CHRONIC PANCREATITIS 2018

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DEFINITION

- Chronic pancreatitis is a syndrome involving a progressive irreversible inflammation, fibrosis, and loss of acinar and islet cells which can manifest in

✓ unrelenting abdominal pain

✓ Exocrine insufficiency

✓ Endocrine insufficiency

EPIDEMIOLOGY

- 87.000 cases annually USA
- 6.7-3.2 per 100.000 population
- The prevalence of chronic pancreatitis increases with age, and the median age at diagnosis ranges between 51 and 58 years.
- Younger ages of onset, including childhood, are mostly related to genetic risk factors.
- A disease of men *5
- black individuals*3

ETIOLOGY

- chronic alcohol abuse (40–70%)
- Tobacco smoking*3
- Non-alcohol-associated and non-tobacco-associated chronic pancreatitis(20–50%) :
  - Ductal obstruction (eg, trauma, pseudocysts, stones, tumors, possibly pancreas divisum)
  - Tropical pancreatitis
  - Systemic disease such as systemic lupus erythematosus, hypertriglyceridemia, possibly hyperparathyroidism
  - Autoimmune pancreatitis
  - Idiopathic pancreatitis(30%)

- GENETIC DISEASE

- **Autosomal dominant** (only sufficient to cause CP)
  - Hereditary pancreatitis (PRSS1 mutations)
- **Autosomal recessive or modifier genes** (cofactor)
  - CFTR mutations
  - SPINK1 mutations
  - Chymotrypsin C mutations
  - Claudin mutations
  - Calcium-sensing receptor gene mutations
  - Others

- **Asymptomatic Pancreatic Fibrosis :**
  - Chronic alcoholism
  - Chronic kidney disease
  - Diabetes mellitus
  - Old age
  - Radiotherapy

Box 1 | **Aetiologies of chronic pancreatitis according to the TIGAR-O system***

- Toxic-metabolic: chronic pancreatitis caused by alcohol abuse, tobacco smoking, hypercalcaemia, hyperlipidaemia, chronic kidney failure, medications or toxins.
- Idiopathic: chronic pancreatitis that is not associated with any known gene mutations, such as early-onset chronic pancreatitis, late-onset chronic pancreatitis and tropical chronic pancreatitis (an early-onset form of non-classic chronic pancreatitis that is almost exclusively observed in tropical countries in the developing world and that is characterized by an aggressive course).
- Gene mutations: chronic pancreatitis caused by Mendelian diseases involving the pancreas, complex genetics or modifying genes (for example, *PRSS1*, *CFTR* and *SPINK1*).
- Autoimmune: steroid-responsive chronic pancreatitis, which can be isolated or syndromic.
- Recurrent and severe acute pancreatitis: chronic pancreatitis that is associated with necrosis (severe necrotizing acute pancreatitis), vascular disease (including ischaemia) and post-irradiation damage.
- Obstructive: chronic pancreatitis that is associated with pancreas divisum (a congenital abnormality of the pancreas), sphincter of Oddi disorders, duct obstruction (for example, from a tumour) and post-traumatic pancreatic duct scars.

PATHOGENESIS

- The pathogenesis of chronic pancreatitis appears to be multifactorial, and is probably initiated by two distinct events.
- The first is a decrease in bicarbonate secretion, due to either functional impairment caused by genetic abnormalities of the ductal cells, or mechanical obstruction such as strictures or tumors.
- The second involves intraparenchymal activation of digestive enzymes within the pancreatic gland,This may be due to **genetic abnormalities** (such as those seen in hereditary pancreatitis) that directly cause impairment in enzyme activation and regulation or predispose to toxic injury from environmental exposures, such as alcohol.

TYPE OF CP

- Calcifying CP
- Obstructive CP
- Autoimmune pancreatitis
- Groove pancreatitis

CLINICAL MANIFESTATIONS

- The two primary clinical manifestations of CP are :
  - abdominal pain
  - pancreatic insufficiency.

ABDOMINAL PAIN

- Abdominal pain is a dominant feature of chronic pancreatitis.
- may be absent in some cases(20%).
- typically epigastric, often radiates to the back.
- often worse 15 to 30 minutes after eating.
- Early may occur in discrete attacks; as the condition progresses, the pain tends to become more continuous.
- Change of pain natural ⇒ complications(CA)

EXOCRINE INSUFFICIENCY

- until over 90 % of pancreatic function is lost.
- ↓ digestive enzymes and bicarbonate → malabsorption :

- Steatorrhea.(>50%)
- Malnutrition
- Malabsorption of the fat soluble vitamins (A, D, E, K) and vitamin B12 may also occur.
- loss of body weight (80%)

ENDOCRINE INSUFFICIENCY

- **Glucose intolerance** (frequently) 26-80%
- diabetes mellitus T3 (late) : calcifying disease or family history.
  - ✓ HbA1C ≥6.5%
  - ✓ FPG ≥126 mg/dl
  - ✓ OGTT, 2 h fasting glucose ≥200 mg/dl
- Metformin lower the risk of (pancreatic CA)
- Diabetes usually insulin requiring
- Episodic hypoglycemia (79%)
- Diabetic ketoacidosis and nephropathy are rare; neuropathy and retinopathy occur more frequently.
- OGTT+ HbA1C should be performed annually in CP.

