Chronic pancreatitis
an increasing Indian Problem

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Disclosure

- On the Speaker's Bureau of
- Ethicon Endosurgery
- Covidien
- Stryker
- Karl Storz
- Olympus

Some history

- Alexander the Great
- Cawley (1788) described a thirty four year old ‘free living man with several corporeal exertions’ who died of diabetes and emaciation and at necropsy had pancreas studded with calculi
- Friedrich (1878) called this drunkard’s pancreas

Introduction

- Pancreatitis is an inflammation of glandular parenchyma leading to injury or possibly irreversible destruction of acinar components.
- This inflammation can
  - Self limited disease which may even be subclinical
  - Acute disease leading to systemic manifestations and life threatening complications
  - Chronic form with fibrosis, calcification and organ insufficiency and irreversible damage to function.

- The development of CP depends upon the –
  - Host
  - Environment (Toxin and cofactors)

- In every patient each may contribute to varying levels.

Toxic and Metabolic (A, N – Alcohol and Nicotine)

- Most common cause of chronic pancreatitis in Western countries. (Alcohol : 50 – 60%; Smoking : 25 – 30%)
- Average threshold – 80 g/day (40 g/day in women) for 5 years.
- It has been demonstrated that acute attacks precede the development of chronic disease.
- Necrosis and pseudocyst formation are more common.

Cofactors in alcohol induced pancreatitis

- genetics,
- smoking,
- intestinal infection,
- high-fat diet,
- compromised immune function,
- gallstones,
- gender,
- hormonal factors, and
- drinking patterns

Role of smoking

- Independently associated with increased risk of chronic pancreatitis (OR – 17.3).
- Smoking cessation reduces the risk by 50%
- Pathway
  - Increases oxidative stress (UGT1A7 mutation)
  - Alters the secretion and composition of the pancreatic juice
  - Causes inflammation

Others

- Hypercalcemia as a result of primary or secondary hyperparathyroidism.
- Calcium
  - increases trypsinogen activation,
  - increases intraductal stone formation,
  - Modifies pancreatic secretion leading to increased protein plug formation.

Idiopathic

- As there is greater research this category is expected to shrink in the future.
- Most common cause in INDIA and CHINA.
- Mutations of SPINK1 gene may contribute to 25% of these patients.
- Bimodal age of distribution – early onset and late onset.

Indian type or idiopathic

- Early onset – Within the first two decades, with considerable delay (around 13 years) in onset of diabetes and exocrine insufficiency.
- Late onset – Higher proportion of organ insufficiency which appears earlier (<5 years).
- Pain is uniformly present in both the groups

Genetic causes

- early activation or failure to inhibit the activated enzyme
- *SPINK1-N34S* gene mutation – found to be positive in nearly 42% patients of idiopathic chronic pancreatitis in INDIA.
- The progression of CP is faster in patients with *SPINK-N34S* mutation than in patients with *PRSS1* mutations

Recurrent and Severe Acute Pancreatitis

- recurrent attacks precipitated by
  - genetic,
  - hereditary,
  - anatomic (pancreas divisum, pancreatic duct stenosis),
  - functional (sphincter of Oddi dysfunction),
  - toxic (alcohol, nicotine), and
  - microlithiasis of the bile ducts

Obstructive (E - Efferent Duct Factors)

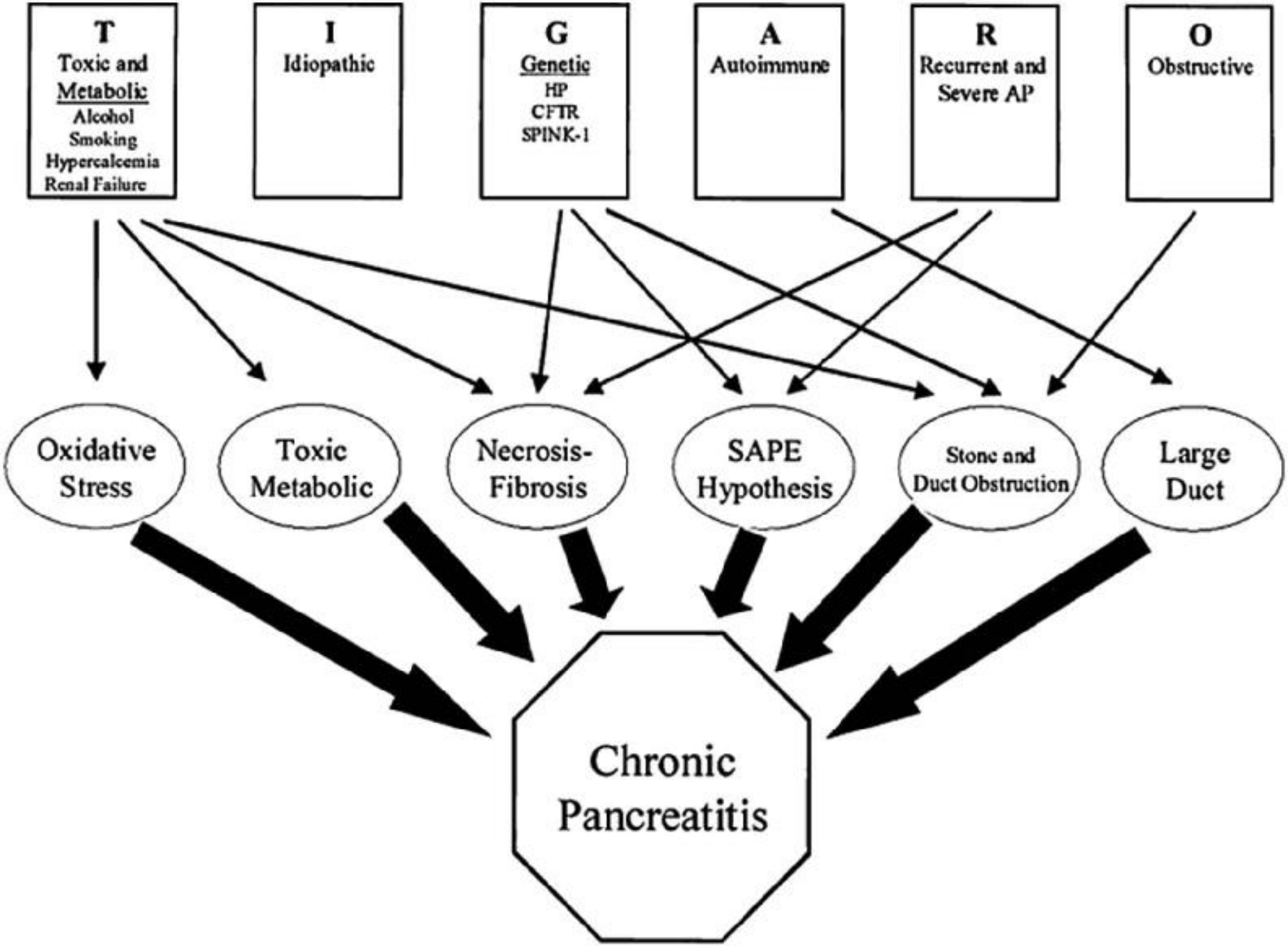
- scars of the pancreatic duct,
- tumors of the ampulla of Vater,
- mucinous duct ectasia,
- tumors of head of the pancreas,
- trauma
- sphincter of Oddi dysfunction
- pancreas divisum,

Obstructive causes

- Obstructive factors can lead to –
  - stagnation and stone formation of pancreatic juice (stone and duct obstruction theory)
  - acute recurrent pancreatitis and periductular fibrosis (necrosis-fibrosis theory)
  - a form of compartment syndrome, due to decreased tissue compliance and increased interstitial pressures

Pathogenesis

- Necrosis-Fibrosis Hypothesis
- Protein-Plug (Stone/Ductal Obstruction) Hypothesis
- Oxidative Stress Theory
- Toxic-Metabolic Theory
- Primary Duct Hypothesis
- Sentinel Acute Pancreatitis Event Hypothesis
- Sustained Intraacinar Nuclear Factor-κB Activation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Large
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Chronic
Pancreatitis

INDIAN perspective

- Recently, Bal Krishnan et al reported on 1,086 patients hailing from all parts of the country.
- Idiopathic pancreatitis was the most common form – 60.2% followed by alcoholic pancreatitis – 38.7%.
- Only 3.8% patients could be clubbed under the traditional banner of tropical chronic pancreatitis.

