Alex Gonzalez Bossolo, MD ECNU

Diplomate of the American board of Internal Medicine and Endocrinology, Diabetes and Metabolism

December 13, 2019

SPED/AACE Meeting

Pancreatic Neuroendocrine Tumors: Endocrinologist Role

San Juan City Hospital
Endocrinology, Diabetes & Metabolism

Disclosure

- No conflicts of interests to disclose.

Outline

Pancreatic Neuroendocrine Tumors (PNETs)

- Background
- Clinical Features
- Imaging and Localization
- Staging
- Biochemical Markers

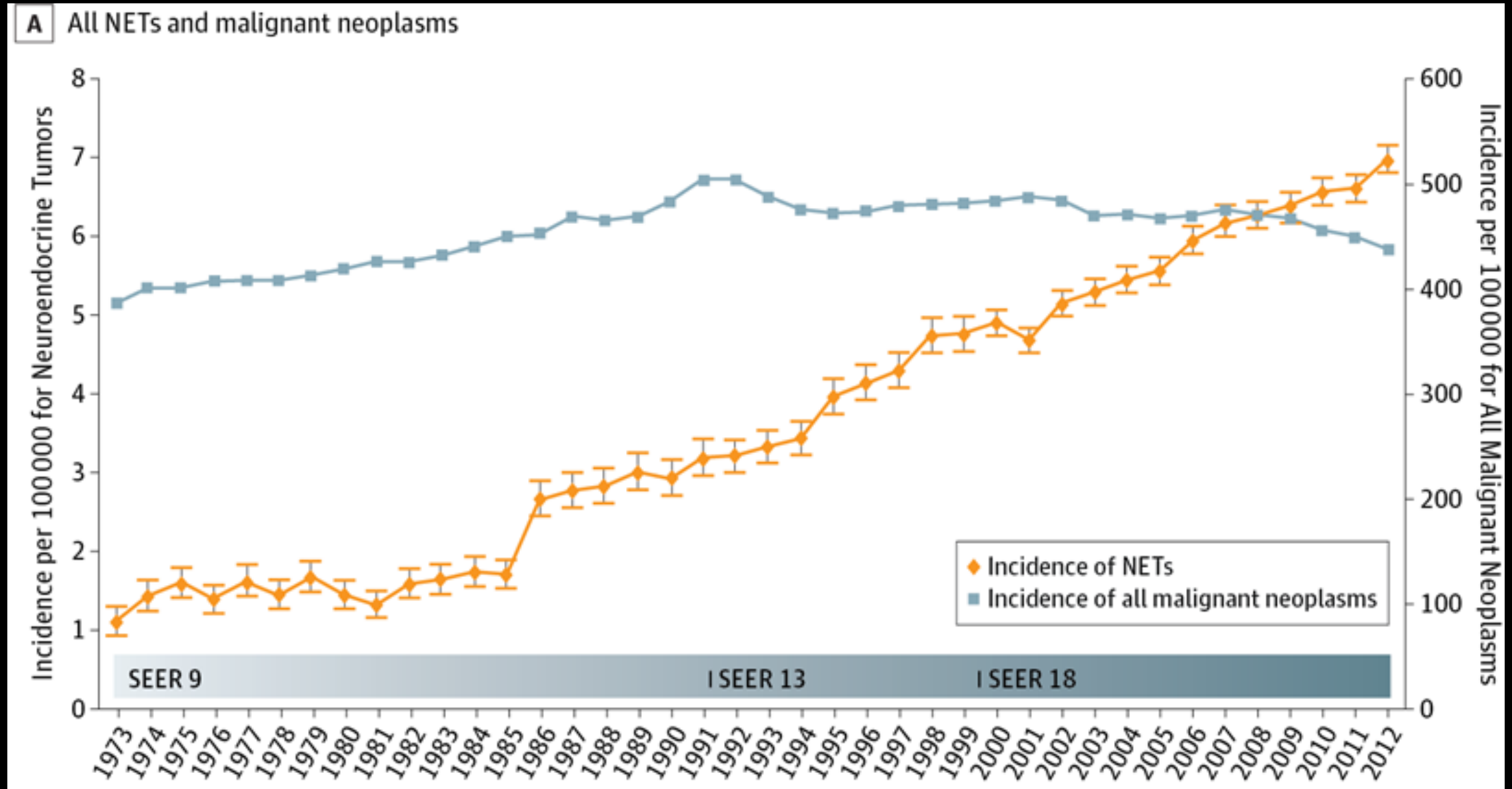
Functional PNETs

Non-Functional PNETs

Background

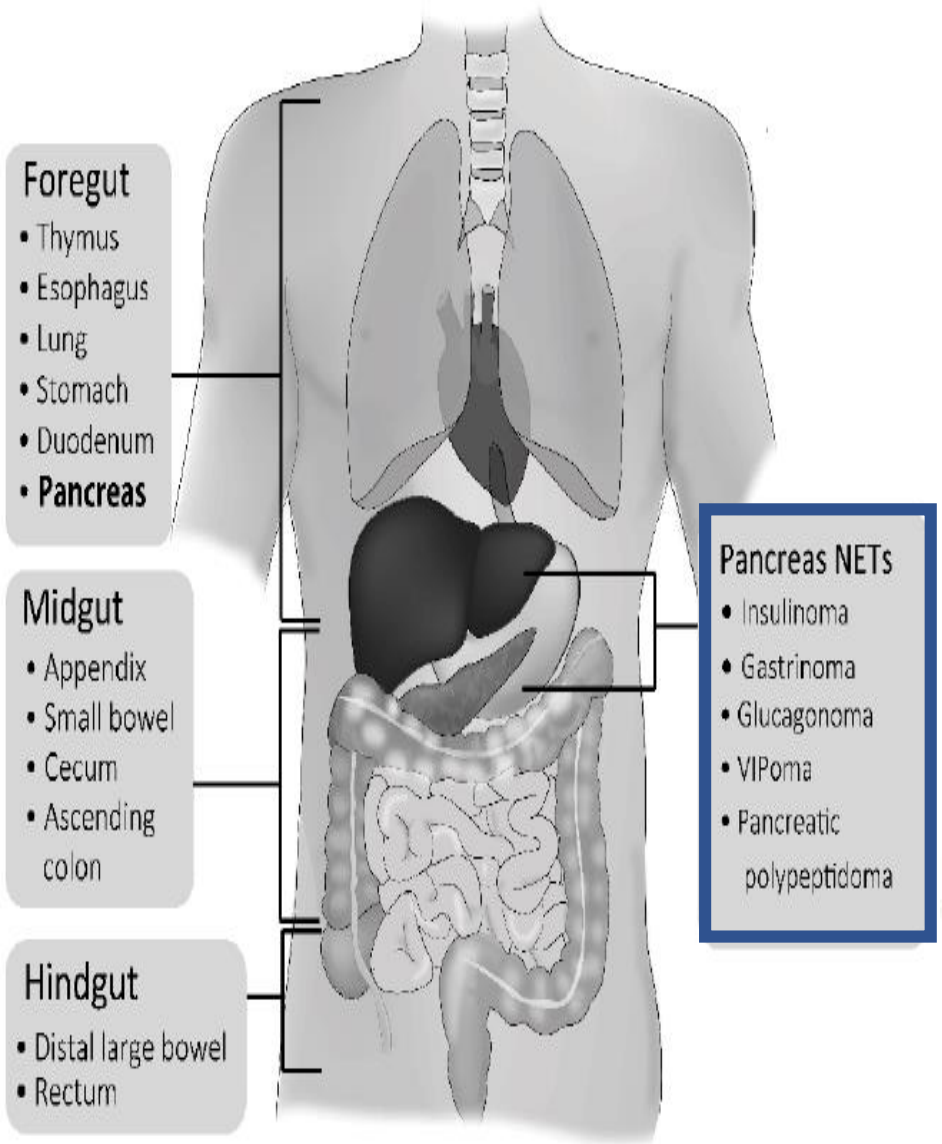
Neuroendocrine neoplasms (NENs), defined as epithelial neoplasms with predominant neuroendocrine differentiation, can arise in most organs.

While some clinical and pathologic features of these tumors are unique to the site of origin, other characteristics are shared regardless of site.



The annual age-adjusted incidence of NETs was 1.09 per 100 000 persons in 1973 and increased to 6.98 per 100 000 persons by 2012

JAMA Oncol. 2017;3(10):1335-1342.



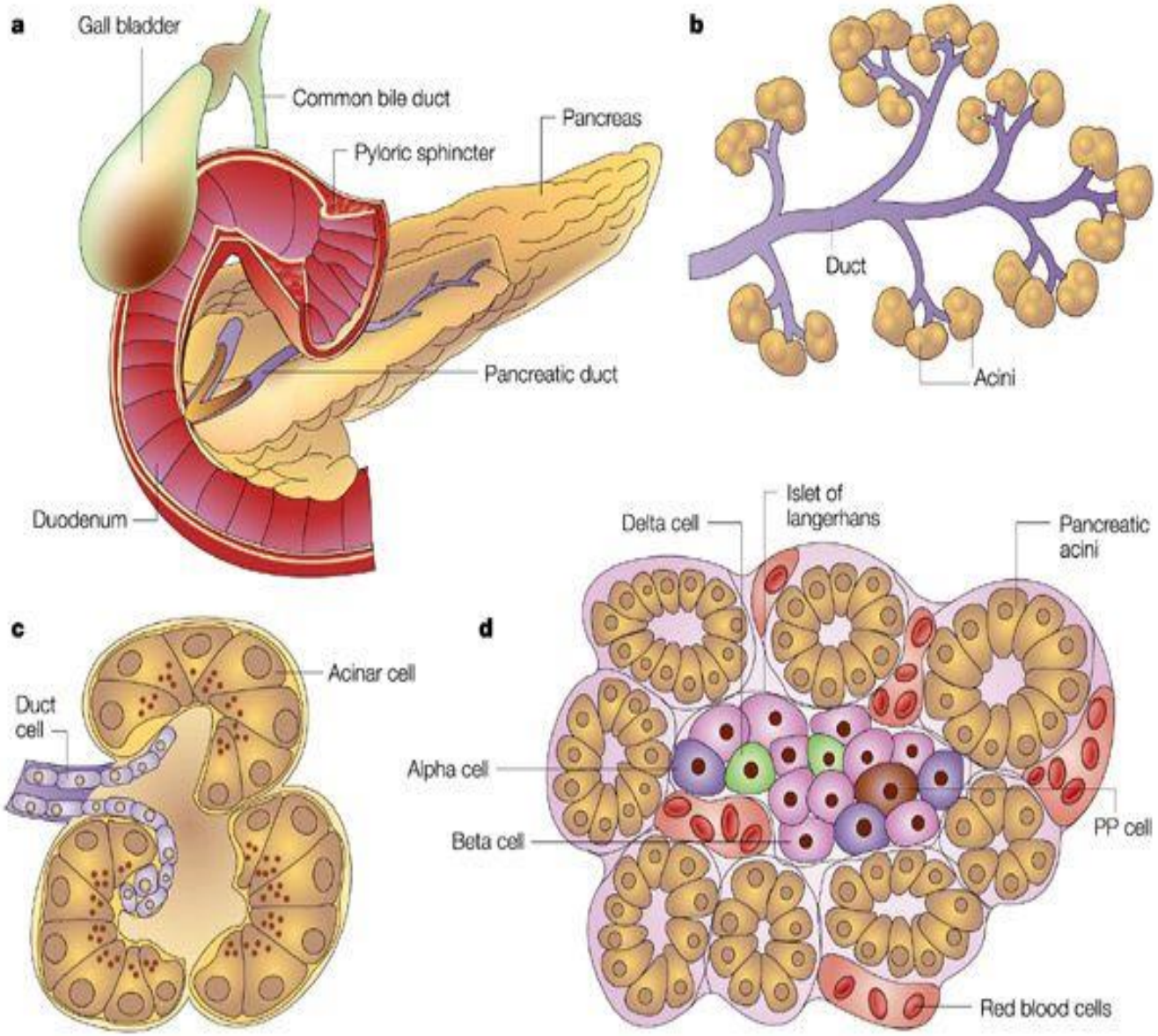
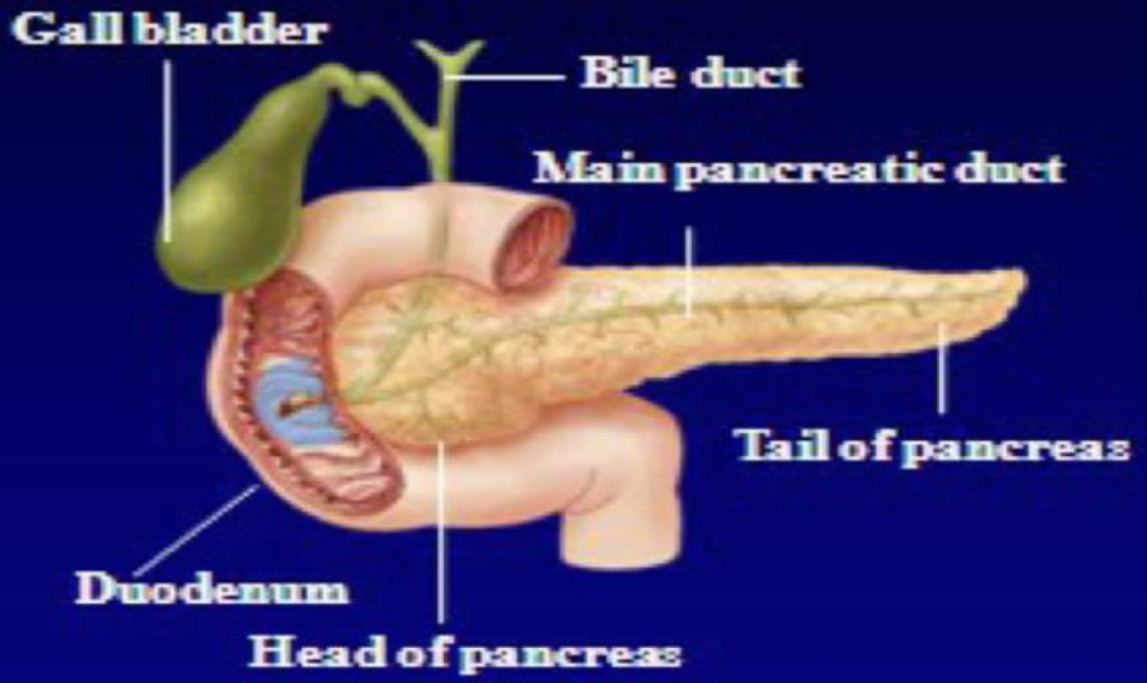


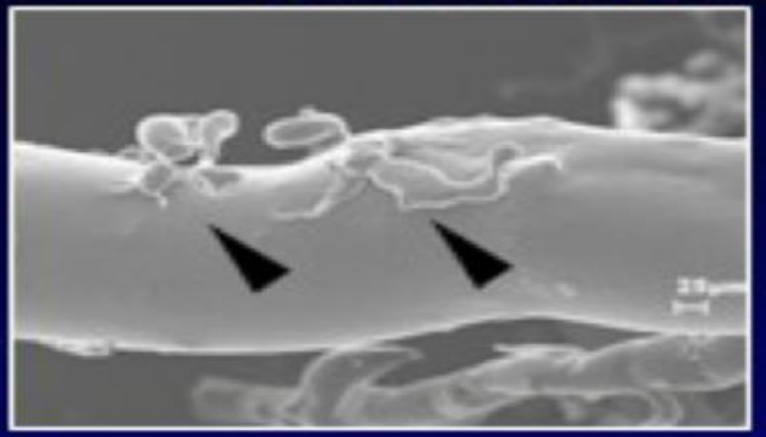
Figure 1. Neuroendocrine tumors are generally classified as foregut, midgut, or hindgut depending on their embryonic origin, ar at least 5 different types of functional tumors.

