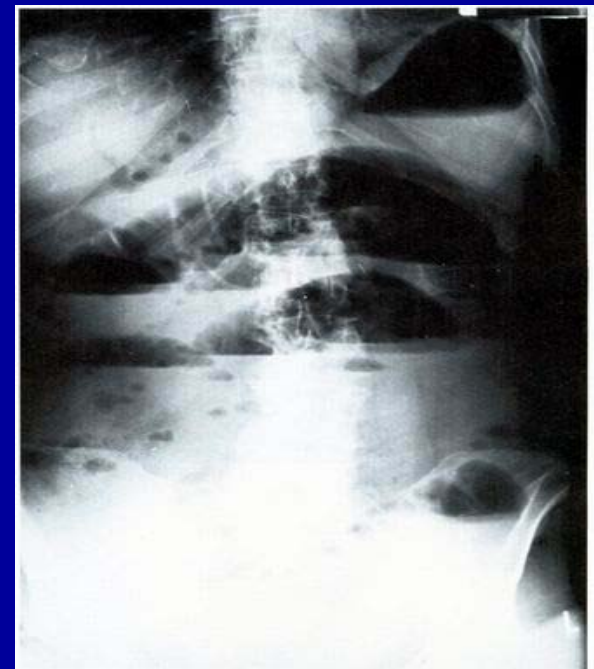
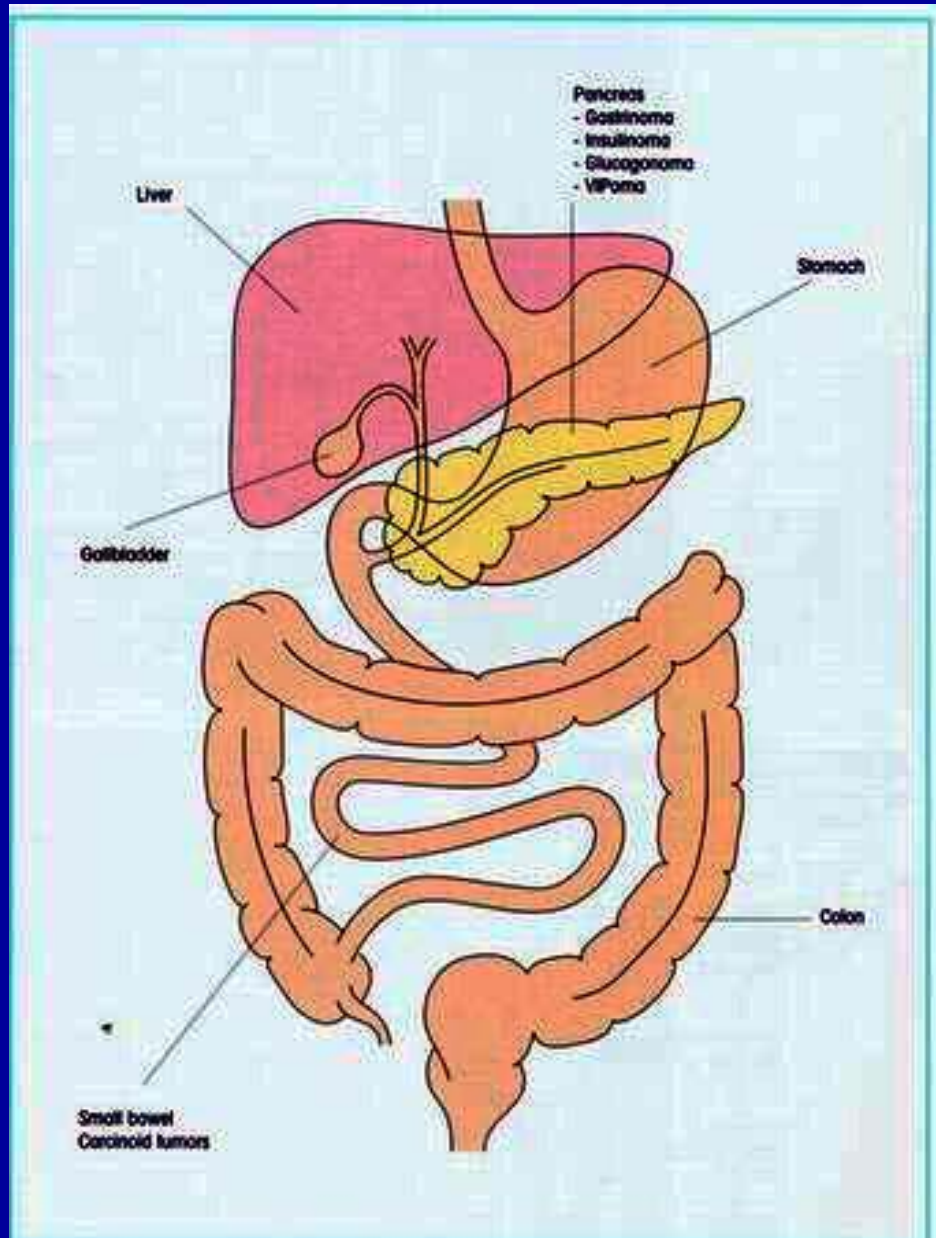


DIAGNOSTIC ALGORITHM AND GUIDELINES FOR GEP TUMORS 2006

Gregory Kaltsas MD FRCP

Endocrine Unit, Department of
Pathophysiology, National University of
Athens

Clinical presentation of GEP tumors



The GEP-tumor Patient May Suffer From

Flushing

Sweating
Cardiorespiratory
failure
Hypotension

Rash

Diabetes
Muscle wasting
Weight loss



Severe diarrhea

Dehydration
Hypokalemia
Hypochlorhydria

Hypoglycemia Peptic Ulcer

STAINS AND LABORATORY STUDIES INDICATED IN THE WORKUP OF NEUROENDOCRINE TUMORS

STAINS

- Basic for diagnosis
 - Chromogranin
 - Synaptophysin
 - Cytokeratin
- Tumor-specific confirmation
 - Gastrin
 - Somatostatin
 - Insulin
 - VIP
 - ACTH
 - Glucagon
 - Prolactin
 - Calcitonin
 - Pancreatic polypeptide

