Endocrine pancreatic neoplasms and palliative surgery

September 9, 2015

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Schulich MEDICINE & DENTISTRY

Western

Objectives

1. Palliation of pancreatic exocrine cancer
2. Clinical presentation and staging of pancreatic endocrine neoplasms (insulinoma, gastrinoma, glucogonoma, 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

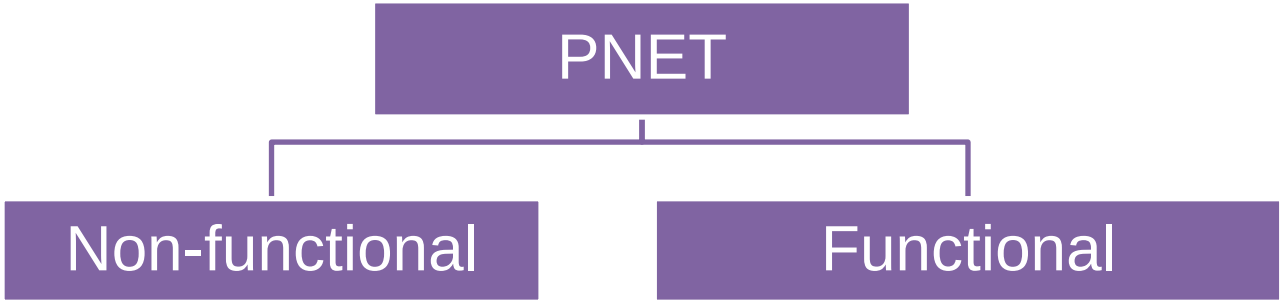
Pancreatic Neuroendocrine Tumours: General Considerations

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

Factor	*Neuroendocrine Tumor (low grade, G1)*	*Neuroendocrine Carcinoma (intermediate grade, G2)*	*Neuroendocrine Carcinoma (high grade, G3)*
Mitotic rate per high-power field	< 2	2-20	> 20
Ki-67 index	< 3%	3-20%	> 20
Necrosis	Absent	—	Present
Size	< 2 cm	> 2 cm	Any size; invasion of adjacent organs, lymph node metastases
Angioinvasion	No	No	Yes
Distant metastases	No	No	Yes



