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# Pancreatic Endocrine Tumours

# Pancreatic Endocrine Tumours

- Rare
- Extremely heterogenous entity
- Research is difficult, given the relative rarity and broad diversity of the disease
- Paucity of prospective data

- Fourth to fifth decade
- Slight female preponderance
- Majority are sporadic
- Inherited Syndromes

# MEN 1

- Autosomal dominant
- Penetrance reaching 100% with age
- Parathyroid
- Enteropancreatic tumours
- Pituitary
- Others

# Molecular Genetics

- Mutation of MEN1 (*MEN1*) gene which is located on chromosome 11 (11q13)
- Codes for a protein called menin
- Generally behaves as a tumour suppressor
- Mutations cause absence or low availability of menin

- Functional Tumours
- Non Functional Tumours

<b>Islet cells</b>	<b>Secreted active agent</b>	<b>Tumour and syndrome</b>
Alpha	Glucagon	Glucagonoma (Diabetes, Dermatitis, DVT)
Beta	Insulin	Insulinoma (hypoglycemia)
Delta	Somatostatin	Somatostatinoma (mild diabetes, cholelithiasis, achlorhydria, steatorrhea)
D	Gastrin	Gastrinoma
A > D	Vasoactive Intestinal Peptide (VIP) and / or other undefined mediators	WDHA (watery diarrhea, hypokalemia, achlorhydria)
	Serotonin (5-HT)	Carcinoid
	ACTH	Cushing disease
	MSH	Hyperpigmentation
<b>Interacinar cells</b>	<b>Secreted active agent</b>	<b>Tumour and syndrome</b>
	Pancreatic polypeptide	Multiple hormonal syndromes
	5-HT	Carcinoid

# WHO Classification

- Well differentiated Endocrine Tumour
  - Benign Behaviour
  - Uncertain Behaviour
- Well differentiated Endocrine Carcinoma
- Poorly differentiated Endocrine Carcinoma

## WHO classification of pancreatic endocrine tumors (Heitz *et al.* 2004)

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### 1. Well-differentiated endocrine tumor

#### 1.1. Benign behavior

Confined to the pancreas, <2 cm in diameter,  $\leq 2$  mitoses per 10 HPF,  $\leq 2\%$  Ki-67-positive cells, no angioinvasion, or perineural invasion

#### 1.2. Uncertain behavior

Confined to the pancreas and one or more of the following features:  $\geq 2$  cm in diameter,  $> 2$  mitoses per 10 HPF,  $> 2\%$  Ki-67-positive cells, angioinvasion, perineural invasion

### 2. Well-differentiated endocrine carcinoma

Low-grade malignant

Gross local invasion and/or metastases

### 3. Poorly differentiated carcinoma

High-grade malignant

$> 10$  mitoses per HPF

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# Localisation

- CECT
- MRI
- PET CT
- Somatostatin Receptor Scintigraphy (SRS)
- EUS
- Intraoperative Ultrasound Scan (IOUS)
- Intraoperative Endoscopic Transillumination