Present status of TCP

- First described by Zuidema from Indonesia.
- Geevarghese described a large series of pancreatic diabetes in association with malnutrition from Kerala state.
- Based on observations in the 1960s and 1970s predominantly in the Indian subcontinent

Classical clinical description

- a child, adolescent or young adult, who presented with recurrent upper abdominal pain, often with diabetes mellitus
- had signs of malnutrition, cyanotic hue of the lips, bilateral enlargement of parotid glands, a pot belly and, sometimes, nutritional edema.
- Demonstration of high blood sugar level and of pancreatic calculi
- 90% of patients required insulin,
- aggressive course of the disease vis-à-vis development of pancreatic cancer

Changing scenario

- Malnutrition is an effect and not a cause of idiopathic CP, cassava is not an aetiology
- SPINK1 gene mutation is associated with TCP in approximately 40% of cases
- phenotype (incidence of DM, requirement of insulin) of Indian patients with ICP is somewhat similar to that reported from other countries
- prognosis of ICP is good both in regards to the pain relief and survival

TCP – a misnomer?

- This change may be due to changing socioeconomic scenario of our country
- Tropical pancreatitis has a geographical rather than etiological connotation
- idiopathic CP in India has a strong genetic predisposition
- prognosis is good with the majority of patients experiencing pain relief and reasonably good life expectancy

Clinical manifestations

- CP may be asymptomatic over long periods of time and can then present with exacerbations.
- Abdominal pain is the commonest symptom. It is epigastric in position radiating to the back. Generally presents about 15 – 30 minutes.
- Early on, it occurs in discreet intervals, later on it becomes continuous. In very late “burnout phase”, pain reduces.
- Change in character of pain, especially cessation should raise suspicion of malignancy.

- Exocrine insufficiency – generally comes only after 90% of the gland has been destroyed. Steatorrhea occurs prior to protein insufficiency as lipolysis is affected more. Also deficiency of Vit A, D, E, K, B12 may be seen.
- Endocrine – Patients with calcifying disease develop DM more than noncalcifying patients. This diabetes generally requires insulin for treatment. Also since α cells are affected there is increased chance of hypoglycemia.

- Weight loss is caused by two factors:
  - at first, patients fear eating because of the accompanying pain
  - weight loss results from malabsorption related to pancreatic insufficiency
- Having said that any recent change in the character of symptoms including appearance of new ones warrants investigations to rule out malignancy

Stage	CLINICAL PICTURE		Morphology	Pancreatic Function	Diagnostics
	Pain	Complications			
A: Early	Recurrent acute attacks	No complications	Morphologic changes detectable with imaging procedures directed to pancreatic parenchyma and ductal system	Normal pancreatic endocrine and exocrine function	EUS, ERP/MRP, CT, secretin
B: Moderate	Increasing number of attacks and increased intensity	Pseudocysts, cholestasis, segmental portal hypertension	Progredient morphologic changes detectable in several imaging procedures	Impairment of pancreatic function in several degrees, but rarely steatorrhea	Transabdominal US, ERP/MRP, EUS, CT, fasting blood glucose, oral glucose tolerance test
C: Advanced	Decreasing pain (“burnout” of the pancreas)	Pseudocysts, cholestasis, segmental portal hypertension	Calculi	Marked impairment of pancreatic function, more often steatorrhea than in other stages; diabetes mellitus	Transabdominal US, ERP/MRP, CT, FE-1, fasting blood glucose, oral glucose tolerance test

Diagnosis of CP

- In advanced stages the diagnosis is easy, but it is challenging in the early stages.
- Laboratory investigations such as amylase and lipase are of limited use as they are neither diagnostic nor therapeutic.
- For many years, the gold standard for diagnosing CP has been ERCP, but now EUS has largely supplanted ERCP as the imaging method of choice.

Comparison of various modalities

Imaging Method	Sensitivity (%)	Specificity (%)
Transabdominal ultrasound	48-96	75-90
Computed tomography	56-95	85-100
Endoscopic retrograde pancreatography	68-100	89-100
Endoscopic ultrasound	85-100	85-100

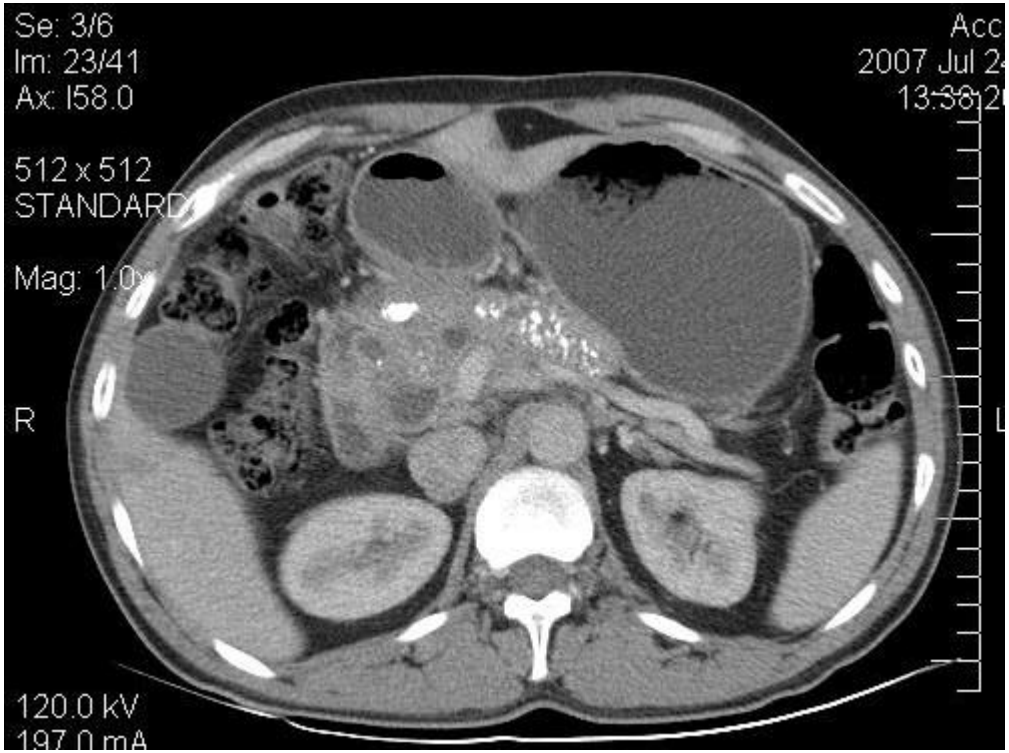
USG

- Diagnostic criteria for CP
  - irregular contour (lobulation),
  - pancreatic duct dilation and irregularity of the main pancreatic duct,
  - loss or reduction of pancreatic parenchyma echogenicity (echo-poor or echo-rich areas),
  - cysts or cavities,
  - pancreatic calcifications

