ENDOCRINE PANCREATIC TUMOURS

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INTRODUCTION

- Pancreatic endocrine tumours are rare, approximately 5 per 1,000,000 per year.
- They comprise 1-2% of all pancreas neoplasms.
- They are either functional or non-functional
- About 20% are non-functional
- Functional tumours maybe benign or malignant.
- Malignancy is defined by the presence of metastasis.

RELEVANT ANATOMY AND PHYSIOLOGY

- The pancreas is divided functionally into
  - **Exocrine Pancreas**
    - 85% of pancreatic mass
  - **Endocrine Pancreas**
    - 2% of pancreatic mass

EXOCRINE PANCREAS

- Secretes a clear, alkaline (pH 7-8.3) solution of 1-2 L/day, containing digestive enzymes.
- secretion is stimulated by
    - Secretin
    - CCK
    - Parasympathetic vagal discharge

ENDOCRINE PANCREAS

- **The pancreatic islets or islets of Langerhans** are the regions of the pancreas that contain its endocrine cells,
- Nearly **one million** islets of Langerhans are in the normal adult pancreas and each contains about **3000 cells**
- The pancreatic islets constitute **1 to 2% of the pancreas volume** and receive 10–15% of its blood flow
- larger islets are located closer to the major arterioles
- smaller islets are embedded more deeply in the pancreatic parenchyma
- **islet cells** originate from neural crest cells, aka **APUD cells**- *Amine precursor uptake and decarboxylation cell.*

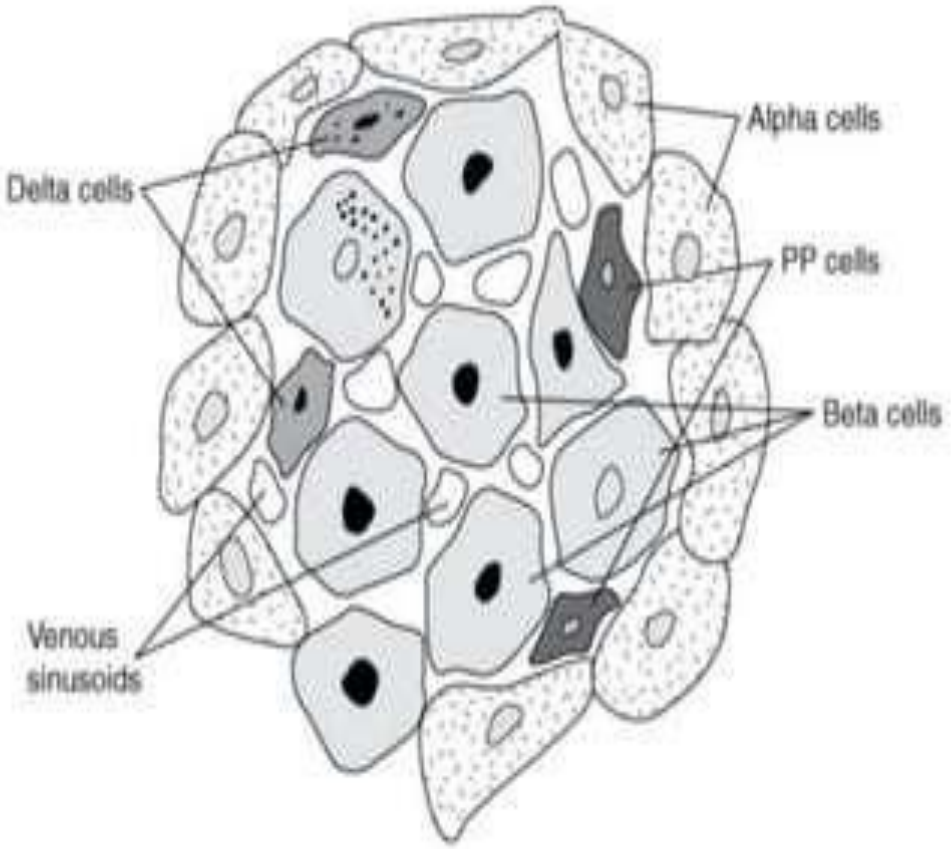
ISLET OF LANGERHANS

Alpha cells (A)

Beta cells (B)

Delta cells (D)

F or polypeptide cells (PP)



Cell Components of a Pancreatic Islet

ORIGIN OF TUMOURS

- Originally, it was thought that pNETs arose from the islets of Langerhans, but more recent investigation has suggested they arise from pluripotent stem cells in the pancreatic ductal/acinar system.

