

Pancreatic Neuroendocrine Tumor (PNET)

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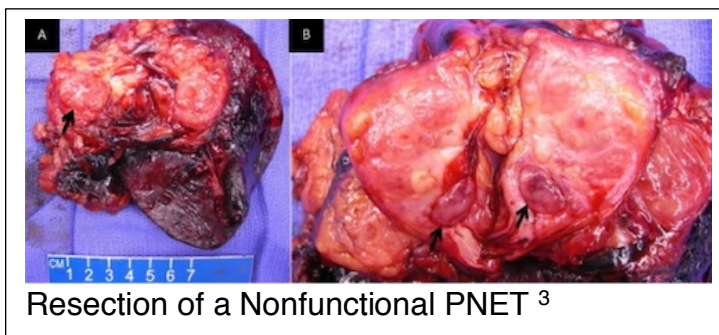
Definitions and Tumors

Definitions

- *Pancreatic Neuroendocrine Neoplasia (PNET)* – Any Neuroendocrine Neoplasia of the Pancreas
 - Previously Known as “Islet Cell Tumors”
- *Pancreatic Neuroendocrine Tumor (PNET)* – Well-Differentiated PNET
- *Pancreatic Neuroendocrine Carcinoma (PNEC)* – Poorly-Differentiated PNET with High-Proliferative Rate

Non-Functional PNET (NF-PNET) ^{1,2}

- The Majority of PNETs are Nonfunctional (60-90%)
- Can Secrete Substances but Do Not Present with Hormonal Syndromes
 - Ex: Chromogranin, Pancreatic Polypeptide, Ghrelin, etc.
- Generally Present Later with a More Indolent and Protracted Course
- Symptoms are Generally Related to Mass Effect:
 - Abdominal Pain
 - Weight Loss
 - Anorexia
 - Nausea and Vomiting
 - Obstructive Jaundice



Functional PNET (F-PNET)

- *Insulinoma* – *See Insulinoma
- *Gastrinoma* – *See Gastrinoma and Zollinger-Ellison Syndrome
- *Glucagonoma* – *See Glucagonoma and Glucagonoma Syndrome
- *VIPoma* – *See Vasoactive Intestinal Peptide-Secreting Tumor (VIPoma)
- *Somatostatinoma* – *See Somatostatinoma
- Other Less Common Functional PNETs:
 - *ACTH-Secreting Tumors* (Cushing Syndrome)
 - *Serotonin-Secreting Pancreatic Neuroendocrine Tumor* (Carcinoid Syndrome)
 - *PTHrp-oma* (Mimics Hyperparathyroidism with Hypercalcemia)

Functional PNET Comparisons

PNET	Percentage of All Functional PNETs ⁴	General Presentation
<i>Insulinoma</i>	35-40% (Most Common)	<u>Whipple's Triad</u> Fasting Hypoglycemia Symptoms of Hypoglycemia Symptomatic Relief with Glucose
<i>Gastrinoma</i>	16-30%	Peptic Ulcer Disease
<i>Glucagonoma</i>	< 10%	<u>4-D Syndrome</u> Diabetes/Glucose Intolerance Dermatoses (NME) DVT Depression
<i>VIPoma</i>	< 10%	<u>WDHA Syndrome</u> Watery Diarrhea Hypokalemia Achlorhydria
<i>Somatostatinoma</i>	< 5%	Diabetes/Glucose Intolerance Cholelithiasis Diarrhea/Steatorrhea

Size and Malignancy

- Most are Large (> 3 cm) and Malignant (60-90%) ⁵⁻⁸
 - 75% Present as Advanced Disease
- Conversely, Insulinomas are Generally Small (< 3 cm) and Benign (93%) ^{9,10}

Association with Multiple Endocrine Neoplasia Type 1 (MEN-1)

- **Most are Sporadic**
- *Insulinoma*: 6% ¹¹
- *Gastrinoma*: 20-30% – The Most Common PNET Associated with MEN-1 ¹²
- *Glucagonoma*: 3-10% ^{6,13,14}
- *VIPoma*: 5% ¹⁵
- *Somatostatinoma*: 35-45% ¹⁶
 - Although MEN-1 is Common in Somatostatinoma, Somatostatinoma is Overall One of the Least Common PNETS in MEN-1 (< 1%) ¹⁶

Most Common Location in the Pancreas MN

- *Insulinoma*: Even Distribution Throughout the Pancreas ¹⁷
- *Gastrinoma*: Head ¹⁸
- *Glucagonoma*: Body and Tail ¹⁹
- *VIPoma*: Body and Tail ²⁰
- *Somatostatinoma*: Head ⁸

Staging

TNM Staging (AJCC 8) ²¹

	T	N	M
1	Limited to the Pancreas (< 2 cm)	Any Regional Lymph Node Involvement	M1a – Liver M1b – Extrahepatic M1c – Both Liver and Extrahepatic
2	Limited to the Pancreas (2-4 cm)		
3	Limited to the Pancreas (> 4 cm) or Invades the Duodenum/CBD		
4	Invades Adjacent Organs or Large Vessels		

- For T Stage – Multiple Tumors are Designated as T(#) (Example: T3(4))
 - If Number of Tumors is Too Numerous or Unavailable – T(m)
- *Note: This System Does Not Apply to High-Grade, Poorly Differentiated Neuroendocrine Carcinoma (PNEC) – These are Staged as an Exocrine Pancreatic Cancer

