The Multidisciplinary Management of Pancreatic Cancer; Have We Made Any Progress?

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Goals

To Discuss:

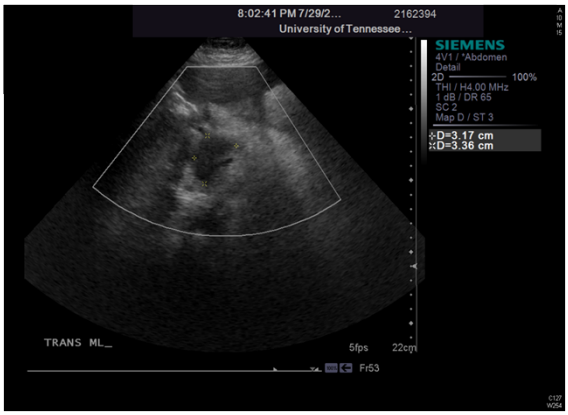
- Epidemiology and risk factors of pancreatic adenocarcinoma
- Staging
- Selection of appropriate surgical candidates
- Technical aspects of surgical resection
- Neoadjuvant and adjuvant treatment options
- Palliation of unresectable disease

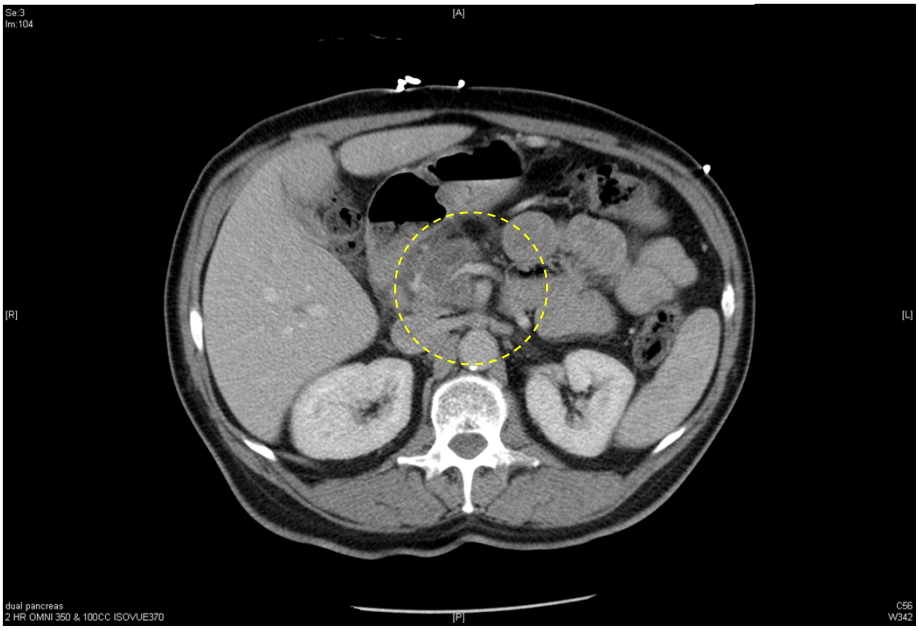
Case Study

- 54yom presents to PCP, then sent to ER:
  - 1 week h/o pruritus/jaundice
  - Epigastric and LUQ pain
  - Significant wt. loss, 15# over 2 weeks
- PMH
  - Bipolar disorder (Depakote, Lexpro)
  - Hypercholesterolemia (Crestor)
- SH
  - 2pk/day smoker
  - Narcotic addiction from previous fracture mgmt
- PE
  - NAD
  - Scleral icterus
  - Mid epigastric tenderness, no mass

Case Study

- Labs
  - Tbili = 5.6
  - AP = 669
  - AST/ALT = 168/329
  - Amylase/lipase WNL
- Abdominal US
  - No IH/EH ductal dilation
  - 3.4 x 3.2 ill defined mass in pancreatic head





Case Study

- ERCP with brushings
  - 20mm distal CBD stricture
  - 10mm upstream CBD
  - Difficult cannulation, but 10-Fr stent placed
  - Brushings show atypical cells
- EUS w/ FNA
  - 4.6 x 2.9cm mass in pancreatic hd
  - PV involvement; proximal SMA abutment
  - uT3 (?T4)N1
  - Adenocarcinoma
- CA19-9 = 55

Case Study

- MD Plan
  - Marginally resectable tumor
    - <50% chance for R0 resection – Loyer classification
  - Neoadjuvant chemoradiation (5-FU/XRT)
  - Restaging
  - Consider surgical resection

Questions

1. **What is the natural history of pancreatic cancer**
2. **Is his presentation typical?**
3. Did he have known risk factors?
4. Was the diagnostic workup appropriate?
5. Is he a surgical candidate and why?
6. Is neoadjuvant treatment justified?