LABORATORY STUDIES

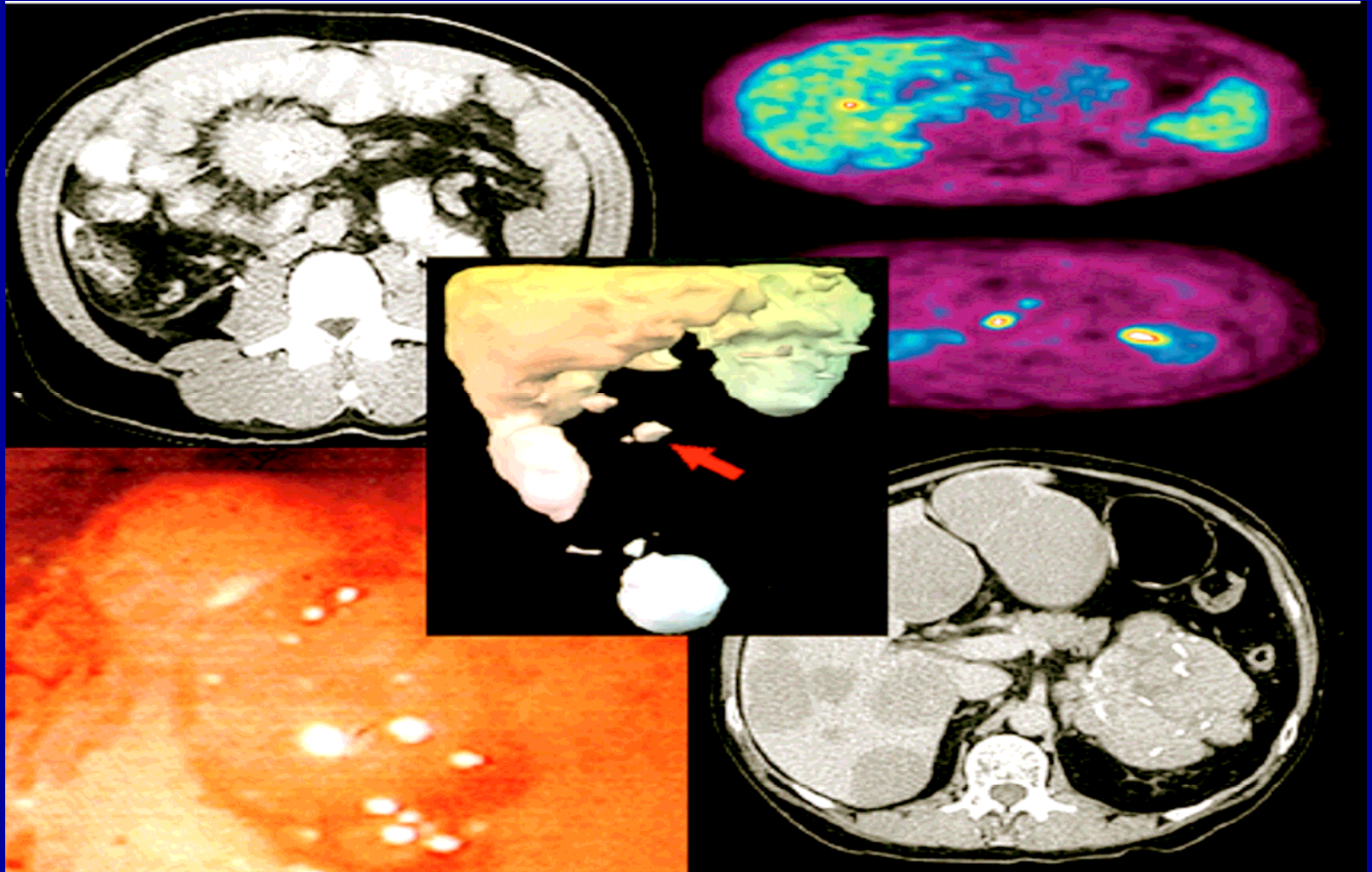
- Chemistries
 - Calcium
 - Phosphorus
 - Electrolytes
 - Magnesium
 - Chloride/
phosphorus ratio

HORMONE-RELATED STUDIES

- (markers)
 - Carcinoid
 - 5-HIAA (24 h urine)
 - Chromogranin A
 - Gastrinoma
 - Gastrin
 - Insulinoma
 - Proinsulin
 - Insulin/glucose ratio
 - C-peptide
 - VIPoma
 - VIP
 - Glucagonoma
 - Glucagon
 - Blood glucose
 - CBC
 - Other pancreas
 - Chromogranin A
 - Somatostatin
 - Pancreatic polypeptide
 - Calcitonin
 - Parathyroid hormone related peptide

- Pheochromocytoma/
paranglioma
 - Metanephrines (plasma and
urine)
 - Catecholamines (urine)
 - Dopamine (urine) (optional)
- Pituitary
 - Growth hormone/IGF-1
 - Prolactin
 - LH/FSH
 - TSH
 - Alpha subunits
 - ACTH
- Ectopic hormones
 - ACTH
 - GRH
 - GHRH

