

Gastro Foundation Fellows Weekend 2017

Chronic Pancreatitis

Jose Ramos

University of the Witwatersrand
Donald Gordon Medical Centre

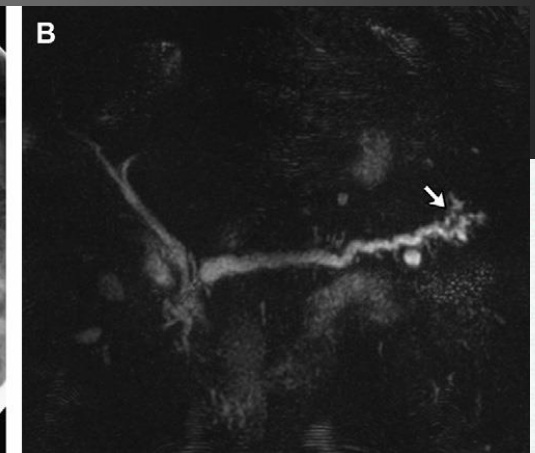
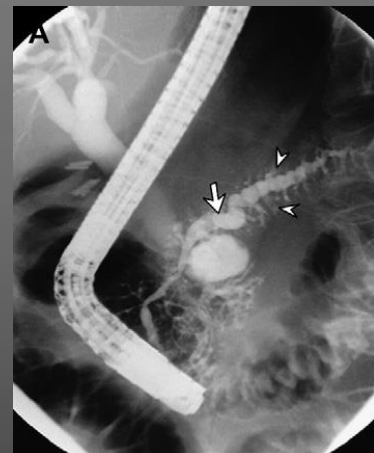


Aetiology in SA

- Alcohol (up to 80%)
- Idiopathic
- Tropical
- Obstruction
- Autoimmune
- Miscellaneous

Diagnosis of CP

- Clinical symptoms
 - Pain
 - Endocrine insufficiency
 - Exocrine insufficiency
 - Complications
- Imaging
 - Pancreatic calcification
 - Ductal dilatation/strictures



Classification of CP

Guideline for the diagnosis and treatment of chronic pancreatitis

P C Bornman, J F Botha, J M Ramos, M D Smith, S van der Merwe, G A Watermeyer, C C M Ziady

S Afr Med J 2010; 100: 845-860.

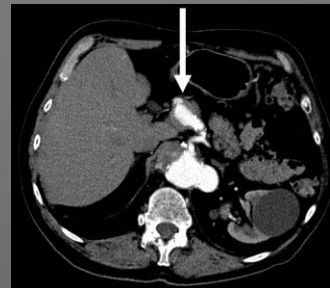
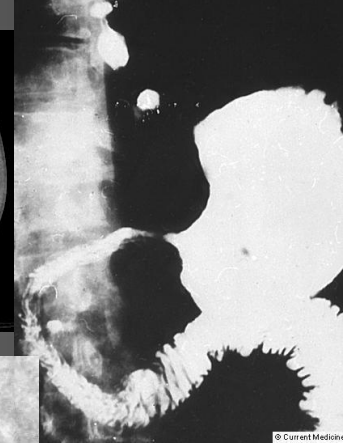
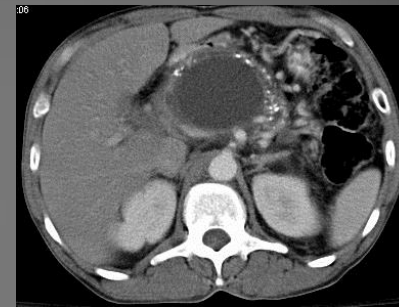
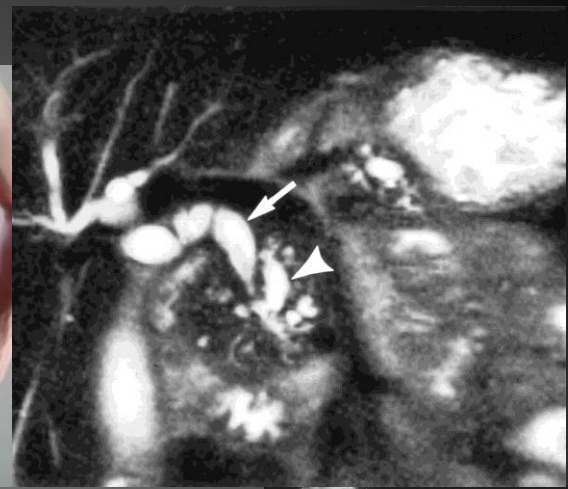
Table II. Cambridge Classification of CP²⁵

Group	Terminology	Findings
0	Normal	Whole gland without abnormal feature
	Equivocal	<3 abnormal branches
1	Mild	>3 abnormal branches
2	Moderate	Abnormal main duct and branches
3	Marked	As above with one or more of the following: <ul style="list-style-type: none">- large cavities (>1 cm)- intraductal filling defects or calculi- ductal obstruction or strictures- gross irregularity- contiguous organ invasion



Problems in CP

- Pain
- Endocrine insufficiency
- Exocrine insufficiency
- Biliary obstruction
- Pseudocysts / fluid collections
- Duodenal obstruction
- Vascular complications
 - Venous thrombosis
 - False aneurysms
- Pancreatic cancer



Management options

Problem	Surgery	Medical	Interventional
Pain	Yes	Yes	Yes
Endocrine insufficiency	No	Yes	No
Exocrine insufficiency	Yes/No?	Yes	No
Biliary obstruction	Yes	No	Yes
Pseudocysts / fluid collections	Yes	No	Yes
Duodenal obstruction	Yes	No	Yes
Vascular complications	No	Yes	Yes
Pancreatic cancer / Suspicion	Yes	Yes	No

Endocrine insufficiency

- HbA1c most reliable test
- Oral agents of limited benefit
- Cause is impaired insulin secretion
- Best managed with insulin replacement

Exocrine insufficiency

Diagnosis of PEI: Pancreatic Function Tests

Co-efficient of fat absorption (CFA)¹

Carbon 13 (¹³C)- mixed triglyceride (¹³C-MTG) breath test¹

Faecal elastase tests (FE-1)²

1. Dominguez-Munoz JE et al. *J Gastroenterol Hepatol*. 2011;26(2):12-16.
2. Sikkens ECM, et al. *Best Pract Res Clin Gastroenterol*. 2010;(24);337-347.

Faecal Elastase Test

- Faecal elastase tests are becoming more prevalent in clinical practice¹
- In 2010, it was reported to be the most popular test used to evaluate PEI²
- Requires a single stool sample²
- Measures the amount of elastase enzyme left in the stool^{1,2}
- Specificity: Approximately 93%
 - Compromised in patients with small bowel disease and type 1 diabetes
 - Risk of false positive result in diarrhoea and other intestinal disorders²

>200 µg/g stool: normal value²

<200 µg/g stool: mild PEI¹

<100 µg/g stool: severe PEI¹

1, Australasian treatment guidelines for the management of pancreatic exocrine insufficiency. 2010:1-89.
2. Sikkens ECM et al. *Best Pract Res Clin Gastroenterol*. 2010;(24):337-347.

Diagnosis of PEI: Practical Approaches (or Non-Pancreatic Function Tests)

In certain conditions, where these tests are not widely available in clinical practice, some practical approaches may aid diagnosis

Assessment of symptoms¹

Pancreatic morphology in patients with CP²

Nutritional parameters in patients with CP³

High probability of PEI in specific patients groups¹

Trials of PERT^{4,5}

1. Dominguez-Munoz JE et al. *J Gastroenterol Hepatol*. 2011;26(2):12-16.
2. Dominguez-Munoz JE et al. *Pancreas* 2012;41(5):724-8.
3. Lindkvist B et al. *Pancreatology* 2012;12:305-310.
4. Sikkens ECM et al. *Best Pract Res Clin Gastroenterol*. 2010;(24):337-347.
5. Toouli J et al. *MJA*. 2010;93(8):461-467.