Pancreatic Ductal Adenocarcinoma

- 85-90% of PC
- 78% in the head
- Most have KRAS2, p16/CDKN4, TP53, SMAD4/DPC4 mutations

Clinicopathologic features of pancreatic malignancies

Classification	Frequency (%)	Author	yr	Survival (5-yr survival after surgical resection)
DIA (incidence per 100 000 patients at risk = 8.37)[69]	85-90[1]	Conlon *et al*[70]	1996	10%
		Winter *et al*[71]	2006	18%
		Poultsides *et al*[72]	2010	19%
SPPN (incidence per 100 000 patients at risk = NA)[69]	0.1-3[73]	Papavramidis *et al*[74]	2005	95%
IPMN (incidence per 100 000 patients at risk = 0.03)[69]		Shin *et al*[75]	2010	Benign: 95% Malignant: 64%
IPMN with simultaneous DIA: (incidence per 100 000 patients at risk = NA)[69]	5[75]	Poultsides *et al*[72]	2010	42%
		Fan *et al*[77]	2010	57%
		Sohn *et al*[78]	2004	43%
Pancreatoblastoma (incidence per 100 000 patients at risk = NA)[69]	0.50[79]	Dhebri *et al*[80]	2004	50%
		Saif *et al*[79]	2007	80%
Undifferentiated (incidence per 100 000 patients at risk = 0.03)[69]	2-7[81]	Paal *et al*[82]	2001	3% (3-yr survival)
		Connolly *et al*[83]	1987	5 mo (average survival)
Medullary carcinoma (incidence per 100 000 patients at risk = NA)[69]	NA	Wilentz *et al*[84]	2000	11% 14 mo (average survival)
Mucinous cystadenocarcinoma (incidence per 100 000 patients at risk = 0.43)[69]	1	Ridder *et al*[85]	1996	56%
Adenosquamous carcinoma (incidence per 100 000 patients at risk = 0.05)[69]	4	Madura *et al*[86]	1999	5-7 mo (median survival)
		Mulkeen *et al*[87]	2006	
Acinar cell carcinoma (incidence per 100 000 patients at risk = 0.02)[69]	2	Holen *et al*[88]	2002	38 mo after surgical resection (median survival) 14 mo for unresectable disease (median survival)

DIA: Ductal infiltrating adenocarcinoma; SPPN: Solid pseudo-papillary neoplasm; IPMN: Intraductal papillary mucinous neoplasm; NA: Not applicable.

World J Gastroenterol, 2011, 17:867-897

Burden of Disease

- 4th leading cause of cancer mortality in the US (lung, colon, breast)
- 2010; 43,140 new cases 36,800 deaths; 26% of all GI-related deaths
- 80% of pancreatic cancer (PC) > 60yo
  - higher incidence in men (1.3) and AA (1.5)
- Declining death rate among men v. increasing mortality among women over last 30 years

Natural History

- Present with abdominal pain, weight loss, anorexia, early satiety, recent onset diabetes and jaundice
- 50% present with distant mets; only **20%** are candidates for resection
- Dismal prognosis: late presentation, aggressive biology, complex surgical management and lack of effective systemic therapies
- Since 1980: improvements in diagnosis, treatment and palliation; however, **22%** (15%) -*1yr OS* and **5%** (3%) -*5yr OS*

Questions

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2. Is his presentation typical?
3. **Did he have known risk factors?**
4. Was the diagnostic workup appropriate?
5. Is he a surgical candidate and why?
6. Is neoadjuvant treatment justified?

Major Risk Factors

- **Smoking; RR=1.5-2.1**
  - PC 2nd to lung cancer in smokers
  - Mechanism unknown
  - RR proportionate to cigarettes/smoke dose
  - Risk persists up to 15y after cessation
- **Diabetes; RR=2.1**
  - 80% with PC have DM-II
  - Not sure if DM is cause or synchronous effect of common exposure
  - PC RR=7.1 in gestational DM (constitutive activation of IGF1R and carcinogenesis)
  - AA have higher incidence and mortality from and DM and PC

Major Risk Factors

- **Obesity/Nutrition**
  - Risk of PC in obese may be similar to DM mechanism
  - Obesity related to up to 20% of all cancer-related deaths
  - PC incidence inversely related to fruits/veges consumed
  - Vit C, folate, lycopene protective?
  - Salt, smoked meats, refined sugars harmful?
- **Pancreatitis**
  - Pancreatitis >5yrs; RR=2.1
  - Hereditary pancreatitis (AD); 40-70% lifetime cumulative risk

Other Risk Factors

- Alcohol
- Occupation
- H. pylori
- Hereditary Factors
  - Peutz-Jeghers
  - BRCA2
  - FAP
  - HNPCC
  - Cystic Fibrosis

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CA19-9

- No single marker suitable for screening
- 70-90% sensitivity; 43-91% specificity; 72% PPV; 81% NPV
- Higher CA19-9 (>200) portends poorer prognosis; postoperative return to normal levels may be associated prolonged survival
- Useless in the setting of biliary obstruction
- Addition of CEA no better than CA19-9 alone