Neoplasia Vol. 19, No. 12, 2017

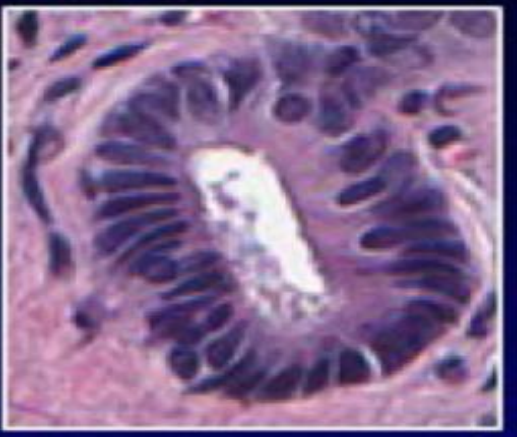
Proliferation of Pancreatic Ductal Cells



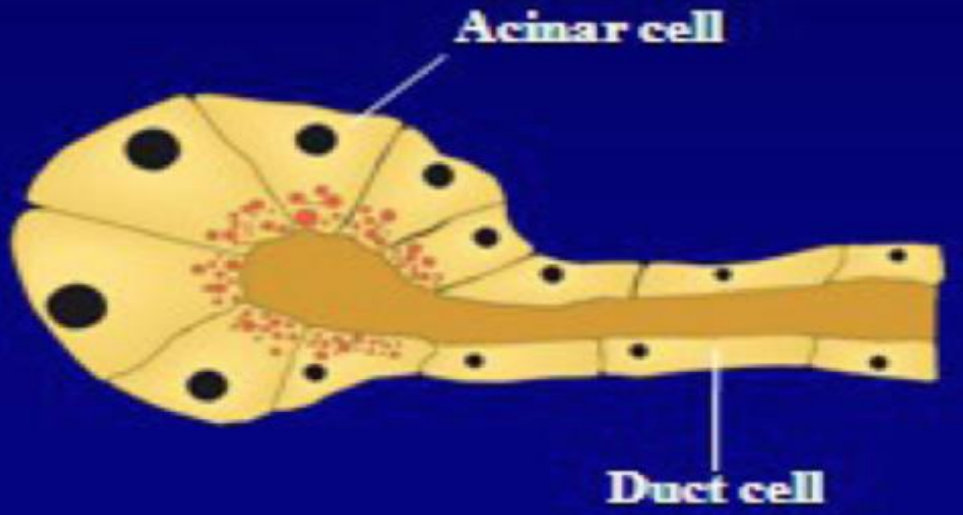
Pancreatic duct glands (PDGs)



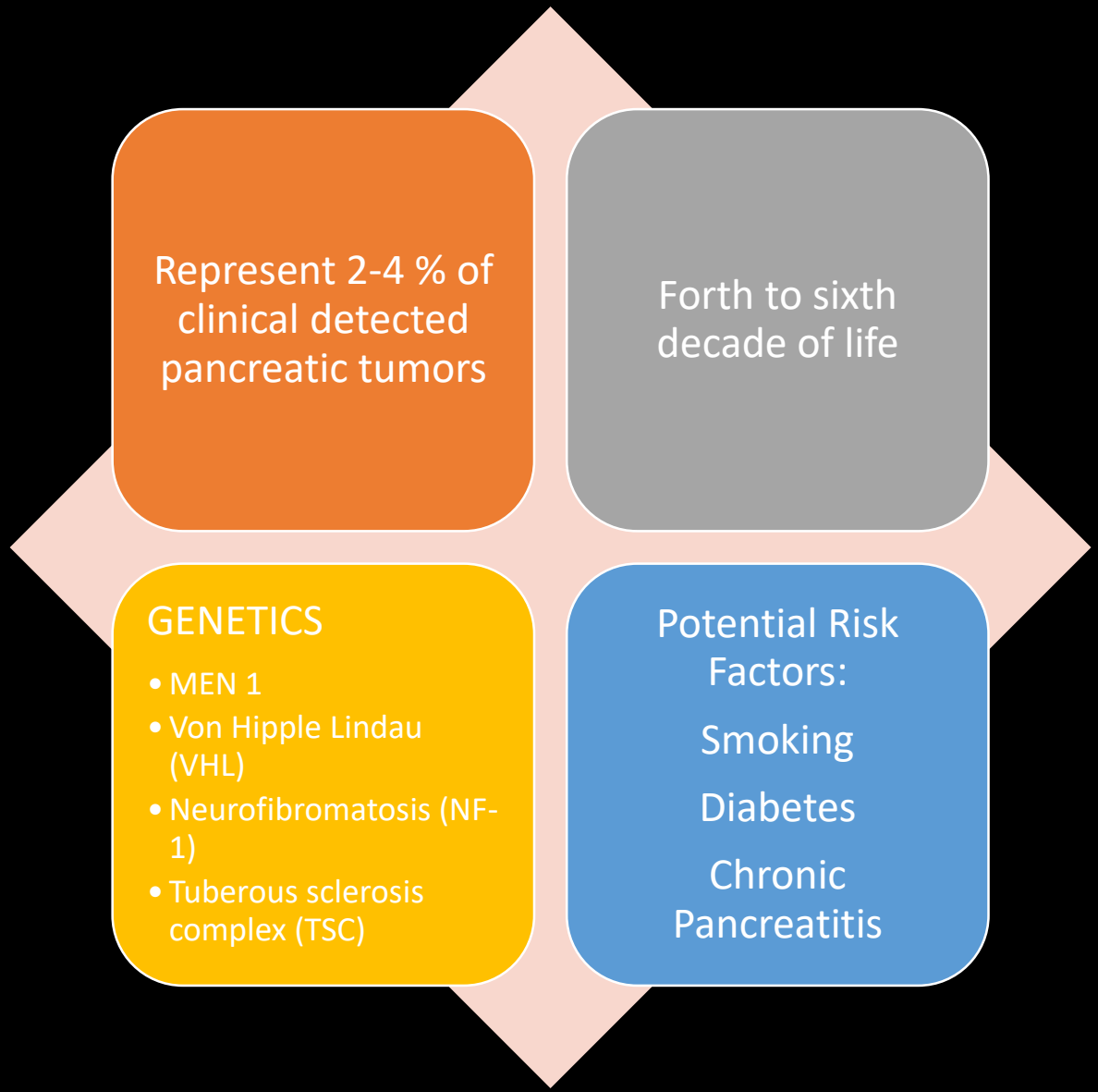
Main duct with PDGs
Strobel et al.,
Gastroenterology (2010)



Cross-section of
a PDG
(H&E stain)



Epidemiology



Cancer. 2015 Feb;121(4):589-97

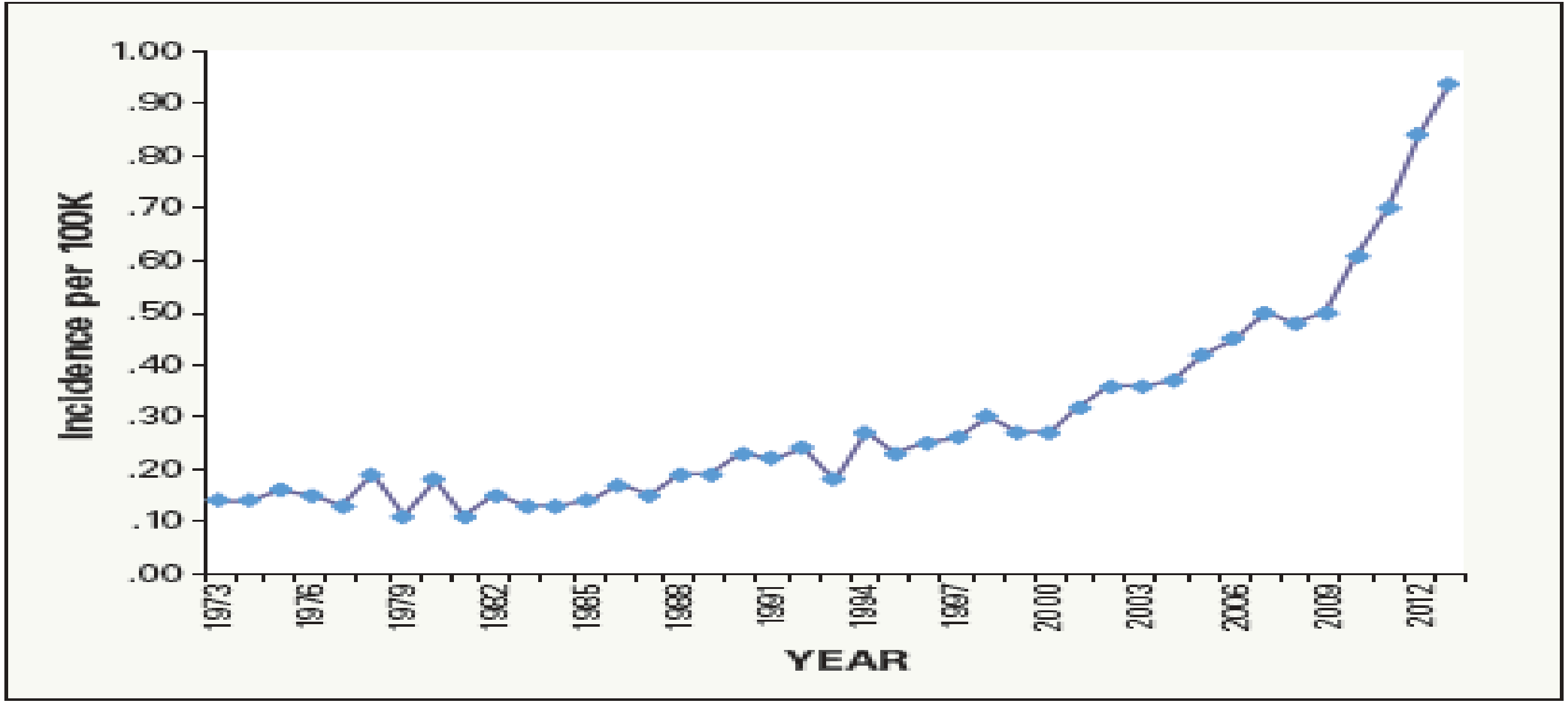
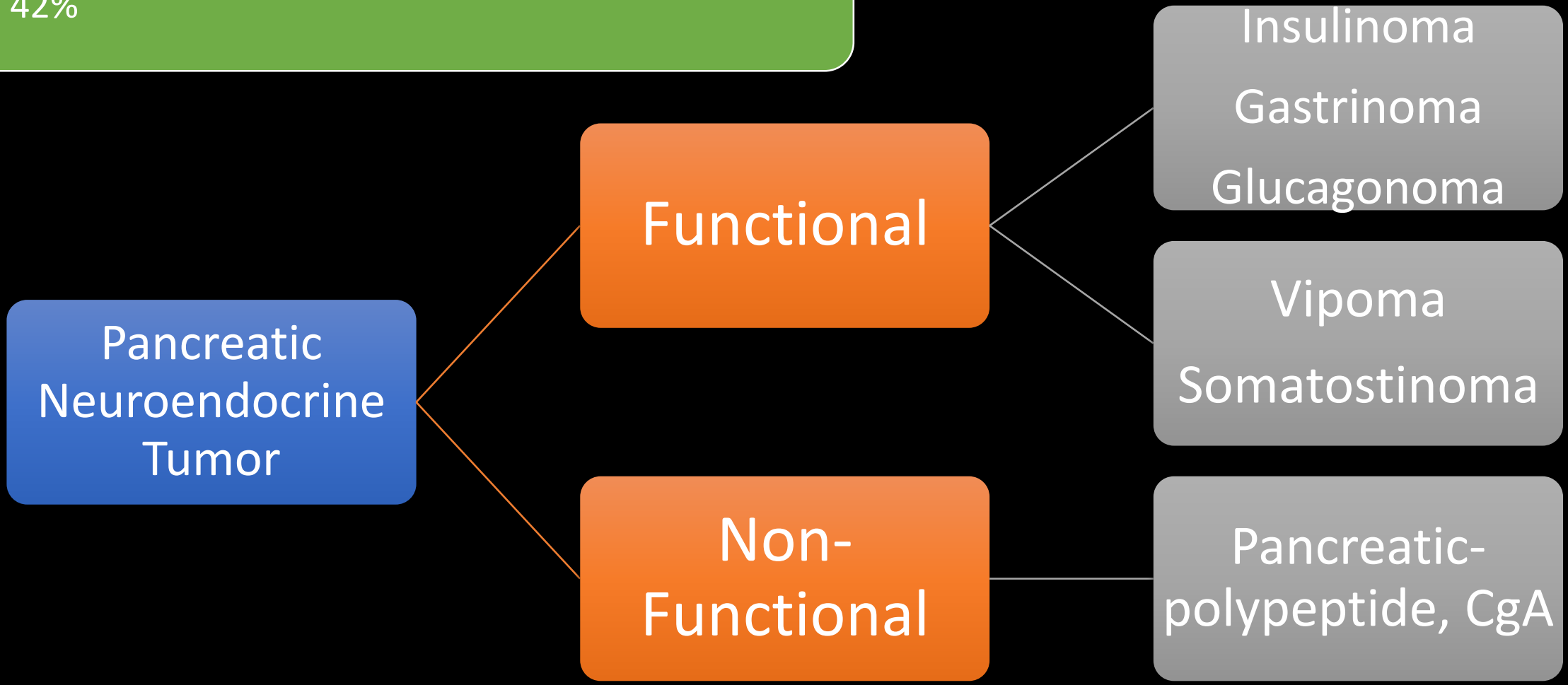


Figure 1. SEER Age-Adjusted Incidence of PNETs by Year of Diagnosis (1973–2013). Data from SEER Database.

GEP = gastroenteropancreatic; NET = neuroendocrine tumor; PNET = pancreatic neuroendocrine tumor; SEER = Surveillance, Epidemiology, and End Results.

The 5-year survival rate for people with a pancreas NET is about 42%



Hosp Pract. 2016 Aug;44(3):109-19

Clinical Presentation

Will depend upon hormonal secretion	
Insulinoma	• Hypoglycemia: confusion, visual change, unusual behavior, palpitations, diaphoresis, and tremulousness.
Gastrinoma	• Peptic Ulcer Disease
Glucagonoma	• Necrolytic Migratory erythema,diabetes, anemia, weight loss
Vasoactive Intestinal Peptide	• Watery Diarrhea, hypokalemia, hypochloridria

Neuro endocrinology

Neuroendocrinology (DOI:10.1159/000471879)
(Accepted, unedited article not yet assigned to an issue)

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Accepted after revision: March 21, 2017

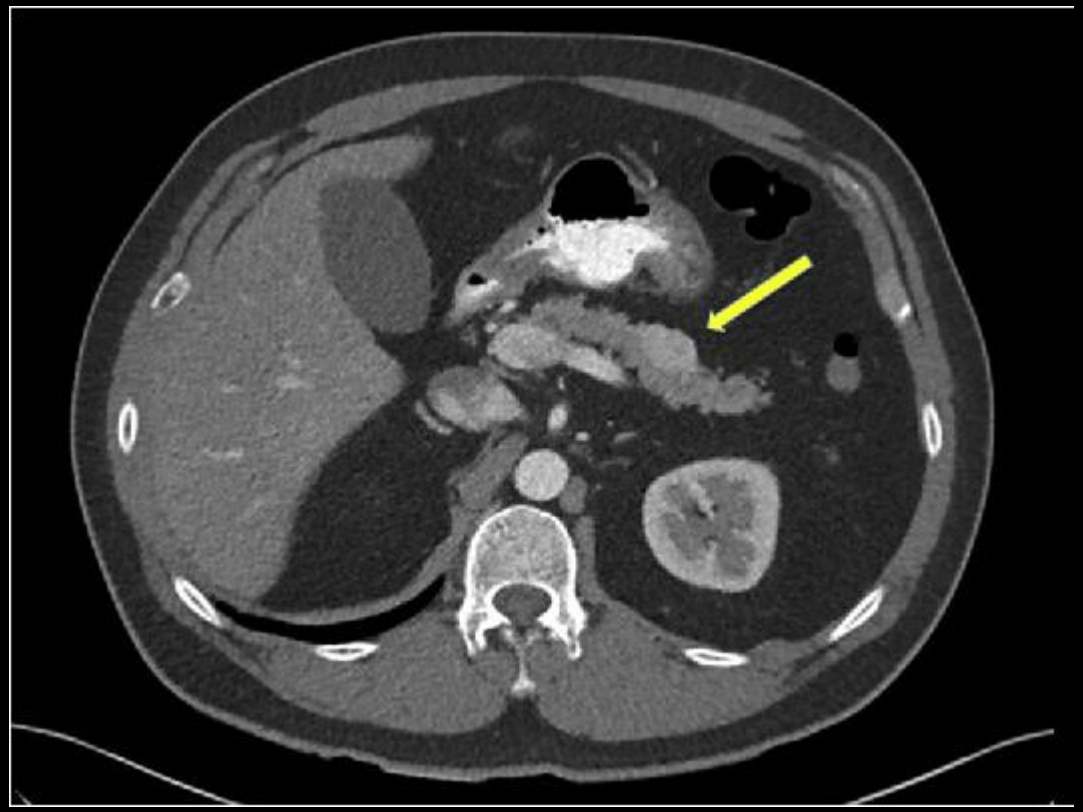
ENETS Consensus Guidelines for the Standards of Care in Neuroendocrine Tumors: Radiological, Nuclear Medicine & Hybrid Imaging

