Endocrine pancreatic neoplasms and palliative surgery

September 9, 2015

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Dr. Ken Leslie
Objectives

1. Palliation of pancreatic exocrine cancer
2. Clinical presentation and staging of pancreatic endocrine neoplasms (insulinoma, gastrinoma, glucagonoma, somatostatinoma and VIPoma)
3. Biochemical presentation and tests of endocrine pancreatic neoplasms
4. Indications and respectability of pancreatic endocrine neoplasms
5. Management of pancreatic endocrine neoplasms
6. Role of neoadjuvant and adjuvant treatment in the management of endocrine neoplasms of the pancreas
7. Survival or pancreatic endocrine neoplasm
Pancreatic Neuroendocrine Tumours: General Considerations
Definition/Classification

- Neoplasms originating from endocrine pancreas

Classification based on:

- Size
- Mitotic rate
- Ki-67 labeling
- Perineural/vascular invasion
- Functional vs. non-functional
## Definition/Classification

<table>
<thead>
<tr>
<th>Factor</th>
<th>Neuroendocrine Tumor (low grade, G1)</th>
<th>Neuroendocrine Carcinoma (intermediate grade, G2)</th>
<th>Neuroendocrine Carcinoma (high grade, G3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic rate per high-power field</td>
<td>&lt; 2</td>
<td>2-20</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Ki-67 index</td>
<td>&lt; 3%</td>
<td>3-20%</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Absent</td>
<td>—</td>
<td>Present</td>
</tr>
<tr>
<td>Size</td>
<td>&lt; 2 cm</td>
<td>&gt; 2 cm</td>
<td>Any size; invasion of adjacent organs, lymph node metastases</td>
</tr>
<tr>
<td>Angioinvasion</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Distant metastases</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Pancreatic Neuroendocrine Tumors

PNET

Non-functional

Functional

- Insulinoma
- Glucagonoma
- Gastrinoma
- VIPoma
- Somatostatinoma
Epidemiology

- < 2% of all pancreatic tumours
- 10% of all NET subtypes
- Incidence 0.32-0.55 per 100 000
  - 6-fold increase in Ontario from 1994 to 2009
- Autopsy prevalence up to 10%

Etiology

- Majority are sporadic

Familial Syndromes

- MEN-1
  - Gastrinoma
  - Non-functional
- VHL
  - Various
- NF-1
  - Somatostatinomas
Clinical Presentation

- Asymptomatic - incidental finding
- Symptomatic
  - Mass effect
  - Syndrome from functional PNET
Diagnosis

• Bloodwork
  • Elevated level of incriminated peptide
  • What about non-functional?
    • Chromogranin A
      • Caution in pts on PPI or with atrophic gastritis
Diagnosis

• Imaging

1. Contrast enhanced CT
   • PNETs enhance in arterial phase
Diagnosis
Diagnosis

- Imaging

1. Contrast enhanced CT
   - PNETs enhance in arterial phase

2. MRI
   - Good for small lesions, sensitivity 74-100%
   - Enhances in arterial phase in T1 phase with gad
   - High signal intensity in T2 phase
Diagnosis

Pancreatic Neuroendocrine Tumors
3. **Somatostatin Receptor Scintigraphy**
   - 74-100% sensitivity
   - Caution with non-functional tumours and insulinoma
   - Additional role for evaluating metastatic spread
Diagnosis
Diagnosis

4. **Endoscopic Ultrasound with FNA**
   - Homogeneous, hypoechoic mass
   - Sensitivity 82-93%, specificity 95%
   - Operator dependent
Diagnosis

Pancreatic Neuroendocrine Tumors
Diagnosis

4. Endoscopic Ultrasound with FNA
   • Homogenous, hypoechoic mass
   • Sensitivity 82-93%, specificity 95%
   • Operator dependent