Imaging Modality Characteristics

Diagnostic modality	Author	Yr	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
US	Giovannini *et al*[176]	1994					
	Böttger *et al*[177]	1998					
	Rösch *et al*[178]	1991	48-95	40-91	92	100	46-64
	Niederau *et al*[179]	1992					
	Palazzo *et al*[180]	1993					
	Tanaka *et al*[231]	1996					
Doppler US	Candiani *et al*[232]	1998					
	Casadei *et al*[124]	1998	50-94	80-100	79	88	81-95
	Calculli *et al*[233]	2002					
EUS	Akahoshi *et al*[234]	1998	98	97	94	100	90
	Legmann *et al*[235]	1998					
Contrast enhanced US	Dietrich *et al*[125]	2008	90	100	100	86	93
CT	Bronstein *et al*[196]	2004	77	100	NA	NA	73
	Megibow *et al*[197]	1995					
MDCT	Park *et al*[214]	2009					
	Vargas *et al*[202]	2004	83-91	63-75	80	87	85-95
	Diehl *et al*[203]	1998					
	Schima *et al*[200]	2002					
MRI-MRCP	Andersson *et al*[212]	2005	83-92	63-85	95	79	89
PET	Maemura *et al*[217]	2008	87-100	67-77	94	100	85-95
	Delbeke *et al*[221]	1999					

PPV: Positive predictive value; NPV: Negative predictive value; US: Ultrasound; EUS: Endoscopic ultrasound; CT: Computed tomography; MDCT: Multi detector computed tomography; PET: Positron emission tomography; NA: Not applicable; MRI: Magnetic resonance imaging.

Imaging Modality Comparison

- Abdominal US
  - Good screening test
  - Best for lesions >3cm
  - Operator dependent
  - Poor predictor of resectability
- Pancreatic Protocol CT
  - MDCT; Thin section (1-3mm), dual phase; allow reformats, reconstructions, and volume rendering
  - >95% detection rate
  - Pancreatic parenchymal phase helps delineate mass and PV phase shows relationships to venous structures and liver mets
  - Should be able to predict resectability >80%

Von Hoff, Pancreatic Cancer, 165-180

Imaging Modality Comparison

- MRI-MRCP
  - Used in patients with iodine contrast allergy or when further treatment planning needed
  - MDCT and MRCP comparable for planning resection; MRCP may be superior in evaluating distant mets, especially liver
  - May be used when vascular involvement equivocal on CT
- PET/CT
  - Screen for hyperglycemia to avoid FN
  - Useful in evaluating metastatic disease $\geq$7mm
  - Useful in assessing tumor viability and response to treatment (SUV < 3 may be positive predictive factor)
  - May change surgical planning based on MDCT alone Ann Surg, 2005; 242:235-243

Preoperative biliary decompression

- Avoids liver decompensation in neoadjuvant therapy
- Performed by ERCP or PTS
- May increase risk of postoperative soft tissue infection and perioperative mortality
- Risk of stent occlusion during preoperative treatment; 15% of patients required stent exchange in Katz (2008) study

Endoscopic Ultrasound (v. MDCT)

- Superior of equal:
  - Detecting PC (98 % v. 86%)
  - Tumor staging (67% v. 41%)
  - LN involvement (44% v. 47%)
  - Tumor resectability similar (68% v. 64%)
  - PV/SV invasion
- Inferior/Drawbacks
  - SMA and SMV involvement
  - Invasive
  - Operator dependent
  - Risk of perforation

My Approach

1. Pancreatic protocol CT CAP for staging and resectability
2. EUS for diagnosis, locoregional staging, confirm resectability
3. MRI of suspicious liver lesion, not amenable to biopsy
4. CT/PET to evaluate suspicious extrahepatic lesion >7mm and not amenable to biopsy (i.e. lung, retroperitoneum)
5. Biliary decompression in patients considered for neoadjuvant treatment or definitive chemotherapy

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AJCC 6th edition TNM staging system for pancreatic cancer

TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
Tis	Carcinoma *in situ*	
T1	Tumor limited to the pancreas, 2 cm or less in greatest diameter	
T2	Tumor limited to the pancreas, greater than 2 cm at greatest diameter	
T3	Tumor extends beyond pancreas but no involvement of celiac axis or superior mestenteric artery	
T4	Tumor involves the celiac axis or the superior mestenteric artery (unresectable)	
NX	Regional nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
MX	Distant metastasis cannot be assessed	
M0	No distant metastasis	
M1	Distant metastasis	
Stage grouping		
Stage 0	Tis N0 M0	Localized within pancreas
Stage I A	T1 N0 M0	Localized within pancreas
Stage I B	T2 N0 M0	Localized within pancreas
Stage II A	T3 N0 M0	Locally invasive, resectable
Stage II B	T1, 2, or 3 N1 M0	Locally invasive, resectable
Stage III	T4 Any N M0	Locally advanced, unresectable
Stage IV	Any T Any N M1	Distant metastases

AJCC: American Joint Committee on Cancer.