- Insulinoma
- Glucagonoma
- Gastrinoma
- VIPoma
- Somatostatinoma

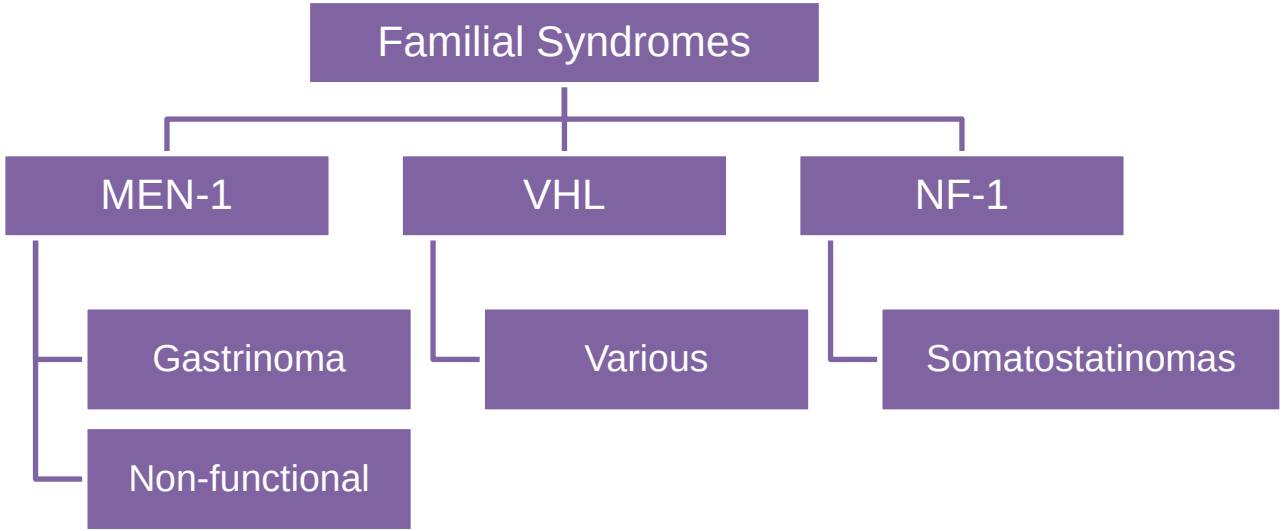
Epidemiology

- < 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%

Halfdanarson TR, *Ann Oncol:* 2008; Cukier M, *J Clin Oncol*: 2012

Etiology

- Majority are sporadic



Clinical Presentation

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

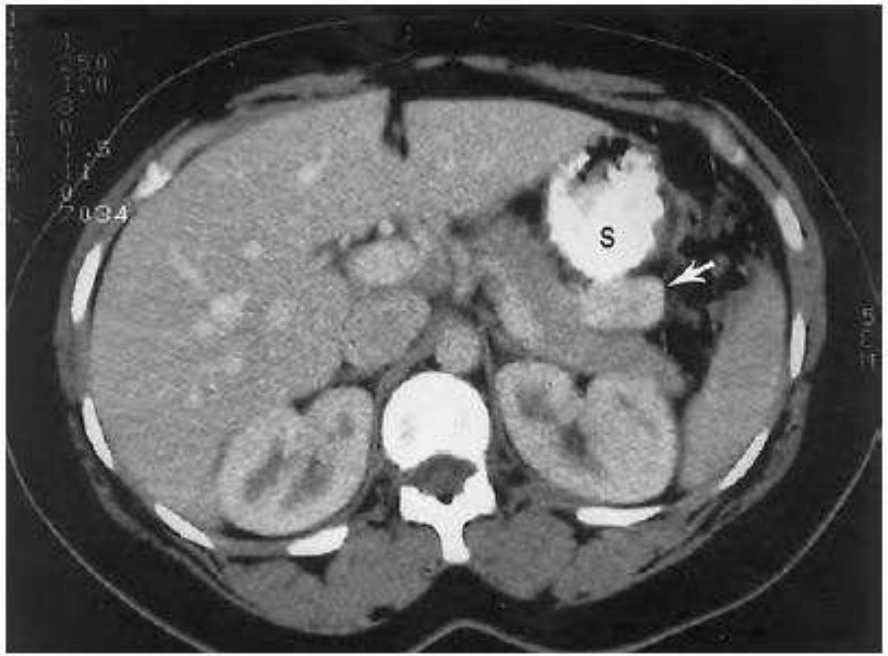
Diagnosis

- 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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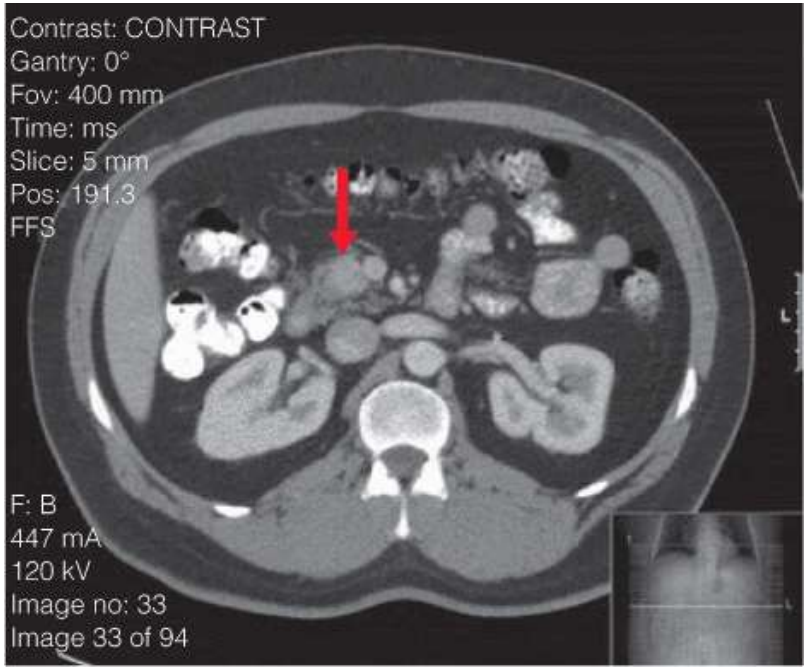
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Time: ms
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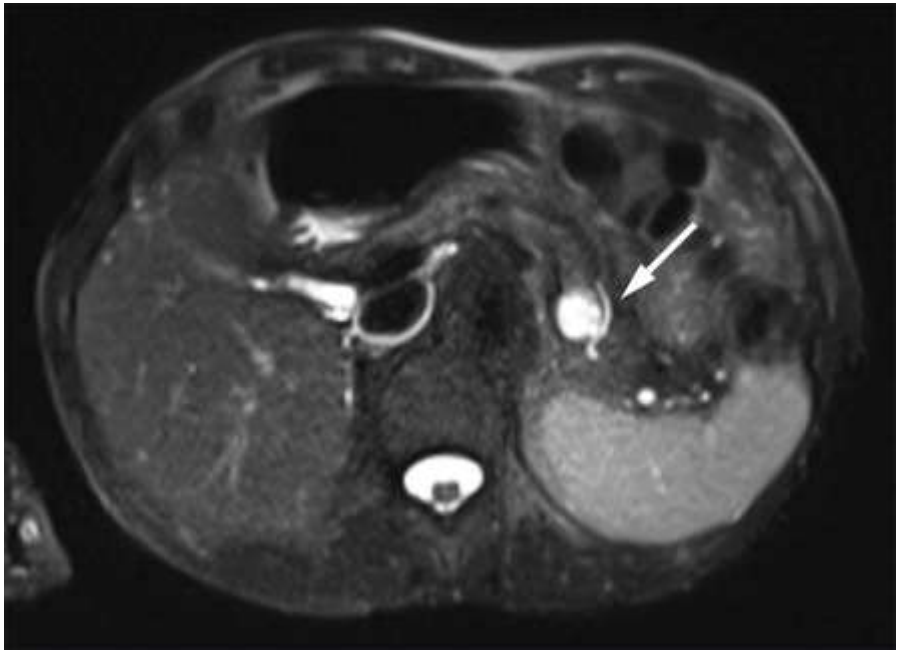
Image 33 of 94