PANCREATIC ENDOCRINE TUMOURS; CELL TYPES AND DISTRIBUTION

CELL TYPE	HORMONE PRODUCE	ENDOCRINE TUMOUR/ SYNDROME	DISTRUBUTION THROUGHOUT THE PANCREAS
ALPHA (A)	GLUCACON	GLUCAGONOMA	UNIFORM THROUGHOUT THE BODY/TAIL
BETA (B)	INSULIN	INSULINOMA	BODY/TAIL
DELTA (D)	SOMATOSTATIN	SOMATOSTATINOMA	UNIFORM THROUGHOUT
F	PP	PPOMA	UNCINATE PROCESS
D 2	VIP	VIPoma/WDHA	UNIFORM THROUGHOUT

HORMONE FUNCTIONS

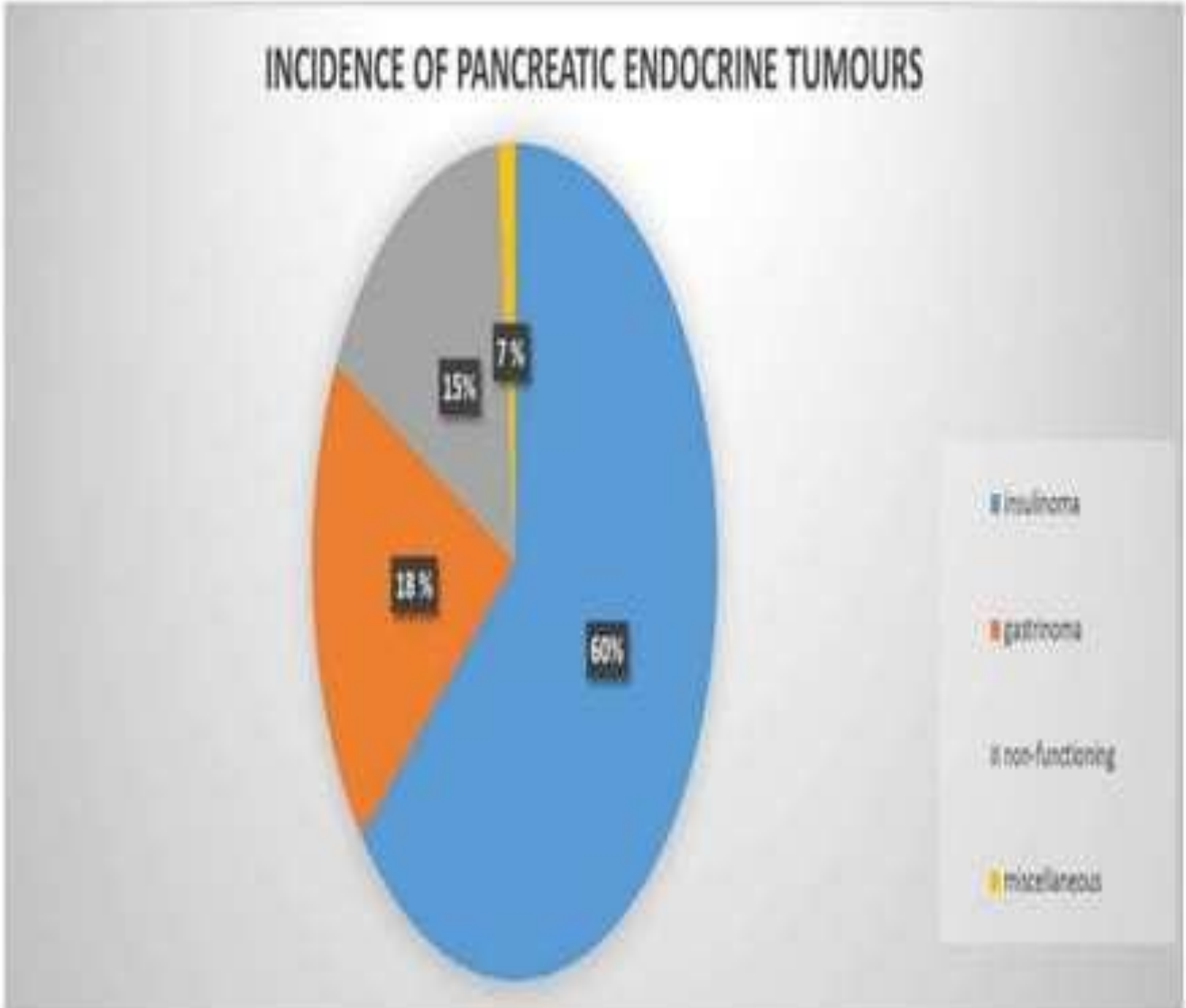
Hormones	Islet Cell	Functions
Insulin	β (beta cell)	Decreased gluconeogenesis, glycogenolysis, fatty acid breakdown and ketogenesis
		Increased glycogenesis, protein synthesis
Glucagon	α (alpha cell)	Opposite effects of insulin; increased hepatic glycogenolysis and gluconeogenesis
Somatostatin	δ (delta cell)	Inhibits gastrointestinal secretion
		Inhibits secretion and action of all gastrointestinal endocrine peptides
		Inhibits cell growth
Pancreatic polypeptide	PP (PP cell)	Inhibits pancreatic exocrine secretion and section of insulin
		Facilitates hepatic effect of insulin
Amylin (IAPP)	β (beta cell)	Counterregulates insulin secretion and function
Pancreastatin	β (beta cell)	Decreases insulin and somatostatin release
		Increases glucagon release