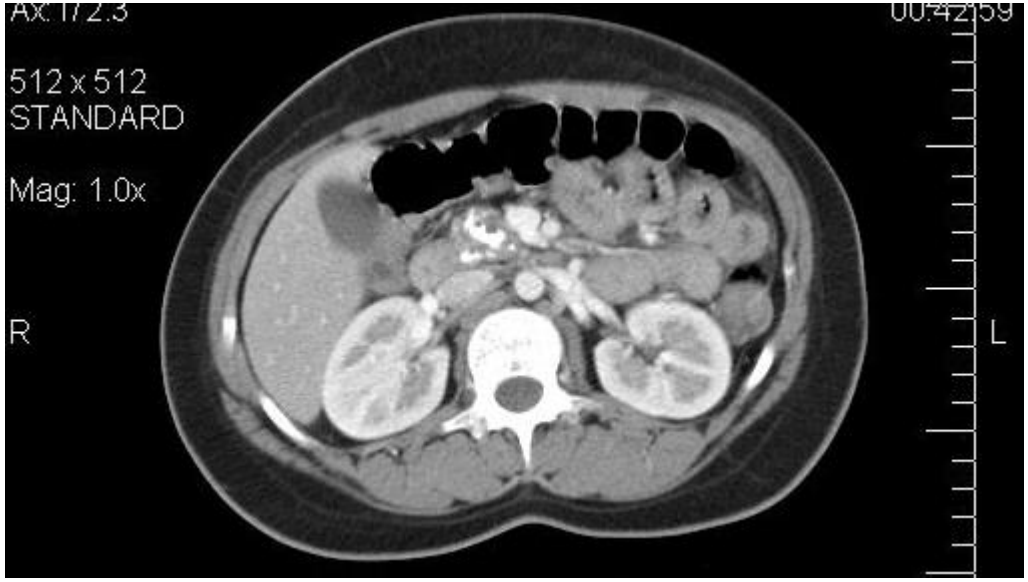
Computed Tomography

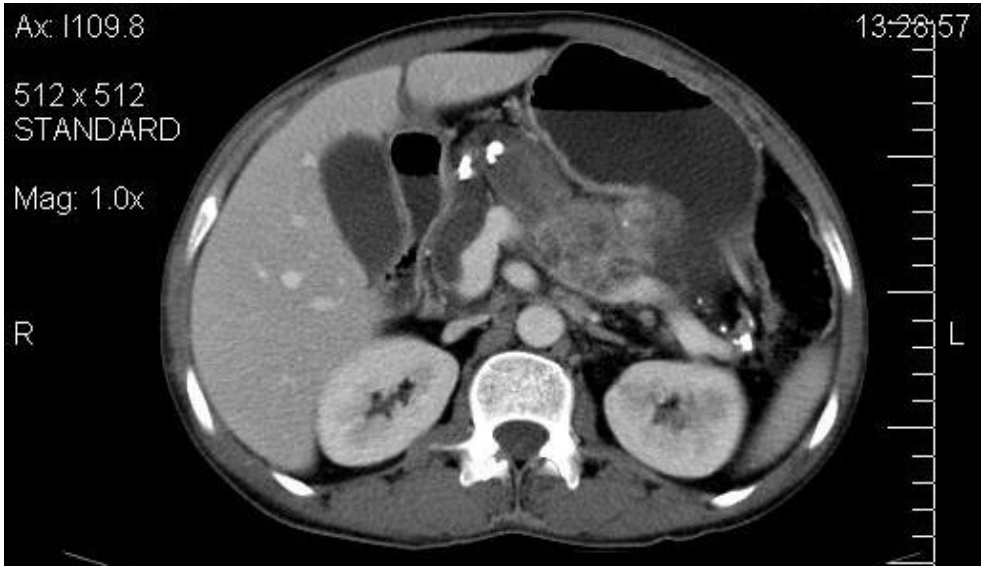
- After oral and i.v. administration of contrast medium, the pancreas can be completely visualized with spiral CT using a slice thickness of 5 mm.
- most sensitive method to detect calculi
- early stages of CP can be easily missed.
- It is important to differentiate CP from pancreatic cancer, a task that may be challenging.
- CT is useful as an initial radiologic test and is helpful to visualize calcifications and duct abnormalities, to exclude complications and other, non-CP etiologies for pain or weight loss

- favor CP are
  - intraductal or parenchymal calcifications,
  - lack of obstructing mass,
  - irregular dilation of the pancreatic duct,
  - relatively limited atrophy of the gland
- favor neoplasia include
  - pancreatic duct dilation with associated mass at the site of obstruction, with
  - associated atrophy of the pancreas,
  - vascular invasion,
  - metastases

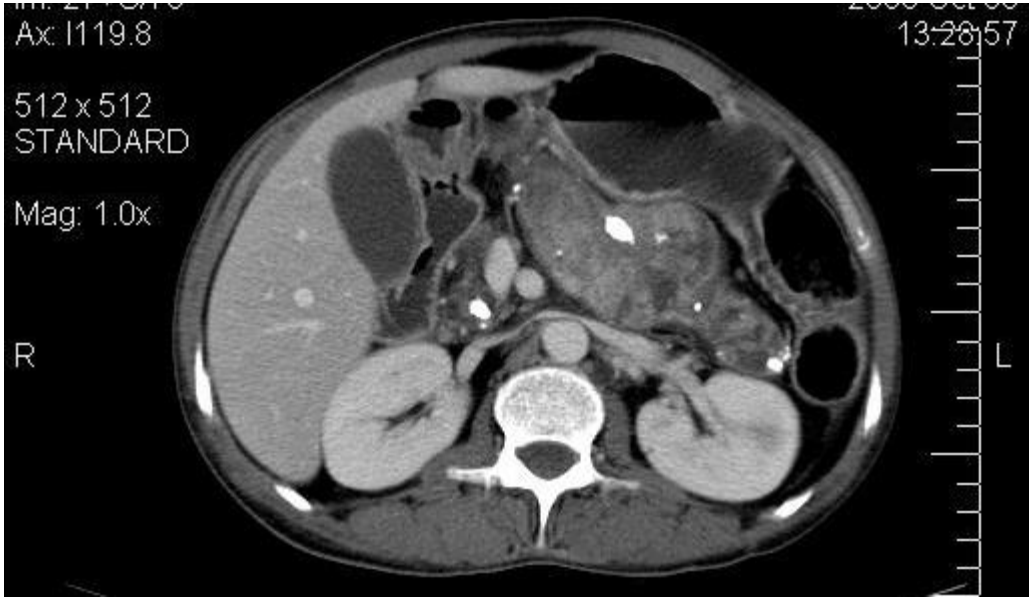


Calculi in the MPD





- Chronic calcific pancreatitis with a mass



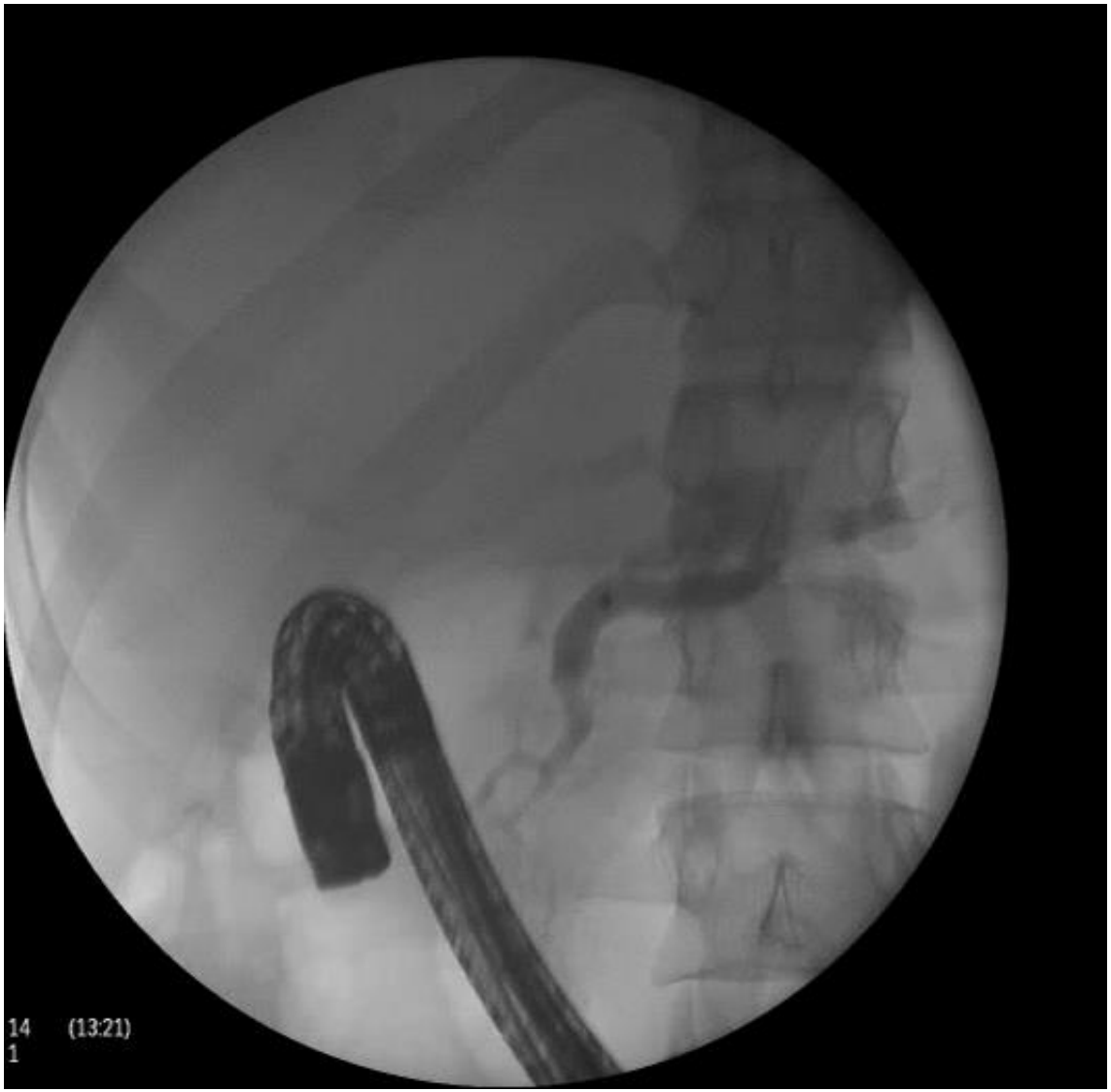
ERP

- Endoscopic retrograde pancreatography (ERP) is the gold standard among all imaging methods for diagnosis and staging of CP, because it has 90% sensitivity and 100% specificity in diagnosis
- era of high-quality imaging tests such as CT and MRI/MRCP, the role of ERP for the diagnosis of CP has greatly decreased.
- Currently, ERP is mainly used as a therapeutic tool in patients with CP and its complications
- invasive method with a low but important rate of post-ERP pancreatitis in 3% to 7% of patients

