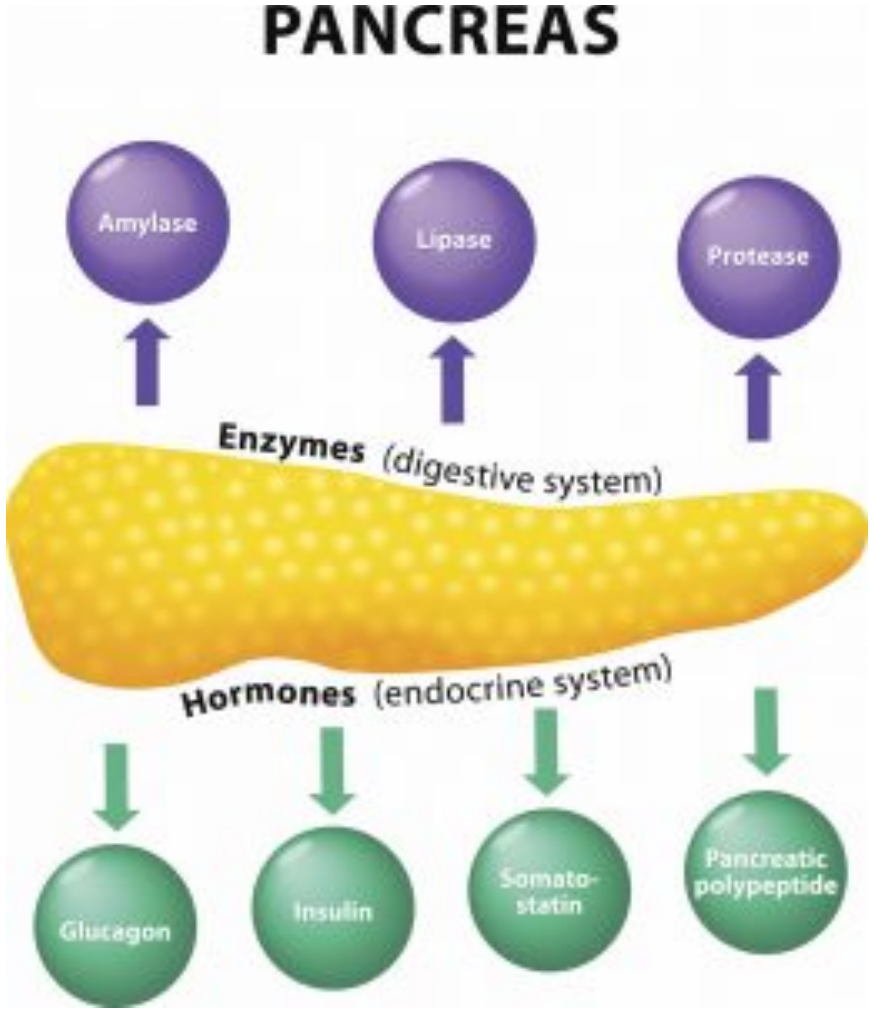
– WHO classification is based on morphology and clinical pathological information (and is independent from presence and type of hormone secretion)

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

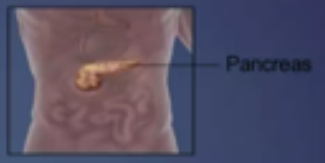


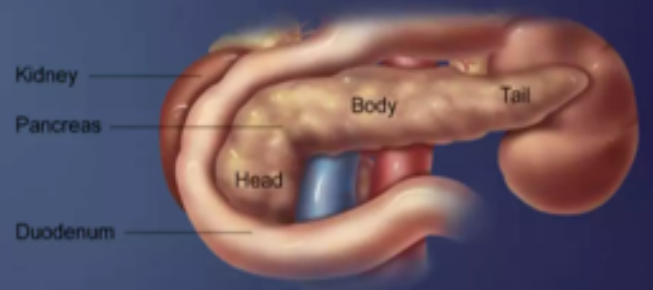
NET of Pancreas

- MC NET of pancreas: non- functiponal.
- MC benign NET of pancreas: Insulinoma.
- MC malignant functional NET of pancreas: Gastrinoma

NET of Pancreas Overview:

- PNETs are rare, slow-growing neoplasms
  - Symptoms from excess hormone production or mechanical problems
  - 7% of all NETs are found in pancreas
  - 1-2% of all pancreatic tumors
- Historically – islet cell tumors