RISK FACTORS

- Environmental – none
- **Syndromes**
  - **MEN 1 (Wermer syndrome)-** parathyroid hyperplasia, pituitary tumours, pancreatic endocrine tumours (30-80 % of patient with MEN 1)
  - von Hippel-Lindau
  - Neurofibromatosis
  - Tuberous sclerosis complex (TSC)
- **GENETICS;**
  - Homozygous deletion or silencing of 5′ CpG island methylation; > 90% of gastrinomas and non-functioning pancreatic tumours.
  - LOH (loss of heterozygosity) at chromosome 11q – functional tumours
  - LOH at chromosome 6q – nonfunctional tumours

TYPES

- INSULINOMAS
- GASTRINOMAS
- NON-FUNTIONAL TUMOURS AND PPomas
- VIPoma
- GLUCAGONOMA
- SOMATOSTATINOMA
- OTHERS



INSULINOMAS

- 60% of all pancreatic endocrine tumours
- The average age at diagnosis 45 years
- Men and women are equally affected
- Equally distributed in the head, body, and tail of the pancreas
- Rarely, they may be located in the duodenum, splenic hilum, or gastrocolic ligament
- 90% < 2 cm in size

INSULINOMAS cont....

- They are encapsulated, firm, yellow-brown nodules that are typically hypervascular
- **Malignancy occurs in 10% of the cases**
- Most are solitary lesions
- **Multicentricity occurs in about 10% of cases and should raise the suspicion of MEN-1**
- Release large amounts of proinsulin (C-peptide and insulin) which cause hypoglycemia

