Surgical Management of Pancreatic Neuroendocrine Tumors

Michael A. Choti, MD, MBA, FACS
Department of Surgery
Johns Hopkins University School of Medicine, Baltimore, MD
Pancreatic Endocrine Tumors (Islet Cell)

- Accounts for about 1% of pancreatic malignancies
- Approximately 50% are non-functional
- Of the functional tumors, 95% are insulinomas or gastrinomas
- Majority are malignant (except insulinoma)
Surgical Management of Pancreatic Neuroendocrine Tumors

1. Approaches to the primary tumor
2. Surgical management of the non-functional PNET
3. Management of functional tumors
4. Surgical therapy for MEN1
Surgical Approaches to Tumors in the Pancreas

- Pancreaticoduodenectomy (Whipple)
- Distal pancreatectomy (+/- splenectomy)
- Total pancreatectomy
- Tumor enucleation
- Central pancreatectomy
- Laparoscopic resection
Pancreaticoduodenectomy (Whipple)
Distal Pancreatectomy

www.bcm.edu/pancreascenter/index.cfm?pmid=9291
Indications for Enucleation of PNET

- The lesion is thought to be a benign or low-grade neoplasm at preoperative evaluation.
- The lesion must be at least 2–3 mm far from the main pancreatic duct.

Laparoscopic Pancreatic Tumor Resection
Hopkins Experience

• 5,250 Pancreatectomies since 1984
• 505 of these were for PNET (9.6%)
• 43% had nodal involvement.
• Type of operation
  – Central – 11 (2.6%)
  – Distal – 184 (44%)
  – Enucleation – 19 (4.6%)
  – Total - 13 (3%)
  – Whipple – 174 (42%)
Long-term Survival of Patients Who Underwent PD for Pancreatic Cancer, by Histologic Type

Ductal adenocarcinoma, n=1175

Neuroendocrine carcinoma, n=98

IPMN with invasive cancer, n=90
Management of the Non-Functional PNET
Pancreatic duct
## Characteristics of Functional Endocrine Tumors of the Pancreas

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Major Clinical Symptom</th>
<th>Predominant Hormone</th>
<th>Percent Malignant</th>
<th>Other Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>Recurrent peptic ulcer</td>
<td>Gastrin</td>
<td>90</td>
<td>Diarrhea/steatorrhea</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>Hypoglycemia (fasting or nocturnal)</td>
<td>Insulin</td>
<td>10</td>
<td>Catecholamine excess</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>Diabetes mellitus, Migratory necrolytic erythema</td>
<td>Glucagon</td>
<td>90</td>
<td>Panhypoaminoaciduria, Thromboembolism, Weight loss</td>
</tr>
<tr>
<td>VIPoma</td>
<td>Watery diarrhea, hypokalemia, achlorhydria (WDHA syndrome)</td>
<td>Vasoactive intestinal polypeptide (VIP)</td>
<td>50</td>
<td>Metabolic acidosis, Hyperglycemia, Hypercalcemia, flushing</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>Diabetes mellitus, Diarrhea/steatorrhea</td>
<td>Somatostatin</td>
<td>80</td>
<td>Hypochlorhydria, Weight loss, Gall bladder disease</td>
</tr>
<tr>
<td>PPoma</td>
<td>Hepatomegaly, Abdominal pain</td>
<td>Pancreatic polypeptide (PP)</td>
<td>80</td>
<td>Occasional watery diarrhea</td>
</tr>
</tbody>
</table>
Operative Management of Sporadic Gastrinomas

Surgical resection results in long-term DFS in 26-100%

Pancreatic Gastrinoma
• Most are solitary and identifiable at laparotomy
• Enucleation with selective lymphadenectomy vs formal resection (pancreaticoduodenectomy, PD)

Duodenal Gastrinoma
• 50% of sporadic tumors are found in duodenum
• Most are submucosal in proximal duodenum
• Duodenotomy with palpation and enucleation for small tumors
• Consider PD for larger or invasive tumors

Norton et al. NEJM (1999)
Gastrinoma (usually duodenal or head of pancreas) →

- Gastrin levels (basal, stimulated as indicated)
- CT/MRI
- As appropriate:
  - Chromogranin A
  - Octreoscan

Recommended:

- Manage gastric hypersecretion with proton pump inhibitors or histamine H2 antagonists
- Trivalent vaccine

Occult
- No primary tumor or metastases on imaging

- Exophytic or peripheral tumors by imaging and surgical removal feasible
- Head
- For deeper or invasive tumors and those in proximity to the main pancreatic duct
- Distal

- Observe (category 2B) or
- Enucleation of tumor(s) and duodenotomy + periduodenal node resection

- Enucleation with duodenotomy + consider periduodenal node dissection
- Pancreateico-duodenectomy + periduodenal lymph node dissection
- Distal pancreatectomy or enucleation (spleen preserving)
Operative Management of Insulinomas

• Most are solitary (90%) and small (90% <2cm)
• 10% malignant

Surgical resection is treatment of choice
• 88% 10-year DFS after resection
• Enucleation is indicted for small tumors at least 2-3mm from main pancreatic duct.
• Intraoperative ultrasonography (15MHz) can be useful for localization
• Ideally suited for laparoscopic approach.
• Consider preoperative tattoo.
Operative Management of Pancreatic Neuroendocrine Tumors in MEN-1

- High incidence of multifocality prompts more controversy regarding surgical management.
- Exploration should be considered in those with biochemically confirmed (e.g. MEN1-gastrinoma), particularly when tumor is visualized.
- Many recommend more aggressive approach (e.g. PD) than sporadic PNET.
- Most will develop new tumors in pancreatic remnant.
- The role of total pancreatectomy is controversial.

