

Periampullary Carcinoma

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Epidemiology of pancreatic cancer

- In 2000, 217,000 new cases of pancreas cancer were reported globally, with 213,000 resultant deaths ([Hariharan et al, 2008](#))
- India and Nigeria have the lowest reported incidence ([Boyle et al, 1989](#); [Mack et al, 1985](#))
- Asian patients with PDA tend to have less aggressive tumors than do non-Asians

Risk Factors Associated with Cancer of the Pancreas

Medical Conditions	Race/Ethnic Factors	Lifestyle and Environmental Factors
Cirrhosis	African-American men and women	Cigarette smoking (dose-response relationship)
Diabetes Mellitus	Native female	Environmental tobacco smoke exposure, particularly early in life
Chronic Pancreatitis	Hawaiians	Alcohol
	Ashkenazi Jews	Residential radon

Dietary Factors	Occupational Exposure to Carcinogens	Selected High-Risk Occupations
High fat/cholesterol	Asbestos	Dry cleaning or chemical plant work
Overweight and obesity	2-naphthylamine	sawmill work
Nitrosamines in food	Benzidine	electrical equipment manufacturing work
	gasoline products	mining and metal working occupations
	DDT, radon	

**HeightRR = 1.81 (CI, 1.31 to 2.52)
when comparing tallest and shortest
height categories for men and
women**

**Previous Surgery
Cholecystectomy**

Inherited Predisposition

Hereditary pancreatitis

Hereditary nonpolyposis colorectal cancer

Hereditary breast and ovarian cancer

Familial atypical multiple mole melanoma syndrome

Peutz-Jeghers syndrome

Ataxia-telangiectasia

Fanconi anemia

Cystic fibrosis

Inherited Predisposition

Strong risk factor in 5% to 10% of cases

Sporadic pancreas cancer - 2 fold higher risk in first degree relative

Familial pancreatic cancer – 9 fold higher risk in first degree relative

BRCA2 are found in 6% to 19% of familial pancreatic cancer patients

PALB2 gene in 3% of familial pancreas cancer patients

No single “pancreas cancer gene” has been identified

High-Risk Genetic Disorders Associated with Familial Pancreatic Cancer

Genetic Syndrome	Gene/Chromosomal Mutation Region	Estimated Increased Risk of PDA
Hereditary pancreatitis	PRSS1 (7q35)	50 to 80 times
Hereditary nonpolyposis colorectal cancer (Lynch II variant)	<i>hMSH2, hMSH1, hPMS2, hMSH3, hPMS1, hMSH6/GTBP</i>	Undefined
Hereditary breast and ovarian cancer	BRCA2 (13q12-q13)	3.5 to 10 times
FAMMM syndrome	p16 (9p21)	20 to 34 times
Peutz-Jeghers syndrome	STK11/LKB1 (19p13)	75 to 132 times
Ataxia-telangiectasia	ATM (11q22-23)	Rare

- Collectively these syndromes account for less than 5% of the familial aggregation of PDA
- Approximately 40% of those with HP will develop PDA when the additional risk factor of cigarette smoking is added.

Tobacco Exposure

- contributing factor in approximately 20% to 25% of the cases of PDA
- smokers have a 70% increased risk of PDA compared with nonsmokers
- dose-response relationship – seen in few studies
- significantly younger mean age (64.0 years) when compared with nonsmoker (66.5 yrs)

Clinical feature

- Jaundice
- Pruritus
- Epigastric pain radiating to the back
- persistent nausea or vomiting
- Pancreatitis
- anorexia, weight loss, and fatigue
- left supraclavicular adenopathy (Virchow node)
- Periumbilical adenopathy (Sister Mary Joseph node)
- Blumer shelf from drop metastases
- Ascites hepatomegaly from metastatic disease
- Palpable abdominal mass.

Lab Investigations

- LFT
- Raised bilirubin, ALP, GGT, 5-NT
- New-onset diabetes mellitus
- carbohydrate antigen 19-9 (CA19-9)
 - not specific for pancreatic cancer
 - patients who test negative for Lewis blood group antigens A and B are unable to synthesize CA19-9
 - marker of treatment response and recurrence

MDCT

- pancreas protocol multidetector CT with dedicated arterial and venous phases and three-dimensional (3D) reconstruction
- Water is given orally, and contrast is given intravenously
- tumor as a low-density (hypodense) lesion within the pancreas, best seen during the venous phase of contrast enhancement
- surrounding visceral vessels
- variations in hepatic arterial anatomy
- Predict surgical respectability – 80 -90 % times

Magnetic resonance imaging (MRI)

- diagnostic sensitivity of 91% for CT, compared with 84% for MRI
- No advantage obtaining both CT and MRI
- renal impairment or sensitivity to the intravenous contrast
- MR cholangiopancreatography (MRCP) is valuable in evaluating and following small cystic lesions of the pancreas