Diagnosis of PEI: Assessment of Symptoms

Common symptoms

- Abdominal pain¹
- Flatulence in adults¹
- Weight loss¹
- Lack of weight gain in children¹
- Steatorrhea¹
- Lack of energy²



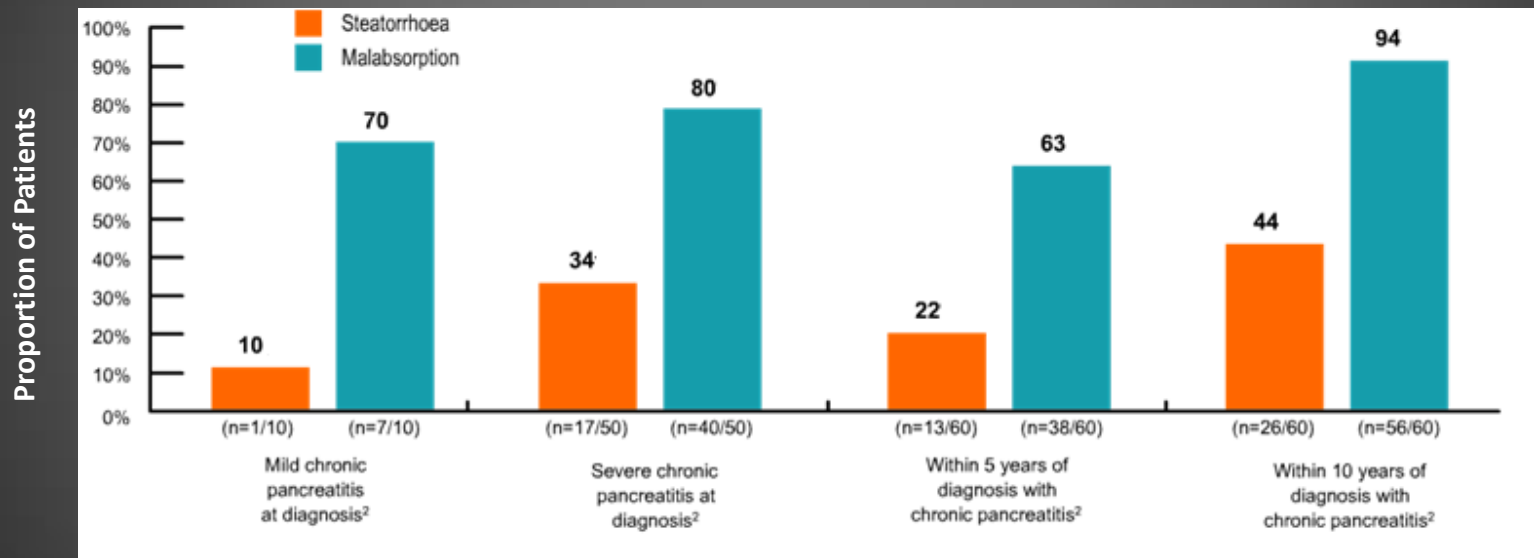
Diagnosis of PEI is commonly based on an assessment of the individual's clinical state and a self-report of bowel movements and weight loss in adults or failure to thrive in children¹

1. Australasian treatment guidelines for the management of pancreatic exocrine insufficiency. 2010:1-89
2. Ockenga J. *HPB*. 2009. 11(suppl.3):11-15.

Assessment of Symptoms: PEI May be Missed in Asymptomatic Patients

- Diagnosis of PEI are often missed in the absence of clinical steatorrhoea¹
- Many patients with malabsorption are asymptomatic²

Presence of Steatorrhoea and Malabsorption in CP Patients



“Every patient with PEI and maldigestion, independent of the degree of steatorrhoea and presence or absence of associated symptoms, should receive PERT”³

1. Imrie CW et al. *Aliment Pharmacol Ther.*2010;32(Suppl. 1):1–25.
2. Dumasy V et al. *Am J Gastroenterol.* 2004; 99(7): 1350-1354.
3. Sikkens ECM et al. *Best Pract Res Clin Gastroenterol.* 2010;(24);337-347.

High Probability of PEI in Specific Patient Groups

Patient groups who have a high likelihood of PEI (>80%)¹

- Chronic pancreatitis with dilated pancreatic duct and/or calcifications²
- Severe necrotising pancreatitis¹
- GI or pancreatic surgery¹
- Unresectable cancer of the pancreatic head¹

In patients where the likelihood of PEI is higher than 80%, PERT could be started even in the absence of confirmatory diagnostic test.

1. Domínguez-Muñoz JE. *J Gastroenterol Hepatol*. 2011; 26(2):12-16.

2. Dominguez-Munoz JE et al. *Pancreas* 2012;41(5):724-728.

GI, gastrointestinal

Treatment of exocrine insufficiency

Guideline for the diagnosis and treatment of chronic pancreatitis

P C Bornman, J F Botha, J M Ramos, M D Smith, S van der Merwe, G A Watermeyer, C C M Ziady

S Afr Med J 2010; 100: 845-860.

Recommendations

- Pancreatic enzyme replacement therapy is recommended in patients with clinical features of exocrine insufficiency.
- Enteric-coated preparations are superior to uncoated therapy for the treatment of malabsorption.
- The preferred dose is a minimum of 25 - 40 000 units of lipase per meal and 10 - 25 000 units of lipase with snacks.
- The response to treatment is measured clinically by weight gain and improvement in symptoms.
- The appropriate dose of enzyme replacement therapy needs to be titrated to maximise response.
- Patients who remain symptomatic despite compliance with maximal enteric-coated enzyme replacement would benefit from the addition of acid-suppressing medication.



CP – indications for intervention

- Chronic pain not responding to non-opiate analgesia
- Biliary obstruction
- Duodenal obstruction
- Confirmed or suspected cancer

Surgery vs interventional endoscopy/radiology?

Long-term Outcomes of Endoscopic vs Surgical Drainage of the Pancreatic Duct in Patients With Chronic Pancreatitis

DJUNA L. CAHEN,* DIRK J. GOUMA,[§] PHILIPPE LARAMÉE,^{||} YUNG NIO,[¶] ERIK A. J. RAUWS,[‡] MARJA A. BOERMEESTER,[§] OLIVIER R. BUSCH,[§] PAUL FOCKENS,[‡] ERNST J. KUIPERS,* STEPHEN P. PEREIRA,[#] DAVID WONDERLING,^{||} MARCEL G. W. DIJKGRAAF,** and MARCO J. BRUNO*

*Department of Gastroenterology and Hepatology, Erasmus Medical Center, Rotterdam, The Netherlands; Departments of [‡]Gastroenterology and Hepatology, [§]Surgery, and [¶]Radiology and ^{**}Clinical Research Unit, Academic Medical Center, Amsterdam, The Netherlands; ^{||}National Clinical Guideline Center, Royal College of Physicians, London, England; and [#]Institute of Hepatology, University College London, London, England

GASTROENTEROLOGY 2011;141:1690-1695

Table 3. Long-term Cost Analysis of Endoscopic and Surgical Treatment

Cost category ^a	Endoscopy (n = 19)	Surgery (n = 19)	Cost difference (95% confidence interval)	P value
Diagnostic procedures	1618	938	681 (38 to 1749)	.043
Therapeutic procedures and hospital stay	28,327	23,173	5153 (-16,895 to 26,963)	.32
Pancreatic insufficiency	1107	926	181 (31 to 328)	.036
Total cost	31,048	25,042	6006 (-16,188 to 27,786)	.29

^aCosts are presented in US dollars and were converted from pound sterling using the 2009 Purchasing Power Parity (\$1 = £0.62).²⁸ http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4.

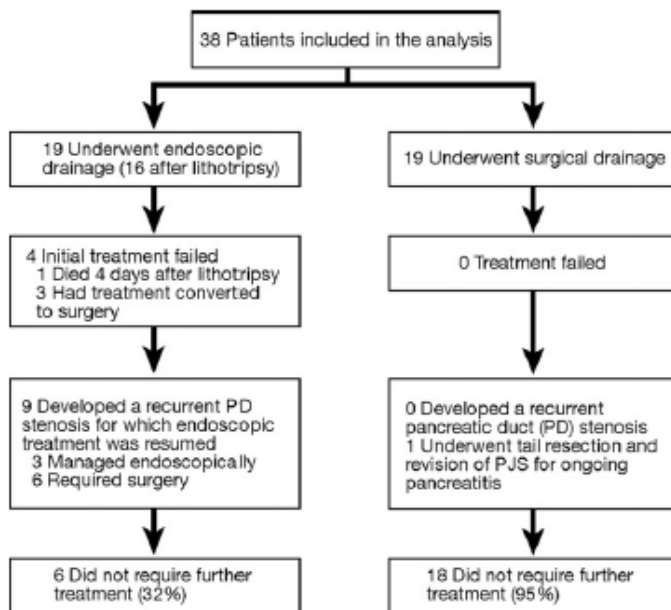


Figure 2. Treatment outcome.

