Objectives

• **Define** Pancreatic Neuroendocrine Tumor (**PNET**)
  – What are PNETs? Are they cancers?
  – How common are PNETs?

• **Identify** PNETs that require treatment
  – When do PNETs require surgery?
  – What surgical options exist for PNETs?

• **Learn** how Yale Cancer Center is improving care for patients with PNETs
A Confusing Tumor!

- The pancreas has dual functions
  - Acts as a digestive organ and a gland secreting hormones

- PNETs are different than pancreatic adenocarcinoma ("pancreas cancer")

- PNETs are part of a broad family of tumors
  - Pancreatic carcinoid, islet cell tumors → old terms

Endocrine - PNET
Epidemiology

- PNETs by the numbers…
  - ~1 case per 100,000 individuals annually
  - ~3% of primary pancreas tumors
  - ~15% of pancreas tumors that undergo surgery
  - 15-17% associated with genetic syndromes
    - MEN1, VHL, NF1, tuberous sclerosis
  - Median age of diagnosis: 60 years

Classifying by Hormone

- **Functional** PNETs – secrete pancreatic hormones
  - Dominant hormone causes symptoms
    - Historically, most cases diagnosed in this manner

- **Non-functional** PNETs – no hormonal symptoms
  - Currently, 50-85% of cases are non-functional
    - Half are asymptomatic and diagnosis is *incidental*

- Symptoms can include abdominal pain, weight loss, nausea, or jaundice

Staging

- **Staging** classifies tumors for treatment planning
  - Characterize the tumor and check for metastases

- **Modalities for staging:**
  - Multiphasic contrast-enhanced CT of the abdomen
    - PNETs are hypervascular → contrast strongly enhances
  - Additional imaging may include nuclear scintigraphy, an MRI, or an endoscopic ultrasound
  - Blood tests for chromogranin A and other hormones; further workup may be needed for functional tumors
Staging

Pancreas
Treatment is Stage-Specific

- **Metastases present? ("Stage 4")**
  - Multidisciplinary approach is key; treatment options exist
  - Surgery may be appropriate in select cases

- **For localized PNET, surgery is the primary modality**
  - **All** functional PNETs (hormone-secreting)
  - **All** symptomatic non-functional PNETs

- **Special cases:**
  - Locally advanced ("unresectable") tumors
  - PNETs associated with genetic syndromes
Incidental PNET?

• For localized disease, staging and biopsy can help predict tumor behavior:

Well-differentiated
Low grade/Ki-67
No enlarged lymph nodes
Smaller tumor size

Lower stage

Poorly-differentiated
High grade/Ki-67
Enlarged lymph nodes
Larger tumor size

Higher stage

• All PNETs have the potential to grow & spread
• Likelihood of spread is very low in subsets of PNETs
Incidental PNET?

• Are some PNETs safe to observe?

• Who are candidates for observation?

At autopsy, 10% have occult PNETs at the time of death from other causes - Average size < 0.5 cm

Well-differentiated pathology

Patients with genetic syndromes can be observed for decades

Small tumor (< 1-2 cm)

Early PNETs have a 10-yr survival rate of 93%

Non-functioning/asymptomatic

No evidence of lymph nodes

Amenable to follow-up and serial radiologic scans

Scarpa A, ..., Falconi M. Mod Path. 2010;23:824.
# Data for Observation

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Tumor Size</th>
<th>Key Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo, 2010</td>
<td>&lt; 4cm</td>
<td>Overall survival with observation same as resection at 11 years (single hospital)</td>
</tr>
<tr>
<td>Duke, 2014</td>
<td>&lt; 2cm</td>
<td>Survival <em>&gt;50% worse</em> in patients observed rather than resected (database study)</td>
</tr>
<tr>
<td>Yale, 2013</td>
<td>&lt; 1cm</td>
<td>Survival at 10 years 95%, although 16% did have lymph node spread (database study)</td>
</tr>
<tr>
<td>MSK, 2016</td>
<td>&lt; 3cm</td>
<td>Overall survival same at 4 years, <em>~25%</em> of observed patients will convert to resection</td>
</tr>
</tbody>
</table>

Lee LC, ... Huebner M. Surgery. Dec 2012.
Summary – Part 1

• PNETs are distinct from pancreatic adenocarcinoma

• They can cause symptoms (from hormones or local effects) or be diagnosed incidentally

• Surgery is recommended if localized and resectable and:
  – Tumor is functional or causing symptoms
  – Incidental tumors >1-2cm or with worrisome features during staging
  – In selected cases of metastatic disease

• Observation possible for highly-selected patients
  – Requires close surveillance/compliance
Goals of Surgery

• Oncologic goals:
  – Maximize local control
    • Ro resection – negative margins
    • Regional lymphadenectomy
  – Prolong survival
  – Improve quality of life (if metastatic or advanced)

• Minimize morbidity:
  – Short-term ⇒ pancreatic leak, infection
  – Long-term ⇒ diabetes, exocrine insufficiency
Considerations for Surgery