Esophagogastroduodenoscopy (EGD)

- gastric outlet obstruction - duodenal stenting
- ERCP - stenting of biliary strictures for metastatic, unresectable, or physiologically unfit patients or

Endoscopic ultrasound (EUS)

- operator dependent
- superior to CT for the detection of lesions smaller than 2 cm not evident on cross-sectional imaging.
- accurately estimate T-stage
- superiority over CT for the detection of venous invasion
- obtain tissue via fine needle aspiration (FNA)

Diagnostic Biopsy

- low-risk patients with resectable lesions - tissue diagnosis is not required
- locally unresectable or metastatic disease
- endoscopically with EUS-FNA best
- Percutaneous US- or CT-guided pancreatic biopsy should be discouraged
- biopsy of the distant lesion (metastasis) if accessible is preferred over biopsy of the primary pancreatic lesion

AJCC Staging of Pancreatic Cancer

7th ed, 2010

Stage	Primary Tumor (T)	Regional Lymph Nodes (N)	Distant Metastases (M)	Description
0	Tis	N0	M0	Carcinoma in situ, includes PanIN3
IA	T1	N0	M0	Tumor limited to the pancreas, ≤2 cm in greatest dimension
IB	T2	N0	M0	Tumor limited to the pancreas, >2 cm in greatest dimension
IIA	T3	N0	M0	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
IIB	T1, T2, T3	N1	M0	Regional lymph node metastasis
III	T4	Any N	M0	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)
IV	Any T	Any N	M1	Distant metastasis

- Localized resectable disease (stages I and II)
 - On CT scan no evidence of metastatic disease
 - a clear tissue (fat) plane between the tumor and the visceral arteries (celiac axis and SMA)
 - 180-degree or less circumferential involvement of the SMV– PV confluence
- Locally advanced unresectable disease (stage III)
 - involvement of the celiac axis or SMA
- Distant metastatic disease (stage IV)

Diagnostic laparoscopy

- detect small surface liver or peritoneal metastases
- ability to evaluate locally advanced disease - limited
- alters subsequent management is reported at between 4% and 40%
- selected patients - tumors greater than 4 cm, left sided tumor, ascitis, small, indeterminate liver or peritoneal lesions seen on CT

Median Survival by Surgical Treatment and AJCC Stage in Months

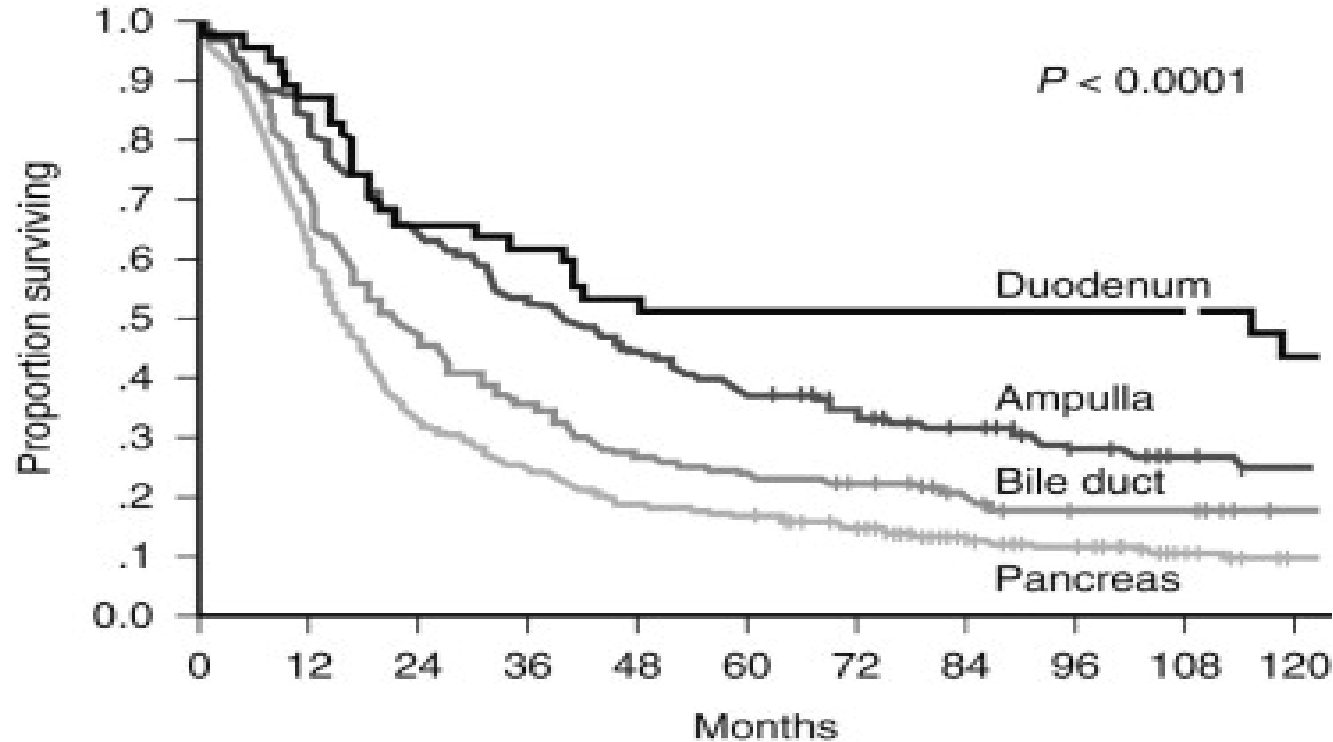
Stage	Nonresected Patients	Resected Patients	All Patients
Ia	6.8	24.1	10.0
Ib	6.1	20.6	9.1
IIa	6.2	15.4	8.1
IIb	6.7	12.7	9.7
III	7.2	10.6	7.7
IV	2.5	4.5	2.5
Total	3.5	12.6	4.4