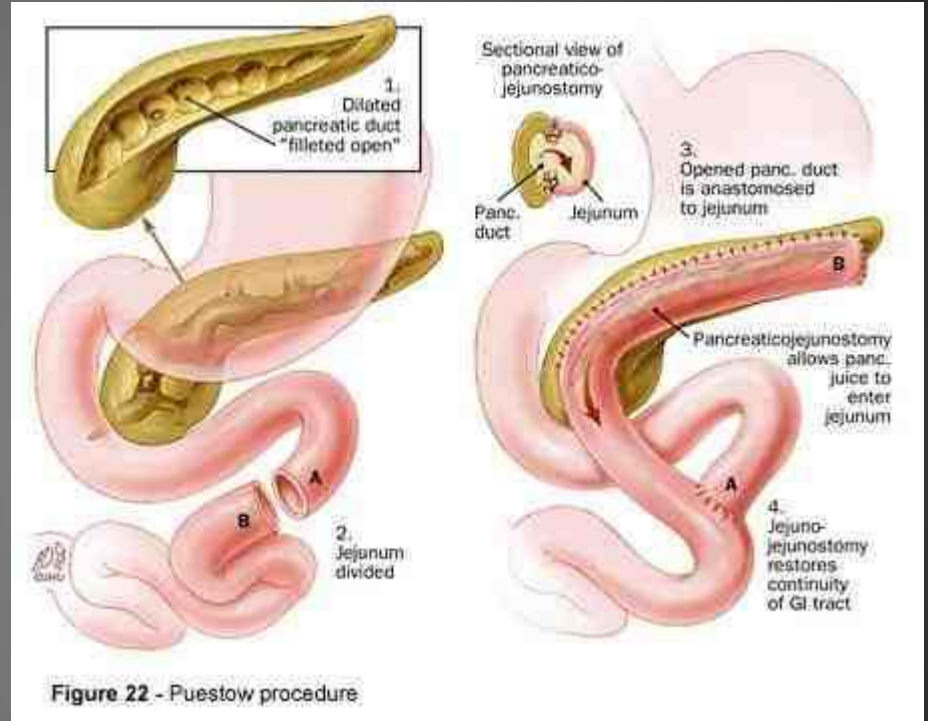
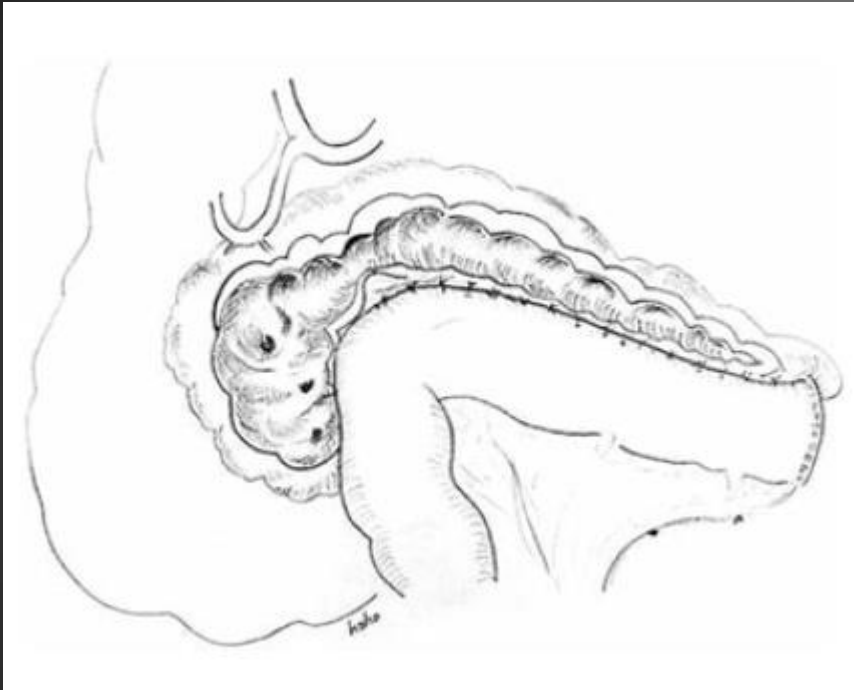
CONCLUSIONS:

In the long term, symptomatic patients with advanced chronic pancreatitis who underwent surgery as the initial treatment for pancreatic duct obstruction had more relief from pain, with fewer procedures, than patients who were treated endoscopically. Importantly, almost half of the patients who were treated with endoscopy eventually underwent surgery.

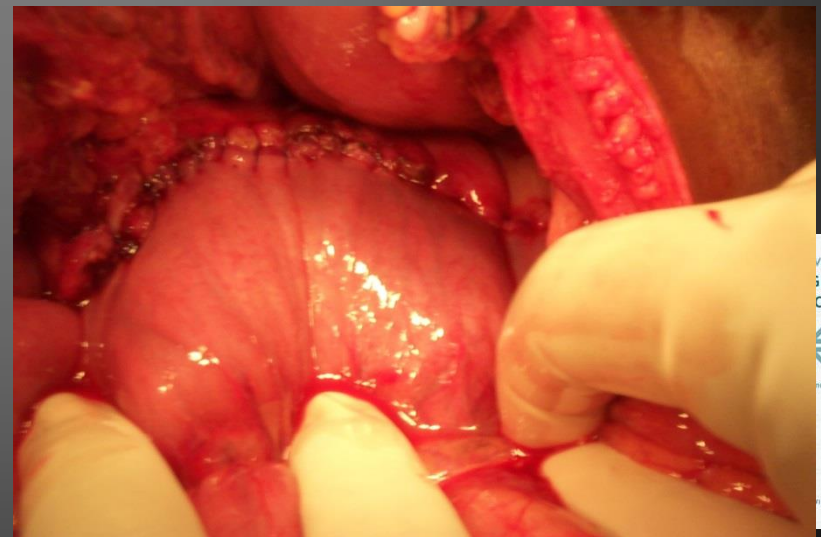
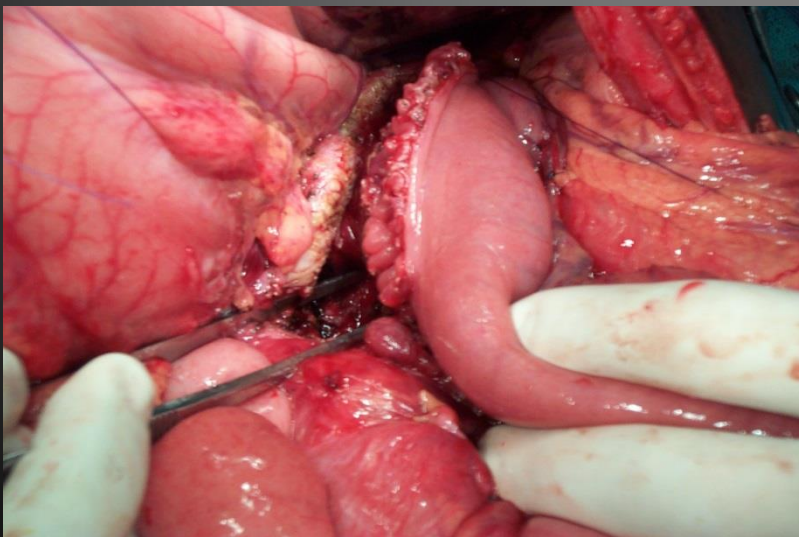
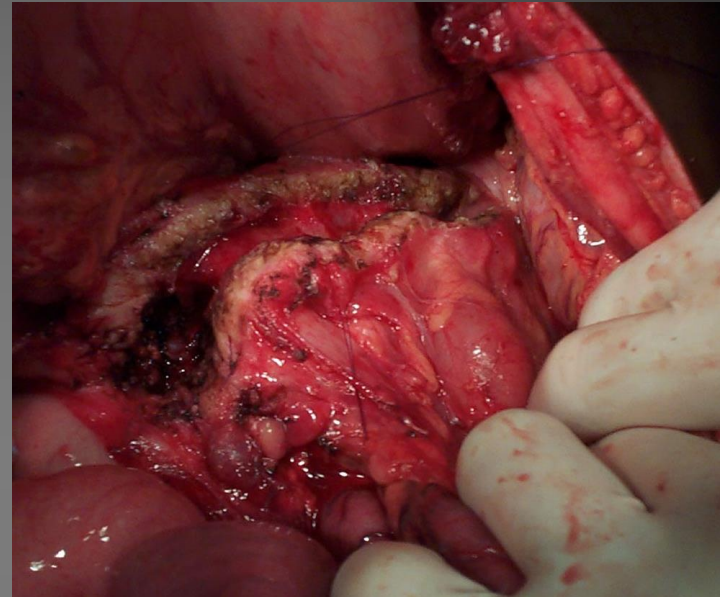
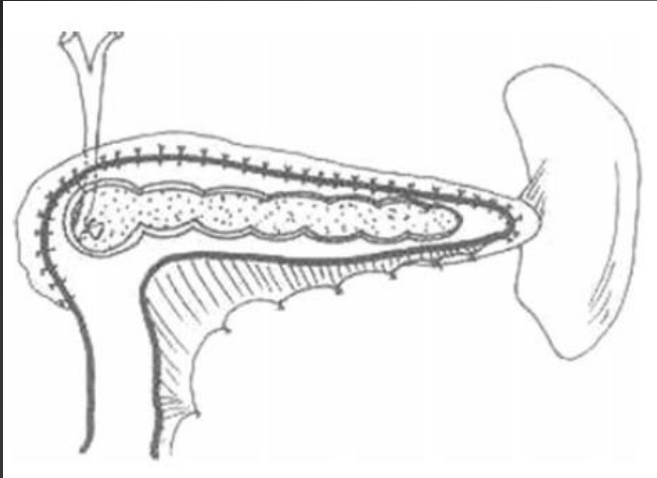
Surgical Procedures