5. Intraoperative Ultrasound
Diagnosis

6. Venous sampling
   - For PNETs failing localization
   - Percutaneous transhepatic portal venous sampling
     - Sequential sampling splenic vein, SMV and PV
   - Arterial stimulation with venous sampling
     - Selective visceral arterial injection with hepatic vein sampling
   - Injection of secretogogue
Diagnosis

PTPVS for Insulinoma

ASVS for Gastrinoma

Pancreatic Neuroendocrine Tumors
Diagnosis - Principles

1. Recognize altered physiology or syndrome
2. Detection of hormone elevations in serum
3. Localization and staging
# Pancreatic Neuroendocrine Tumors

## AJCC/WHO 2010 TNM Staging

<table>
<thead>
<tr>
<th><strong>Primary Tumor (T)</strong></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ (includes PanInIII)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor limited to pancreas, ≤ 2 cm in size</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor limited to pancreas, &gt; 2 cm in size</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor extends beyond the pancreas but without involvement of celiac axis or superior mesenteric artery</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor involves the celiac axis or superior mesenteric artery</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th><strong>Regional Lymph Nodes (N)</strong></th>
<th><strong>Description</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>NX</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis</td>
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<table>
<thead>
<tr>
<th><strong>Distant Metastasis (M)</strong></th>
<th><strong>Description</strong></th>
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<tbody>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

## Anatomic Stage | TNM Stage
---|---|---|---|
0 | Tis | N0 | M0 |
IA | T1  | N0 | M0 |
IB | T2  | N0 | M0 |
IIA | T3  | N0 | M0 |
IIB | T1  | N1 | M0 |
| T2  | N1 | M0 |
| T3  | N1 | M0 |
III | T4  | Any N | M0 |
IV | Any T | Any N | M1 |
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<td>T1</td>
<td>Tumor limited to pancreas, &lt;2 cm in size</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor limited to pancreas, 2-4 cm</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor limited to pancreas, &gt; 4 cm or invading duodenum or bile duct</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or wall of large vessels (celiac axis or SMA)</td>
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Pancreatic Neuroendocrine Tumors
ENETS TNM Staging

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<tr>
<td></td>
<td>N0</td>
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<tr>
<td></td>
<td>M0</td>
</tr>
<tr>
<td>IIa</td>
<td>T2</td>
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<td>M0</td>
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<tr>
<td>IIb</td>
<td>T3</td>
</tr>
<tr>
<td></td>
<td>N0</td>
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<td></td>
<td>M0</td>
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<td></td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
</tr>
<tr>
<td></td>
<td>Any N</td>
</tr>
<tr>
<td></td>
<td>M1</td>
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Management Principles

Operative management
- Locoregional
- Metastatic

Non-operative management
- Biotherapy
- Chemotherapy
- Targeted therapy
Locoregional Disease

- Complete surgical resection primary approach
- Negative margins and regional lymphadenectomy
- 5-year survival all PNETs 55-64%
- Aggressive multivisceral resection for locally advanced disease same survival benefit
  - Higher recurrence rate (47-100%)
Operative Metastatic Disease

- Most common site: liver
- > 50% of patients with PNETs have hepatic mets
- Debulking surgery
  - 48% 5-year overall survival (>90% tumor burden reduction)
- Complete metastasectomy when feasible
  - 61-69% 5 year overall survival
Operative Metastatic Disease

- Local ablative therapy
  - Poor surgical candidates
  - Bilobar disease combined with resection
  - RFA, HAE, cryoablation, EtOH ablation

- Liver transplantation
  - Mets confined to liver
  - 5-year overall survival 47-58% and disease free survival 20%
Operative Metastatic Disease

- Liver transplantation cont’d
  - ENETS 2012 guidelines
    - Patients refractory to other treatments
    - Favourable tumours
      - Low Ki-67
      - Normal E-cadherin
      - Histologically well-differentiated
      - No extra-hepatic disease
      - < 50 years old