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

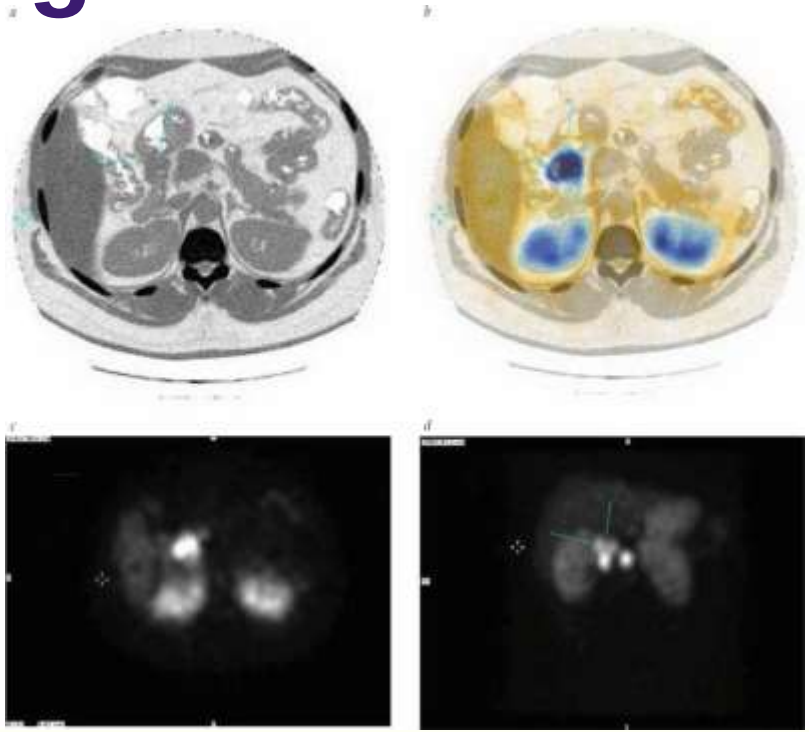
Diagnosis



Diagnosis

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

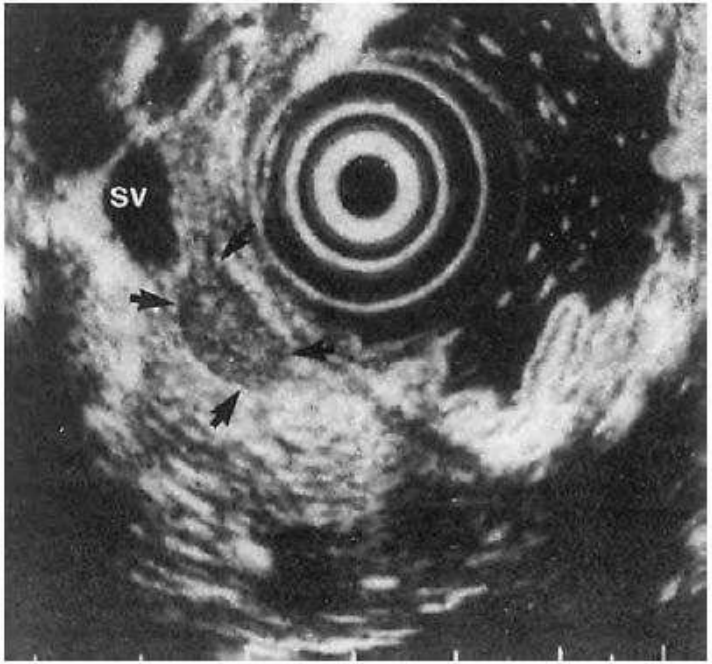
Diagnosis



Diagnosis

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

Diagnosis



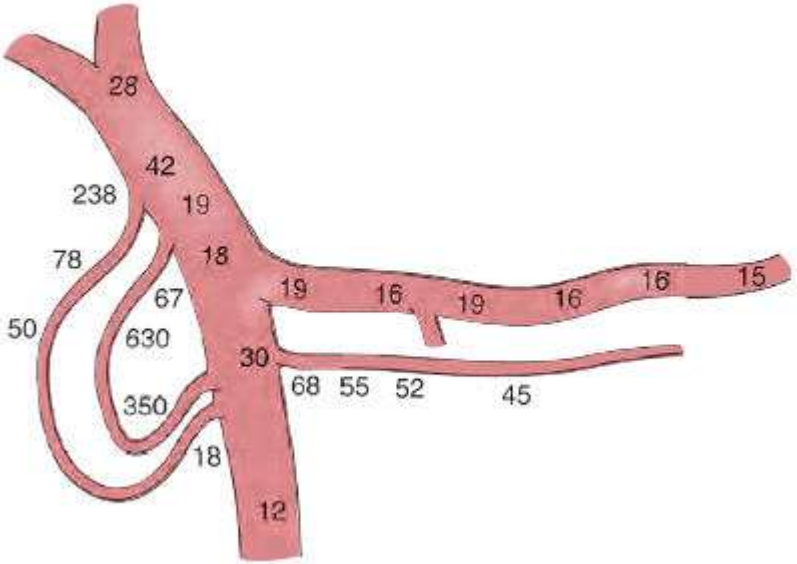
Diagnosis

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

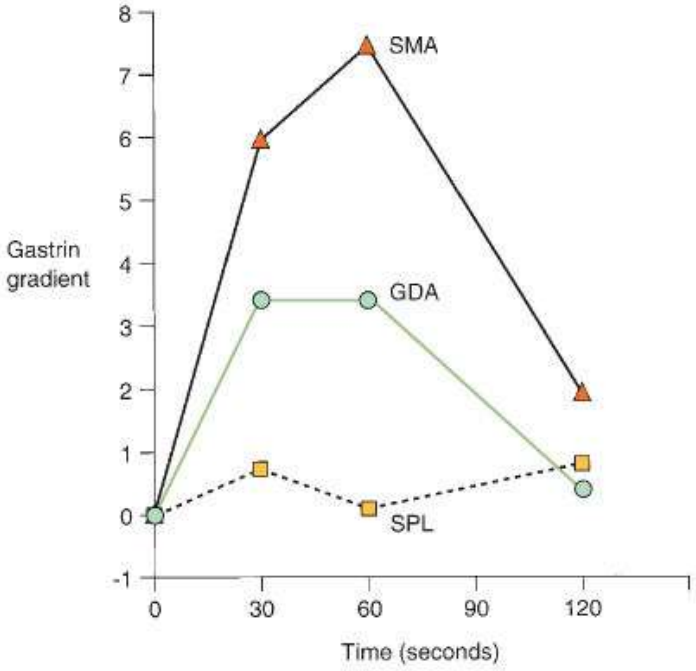
Diagnosis

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

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

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

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

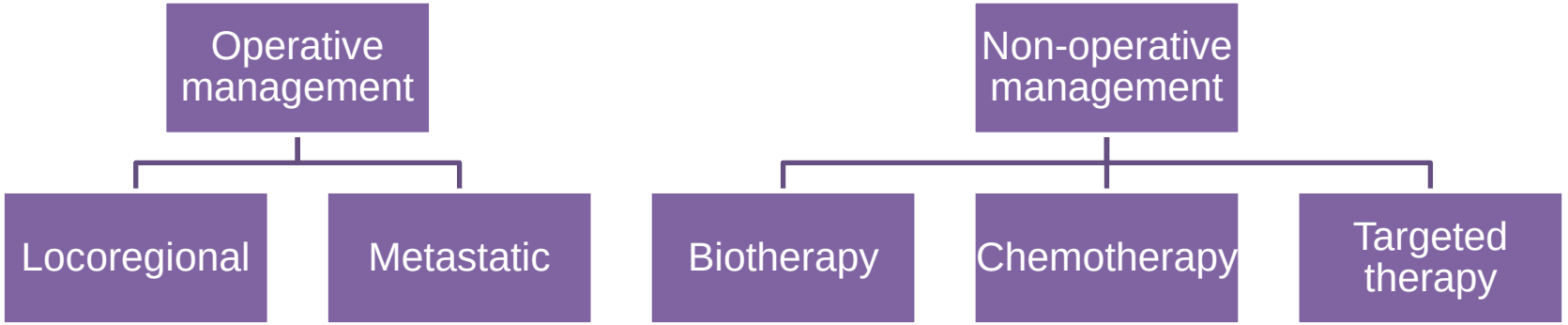
Pancreatic Neuroendocrine Tumors

ENETS TNM Staging

Primary Tumor (T)	*Description*
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor limited to pancreas, **<2 cm in size**
T2	Tumor limited to pancreas, **2-4 cm**
T3	**Tumor limited to pancreas, > 4cm or invading duodenum or bile duct**
T4	**Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or wall of large vessels (celiac axis or SMA)**
Regional Lymph Nodes (N)	*Description*
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis
Distant Metastasis (M)	*Description*
M0	No distant metastasis
M1	Distant metastasis

Anatomic Stage	*TNM Stage*		
I	T1	N0	M0
IIa	T2	N0	M0
IIb	T3	N0	M0
IIIa	T4	N0	M0
IIIb	Any T	N1	M0
IV	Any T	Any N	M1