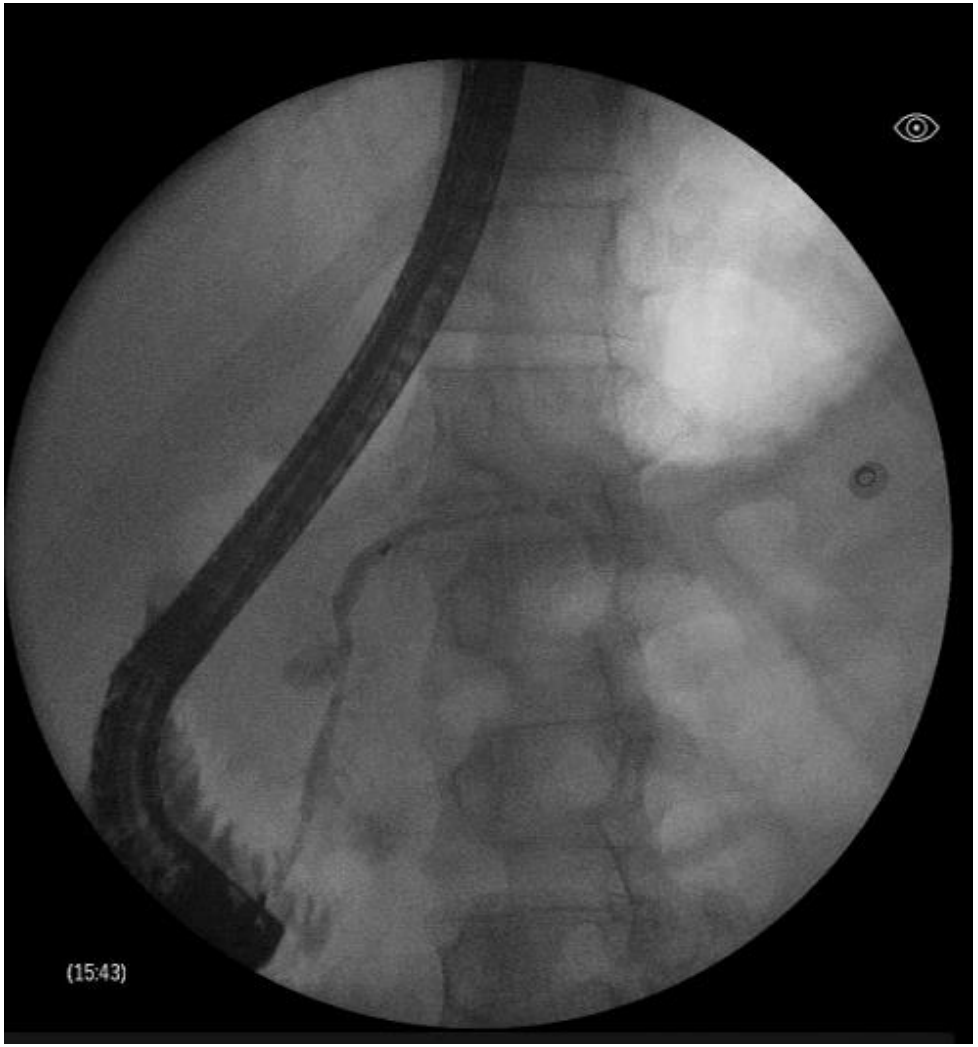
Cambridge Criteria of Chronic Pancreatitis (1984)

Stage	Typical Changes
Normal	Normal appearance of side branches and main pancreatic duct
Equivocal	Dilation or obstruction of less than three side branches; normal main pancreatic duct
Mild	Dilation or obstruction of more than three side branches; normal main pancreatic duct
Moderate	Additional stenosis and dilation of main pancreatic duct
Severe	Additional obstructions, cysts, and stenosis of main pancreatic duct; calculi

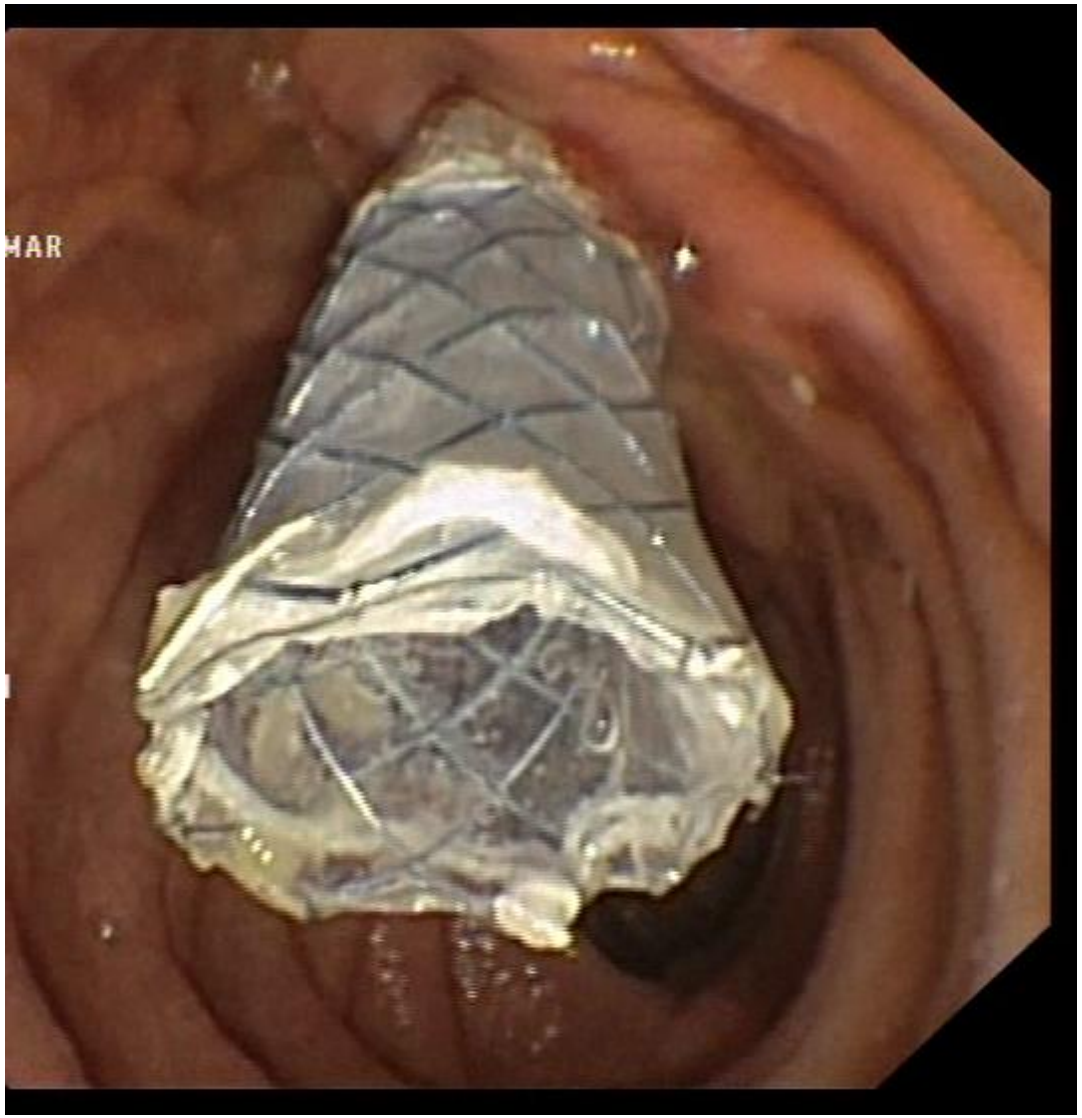
Dilated MPD



MPD communicating with pseudocysts in head



Deployment of bumpy stent



EUS

- Endoscopic ultrasonography (EUS) visualizes both the pancreatic ducts and the parenchyma
- The main disadvantage is that, there is often relatively poor interobserver agreement for EUS, even among expert endosonographers, which limits the diagnostic accuracy and overall utility of EUS for diagnosing CP