Anders Sundin[1], Rudolf Arnold[2], Eric Baudin[3], Jaroslaw B Cwikla[4], Barbro Eriksson[5], Stefano Fanti[6], Nicola Fazio[7], Francesco Giammarile[8], Rodney J. Hicks[9], Andreas Kjaer[10], Eric Krenning[11], Dik Kwekkeboom[12], Catherine Lombard-Bohas[13], Juan M O´Connor[14], Dermot O´Toole[15], Andrea Rockall[16], Bertram Wiedenmann[17], Juan W Valle[18], Marie-Pierre Vullierme[19], all other Antibes Consensus Conference participants

	CT	MRI	US/EUS	68-GaDOTATATE
Sensitivity % (mean)	82%	79%	86%	92%
Specificity % (mean)	96%	100%	92%	85%

Computed Tomography (CT)

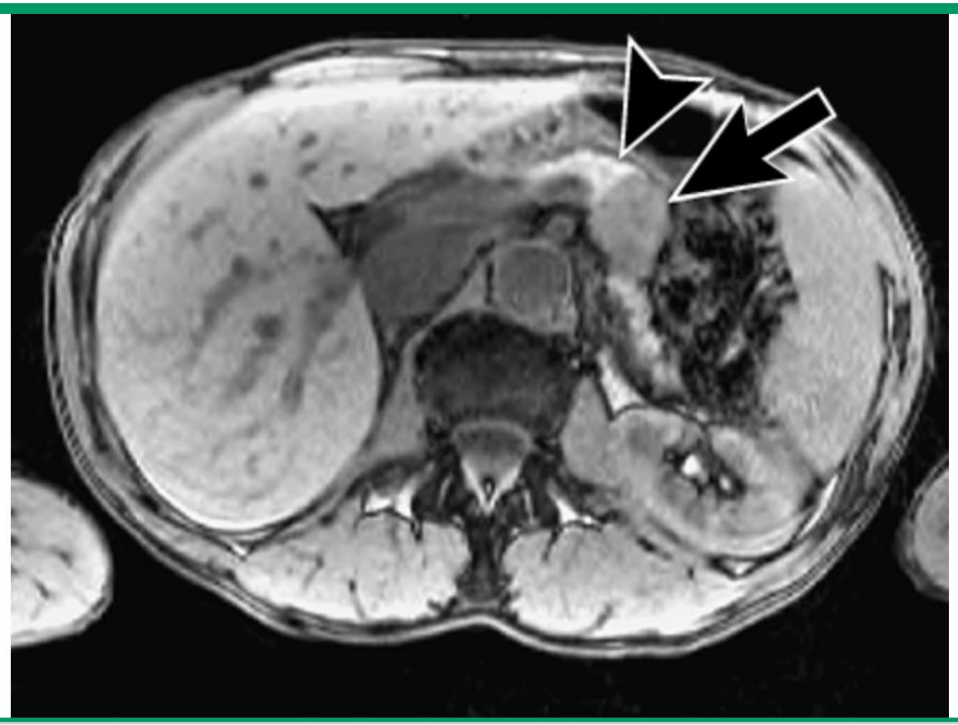
- CT scans are noninvasive and readily available.
- More than 80 % sensitivity for tumors more than 2 cm.
- Symptomatic but nonfunctioning tumors, are usually large (>3 cm) at the time of diagnosis.
- The sensitivity of contrast-enhanced CT for these tumors approaches 100 percent, and it is considered the imaging study of choice



Magnetic Resonance Imaging (MRI)

- Second Line
- Hypointensity on T1
- Hyperintensity on T2
- High specificity

T1-weighted MRI image of a neuroendocrine tumor of the pancreas



Malignant neuroendocrine tumor of the pancreas. T1-weighted gradient echo image of abdomen demonstrates mass (arrow) near junction of pancreatic body and tail. Note that mass (arrow) is lower in signal intensity than adjacent normal pancreatic parenchyma (arrowhead).

Nuclear Imaging

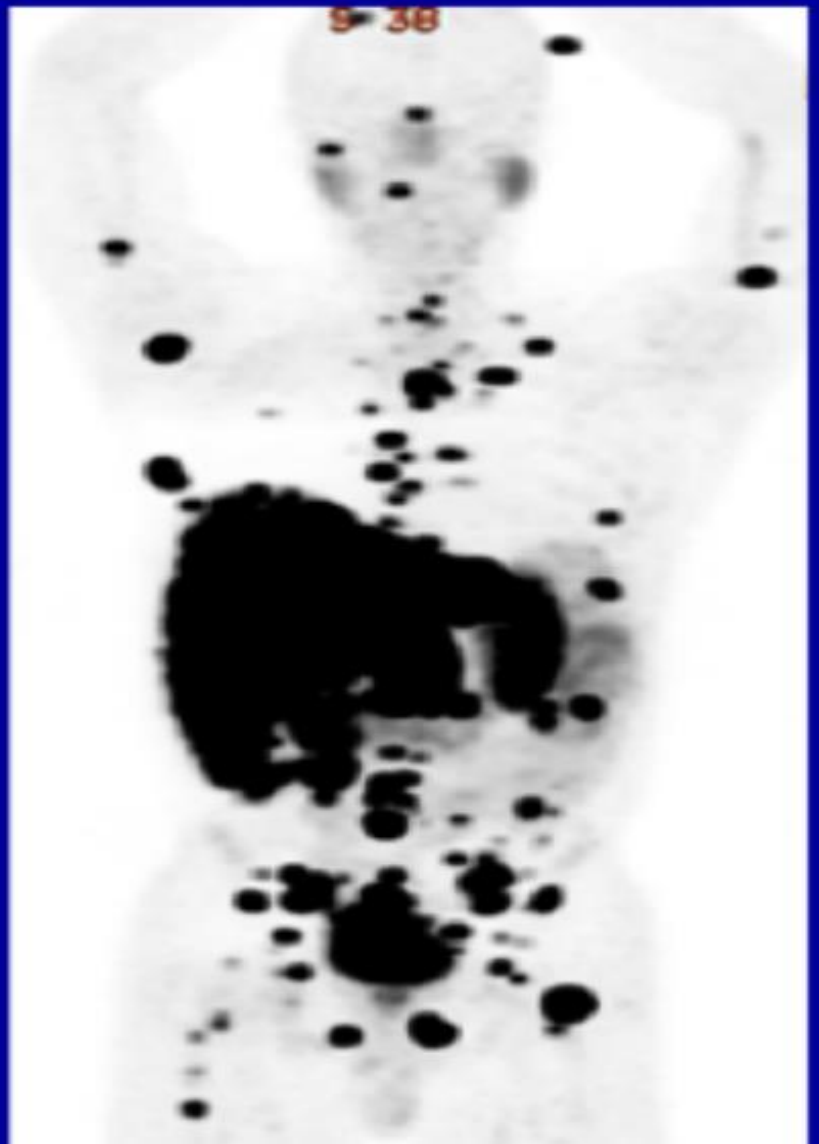
Somatostatin receptor scintigraphy (SRS) (Octreoscan)

- Most well-differentiated NETs express high levels of somatostatin receptors and can therefore be imaged with radiolabeled somatostatin analogs.

68 Ga-PETCT/DOTATATE

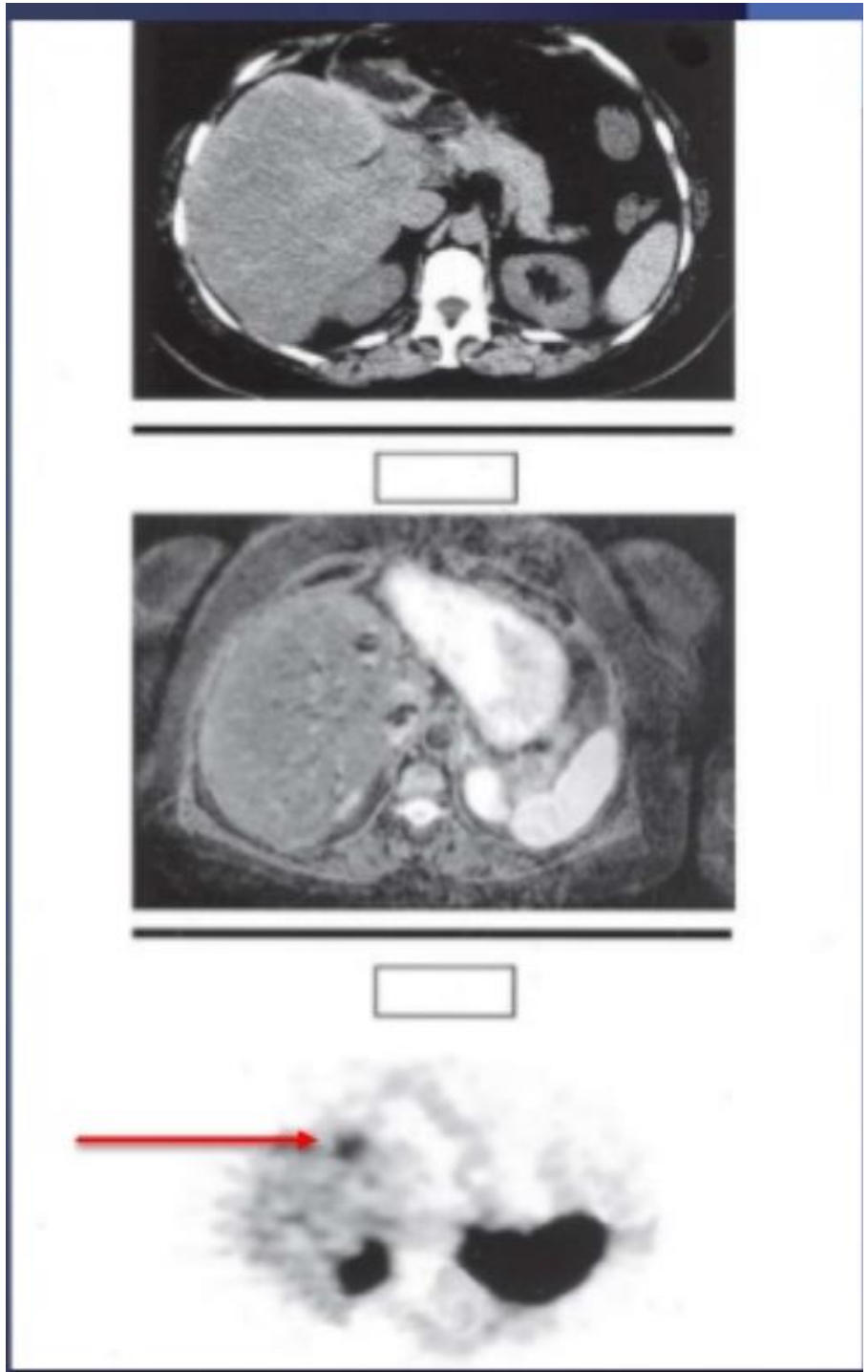
- These novel PET modalities offer higher spatial resolution than conventional SRS scanning and are associated with improved sensitivity for detection of small lesions.

Octreoscan vs. PET/CT with ^{68}Ga-DOTA-Octreotide



J Nucl Med 2007; 48(4):508-518.

- Comparison of a CT (Top), MRI (Middle) and a SRS scan(Bottom).
- Neither the CT scan or the MRI showed the lesion of the liver in a patient with a Zollinger Ellison syndrome



Neuroendocrine tumors of the pancreas TNM staging AJCC UICC 8th edition

Primary tumor (T)

T category	T criteria
TX	Tumor cannot be assessed
T1	Tumor limited to the pancreas,* <2 cm
T2	Tumor limited to the pancreas,* 2 to 4 cm

Regional lymph nodes (N)

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node involvement
N1	Regional lymph node involvement

Distant metastasis (M)

M category	M criteria
M0	No distant metastasis
M1	Distant metastases
M1a	Metastasis confined to liver
M1b	Metastases in at least one extrahepatic site (eg, lung, ovary, nonregional lymph node, peritoneum, bone)
M1c	Both hepatic and extrahepatic metastases

Prognostic stage groups

When T is...	And N is...	And M is...	Then the stage group is...
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	II
T4	N0	M0	III
Any T	N1	M0	III
Any T	Any N	M1	IV

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer control.

Table 2. Histologic Grading System for Gastroenteropancreatic NETS Adopted by ENETS (2006), AJCC (2009), and WHO (2010)

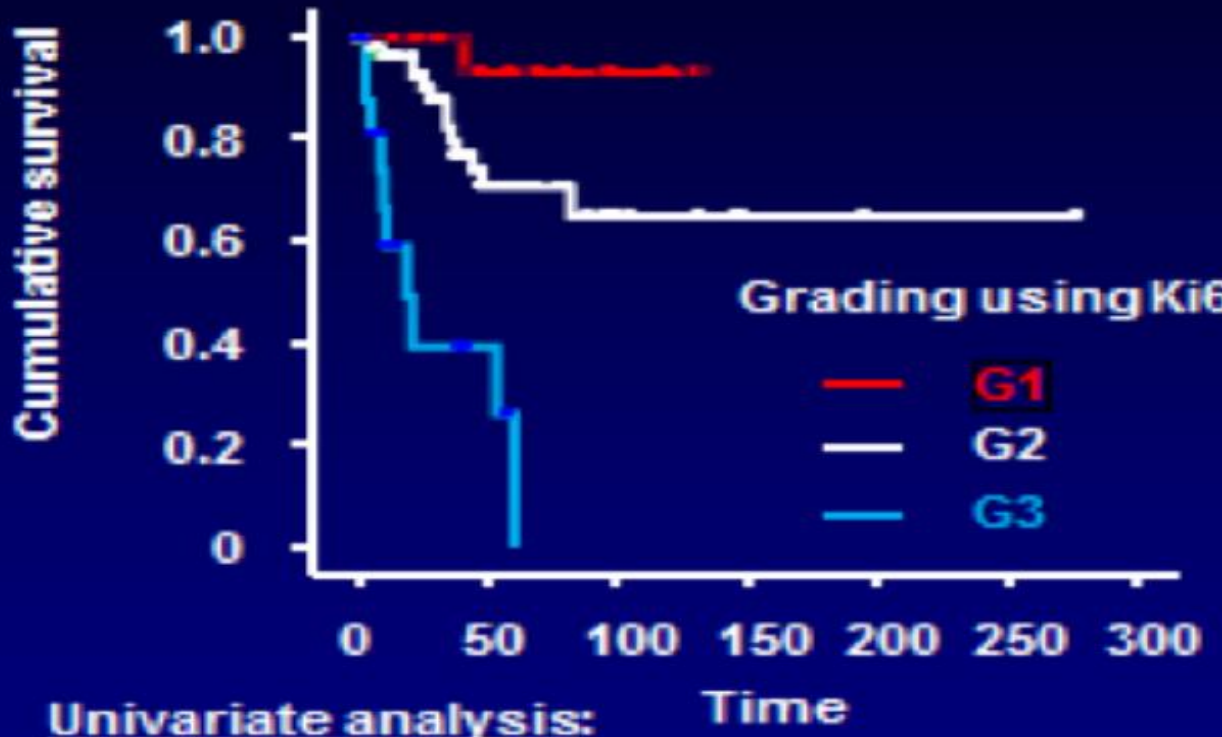
Grade	Mitotic Rate	Ki-67 Index	Differentiation
Low (G1)	< 2/10 HPF	≤ 2%	Well-differentiated NET
Intermediate (G2)	2–20/10 HPF	3% to 20%	Well-differentiated NET
High (G3)	> 20/10 HPF	> 20%	Poorly differentiated NEC

AJCC = American Joint Committee on Cancer; ENETS = European Neuroendocrine Tumor Society; HPF = high-power field; NEC = neuroendocrine carcinoma; NET = neuroendocrine tumor; WHO = World Health Organization.