Pancreatic Neuroendocrine Tumors
Non-Operative Management

• Biotherapy
  • Somatostatin analogues (Octreotide) or interferon
  • Alleviate hormonal excess states
  • Symptomatic relief
  • Tumoristatic effects
Non-Operative Management

• **Chemotherapy**
  - Advanced metastatic PNETs
  - Well-differentiated PNETs
    - Streptozocin, 5-FU and doxorubicin – 20-45% response
    - Temozolomide + capecitabine – up to 70% response
  - Poorly-differentiated PNETs
    - Cisplatinum + etoposide
Non-Operative Management

• Targeted Therapy
  • Everolimus – mTOR inhibitor
    • 11 versus 4.6 month progression-free survival vs placebo (RADIANT-3 2010)
  • Sunitinib – tyrosine kinase inhibitor
    • 11.4 vs 5.5 month progression-free survival vs placebo
  • Peptide Receptor Radionuclide therapy (PRRT)
    • 34 and 54 mo progression-free and overall survival
Non-functional PNETs
Epidemiology

- Majority of PNETs
- 1-3 per 1,000,000
- 60% are malignant

Non-functional PNETs
Clinical Syndrome

- Asymptomatic incidental findings
- Symptomatic from mass effect
  - Gastric outlet obstruction
  - Jaundice
  - Pain

Non-functional PNETs
Biochemical Profile

- Chromogranin A elevation
- Pancreatic polypeptide elevation
Localization

- Cross-sectional imaging
- SRS
- EUS +/- FNA for locoregional disease
- Percutaneous liver biopsy for metastatic disease
Management

- Locoregional -> complete surgical resection
- Metastatic + resectable -> complete surgical resection
- What about incidentalomas?
  - Unclear role for observation vs. resection
    - <2cm, low Ki67, no invasion/metastasis
    - Biochem + imaging q6-12mo
Non-functional PNETs

Localized disease

- Contrast-enhanced multiphase CT or MRI
- ± EUS
- SRS
- Chromogranin A level and pancreatic polypeptide level

Small (< 2 cm)
- Head: pancreatoduodenectomy or enucleation (if > 3 mm from main pancreatic duct)
- Body/tail: distal pancreatectomy

Large (> 2 cm)
- < 1 cm, asymptomatic, poor surgical risk: consider observation
- Head: pancreatoduodenectomy
- Body/tail: distal pancreatectomy with splenectomy
Insulinomas
Epidemiology

- Most common *functional* PNET
- 1-2 per 1 000 000
- 85-95% exhibit benign behaviour
- 5% associated with MEN-1
Clinical syndrome

- Whipple’s triad
  1. Hypoglycemic symptoms
  2. Hypoglycemia at time of symptoms
  3. Resolution of symptoms with eating/glucose

- Hypoglycemic symptoms
  - Confusion, seizure, coma, personality change
  - Palpitations, trembling, diaphoresis, tachycardia

- Weight gain
Biochemical Profile

• 72-hour monitored fast
  • q6h glucose, insulin, c-peptide, proinsulin and β-hydroxybutyrate
  • Measure above when pt symptomatic
  • Positive results
    • Glucose < 3 mmol/L
    • Insulin > 3µU/mL
    • C-peptide > 0.2 nmol/mL
    • Proinsulin > 5 pmol/mL

Insulin:glucose > 0.3
Localization

- Cross-sectional imaging
  - Usually diagnostic for lesions >1 cm
- EUS +/- FNA
- Limited role for SRS
  - Do not overexpress somatostatin receptors
- Venous sampling if other modalities failed
- Intraoperative ultrasonography
Management

- Preoperative glucose control
  - Diazoxide to inhibit insulin release and increase glycogenolysis
  - Somatostatin analogues
- Vast majority are benign and dictates surgical intervention
Management