Management Principles



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

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

Clinical Syndrome

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

Biochemical Profile

- Chromogranin A elevation
- Pancreatic polypeptide elevation

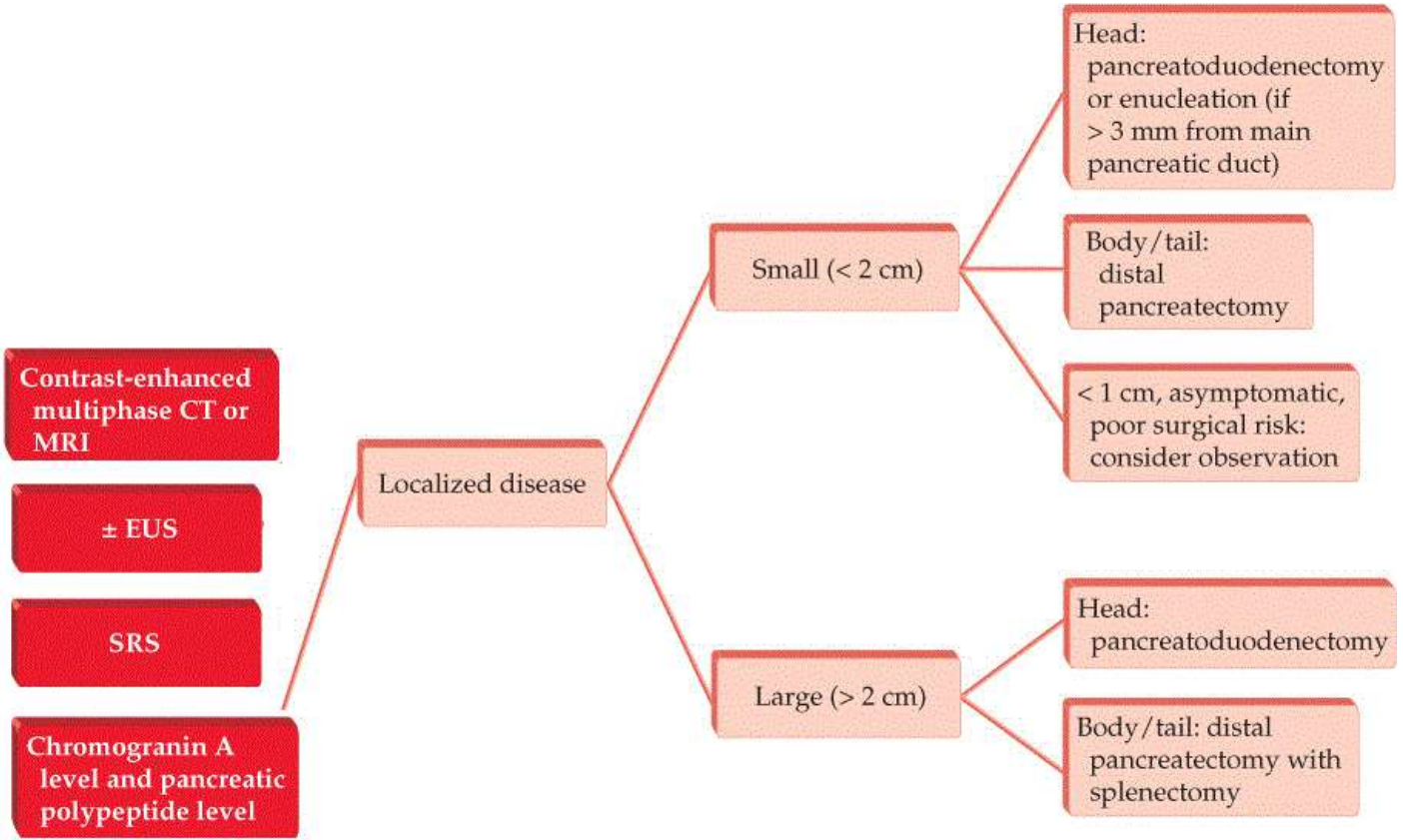
Localization

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

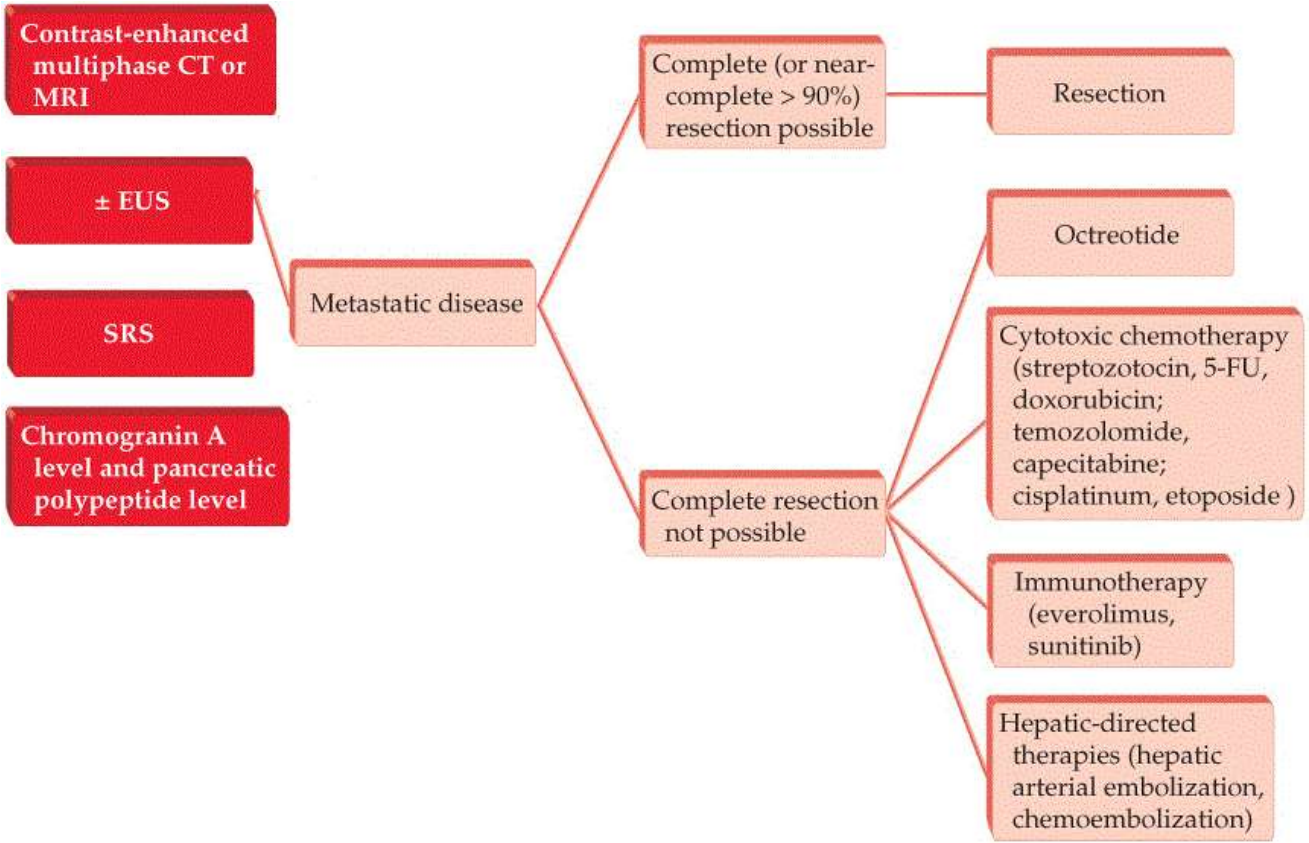
Management

- 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



Non-functional PNETs



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

    } Insulin:glucose > 0.3

    - C-peptide > 0.2 nmol/mL
    - Proinsulin > 5 pmol/mL

Localization

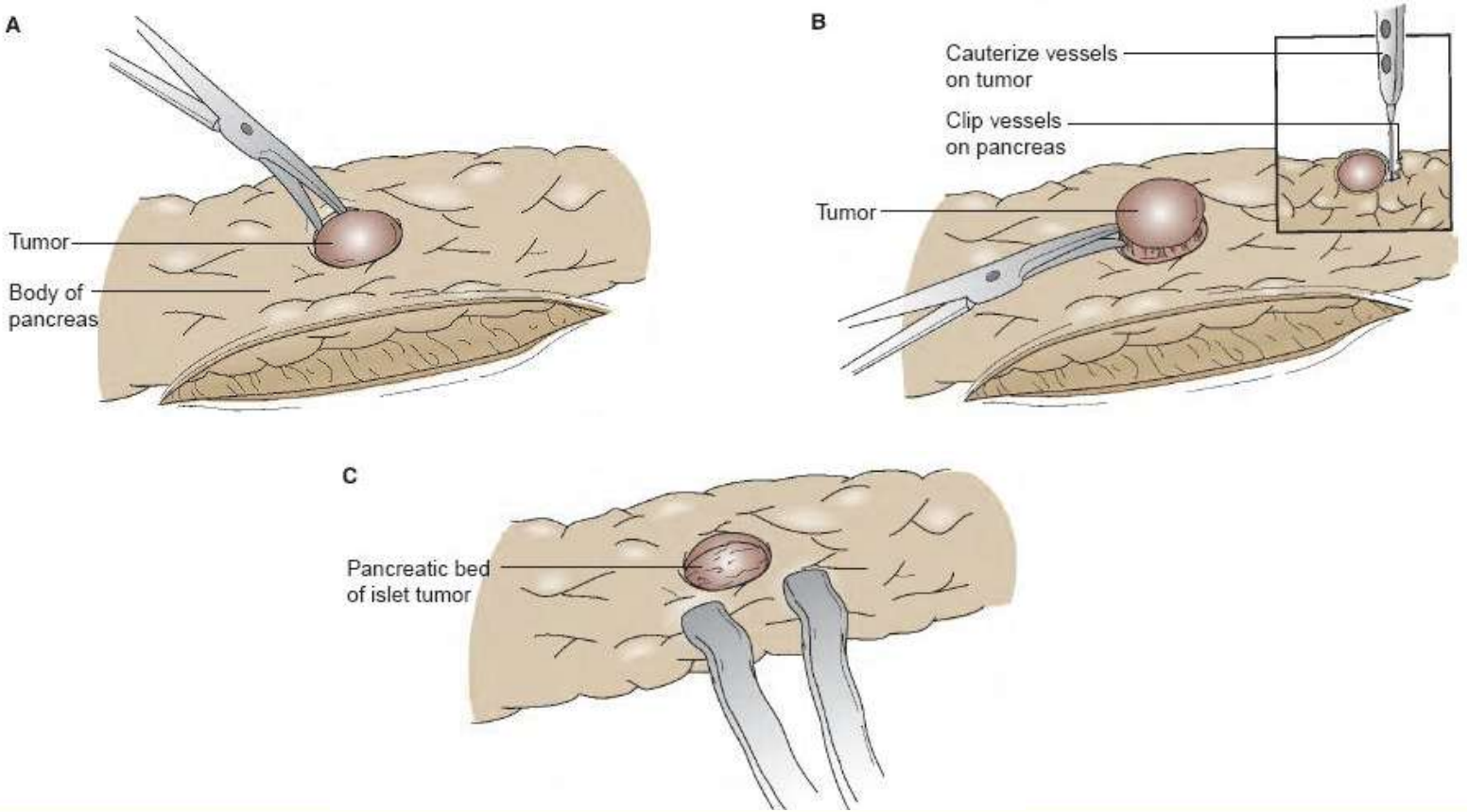
- Cross-sectional imaging
  - Usually diagnostic for lesions >1 cm
- EUS +/- FNA
- Limited role for SRS
  - Do not overexpress somatostatin receptors
- Venous sampling if other modalities failed
- Intraoperative ultrasonography