• Selecting a surgical approach?
  – Tumor location is paramount
  – Need for lymphadenectomy
  – Patient tolerance for procedure scope

• Three main procedures:
  – Enucleation
  – Distal pancreatectomy
  – Pancreaticoduodenectomy (Whipple)
Enucleation

- Limited removal of PNET
- Spares normal pancreas
- Lowest complication rate
- Tumor must be away from duct, located in body/tail
- Most frequently performed for *insulinoma*

Distal Pancreatectomy

- Tumor location in body or tail of pancreas

- Multiple approaches:
  - Open (traditional)
  - Laparoscopic
  - Robot-assisted

- Splenectomy?
  - Case-by-case decision
  - If removed, vaccinations provide excellent coverage

Distal Pancreatectomy/Splenectomy
Pancreaticoduodenectomy

- Tumor location in head of pancreas

- Removes the following:
  - Bile duct
  - Duodenum (first part of small intestine)
  - Gallbladder
  - Small part of stomach (sometimes)

- Remaining pancreas, bile duct, and stomach are re-connected

- Able to eat just as before surgery
Modern Era Pancreaticoduodenectomy

- High-volume hospitals and surgeons
  - 2006-2016, n=403

- Operative Mortality
  - 1970’s - 15-20%
  - 2000’s - <3%
  - YNHH, 1.9%

- Length of Stay
  - 1970’s – 25-35d
  - 2000’s – 8-11d
  - YNHH, 7.7d

- Morbidity?
  - Serious ~15-30%

- Nasogastric Tube
- Gastrostomy/Jejunostomy
- Operative Drain(s)

YNHH, 1.9%
Can Drains Be Omitted?

- **Highly selective drainage**
  - Drains placed for concern for anastomotic fidelity or in obvious contaminated field
  - Series of 237 patients analyzed with 3 deaths (1.3%)
  - Operative drains in 7 patients (3%)

<table>
<thead>
<tr>
<th></th>
<th>Length of stay, median days (IQR)</th>
<th>6 (5 – 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tolerance of diet, median days (IQR)</td>
<td>4 (3 – 5)</td>
<td></td>
</tr>
<tr>
<td>Need for readmission</td>
<td>54 (22.8%)</td>
<td></td>
</tr>
<tr>
<td>Need for reoperation</td>
<td>14 (5.9%)</td>
<td></td>
</tr>
<tr>
<td>Postoperative drainage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous</td>
<td>29 (12.2%)</td>
<td></td>
</tr>
<tr>
<td>Operative</td>
<td>12 (5.1%)</td>
<td></td>
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</tbody>
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<table>
<thead>
<tr>
<th>Morbidity</th>
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<tbody>
<tr>
<td>Pancreatic fistula</td>
<td>19 (8.0%)</td>
</tr>
<tr>
<td>Biliary-/enteric anastomotic leak</td>
<td>5 (2.1%)</td>
</tr>
<tr>
<td>Intraabdominal abscess</td>
<td>11 (4.6%)</td>
</tr>
<tr>
<td>Need for post-operative transfusion</td>
<td>22 (9.3%)</td>
</tr>
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- **Conclusion:** In properly selected patients, operative drains can be avoided safely.

Can NGT Be Omitted?

**Hypothesis:**
The majority of patients undergoing a Whipple procedure can forgo routine NG tube placement.

<table>
<thead>
<tr>
<th></th>
<th>Routine NGT</th>
<th>Selective NGT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Re-insertion/insertion of NGT</strong></td>
<td>15 (12.0%)</td>
<td>10 (8.0%)</td>
<td>0.292</td>
</tr>
<tr>
<td><strong>Time to Diet Tolerance, days</strong></td>
<td>Mean (SEM)</td>
<td>9.15 (1.60)</td>
<td>4.9 (0.40)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>3 – 163</td>
<td>3 – 33</td>
</tr>
<tr>
<td><strong>Length of Stay, days</strong></td>
<td>Mean (SEM)</td>
<td>10.47 (1.01)</td>
<td>6.82 (0.36)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>5 – 86</td>
<td>4 – 35</td>
</tr>
</tbody>
</table>

**Conclusion:** As in other forms of abdominal surgery, selective NGT placement appears an acceptable treatment strategy, with no increase in NGT replacement, LOS, dietary tolerance, or operative morbidity.

Special Cases for Surgery

- **Metastatic disease?**
  - Small volume can be targeted for resection
  - Large volume in symptomatic patients may benefit from debulking

- **Palliation?**
  - Biliary bypass for jaundice
  - Gastroenteric bypass for obstruction
  - Cholecystectomy for patients receiving somatostatin therapy
Summary – Part 2

• The goals of surgery are to control the disease and increase quality of life with minimal morbidity

• PNETs are usually removed via three operations: pancreaticoduodenectomy (Whipple), distal pancreatectomy, or enucleation

• Choice of operation is largely dictated by location of the tumor

• Pancreatic surgery is now routinely done with excellent outcomes at high-volume centers