CLINICAL PRESENTATION

- **NEUROGLYCOPENIC SYMPTOMS**

- headache
- lethargy
- dizziness
- diplopia
- amnesia

- CATECHOLAMINE RELEASE

- trembling
- sweating
- palpitations
- nervousness
- hunger

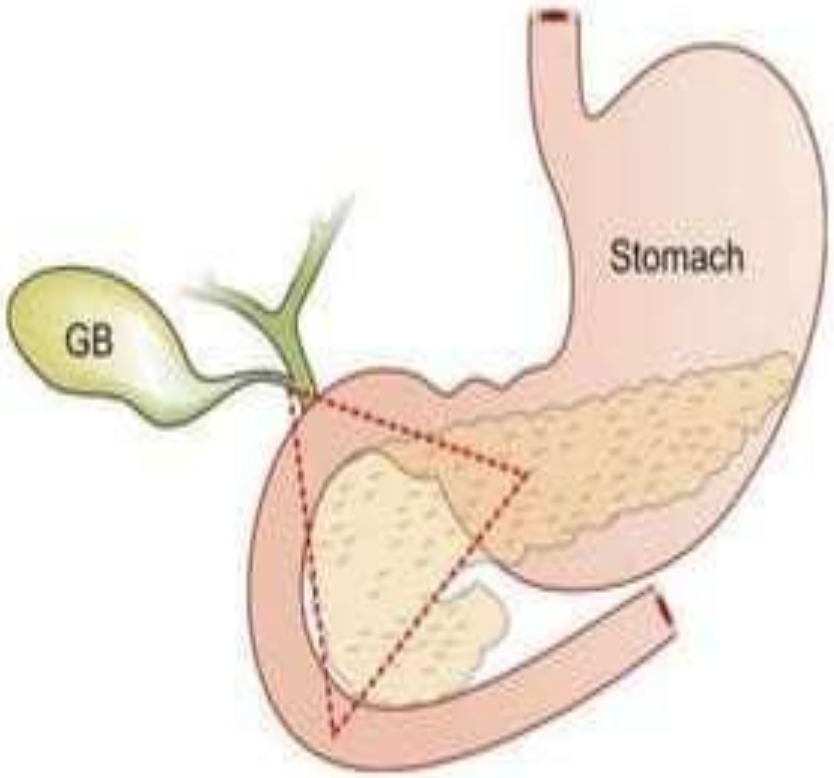
- weight gain
- **Whipple's Triad**
- low glucose level (<50 mg/dL)
- symptoms of hypoglycemia
- symptoms resolve with administration of glucose

GASTRINOMA

- **2nd most common**
- Mean age of patients is 50 years
- Slight male predominance (60%)
- **Gastrinomas produce ZES (Zollinger Ellison syndrome) by overproduction of gastrin**
- Over 60% are malignant (*Most common malignant endocrine pancreatic tumour is gastrinoma*)
- Metastases may also involve the lungs or bone
- 90% of gastrinomas are located within **Passaro's triangle- gastrinomas triangle**

PASSARO'S TRIANGLE

1. Junction between the **head and neck of the pancreas**
2. Junction of **cystic duct with CBD**
3. Junction between the **2nd and 3rd parts of the duodenum**



CLINICAL PRESENTATION

- Severe form of peptic ulcer disease
  - refractory to standard treatment
  - atypical location – jejunal ulcers
- upper abdominal pain
- GI bleeding
- weight loss, nausea, vomiting
- GERD
- **Diarrhea relieved by NG suction**

VIPoma

- VIPomas originate from neoplastic D2 cells aka **WDHA or Verner-Morrison syndrome**
- exceedingly rare tumors
- bimodal age distribution
  - most patients are middle aged
  - 10% < 10 years
- usually solitary located in body or tail
- 2/3 are malignant

CLINICAL PRESENTATION

- profuse, watery, iso-osmotic secretory diarrhea
  - may exceed 3 L/day
  - independent of food intake
  - doesn't resolve with NG suction
  - devoid of blood, fat, or inflammatory cells
- weight loss
- crampy abdominal pain
- dehydration
- electrolyte abnormalities
- metabolic acidosis (due loss of large amount of bicarbonate from pancreatic secretion)

- 75% hypochlorhydia or achlorhydria
- 20% flushing
- **WDHA;**
  - **Watery**
  - **Diarrhea**
  - **Hypokalemia**
  - **Achlorhydria**