Bilimoria KY, et al, 2007a: Validation of the 6th edition AJCC pancreatic cancer staging system: report from the National Cancer Database. Cancer 110(4):738-744.

Surgical Treatment

- Surgical resection - only potentially curative therapy
- Only 20% to 30% patients candidate for curative resection
- right-sided tumors - pancreatoduodenectomy
- left-sided tumors – distal pancreatectomy
- extensive parenchymal involvement - total pancreatectomy

Riall et al, 2006: Resected periampullary adenocarcinoma: 5-year survivors and their 6- to 10-year follow-up. *Surgery* 140[5]:764-772.)



Kaplan-Meier actuarial 10-year survival by site of tumor origin after right-sided pancreatectomy for pancreatic and periampullary adenocarcinoma. Results from a cohort of **890 patients** treated by pancreatoduodenectomy (pancreas, n = 564; ampulla, n = 144; bile duct, n = 135; duodenum, n = 47). The first 5 years of the curve represent the actual **5-year survival** because no patients were censored during that time. Five-year actual survival rates were 17% for pancreas, 37% for ampulla, 23% for bile duct, and 51% for duodenum. **Ten-year actuarial survival** rates were 9% for pancreas, 25% for ampulla, 17% for bile duct, and 44% for duodenum. All patients were censored after 5 years, so all 890 were at risk for recurrence.

Adjuvant Therapy

Reference	No. Patients	EBRT Dose (Gy)	Chemotherapy	Survival				
				Median	1 yr	2 yr	3 yr	5 yr
GITSG (Kaiser & Ellenberg, 1985)	22 Surgery alone	None	None	11 mo	49%	15%		NR
	21 Adjuvant tx	40 split course	5-FU bolus	20 mo	63%	2%		NR
EORTC (Klinkenbijl et al, 1999)	54 Surgery alone	None	None	12.6 mo	40%	23%		10%
	60 Adjuvant tx	40	5-FU CI	17.1 mo	65%	37%		20%
ESPAC-1 (Neoptolemos et al, 2004)	69 Surgery alone	None	None	16.9 mo				11%
	75 Chemo tx	None	5-FU bolus	21.6 mo				29%
	73 Chemorad tx	40 split course	5-FU bolus	13.9 mo				7%
	72 Chemorad plus additional chemo	40 split course	5-FU bolus	19.9 mo				13%

RTOG (Regine et al, 2008), pancreatic head subset	221 5-FU arm	50.4	5-FU CI	NR	68%	33%		
	221 Gem arm	50.4	Gem + 5FU CI	NR	69%	39%		
	194 5-FU arm	50.4	5-FU CI	16.9 mo			32%	
	187 Gem arm	50.4	Gem + 5FU CI	20.6 mo			21%	
CONKO-001 (Neuhaus et al, 2008)	175 Surgery alone	None	None	20.2 mo	72.5%	42%	20.5%	11.5%
	179 Gem arm	None	Gem	22.8 mo	72.5%	47.5%	34%	22.5%
ESPAC-3 (Neoptolemos et al, 2009)	551 5-FU/LV arm	None	5-FU/LV	23.0 mo				
	537 Gem arm	None	Gem	23.6 mo				
JSAP-02 (Ueno et al, 2009)	60 Surgery alone	None	None	18.4 mo	75%	40%		11%
	58 Gem arm	None	Gem	22.3 mo	78%	48%		24%

- adjuvant therapy for pancreatic cancer has a survival benefit
- optimal chemotherapeutic regimen and the role of radiotherapy – controversial
- RTOG-0848 – phase III ongoing study

Neoadjuvant Therapy

- Downstaging the tumor such that an R0 resection is possible in borderline resectable tumor
- Systemic therapy would be given up front, eliminating the risk of delayed or incomplete treatment postoperatively
- patients who manifest metastatic disease following neoadjuvant therapy would avoid an operation unlikely to be beneficial
- Radiation more effectively given before tissues are devascularized by surgery.