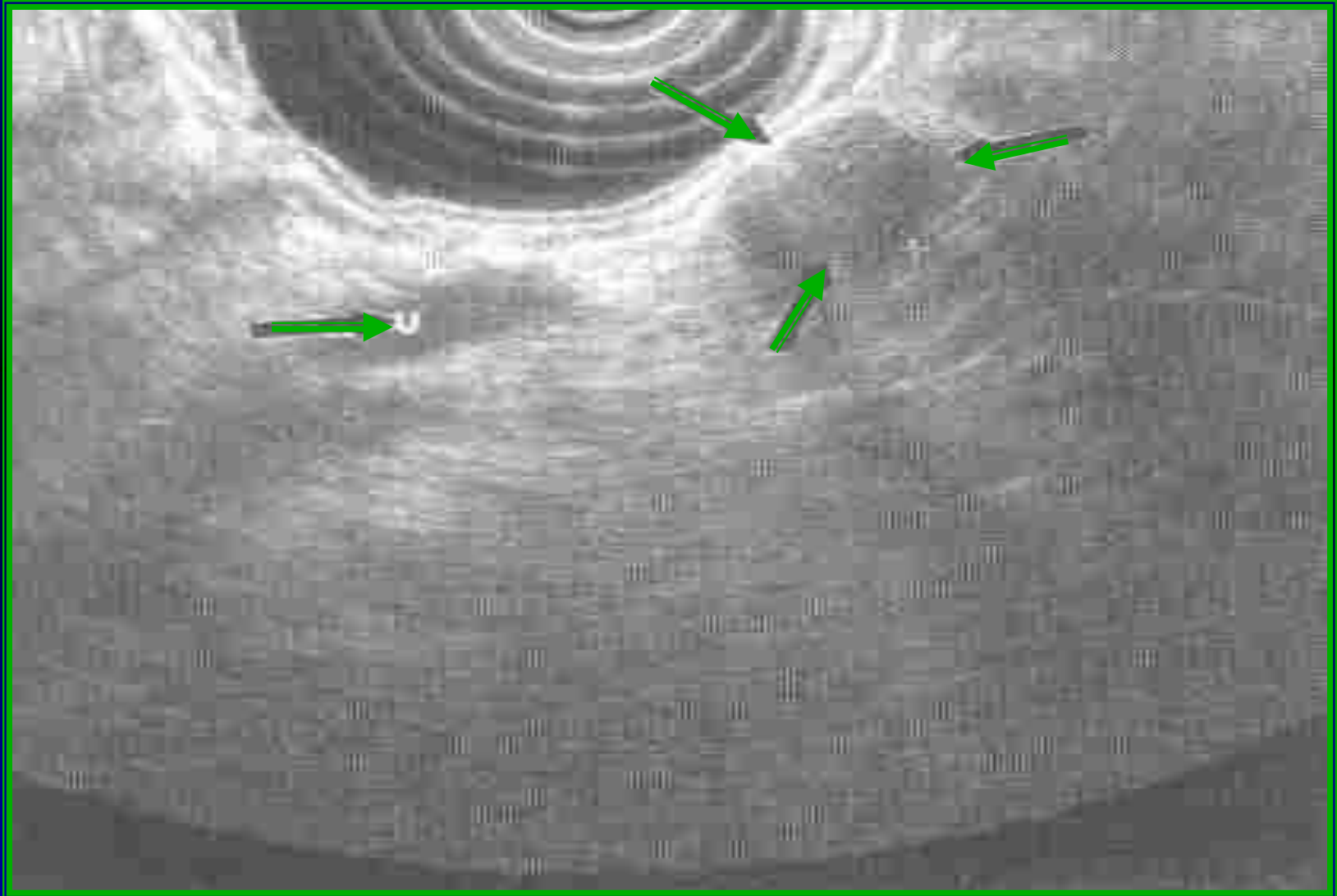
# SRS

- Localisation
- Metastasis detection
- Somatostatin Type 2 receptors
- Gastrinomas
- Carcinoids
- Non Functioning PET
- Glucagonoma

# Endoscopic Ultrasound (EUS)

- Tumours as small as 2-3mm in diameter in pancreas head and duodenal wall can be identified
- Sensitivity(70 – 90%)
- Specificity ( almost 100%)
- EUA guided FNAC can be done