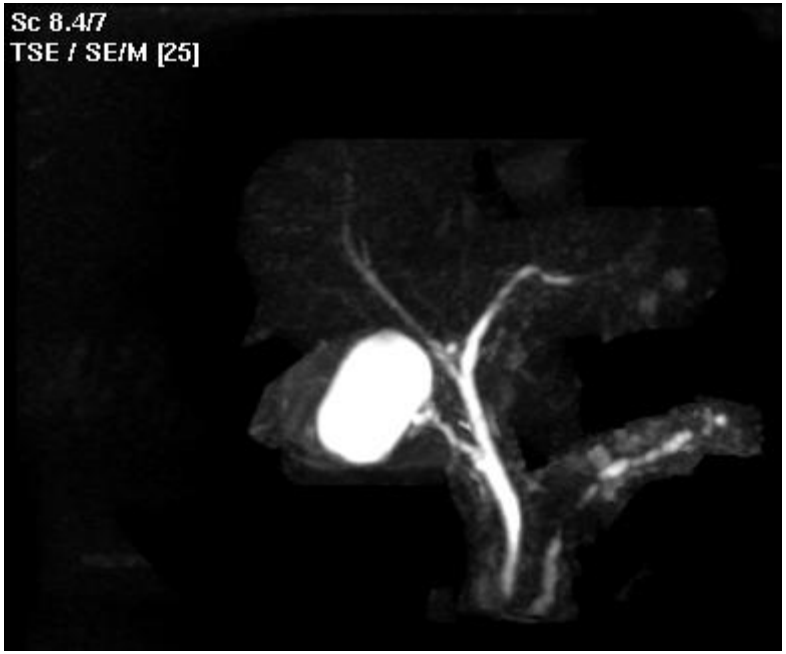
EUS

Milwaukee Criteria of Chronic Pancreatitis

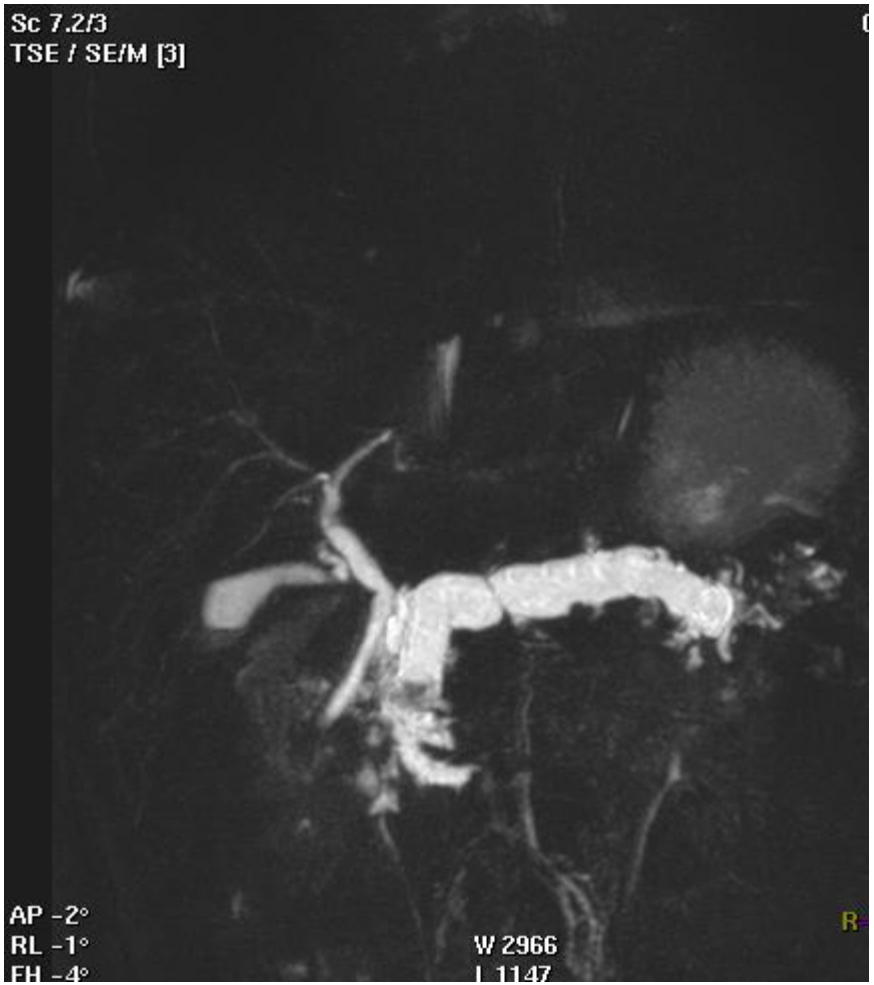
Parenchymal Features
Gland size, cysts
Echo-poor lesions (focal areas of reduced echogenicity)
Echo-rich lesions >3 mm in diameter
Accentuation of lobular pattern
Ductal Features
Increased duct wall echogenicity
Narrowing or dilation (main pancreatic duct, side branches)
Calculi

Magnetic Resonance Imaging and Cholangiopancreatography

- More sensitive for the diagnosis of CP than CT or US.
- MRI/MRCP detects early parenchymal changes of CP and ductal abnormalities.
- Use of secretin-stimulated MRI/MRCP provides a dynamic test to characterize the pancreatic duct and pancreatic parenchyma.
- Useful to detect early parenchymal changes suggestive of CP, such as abnormal decreased signal intensity on fat-suppressed T1-weighted images and delayed or limited enhancement after gadolinium administration



MRI with MPD calculi



MRI in pancreatic divisum

Treatment

- The goals of treatment include
  - pain management,
  - correction of pancreatic insufficiency, and
  - management of complications
- The natural history of chronic pancreatitis cannot be altered by any specific procedure/agent, all treatment is in a sense “palliative”

Pain management

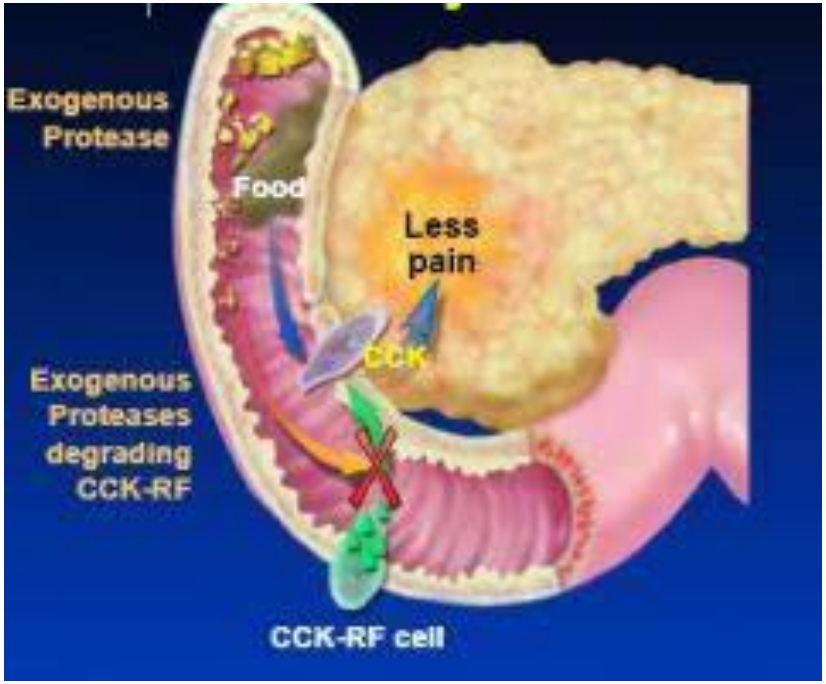
- Source of pain
  - pancreatic hyper stimulation,
  - ischemia and acidosis,
  - obstruction of larger or small ducts,
  - inflammation or neuropathic mechanisms
- The first step in alleviating pain is to recognize the underlying cause of chronic pancreatitis and to treat the underlying etiology to reduce progressive pancreatic damage.

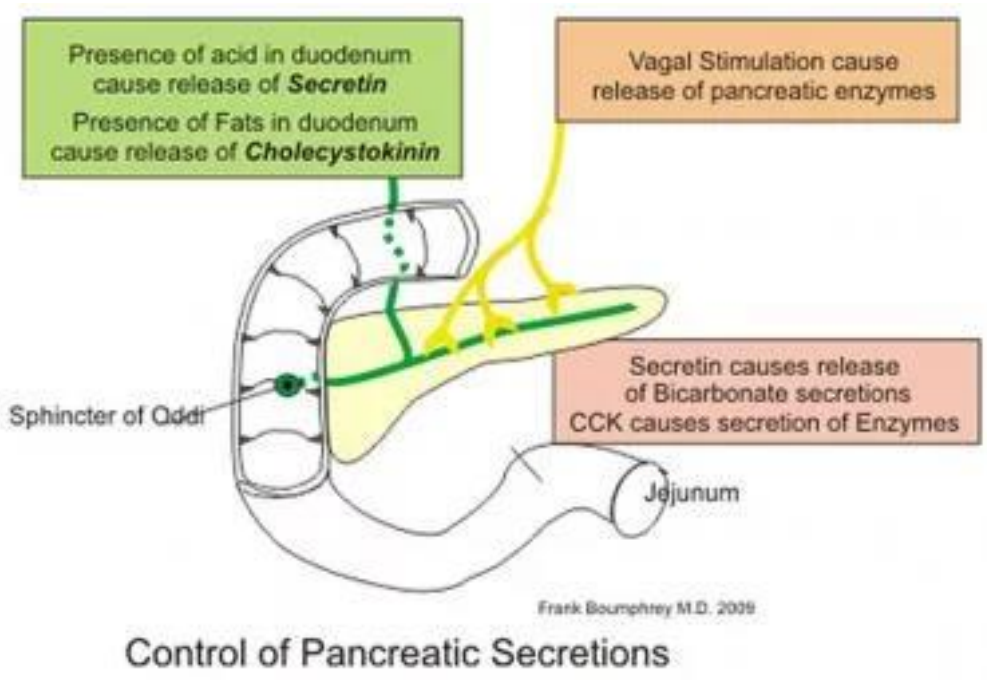
Step wise approach

- Cessation of alcohol intake — Imperative, particularly if this is the underlying etiology of pancreatitis. Patients continue drinking have increased mortality.
- Small meals and hydration — Small meals that are low in fat may help. Keeping patients well hydrated may help prevent flares of pancreatitis.
  - Supplementation with medium chain triglycerides (MCTs) and hydrolyzed peptides, resulted in improvement in pain, which in some patients was sustained after stopping this oral supplement. This mixture resulted in a minimal increase in plasma CCK levels.
- Cessation of smoking

Enzyme supplements

- Suppresses pancreatic exocrine secretion by breaking the feedback loop to relieve pain in some patients. High doses of the non-enteric coated enzymes were used in the clinical trials. They should also be treated with acid suppression. Generally about 10% of pancreatic lipase is sufficient prevent steatorrhea.