- Drainage
 - Ductal drainage (Puestow)
 - Cyst-drainage
- Duodenal preserving resection + drainage (DPPHR)
 - Frey
 - Beger
 - Various options (Izbicki, Berne)
- Head resection
 - Whipple
 - PPPD
- Distal pancreatectomy
- Total pancreatectomy

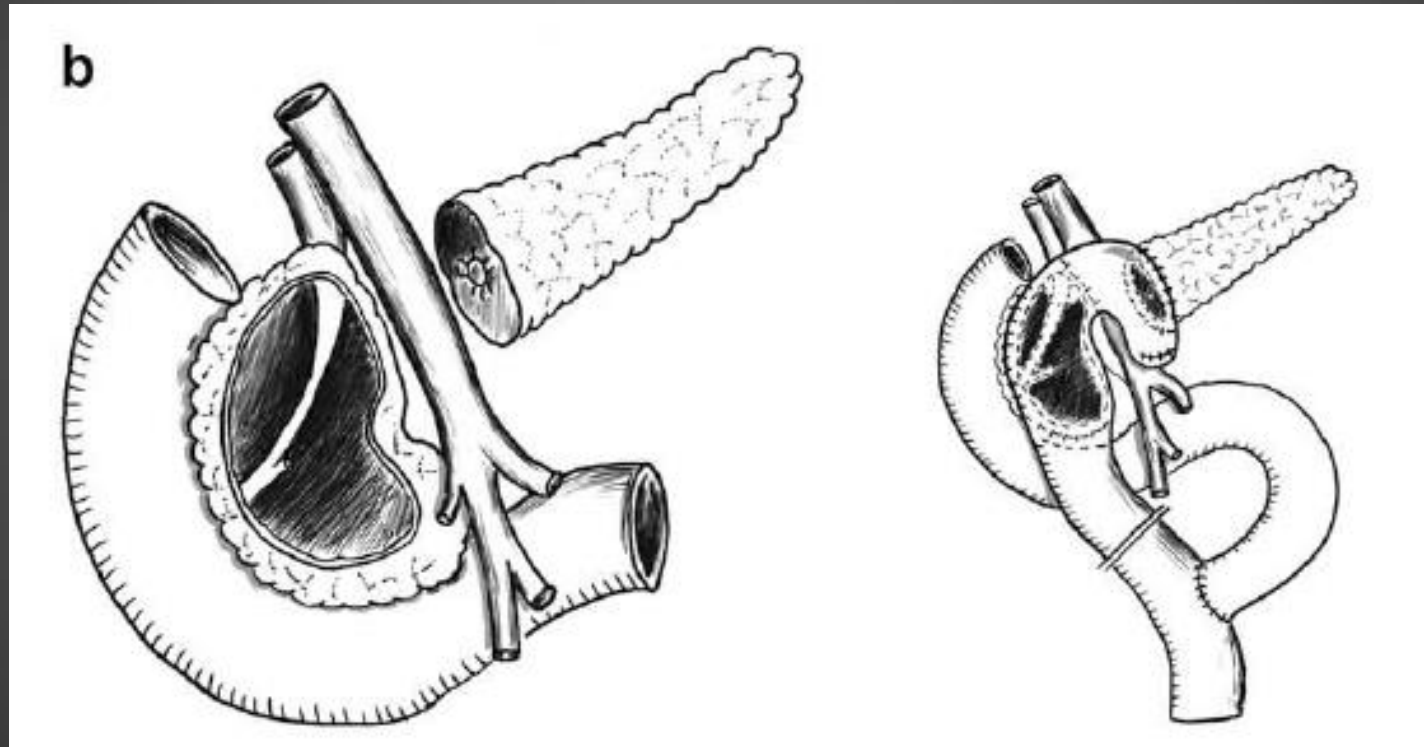
Puestow



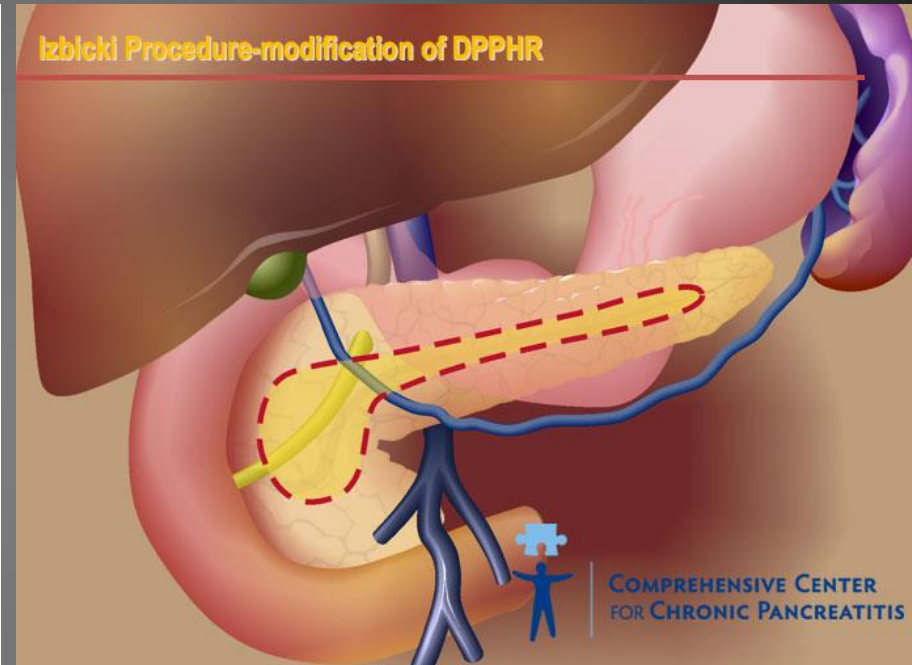
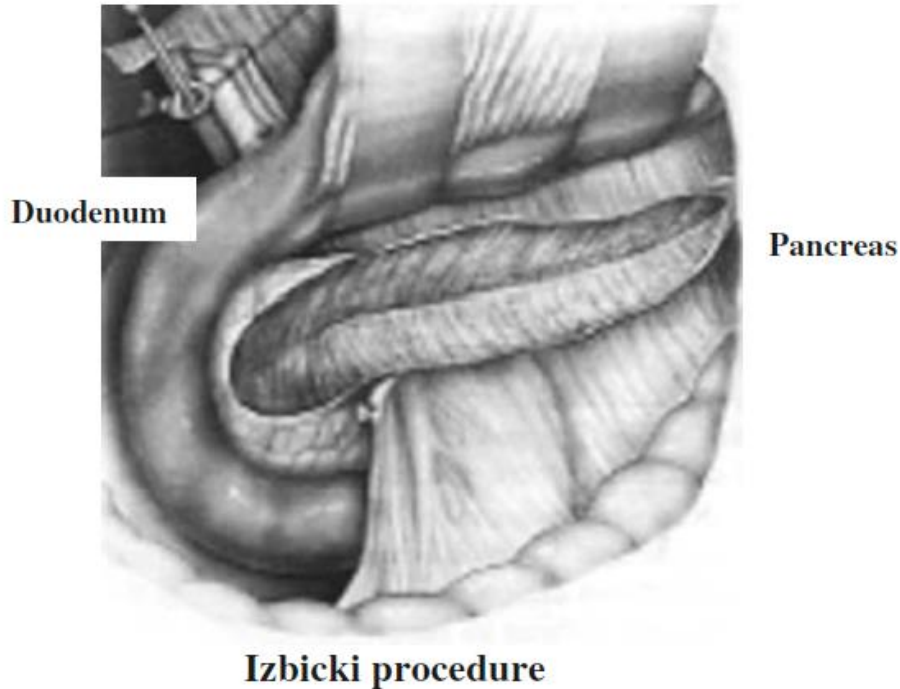
Frey operation