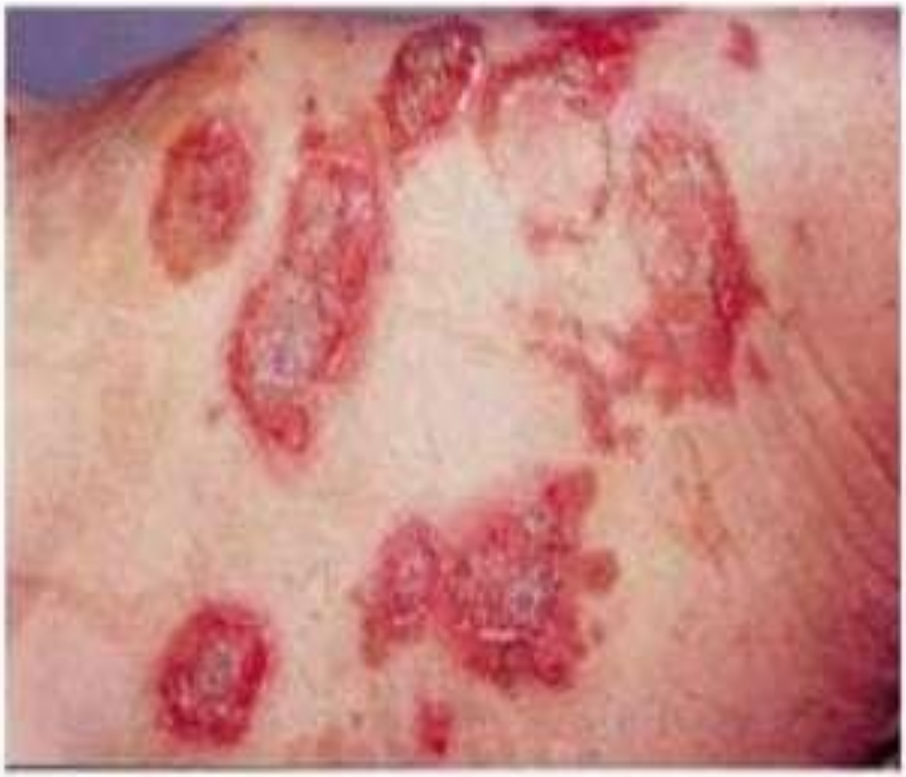
GLUCAGONOMA

- exceedingly rare tumors
- 2-3 times more common in women
- averaging 5-10 cm
- highly vascular
- 65-75% are found in the body or tail
- malignancy occurs in 50-80% of patients
- 5-17% are associated with MEN 1
- **Glucagon is a catabolic hormone, and most patients present with malnutrition.**

CLINICAL PRESENTATION

- weight loss
- hyperglycemia, with 76-94% having diabetes
- normochromic normocytic anemia
- fat-soluble vitamin deficiency
- hypoaminoacidemia
- thromboembolism
- diarrhea
- vulvovaginitis

- **Migratory necrolytic dermatitis**
  - found in 2/3 of patients
  - due to **severe amino acid deficiency**
  - begins as erythematous patches that spread radially
  - bullae develop then slough with bacterial or fungal superinfection
  - healing begins in center, takes 2-3 weeks, leaving hyperpigmented skin



SOMATOSTATINOMA

- Exceedingly rare tumors
- solitary, large tumors > 2 cm
- patients are usually in their 5th or 6th decade of life
- most are in the head of pancreas
- majority are malignant
- may be associated with neurofibromatosis
- **Somatostatin inhibits pancreatic and biliary secretions**

CLINICAL PRESENTATION

- Steatorrhea
- Cholelithiasis
- Diabetes
- Hypochlorhydria
- They present **gallstones** due to bile stasis, **diabetes** due to inhibition of insulin secretion, and **steatorrhea** due to inhibition of pancreatic exocrine secretion and bile secretion

NONFUNCTIONAL TUMORS & PPomas

- **20% of Pancreatic endocrine tumours are nonfunctional**
- PPomas are classified as nonfunctional
- **2/3 are malignant**
- 60-80% of malignant tumors have distant metastases at the time of diagnosis
- Typically larger (4-5 cm)

CLINICAL PRESENTATION

- Abdominal pain
- Jaundice (obstructive)

OTHER PANCREATIC ENDOCRINE TUMORS

- **Tumors which secrete;**
  - gastrin-releasing factor
  - adrenocorticotropic hormone
  - neurotensin
  - calcitonin
  - enteroglucagon
  - CCK
  - gastric inhibitory peptide
  - leutenizing hormone

DIAGNOSIS

- Diagnosis is obtained from, evaluate for ***features of an endocrine syndrome***, biochemical detection of ***circulating hormone***, ***localization*** of tumour by imaging.

ROLE OF IMAGING

- CT Scan
- MRI
- SRS
- PET scan
- EUS
- ANGIOGRAPHY
- INTRAOPERATIVE ULTRASOUND

CT SCAN

- CT is the most common initial imaging study in the evaluation of patients with pNETs. **Triple-phase contrast CT** is the optimal study as pNETs are typically best visualized during the arterial phase. They usually appear as **spherical, hyper-dense, and hyper-vascular mass that rarely obstruct the pancreatic duct.**
- The reported ***sensitivity of CT ranges from 62-83%*** with a **specificity of 83-100%**

MRI

- The sensitivity of MRI ranges from 85-100% with a specificity of 75-100%.
- Not as commonly used as CT, **MRI is most often ordered when lesions are too small to be visualized on CT.**
- **In detecting and following liver metastases, MR has been suggested to be superior to CT**