# EUS



# Intraoperative Ultrasound Scan (IOUS)

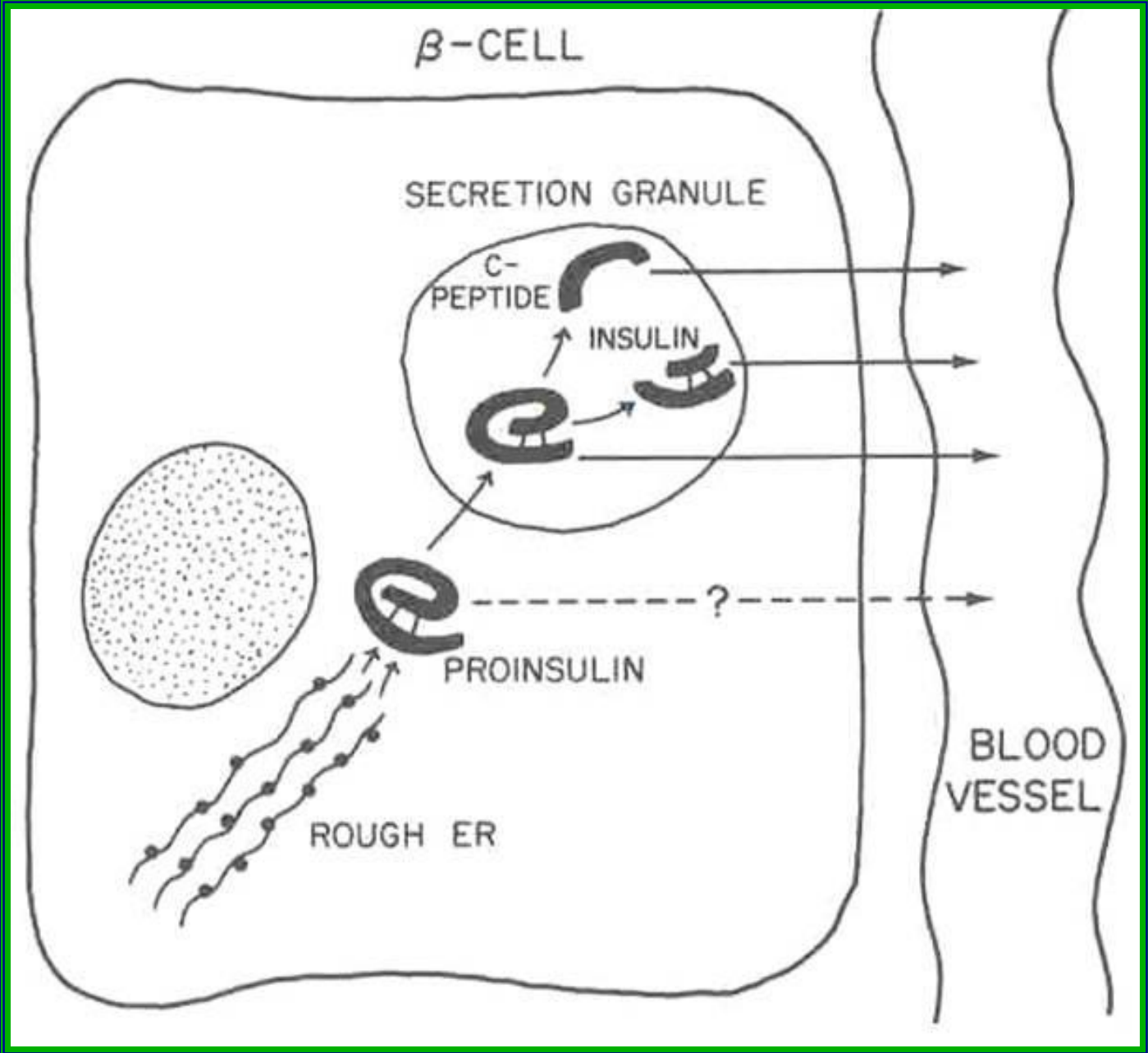
- Most sensitive technique for intraoperative localisation
- Combination of palpation and IOUS detects 75 – 100% of insulinomas
- Useful for gastrinomas arising from pancreas
- Sensitivity falls in extrapancreatic sites

# Insulinoma

- Most common sporadic pancreatic endocrine tumour
- 90% benign
- Usually solitary and well encapsulated
- 10% - Multiple
- 10% - MEN 1