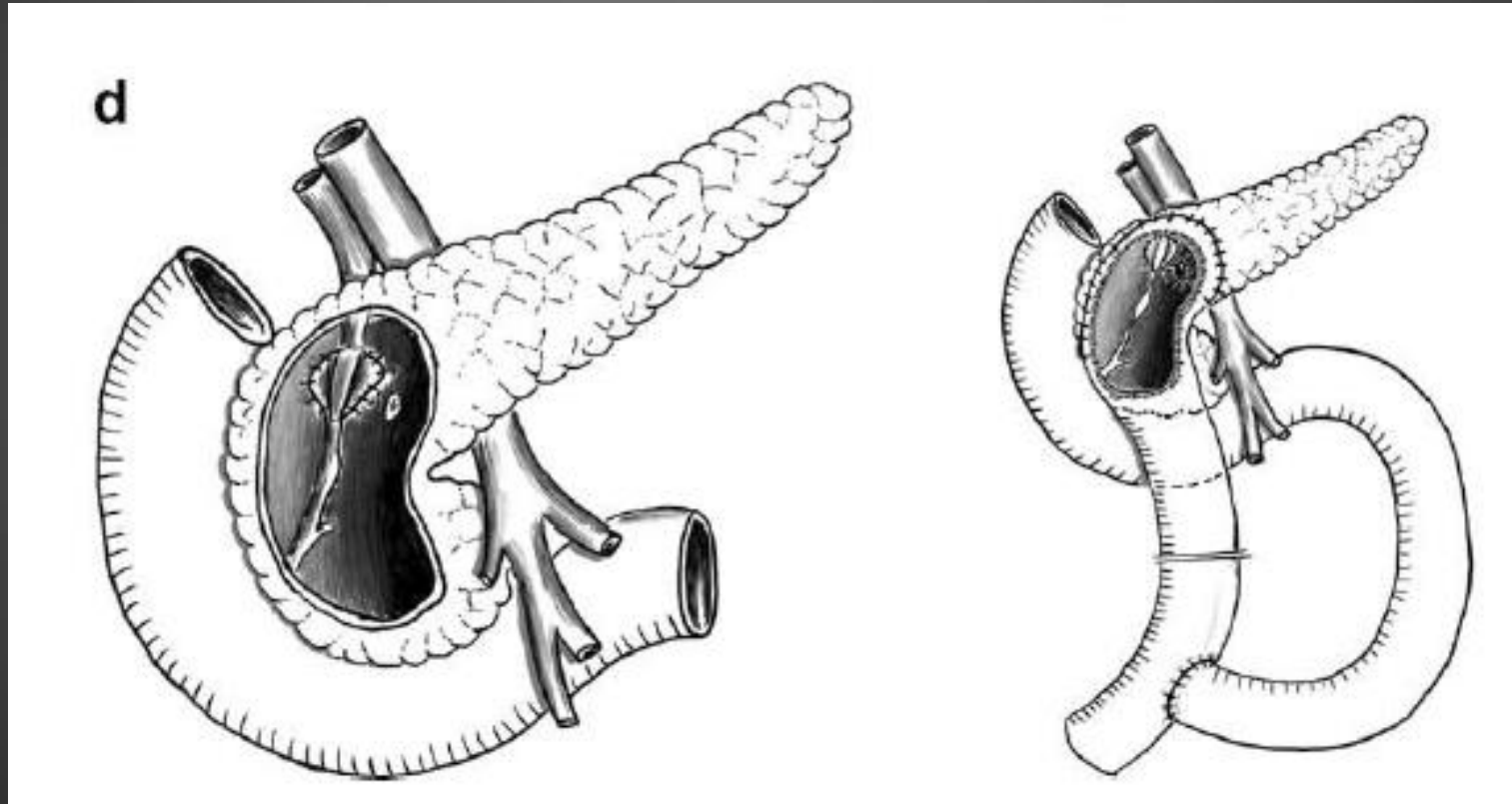
Beger operation



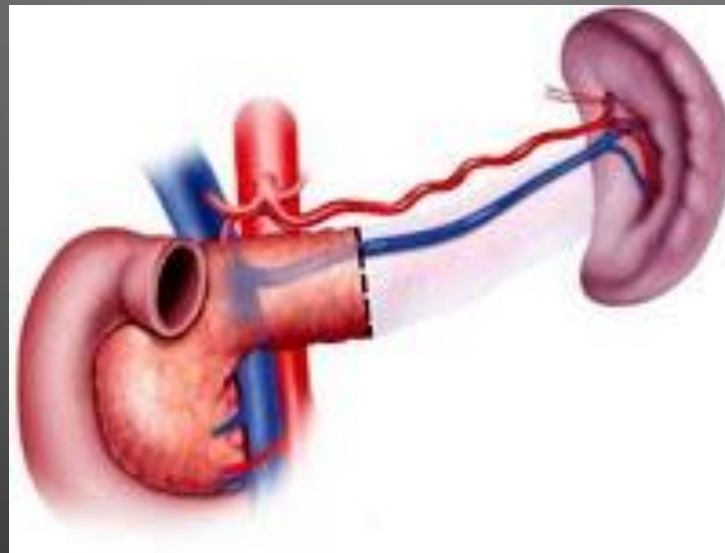
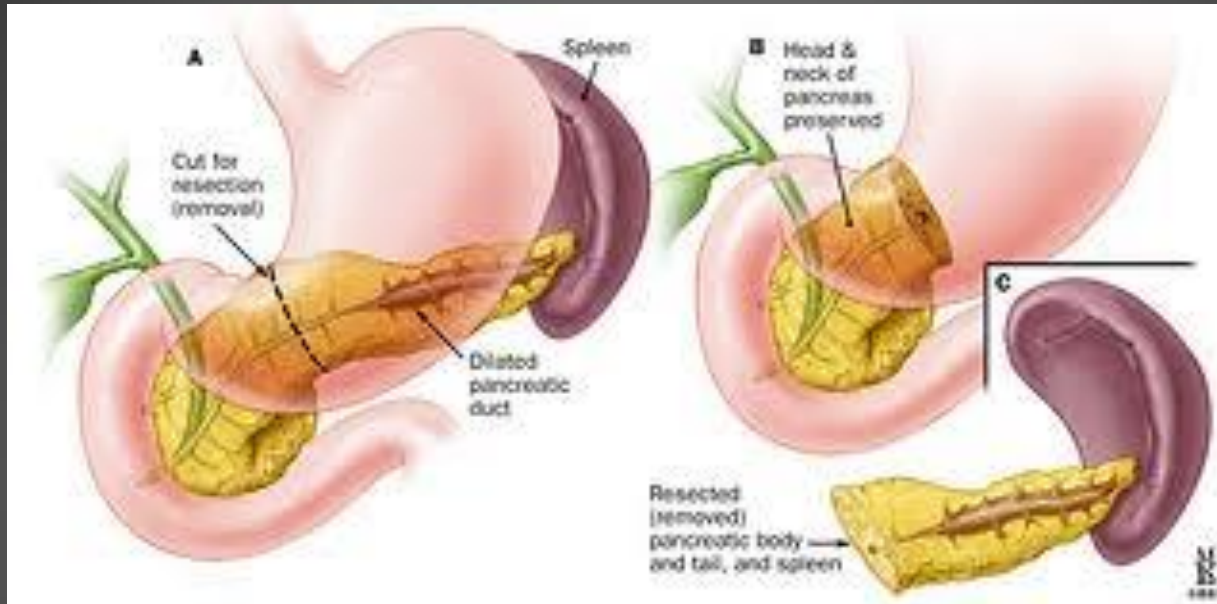
Izbicki operation