Imaging of GEP tumors

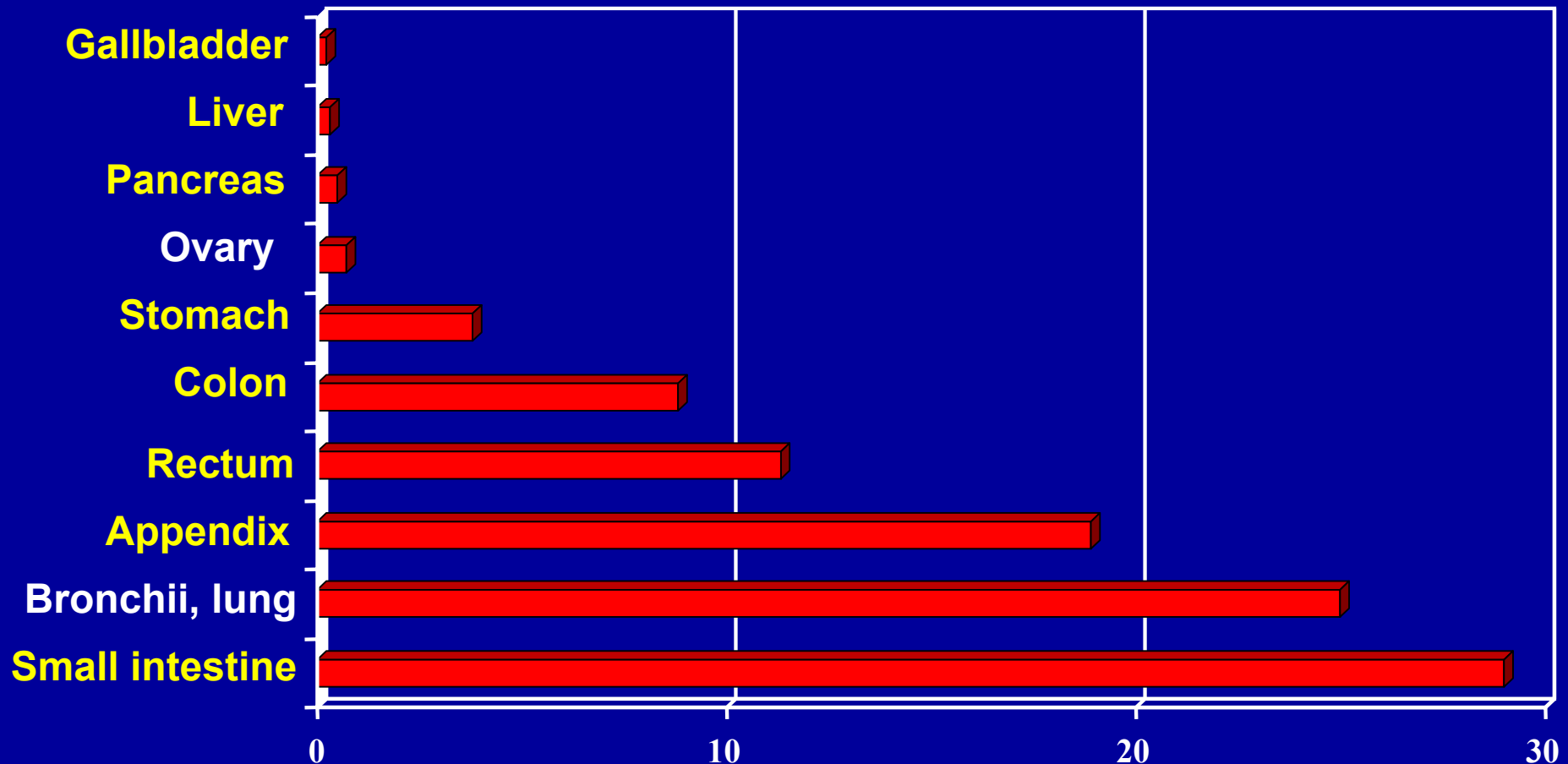


'Carcinoid' GE(P) Tumors

- 1% autopsies
- Indolent (grade 1); malignant (grade 2 & 3)
- Association with **MEN-1** (10-15%), NF1, Von Hippel Lindau
- **Familial Risk** SIR 4.35 (small intestinal), 4.65 (colon)
- Can be associated with **other malignancies** (**midgut, hindgut**) SIR for second small intestinal cancer 24.16
- Genetic screening (**Familial Syndromes**)

ANALYSIS OF 8305 CARCINOID TUMORS

Distribution of Carcinoid Tumors by Site (ERG, TNCS and SEER Registries)



Modlin 1997

Gastric GEP tumors

	<i>Type I</i>	<i>Type II</i>	<i>Type III</i>
% gastric GEP	70-80%	5-6%	14-25%
Tumor features	Single/multiple, small (<1-2 cm), polypoid, intramucosa	Usually multiple polypoid	Single, polypoid, ulceration
Associations	ABG	ZES/MEN-1	Sporadic
Histology	Well differentiated	Well differentiated	Well/poorly differentiated, mixed carcinoma
Plasma Gastrin	↑↑	↑↑	-
Gastric pH	↑↑	↓↓	-
Risk metastases	2-5%	10-30%	50-100%
Tumor death	0%	<10%	Well dif. 25-30% Poorly dif. 75-87%

Gastric GEP tumors

- Gastroscopy with multiple biopsies from tumor and non-tumor tissue for histopathological diagnosis to distinguish between the different types of gastric GEP tumors
- Indicates the size, location and invasion of primary tumor
- Excludes infection with *Helicobacter pylori*