Management of Metastatic NET Disease

- Widespread metastasis
  - Surgical debulking indicated, in many series, provides symptomatic relief
  - Hepatic resection
    - Wedge resection or hepatic lobectomy
  - Hepatic artery ligation or percutaneous embolization
  - Reports of tumor regression with hepatic artery occlusion combined with chemo
    - Multimodal therapy needs further evaluated
Carcinoid Tumors

**MANAGEMENT OF RECURRENT OR UNRESECTED DISEASES**

- **Resectable (liver only)**
  - **Asymptomatic**
    - **Resectable**
    - **Observe with markers and scans every 3-6 mo**
    - **Octreotide**
    - **Clinical trial**
  - **If clinically significant progression, see below**

- **Unresectable**
  - **Observe with markers and scans every 3-6 mo**
  - **Octreotide**
  - **Clinical trial**
  - **Consider prophylactic cholecystectomy**

**Distant metastases**
- Imaging: CT/MRI
- Resect primary tumor if locally symptomatic primary or if complete resection can be achieved

- **Clinically significant tumor burden**
  - **Significant progression or Local effects**
  - **Octreotide**
  - **Echocardiogram**

- **Liver**
  - **Resectable**
  - **Wedge resection or radiofrequency ablation or partial hepatectomy**
  - **Consider prophylactic cholecystectomy**

- **Bone**
  - **Regional/mesenteric lymph nodes**
  - **CT/¹8F-fluorodeoxyglucose positron emission tomography (¹8F-FDG PET)**

**Additional Information**
- **Octreotide 150-250 mcg SC TID or octreotide LAR 20-30 mg IM every 4 weeks.** Dose and frequency may be further increased for symptom control as needed. Short-acting octreotide can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.
- **Triple-phase CT technique.**
- **If signs and symptoms of heart disease or planning major surgery.**
- **Including removal of intestinal primary.**
- **Includes ablative techniques such as radiofrequency, microwave, and cryotherapy.** There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.
- **Regional chemotherapeutic protocols.**
- **Cytotoxic agents such as temozolomide, dacarbazine, 5-fluorouracil, and capcitabine can be used in patients with progressive metastases for whom there are no other treatment options.** Objective radiographic responses are rare and no chemotherapy drug or regimen has demonstrated a progression-free or overall survival benefit.
Isolated Liver Metastases from Neuroendocrine Tumors: Does Resection Prolong Survival?

![Survival Curve Diagram](image)

- **Resected (n=15)**
- **Unresected (n=23)**

\[ p=0.003 \]

Time after Liver Resection (months)
301 patients undergoing surgical management for hepatic NET metastases 1985-2008, 8 major hepatobiliary centers.

**Results:**
- 34% patients had a hormonally active tumor
- The majority of patients (55%) had bilateral liver disease
- 78% resection, 3% ablation alone, and 19% resection + ablation
- Margin status: R0/R1 in 78%, 22% incomplete (R2) debulking
- Carcinoid most common NET histological sub-type (54%)
- Overall 3-, 5-, and 10-yr survival was 82%, 73%, and 54%, respectively
- Factors associated with an increased risk of worse overall survival
  - poor tumor differentiation, R2 margin status, non-functional
- Hormonally functional NET w/R0/R1 resection benefited the most from surgery
- No difference in survival following R0/R1 versus R2 resection for non-functional hepatic NET metastasis

Mayo et al. Ann Surg Oncol. 2010
Surgery Versus Intra-arterial Therapy for NET Liver Metastasis

Proportion surviving

\[ P < 0.001 \text{ (log-rank)} \]

\[ n = 753 \text{ (IAT = 414; surgery = 339)} \]

Surgery (123 months) vs. IAT (33.5 months)

Hepatic Neuroendocrine Metastases:  
Intraoperative Detection of the Occult Primary Tumor

112 patients undergoing liver resection/ablation for synchronous NET metastases  
1988 - 2008 at JHH

<table>
<thead>
<tr>
<th></th>
<th>Carcinoid</th>
<th>Panc</th>
<th>Unknown</th>
<th>p-value</th>
<th>Total</th>
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<tr>
<td>Pre-op Diagnosis</td>
<td>28 (65%)</td>
<td>37 (90%)</td>
<td>0</td>
<td>0.008</td>
<td>65 (73%)</td>
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<td>Intra-op Diagnosis</td>
<td>14 (32.5%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>0.09</td>
<td>16 (18%)</td>
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<tr>
<td>Post-op Diagnosis</td>
<td>1 (2.3%)</td>
<td>2 (5%)</td>
<td>0</td>
<td></td>
<td>3 (3.4%)</td>
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<tr>
<td>No Diagnosis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>5</td>
<td></td>
<td>5 (5.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>43 (48%)</td>
<td>41 (52%)</td>
<td>5</td>
<td></td>
<td>89 (100%)</td>
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</tbody>
</table>
Alternative Lengthening of Telomeres (ALT) Predicts Site of Origin in Neuroendocrine Tumor Liver Metastases

- Analysis of Tissue Microarrays (TMA) from 90 patients with resected liver metastases from NET
- 29% of tumors were ALT +

- ALT+ associated with oligometastases and unilobar disease
- In advanced pNET, ALT+ associated with improved survival
Summary

1. Surgical resection of local or regional disease is the treatment of choice when possible.

2. The choice of surgical approach depends on the tumor size, location, and malignant potential.


4. In metastatic disease, resection or ablation should be offered when complete removal can be achieved, although rarely curative.

5. Cytoreductive (incomplete) resection/ablation may offer a survival benefit and should be considered.

6. New predictive and prognostic biomarkers may be useful in managing patients in the future.