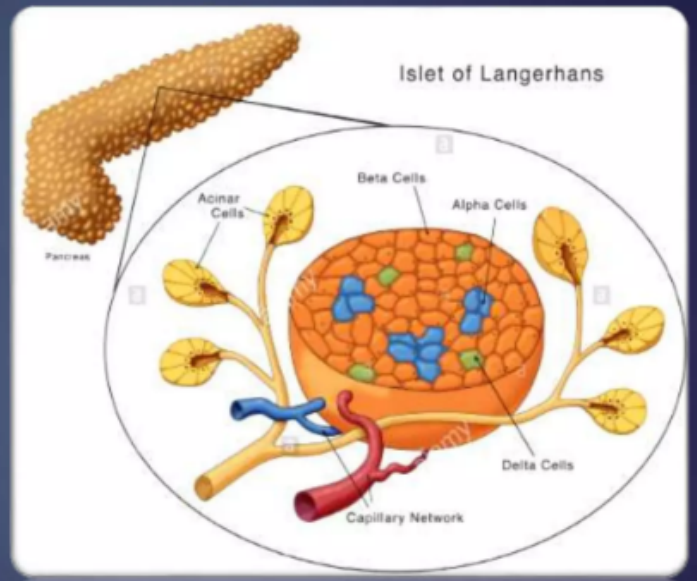




Amin, Mahul B., ed. (2017). "30 - Neuroendocrine Tumors of the Pancreas". AJCC Cancer Staging Manual (8 ed.). Springer. pp. 415–416. ISBN 978-3-319-40617-6.

ORIGIN

- Debated
- Arise from pluripotent stem cells in pancreatic ductal acinar system and not from pancreatic islet themselves



Schimmack S, et al: The diversity and commonalities of gastroenteropancreatic neuroendocrine tumors, *Langenbecks Arch Surg* 396:273– 298, 2011.

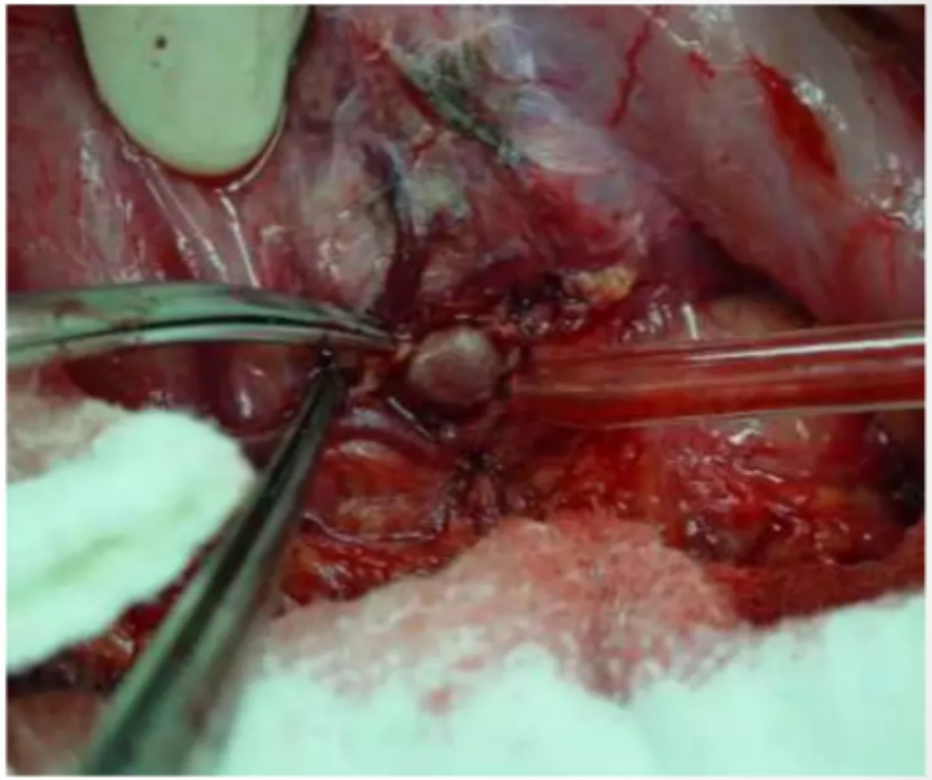
Pancreatic NETs Types

Tumor	Islet cell type	Predominant hormone produced	Malignant potential
Gastrinoma	Gamma	Gastrin	Very high
Insulinoma	Beta	Insulin	Low
Glucagonoma	Alpha	Glucagon	Very high
VIPoma	Delta	Vasoactive intestinal peptide	High
Somatostatinoma	Delta	Somatostatin	Very high
PPoma	PP cells	Pancreatic polypeptide	Very high