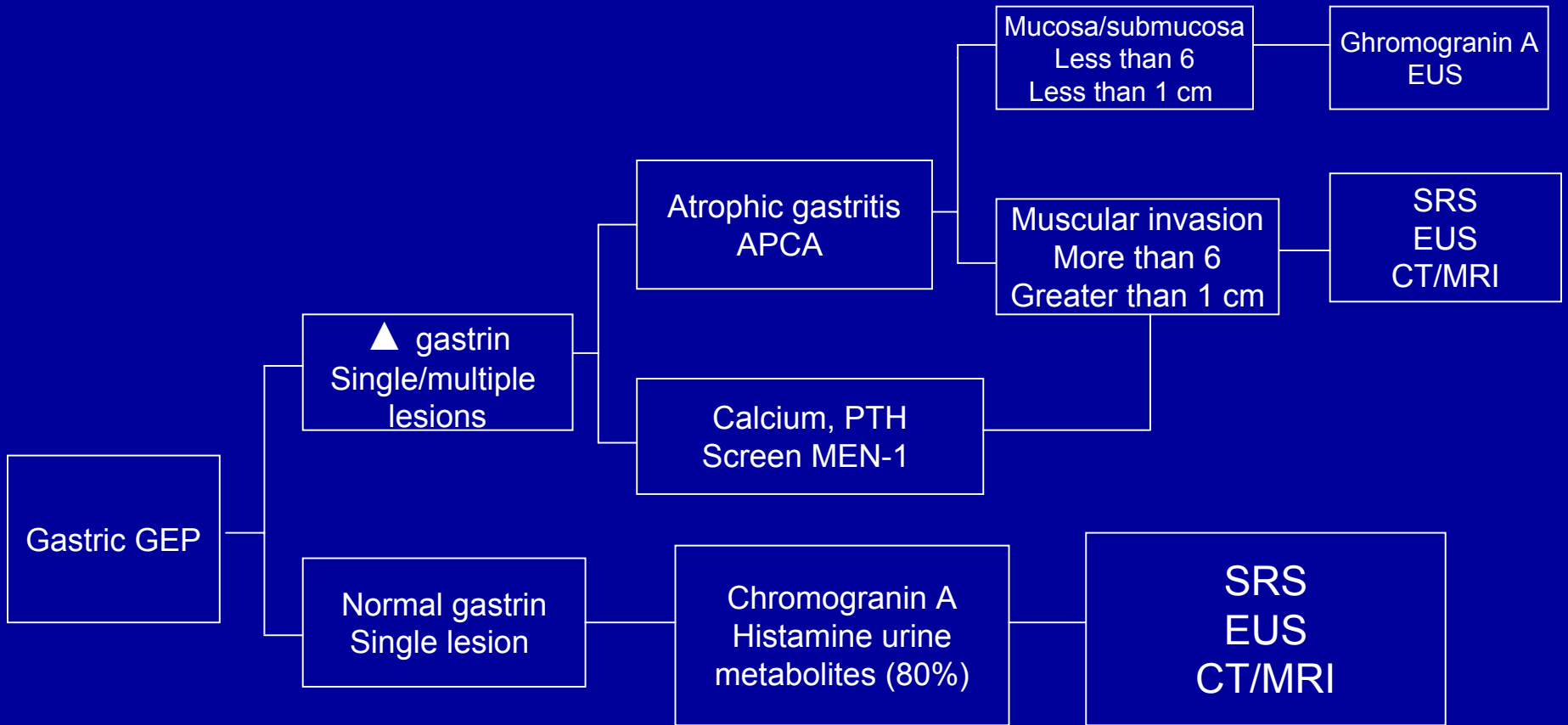
Gastric GEP tumors

- Parietal cell & intrinsic factor antibodies, B₁₂ levels
- Serum Chromogranin A, gastrin, histamine urine metabolites (Type 3 & 1)
- Screen for MEN-1 (ionized Calcium, PTH, pituitary hormones)

Gastric GEP tumors

- Endoscopic US (EUS) to assess invasiveness if size > 1cm
- Octreotide scan (SRS), CT/MRI*, if invasiveness and tumor size > 1cm
- Octreotide scan (SRS), CT/MRI* if type 3 and poorly differentiated tumors

* US of abdomen



Diagnostic algorithm for gastric GEP tumors

GEP tumors of the duodenum



- Gastrin (G) cells
- Somatostatin (D) cells
- Serotonin (EC) cells

Duodenal GEP tumors

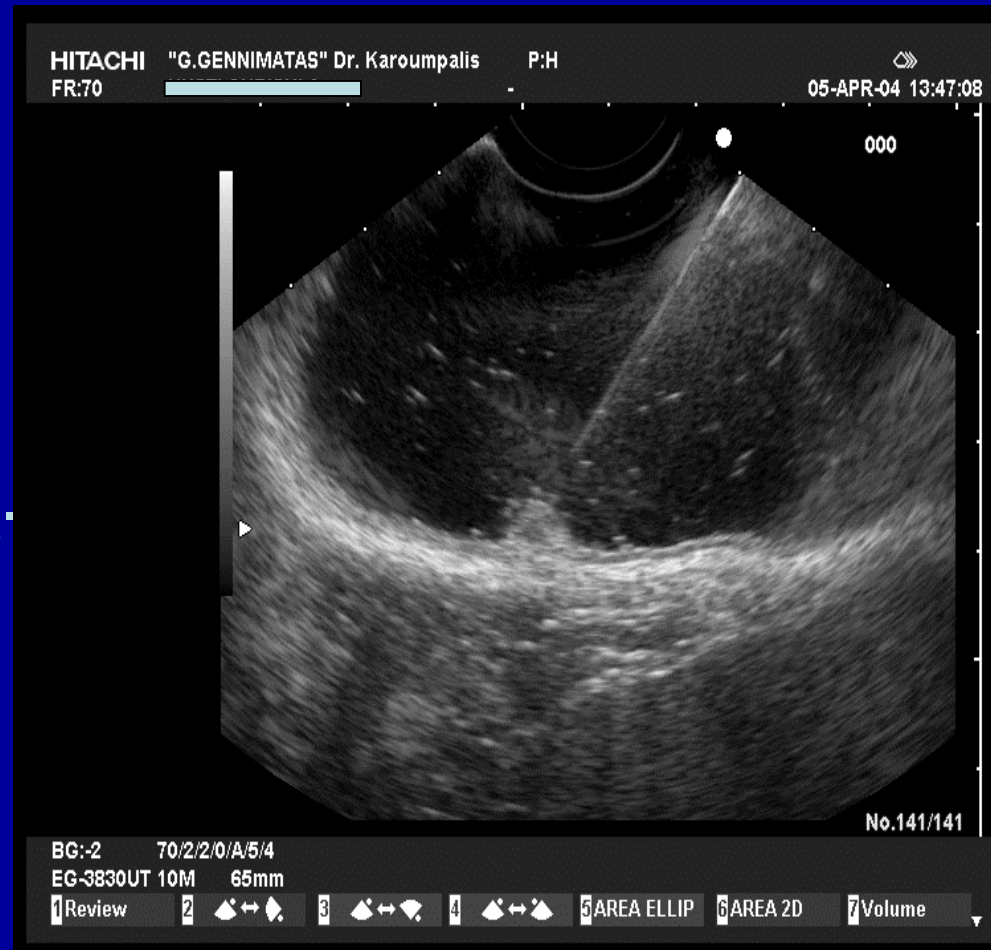
- Endoscopy with biopsy for histopathological diagnosis to distinguish between the different types of duodenal tumors
- Indicates size, location and degree of invasion of primary tumor

Duodenal GEP tumors

- Chromogranin A is the most reliable tumor marker
- Levels of other tumor markers vary depending on the type of tumor (gastrin, calcitonin, somatostatin, urinary 5-HIAA)
- Additional work-up for those suspected for
 - Von Recklinghausen's disease (D cells)
 - Zollinger-Ellison syndrome (G cells)
 - Gangliocytic paragangliomas (ampullary region)

Duodenal GEP tumors

- EUS
- Contrast-enhanced CT/MRI abdomen
- SRS
- (5-HTP PET, *L*-dopa-PET)



Pancreatic Endocrine Cancer (Islet Cell)