Management

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

Management

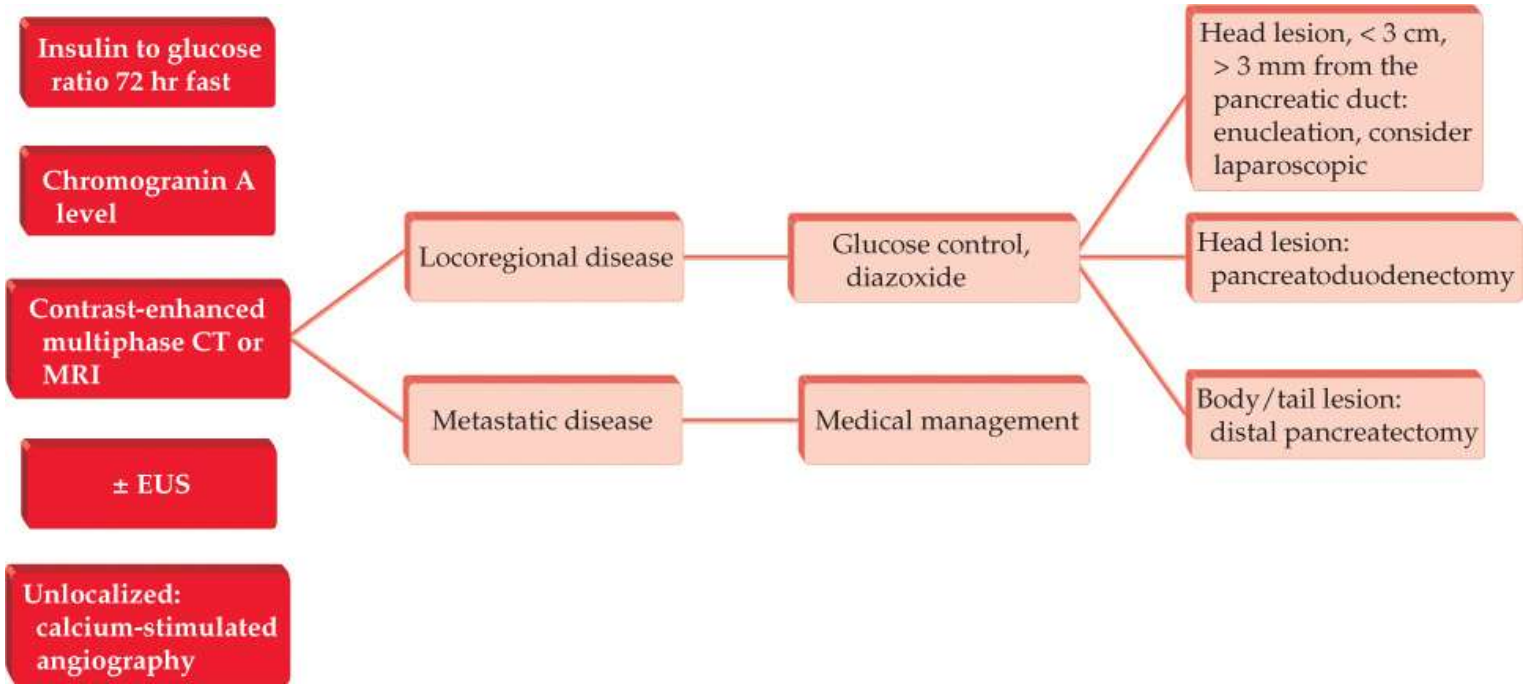
- Operative approaches
  - Parenchymal-preserving techniques
    - Enucleation
    - Central pancreatectomy
  - Distal pancreatectomy
  - Pancreaticoduodenectomy
  - Lymphadenectomy in large or invasive tumors


A
Tumor
Body of pancreas
B
Cauterize vessels on tumor
Clip vessels on pancreas
Tumor
C
Pancreatic bed of islet tumor

Laparoscopic Enucleation

Laparoscopic Central Pancreatectomy

Insulinomas



Gastrinoma


- 2014
THE OHIO STATE UNIVERSITY
WEXNER MEDICAL CENTER
SSON, M.D.
URGERY
1992
RONALD M. FERGUSON, M.D., PH.D.
CHAIR OF SURGERY
1993–1999
E. CHRISTOPHER ELLISON, M.D.
CHAIR OF SURGERY
1999–2013
2013–
2000

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%)

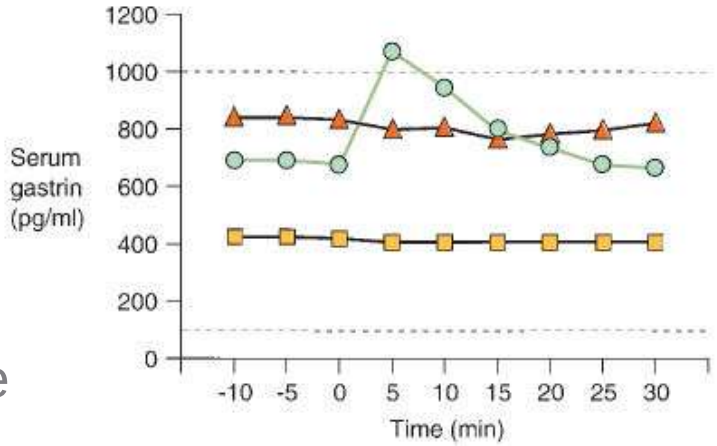
Biochemical Profile

- 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+})

Gastrinoma
Antral G cell hyperplasia
Conditions associated with achlorhydria 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

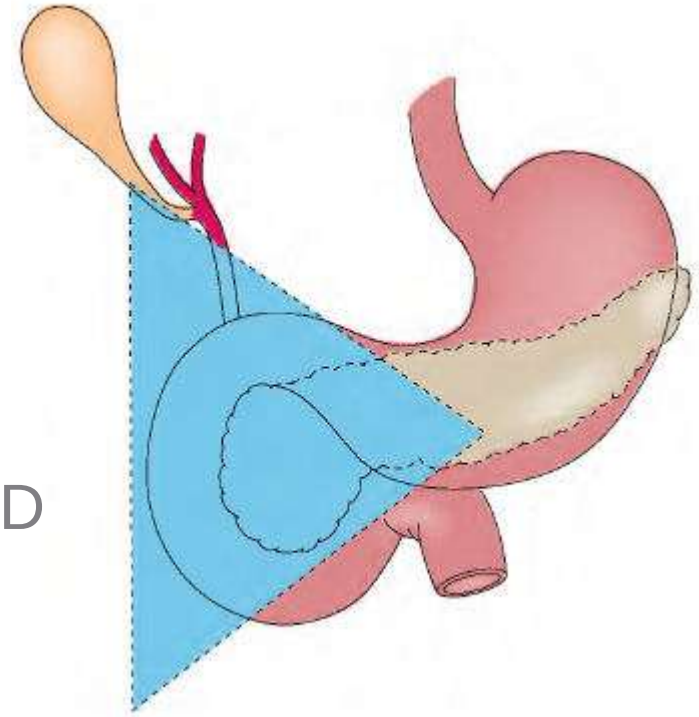
Biochemical Profile

- Elevated serum gastrin
  - Stop PPI 2/52
  - Fasting > 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+})