# Diagnosis

- Whipples Triad
- Neuroglycopenic symptoms
- Adrenergic symptoms

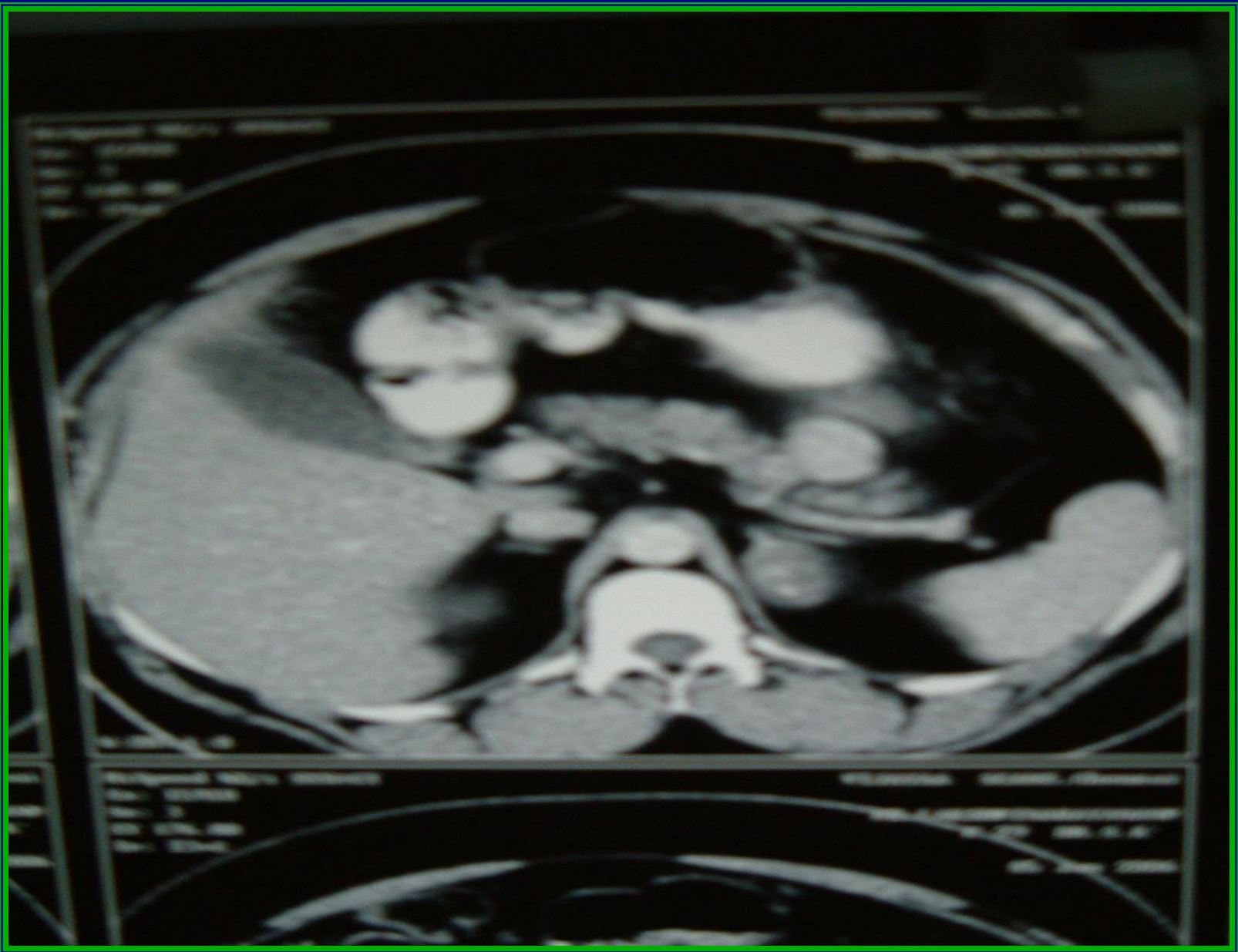