- Endocrine carcinoma accounts for no more than 1,000 cases a year in the U.S (autopsies 1%).
- Tumor classifications:
 - functioning (hormone producing → syndrome)
 - nonfunctioning (? production bioactive substances ⇌ syndrome)
- Most endocrine cell tumors are nonfunctioning
- 90 % of nonfunctioning tumors are malignant

Name	Peptide Secreted	Incidence <small>New cases/million population</small>	Tumour Location	Malignant %	Associated with MEN-1 %
Zollinger-Ellison Syndrome	Gastrin	1-1.5	Duodenum 60% Pancreas 40%	60-90%	25%
Insulinoma	Insulin	1-2	Pancreas	10%	5%
VIPoma (Verner Morrison)	VIP	0.1	Pancreas 90%	40-70%	5%
Glucagonoma	Glucagon	0.01-0.1	Pancreas	50-80%	10%
Somatostatinoma	Somatostatin	<0.1	Pancreas 55% Duodenum 45%	70%	45%
GRFoma	Growth hormone releasing hormone	<0.1	Pancreas 30% Lung 50% Jejunum 15%	60-70%	15%
ACTHoma	ACTH	<0.1	Pancreas 90%	95%	Rare
PPoma	(Pancreatic polypeptide)	2-4	Pancreas 100%	60-80%	20-40%

Glucagonoma Rash



- Migratory Necrotizing Erythema
 - Hyperpigmentation of healing lesions

Pancreatic GEP tumors

- Chromogranin A is a general tumor marker increased in all types of endocrine pancreatic tumors
- Pancreatic polypeptide (PP) is a further general tumor marker
- Hormone determination is performed according to the secretory syndrome although mixed syndromes may also occur

Pancreatic GEP tumors

- Dynamic tests (insulinoma, gastrinoma, MEN-1)
- Screening for MEN-1 (15-30%)
- Von Hippel Lindau's syndrome

Pancreatic GEP tumors

- EUS combined with biopsies is the most sensitive method pancreatico-duodenal tumors
- SRS
- US, CT, MRI
- 5-HTP or *L*-dopa PET
- Intraoperative US

Small intestine GEP tumors

- Chromogranin A universally elevated
- High levels inversely correlate with survival
- 5-HIAA 24h urine measurement
- Serotonin is not a reliable marker
- Relevant hormones when other secretory syndromes present

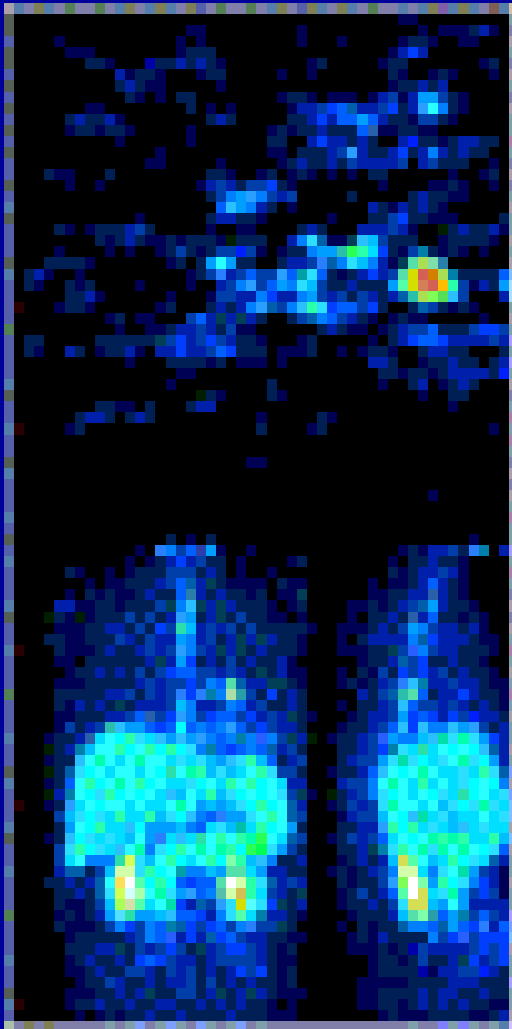
Small intestinal GEP tumors

- SRS (primary, lymph nodes, known and unknown metastases)
- CT/MRI of positive areas to estimate the size of lesions (mesenteric lymph nodes +/- desmoplastic reaction)
- Echocardiography in patients with carcinoid syndrome
- Bone scan (MRI) if bone lesions negative SRS