Improvement of NET Grading System using Mitoses and Ki-67

Well differentiated NENs		
Grade	Ki-67 index (%)	Mitotic count (10 HPF)
NET G1	< 3	< 2
NET G2	3–20	2–20
NET G3	> 20	> 20
Poorly differentiated NENs		
NEC G3	>20	
Small cell type Large cell type		
Mixed neuroendocrine-nonneuroendocrine neoplasm(MiNEN)		

WHO classification 2017



Univariate analysis:

G1 vs. G2: p = 0.040

G1 vs. G3: p < 0.0001

G2 vs. G3: p < 0.0001

Rindi G, et al. Virchows Arch. 2006;449:395-401.

Pape UF, et al. Cancer. 2008;113:256-65.

Circulating Biomarkers

Chromogranin A (CgA)

- Elevated CgA levels are noted in 50 to 100% of patients with PNETs .
- Levels depend upon tumor mass, burden or progression and malignant nature of the tumor.
- False elevations
  - Renal insufficiency
  - Essential HTN
  - Use of PPIs
  - Not seen with CgB levels

Pancreatic Polypeptide (PP)

- It has a sensitivity of 63% in PNETs.
- Combined with CgA
  - sensitivity increases to 94% in PNETs

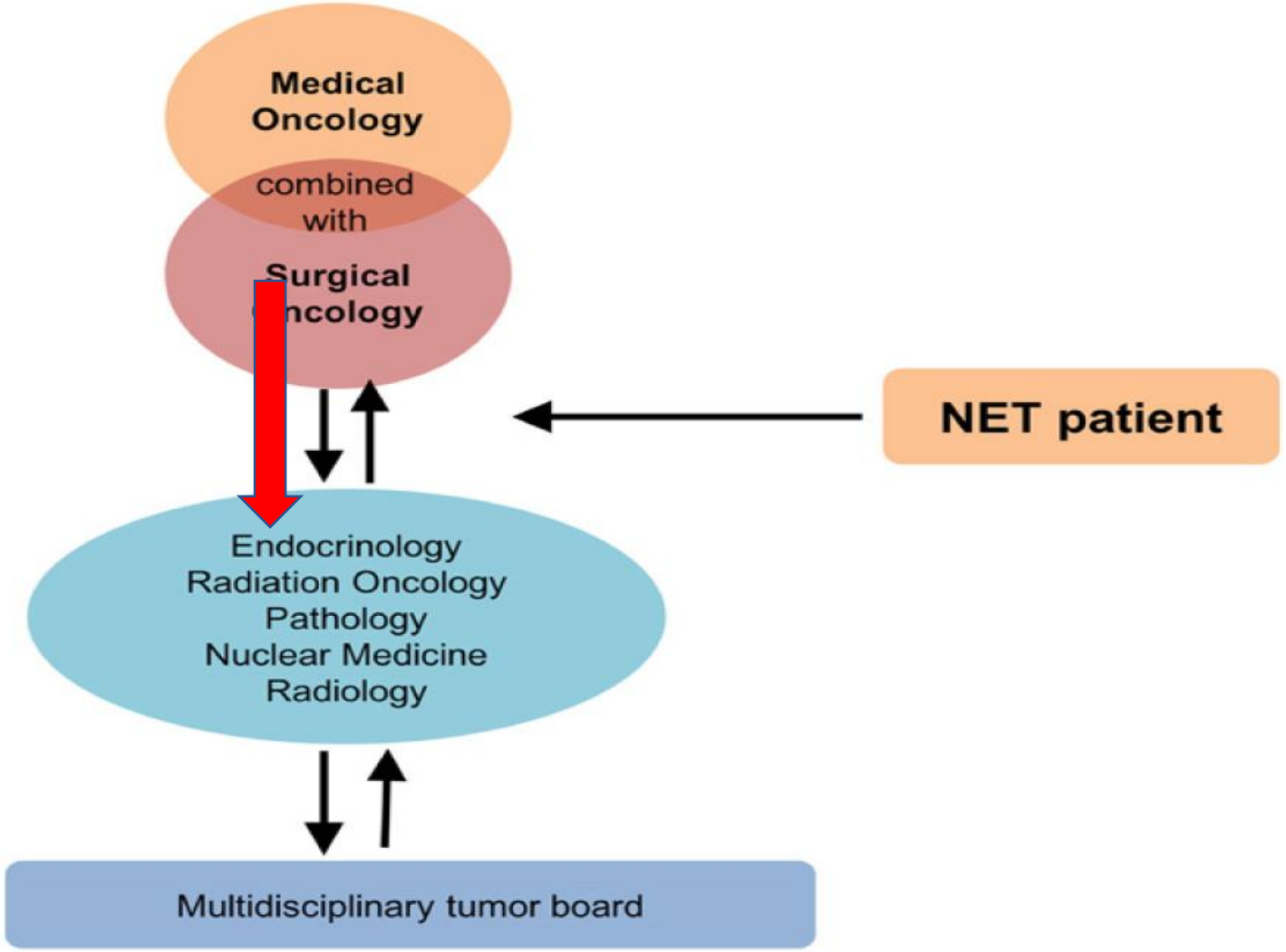


Figure 2. Neuroendocrine multidisciplinary team.

FUNCTIONAL PNETS

Insulinoma

0.4 cases per 100,000 person years

Most appears in the fifth decade

Most common Pancreatic Neuroendocrine Tumor

Cancer. 2015 Feb;121(4):589-97

Symptoms

Neuroglycopenic

- Confusion
- Visual changes
- Unusual behavior

Sympathoadrenal

- Palpitations
- Diaphoresis
- Tremulousness

As many as 20 percent of patients had been misdiagnosed with a neurologic or psychiatric disorder before the insulinoma was recognized

Mayo Clin Proc. 1976;51(7):417.

Pathogenesis of Hypoglycemia in Insulinoma Patients

FIGURE 1. Plasma glucose, glucagon, and insulin concentrations in insulinoma patients and normal subjects during an 8-h fast.

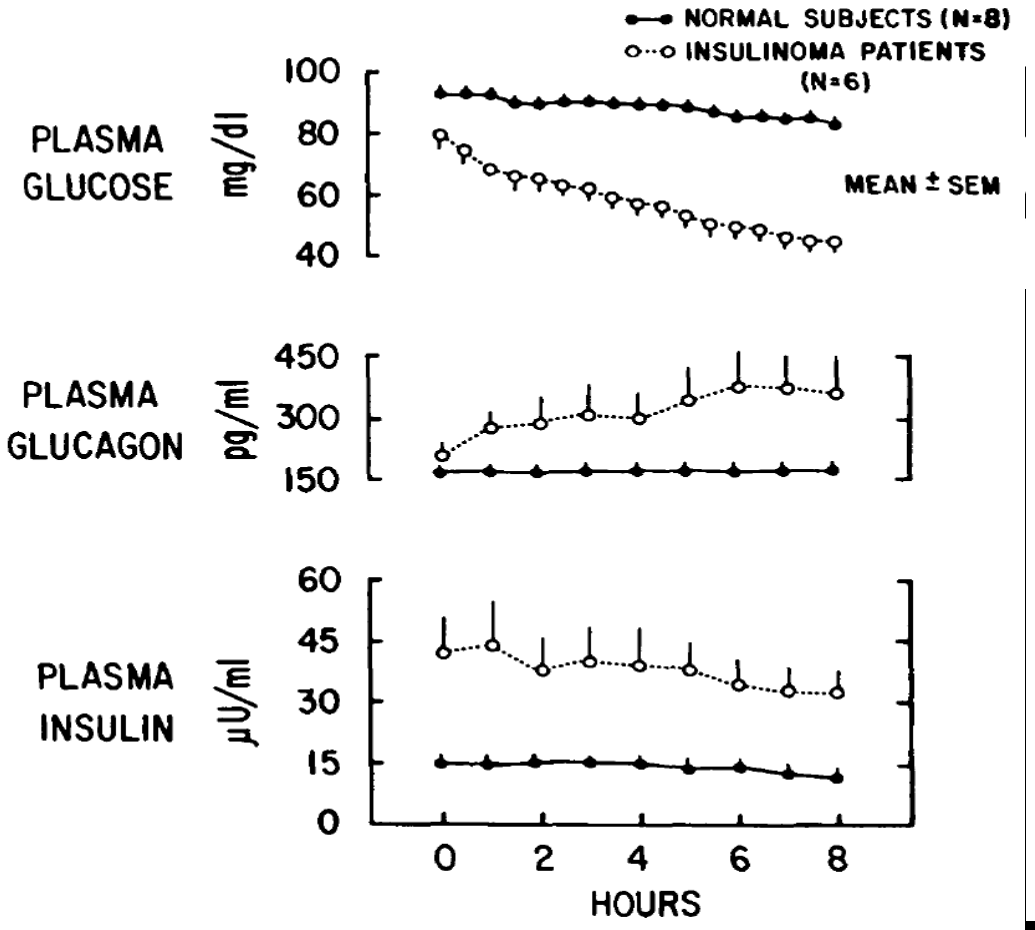
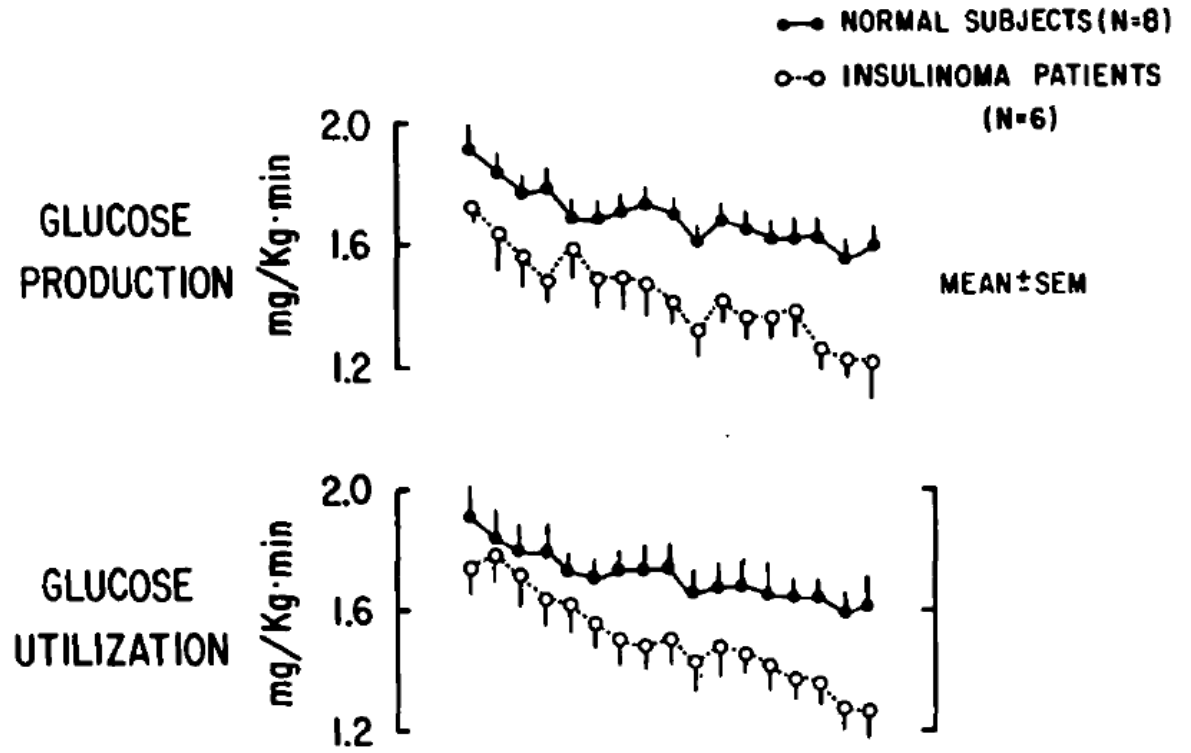
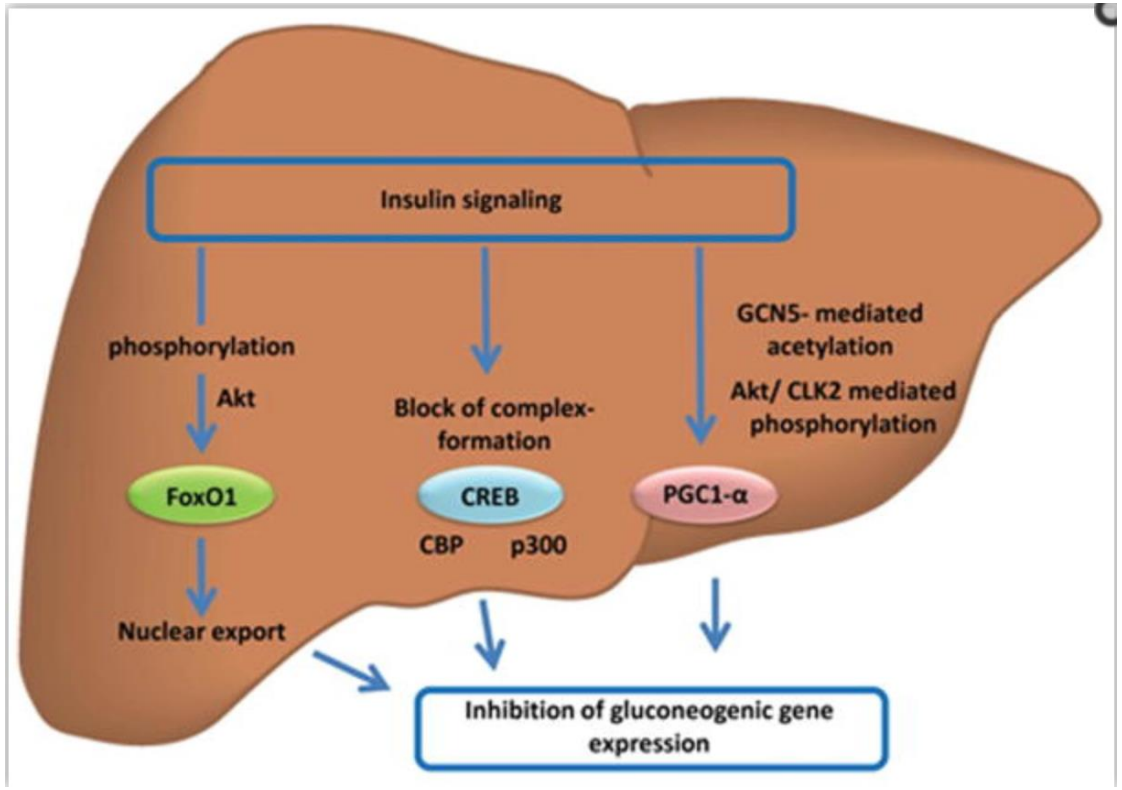


FIGURE 2. Rates of glucose production, utilization, and clearance and the cumulative glucose balance in insulinoma patients and normal subjects during an 8-h fast.





Extrahepatic effects of insulin that regulate hepatic gluconeogenesis.

Organ/tissue	Action	Effect on liver	Reference
Pancreatic alpha cells	Secretion of glucagon ↓	Transcriptional regulation of gluconeogenic genes	12–[14], [16]
White adipose tissue	Lipolysis ↓	Reduction of free fatty acid delivery to the liver	10,14,17
Skeletal muscle	Proteolysis ↓	Reduction of amino acid flux to the liver	10,14
Central nervous system	Pleiotropic manner	Multiple effects	18

Ann N Y Acad Sci. 2018 January ; 1411(1): 21–35.