Analgesia

- A short course of opiates coupled with low dose amitriptyline (10 mg nightly for three weeks to determine efficacy) and a NSAID will break the pain cycle.
- Chronic opioid analgesia may be required in patients with persistent significant pain - morphine sulfate continuous release or fentanyl patches; pregabalin has been shown to be effective in some trials.

Antioxidant therapy

- Conflicting evidence
- A trial from AIIMS shows positive results.
- The antioxidant supplementation included daily doses of 600 g organic selenium, 0.54 g ascorbic acid, 9000 IU -carotene, 270 IU - tocopherol and 2 g methionine.
- After 6 months, the reduction in the number of painful days per month was significantly higher in the antioxidant group compared with the placebo group.

Endoscopy

- The rationale for this approach is based upon the hypothesis that ductal hypertension due to sphincter of Oddi dysfunction or strictures of the main pancreatic duct lead to pain.
- Decompressing an obstructed pancreatic duct can be associated with pain relief in some patients.
- A small RCT found that surgical drainage was more effective in relieving obstruction and achieving pain relief' however many centers use endoscopy as first line.

Recommendations

- Patients with proximal stenosis and no calcifications or inflammatory mass may be treated endoscopically. If two to three repetitive endoscopic treatments fail, the option of surgery must be evaluated.
- In patients with distal duct obstruction, calcifications, or local complications, surgery is superior to endoscopic treatment.
- Pancreatic pseudocysts may be treated endoscopically. If endoscopic treatment fails, a surgical drainage procedure is recommended.

Options	Indications
Interventional External Drainage	Temporary treatment infected pseudocyst
	Frequently followed by definitive surgical treatment if internal drainage is not possible
Internal Drainage	Effective therapy of pseudocysts
Endoscopic cystogastrostomy/endoscopic cystoduodenostomy	If anatomically possible: less invasive than surgery Problems with recurrence and catheter dislocation
Endoscopic Ductal Drainage	
ePT	Pancreas divisum, sphincter of Oddi dysfunction
ePT + dilation + stenting of pancreatic duct	Proximal stenosis of PD
ePT + lithotripsy and stone extraction	Pancreatolithiasis
ePT + bile duct stenting	Bile duct stenosis
	Caution: Poor outcome of endoscopic treatment if:
	Distal stenosis of pancreatic duct
	Parenchymal calcifications

ESWL

- No clear role, no definite trials.
- ESWL is used mostly in Europe.
- Many patients with stones (even with ductal dilation) are asymptomatic, while those with symptoms generally have pain due to small duct obstruction and other factors such as parenchymal inflammation and ischemia.

Surgery

- Surgery has generally been considered for patients who fail medical therapy, or as first line therapy if there is suspicion of pancreatic cancer.
- Upto 15 percent of patients in surgical series had unrecognized pancreatic cancer at the time of the procedure
- Three broad types –
  - decompression/drainage operations
  - pancreatic resections
  - denervation procedures

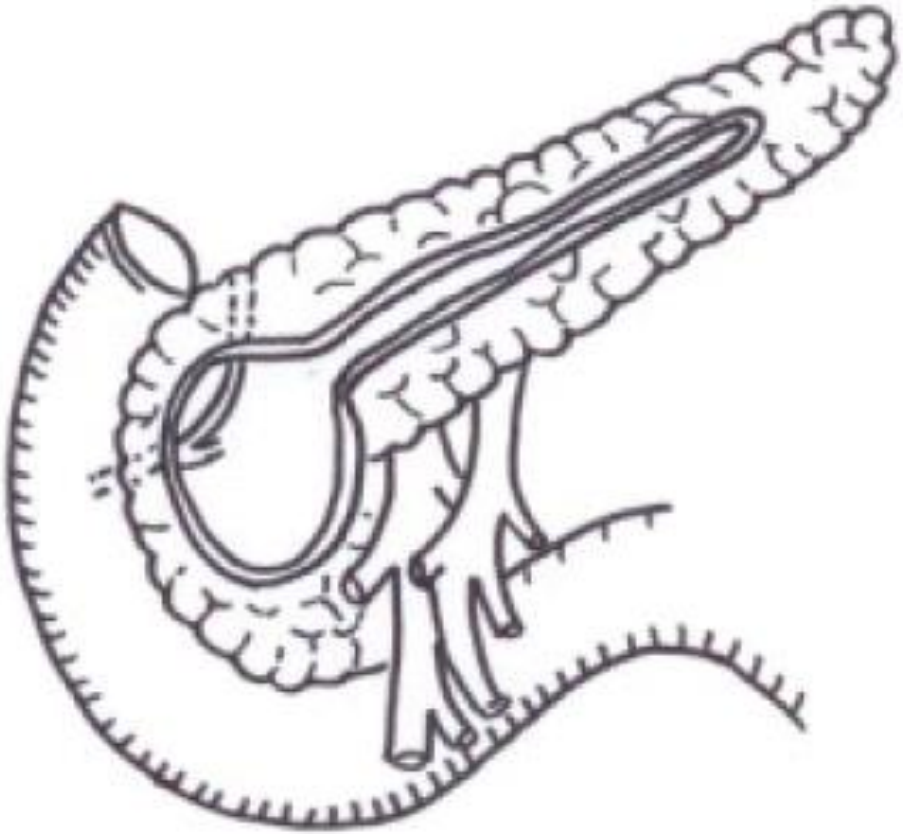
Indications for Surgery in Chronic Pancreatitis

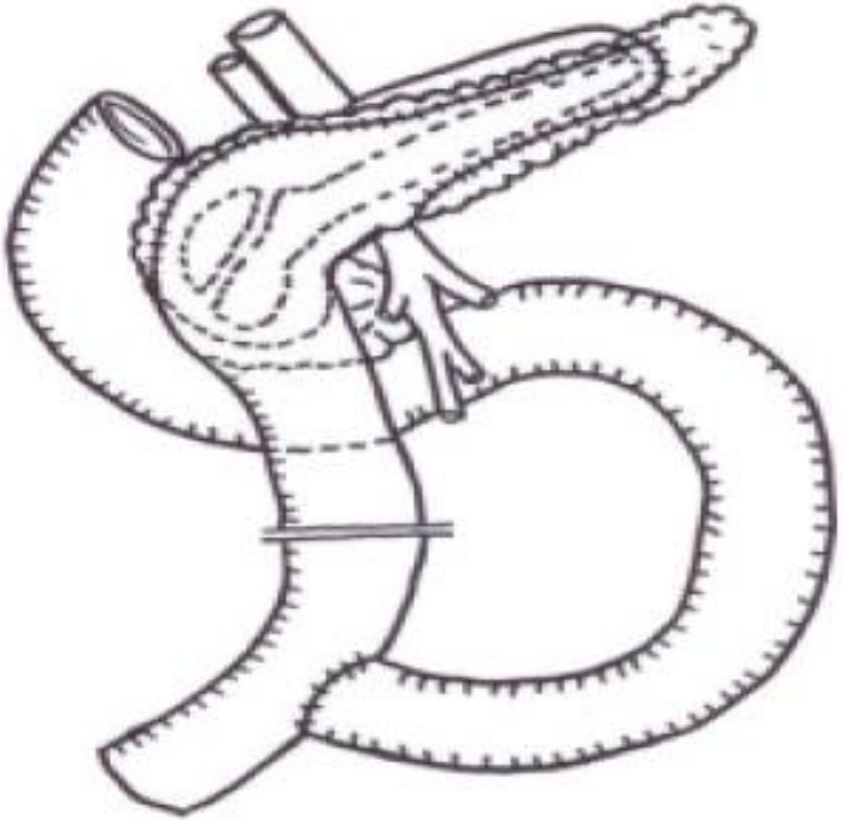
- Intractable pain
- Symptomatic local complications
- Unsuccessful endoscopic management
- Suspicion of malignancy