LABORATORY TESTS

- Amylase and lipase may be slightly elevate but are more commonly normal.
- The complete blood count, electrolytes
- liver function tests are typically normal.
- Bilirubin and alkaline phosphatase normal. ↑ (bile duct comp).
- Elevated ESR, IgG4, RF , ANA, and ASMA (AIP)

COMPLICATIONS

- pseudocysts formation
- bile duct or duodenal obstruction(5-10%)
- pancreatic ascites or pleural effusion
- splenic vein thrombosis,PHT
- pseudo aneurysms
- acute attacks of pancreatitis
- pancreatic cancer

Box 3 | **Diagnostic criteria for chronic pancreatitis**

The diagnosis of chronic pancreatitis involves several criteria[3,125,128].

- Recurrent bouts of pain with or without ≥3-fold the normal upper limit of amylase or lipase levels and one or more of the following criteria:
- Radiological evidence comprising strictures and dilatation in side branches and/or the main pancreatic duct and/or intraductal and/or parenchymal pancreatic calcifications by contrast-enhanced CT and magnetic resonance cholangiopancreatography.
- Histological proof of chronic pancreatitis from biopsy samples undertaken by endoscopic ultrasonography or from a surgically resected specimen.

DIAGNOSIS

- Tests of Pancreatic **Function**
  - Direct T
  - Indirect T
- Tests of Pancreatic **Structure** (Imaging)

TABLE 59-3 Available Diagnostic Tests for Chronic Pancreatitis*

Tests of Pancreatic Structure	Tests of Pancreatic Function
EUS	Direct hormonal stimulation (with pancreatic stimulation by secretin or CCK or both): Using oroduodenal tube† Using endoscopy†
MRI with MRCP, with or without secretin stimulation	Fecal elastase
CT	Serum trypsinogen (trypsin)
ERCP	Fecal chymotrypsin
Abdominal US	Fecal fat
Plain abdominal film	Blood glucose level

DIRECT TEST

➢ Secretin test

- Administer 0.2 µg/kg of recombinant secretin,
- samples collected via a Dreiling tube or endoscope over 60 m
- The fluid samples are analyzed for bicarbonate concentration,
- Abnormal test is defined as all samples with bicarbonate concentrations < 80 mEq/L.
- Sen.(97%) + Sp(80-90%)
- Need (30-50%) damage to the gland

INDIRECT TESTS

Table 1 | **Sensitivity and specificity of the available non-invasive pancreatic function tests***

Test	Marker	Mild exocrine deficiency	Moderate exocrine deficiency	Severe exocrine deficiency	
		Sensitivity (%)	Sensitivity (%)	Sensitivity (%)	Specificity (%)
Pancreatic elastase tests (faeces)	Marker for pancreatic enzyme secretion	54	75	95	85
Qualitative faecal fat test	Marker for steatorrhoea	0	0	78	70
Chymotrypsin activity in faeces	Marker for pancreatic enzyme secretion	<50	60	80–90	80–90
^{13}C (mixed triglyceride) breath test	Marker for impaired fat digestion	ND	ND	90–100	80–90

ND, not determined. *Sensitivity and specificity compared with invasive pancreatic function tests (secretin and secretin–pancreozymin-stimulated tube tests were used as reference methods)[106].

CONCLUSION

- none of the non-invasive pancreatic function tests is sensitive enough to diagnose slight-to-moderate exocrine pancreatic insufficiency reliably, and these tests are generally unnecessary for advanced disease..

IMAGING TESTS

- Plain films : Calcifications within the pancreatic duct (30 %)
- Calcifications: alcoholic pancreatitis> hereditary and tropical> idiopathic pancreatitis
- US : Parenchyma Se.(60-70%) Sp.(80-90%)
- CT :Parenchyma + complications Se.(75-90%) Sp.(85%)
- MRCP : Ducts + S/function Se.(85%) Sp.(100%)
- ERCP :Ducts , invasive + therapy Cambridge class
- However, some patients with early chronic pancreatitis have a normal pancreatogram
- If suspected despite a normal ERCP,(EUS or PFT) considered