Secular Trends in the Presentation and Management of Functioning Insulinoma at the Mayo Clinic, 1987–2007

Kimberly A. Placzkowski, Adrian Vella, Geoffrey B. Thompson, Clive S. Grant, Carl C. Reading, J. William Charboneau, James C. Andrews, Ricardo V. Lloyd, and F. John Service

J Clin Endocrinol Metab, April 2009, 94(4):1069–1073

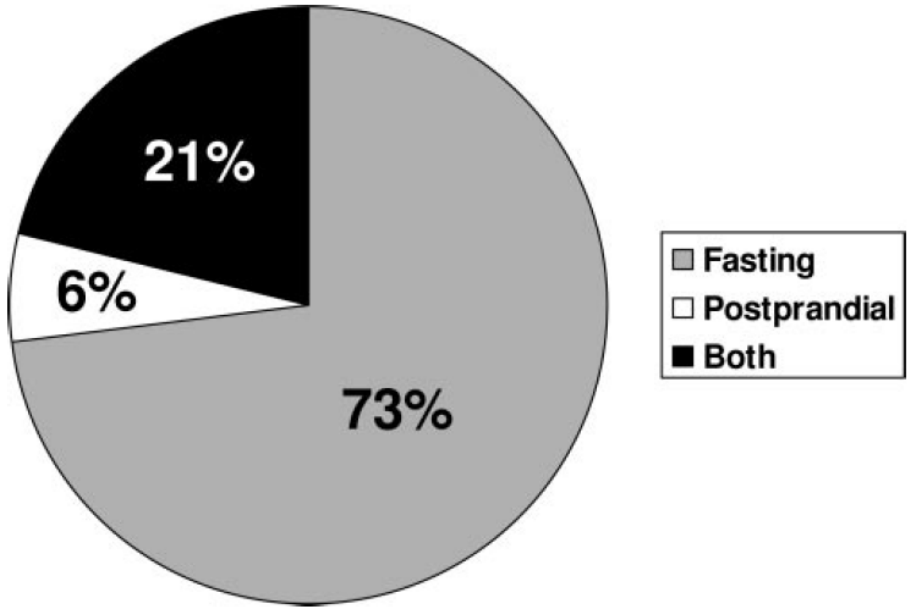


FIG. 1. Distribution of the timing of hypoglycemia symptoms in 214 patients with functioning insulinoma.

TABLE 1. Inpatient *vs.* outpatient evaluation by quartile of study period

Quartile	1987–1992, n (%)	1993–1997, n (%)	1998–2002, n (%)	2003–2007, n (%)
n	54	52	62	69
Inpatient	33 (61)	32 (62)	15 (24)	10 (15)
Outpatient	18 (33)	15 (28)	40 (65)	50 (72)
Outside data	3 (6)	5 (10)	7 (11)	9 (13)

Tumor Distribution

87 percent presents as single benign tumors.

7 percent presents as multiple

6 percent are malignant, defined as the presence of metastases

Mayo Clin Proc. 1991;66(7):711

Management

DIAGNOSIS

TUMOR LOCALIZATION

TREATMENT

Diagnosis

- Documentation of Whipple’s triad is essential to the diagnosis of a hypoglycemic disorder.

Glucose (mg/dL)/(mmol/L)	Insulin (microU/mL)/(pmol/L)	C-peptide (nmol/L)/(ng/mL)	Proinsulin (pmol/L)	Beta-hydroxybutyrate (mmol/L)	Glucose increase after glucagon (mg/dL)/(mmol/L)	Circulating oral hypoglycemic agent	Antibody to insulin	Diagnostic interpretation
<55/3	<3/20.8	<0.2/0.6	<5	>2.7	<25/1.4	No	No	Normal
<55	>>3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
<55	>>3	>>0.2¶	>>5¶	≤2.7	>25	No	Pos	Insulin autoimmune
<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF$^{\Delta}$
<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin (or IGF)-mediated

TABLE 2. Localization procedures

Quartile	1987–1992	1993–1997	1998–2002	2003–2007
Noninvasive localization studies				
n	54	52	62	69
Percent done	100	100	100	100
Percent positive	74	71	77	80
Invasive localization studies				
n	0	11	24	26
Percent done	0	21	39	38
Percent additional positive	0	8	21	20
Percent blind pancreatic exploration	26	21	2	0

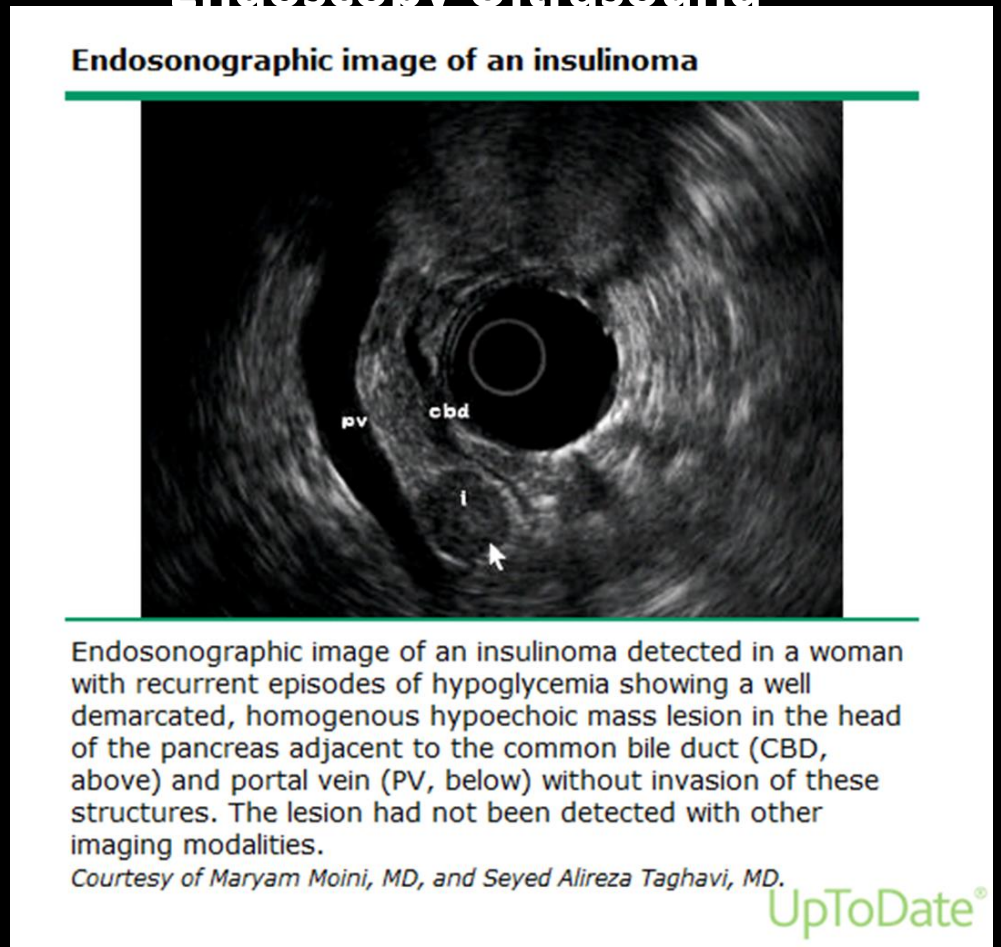
Localization

- Considering all quartiles of study, CT scan had an accuracy rate of 55%, US of 61%, and MRI of 42% for the detection of functioning insulinomas.

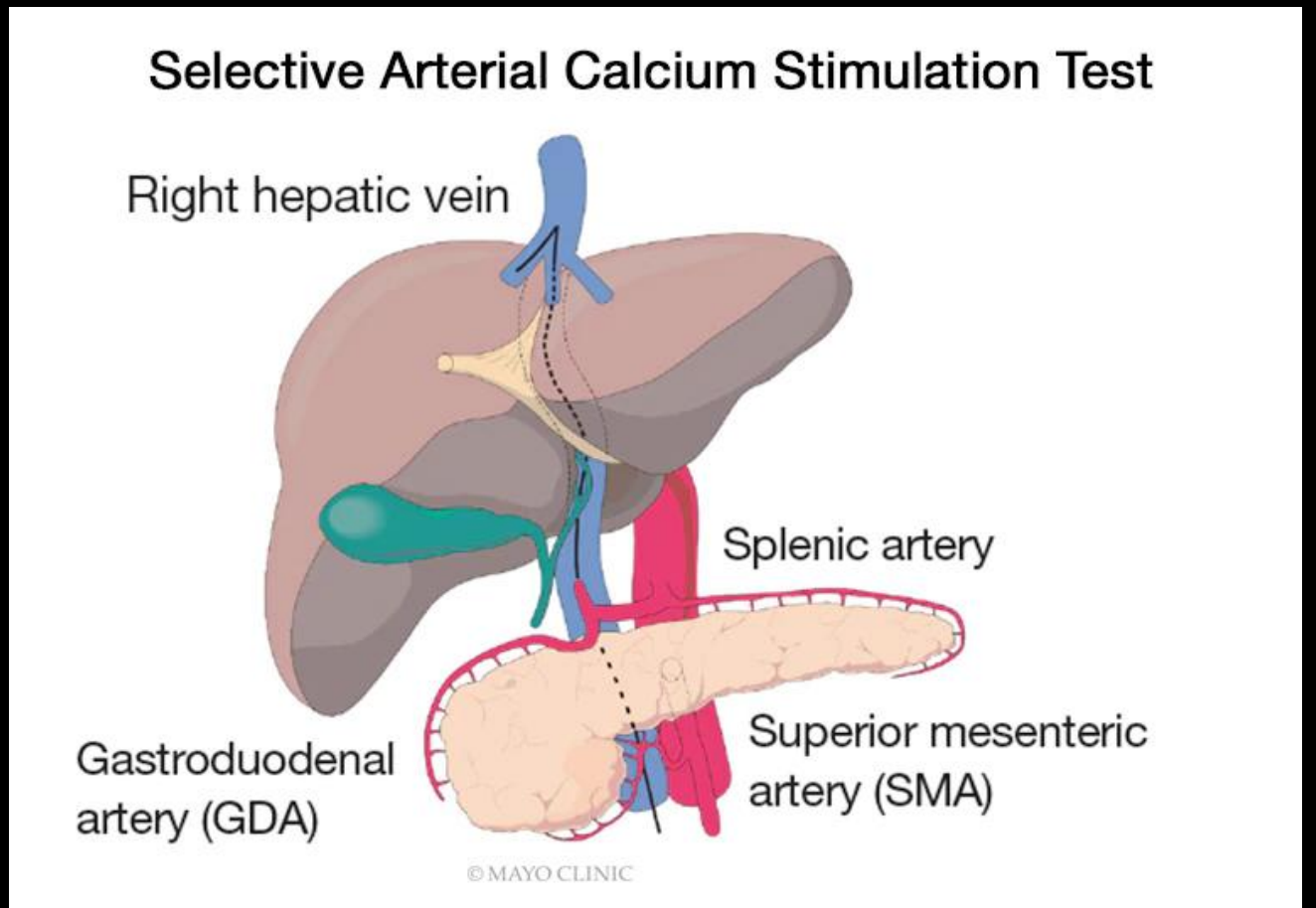
Clin Endocrinol Metab, April 2009, 94(4):1069–1073.

Unable To localize

Endoscopy Ultrasound



Selective Arterial Calcium Stimulation Test (SACST)



Unable To Localize

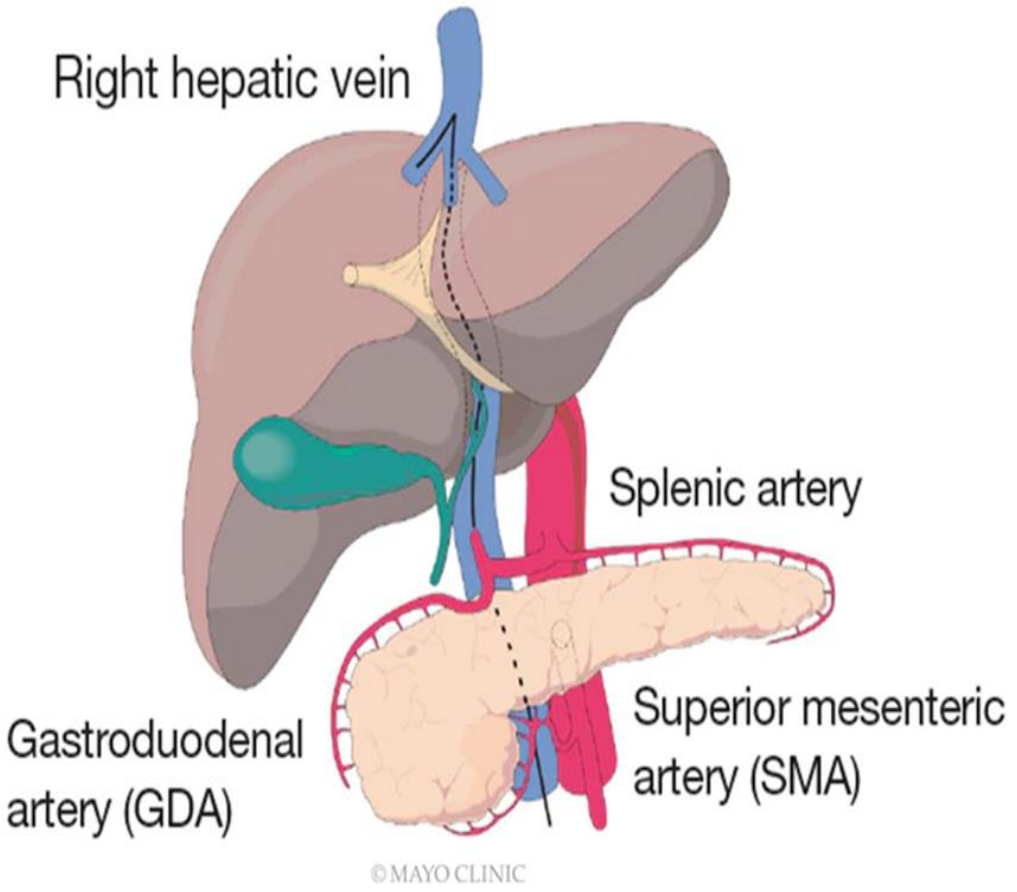
Endoscopic Ultrasound

- In small case series, the sensitivity of endoscopic ultrasound for the detection of insulinoma confirmed by surgery ranged from 82 to 85 percent.

SACST

- In the Mayo Clinic series of 237 patients with insulinoma, the sensitivity of SACST for localization of insulinoma was 93 percent.

Selective Arterial Calcium Stimulation Test



Artery	Time, seconds	Serum hepatic vein insulin, microU/ mL
Superior mesenteric	0	41
	20	65
	40	333
	60	441
Gastroduodenal	0	30
	20	35
	40	38
	60	36
Splenic	0	31
	20	26
	40	26
	60	31

Calcium stimulates the release of insulin from hyperfunctional beta cells but not normal beta cells

Treatment

Resection of primary tumor

- First Choice of treatment

Medical Therapy

- Unable to surgery
- Metastatic disease
- Multiple Comorbid Conditions

Medical therapy

Diazoxide

- Diminishes insulin secretion in doses of 120mg/day.
- Marked adverse events of edema and hirsutism

Octreotide

- At high doses inhibits the secretion of insulin, glucagon and thyroid stimulating hormone
- Use only for patient with hypoglycemia refractory to diazoxide
- Lanreotide can also be used

Verapamil and Phenytoin

- Last choice
- Scarce data

Types of Surgery

- Enucleation of the insulinoma
- Partial distal pancreatectomy
- Enucleation of the insulinoma and partial pancreatectomy
- A Whipple procedure (removal of the head of the pancreas, gastrectomy, duodenectomy, and splenectomy)
- Total pancreatectomy

Recurrence and Survival

The cumulative incidence of recurrence was 6 percent at 10 years and 8 percent at 20 years.

The overall survival rate of patients with insulinoma did not differ from that expected in the general population.

Mayo Clin Proc. 1991;66(7):711.

Liver Directed Metastatic Disease

Resection	• Considered only for patients with a very limited number of metastases.
Hepatic artery embolization	• Since the blood supply from liver metastases differs from healthy hepatocytes, embolization will produce minimal damage to the normal liver parenchyma
Liver transplantation	• No long-term data
Chemotherapy	• Streptozocin/doxorubicin

Case # 1

A 42-year-old woman has been evaluated on multiple occasions for frequent symptoms of tachycardia, sweating, tremor, and anxiety that are relieved by food intake. The spells are disruptive and have become noticeable over the past 6 months.

Recently, at the time of a routine blood draw and after a 8-hour fast, the patient was found to have a venous glucose concentration of 48 mg/dL (2.7 mmol/L).

The patient has no notable medical history and is not taking any medication. She has never had surgery. She exercises regularly, and over the past 2 years she has participated in 4 half-marathons.