- M.D. Anderson group has recently published reports of two phase II trials of either gemcitabine-based neoadjuvant chemoradiotherapy or preoperative gemcitabine and cisplatin chemotherapy in addition to chemoradiation.

Palliative Therapy

- unresectable and/or metastatic disease
- Endoscopic therapy and interventional radiology - palliation of biliary obstruction and gastric outlet obstruction
- surgical palliation through gastrojejunostomy and Roux-en-Y hepaticojejunostomy
- celiac plexus nerve block at the time of exploration

Palliative Chemotherapy

- intention of prolonging life while preserving or improving quality of life
- [Burris and colleagues](#) 1967 in their landmark study, which showed a significant prolongation in OS, as well as a concurrent clinical benefit response, in patients with advanced pancreatic cancer treated with gemcitabine compared with the previous standard chemotherapy (5-FU)

- Erlotinib – FDA approval
- FOLFIRINOX - 5-FU, leucovorin, irinotecan, and oxaliplatin

Perioperative Management

- Perioperative Anticoagulation –
 - low-molecular-weight heparin (LMWH)
 - compression stockings to wear intraoperatively and for their entire inpatient stay
- Antibacterial Prophylaxis –
- at induction of anesthesia
- High-volume pancreatic surgical centers are consistently reporting mortality rates of less than 2% and morbidity rates of 36% ([Büchler et al, 2003](#); [Cameron et al, 2006](#); [Wagner et al, 2004](#)).

Octreotide Analogues

- Prophylactic administration of somatostatin or its analogue does not uniformly reduce the incidence of pancreatic anastomotic leak, overall morbidity, or mortality after pancreatic resection ([Li-Ling & Irving, 2001](#)).
- use of prophylactic somatostatin in high-risk patients (soft pancreas, small duct)
- Somatostatin is applied intraoperatively (200 µg subcutaneously), followed by three daily doses of 200 µg octreotide for 5 days

Preoperative Biliary Drainage

- Jaundiced patient - increased risk of coagulopathy, malabsorption, malnutrition, and immune dysfunction
- Jaundice (bilirubin level >5.8 mg/dL) is a significant risk factor for postoperative hemorrhage ([Martignoni et al, 2001](#)).
- [Sewnath and colleagues \(2002\)](#) found in a meta-analysis no difference in the overall death rate among patients who had PBD and those who had surgery without PBD.

- Overall complication rate was adversely and significantly affected by PBD, and the hospital stay was also prolonged.

PBD

- colangitis
- Severe complication of jaundice

Fast-Track Surgery ([Basse et al, 2002](#))

- Thoracic Epidural analgesia ([Fotiadis et al, 2004](#))
 - shorter duration of postoperative ileus
 - attenuation of the stress response
 - fewer pulmonary complications
 - improved postoperative pain and mobility
 - patient perception of a quicker recovery
- standardized regimen of early feeding and mobilization
- reduce hospital stay

Standard PD vs PPPD

- Meta-analysis ([Diener et al, 2008b](#)).
- classical Kausch-Whipple procedure and the pylorus-preserving Whipple procedure are comparable with regard to perioperative morbidity and mortality and long-term outcome
- PPPD should be designated the “standard” procedure for pancreatic and periampullary neoplasm([Bell, 2004](#))
- Hemigastrectomy should be performed only when gastric or proximal duodenal invasion or grossly abnormal peripyloric nodes are evident.

Vascular Resection

- systematic review ([Siriwardana & Siriwardena, 2006](#)) evaluated 52 manuscripts with 6333 patients
- 1646 of these patients (26%) underwent synchronous portal and superior mesenteric vein resection
- The median operation time was 513 minutes (range, 168 to 1740 minutes),
- median blood loss was 1750 mL (range, 300 to 26,000 mL),
- median time for PV occlusion was 20 minutes (range, 7 to 302 minutes).

- The long-term survival was 13 months (range, 1 to 109 months) after portal and superior mesenteric vein resection.
- The 1-, 3-, and 5-year overall survival rates of 1351 patients undergoing portal and superior mesenteric vein resection was 50%, 18%, and 8%, respectively.
- In 15% of pancreatic operations in which portal or mesenteric vein resection had to be performed, arteries were also resected. These included the common hepatic artery (50%), SMA (20%), celiac axis (10%), and other arteries ([Siriwardena & Siriwardena, 2006](#)).