Decompression procedures

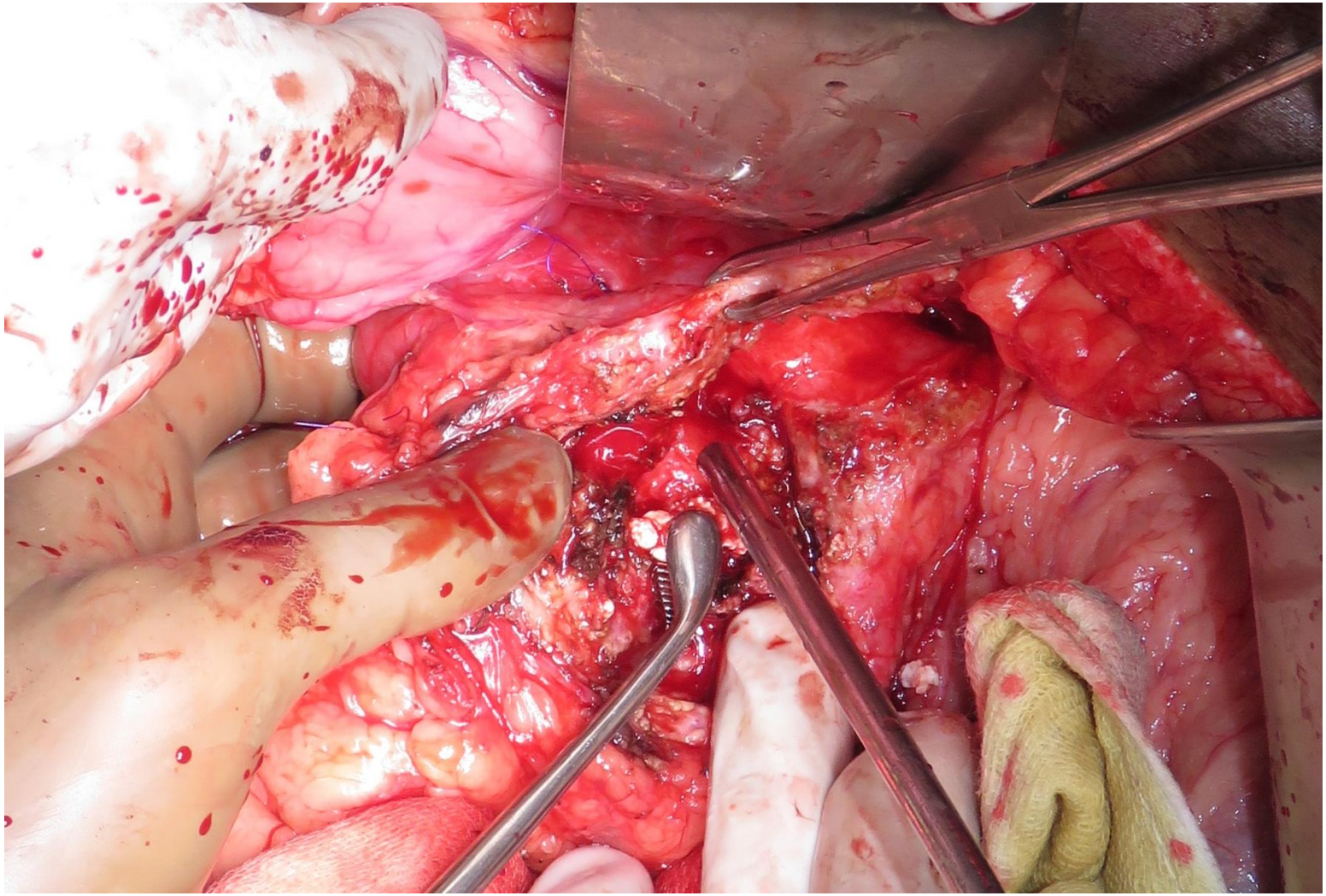
- Patients with refractory pain who have a dilated main pancreatic duct
- The data suggest that short-term pain relief is achieved in approximately 80 percent of patients. Morbidity and mortality related to the operation are generally low when the procedure has been performed by experienced surgeons (0 to 5 percent).