CA Cancer J Clin 2010;60:277-300

Stage	Stage Distribution (%)	5-yr OS (%)
Localized	7	22
Regional	26	9
Distant	53	2

Surgical Treatment

- Surgical resection is the only opportunity for cure
- 5% mortality and > 50% morbidity
- Best results achieved in high volume centers
  - More likely to be resected
  - More likely to receive multimodal therapy
  - Mentorship is important
- Only 20% are surgical candidates
- How do we determine resection candidates?
  - define resectability in multidisciplinary setting
  - Historically ill defined; often determined intraoperatively

M.D. Anderson criteria for PC resectability

Vessel	Resectable	Borderline resectable	Locally advanced
SMA	No extension; normal fat plane between the tumor and the artery	Tumor abutment ≤ 180° (one half or less) of the circumference of the artery; periarterial stranding and tumor points of contact forming a convexity against the vessel improve chances of resection	Encased (>180°)
Celiac axis/hepatic artery	No extension	Short-segment encasement/abutment of the common hepatic artery (typically at the gastroduodenal origin); the surgeon should be prepared for vascular resection/ interposition grafting	Encased and no technical option for reconstruction usually because of extension to the celiac axis/ splenic/left gastric junction or the celiac origin
SMV/PV	Patent	Short-segment occlusion with suitable vessel above and below; segmental venous occlusion alone without SMA involvement is rare and should be apparent on CT images	Occluded and no technical option for reconstruction

SMA, superior mesenteric artery; SMV/PV, superior mesenteric vein/portal vein; CT, computed tomography.

Annals of Surgical Oncology, 2006;13:1035-1046

Katz subtypes for borderline resectable PC

- ***Subtype A***
  - Abutment of SMA/celiac axis ≤180º
  - Abutment or encasement (>180º) of short segment hepatic artery
  - Short-segment occlusion of SMV, PV, SMV-PV confluence amenable to resection and reconstruction
- ***Subtype B***
  - Concern for possible extrapancreatic metastatic disease
  - Known N1 disease
- ***Subtype C***
  - Marginal performance status (Zubrod 3)
  - Severe preexisting co morbidities requiring extensive evaluation or treatment prior to operation
- **Preoperative chemotherapy and/or chemoradiation recommended in all subtypes; aim is to increase probability of R0 resection**

JACS 2008;206:833-846

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5. Is he a surgical candidate on restaging and why?
6. **Is neoadjuvant treatment justified?**

Rationale for preoperative therapy

1. Evaluate natural history of the disease
    1. Surgical candidates have stable or responding disease
2. Early treatment of micrometastatic disease; present in most patients
3. Intact tumor blood supply
4. Therapy tolerance/compliance not impeded by surgical recovery
5. Potential for tumor downstaging (peripheral sterilization); able to achieve R0 resection in > 85%
6. Litmus test for patients with marginal PS

Preoperative Chemotherapy + Concurrent Radiation for Borderline Resectable Pancreatic Cancer

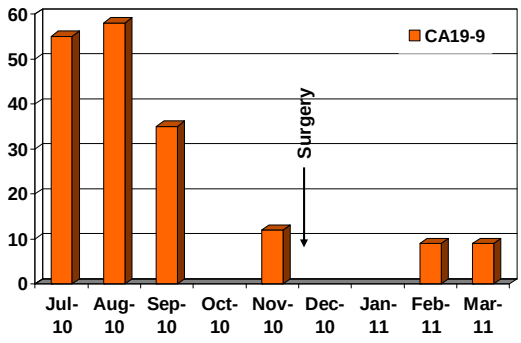
Stokes et al, *Ann Surg Oncol* (2011) 18;619-627

- 40/170 borderline resectable
- 34/40 (85%) completed preoperative capecitabine + 50Gy (20/4 or 28/6)
- 16 (46%) resected; R0 in 88%
- Median OS = 23mo; comparable to resectable patients

Katz et al, *JACS* (2008) 206;833-846

- 160/ 2454 borderline resectable
- 125/160 completed preoperative Gem combo for 2-4mo; restaging; 5-FU, paclitaxel or Gem + 50Gy; restaging; surgery
- 66/160 (41%) resected; R0 in 94%
  - 13/79 taken to the OR not operable
- Median OS = 40mo in resected v. 13mo in unresected; 18mo overall
- OR = 5.4 for surgical resection in patients with >50% drop in preoperative CA19-9

- **Is he a better surgical candidate now?**
  - Stable disease, no mets
  - Good PS
  - Declining CA19-9



Surgery 12/2/10

- Pylorus-preserving whipple procedure w/ PV resection
- Intraop – Circumferential PV invasion, SMA abutment
- Pathology
  - 3.1cm poorly differentiated ductal adenocarcinoma
  - Pancreatic neck, CBD, PV, SMA margins negative for malignancy
  - No LVI, +PNI
  - 13 LN w/o malignancy
  - <20% viable tumor

Surgical Options

- 20% of patients resectable; nearly 80% of lesions in the pancreatic head
- Pancreaticoduodenectomy (Whipple procedure) the most common operation for cure
- Distal Pancreatectomy ± splenectomy indicated for tumors left of SM vessels
- R0 resections portend equal survival regardless of location, however, body/tail lesions present at later stage due to lack of symptoms
- Total pancreatectomy rarely indicated for PC; OS is similar, but M&M higher and QOL poorer