# Diagnosis

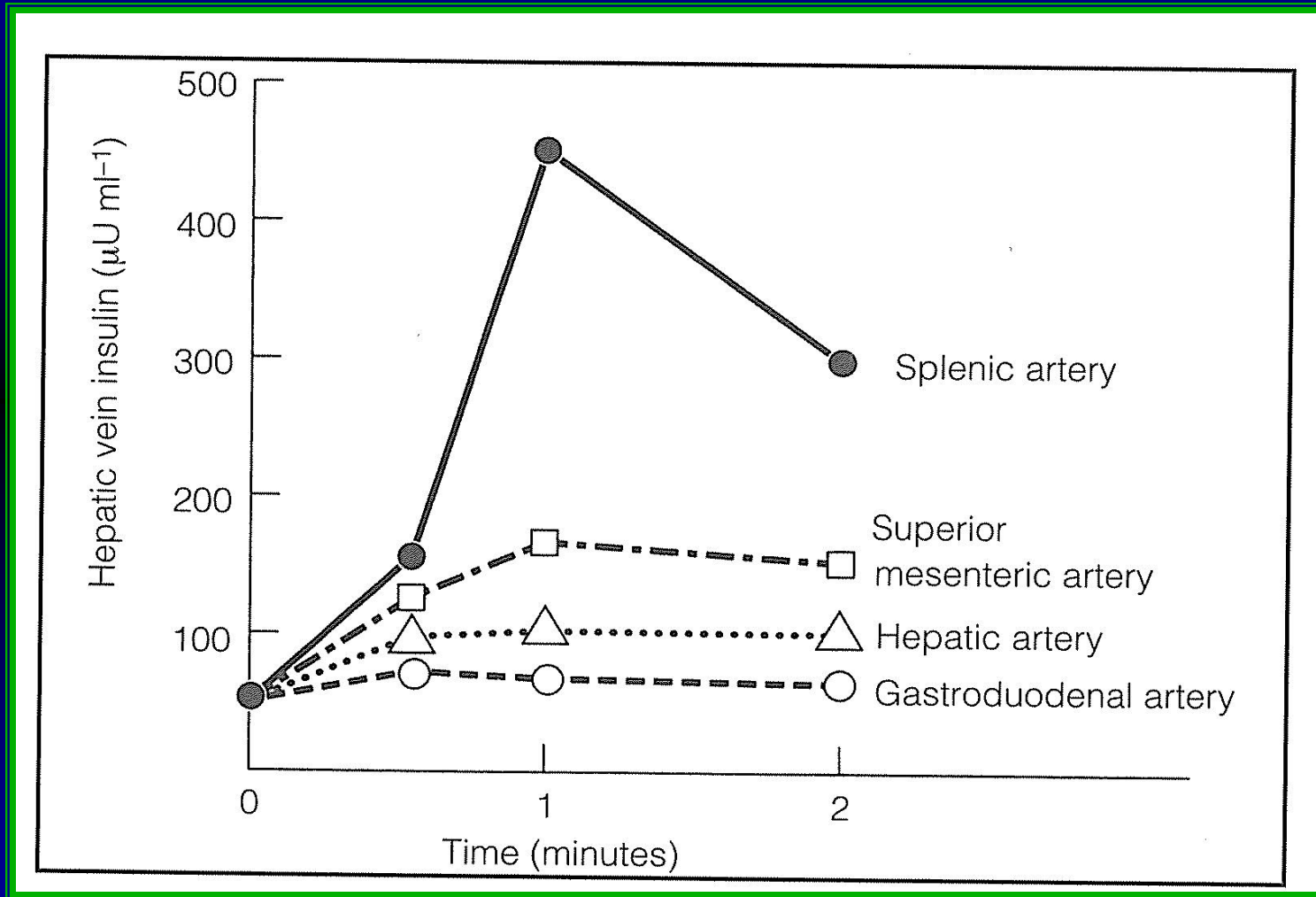
- Supervised Standard 72 hour fasting test
- Insulin glucose ratio  $> 4$
- C – Peptide assay
- Pro insulin

