Rising Incidence of Neuroendocrine Tumors

Dasari V, Yao J, et al. JAMA Oncology 2017
Overview
Pancreatic Neuroendocrine Tumors

- Tumors which arise from endocrine cells of the pancreas
- 5.6 cases per million
  - 3% of pancreatic tumors
- Median age at diagnosis 60 years
- More indolent course compared to adenocarcinoma
  - 10-year overall survival 40%
- Usually sporadic but can be associated with hereditary syndromes
  - Core genetic pathways altered in sporadic cases
    - DNA damage repair (*MUTYH*)
    - Chromatin remodeling (*MEN1*)
    - Telomere maintenance (*MEN1, DAXX, ATRX*)
    - mTOR signaling
  - Hereditary: 17% of patients with germline mutation

# Pathology Classification

<table>
<thead>
<tr>
<th>World Health Organization (WHO)</th>
<th>European Neuroendocrine Tumor Society (ENETS)</th>
<th>American Joint Committee on Cancer (AJCC)</th>
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<tbody>
<tr>
<td><strong>Grade</strong></td>
<td><strong>Ki-67</strong></td>
<td><strong>TNM</strong></td>
</tr>
<tr>
<td><strong>Low</strong></td>
<td>$\leq 2%$</td>
<td>T1: limit to pancreas, $\leq 2\text{ cm}$ T2: limit to pancreas, 2-4 cm T3: limit to pancreas, $&gt;4\text{ cm}$, invades duodenum, bile duct T4: beyond pancreas, invasion adjacent organs or vessels</td>
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<tr>
<td><strong>Intermed</strong></td>
<td>3-20%</td>
<td>No: node negative N1: node positive</td>
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<tr>
<td><strong>High</strong></td>
<td>$&gt;20%$</td>
<td>M0: no metastases M1: metastases</td>
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<td>$&gt;2$</td>
<td>T1: limit to pancreas, $\leq 2\text{ cm}$ T2: $&gt;\text{limit to pancreas, 2 cm}$ T3: beyond pancreas, no celiac or SMA involvement T4: involves celiac or SMA</td>
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<td></td>
<td>2-20</td>
<td>No: node negative N1: node positive</td>
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<tr>
<td></td>
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<td>M0: no metastases M1: metastases</td>
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Classification Based on Functionality

• **Nonfunctioning tumors**
  – No clinical symptoms (can still produce hormone)
  – Accounts for 40% of tumors
  – 60-85% present with liver metastases

• **Functioning tumors**
  – Dominant hormone hypersecretion leads to clinical manifestation
  – Tumor types:
    • Insulinoma
    • Glucagonoma
    • Somatostatinoma
    • Gastrinoma
    • VIPoma
    • Others
Workup and Treatment of Nonfunctioning Neuroendocrine Tumors
Diagnostic Workup
Nonfunctioning Tumor

• Multiphasic contrast-enhanced CT abdomen/pelvis (thin cuts)
  – Hypervascular lesion
• EUS-guided FNA
• +/- Somatostatin receptor scintigraphy
• +/- MRI (suspected liver metastases)
• Serum biomarkers
  – Chromagranin A (CGA)
  – Consider: Urine 5-HIAA, pancreatic polypeptide (PP)
Fundamental Principles of Surgery

• Goals of surgery
  – Maximize local control
  – Increase quality of life
  – Prolong survival
  – Ro resection (negative margins)

• Minimize
  – Short term morbidity: surgery
  – Long term morbidity: insulin dependence, GI dysfunction
Specific Surgical Scenarios

- **Localized, nonmetastatic:** resect if complete resection feasible
  - Median survival 7.1 years
  - ~50% of patients recurrence-free at 2.7 years

- **Incidental finding of tumor <2 cm (malignant potential may exist)**
  - Carefully consider observation (serial imaging)
  - Resect for rapid changes

- **Locally advanced, nonmetastatic, unresectable**
  - Consider operative bypass (biliary obstruction, gastric outlet obstruction, bleeding)
  - Median survival: 5 years

- **Limited metastases**
  - Consider staged approach

Kuo E, Salem R. Ann Surg Onc 2013
Surgical Armamentarium

- Pancreatectomy
  - Pancreaticoduodenectomy
  - Distal pancreatectomy
  - Enucleation

- Lymphadenectomy

- Limited liver metastasis
  - Staged approach
  - Synchronous: selectively consider resection in same setting as pancreatectomy

- Palliative operations
  - Biliary bypass
  - Gastric bypass
Pancreatic Tail Neuroendocrine Tumor
Laparoscopic Distal Pancreatectomy and Splenectomy