Staging Laparoscopy

- Introduced in late 1980's
- Liver, peritoneum, porta hepatis, transverse mesocolon, lesser sac examined for occult mets
- Likely more applicable in body and tail tumors and/or when imaging findings are equivocal
- Large volume centers show up-staging in 4-54% of cases (majority of patients evaluated prior to present quality CT)
- Likely to change operative management <10% of time when combined with high quality imaging JACS, 2008;206:445-450; Br J Surg 2001;88:325-337
- LUS may increase sensitivity; peritoneal fluid washings controversial
- Not widely accepted yet, adds cost, adds OR time

Whipple procedure (PD)

- First described by Walter Kausch in 1912
- Later popularized by Allan Whipple
- *En bloc* removal of pancreatic head, duodenum/proximal jejunum, common bile duct, gallbladder, pylorus/distal stomach and regional LN's
- Pancreatic fistula is the most significant complication (20%)

Pylorus-preserving PD (PPPD)

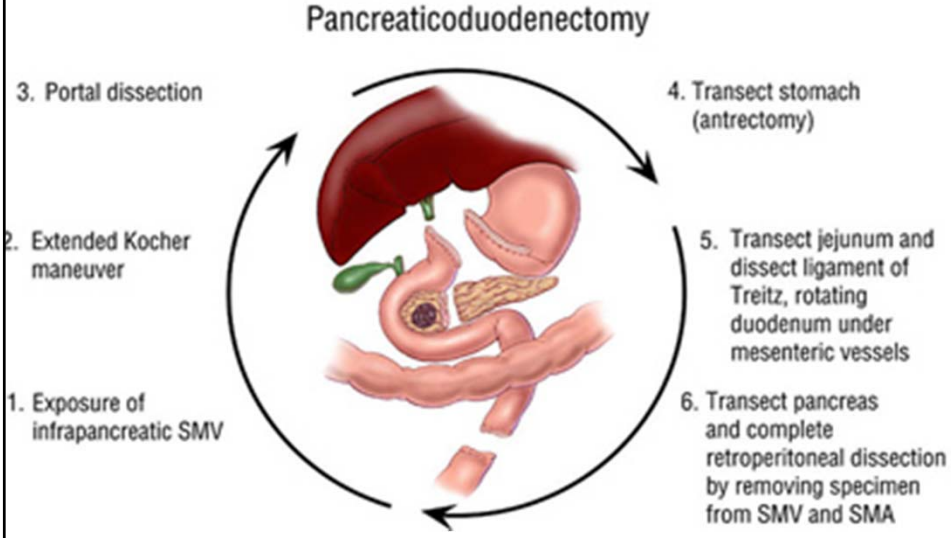
- Introduced by Watson in 1942 and popularized by Traverso/Longmire in 1978
- Advantages:
  - Preserves gastric reservoir and function
  - Improved post operative weight gain and QOL
  - Oncologically equal to PD
- Higher incidence of delayed gastric emptying

Laparoscopic Pancreatic Resection

- Lap distal pancreatectomy most common operation
  - Safe and feasible
  - Oncologically equal?
  - M&M, LOS similar
  - I perform open resection for known PC
- Lap PD
  - First described in 1994 by Gagner and Pomp
  - Kendrick et al (Mayo) have greatest experience to date
    - Safe, feasible
    - M&M comparable to open approach
    - Hope to show advantage in QOL

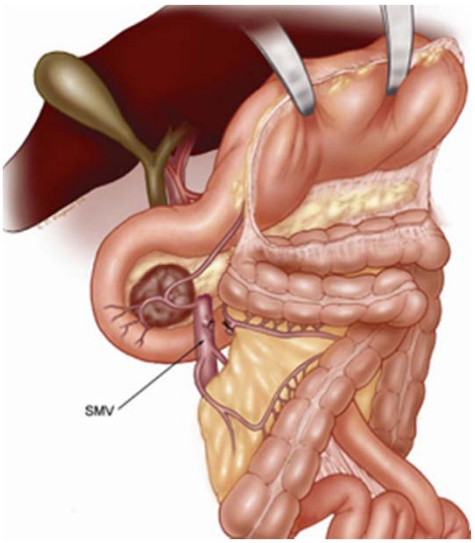
Radical Pancreatic Resection

- Vein resections with reconstruction are safe and outcomes similar to PD alone
- Arterial resections are limited to select group of patients, as most of these patients have advanced disease
- No oncologic benefit to extended lymphadenectomy; possible increased morbidity
  - Japanese v. American approach to GI malignancy