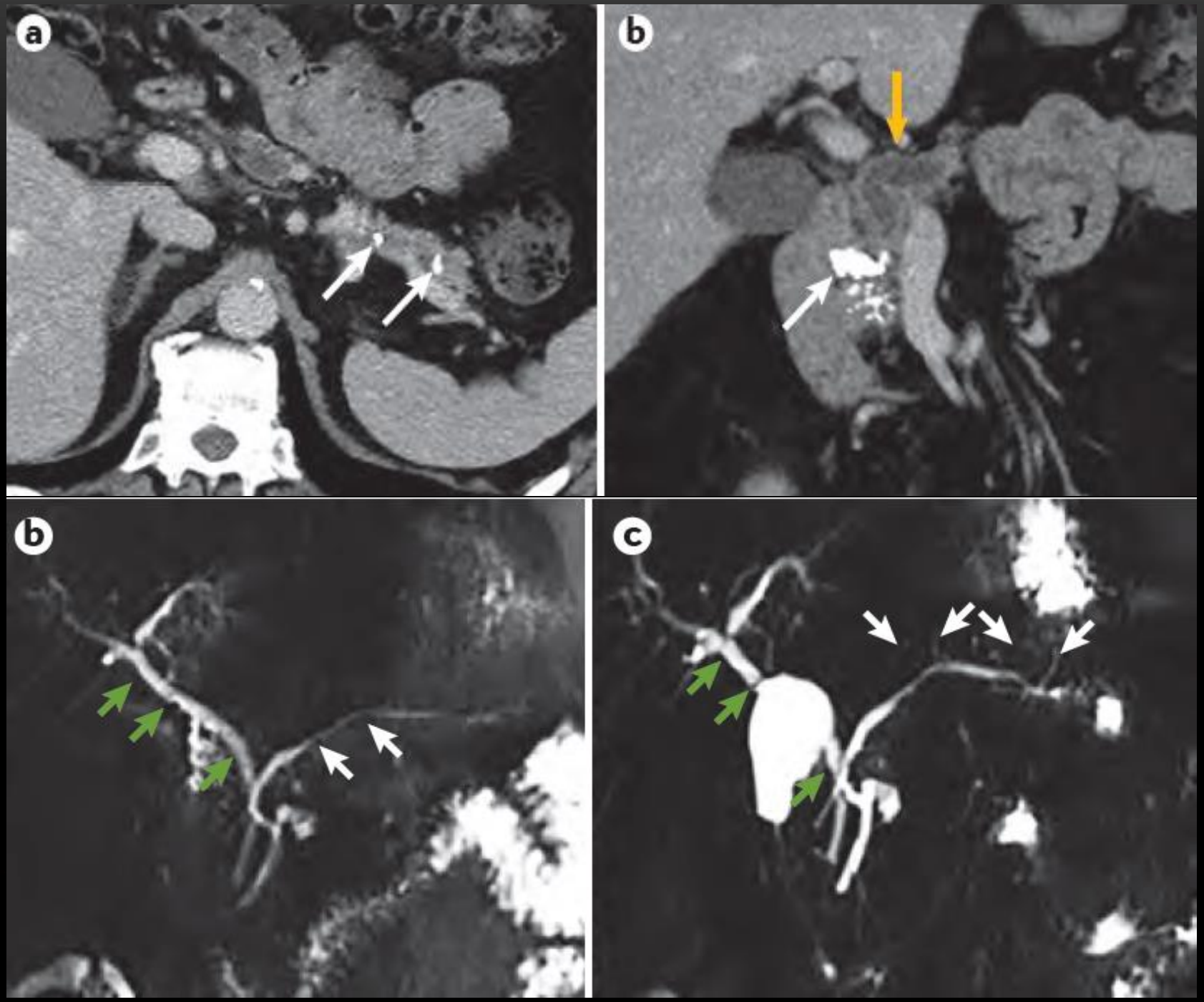

a
b
b
c

TABLE 59-4 Grading of Chronic Pancreatitis by US or CT

Grade	US or CT Findings
Normal	No abnormal findings on a good-quality study visualizing the entire gland
Equivocal	One of the following: Mild dilatation of the pancreatic duct (2-4 mm) in the body of the gland Gland enlargement ≤ 2-fold normal
Mild/moderate	One of the preceding findings plus at least one of the following: Pancreatic duct dilatation (>4 mm) Pancreatic duct irregularity Cavity/cavities < 10 mm Parenchymal heterogeneity Increased echogenicity of duct wall Irregular contour of the head or body Focal necrosis or loss of parenchyma
Severe	Mild/moderate features plus one or more of the following: Cavity/cavities > 10 mm Intraductal filling defects Calculi/pancreatic calcification Duct obstruction (stricture) Severe duct dilatation or irregularity Contiguous organ invasion

EUS

- Most sensitive(97%) imaging for diagnosis early stages of CP.
- Provides high-resolution imaging of the pancreatic parenchyma and ductal structure+**stones**
  - Parenchymal features : hyperechoic foci, hyperechoic strands, lobularity, and cysts.
  - Ductal features : main duct dilation, duct irregularity, hyperechoic duct margins, visible side branches, and stones
- presence of **>4 , highly suggestive** of CP

TABLE 59-6 Diagnosis of Chronic Pancreatitis on EUS

Standard EUS Grading System		Rosemont Criteria for EUS Diagnosis	
Parenchymal abnormalities	Hyperechoic foci Hyperechoic strands Lobularity of contour Cysts	Major features	Hyperechoic foci with shadowing (Major A) Main pancreatic duct calculi (Major A) Lobularity with honeycombing (Major B)
Ductal abnormalities	Main duct dilatation Main duct irregularity Hyperechoic ductal walls Visible side branches Calcification	Minor features	Lobularity without honeycombing Hyperechoic foci without shadowing Stranding Cysts Irregular main pancreatic duct contour Main pancreatic duct dilatation Hyperechoic duct margin Dilated side branches
In the standard EUS grading system, each finding counts equally, and the score is the total number of findings. In the Rosemont system, the diagnostic strata are as follows:			
Most consistent with chronic pancreatitis		One Major A feature and ≥3 minor features ***or*** One Major A feature and Major B feature ***or*** Two Major A features	
Suggestive of chronic pancreatitis		One Major A feature and <3 minor features ***or*** One major B feature and ≥3 minor features ***or*** ≥5 minor features	
Indeterminate for chronic pancreatitis		3-4 minor features ***or*** One major B feature with <3 minor features	
Normal		≤2 minor features	