# Localisation

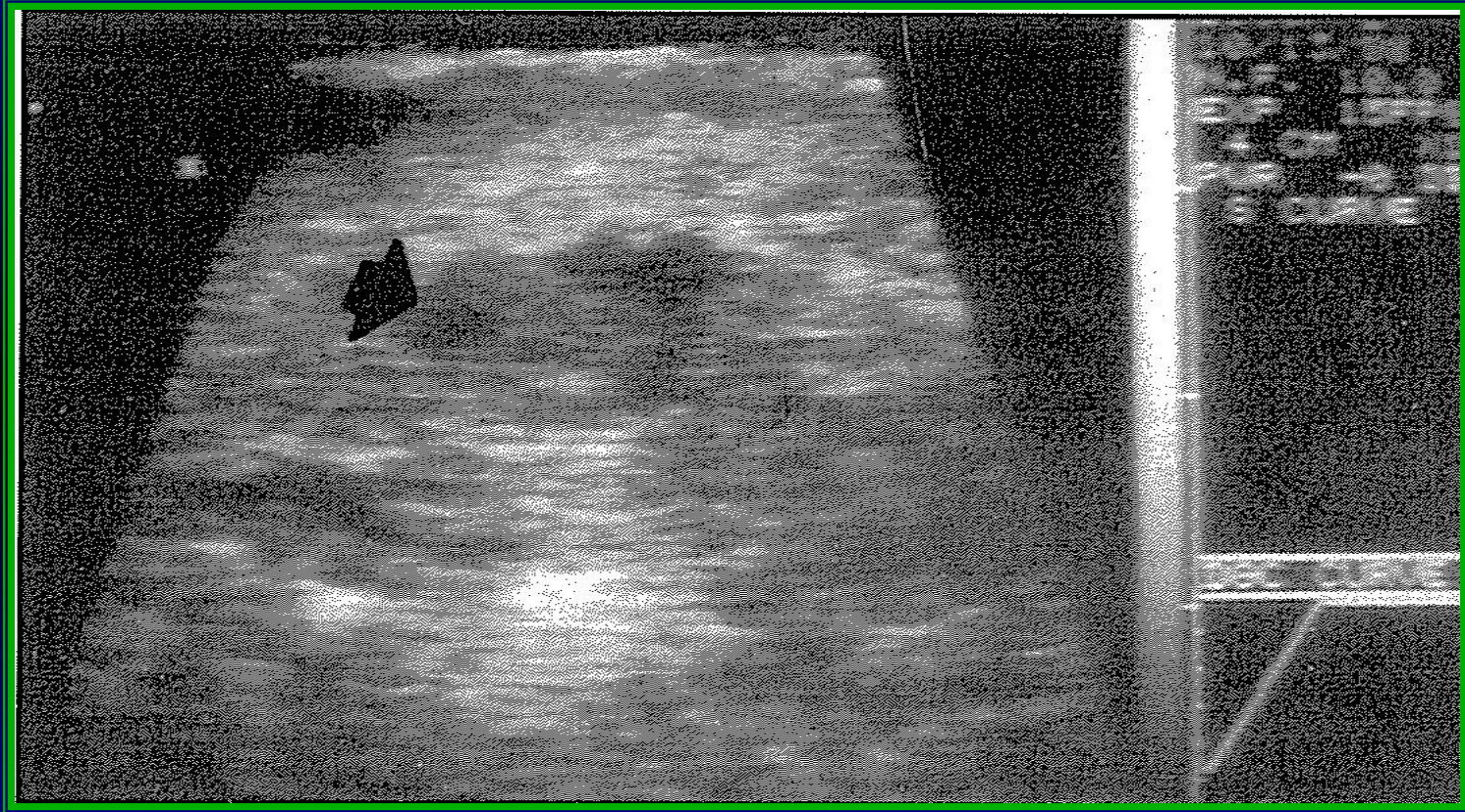
- C T Scan
- MRI
- PET CT
- SRS – Not very useful
- EUS
- Calcium Angiogram
- Intraoperative Ultrasound ( IOUS)
- IOUS and bidigital palpation very useful