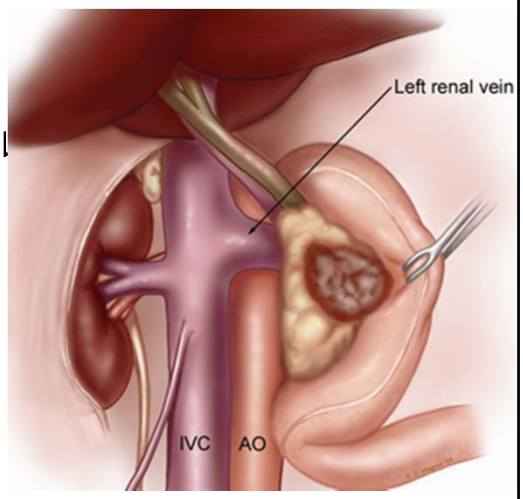
STEP 1

- Enter lesser sac
- TD hepatic flexure
- ID SMV; ligate tributaries



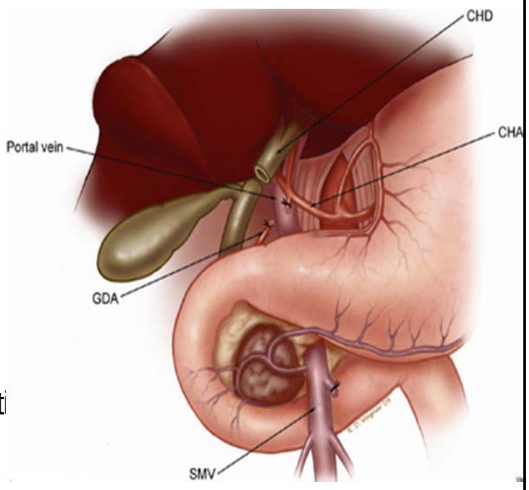
STEP 2

- Kocher maneuver to l lateral aorta
- Remove tissue anterior to IVC



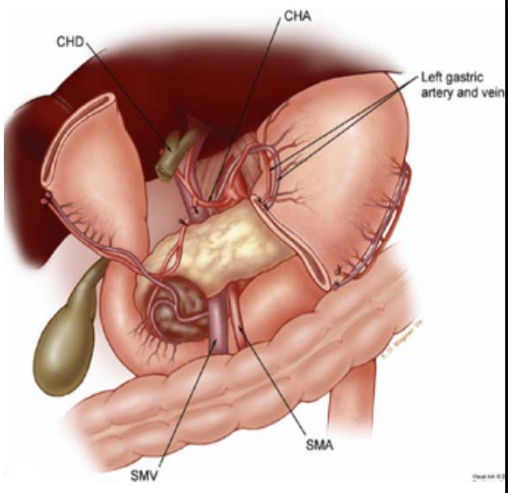
STEP 3

- Dissection of porta hepatis
- Ligate GDA
- ID portal vein
- Transect common hepati duct



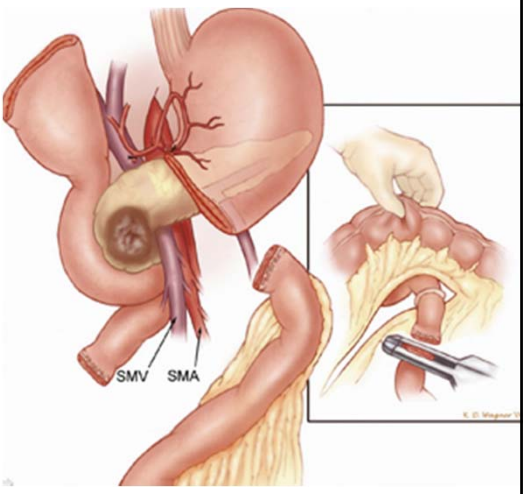
STEP 4

- Transect distal stomach
- Leave 2cm duodenal cuff for PPPD



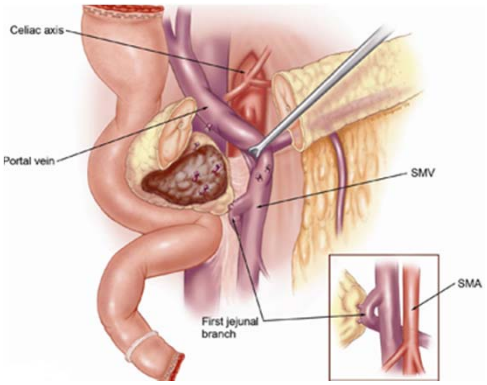
STEP 5

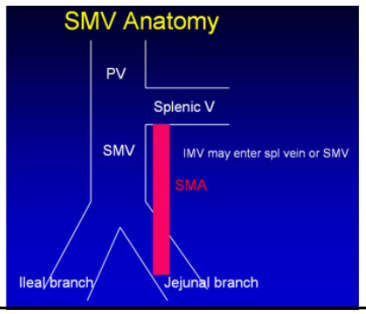
- Transect proximal jejunum



STEP 6a

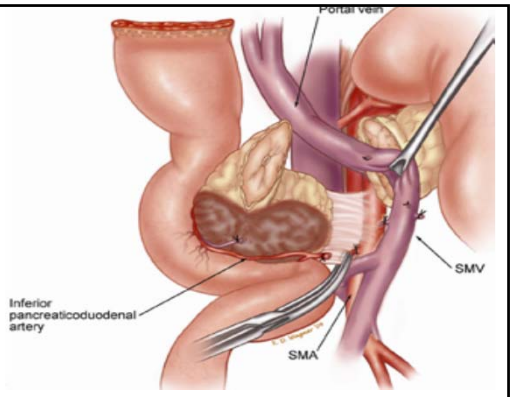
- Pancreatic head and uncinate separated from PV-SMV
- Pancreas transected at level of PV and reflected laterally