- portal and superior mesenteric vein should be performed when adherence or infiltration of the tumor is present to achieve R0 resection
- perioperative morbidity, mortality, and long-term survival are identical
- resection of the SMA, celiac trunk, or hepatic arteries is technically feasible – but does not leads to any improvement of long-term outcome

Multivisceral Resections

- en bloc resection of contiguously involved organs can be performed safely ([Sasson et al, 2002](#)).
- No difference was reported with regard to perioperative morbidity (35%) and mortality (3%) compared with standard resection
- The main aim of the extended procedure must be an R0 resection because this is the most important predictor of long-term survival ([Wagner et al, 2004](#)).

- mesocolon, colon, adrenal glands, liver, and stomach – can be resected
- morbidity is increased
- The 5-year survival rate was 16%, and the median survival of 26 months is much better than the 6 to 9 months reported for patients who are not resected at all.

Lymphadenectomy

- consensus conference - Castelfranco Veneto, Italy ([Pedrazzoli et al, 1999](#))
- The three stages of radicality for PD have been named *standard*, *radical*, and *extended radical*, depending on the nodal stations removed.
- For body and tail of pancreas - two different procedures are identified: *standard and radical*.
- Japan Pancreas Society, 1993 – rules followed

- Japan, extended lymphadenectomy was widely used in the late 1980s and 1990s because of the initial reports of [Ishikawa and colleagues \(1988\)](#) and [Manabe and colleagues \(1989\)](#), who advocated an extension of the PD
- survival rates were significantly increased in the extended lymphadenectomy groups
- the largest retrospective studies ([Hirata et al, 1997](#); [Mukaiya et al, 1998](#)), which together included 1330 patients, did not reproduce these results

- Six prospective, nonrandomized studies - revealed no significant differences in mortality rate and long-term survival
- for node-negative cancer, extended lymphadenectomy significantly improved the 5-year survival rates ([Popiela et al, 2002](#))
- extended lymphadenectomy was associated with an increased rate of severe diarrhea in the early postoperative phase

- Four randomized controlled trials ([Farnell et al, 2005](#); [Michalski et al, 2007](#); [Nimura et al, 2004](#); [Pedrazzoli et al, 1998](#); [Yeo et al, 2002](#)) - metaanalysis – no difference in morbidity, mortality, and survival
- Standard lymphadenectomy included the dissection of lymph nodes at the anterior and posterior pancreatoduodenal side, at the pylorus, bile duct, and superior and inferior part of the pancreatic head and body

- Extended procedure, additional lymph nodes were dissected within the complete circumference at the aorta, the inferior and superior mesenteric arteries, and the celiac trunk
- The largest study on this subject enrolled 294 patients; it was published in 2002 and updated in 2005 by Yeo and colleagues. significant increase in morbidity was reported in the extended lymphadenectomy group (29% vs. 43%; $P < .01$), which was mainly due to higher rates of delayed gastric emptying and pancreatic fistula.