- Operative approaches
  - Parenchymal-preserving techniques
    - Enucleation
  - Central pancreatectomy
  - Distal pancreatectomy
  - Pancreaticoduodenectomy
  - Lymphadenectomy in large or invasive tumors
Laparoscopic Enucleation

Laparoscopic Central Pancreatectomy
Insulinomas

- Insulin to glucose ratio 72 hr fast
- Chromogranin A level
- Contrast-enhanced multiphase CT or MRI
- ± EUS

Locoregional disease
- Glucose control, diazoxide

Metastatic disease
- Medical management

Head lesion, < 3 cm, > 3 mm from the pancreatic duct: enucleation, consider laparoscopic

Head lesion: pancreatoduodenectomy

Body/tail lesion: distal pancreatectomy
Pancreatic neuroendocrine tumours

Gastrinoma
Pancreatic neuroendocrine tumours
Epidemiology

- Second most common functional PNET
- 0.3 to 5 per 1,000,000 per year
- 60-90% exhibit malignant behaviour
- 25-40% associated with MEN-1
Clinical Syndrome

- Abdominal pain (90%)
- Refractory peptic ulcer disease (90%)
- Diarrhea (50%)
Biochemical Profile

- Elevated serum gastrin
  - Stop PPI 2/52
  - Fasting > 1000pg/mL
- Secretin or Ca\(^{2+}\) stimulation test
  - 2 U/kg secretin or calcium gluconate
  - Serial gastrin 30min or 3 hrs (Ca\(^{2+}\))
  - > 200 pg/mL or > 400 pg/mL (Ca\(^{2+}\))

Gastrinomas

Gastrinoma
Antral G cell hyperplasia
Conditions associated with achlorhydia or reduced gastric acid secretion
Pernicious anemia
Chronic atrophic gastritis
Proton pump inhibitor therapy

Conditions associated with gastric acid hypersecretion
*Helicobacter pylori* infection
Gastric outlet obstruction
Truncal vagotomy
Retained gastric antrum (in patients who have undergone prior antrectomy)
Short bowel syndrome
Renal failure
Biochemical Profile

- Elevated serum gastrin
  - Stop PPI 2/52
  - Fasting > 1000 pg/mL
- Secretin or Ca²⁺ stimulation test
  - 2 U/kg secretin or calcium gluconate
  - Serial gastrin 30min or 3 hrs (Ca²⁺)
  - > 200 pg/mL or > 400 pg/mL (Ca²⁺)
Localization

- Gastrinoma triangle
  - Neck of the pancreas
  - Junction of D2 and D3
  - Junction of cystic duct and CBD
Localization

- Cross-sectional imaging
  - CT with IV + oral contrast to enhance duodenum
- SRS 53-72% sensitivity
- EUS 67-100% sensitivity
- Venous sampling if not localized
Management

- Preoperative optimization
  - PPI
  - MEN-1 -> screen for hyperCa and parathyroid adenoma
    - Treat prior to OR
Management

• Operative approaches
  • Parenchymal-preserving techniques
    • Enucleation
    • Central pancreatectomy
  • Distal pancreatectomy
  • Pancreaticoduodenectomy
• Lymphadenectomy in large or invasive tumors
Management

• Operative approach in cases failing localization
  • Mobilization of duodenum and pancreas
  • Palpation and intraoperative ultrasonography
  • Duodenal transillumination and duodenotomy
  • Small duodenal lesion can be enucleated with lymphadenectomy
Gastrinomas

Outcomes

- 15 year disease-free survival
  - 41-46%
- 15 year disease-specific survival
  - 98% in operated patients
  - 74% for unoperated patients
Glucagonoma
Epidemiology

- 0.1 per 1,000,000
- 50-80% exhibit malignant behaviour
- Metastatic at initial presentation in 78-90%
- 10% associated with MEN-1
Clinical Syndrome

- Diabetes
- Necrolytic migratory erythema (70%)
- DVT (Factor X-like mediator release from tumour)
- Weight loss and malnutrition
- Anemia from bone marrow suppression
Clinical Syndrome