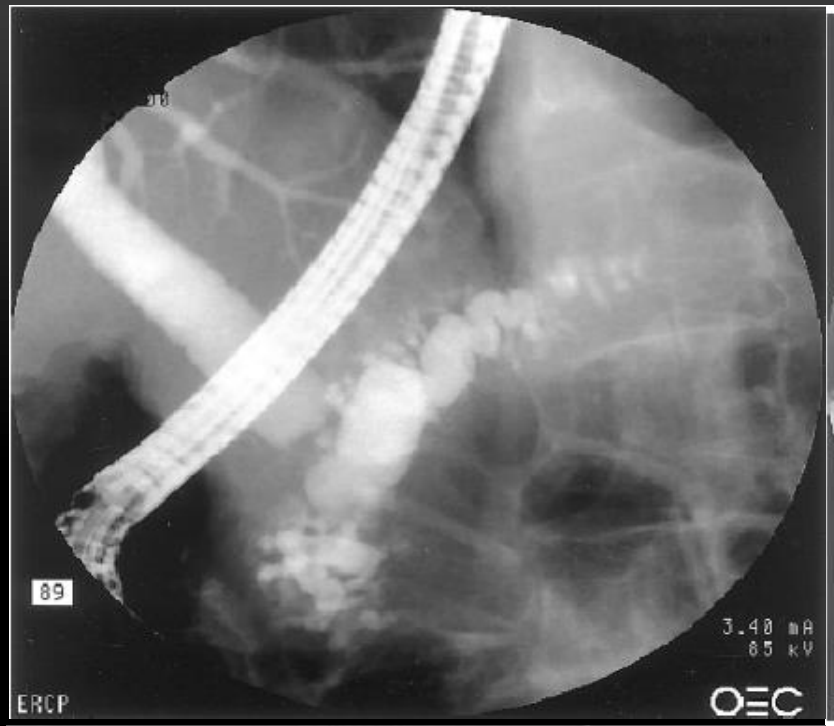
ERCP

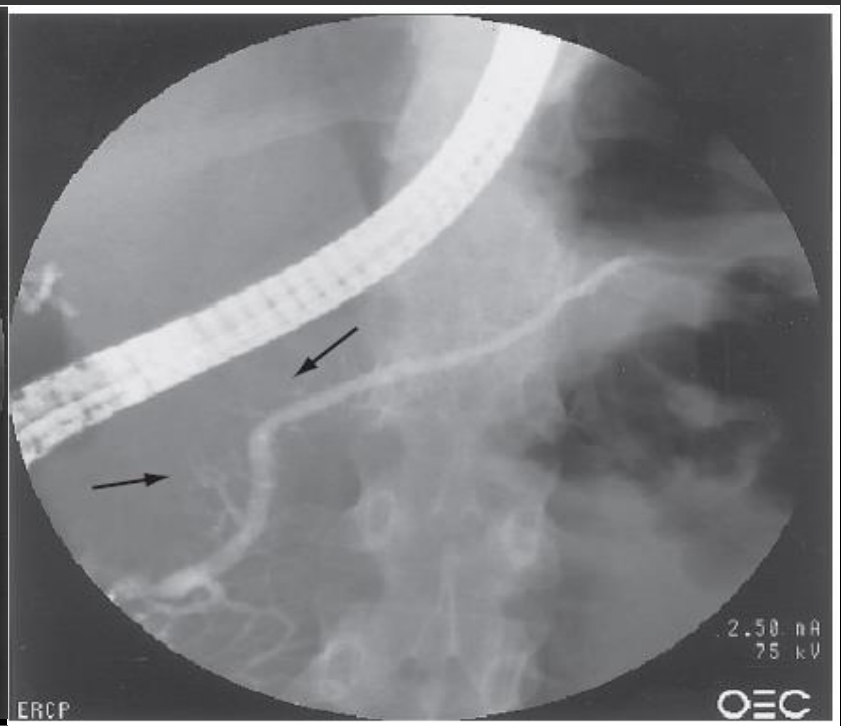
- PD changes (only) …… main and branched duct.
- invasive (AP 15%)
- therapeutic indications.
- Cambridge classification

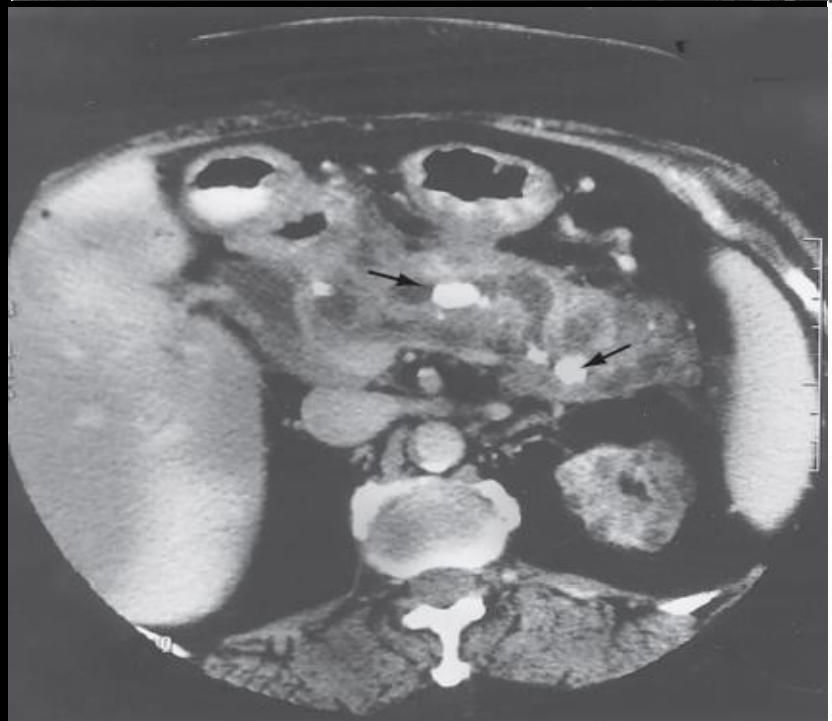
TABLE 59-5 Cambridge Grading of Chronic Pancreatitis Based on Findings on Pancreatography