Freys' procedure

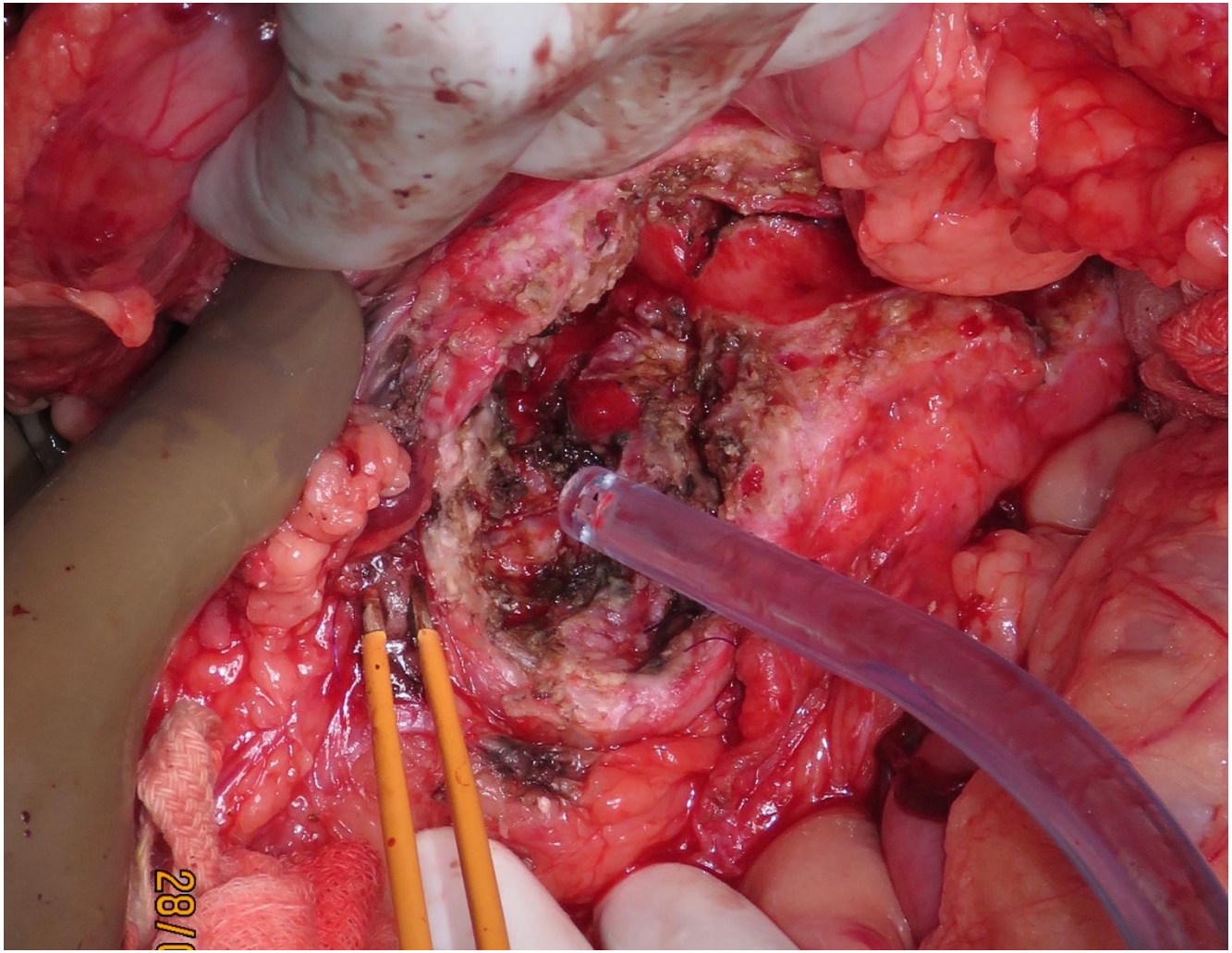




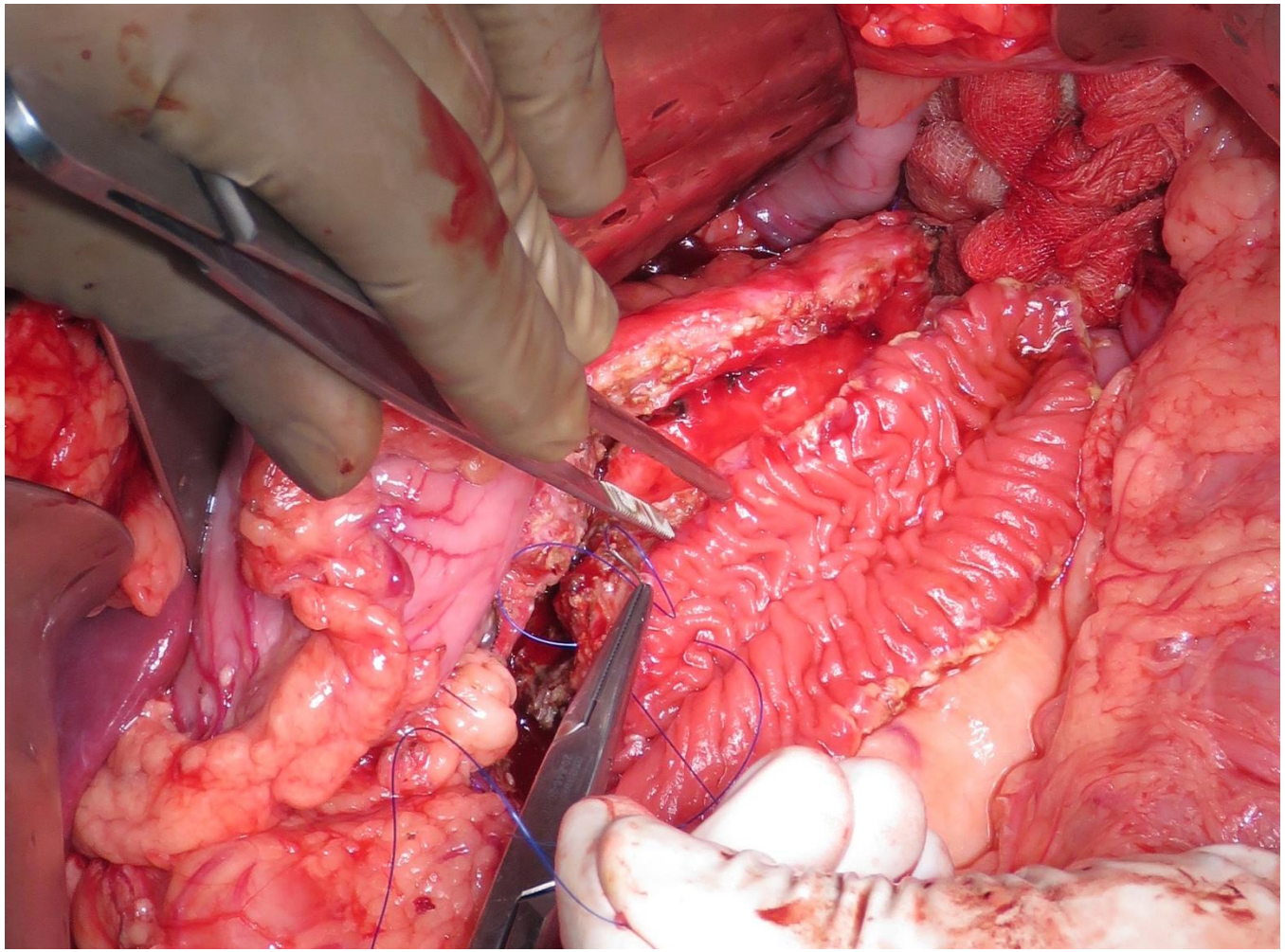
Stone extraction and head coring



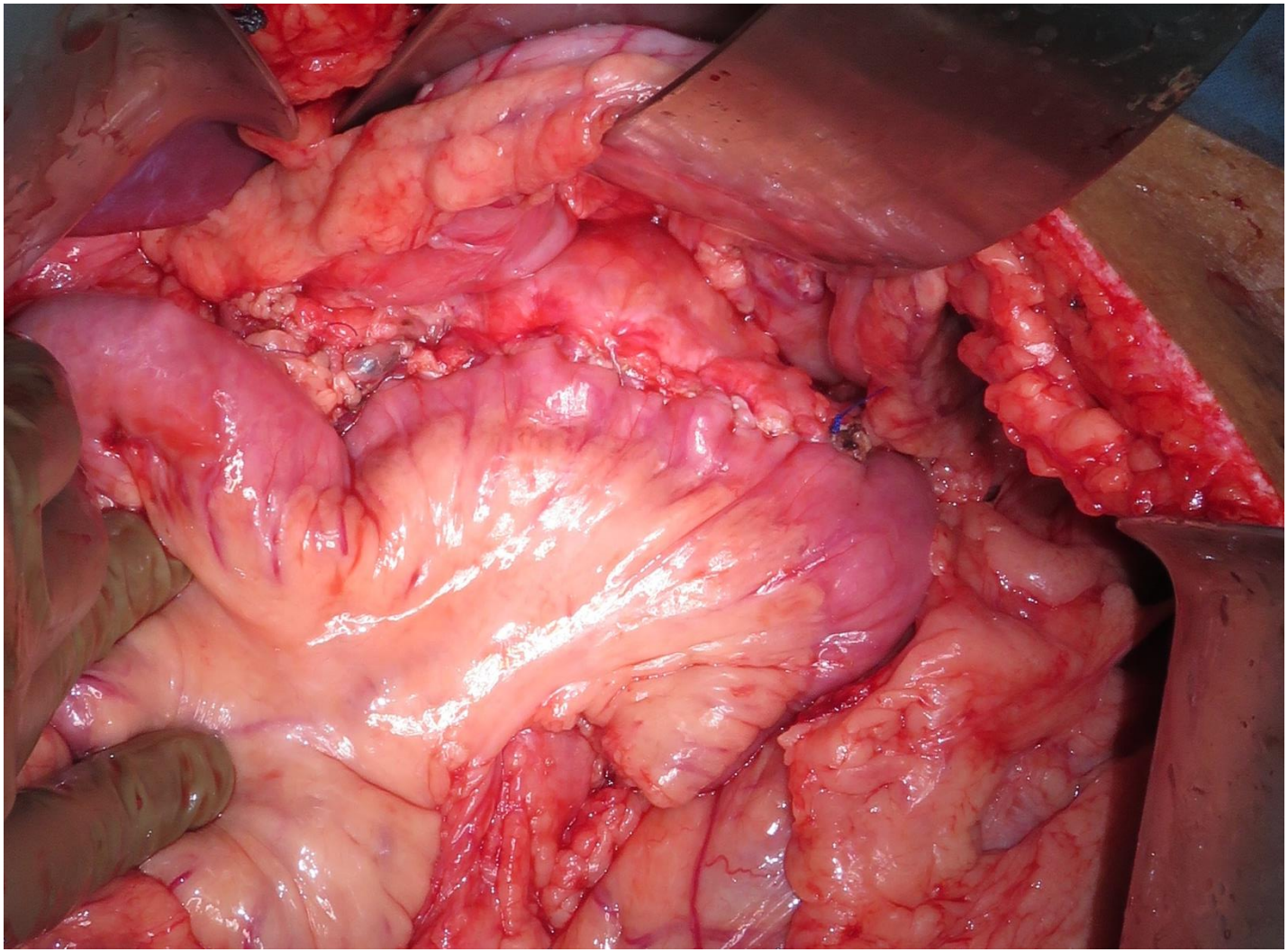
Completed head coring



Pancreaticojejunostomy in progress



Completed pancreatojejunostomy



Resection

- Vast majority of patients are seen with a ductal obstruction in the pancreatic head, frequently associated with an inflammatory mass. In these patients, pancreatic head resection is the procedure of choice.
- In patients with small-duct disease (diameter of the pancreatic duct <3 mm) and no mass in the pancreatic head, a V-shaped excision of the anterior aspect of the pancreas is a safe approach, with effective pain management

Surgical Techniques	Indications and Recommendations
Pure Drainage Operations	
Cystojejunostomy	Surgical procedure of choice for isolated pseudocysts
	Caution: Intraoperative frozen section to exclude a cystic neoplasm!
Laterolateral pancreaticojejunostomy	Ductal dilation > 7 mm, without inflammatory mass
Partington-Rochelle procedure	
Caudal drainage: Puestow-procedure	Rare indications, replaced by other procedures
Resection Procedures	
Pancreatic head resections	Always include a ductal drainage
	Procedures of choice if inflammatory mass in the head of the pancreas
	All techniques have comparable results
PD and ppPD	Procedure of choice in suspected malignancy and in irreversible duodenal stenosis
DPPHR Techniques	*Caution:* Intraoperative frozen section to exclude malignancy!
DPPHR, Beger	Procedures of choice if inflammatory mass in the head of the pancreas
V-shaped excision	Small-duct disease (diameter of pancreatic duct < 3 mm)
Segmental resection	Rare cases, e.g., isolated ductal stenosis in the body (e.g., posttraumatic) in patients without diabetes
Total pancreatectomy	Rare cases with severe changes in the entire pancreas and preexisting IDDM

Our data

- See 150 new cases of CP yearly
- Operate about 55 cases annually now
- Total operated cases are now over 1000
- We see an incidence of 6% of cancer in operated cases
- Mortality of surgery is 1 case in 25 years

Our data

- We prefer to do head coring with Roux – en – Y lateral pancreaticojejunostomy.
- On long term follow up we have seen that
  - surgery basically has a role in pain relief, about 70% of the patients are completely pain free and another 20 %have reduced frequency and intensity.
  - There is no change in the progression of the disease i.e., incidence diabetes mellitus in the patients is not changed
  - About 2-3% patients develop benign CBD stricture after surgery which may require a hepaticojejunostomy.