Glucagonoma
Biochemical Profile

- Hyperglycemia
- Elevated serum glucagon $> 1000$ pg/mL
- Hypoproteinemina
- Hypoaminoacidemia
Localization

- Most in pancreatic tail
- Cross-sectional imaging
- SRS
- EUS +/- FNA
- Portal venous sampling if not localized
Management

• Preoperative optimization
  • Tight blood glucose control
  • Correction of malnutrition
    • Zinc deficiency common
    • Amino acid replacement
  • Somatostatin analogue therapy
  • Consider anticoagulation therapy
Management

• Operative approaches
  • Formal anatomic resection with lymphadenectomy
    • Distal pancreatectomy
    • Pancreaticoduodenectomy
  • +/- cholecystectomy (?long-term SSA use)
Somatostatinoma

Pancreatic neuroendocrine tumours
Epidemiology

- 0.1 per 1,000,000
- 70-80% exhibit malignant behaviour
- 45% associated with MEN-1
Clinical Syndrome

- Diabetes
- Cholelithiasis
- Malabsorption
- Steatorrhea
- Abdominal pain (39%)
- Jaundice (28%)
- GI Bleeding (22%)
Biochemical Profile

• Elevated fasting serum somatostatin
  • > 160 pg/mL
Localization

- Common in head of pancreas or duodenum
- Cross-sectional imaging
- SRS
- EUS +/- FNA
Management

• Operative approaches
  • Formal anatomic resection with lymphadenectomy
    • Distal pancreatectomy
    • Pancreaticoduodenectomy
  • + cholecystectomy
VIPoma

Pancreatic neuroendocrine tumours
Epidemiology

- 0.1 per 1,000,000
- 40-70% exhibit malignant behaviour
- Metastatic at initial presentation in 50%
- 5% associated with MEN-1
Clinical Syndrome

- Verner-Morrison (WDHA) Syndrome
- Watery Diarrhea
  - Persists despite fasting
- Hypokalemia
- Achlorhydria
Biochemical Profile

- Hypokalemia
- Achlorhydria
- Elevated serum VIP
Localization

- Most common in body and tail
- Extrapancreatic mets
  - Adrenals, retroperitoneum, mediastinum, small bowel, kidney, colon
- Cross-sectional imaging, SRS, EUS
Management

- Preoperative optimization
  - Temporize diarrhea with SSA
  - Correction of electrolyte abnormalities
  - Correction of malnutrition
Management

Operative approaches

- Formal anatomic resection with lymphadenectomy
  - Distal pancreatectomy
  - Pancreatoduodenectomy
  - + cholecystectomy
Surgical Palliation of Pancreatic Cancer
Biliary Obstruction

- 65-75% adenocarcinomas present with symptomatic biliary obstruction
- 81% will develop obstruction
- 20% develop pruritis
- Untreated -> cholangitis, cholestasis, liver failure
- Cause of death in up to 40% without palliative care
Surgical Palliation of Pancreatic Cancer

Biliary Obstruction

Operative
- Cholecystojejunostomy
- Choledochojejunostomy
- Hepaticojejunostomy

Non-operative
- Stent
  - Plastic
  - Metal
Open Biliary Bypass

- Hepatico-J vs. Choledocho-J vs. Cholecysto-J
  - Choledocho > cholecysto in short and long-term
- Roux-en-Y vs Loop
- 2-15% rate of recurrent jaundice
- High morbidity (60%) and mortality (23%)
Open Biliary Bypass

4b. Roux-en-Y Hepaticojunostomy Procedure performed for cholangiocarcinoma and biliary injuries.