Case # 1

- On physical examination, her resting heart rate is 65 beats/min and blood pressure is 120/60 mm Hg. Her height is 63 in (160 cm), and weight is 118 lb (53.6 kg) (BMI = 20.9 kg/m2).
- An outpatient fast is undertaken. The patient last ate at 6:00 PM the preceding day and presents to the endocrine testing center at 8:00 AM.
- Symptoms occur at 9:45 AM. A point-of-care glucose value is 49 mg/dL.

The patient's glucose concentration is 49 mg/dL . Imaging studies of the pancreas would be indicated on the basis of which of the following sets of laboratory values?

Answer	Insulin	C-Peptide	Proinsulin	Glucose Rise after Glucagon (D)	Insulin Antibodies	Sulfonylurea Screen
A.	3.2mIU/mL (22.2 pmol/L)	4.0 ng/mL (1.3 nmol/L)	16 pg/mL (1.8 pmol/L)	31 mg/dL (1.7 mmol/L)	Negative	Negative
B.	15.0mIU/mL (101.2 pmol/L)	4.5 ng/mL (1.5 nmol/L)	32 pg/mL (3.6 pmol/L)	31 mg/dL (1.7 mmol/L)	Negative	Positive
C.	112.0mIU/mL (777.8 pmol/L)	<2.0 ng/mL (<0.7 nmol/L)	<5 pg/mL (<0.6 pmol/L)	38 mg/dL (2.1 mmol/L)	Negative	Negative
D.	212.0mIU/mL (1472.3 mmol/L)	10.3 ng/mL (3.4 nmol/L)	230 pg/mL (26.1 pmol/L)	45 mg/dL (2.5 mmol/L)	Positive	Negative
E.	5.0mIU/mL (34.7 pmol/L)	<2.0 ng/mL (0.7 nmol/L)	<5 pg/mL (<0.6 pmol/L)	5 mg/dL (0.3 mmol/L)	Negative	Negative

The patient's glucose concentration is 49 mg/dL . Imaging studies of the pancreas would be indicated on the basis of which of the following sets of laboratory values?

Answer	Insulin	C-Peptide	Proinsulin	Glucose Rise after Glucagon (D)	Insulin Antibodies	Sulfonylurea Screen
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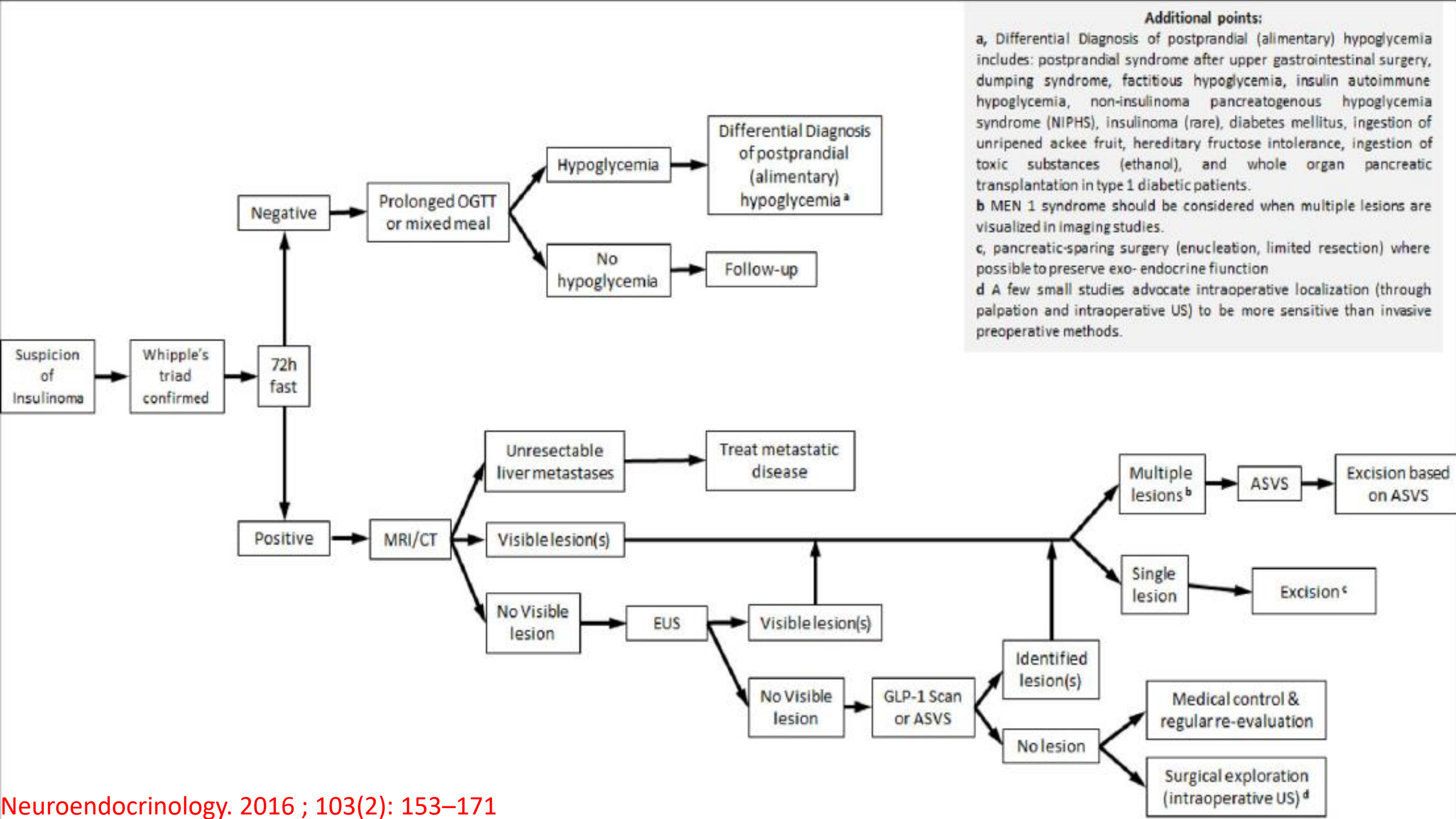
B.	15.0mIU/mL (101.2 pmol/L)	4.5 ng/mL (1.5 nmol/L)	32 pg/mL (3.6 pmol/L)	31 mg/dL (1.7 mmol/L)	Negative	Positive
C.	112.0mIU/mL (777.8 pmol/L)	<2.0 ng/mL (<0.7 nmol/L)	<5 pg/mL (<0.6 pmol/L)	38 mg/dL (2.1 mmol/L)	Negative	Negative
D.	212.0mIU/mL (1472.3 mmol/L)	10.3 ng/mL (3.4 nmol/L)	230 pg/mL (26.1 pmol/L)	45 mg/dL (2.5 mmol/L)	Positive	Negative
E.	5.0mIU/mL (34.7 pmol/L)	<2.0 ng/mL (0.7 nmol/L)	<5 pg/mL (<0.6 pmol/L)	5 mg/dL (0.3 mmol/L)	Negative	Negative



Neuroendocrinology. 2016 ; 103(2): 153–171

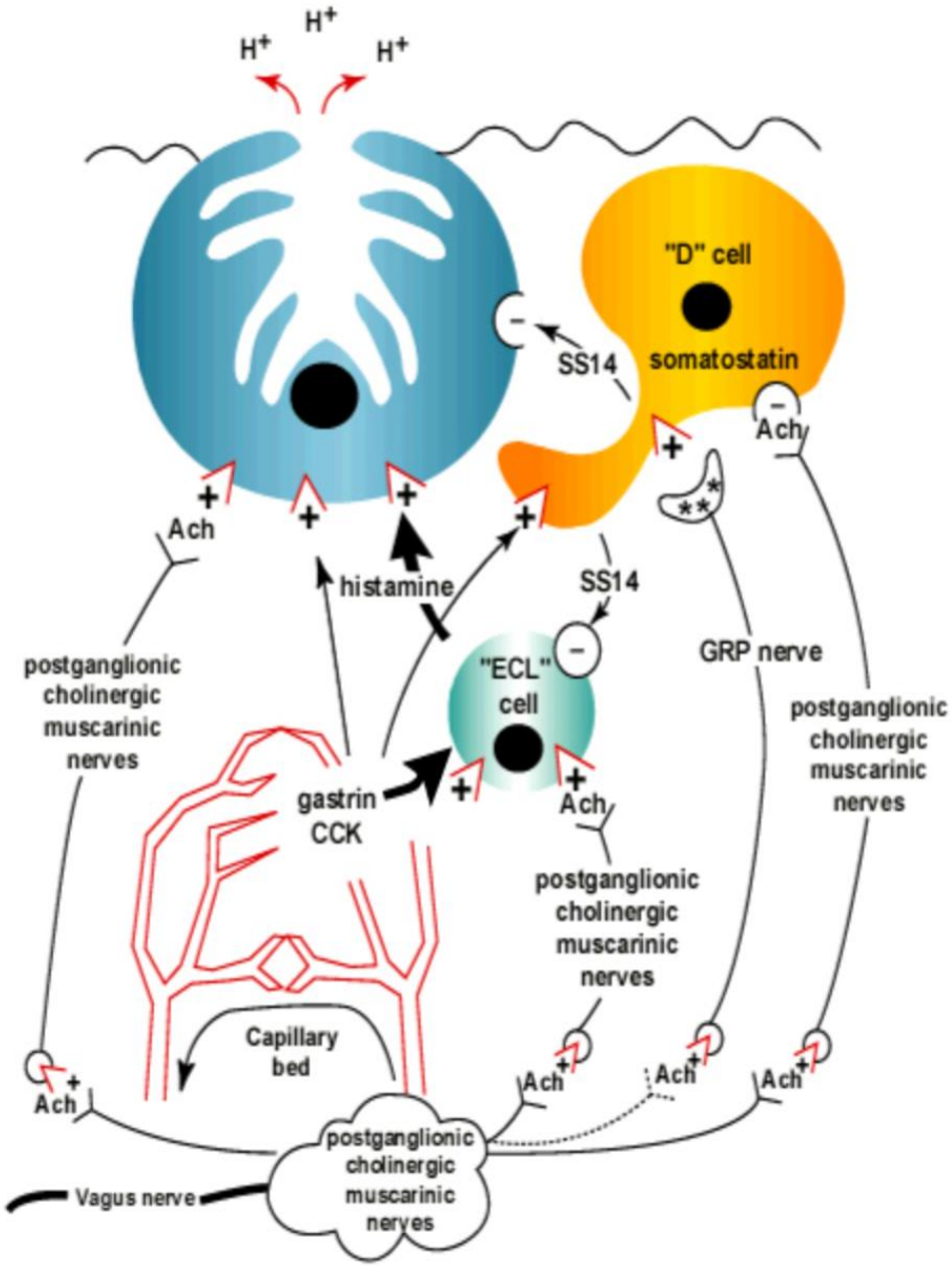
Gastrinoma (Zollinger-Ellison Syndrome)

Annual incidence 0.5 to 2 per million population.

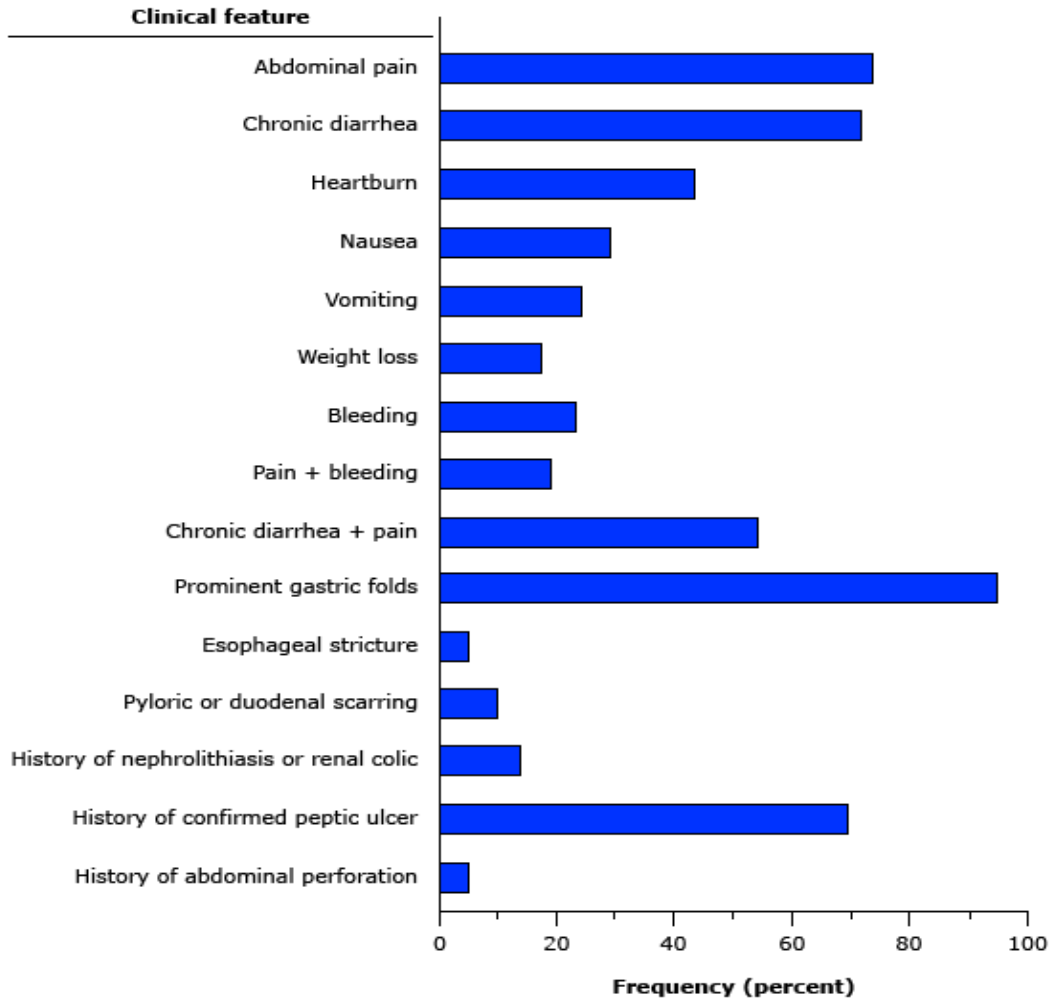
80 percent are sporadic, 20 percent occurs in MEN1 patients.

Only 25 percent of gastrinomas occurs in the pancreas.

Regulation of acid secretion



Presenting symptoms and signs in patients with Zollinger-Ellison syndrome



The presence or absence of clinical symptoms or signs at the initial assessment in 261 patients with Zollinger-Ellison syndrome (ZES). Prominent gastric body folds, esophageal stricture, and pyloric or duodenal scarring were determined by upper gastrointestinal endoscopy; a confirmed peptic ulcer was assessed by upper gastrointestinal endoscopy or radiographic studies.

Data from: Roy PK, Venzon DJ, Shojamenesh H, et al, Medicine (Baltimore) 2000; 79:379

Diagnosis

Gastrin level 10 times upper normal limit (1000 pg/mL) with a low gastric pH (<2).

If gastric PH > 2, rule out secondary causes of hypergastrinemia

Secretin stimulation test: (inconclusive gastrin levels)

- Secretin stimulates gastrin from gastrinoma cells
- Secretin inhibits gastrin from normal parietal cells

Surgical Management

- Gastrinomas located in the head of the pancreas can generally be enucleated.
- Those in the body and tail are removed through a distal pancreatectomy.