Grade	Main Pancreatic Duct	Side Branches
Normal	Normal with filling of duct to side branches	Normal
Equivocal	Normal	<3 Abnormal
Mild	Normal	≥3 Abnormal
Moderate	Abnormal	≥3 Abnormal
Severe	Abnormal with at least one of the following: Large cavity (>10 mm) Obstruction or stricture Filling defect(s) Severe dilatation or irregularity	≥3 Abnormal

- This classification scheme correlated with the degree of pancreatic dysfunction


89
3.40 mA
85 kV
ERCP
OEC


2.50 mA
75 kV
ERCP
OEC



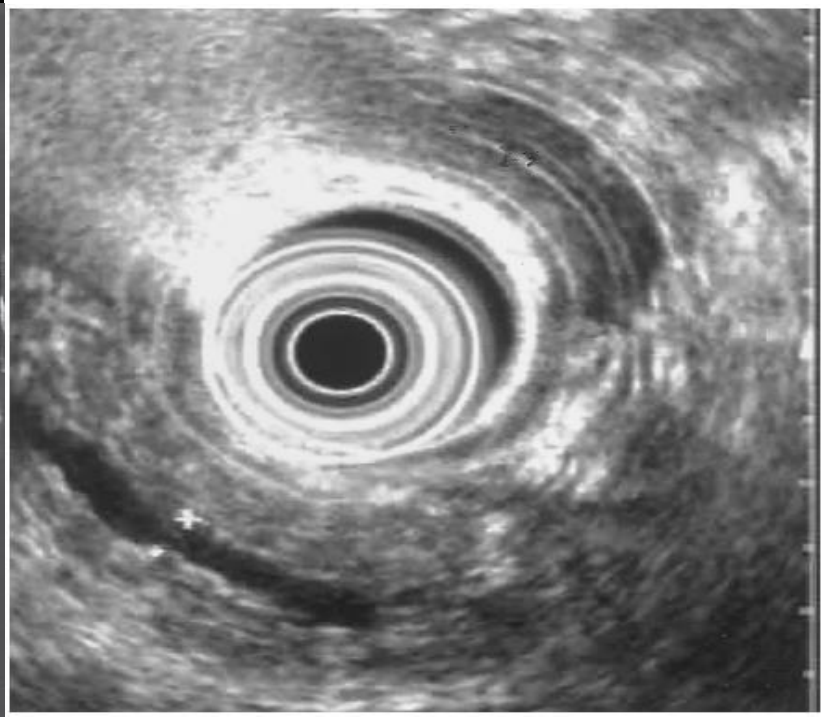


Table 1. Diagnostic Tests for Chronic Pancreatitis

Imaging tests	
EUS	Two systems of reporting are used: standard terminology and Rosemont criteria.[5] EUS allows detailed examination of both the pancreatic parenchyma and the pancreatic duct.
MRI with MRCP	Administration of secretin during MRCP improves the quality of imaging of the pancreatic duct and may allow the pancreatic secretory capacity to be estimated. MRI cannot visualize calcification.
CT	CT images the pancreatic parenchyma well, with less ductal detail than MRI.
ERCP	ERCP provides the most detailed images of the pancreatic duct but is rarely used for diagnosis.
Ultrasonography	Ultrasonography has limited ability to image the pancreas, but it is of low cost and has no ionizing radiation.
Functional tests	
Secretin test	Administration of a supraphysiologic dose of secretin produces maximal pancreatic stimulation; pancreatic juice is collected with a Dreiling tube or an endoscope and analyzed for bicarbonate concentration.
Fecal elastase	Low levels in the stool (<200 μg/g of stool) are seen in patients with advanced chronic pancreatitis.
Serum trypsin	Low levels (<20 mg/dL) are seen in patients with advanced chronic pancreatitis.

MANAGEMENT OF PAIN

- The first step is recognize the **underlying cause** of CP:
  - Pancreatic **neural** remodeling(Med/ET?)
  - Increased intraductal and parenchymal **pressure** (ET)
  - Pancreatic **ischemia**
  - Acute **inflammation** during an acute relapse.
  - **Complications** (pseudocysts, CBD, cancer).(ET?/Sur)

Box 2 | **Causes of pain in chronic pancreatitis**

Primary (genuine) pancreatic pain

- Duct obstruction and tissue hypertension
- Active inflammation
- Tissue ischaemia
- Altered nociception, owing to cholecystokinin-related changes in pain threshold, local nerve damage (neuropathic pain), peripheral and central sensitization of the nervous system and increased sympathetic drive

Secondary pain

- Local complications, including pseudocysts, an inflammatory mass in the pancreas, small bowel strictures and adenocarcinoma
- Remote complications, including obstruction of the bile duct and duodenum, peptic ulcer due to changes in blood flow, bacterial overgrowth due to changes in motility, mesenteric ischaemia after acute pancreatitis, small bowel strictures after acute pancreatitis and diabetes mellitus type 3c-related visceral neuropathy

Treatment-related pain

- Surgical and/or endoscopical complications
- Adverse effect to medication (opioid-induced bowel dysfunction and opioid-induced hyperalgesia)