4a. Roux-en-Y Choledochojunostomy used to reconstruct the biliary system.
Endoscopic Biliary Drainage

- ERCP, may require rendezvous
- Plastic stents -> retrievable
- Self-expandable metal stents -> non-retrievable
  - Covered or uncovered
- 90% success rate of placement
Endoscopic Biliary Stent Placement
Endoscopic Biliary Drainage

- 5% early complication rate
  - Pancreatitis
  - Bleeding
  - Cholangitis

- Late complications
  - Up to 17-38% obstruction
  - Migration
    - Up to 20% in covered SEMS
Endoscopic Biliary Drainage

- Plastic vs. SEMS
  - Cochrane 2006 – SEMS lower risk of 4-6month obstruction
  - Plastic median patency 1.8-4.2 months
  - SEMS median patency 3.6-9.1 months
  - Plastic cheaper individually ($20 vs $900)
  - 28% fewer procedures with SEMS for stent-related issues
  - Cost savings favour plastic up to 4 months
Bypass vs. Endoscopic Drainage

- Lower risk of complication (RR 0.6) of endoscopic drainage
- Higher risk of recurrent biliary obstruction (RR 18) with endoscopic drainage
Surgical Palliation of Pancreatic Cancer

Biliary Obstruction

Potentially resectable?

No

Life expectancy >4mo

Yes

SEMS

No

Plastic stent

Yes

Unresectable at OR

No

Biliary bypass

Yes

Resect
Gastric Outlet Obstruction

- 10-25% adenocarcinoma have symptoms of gastric outlet obstruction from duodenal invasion
- Presenting symptom in 6% of patients
- 10-25% who undergo OR without bypass develop GOO prior to death
Surgical Palliation of Pancreatic Cancer

GOO

Operative

Gastrojejunostomy

Prophylactic

Laparoscopic

Non-operative

Stent

Open
Gastrojejunostomy

- Laparoscopic vs open equivocal
- Antecolic vs retrocolic
- 2% recurrence of GOO
Endoscopic Enteral Stent

- 20-22mm diameter, 60-90mm length SEM
- +/- fluoroscopy
- 80-90% clinical success
- 25-30% late complications
  - Stent obstruction or migration
Surgical Palliation of Pancreatic Cancer

Enteral Stent Placement
Surgical vs Endoscopic

- Recurrent GOO higher with endoscopic stents
- SUSTENT RCT 2010
  - Stent quicker return to eating
  - Proportion of patients tolerating diet at 30 and 60d higher in surgical cohort
- Predicting survival key to determine intervention
Surgical vs Endoscopic

- Risk factors for < 6 months survival after palliative bypass:
  - Distant metastasis
  - Severe preop nausea + vomiting
  - Lack of preop biliary stent
Surgical Palliation of Pancreatic Cancer

**GOO**

**Potentially resectable?**

- No
  - Life expectancy > 2mo
    - Yes: Gastrojejunostomy
    - No: Uncovered SEM

- Yes
  - Unresectable at OR
    - Yes: Gastrojejunostomy
    - No: Resect
Prophylactic Bypass

- 33% of patients unresectable at OR
  - Biliary bypass alone 19% rate of GOO
  - Double loop bypass (biliary + gastroj) 0%
  - Stopped early @ interim analysis
  - NNT to prevent reoperation for GOO was 6
Prophylactic Bypass

- 33% of patients unresectable at OR
  - Biliary bypass alone 19% rate of GOO
  - Double loop bypass (biliary + gastroj) 0%
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  - NNT to prevent reoperation for GOO was 6
Pain

- Celiac plexus neurolysis
  - If unresectable at OR: 20ml of 50% EtOH injected, 10 ml on either side of the aorta at level of celiac axis
  - Improved pancreatic cancer pain control versus placebo at 2, 4 and 6 months (RCT, Lillemoe Ann Surg 1993)
  - EUS-guided celiac plexus block – 85% response rate
  - Cochrane reduced subjective pain at 4 and 8 weeks
  - Reduced overall opioid consumption
Surgical Palliation of Pancreatic Cancer

EUS Celiac Plexus Neurolysis