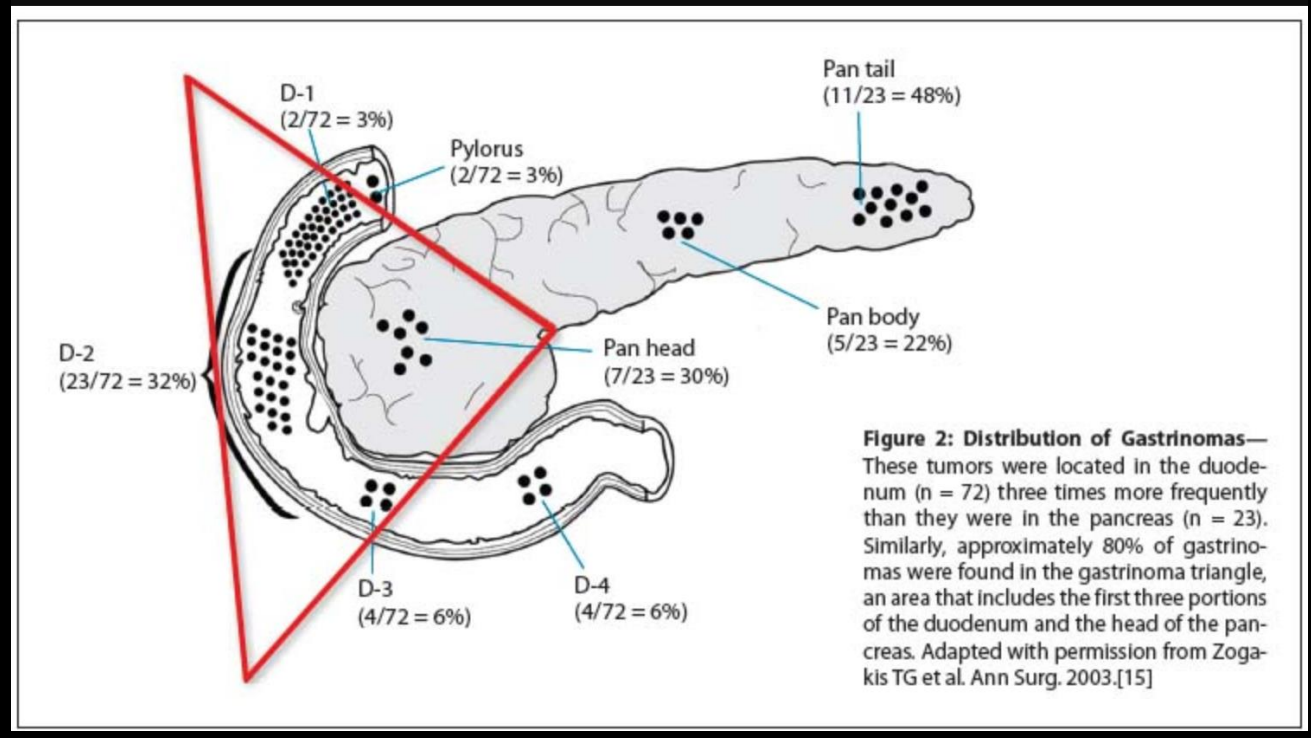


Figure 2: Distribution of Gastrinomas—These tumors were located in the duodenum (n = 72) three times more frequently than they were in the pancreas (n = 23). Similarly, approximately 80% of gastrinomas were found in the gastrinoma triangle, an area that includes the first three portions of the duodenum and the head of the pancreas. Adapted with permission from Zogakis TG et al. Ann Surg. 2003.[15]

Oncologist. 2014;19(1):44. Epub 2013 Dec 6.

Post-Treatment Surveillance

Three to 12 months post-resection: History and PE, serum gastrin level, CT or MRI.

1 > year post-resection to a maximum of 10 years: History and PE with serum gastrin level every 6 to 12 months. Imaging studies as clinically indicated.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (Accessed on November 16, 2019).

Case # 2

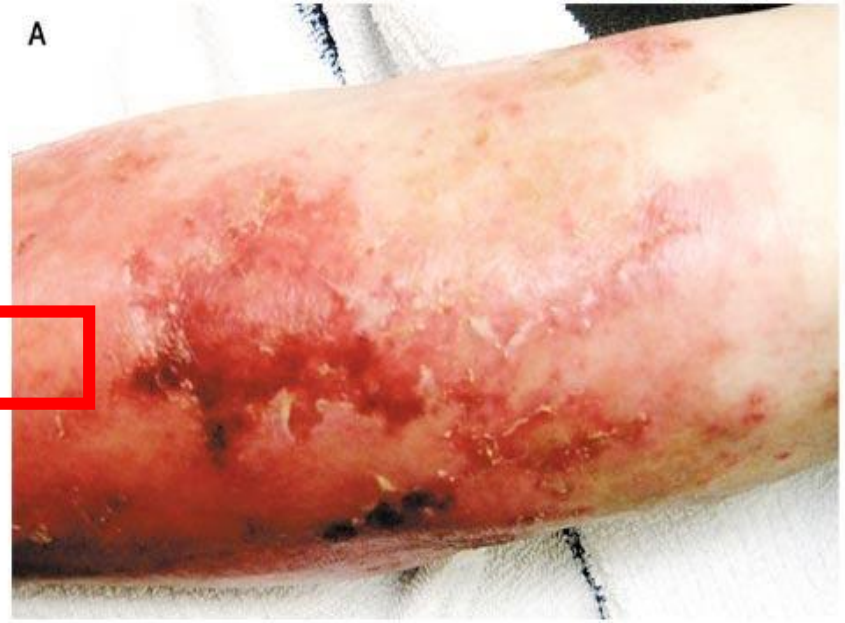
A 71-year-old man with a history of chronic obstructive pulmonary disease, and benign prostatic hypertrophy developed new-onset diabetes mellitus and presents with fatigue, 20-lb weight loss, diarrhea and nocturia.

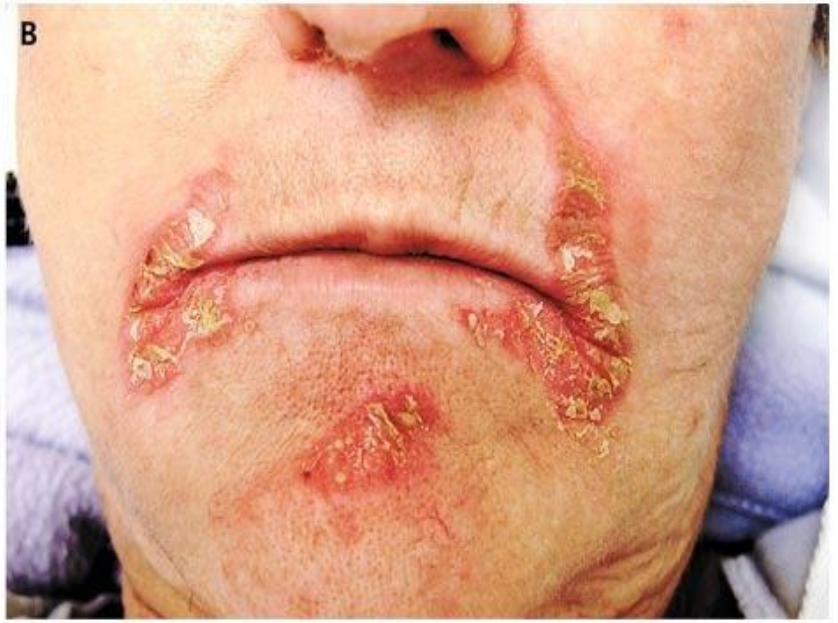
His fasting blood glucose level is 256 mg/dL. One year ago his fasting blood glucose was 102 mg/dL.

On physical examination, he is a cachetic elderly man with a violaceous skin rash across his shins and mouth (see image)

Which of the following will likely reveal the etiology of his diabetes?

- Elevated Gastrin levels
- Elevated somatostatin levels
- Elevated Glucagon levels
- Elevated free cortisol levels





Glucagonoma

Annual incidence of 0.01 to 0.1 new cases per 100,000.

Mostly presents in the distal pancreas

Most of them are sporadic, about 20 percent presents with Multiple Endocrine Neoplasia 1 [MEN 1]

50-80% are metastatic at diagnosis.

Medicine (Baltimore). 1996;75(2):53.

Clinical Features “Glucagonoma Syndrome”

Weight loss

- 80 percent
- Catabolic action of glucagon and through glucagon-like peptides such as GLP-1.

Hyperglycemia

- Up to 95 percent of patients
- However, only 40 percent develops diabetes mellitus

Necrolytic Migratory Erythema (NEM)

- Is the presenting feature in 70 percent of the patients
- Not specific for glucagonoma syndrome
- Biopsy is needed for diagnosis.

Diagnosis

- Glucagon Levels
  - Requires a plasma glucagon level over 500 pg/mL (< 50 pg/mL).
  - Rule out conditions that cause moderate hyperglucagonemia
    - hypoglycemia, fasting, trauma, sepsis
    - acute pancreatitis, abdominal surgery.
    - Cushing's syndrome,renal and hepatic failure .

Tumor Localization

- Computed Tomography (CT)
- Magnetic Resonance Imaging (MRI)
- Somatostatin receptor Scintigraphy
- Functional PET imaging with Ga-68 DOTATATE and Ga-68 DOTATOC
- Endoscopic Ultrasound

Management

- Preoperative
  - Supportive care and management of hyperglycemia
  - If malnutrition : Total Parenteral Nutrition
  - Octreotide
    - Inhibits the catabolism effects of glucagon
    - Improves the malnutrition, Necrolytic Migratory erythema, hyperglycemia and neurologic symptoms.

Management

- Pancreatic Resection
  - The type of pancreatic resection is dictated by the site and extent of the tumor at the time of laparotomy.
  - Resection results in a cure rate of only about 30 percent.

Liver Directed Metastatic Disease

Resection	• Considered only for patients with a very limited number of metastases.
Hepatic artery embolization	• Since the blood supply from liver metastases differs from healthy hepatocytes, embolization will produce minimal damage to the normal liver parenchyma
Liver transplantation	• No long-term data
Molecular target oral therapy	• Everolimus/Sunitinib

Post-Treatment Surveillance

Three to 12 months post-resection: History and PE, serum glucagon level, CT or MRI.

1 > year post-resection to a maximum of 10 years: History and PE with serum glucagon level every 6 to 12 months. Imaging studies as clinically indicated.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (Accessed on November 16, 2019).

Vasoactive intestinal polypeptide (VIPoma)

1 in a million people per year

Bimodal epidemiology

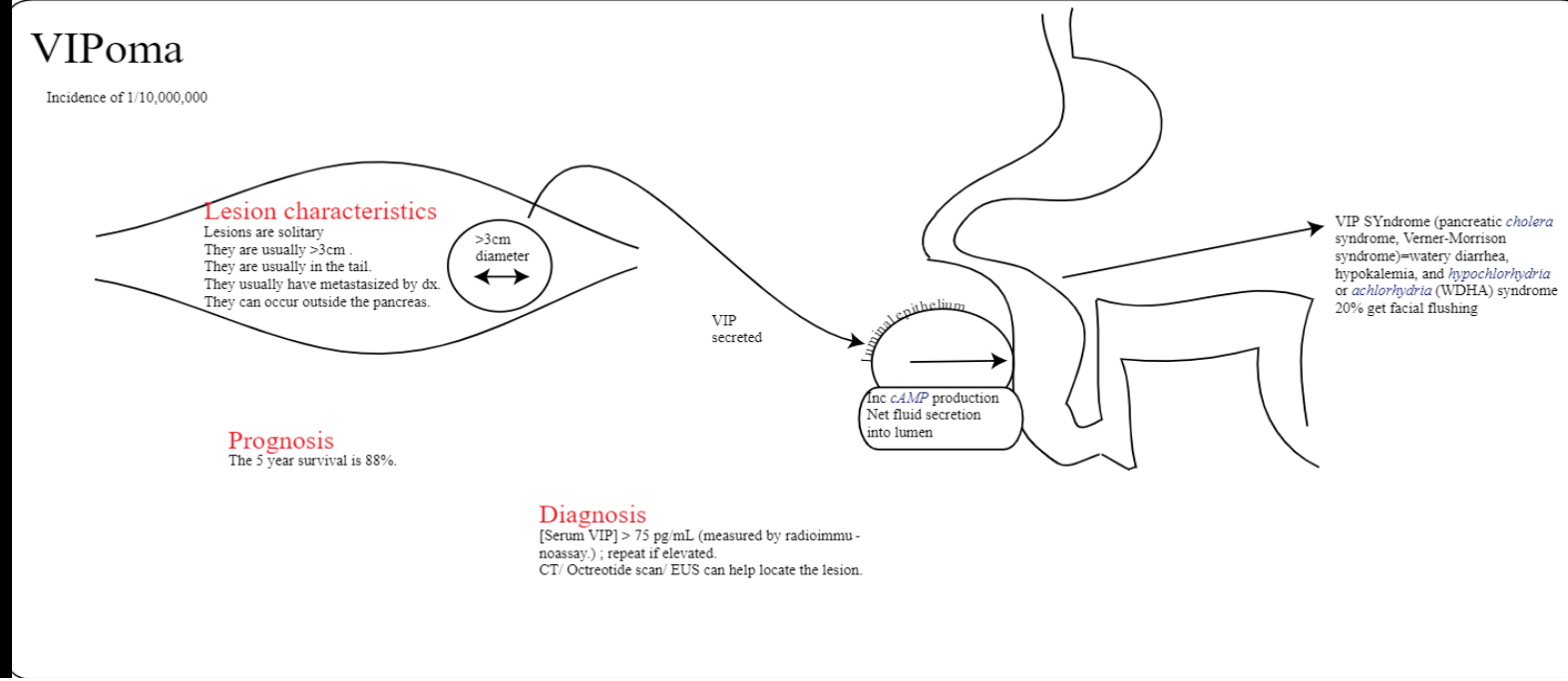
- Age 2-4 and third to fifth decade

60 to 80 percent have metastasized upon diagnosis

Mostly are sporadic

- 5 percent related to Multiple Endocrine Neoplasia Type 1

Pathophysiology



Pathophysiology of clinical manifestations of the VIPoma syndrome

Biologic action of VIP	Clinical signs
Stimulates secretion and inhibits absorption of sodium, chloride, and water in the bowel	Secretory diarrhea
	Dehydration
	Weight loss
Stimulates potassium secretion in the large bowel	Hypokalemia
Inhibits gastric acid secretion	Hypochlorhydria
Induces vasodilation	Flushing
Stimulates bone resorption	Hypercalcemia
Enhances glycogenolysis	Hyperglycemia

VIP: vasoactive intestinal polypeptide.

Clinical features

- VIPoma syndrome
  - Watery diarrhea
    - Persists with fasting
  - Hypokalemia
  - Hypochlorhydia

- Laboratory Features
  - Low Osmotic Gap (< 50 mOsm/kg)
  - Hypochlorhydria
  - Hyperglycemia
  - Hypercalcemia
    - Co-existance of Hyperparathyroidism
    - Hyperalbuminemia
- Diagnosis
  - Elevated vasoactive intestinal polypeptide (VIP) concentration >75 pg/mL

Treatment

Electrolyte replacement

- Many patients require more than 5 L of fluid and 350 mEq of potassium daily.