# Calcium Angiogram



# Intraoperative USS



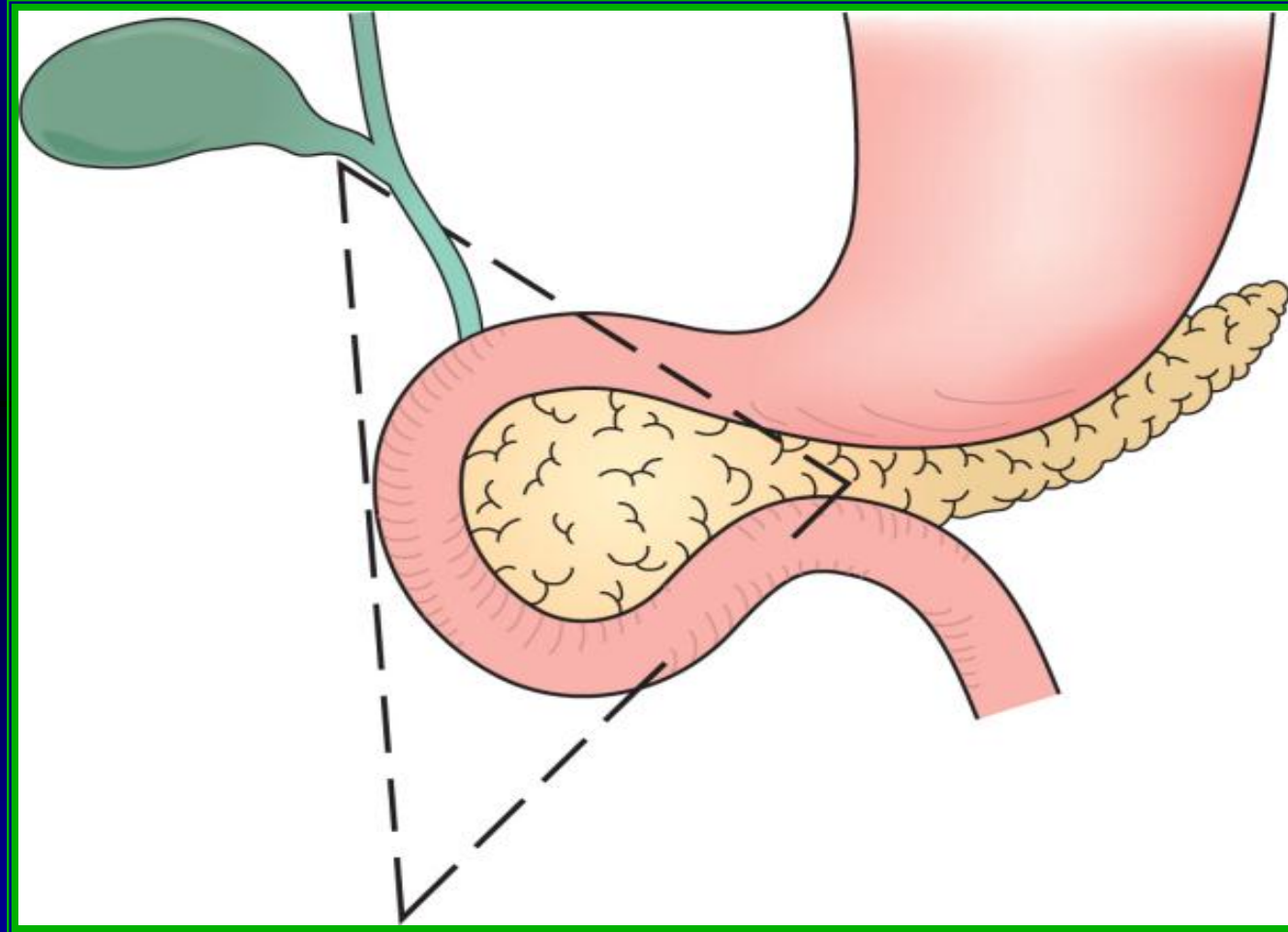
# Treatment

- Site
- Relationship to important structures
- MEN I
- Enucleation
- Spleen preserving distal pancreatectomy
- Laparoscopic approach
- **Blind distal pancreatectomy in case of non localisation of insulinoma not advocated**

# Gastrinoma

- Zollinger – Ellison syndrome
- Commonest pancreatic endocrine tumour associated with MEN 1
- Refractory ulcers
- Multiple ulcers
- Recurrent ulcers
- Unusual sites