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

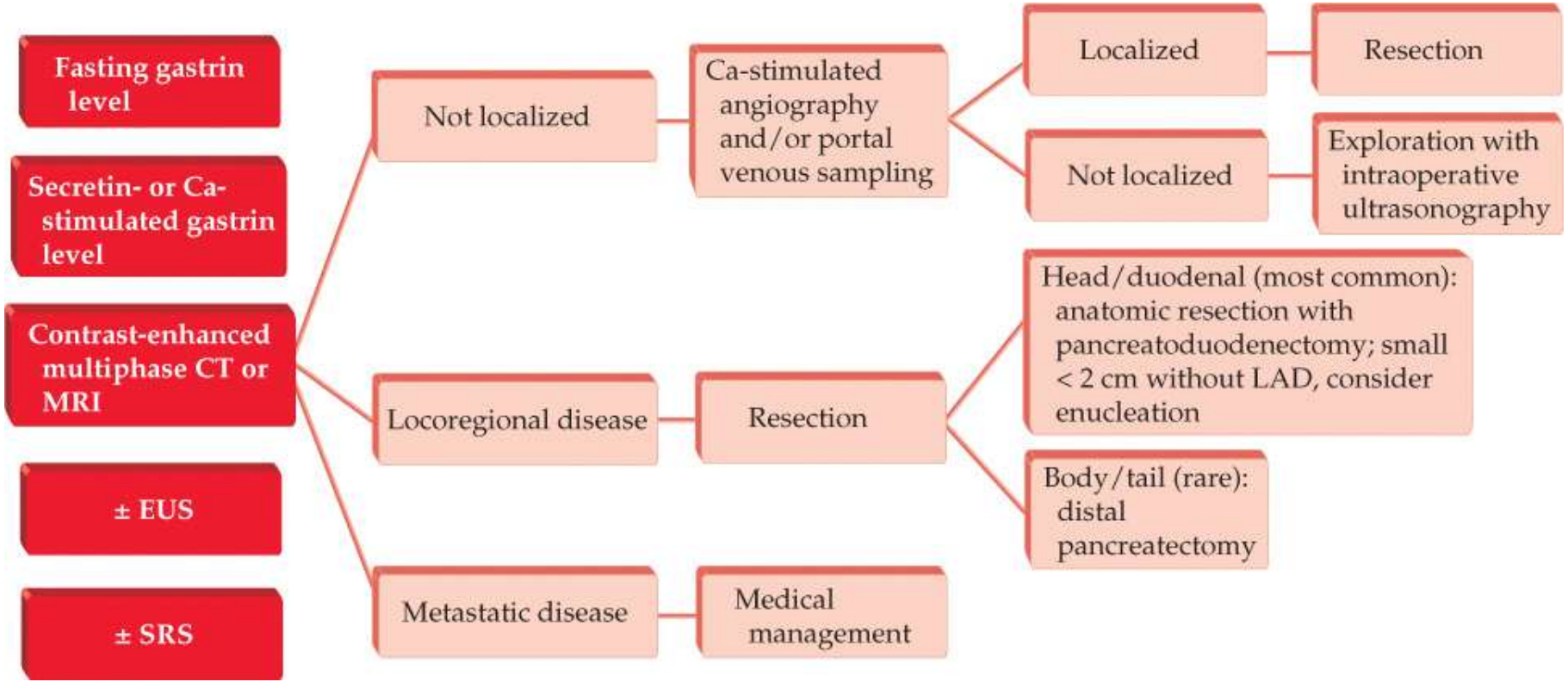
Management

- 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

Outcomes

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

Gastrinomas



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

Biochemical Profile

- Hyperglycemia
- Elevated serum glucagon > 1000 pg/mL
- Hypoproteinemia
- 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

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

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
- **W**atery **D**iarrhea
  - Persists despite fasting
- **H**ypokalemia
- **A**chlorhydria

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
    - Pancreaticoduodenectomy
  - + cholecystectomy

Surgical Palliation of Pancreatic Cancer

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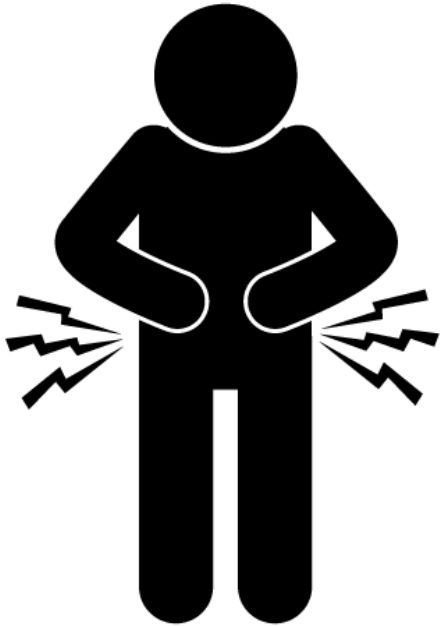
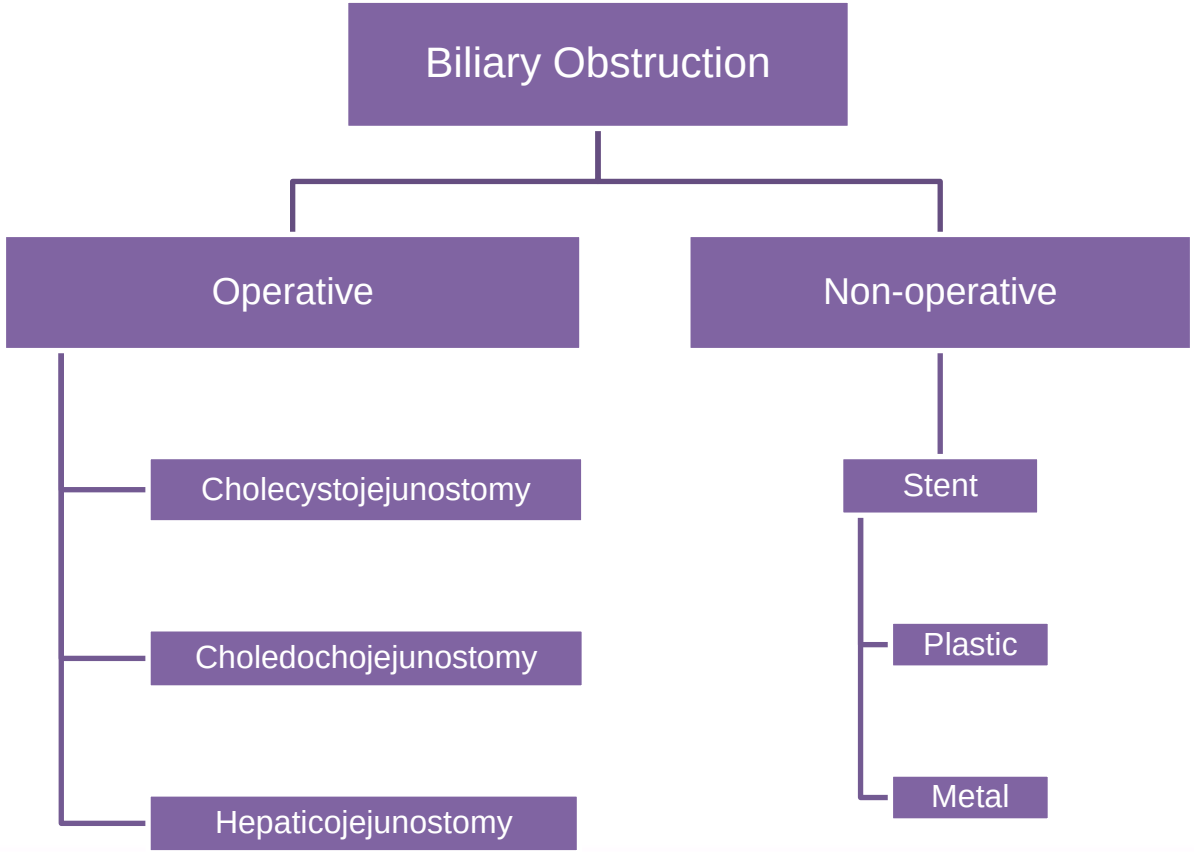
Western