Relative frequency: Asymptomatic >Insulinoma > Gastrinoma > Glucagonoma > VIPomas > Somatostatinoma > Others

Insulinoma

- Most common 60%
- Origin- β cells almost universally within the pancreas (1/3head – 1/3 body – 1/3 tail)
- F>M
- **90% benign, 10% malignant**
- Most solitary, 10% multiple
- 21% MEN 1 – insulinomas
- The median age at diagnosis- 47yrs



Clinical Presentation

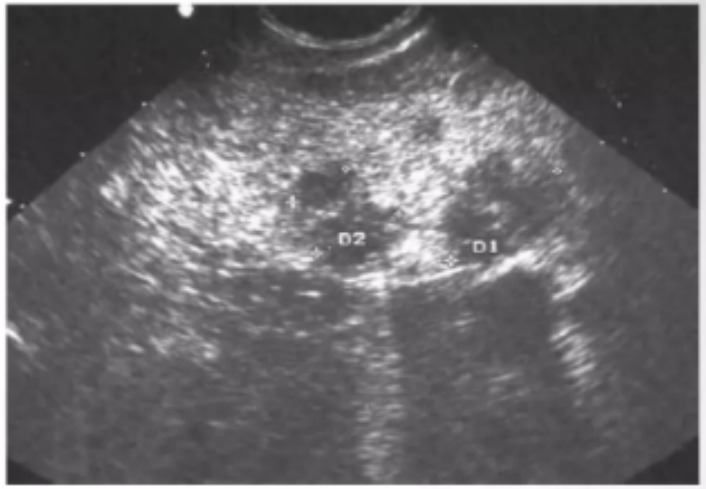
- Whipple's triad - (1) symptoms of hypoglycemia, (2) plasma glucose level <2.2 mmol/l (<40 mg/dl), and (3) relief of symptoms with administration of glucose.
  - Weight gain
  - Diagnosis:

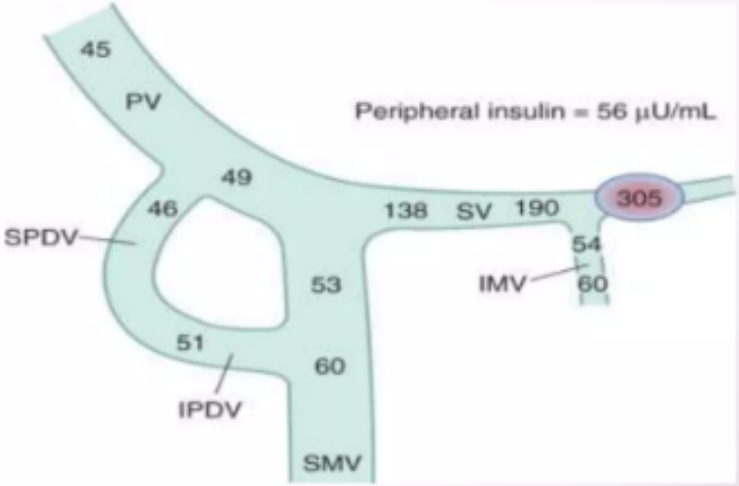
    -72hrs fasting test

    - Neuroglycopenic symptoms
    - Serum glucose<45mg/dl
    - Serum level of insulin >5μU/L
    - Serum C-peptide(>0.7ng.ml),Proinsulin >6.5 pmol

Invasive

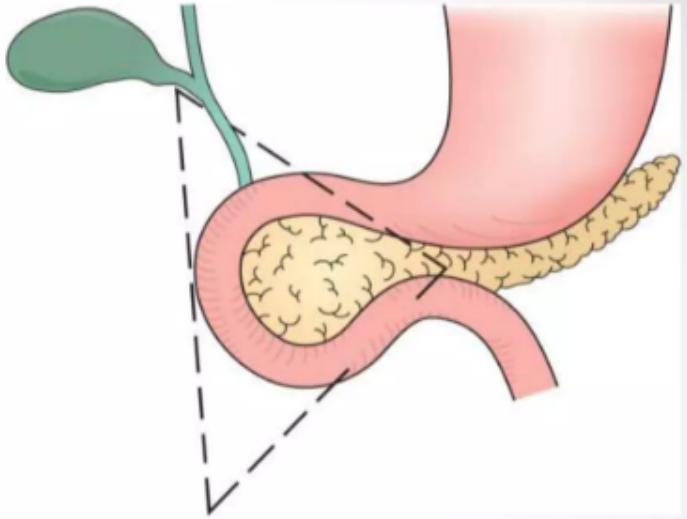
- Selective angiography
- EUS – 77%, EUS guided FNA
- Portal Venous sampling-80%
- Calcium angiogram-90%
- IOUS-90%