# Gastrinoma triangle

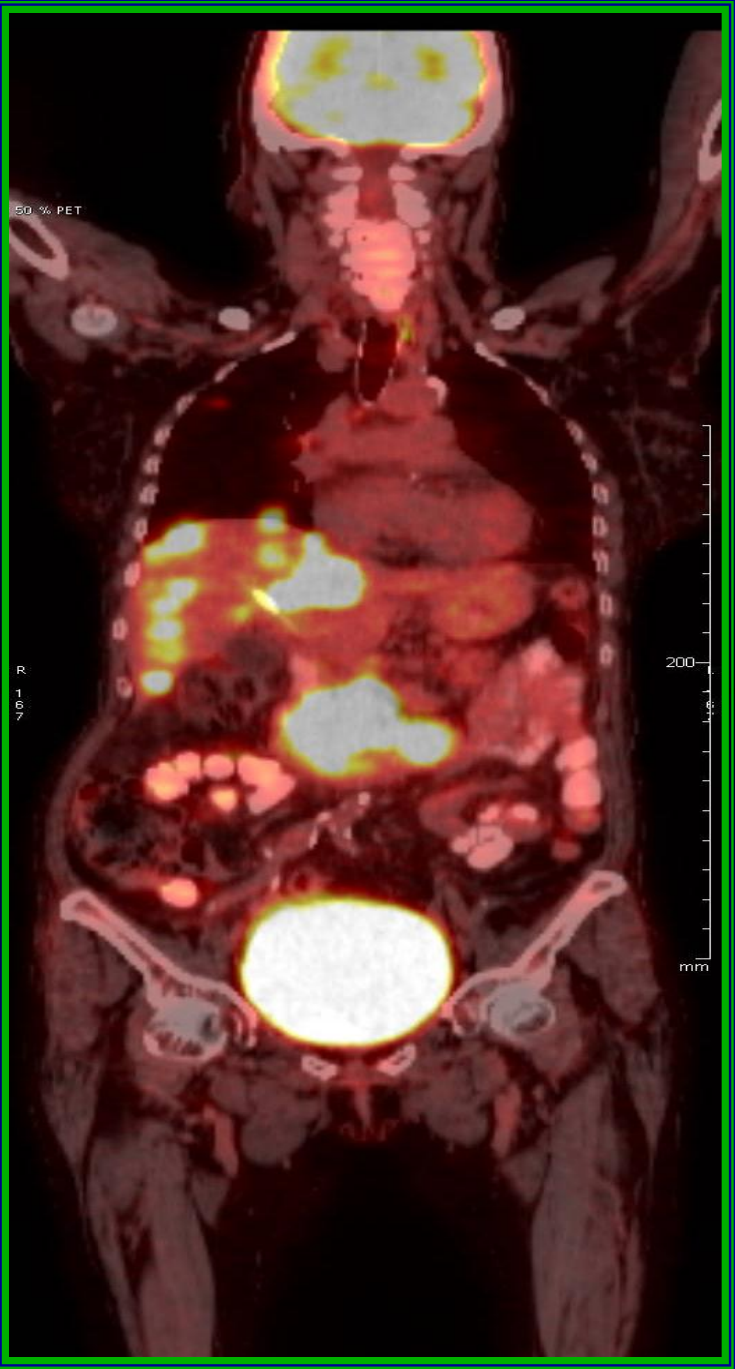


# Diagnosis

- Basal Acid Output > 15 meq/ hr
- Gastric pH < 2.5
- Fasting serum gastrin > 500 pg/ml
- **Secretin provocation test - > 200 pg / ml**

# Localisation

- CT Scan
- MRI
- PET CT
- SRS
- EUS
- IOUS
- Intraoperative endoscopic transillumination



# Treatment

- Medical management with PPI should be started after establishing a biochemical diagnosis.
- About 60% have lymph nodes or liver metastasis at time of initial surgical exploration
- Type of surgery is based on whether Sporadic or associated with MEN 1
- Total gastrectomy rarely indicated

- Sporadic Gastrinoma – Excision with regional lymph nodal clearance
- MEN I Gastrinomas - Type of Surgical Treatment and timing - controversial

# Nonfunctioning PET

- Most common Pancreatic endocrine tumour
- Mass effect, Abdominal Pain, Bleeding
- Sporadic – Resection

## MEN 1

- < 2 cm
- > 2cm

# Hepatic metastasis

- Hepatic resection
- Selective Hepatic artery embolisation
- Radio Frequency Ablation
- Cryoablation
- Liver transplantation

# Systemic therapy

- Pharmacotherapy
- Somatostatin analogs
- Alpha inteferon
- Cytotoxic chemotherapy

# Future

- Somatostatin receptor Radionucleides
- VEGF Inhibitors
- Tyrosine Kinase Inhibitors

- Rare tumors
- Nonfunctioning tumours are now more common
- With the exception of insulinoma majority are malignant
- MEN 1
- Treatment protocols vary depending on sporadic or MEN 1

- Hepatic metastases
- Systemic therapy
- Newer agents



**Thank You**