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

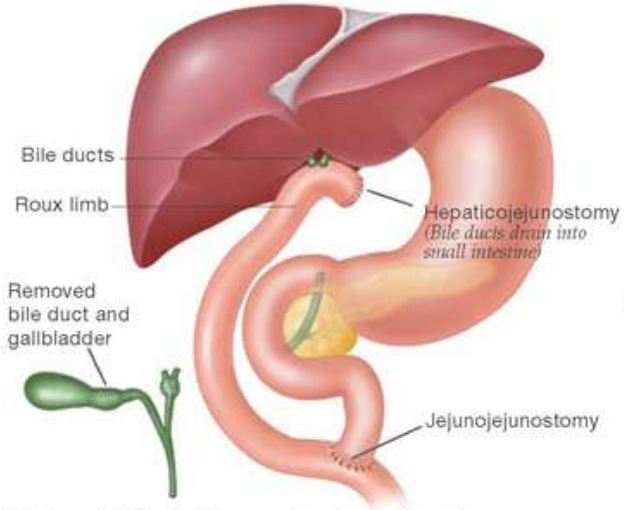
Surgical Palliation of Pancreatic Cancer



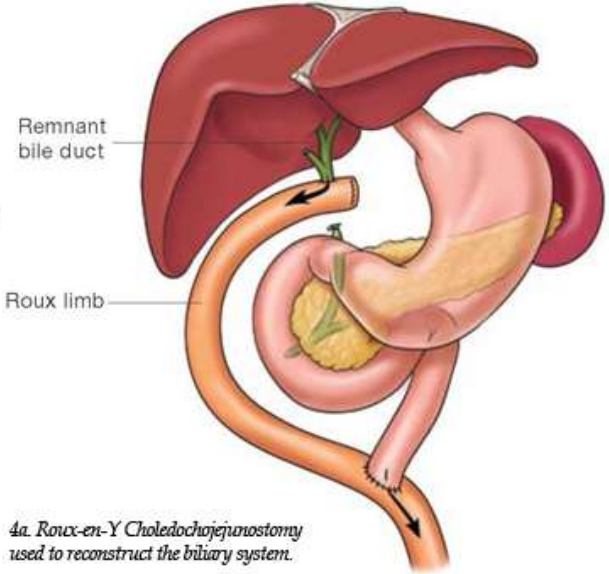
Open Biliary Bypass

- 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%)

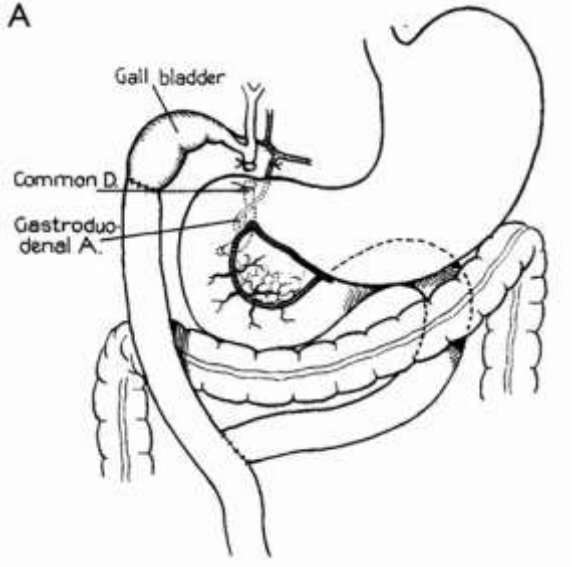
Open Biliary Bypass



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



4a. Roux-en-Y Choledochojejunostomy 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