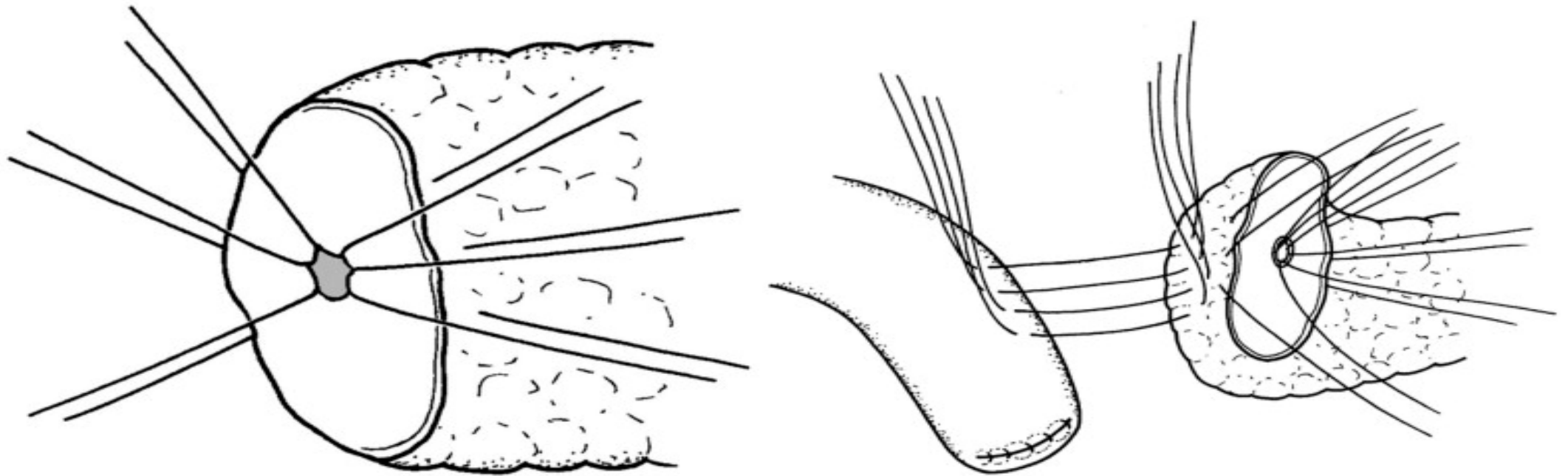
Summary

- extended lymphadenectomy does not improve survival but may increase morbidity
 - follow-up publication and a study on quality of life (QOL) of the same patient group ([Riall et al, 2005](#))
 - Mayo Clinic by [Farnell and colleagues \(2005\)](#)
 - Japan by Nimura and colleagues (2004)

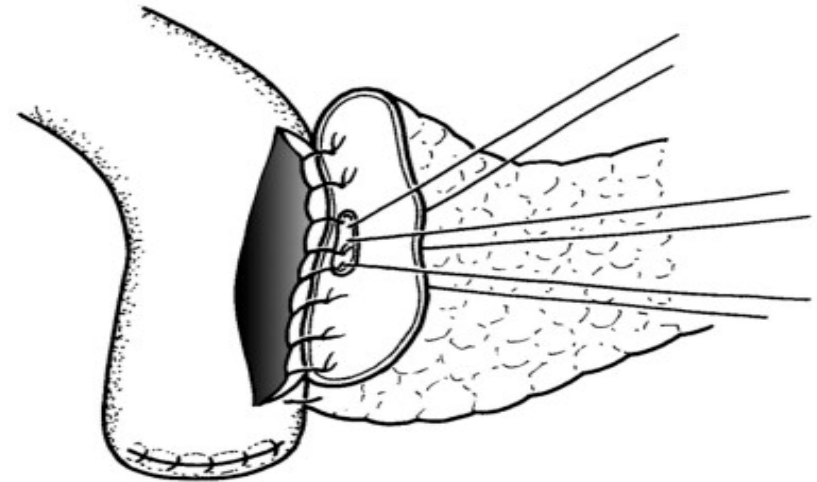
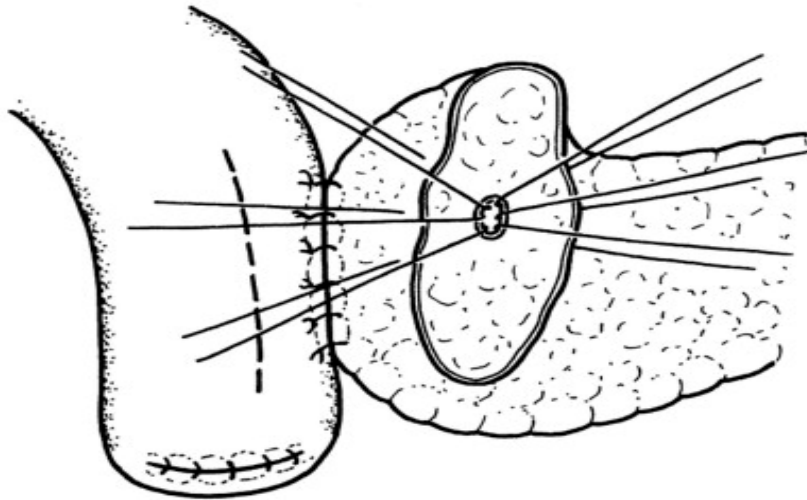
Reconstruction After Pancreatic Resection and Management of the Pancreatic Remnant