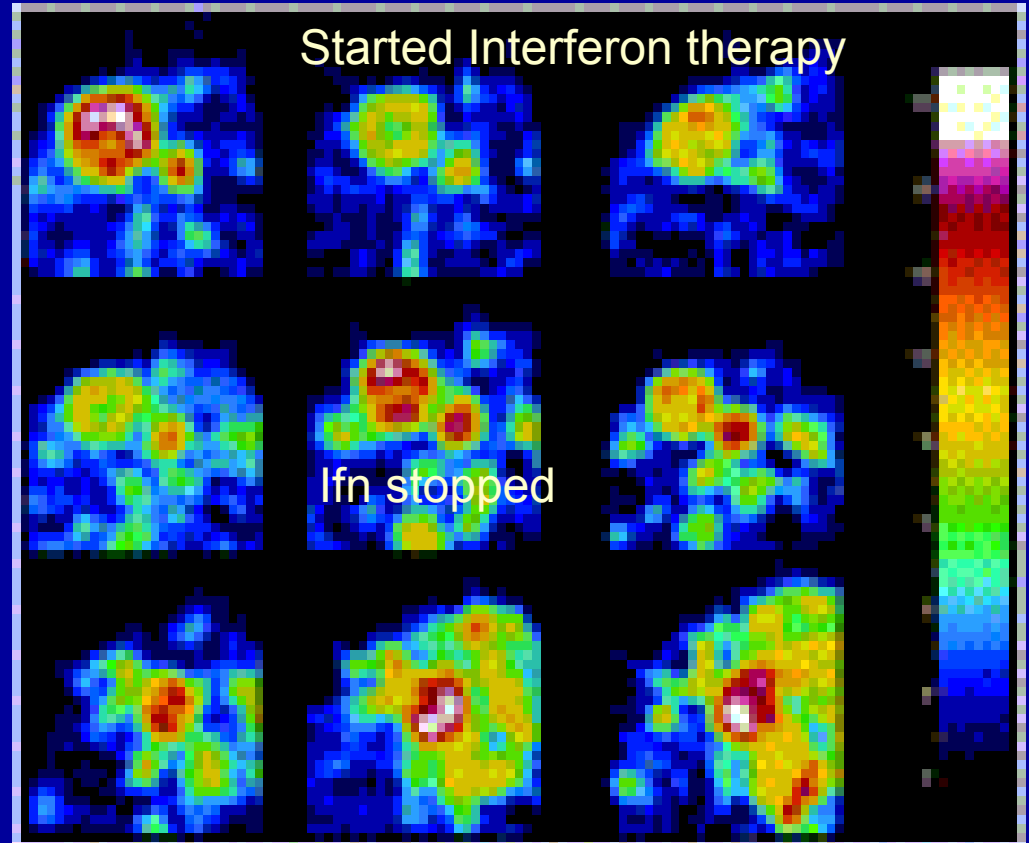
Small intestinal GEP tumors

- Unknown primary
 - Colonoscopy
 - Small bowel enteroclysis
 - CT/MRI enteroclysis
 - Capsule endoscopy
 - Double balloon enteroscopy

11C-5HTP PET Imaging



Unknown primary
Bronchial carcinoid

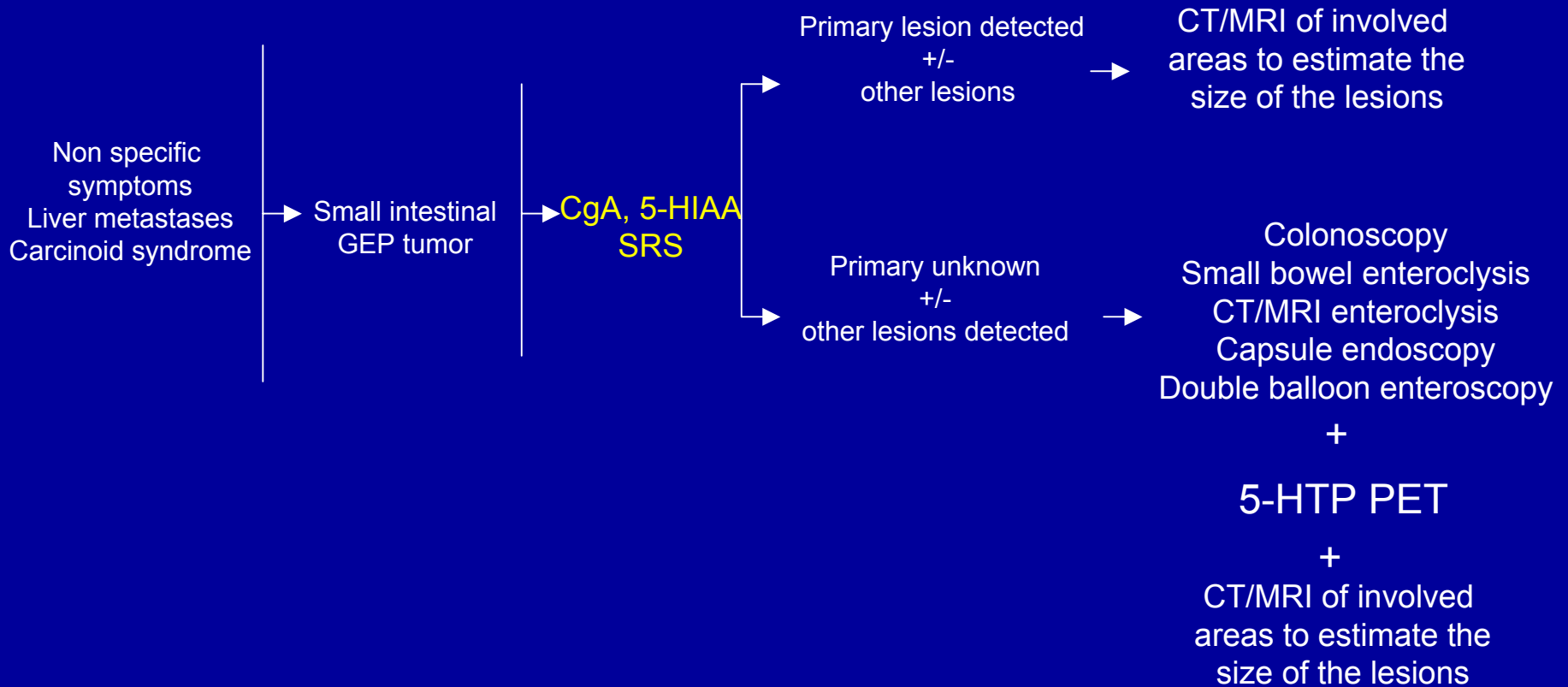


Liver metastases from midgut carcinoid

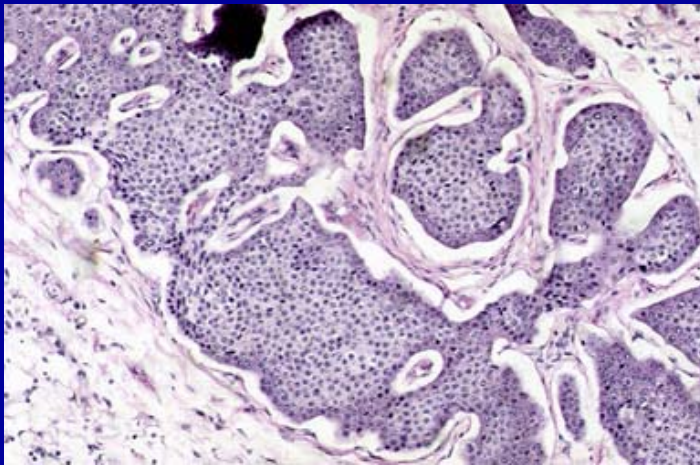
Small intestinal GEP tumors

- Multiple lesions (13-27%)
- Other synchronous or metachronous malignancies (GI tract, breast, lymphoid system)