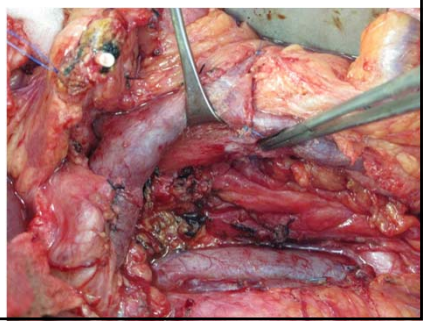




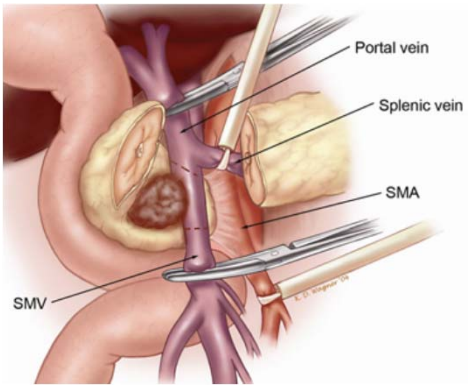
STEP 6b

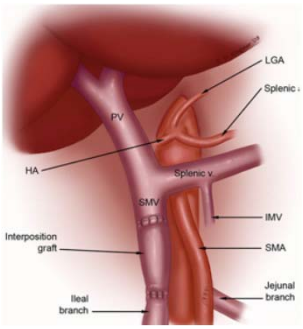
- Medial retraction PV-SMV to facilitate dissection of lateral SMA
- Most important step oncologically
- Specimen removed

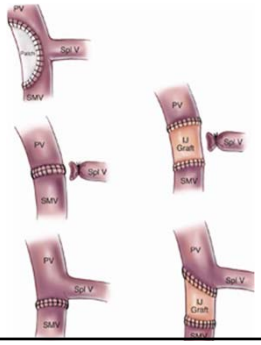




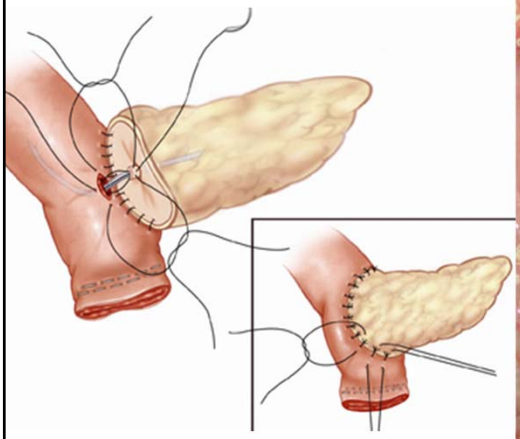
Vein Resection Anatomy

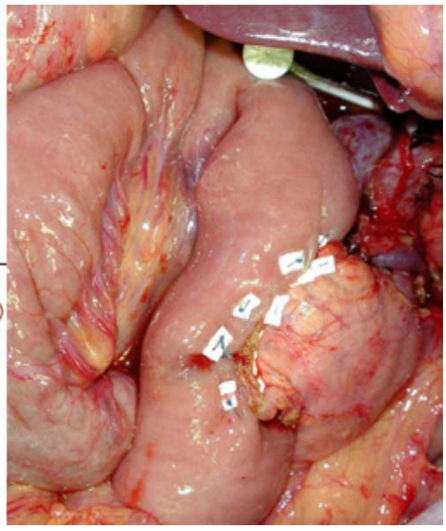




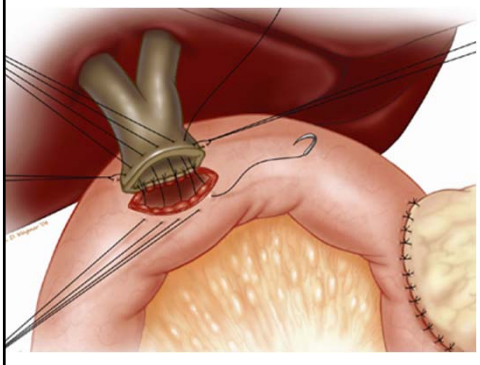


Duct-to-mucosa reconstruction

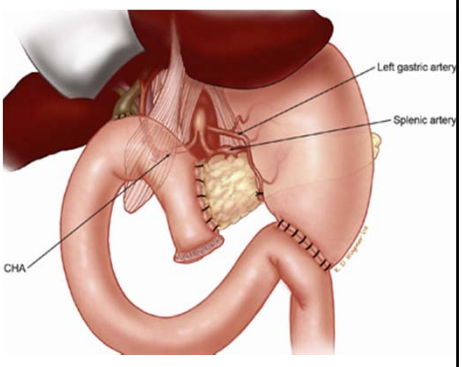




Hepaticojejunostomy



Completed reconstruction



All photos/images courtesy of Douglas B. Evans, MD

Rationale for adjuvant therapy

- Poor long term survival with surgery alone (10 - 20mo median survival)
- Up to 50% rate of incomplete resection worldwide
- High rate of locoregional recurrence and tendency toward early mets in resected patients