PAIN MANAGEMENT

- ***Medical Therapy***
  1. General recommendations
  2. pancreatic enzyme supplementation
  3. Analgesics
  4. Octreotide
- ***Endoscopic Therapy***
- ***Surgical therapy***

1- GENERAL RECOMMENDATIONS

- Cessation of alcohol intake (↓ mortality)
- Small meals and hydration (MCTs??) :minimal increase in plasma CCK levels or antioxidant effects
- Cessation of smoking: ⟹ (CP and cancer)
- Diet :
  - ✓ 2.000 – 3.000 cal (20% fat)
  - ✓ 1.5 – 2 g/kg protein
  - ✓ 5 – 6 g/kg car
  - ✓ 50 – 75 g fat

2-PANCREATIC ENZYME SUPPLEMENTS

- Suppressing pancreatic exocrine secretion, relieve pain in **some** patients.
- Enteric-coated microspheres or mini-microspheres of <2 mm in size are the preparations of choice for PEI.
- Viokace is the only non-enteric coated approved by FDA
- along with meals and snacks (w/PPI or H2)
- A minimum lipase dose of 40,000–50,000 PhU is recommended with main meals, and half that dose with snacks.(H/c=stricture)

2- PANCREATIC ENZYME SUPPLEMENTS

- The **efficacy** evaluated by symptoms and nutritional status ,or PFT (CFA or 13C-MTG-BT) with oral enzymes??
- If unsatisfactory clinical response,
  - ↑ dose (doubled or tripled)
  - PPI
  - another cause?? (if failed above)
- large duct disease(alcohol) or advance disease (note benefit)

TABLE 59-7 Enzyme Products for the Treatment of Chronic Pancreatitis

Product	Formulation	Lipase Content per Pill or Capsule (USP units)
Creon	Enteric-coated capsule	3000; 6000; 12,000; 24,000; 36,000
Zenpep	Enteric-coated capsule	3000; 5000; 10,000; 15,000; 20,000; 25,000
Pancreaze	Enteric-coated capsule	4200; 10,500; 16,800; 21,000
Ultresa	Enteric-coated capsule	13,800; 20,700; 23,000
Pertzye	Enteric-coated with bicarbonate	8000; 16,000
Viokase	Non–enteric-coated tablet*	10,440; 20,880

3-ANALGESICS

- if pancreatic enzyme therapy fails to control pain.
- Analgesic treatment the principles of the 'pain relief ladder' provided by the WHO

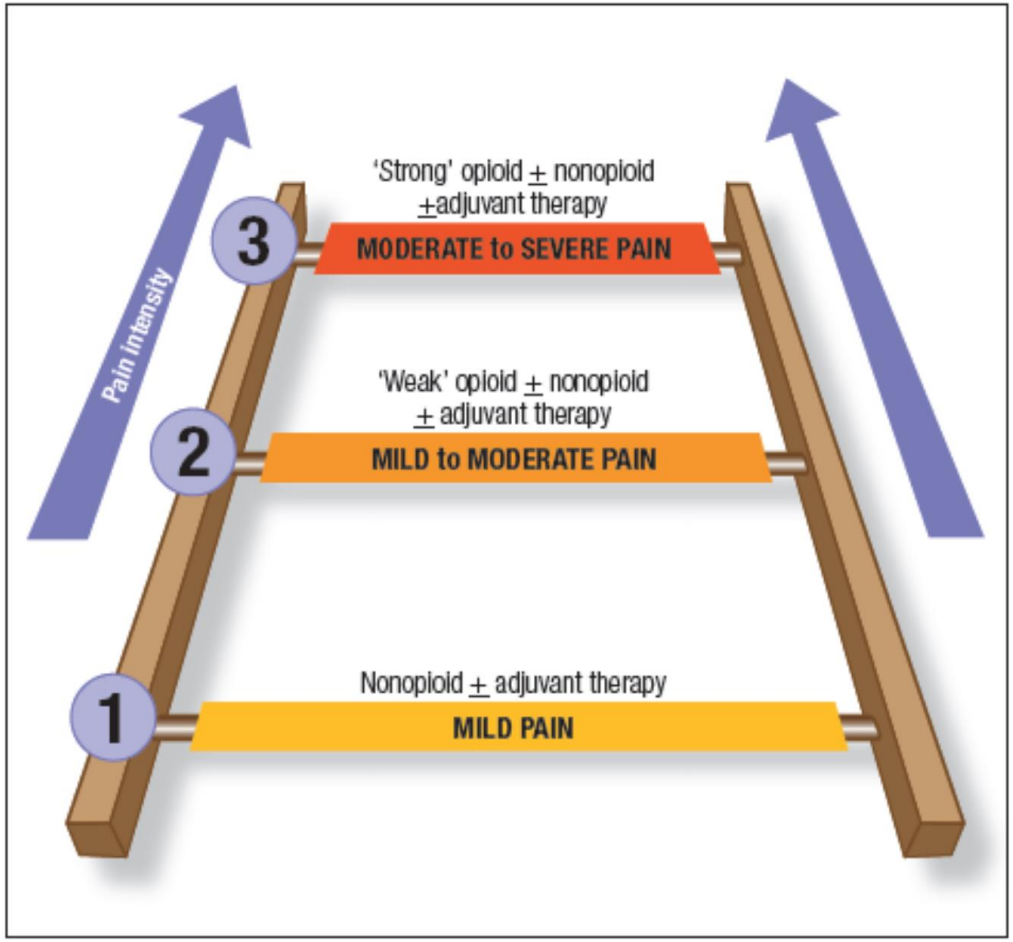


Figure 1. WHO Three-step Pain Ladder. This analgesic step ladder has been the treatment standard most used during the past 3 decades.