SRS – somatostatin-receptor scintigraphy

- Many pancreatic endocrine tumours overexpress somatostatin receptor subtype 2.
- SRS is useful if tumours are not evident in CT/MRI. Sensitivity is 80% excluding insulinoma.
- In insulinomas somatostatin receptors are present only at low levels or absent entirely.
- Used for metastatic disease

PET SCAN

- PET imaging with 18F-Fluorodeoxyglucose (FDG) does not visualize pNETs well, given that most tumours are well differentiated with a **low metabolic rate.**

EUS- endoluminal ultrasound scan

- In addition to radiologic examination of the pancreas, EUS offers the additional benefit of obtaining biopsies for diagnosis.
- EUS is most useful in identifying small insulinomas.
- EUS has the added benefit of being able to tattoo smaller lesions for easier intraoperative identification, facilitating laparoscopic resection.

INSULINOMA

- **Laboratory Studies**
  - low glucose l levels (< 50 mg/dL)
  - insulin levels > 7 U/mL
  - insulin/glucose ratio > 0.3
  - **C-peptide to confirm endogenous source of insulin (marker of insulin secretion)**
- **Localization**
  - CT and MRI for larger tumors
  - EUS can detect small tumors (<2 cm in size)
  - angiography showing a "blush"

GASTRINOMA

- **Laboratory findings**
  - fasting serum gastrin level 200-1000 pg/mL
    - H2 blockers should be stopped 1 week prior to testing, and PPI 3 weeks
  - basal acid output > 15 mEq/L
- **Endoscopy**
  - multiple ulcers
  - large gastric rugal folds
  - mucosal edema
  - jejunal hypermotility

- **Localization**
  - CT (not C for small tumors)
  - MRI (liver metastases)
  - SRS with radiolabeled octreotide
  - EUS

VIPoma

- **Laboratory findings**
  - serum levels of VIP > 150pg/mL after an overnight fast
- **Localization**
  - CT or SRS
  - intraoperative U/S will localize most tumors if pre-operative
  - studies are inconclusive

GLUCAGONAMA

- Laboratory findings
  - fasting glucagon level > 50 pmol/L
- Localization
  - CT easily detects them
  - angiography is also successful because of vascularity

SOMATOSTATINOMA

- Laboratory
  - elevated somatostatin levels
- Localization
  - CT
  - Dx of somatostatinomas is rarely made preoperatively

NONFUNCTIONING TUMOUR

- localization with CT or MRI

ROLE OF TUMOUR MARKERS

- A variety of tumor markers have been proposed for functional and non-functional pNETs. The most common of these is **chromogranin A (CgA)**, an acid soluble protein that is found in secretory granules of neuroendocrine cells, **CgA is sensitive** with elevated levels present in 72-100% of patients.
- others, such as **neuron-specific enolase (NSE), pancreatic polypeptide, pancreastatin,** and **human chorionic gonadotropin** have been proposed but less sensitive.
- Note higher CgA correlate with tumour burden

TREATMENT

- The principle of treatment ;
  - **Preoperative optimization-** *dehydration, dyselectrolytemia, acid-base disturbance, hypoglycemia*
  - **Laparotomy or laparoscopic**
    - Access –upper midline, bilateral subcostal, mechanical ring retractor- Bookwalter
    - Inspect for metastasis; liver, lymph node
    - Mobilization of the pancreas
      - Expose through the lesser sac
      - Kocher's maneuver to mobilize the head
      - Mobilization from the tail to completely free the pancreas
      - Examination of the pancreas; inspect, palpate, intraop ultrasound(correlate with preop)
    - Excision of tumour; enucleation, distal pancreatectomy, central pancreatectomy, pancreaticoduodenectomy
    - Drain

- **Gastrinomas;**
  - examination of the gastrinomas triangle
  - Intraoperative endoscopy- transilluminate the duodenum
  - 3 cm duodenectomy, palpate for tumours < 1 cm
  - Total gastrectomy for ZES with gastric carcinoid that may arise from prolonged hypergastrinemia and for patient who cant tolerate PPI

Enucleation

Historically, enucleation has been reserved for;

- Insulinomas
- small, less than 2 cm, non-functional tumours that are distant from the pancreatic duct.(???)
- One of the prime arguments against enucleation lies in difficulty with fully evaluating the regional lymph nodes, particularly if curative resection is the goal. Therefore, enucleation should be limited to patients with **insulinomas** which tend to be on the benign end of the pNET spectrum

- few studies comparing enucleation to formal pancreatic resections.
- there are advantage in operative time, blood loss, post-operative endocrine/exocrine pancreatic function, and hospital/ICU stay in the enucleation group.