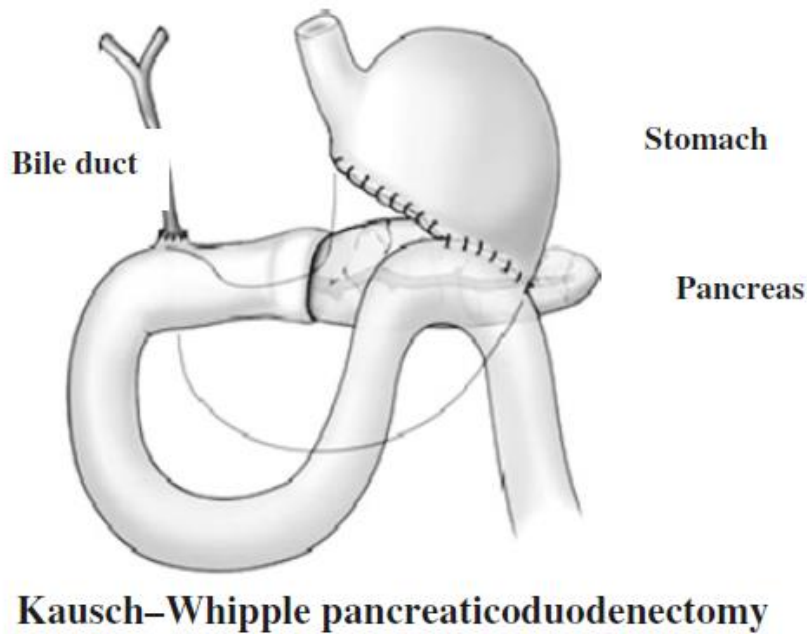
Berne operation



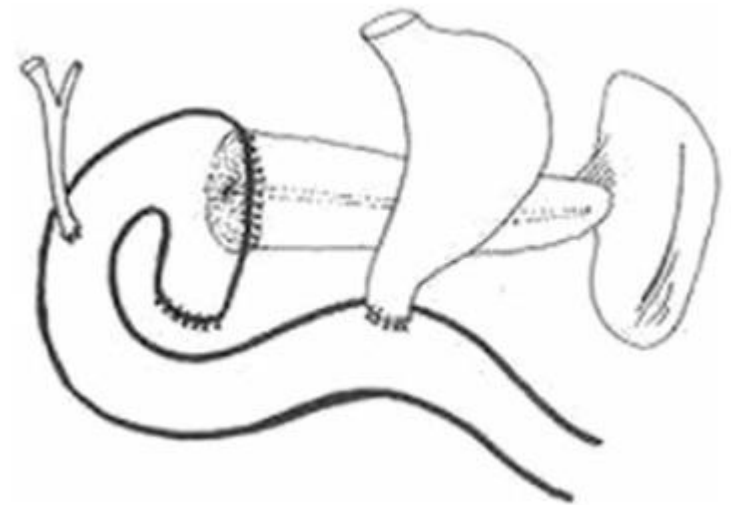
Distal pancreatectomy



Pancreaticoduodenectomy



Classical Whipple

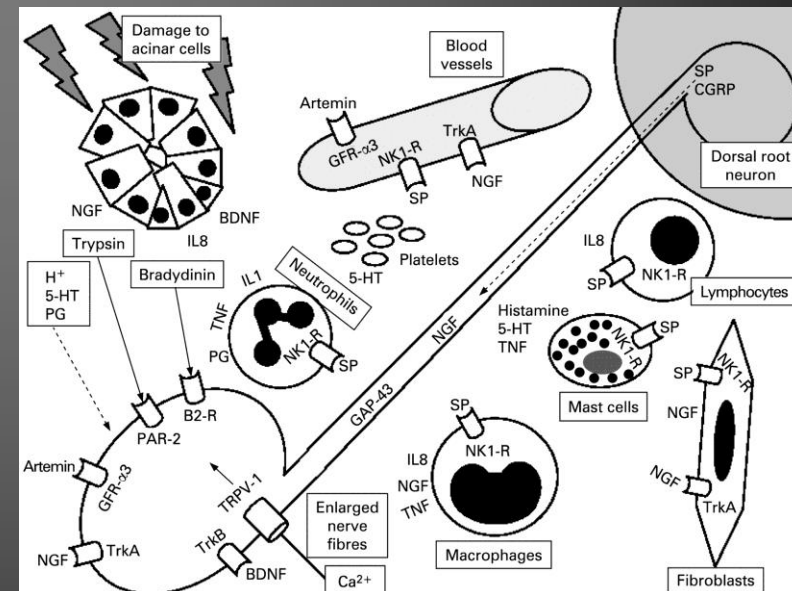
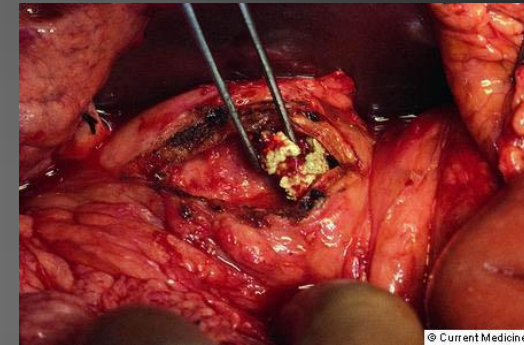
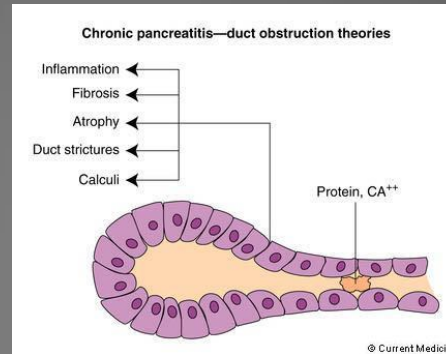


Pylorus-preserving PD

Which operation should we perform for chronic pain?

What factors cause pain?

- Ductal and parenchymal hypertension
- **Ductal dilatation**
- Inflammatory mass
- **Parenchymal ischaemia**
- Neurogenic inflammation
- **Peripheral and central nerve sensitization**
- Parenchymal and ductal calcification
- **Biliary and duodenal obstruction**



The ideal operation?

- Resolve pain
 - Decompress parenchyma and ductal system
 - Reduce volume of or remove inflammatory mass
- Low morbidity and mortality
- Limited impact on pancreatic function
 - Exocrine insufficiency
 - Endocrine insufficiency
- Improve QOL in short and long term

Frey Operation

Johannesburg Hospital series 1997

Interim analysis of Late outcome

- Pain relief 35 / 38 (92%)
- Jaundice 0 / 38
- Pancreatitis 2 (?)
- Pain 4
- Diabetes *initial* 12 (29%)
new 1
- Steatorrhoea *initial* 11 (27%)
new 2

Guideline for the diagnosis and treatment of chronic pancreatitis

P C Bornman, J F Botha, J M Ramos, M D Smith, S van der Merwe, G A Watermeyer, C C M Ziady

S Afr Med J 2010; 100: 845-860.

Table IV. The most common surgical options for CP

Procedures	Indications
Resection:	
- pancreaticoduodenectomy	- suspicion of malignancy
- distal pancreatectomy	- disease confined to the body and tail of the pancreas
Duodenal-preserving resection of the head of the pancreas	- inflammatory mass of the head of the pancreas, with or without a dilated pancreatic duct
Pancreatico-jejunostomy	- dilated pancreatic duct without inflammatory mass in the head of the pancreas.

Recommendation

In carefully selected cases, surgery has an important role to play in the management of intractable pain in CP. The choice of surgery is governed to a large extent by the size of the pancreatic duct and the presence or absence of an inflammatory mass in the head of the pancreas. The principles of surgery are to minimise morbidity and mortality and to preserve exocrine and endocrine pancreatic function. The classic Whipple's operation has now been superseded by organ-preserving resection. Surgery should be performed in specialised centres, with the emphasis on a multi-disciplinary approach.

Summary and conclusion

The role of endoscopic therapy for pain control in uncomplicated disease is limited, while organ-preserving operations in carefully selected patients with intractable pain may provide long-term relief.



Meta analysis

A meta-analysis of the long-term effects of chronic pancreatitis surgical treatments: duodenum-preserving pancreatic head resection versus pancreatoduodenectomy

LÜ Wen-ping, SHI Qing, ZHANG Wen-zhi, CAI Shou-wang, JIANG Kai and DONG Jia-hong

Chinese Medical Journal 2013;126 (1)

Conclusion DPPHR and PD result in equal pain relief, mortality, and pancreatic function; however, DPPHR provides superior long-term outcomes.

Wits University
Donald Gordon
Medical Centre



Patient-centred. Independent. Academic.