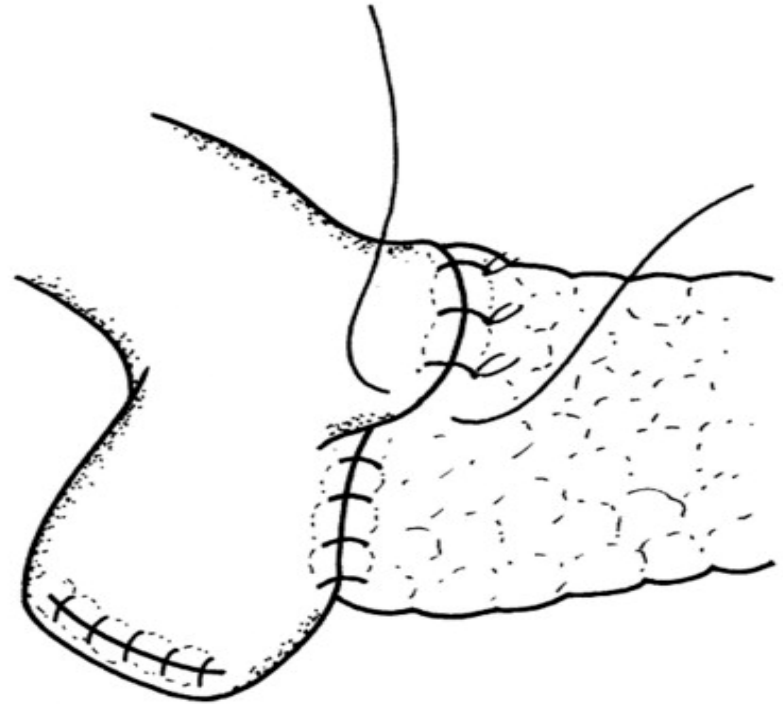
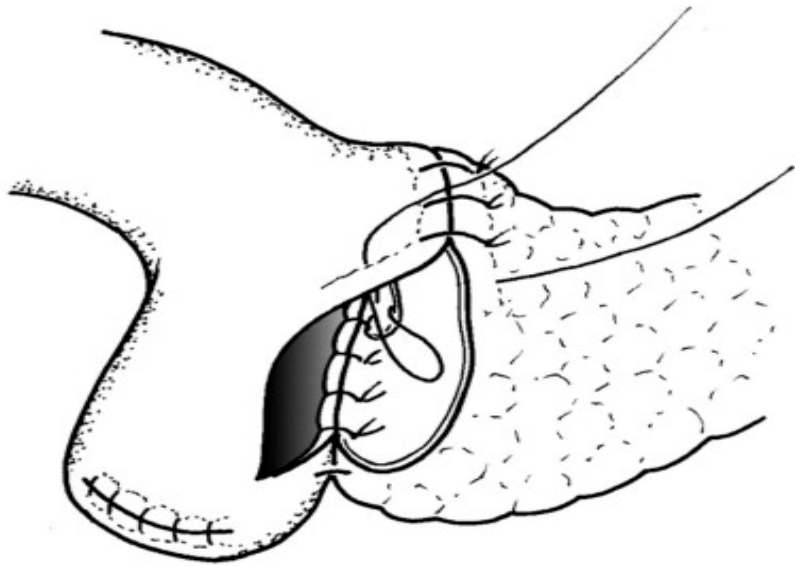
- basic tenets of a safe anastomosis are -
 - careful handling of the pancreatic tissues
 - a tension-free adaptation
 - good perfusion
 - no distal obstruction
- *dunking procedure*
- *duct-to-mucosa technique*
- pancreatogastrostomy (PG) ([Zenilman, 2000](#))
- surgeon's concentration on meticulous execution of the chosen technique ([Trede et al, 2001](#))

standardized technique of PJ performed in an end-to-side fashion with a retrocolic jejunal limb ([Z'graggen et al, 2002](#))