Gastrinoma /Zollinger-Ellison Syndrome

- Second most frequent
- 1-2 / million
- 60% malignant
- 75 % sporadic
- M>F
- Average age -50 years,5 to 10 years earlier in MEN-1
- 25 % MEN-1



Oberg K, Eriksson B. Endocrine tumours of the pancreas. Best Pract Res Clin Gastroenterol 2005;19:753–81.

ZES contd.

- Clinical Features
  - Abdominal Pain 70%
  - Diarrhea 70%
  - Heartburn 50%
  - Nausea 25%
  - Vomiting 20%
  - Weight Loss 15%

Fasting Serum Gastrin (Cessation of PPI for 1 week) > 150pg/ml

Basic acid output > 15 mmol/h

Provocative test(Secretin stimulation test) -Rise by 200 pg/mL or more

VIPOMA(Verner-Morrison Syndrome)

- 0.05-0.2 new cases per million adults
- Third most common neuroendocrine tumor of the pancreas
- Solitary, found in body or tail.
- 2/3 malignant
- Male-to-female ratio in children - 1:1,

  in adults. - 1:3

Clinical features

- Variable features
  - Achlorhydria or hypochlorhydria
  - Hypercalcemia
  - Hyperglycemia
  - Flushing with rash.
- Constant features
  - Watery Diarrhea
  - Hypovolemia
  - Hypokalemia
  - Acidosis

WDHA SYNDROME

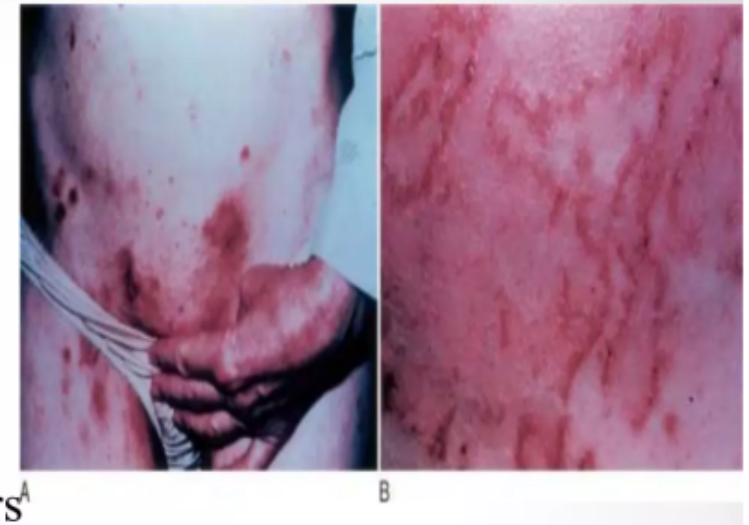
VIPoma contd.

- Diagnostic triad
  - Secretory diarrhea
  - High levels of circulating VIP > 150pg/ml
  - A pancreatic tumor
- Localization
  - SRS - 91% of primary tumors and 75% of metastases.

Nikou GC, et al. H*epatogastroenterology* 2005

- Management
  - Correction of metabolic abnormality
  - Octreotide

Glucagonoma



- Tumor of islet alpha cells
- Mainly body and tail
- 1% of all neuroendocrine tumors
- Mean age of 55 years (19-84 years).
- Nearly all are malignant
- Migratory necrolytic erythema
- 4D syndrome (dermatitis, diabetes, diarrhea, DVT)
- Plasma glucagon >1000pg/ml: Diagnostic

Somatostatinoma

- Rare
- 70% to 90% of tumors – malignant
- Location – usually head
- Clinical findings – unpredictable
  - Diarrhea
  - Gallstones – 59 %
  - Steatorrhea
  - Mild diabetes – 75%

THANK YOU