4-OCTREOTIDE

- decreases pancreatic secretion
- reduces circulating CCK levels.
- some direct antinociceptive effect.

ENDOSCOPIC THERAPY

ENDOSCOPIC THERAPY

- first-line therapy for painful uncomplicated CP (after F Med)
- **Decompressing** obstructed pancreatic duct ,relief pain 60%.
- The clinical response evaluated at 6–8 weeks;
- If unsatisfactory,

  endoscopists, surgeons, and radiologists
- **surgical** options considered, in patients with a predicted poor outcome following endoscopic therapy.

- **To Management of :**

- pancreatic stones(18%)
- main pancreatic duct strictures(50%)
- Endoscopic ultrasound-guided celiac plexus block
- Pancreatic pseudocysts
- Chronic pancreatitis-related biliary strictures.

PD STONES

- **ESWL** as a first step for radiopaque stones≥5mm obstructing the MPD combined or not with endoscopic extraction of stone fragments depending on **expertise** of the center Endoscopic
- Complete or partial pain relief (62 to 86 %)
- Contraindications coagulation disorders, pregnancy, cardiac pacemakers or defibrillators, and presence of bone, calcified aneurysms, or lung tissue
- **Endoscopic extraction** alone only for stones<5mm, head or body of the pancreas.
- Intraductal (laser and electrohydraulic) lithotrips only after failure ESWL

PD STONES

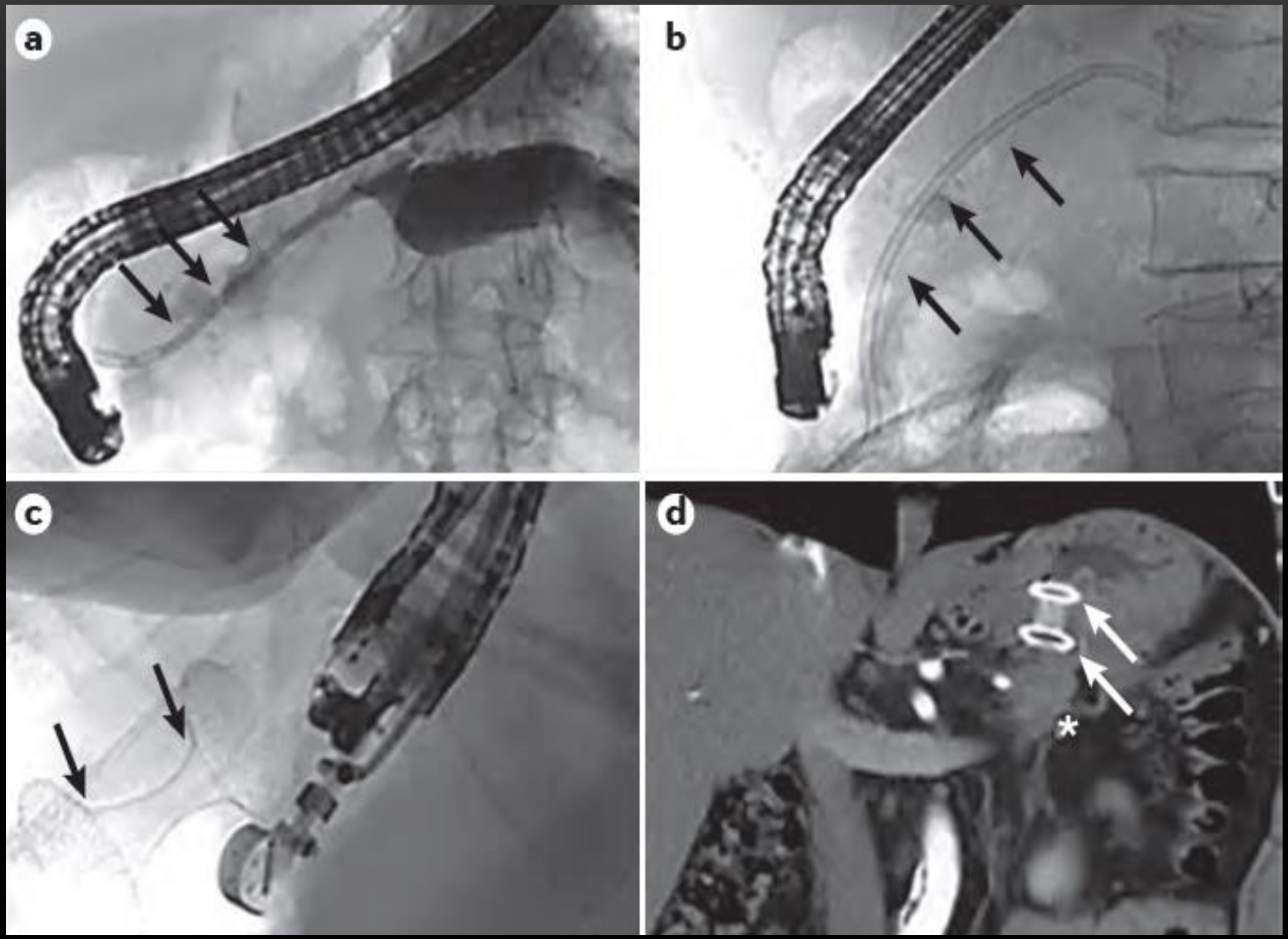
- Factors for long-term success with endoscopic therapy