TABLE 1. *Overall survival data from completed randomized trials of adjuvant therapy for patients with resected pancreatic cancer*

Study (year)	Number of patients	Treatment assignment	Median survival (months)	*P* value
GITSG[1] (1985)	49	Chemoradiation vs. Observation	21.0 vs. 10.9	.035
ESPAC-1[16] (2004)	289	Chemotherapy vs. No chemotherapy	20 vs. 15.5	.009
		Chemoradiation vs. No chemoradiation	15.9 vs. 17.9	.05
EORTC[18] (2007)	120	Chemoradiation vs. Observation	15.6 vs. 12.0	.165
CONKO[19] (2007)	368	Gemcitabine vs. Observation	22.1 vs. 20.1	.06
RTOG[20] (2008)	380[a]	Gemcitabine with 5-FU/EBRT vs. 5-FU with 5-FU/EBRT	20.5 vs. 16.9	.05

5-FU, 5-fluorouracil; EBRT, external-beam radiation.
[a] Head tumors.

TABLE 4. *Eligibility criteria for an optimal trial of adjuvant therapy and criteria used in completed or ongoing clinical trials of adjuvant therapy in patients with resected pancreatic cancer*

Optimal trial design vs. reported adjuvant therapy trials[a]	Pretreatment high-quality CT or MRI	Defined radiographic criteria for resectability	Standardized system for assessment of surgical margins	Postoperative imaging before enrollment
Optimal Trial Design	Yes	Yes	Yes	Yes
GITSG	No	No	No	No
EORTC 40891	No	No	No	No
ESPAC-1	No	No	No	No
EORTC 40013	Yes	No	No	No
ESPAC-3	Yes	No	Yes	No
RTOG 9704	No	No	No	Yes
ACoSOG ZQ5201	No	No	No	Yes
JHMI	No	No	Yes	Yes

CT, computed tomography; MRI, magnetic resonance imaging.
[a] Refer to text for full name of trials and further details.

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Ongoing Adjuvant Trials

- ECOG 2204
  - Phase II; 126 patients; endpoint = toxicity
  - Resection, then Gem/Bev or Gem/Cetux
  - Targeted therapy safe, but no additional benefit
- ACOSOG Z05031
  - Phase II
  - 5-FU/Cis/XRT/IFNa
  - MS = 25.4mo; 2yr OS = 55%
  - IFNa toxic; outcomes noteworthy
- ACOSOG Z5041
  - Gem/Erlotinib, Sx, Gem/Erlotinib
  - Help define significance of XRT
  - May select out better candidates for surgery
- ESPAC-4
  - Sx, Gem v. Gem/Erl
- FOLFIRINOX

Adjuvant Therapy (cont)

- 5-FU + XRT, followed by Gemcitabine based regimen is current standard adjuvant regimen
- Radiation alone (IORT or EBRT) offers local control but no survival advantage
- Additional survival benefit of chemoradiation to adjuvant chemotherapy is unknown
- Optimal sequencing of adjuvant treatment also in question

Palliation of Unresectable Disease

- 80+% unresectable at diagnosis
- Median survival is 7mo in locally advanced/unresectable patients and <3mo in metastatic patients
- Problems include biliary obstruction, gastric outlet obstruction, pain, severe malnutrition
- Palliative intervention can improve QOL and survival
- Get MD team, including palliative care team, involved early

Nutritional Support

- Tx steatorrhea with enzyme supplementation
- High caloric/high protein/high taste foods
- Enteral feeding controversial
- Get nutritionist involved early

Palliative Options

- Surgical biliary and gastric bypass
  - Up to 25% of unresectable patients may develop GOO
  - Traditionally done at time of laparotomy for planned resection
  - Feasible laparoscopically
- Endoscopic biliary and GI stenting
  - High patency and low migration rates in self-expanding metallic stents
  - Decrease LOS, lower morbidity, earlier po intake than surgical bypass, less expensive
  - First line treatment in appropriate patients
- Percutaneous Transhepatic Stenting is indicated in patients who have failed endoscopic stenting

Celiac Plexus Neurolysis

- Can be performed surgically, percutaneously and endoscopically
- 50-100% ethyl alcohol injected into celiac plexus for chemical splanchnicectomy
- RR > 70% but durability variable; can be repeated

What have we learned?

1. Significant advances in imaging and defining surgical candidates
2. Safe surgical resection/palliation with minimally invasive options
3. Further defining appropriate surgical candidates from the “borderline resectable” group
4. Best outcomes are achieved at high volume centers with multidisciplinary teams and mindset
5. We will not cure this disease with safer, more aggressive surgery

Areas for improvement

- Well designed, randomized neoadjuvant and adjuvant clinical trials
  - New cytotoxic and targeted agents
  - Optimal sequencing of current agents
  - Is there a real role for radiation therapy?
- Standardized treatment algorithms within institutions based on available data
  - i.e Gemzar, restage, 5-FU/XRT, restage, surgery, adjuvant gemzar
- Good database management
- Continue to promote risk reduction
- Continued research to identify predisposing factors and screening markers
- Promote awareness and collaboration