TNM Stage ²¹

Stage	T	N	M
I	T1	N0	M0
II	T2-3	N0	M0
III	T4	N0	M0
	Any T	N1	M0
IV	Any T	Any N	M1

WHO 2010 Grading ²²

Grade	Differentiation	Ki-67 Index	Mitotic Count (/10 HPF)
G1 (Low)	Well	≤ 2%	< 2
G2 (Intermediate)	Well	3-20%	2-20
G3 (High)	Poorly	> 20%	> 20

Diagnosis

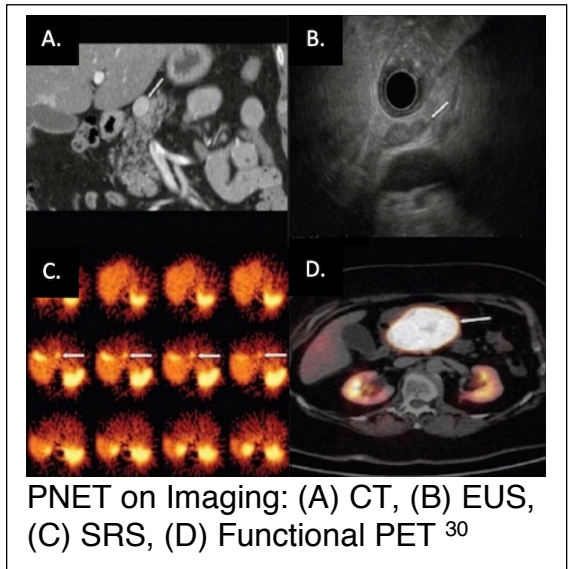
Diagnosis

- *Insulinoma*: High Insulin Levels During an Episode of Hypoglycemia ²³
 - ***See Insulinoma**
- *Gastrinoma*: High Fasting Serum Gastrin (FSG) and Measurement of Gastric pH ²⁴
 - Secretin Stimulation Test if Initial Findings are Not Diagnostic
 - ***See Gastrinoma and Zollinger-Ellison Syndrome**
- *Glucagonoma*: High Fasting Glucagon ²⁵
 - ***See Glucagonoma and Glucagonoma Syndrome**
- *VIPoma*: High Plasma VIP ²⁶
 - ***See Vasoactive Intestinal Peptide-Secreting Tumor (VIPoma)**
- *Somatostatinoma*: High Fasting Plasma Somatostatin ²⁷
 - May Be Made by Biopsy/Histology if Classic Presentation is Absent
 - ***See Somatostatinoma**

Localization

- Initial Imaging: Noninvasive (CT or MRI)
- Somatostatin Receptor Imaging
 - Consider if Initial Imaging Fails to Localize
 - Options:
 - *Somatostatin (Octreotide) Receptor Scintigraphy (SRS)* – Classic Test Used
 - *Functional PET Scan (Ga-68 DOTATATE)* – Becoming More Prevalent with Higher Sensitivity

- Insulinomas Demonstrate Relatively Low Somatostatin Receptor Expression (May Be More Difficult to Detect than Other PNETs) ^{28,29}
- If Noninvasive Imaging Fails: Invasive Imaging
 - *Endoscopic Ultrasound (EUS)* – Generally Preferred Next Step
 - *Selective Arterial Stimulation with Hepatic Venous Sampling*
 - Use: Insulinoma (Calcium Stimulation) or Gastrinoma (Secretin Stimulation)
 - *Selective Visceral Angiography*
- For Gastrinoma, Consider **Surgical Exploration** with Palpation or Intraoperative Ultrasound if High Suspicion but All Imaging Negative



Treatment

Surgical Resection (Treatment of Choice)

- Small (< 2-3 cm): **Enucleation**
 - *Enucleation is Controversial for the More Malignant PNETs (VIPoma, Somatostatinoma, or Glucagonoma)
- Large (> 2-3 cm): **Surgical Resection**

See Individual Pages for Specifics on Management

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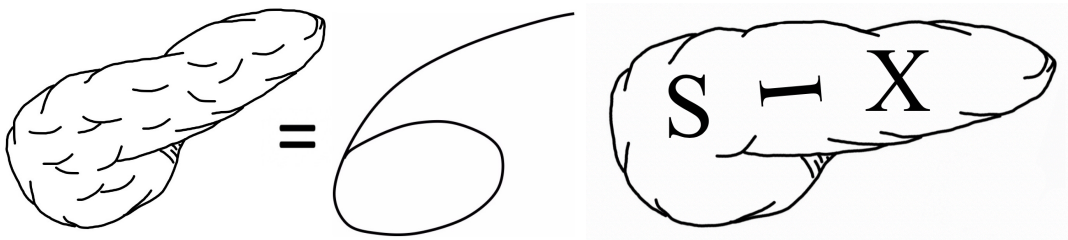
Pancreatic Neuroendocrine Carcinoma (PNEC)

- Poor Prognosis with Rapid Disease Progression
- Resectable Disease: Surgical Resection with Adjuvant Chemotherapy
- Unresectable Disease: Palliative Chemotherapy

Mnemonics

Most Common Site of PNET's ³¹

- “6: The Number of the Pancreas”
 - Pancreas Looks Like a #6
 - *Used in Other Mnemonics: Pseudocyst and Chronic Pancreatitis
- “SIX” Written on Pancreas:
 - “S” in Head: gaStrin and SomatoStatin
 - “I” Anywhere: Insulin
 - “X” in Body/Tail: Glucagon and VIP



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