University of the Witwatersrand

Surgical and Endoscopic Treatment of Pain in Chronic Pancreatitis: A Multidisciplinary Update

Y. Issa^a H.C. van Santvoort^b H. van Goor^c D.L. Cahen^d M.J. Bruno^d
M.A. Boermeester^a

^aDepartment of Surgery, Academic Medical Center, Amsterdam, ^bDepartment of Surgery, University Medical Center, Utrecht, ^cDepartment of Surgery, Radboud University Medical Center, Nijmegen, and ^dDepartment of Gastroenterology, Erasmus Medical Center, Rotterdam, The Netherlands

Dig Surg 2013;30:35–50

<i>Surgery</i>	Year	Comparison	n	Events	Results	Notes
Klempa [115]	1995	Beger vs. PD	43	36–66	Beger: less pain (100 vs. 70%), shorter hospital stay, better pancreatic function, equal mortality and morbidity	No allocation concealment, not powered, and no ITT analysis
Büchler [113]	1995	Beger vs. PPPD	40	6	Beger: more pain relief (75 vs. 40%) and better pancreatic function; comparable hospital mortality, overall morbidity, mean hospitalization time, and hospital readmission	No allocation concealment, not powered, and no ITT analysis
Izbicki [105]	1995	Frey vs. Beger	42	18*	Frey: less morbidity (9 vs. 20%); comparable pain relief (94 and 95%), increase in quality of life and pancreatic function	No ITT analysis
Izbicki [151]**	1997	Frey vs. Beger	74	30*	Frey: less morbidity (22 vs. 32%); comparable pain relief (93 vs. 95%), increase in quality of life and pancreatic function	No allocation concealment, not powered, and no ITT analysis
Müller [152]	1997	Beger vs. PPPD	20	26*	Beger: less frequent delayed gastric emptying; comparable rates of pain relief, hospital readmission, and weight gain	No allocation concealment, not powered, and no ITT analysis
Izbicki [84]	1998	Frey vs. PPPD	61	24*	Frey: lower morbidity (19 vs. 53%), quality of life improvement (71 vs. 43%); equal pain relief (94 vs. 95%)	No ITT analysis
Farkas [114]	2006	Beger vs. OPPHR	40	12*	OPPHR: shorter operation time, less morbidity (0 vs. 40%), shorter hospital stay, and more increase in body weight; comparable hospital mortality, total relief of the symptoms (85 vs. 90%), pancreatic function, and hospital readmission	No allocation concealment, not powered, and no ITT analysis
Köninger [153]	2008	Beger vs. Bern	65	24	Berne: shorter operative time (46 min) and shorter hospital stay (11 vs. 15); equal quality of life; 3 patients in the Berne group were re-operated on during the follow-up period due to ongoing pancreatitis and bile duct obstruction	Low risk of bias



Long-term follow-up						
Strate [95]	2005	Frey vs. Beger	74	104*	Comparable pain relief, morbidity, mortality, quality of life, and pancreatic function	Long-term follow-up [151]
Strate [150]	2008	Frey vs. PPPD	46	84*	Comparable pain relief, quality of life, and pancreatic function	Long-term follow-up [84]
Müller [148]	2008	Beger vs. PPPD	40	168	No difference on the long term in terms of pain relief, quality of life, and pancreatic function	Long-term follow-up [113]
Endoscopy versus surgery						
Dite [13]	2003	Endoscopy vs. surgery	72	60	Surgery: higher complete or partial pain relief (86 vs. 61%), more increase in weight (47 vs. 29%) Surgery: 20% drainage vs. 80% resectional procedures Endoscopic therapy: without ESWL	Pseudo-randomization, no allocation concealment, not powered, lack of baseline characteristics, and no ITT analysis
Cahen [12]	2007	Endoscopy vs. surgery	39	24	Surgery: higher complete or partial pain relief (75 vs. 32%), better physical quality of life; comparable morbidity Surgery: pancreaticojejunostomy Endoscopic therapy: with ESWL	Low risk of bias
ESWL versus ESWL + endoscopy						
Dumoncaeu [33]	2007	ESWL vs. ESWL + endoscopy	55	24	Comparable results in terms of pain relapse and morbidity; treatment costs per patient were 3 times higher in the ESWL + endoscopy group	Low risk of bias

* Median. ** Part of the patients same as [105]

PD = Pancreaticoduodenectomy; PPPD = pylorus-preserving pancreaticoduodenectomy; OPPHR = organ-preserving pancreatic head resection; ITT = intention to treat.

Comments:

Both Beger and Frey procedures compare favorably with the (pylorus-preserving) pancreaticoduodenectomy in terms of morbidity and mortality, length of hospital stay, weight gain, nutrition, and quality of life. Pylorus preserving pancreaticoduodenectomy should be reserved for patients suspected of carcinoma.

Given the lower morbidity rate with a comparable effect on pain control and quality of life, a Frey procedure is preferred over a Beger procedure

Pain relief after Frey's procedure for chronic pancreatitis

S. Negi, A. Singh and A. Chaudhary

British Journal of Surgery 2010; 97: 1087–1095

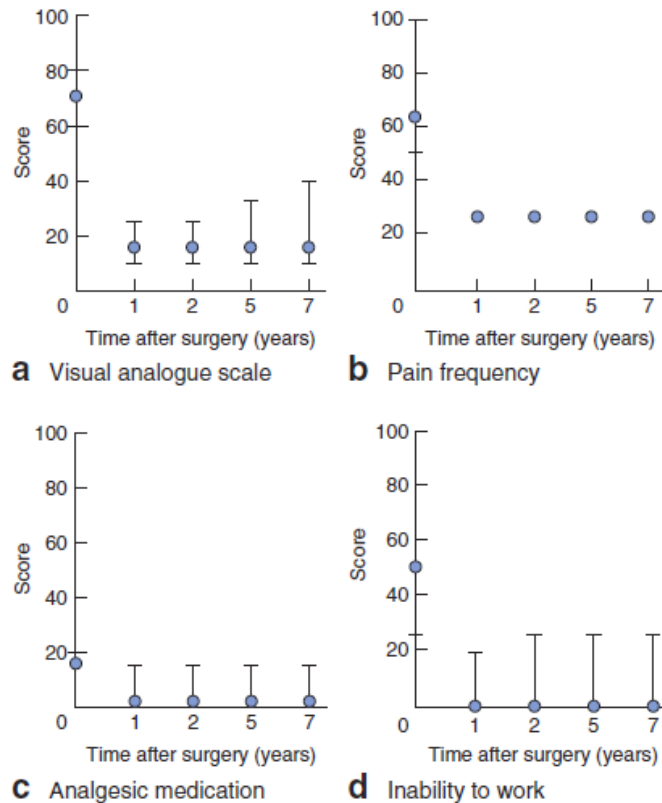


Fig. 2 Median (interquartile range) of Izbicki pain score components before operation, and 1, 2, 5 and 7 years later: **a** a visual analogue score, **b** frequency of pain attacks, **c** analgesic medication use and **d** inability to work

Table 3 Logistic regression analysis of factors associated with failure to achieve complete pain relief after local head resection with lateral pancreaticojejunostomy

	Odds ratio	P
Opiate medication use (yes versus no)	30.14 (1.95, 466.55)	0.015
Continuous pattern of pain (yes versus no)	22.65 (1.48, 347.95)	0.025
Duration of symptoms ≥ 6 years (yes versus no)	5.24 (0.52, 52.80)	0.160
Postoperative complications (yes versus no)	10.52 (1.26, 87.99)	0.030
Age ≥ 38 years (yes versus no)	7.87 (0.96, 64.30)	0.054

Conclusion: Frey's procedure leads to significant and sustained long-term pain relief in patients with chronic pancreatitis. Patients should be referred for surgery before opiates are needed to relieve pain.

Early and late postoperative changes in the quality of life after pancreatic surgery

Orlin Belyaev • Torsten Herzog • Ansgar M. Chromik •
Kirsten Meurer • Waldemar Uhl

Langenbecks Arch Surg (2013) 398:547–555

Preoperative (n=174) Early postoperative (n=133) Late postoperative (n=83)

	Chronic pancreatitis	49 (28.2 %)	38 (28.6 %)	34 (41.0 %)
<i>PD</i> pancreatoduodenectomy, <i>DP</i> distal pancreatectomy, <i>TP</i> total pancreatectomy, <i>NR</i> non-resective surgery, <i>n.a.</i> not applicable	Procedure			
	PD	56 (32.2 %)	49 (36.8 %)	39 (47 %)
	DP	25 (14.4 %)	20 (15.1 %)	18 (21.7 %)
	TP	23 (13.2 %)	19 (14.3 %)	10 (12 %)
	NR	70 (40.2 %)	45 (33.8 %)	16 (19.3 %)

^aRelated to the number of resections only

Conclusions In patients with pancreatic disease, diagnosis determined QoL preoperatively and late after surgery, while in the early postoperative period, type and extent of surgery was the leading factor. **Total pancreatectomy had a profound negative effect on QoL and should be reserved for carefully selected patients only.**

Timing of Surgery

Clinical Outcome in Relation to Timing of Surgery in Chronic Pancreatitis

A Nomogram to Predict Pain Relief

Usama Ahmed Ali, MD; Vincent B. Nieuwenhuijs, MD, PhD; Casper H. van Eijck, MD, PhD; Hein G. Gooszen, MD, PhD; Ronald M. van Dam, MD, PhD; Olivier R. Busch, MD, PhD; Marcel G.W. Dijkgraaf, MD, PhD; Femke A. Mauritz, MD; Sjoerd Jens, MD; Jay Mast, MD; Harry van Goor, MD, PhD; Marja A. Boermeester, MD, PhD; for the Dutch Pancreatitis Study Group

Arch Surg. 2012;147(10):925-932.