Pancreatectomy

- **Central**; Small tumours that lie in the pancreatic neck or body and are close to the pancreatic duct.(better preserves pancreatic function and maintain GI continuity)
- **Distal pancreatectomy**; lesions in body and tail.
- **Pancreaticoduodenectomy**; is the standard of care for pNETs found in the head of the pancreas.
- **Total pancreatectomy** is associated with increase morbidity
- Complete oncologic resections for include distal pancreatectomy with or without splenectomy, and pancreaticoduodenectomy

- **Metastatic disease;**
  - **Insulinoma**; *resection of gross disease, octreotide, systemic chemotherapy(5fu, cisplatin, etoposide)*
  - **Gastrinoma;** PPI, octrotide.
  - Liver metastasis- chemoembolization, radiofrequency ablation

Cytoreductive surgery

- consensus guidelines agree that aggressive resection of the primary tumor, regional lymph nodes, and liver/distant metastases should be pursued if greater than 90% of the tumor burden can be resected.
- most pNETs have a relatively indolent course compared to other pancreatic neoplasms, and that tumor debulking, while not curative, provides the theoretical advantages of symptom control in functional tumors. Prolong survival have been shown.

- A retrospective review of 170 NETs who underwent palliative debulking found that 96% of those with symptoms had resolution post-operatively, and reported a 5- and 10-year survival rate 61% and 35%.
- This is a great improvement over a 5-year survival rate of 30-40% for patients with untreated liver metastases

Targeted therapy

- **Everolimus,** an oral mTOR signaling inhibitor, has shown some effect in treating pNETs.
- **Sunitinib;** Sunitinib is an oral tyrosine kinase inhibitor that is known to target VEGF receptors. Under investigation.

PROGNOSIS

- With treatment;
  - normal life expectancy for benign insulinoma
  - 5 years for malignant insulinomas
  - In gastrinomas, 5-yr survival 90% for patients without metastasis, 5-yr survival < 50% for patients with bulky metastasis
  - VIPoma; only 1/3 are cured after resection
  - Glucagonoma; - 5-yr survival 85% if no metastases present, 5-yr survival 60% if metastases present
  - Somastatinoma; cure rarely achieved
  - Nonfunctional tumours; 5-yr survival approximately 50%
- MEN 1 associated pNET has a poor prognostic factor; reduces life expectancy by about 10 years.

CONCLUSION

- The management of pancreatic endocrine tumors requires a thorough understanding of the ***biological behavior*** of these tumors and the essential role of surgical intervention in providing both potential cure and symptom relief.
- Challenges remain in the localization of these tumors although modern imaging technology identifies the tumor in most cases preoperatively.
- Patients with MEN1-associated neuroendocrine tumors often have more aggressive and multifocal tumors, thus mandating a different surgical approach and preoperative evaluation.
- Resection of tumor burden, including recurrences, remains the most effective method to control the debilitating symptoms caused by hormone overproduction.

REFERENCES

- McKenna, L. R., & Edil, B. H.Update on pancreatic neuroendocrine tumors. Gland Surgery.2014: 3(4) 258–275.
- Vortmeyer AO, Huang S, Lubensky I, et al. Non islet origin of pancreatic islet cell tumors. J Clin Endocrinol Metab 2004;89:1934-8.
- Grant CS. Insulinoma. Best Pract Res Clin Gastroenterol.2005;19:783-98.
- Sarmiento JM, Heywood G, Rubin J, et al. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg 2003;197:29-37.

- Taylor S, Mark E. Endocrine tumours of the pancreas. Maingot's abdominal operation. 12th edition.1211-1225
- William E. Fisher, et al. Pancreas. Schwartz's Principles of Surgery. 10th edition.1390-1393
- James C.et al. Endocrine pancreas. Sabiston Textbook of Surgery, 18th ed.
- SRB. Manual of surgery. 4th edition