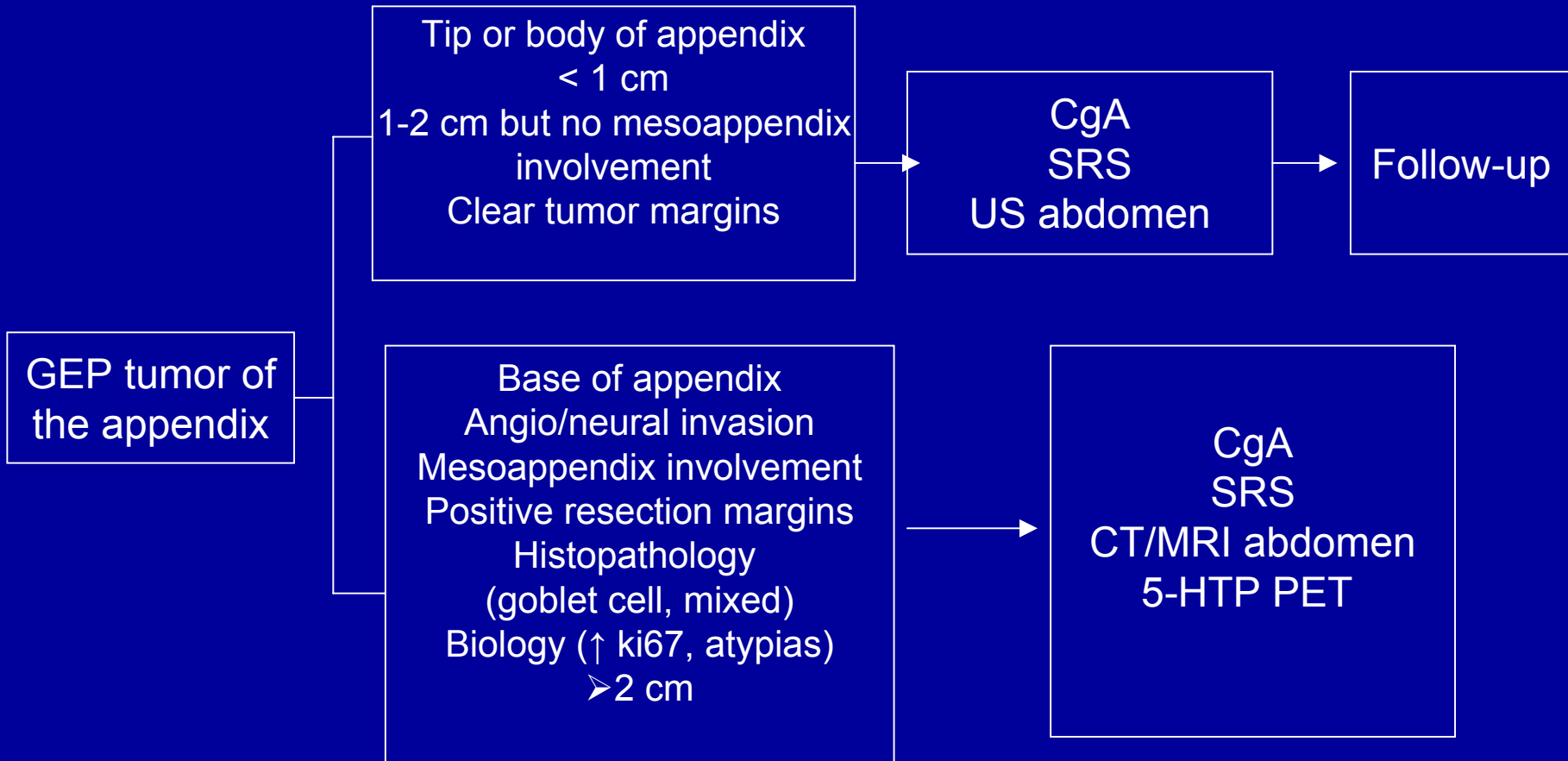
Small intestinal GEP tumors



GEP tumors of the appendix



GEP tumors appendix



GEP tumors of the colon

- Full colonoscopy to exclude concomitant colonic disease and presence of synchronous carcinoma
- CgA (non-functioning)
- CgA levels reflect tumor burden
- 5-HIAA levels is symptoms of carcinoid syndrome (EC cell)

GEP tumors of the colon

- SRS (sensitivity not established)
- CT/MRI staging (thorax, abdomen, pelvis)
- Bone scan
- 5-HTP PET scan

GEP tumors of the rectum

- Endoscopy
- EUS for pre-operative assessment (size, depth of invasion, lymph node involvement)

GEP tumors of the rectum

- CgA
- PP, enteroglucagon (L cells)
- Specific hormones when secretory syndrome (5-HIAA very rare)

- SAP, β -HCG

GEP tumors of the rectum

- SRS (background activity)
- CT/MRI assess lesions with local extension and involvement of other pelvic structures and resectability
- 5-HTP PET scan