266 patients

Table 4. Multivariable Analysis of Risk Factors Associated With Pain Relief

Timing of Surgery	Odds Ratio (95% CI) ^a	P Value
Reported duration of pain ≤3 y	1.81 (1.02-3.37)	.03
No preoperative opioid use	2.14 (1.23-3.96)	.006
Endoscopic treatments, No. (≤5 procedures)	2.46 (1.10-6.27)	.04

Conclusions: The timing of surgery is an important risk factor for clinical outcome in CP. Surgery may need to be considered at an earlier phase than it is now, preferably within 3 years of symptomatic CP

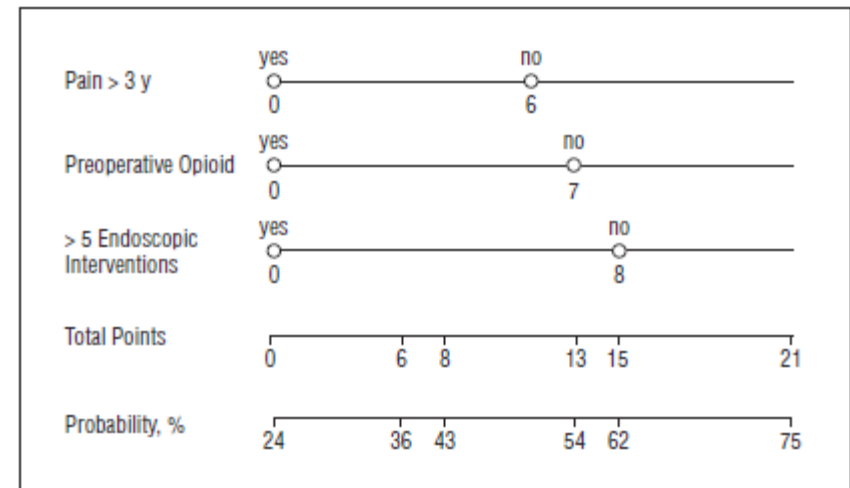


Figure. Nomogram indicating the probability of long-term pain relief in patients operated on for chronic pancreatitis. Points are assigned to patients according to the 3 risk factors (upper part of the nomogram). The probability for achieving pain relief corresponds with the sum of points for that patient (bottom 2 lines).

Surgery for chronic pancreatitis decreases the risk for pancreatic cancer: A multicenter retrospective analysis

Junji Ueda, MD, PhD,^a Masao Tanaka, MD, PhD, FACS,^a Takao Ohtsuka, MD, PhD,^a Shoji Tokunaga, PhD,^b and Tooru Shimosegawa, MD, PhD,^c for the Research Committee of Intractable Diseases of the Pancreas, *Fukuoka and Sendai, Japan*

Surgery 2013;153:357-64.

506 patients who were followed-up for at least 2 years after diagnosis of chronic pancreatitis.

19 developed pancreatic cancer (3.7%)

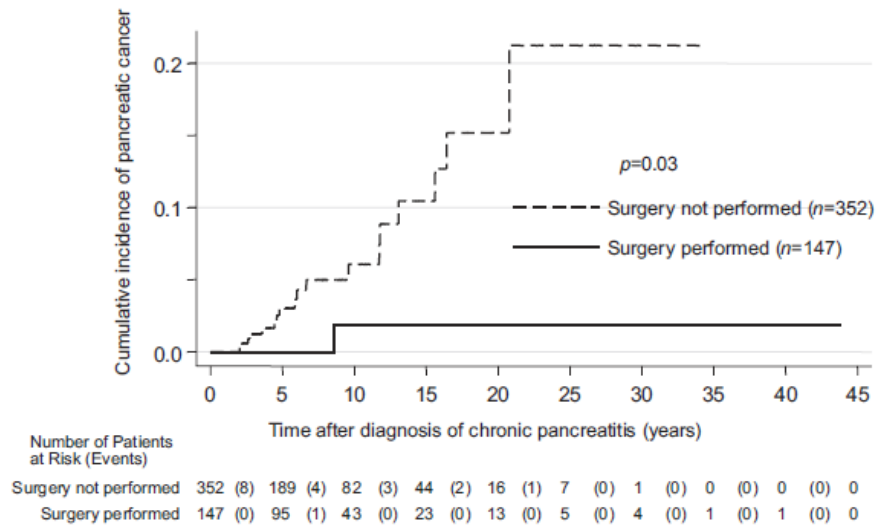


Fig 2. Cumulative incidence of pancreatic cancer in patients with chronic pancreatitis who were followed for 2 years or more. Incidence in patients with or without surgery for chronic pancreatitis after diagnosis of chronic pancreatitis is shown separately.

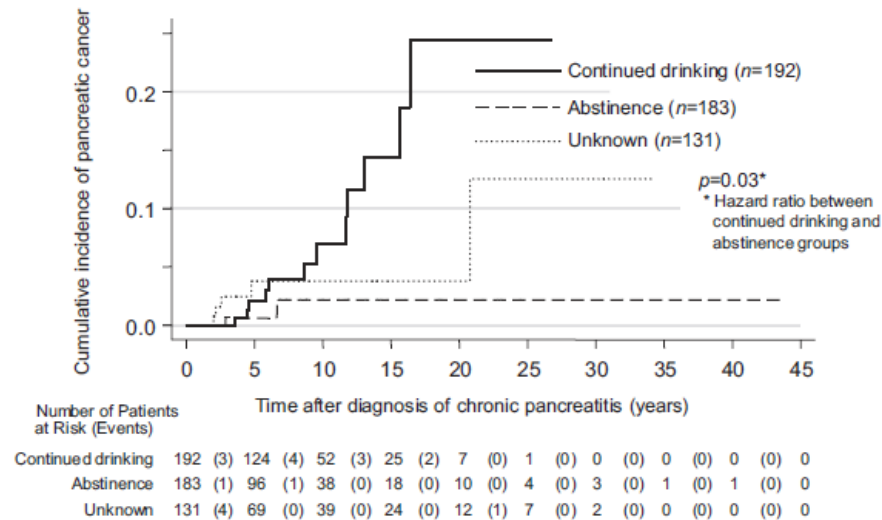


Fig 3. Cumulative incidence of pancreatic cancer in patients with chronic pancreatitis who were followed for 2 years or more, according to drinking habits after diagnosis of chronic pancreatitis.

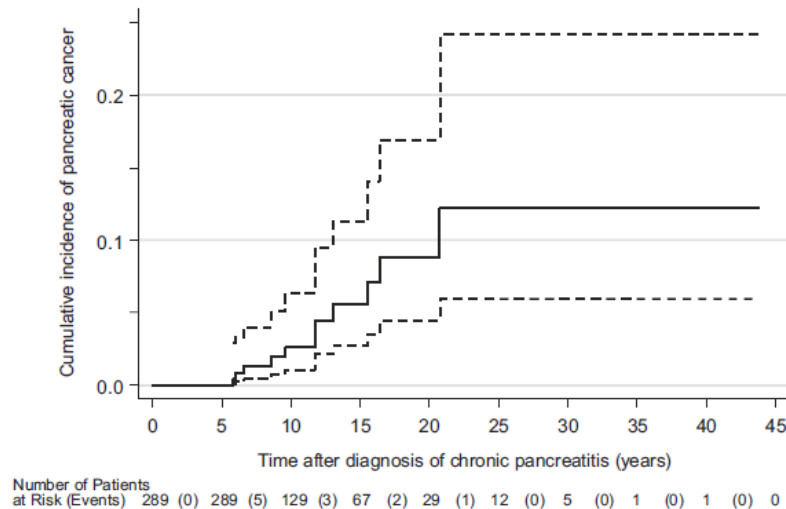


Fig 4. Cumulative incidence of pancreatic cancer in 289 patients with chronic pancreatitis who were followed for 5 years or more. *Dotted lines* show 95% confidence interval.

- Occurrence of pancreatic cancer:
 - 5.1% in pts not undergoing surgery
 - 0.7% in pts undergoing surgery
 - Higher in pts who continued to drink

Conclusions

- Important to diagnose the presence of CP and to detect and treat endocrine and exocrine dysfunction
- Surgery plays a major role in the management of symptomatic CP
- Combination or head resection with ductal drainage (Frey) best option
- Early surgery with avoidance of opiate use and multiple endoscopic intervention beneficial
- Surgery may help to maintain pancreatic function and possibly reduce cancer risk