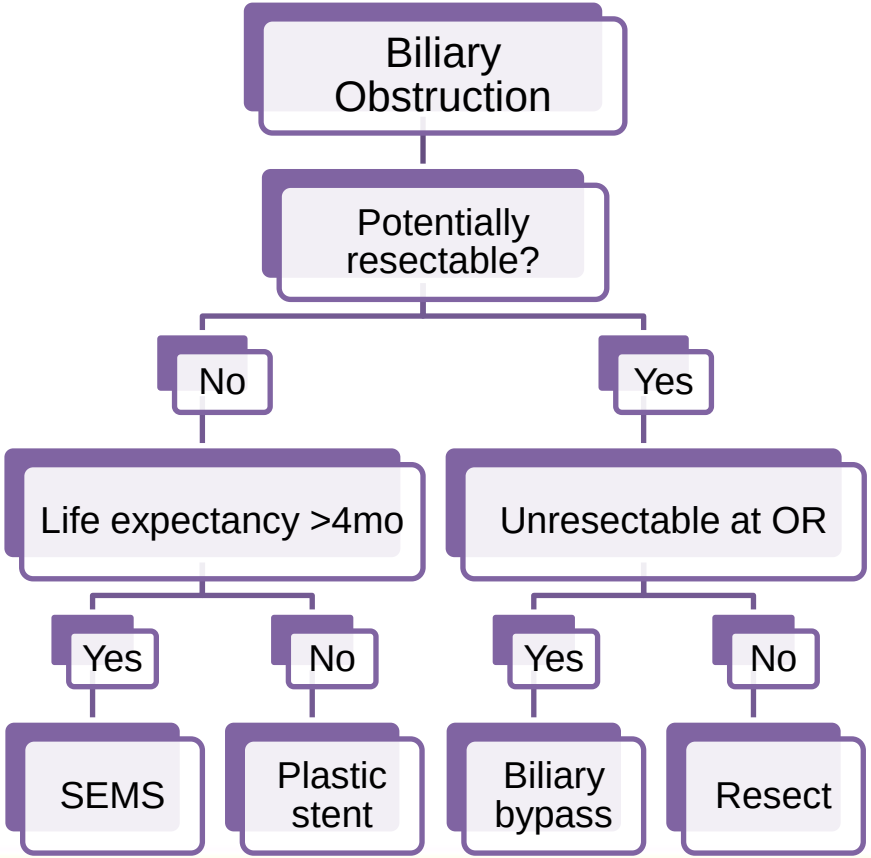
Endoscopic Biliary Drainage

- 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



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

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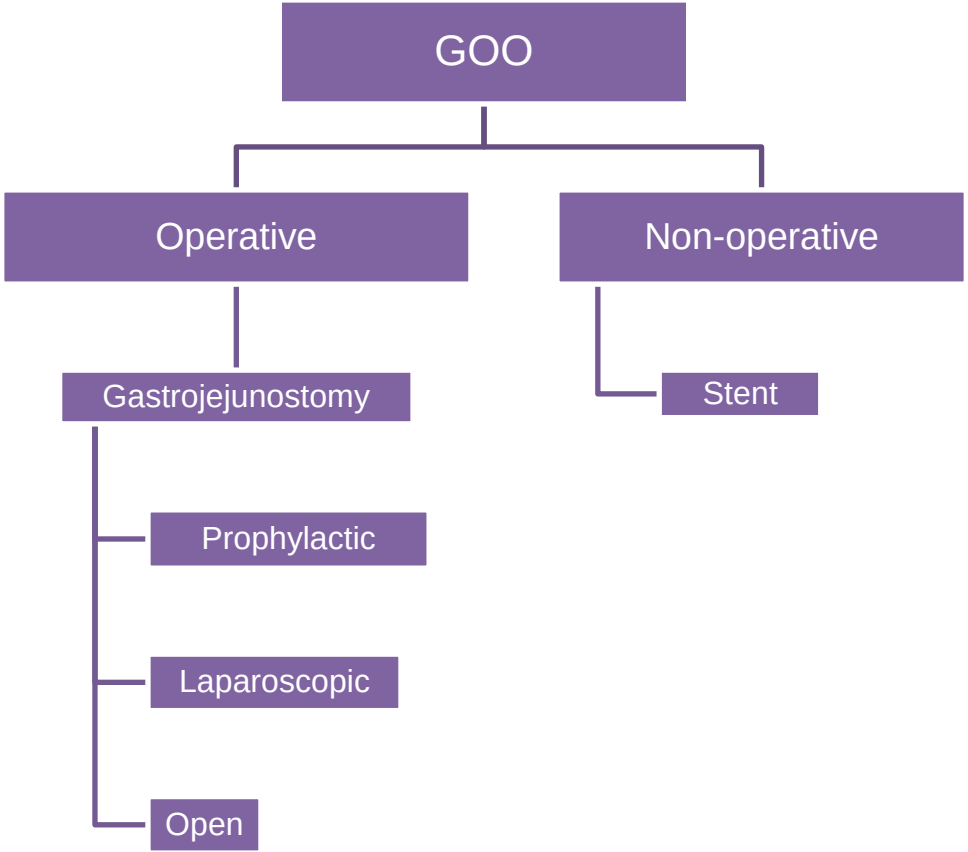
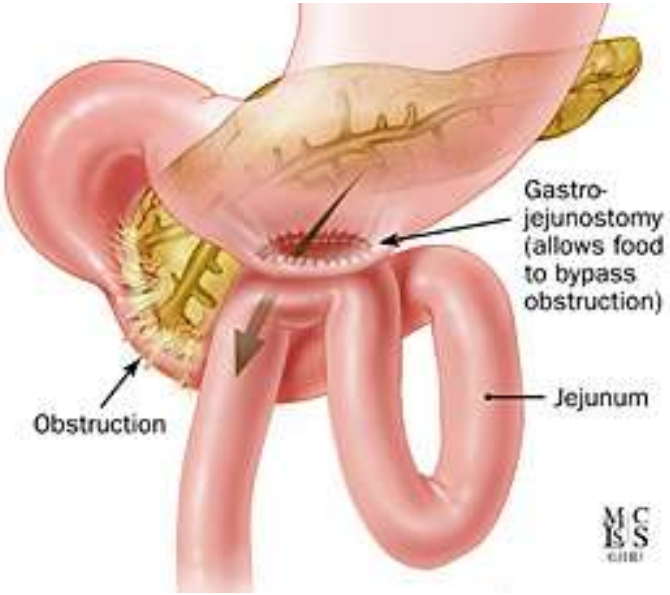


Gastrojejunostomy

- 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

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

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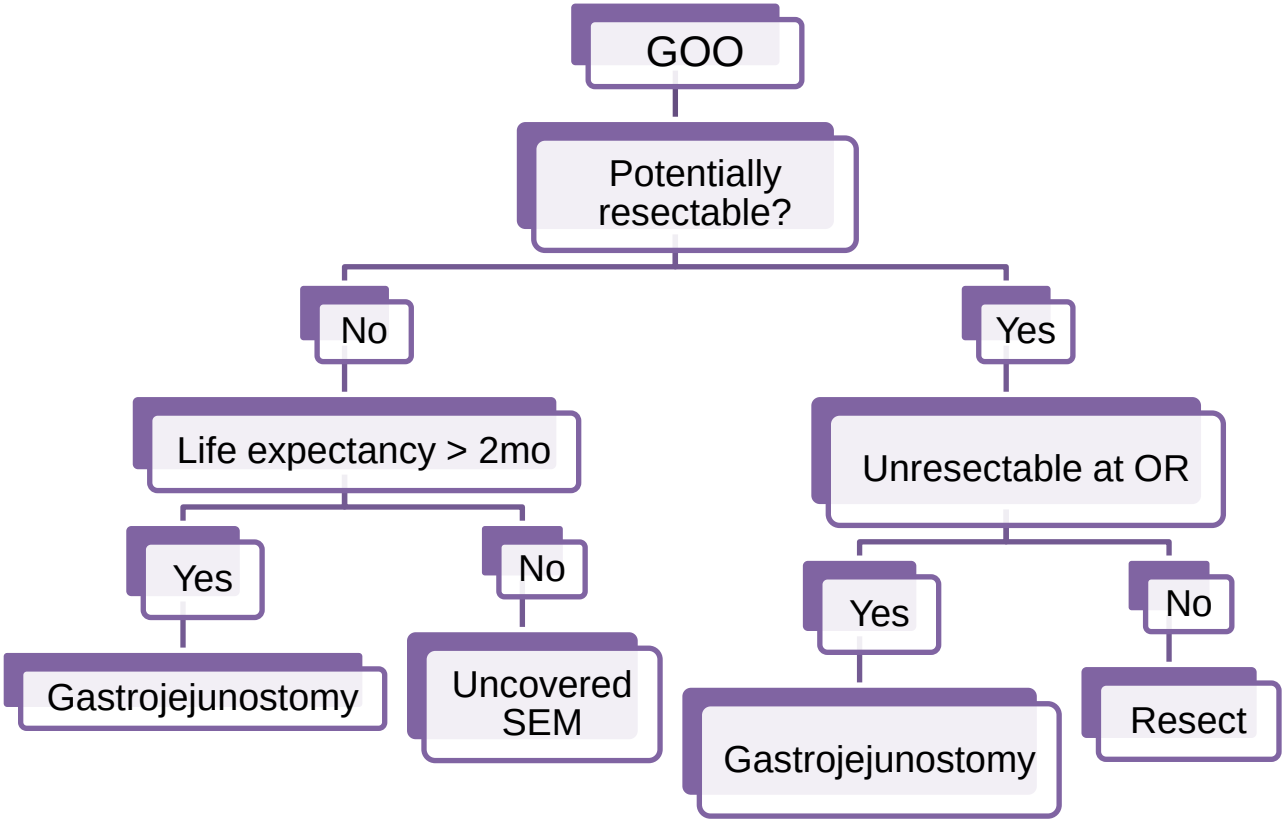

Prophylactic Bypass

- 33% of patients unresectable at OR
- Hopkins group RCT (Lillemore KD, *Ann Surg*, 1999)
  - Biliary bypass alone 19% rate of GOO
  - Double loop bypass (biliary + gastroj) 0%
- Dutch group RCT (Van Heek NT, *Ann Surg*, 2003)
  - Stopped early @ interim analysis
  - NNT to prevent reoperation for GOO was 6

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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

EUS Celiac Plexus Neurolysis


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