Somatostatin analogs

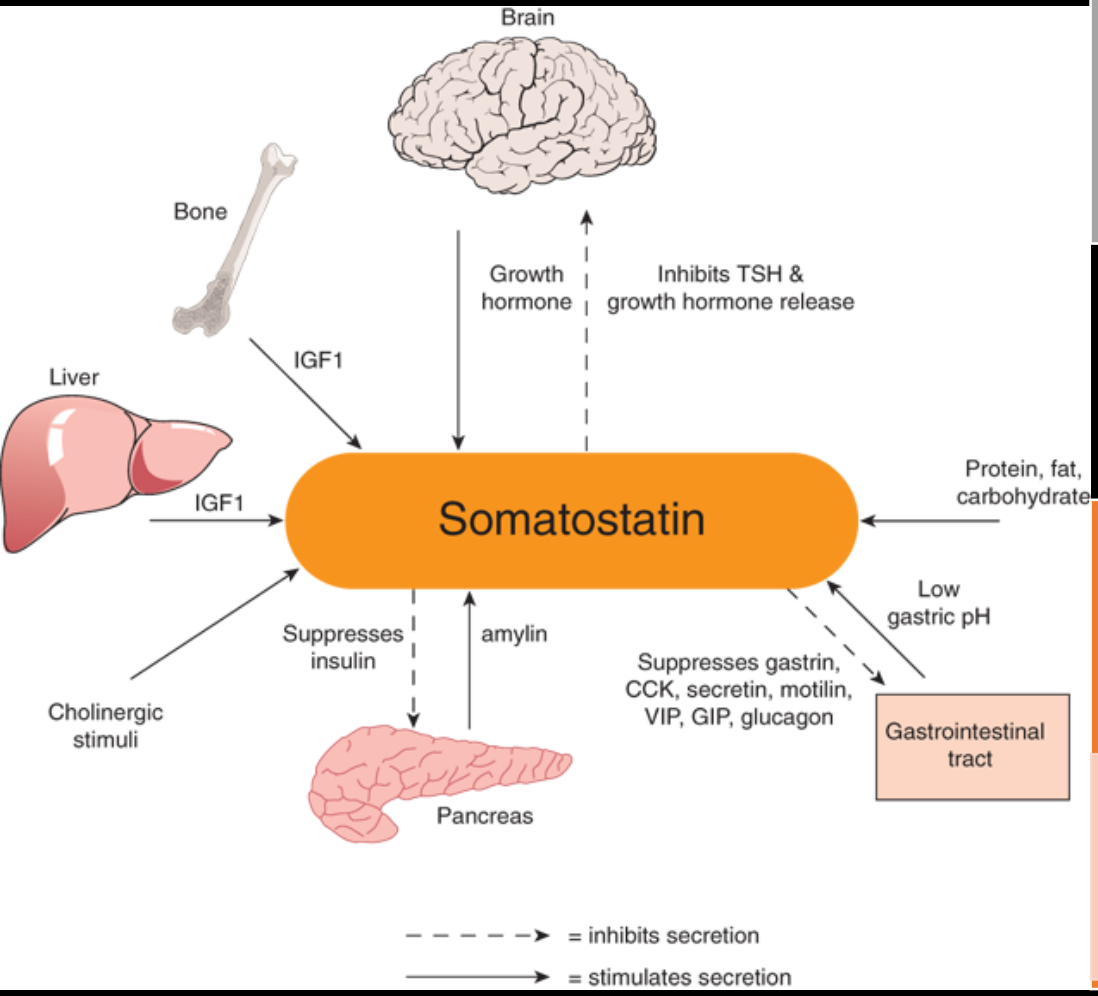
- inhibit the secretion of vasoactive intestinal polypeptide (VIP) and are the treatment of choice to control diarrhea in patients with VIPoma

Pancreatic Resection

- 60 percent already metastasized to bone, lymph nodes, liver and kidney

Somatostatinoma

- Neuroendocrine tumor from D- cell origin that secretes excessive amounts of somatostatin
- Annual incidence of 1 in 40 million
- 55 percent are in the pancreas
- 35-45 percent of somatostatinoma occurs in the MEN-1 patients



Somatostatin is a tetradecapeptide that normally acts in a paracrine manner to inhibit secretion of many hormones, including insulin, glucagon, gastrin, and growth hormone.

Somatostatinoma syndrome

Cholelithiasis	Glucose Intolerance	Diarrhea, steatorrhea

Management

Pancreatic Resection

- Surgical Treatment of choice

Advance Disease

- Octreotide/Lanreotide

Molecular Target therapy

- everolimus, sunitinib

Post-Treatment Surveillance

Three to 12 months post-resection: History and PE, serum somatostatin level, CT or MRI.

1 > year post-resection to a maximum of 10 years: History and PE with serum somatostatin level every 6 to 12 months. Imaging studies as clinically indicated.

National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf (Accessed on November 16, 2019).

Non-Functioning PNETs

Nonfunctional PNETS (NF-PNETs) represent 30 to 50% of all PNETs.

Characteristically, NF-PNETs are large, and 60 to 85% of patients have liver metastases at the time of diagnosis .

Most of them are found incidentally on abdominal imaging studies.

Clinical Features

- Abdominal Pain
- Weight Loss
- Nausea
- Vomiting

Published in final edited form as:
Endocr Pract. 2015 May ; 21(5): 546–553. doi:10.4158/EP14465.DSC.

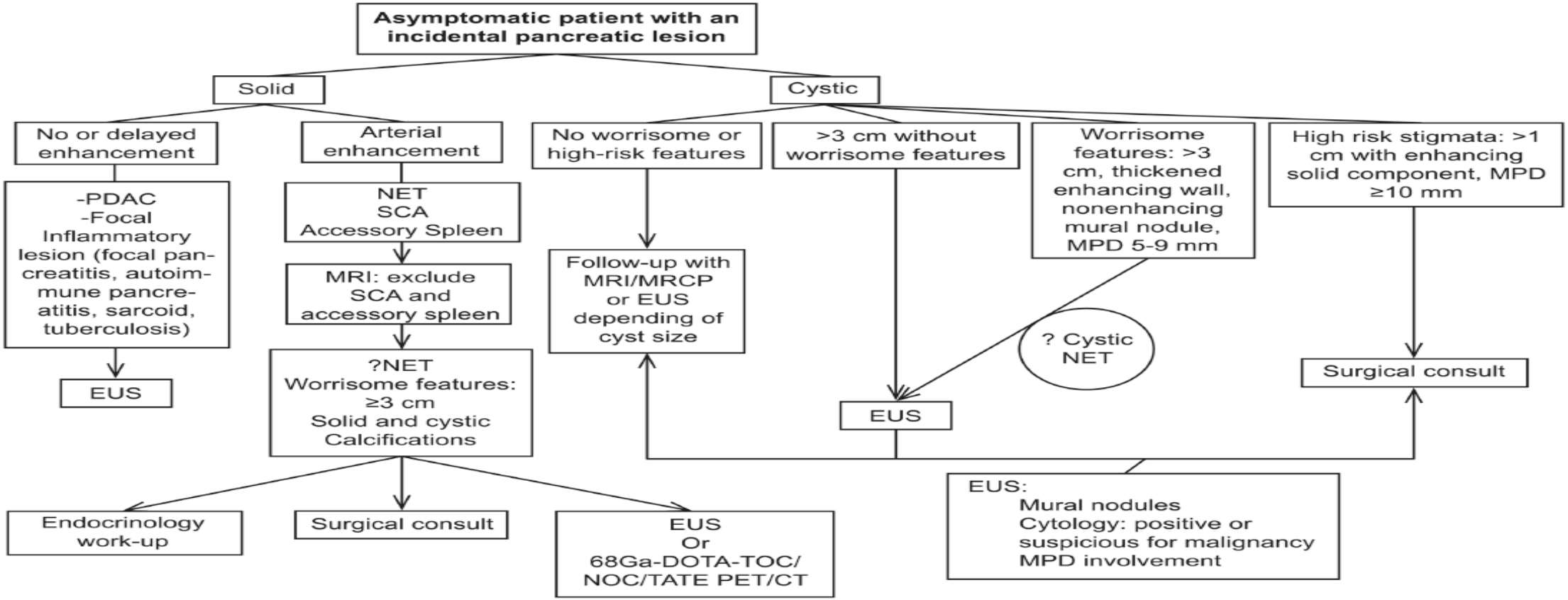


Fig. 1.

Flow-chart for imaging work-up of incidental pancreatic lesions. *CT* = computed tomography; *MPD* = main pancreatic duct; *MRI* = magnetic resonance imaging; *NET* = neuroendocrine tumor; *PDAC* = pancreatic ductal adenocarcinoma; *PET* = positron emission tomography; *SCA* = serous cystadenoma.

Biochemical Diagnosis

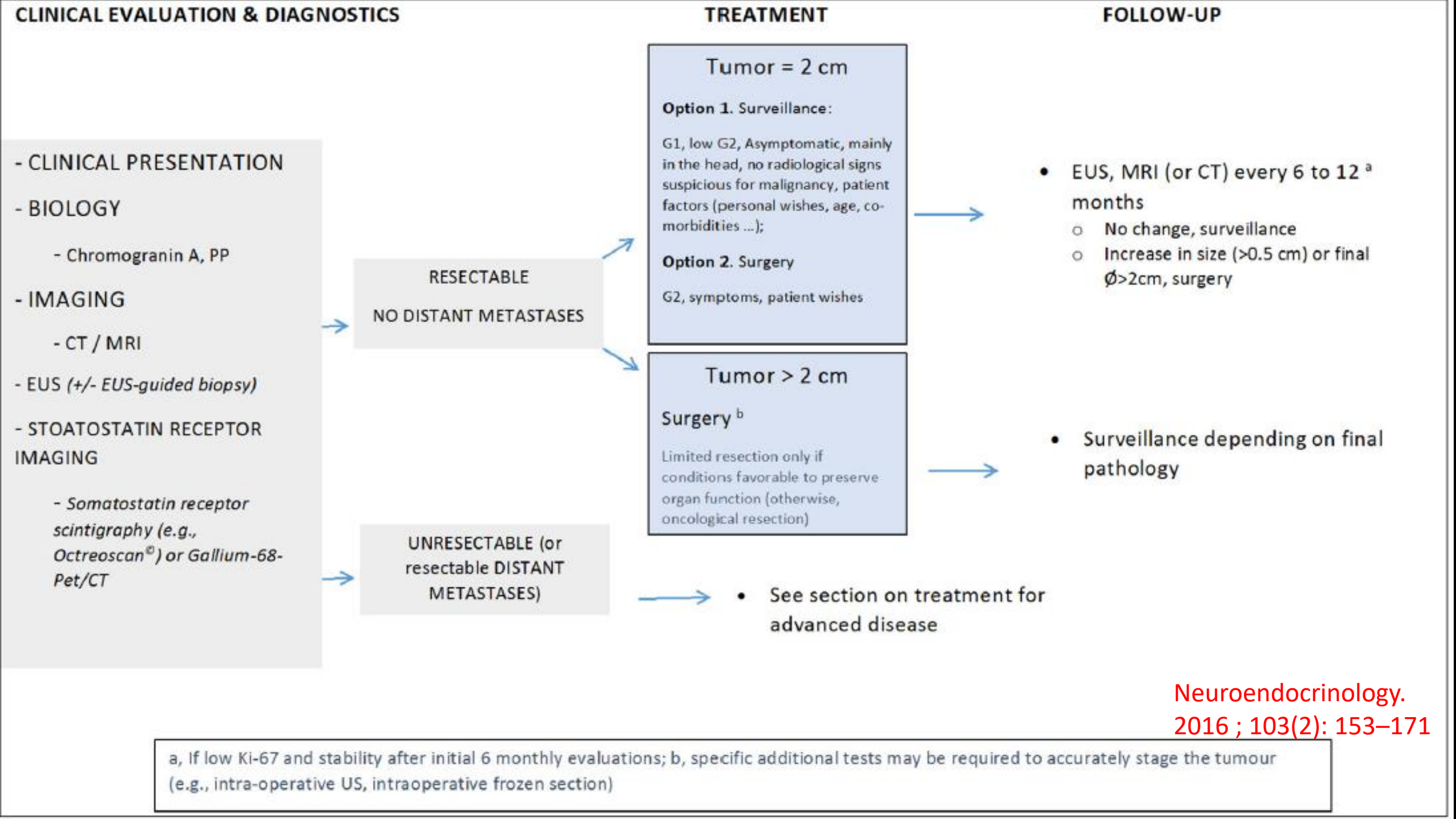
Chromogranin A (CgA)

- Related to tumor burden and metastasis
- Clinical marker for therapeutic response
- Very sensitive, not specific

Pancreatic Polypeptide (PP).

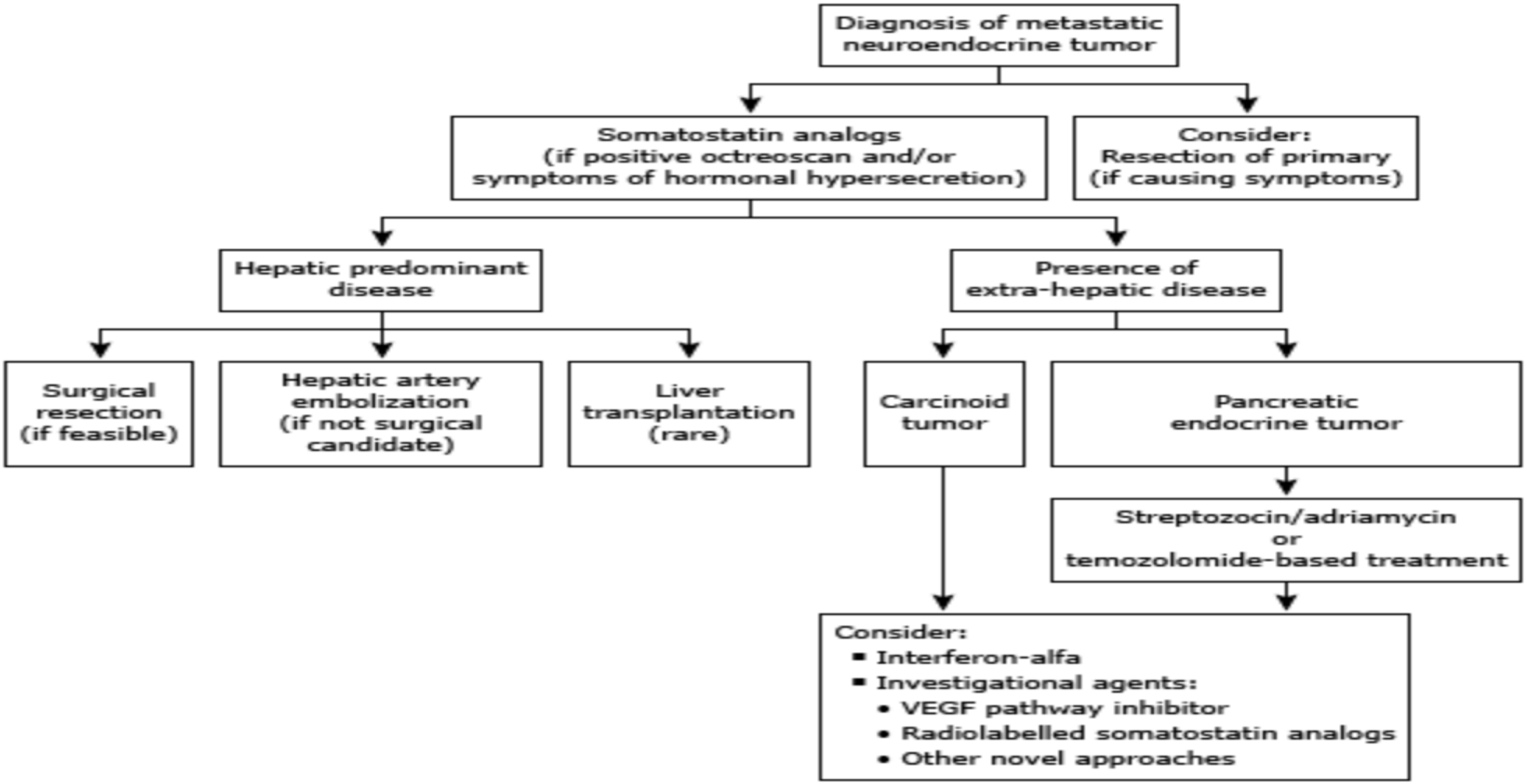
- Produced F cells of the pancreas
- Useful when CgA is negative

Neuron-specific enolase (NSE)



Neuroendocrinology. 2016 ; 103(2): 153–171

Algorithm for treatment of metastatic neuroendocrine tumors



VEGF: vascular endothelial growth factor.

Graphic 79461 Version 4.0

Table 1. Functional PNETs: Symptoms and Laboratory Findings

Tumor	Symptoms	Laboratory Findings Useful for Diagnosis
Insulinoma	Whipple triad (symptoms of hypoglycemia, low plasma glucose level, relief of symptoms with glucose administration), dizziness, irritability, sweating, fits, coma	Elevated serum insulin level, proinsulin level, and/or C-peptide level
Gastrinoma	GERD, duodenal ulcers with bleeding or perforation, diarrhea, weight loss, response to PPIs	Fasting gastrin level 10× normal, low gastric pH
Glucagonoma	Diabetes, necrolytic migratory erythema, diarrhea, stomatitis	Fasting glucagon level 10× to 20× normal
VIPoma	Severe diarrhea, weight loss, hypokalemia	VIP levels > 75 pg/mL
Somatostatinoma	Gallstones, weight loss, diarrhea, steatorrhea, diabetes	Somatostatin > 30 pg/mL
PPoma	No specific symptoms; weight gain, constipation; elevated pancreatic polypeptide level (although this is not a very accurate criterion for diagnosis)	Elevated pancreatic polypeptide level in response to secretin

GERD = gastroesophageal reflux disease; PNET = pancreatic neuroendocrine tumor; PPIs = proton pump inhibitors; VIP = vasoactive intestinal polypeptide.

https://www.cancernetwork.com/AccessedNov212019

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INCA International Neuroendocrine Cancer Alliance

THINK ZEBRA

If you don't suspect it,
you can't detect it.

Questions