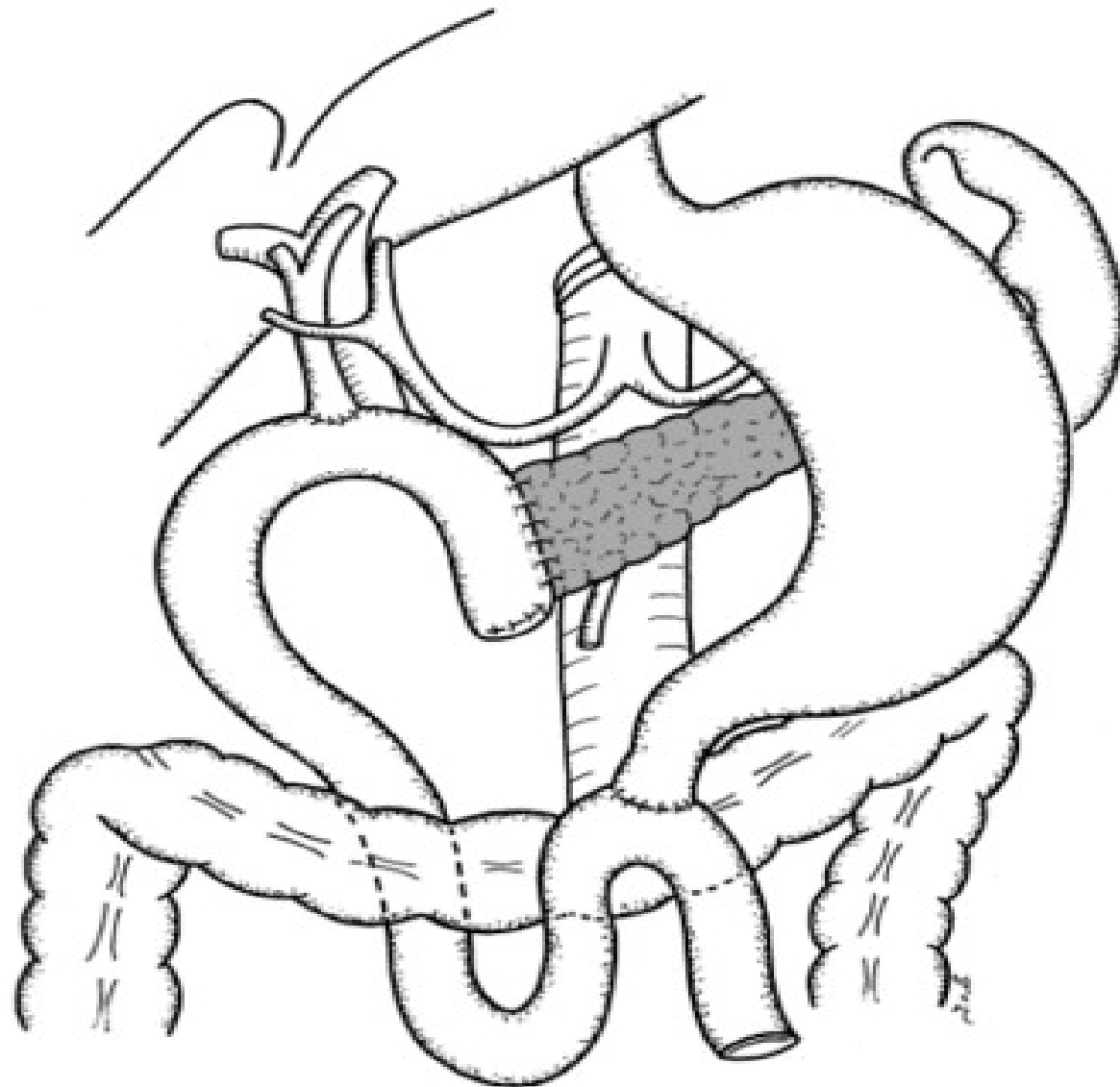
two layers with duct-to-mucosa adaptation using monofilament absorbable polydioxanon sutures (PDS 5/0) with an atraumatic JRB-1 (5/8) needle.





- pylorus preservation does not seem to increase the frequency of DGE ([Horstmann et al, 2004](#)).
- Retrocolic reconstruction –
 - jejunal limb venous congestion – DGE
 - gastric distension, which can lead to angulation of the anastomosis
 - close proximity of the duodenojejunosomy to the PJ also predisposes the occurrence of DGE in the event of a small PJ leak or transient postoperative remnant pancreatitis.

- antecolic reconstruction (Riediger et al, 2003) predisposes the relatively fixed stomach to angulation or torsion
- The risk of DGE caused by local inflammation is reduced by placing the duodenojejunostomy in the infracolic compartment through a separate mesenteric window, away from the pancreatic and biliary anastomoses



Drain

- Placement of drains did not translate into a reduction in surgical morbidity ([Conlon et al, 2001](#))
- drain group developed intraperitoneal sepsis, fluid collection, or fistula
- recently published meta-analysis of prophylactic drainage after GI surgery ([Petrowsky et al, 2004](#))
- drains do not reduce complications following hepatic, colorectal, or rectal resection with primary anastomosis, and drains should not be used following such procedures

NG Tube

- A meta-analysis on the need for NG decompression does not decrease the risk of postoperative nausea, vomiting, aspiration, wound dehiscence, and anastomotic leak ([Cheatham et al, 1995](#)).
- fever, atelectasis, and pneumonia were significantly less common, and days to first oral intake were significantly fewer, in patients managed without NG tube.

Table I. Four final definitions summarizing the current pancreatic fistula concept according to the literature*

1. Output > 10 mL/d of amylase-rich fluid postoperative (postop) day 5 or for > 5 days.
 2. Output > 10 mL/d of amylase-rich fluid after postop day 8 or for > 8 days.
 3. Output between 25 mL/d and 100 mL/d of amylase-rich fluid after postop day 8 or for > 8 days.
 4. Output > than 50 mL/d of amylase-rich fluid after postop day 11 or for > 11 days.
-

Table II. Main parameters for POPF grading

<i>Grade</i>	<i>A</i>	<i>B</i>	<i>C</i>
Clinical conditions	Well	Often well	Ill appearing/ bad
Specific treatment*	No	Yes/no	Yes
US/CT (if obtained)	Negative	Negative/ positive	Positive
Persistent drainage (after 3 weeks)†	No	Usually yes	Yes
Reoperation	No	No	Yes
Death related to POPF	No	No	Possibly yes
Signs of infections	No	Yes	Yes
Sepsis	No	No	Yes
Readmission	No	Yes/no	Yes/no

Thank You