- 72 year old female presents with 3.3 cm incidental pancreatic mass
- EUS-FNA: neuroendocrine tumor
- No metastases on staging workup
Workup and Treatment of Functioning Neuroendocrine Tumors
General Principles For Functioning Pancreatic Neuroendocrine Tumors

• Biochemical workup for clinical symptoms
• Biochemical diagnosis should precede localization study
• Goals of surgery
  – Alleviate clinical symptoms
    • Remove primary hormone secreting primary tumor and lymph nodes
  – Prolong survival
Insulinoma

- Most common functioning PNET
- Sporadic or part of MEN1
- Rarely malignant
- Clinical presentation
  - Whipple’s triad
- Biochemical workup
  - Serum glucose, C-peptide, proinsulin, insulin, sulfonylurea
- Imaging
  - CT, EUS
  - Selective arteriography (calcium stimulation, hepatic v sampling)
  - Even distribution throughout pancreas
Insulinoma
Surgical Options

• Types of operations
  – Enucleation often feasible
    • Roux-en-Y pancreaticojejunostomy for large defects at risk for pancreatic leak
  – Distal pancreatectomy
  – Pancreaticoduodenectomy
• No blind resections
Insulinoma

- 80 year old male with hypoglycemic episodes
- Biochemical workup consistent with insulinoma
- Localization studies: CT

- Pancreaticoduodenectomy with extended lymphadenectomy
- Immediate resolution of hypoglycemia
- >1.5 years postop symptom free
**Gastrinoma (Zollinger-Ellison Syndrome)**

- 2\textsuperscript{nd} most common functioning PNET
- Sporadic and inherited variants (20\% with MEN1)
- **Clinical presentation**
  - Long history ulcers, abdominal pain, diarrhea, GERD, prolong acid-suppressive medication, PUD surgery
- **Biochemical workup**
  - Serum gastrin >1000 pg/mL, or >200 pg/dL with secretin stimulation test
  - Gastric pH ≤2
  - MEN1 workup (PHPT)
- **Imaging and localization**
  - EUS, CT, octreotide scan, operating room
  - Small tumor usually duodenum, pancreatic head or uncinate process (gastrinoma triangle)
Gastrinoma
Surgical Options

- Sporadic tumors should be resected
- Surgery
  - Intraoperative ultrasound, palpation, duodenotomy
  - Resection of primary tumor
    - Enucleation
    - Pancreaticoduodenectomy
    - Duodenotomy and wedge resection
  - Lymphadenectomy
- Consider hepatectomy selectively if all tumor can be removed
- MEN1: Resection if >2 cm tumor
Management Rare Functioning PNET

• Glucagonoma
  – Pancreatic tail
  – Malignant, frequently metastases at presentation
  – Diabetes, dermatitis (necrolytic migratory erythema), diarrhea, DVT
  – Fasting glucagon >50
  – Resect if locoregional disease

• Vasactive Intestinal Polypeptide-Secreting Tumor (VIPoma)
  – Body/tail
  – Watery diarrhea, hypokalemia, achlorydria

• Somatostatinoma
  – Pancreatic head, duodenum
  – Diabetes, diarrhea, gallstones

• Adrenocorticotropic-Secreting
  – Cushing syndrome
Neuroendocrine Tumors Associated with Hereditary Syndromes
Hereditary Syndromes
Overview

- Genetics counseling and cancer screening necessary
- Multiple endocrine neoplasia type 1 (MEN-1)
  - 50% will have gastrinomas
  - <5% of insulinomas
  - Surgery
    - Resect for tumors >2 cm, or tumors increasing on serial imaging
    - Pancreas preservation if technically feasible (enucleation)
- Von Hippel-Lindau (VHL)
  - 10-17% of patients will develop non-functioning PNET
- Neurofibromatosis type 1 (von Recklinghausen’s syndrome)
  - <10% of patients will develop PNET (somatostatinoma of duodenum)
- Tuberous sclerosis complex (TSC)
  - <1% of patients develop PNET
Survival and Surveillance
Overall Survival

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Surveillance After Resection

• Up to 42% of patients will recur
  – Lymph node ratio, Ki-67 index
  – All recurrences happen within 10 years

• Strong, evidence-based consensus guidelines do not exist
  – History and physical every 6-12 months
  – Biochemical markers every 6-12 months
  – Consider cross-sectional imaging (no routine octreotide scan)

Summary
Pancreatic Neuroendocrine Tumors

- Rising incidence
- Survival generally longer than adenocarcinoma
- Surgical management largely dictated by functional status
- Functional tumors: separate biochemical and localization workup
- Surgical resection
  - Nonfunctioning tumors: prolongs progression-free survival
  - Functioning tumors: alleviates hormone drive clinical symptoms