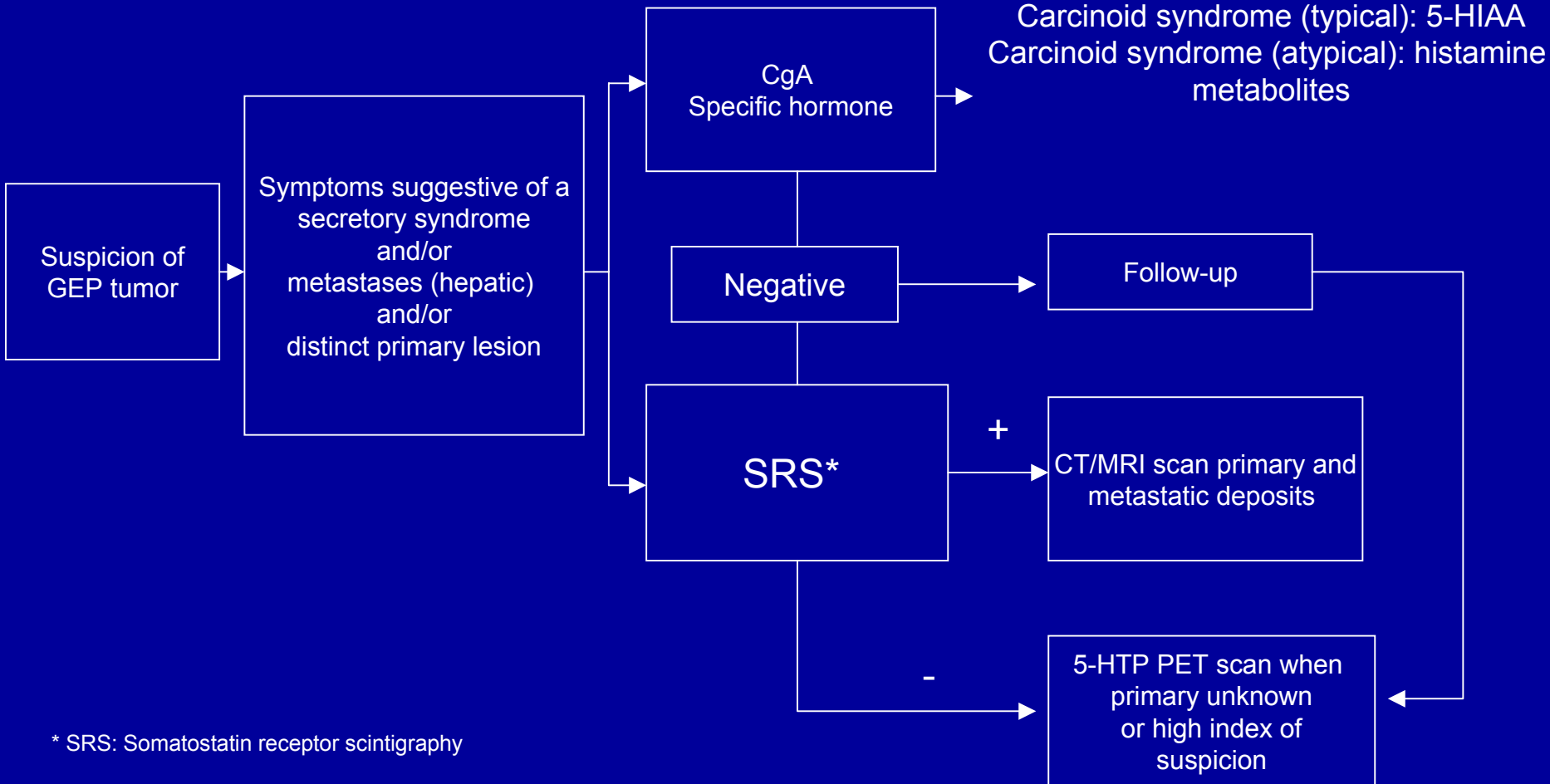
Specific tests for diagnosing GEP tumors

<i>Syndrome</i>	<i>Test</i>	<i>Result</i>
All GEP tumors	Serum chromogranin	↑
Foregut carcinoids	24h 5-HIAA	↑ 20%
Midgut carcinoids	24h 5-HIAA Tachykinins	↑ 75% ↑ 70%
Hindgut carcinoids	24 5-HIAA	Not raised
NF pancreatic	PP	↑ 80%
Insulinoma	Fasting insulin	↓ glucose, ↑ insulin
Gastrinoma	Fasting gut hormones	↑ gastrin, ↑ gastric acid
Glucagonoma	Fasting gut hormones	↑ glucagon, enterogluc
VIPoma	Fasting gut hormones	↑ VIP
Somatostatinoma	Fasting gut hormones	↑ somatostatin
Ectopic hormones	GHRH, ACTH, HCG	↑

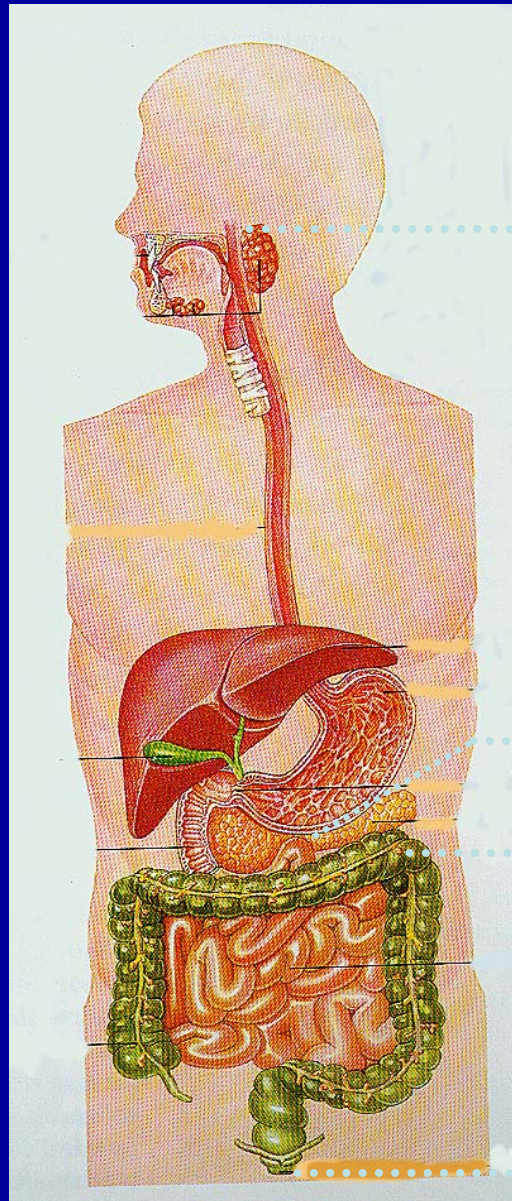
Investigations for localization and staging

- For foregut and midgut tumors SRS is the investigation of choice for localisation of primary and metastatic deposits
- CT/MRI is indicated if SRS is negative and for estimation of the exact size of lesions
- For hindgut tumors colonoscopy followed by CT or MRI is the best option as SRS can be negative
- For secondary lesions SRS is the modality of choice
- ? 5-HTP PET

Diagnostic Algorithm for GEP tumors



Type, Distribution and Frequency of GEP, NET



	Relative frequency	Function	Histology
Foregut	29%	✓ Functional	Islet cell
Midgut	57%	✓ Functional	Carcinoid
Hindgut	14%	Non-functional	Carcinoid

Werner-Morrison Syndrome (VIPoma, Pancreatic Cholera)

- Hormone secreted:
 - Vasoactive Intestinal Polypeptide (VIP)
- Syndrome:
 - Severe, watery diarrhea
 - Severe hypokalemia
 - Dehydration
 - Achlorhydria
- Usually metastatic when discovered

Glucagonoma Syndrome

- Location:
 - Pancreas
- Syndrome:
 - Weight loss
 - Rash, may be severe
 - Diarrhea
 - Anemia
 - Diabetes
- Rash responds to intravenous amino-acids
- Usually metastatic when discovered