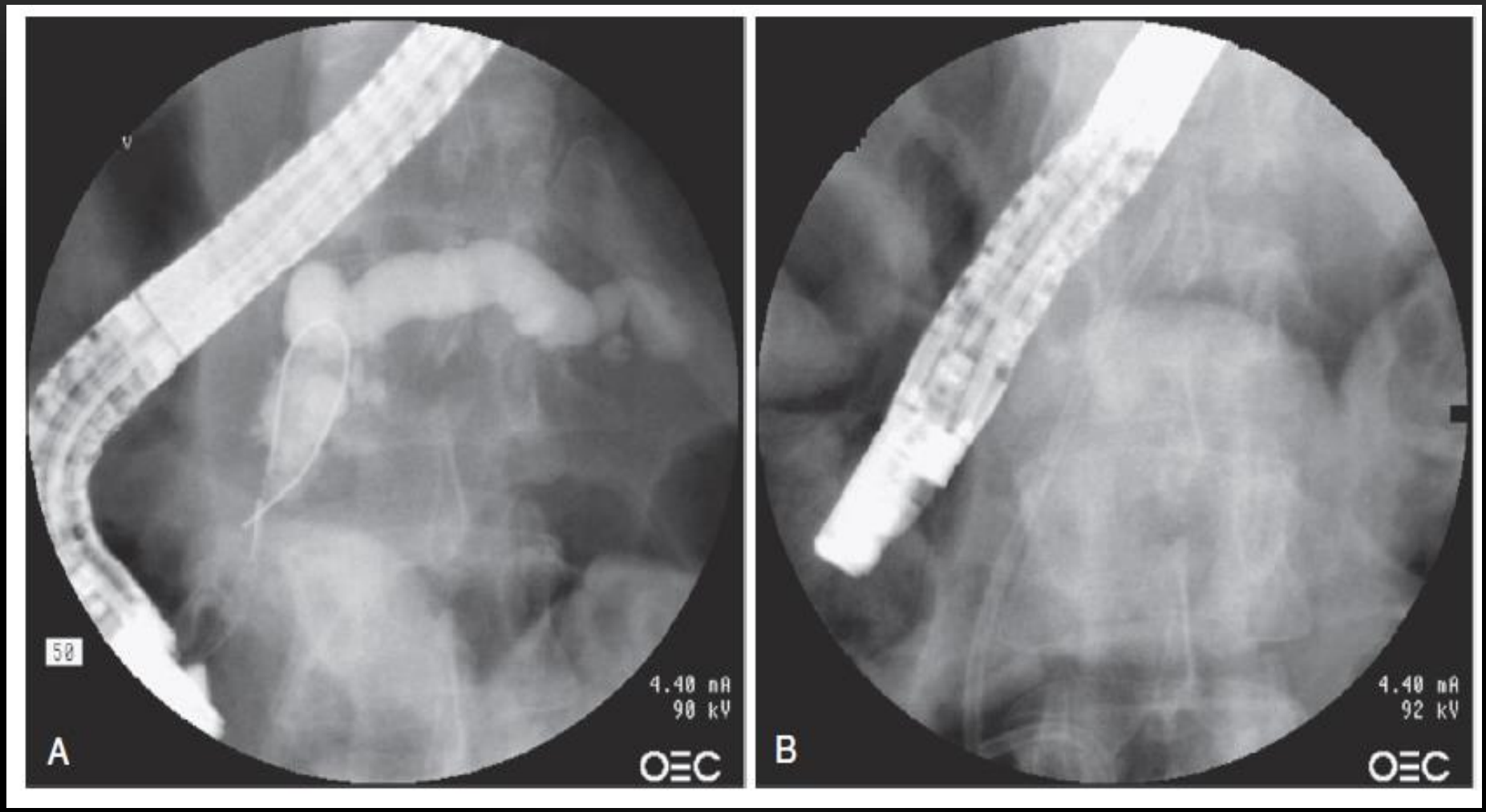
  - Location head of the pancreas.
  - Shorter disease duration with less-frequent attacks of pain,
  - Complete clearance of the main PD
  - Absence main PD stricture
  - Discontinuation of alcohol and tobacco use

MPD STRICTURES

- Pancreatic sphincterotomy
- Biliary sphincterotomy (if*)
- Stricture dilation
- A single 10-Fr plastic stent, with stent exchange planned within 1 year even in asymptomatic patients to prevent complications stent occlusion(usually occlusion within 2–3 months)
- Simultaneous placement of multiple, side-by-side, pancreatic stents could be applied primary or in patients with MPD strictures persisting after 12 months of single plastic stenting.
- At this time point, available options (e. g., endoscopic placement of multiple simultaneous MPD stents, surgery)

- Relief pain (65-84%) of patients.
- At the time of endoscopic intervention, brushings for cytology can be performed to assess for occult malignancy
- **Adverse events**
  - Pain
  - AP
  - stent (occlusion, migration)
  - pancreatic (infection, perforation)
  - stone formation
  - bleeding


a
b
c
d
*


50
4.40 mA
90 kV
A
OEC
4.40 mA
92 kV
B
OEC

EUS-GUIDED ACCESS AND DRAINAGE (ESGAD) OF THE MPD

- Indicated for a symptomatic MPD obstruction and failed conventional transpapillary
- MPD drainage:
  - puncturing MPD through **gastric or duodenal wall**
  - obtaining apancreatogram
  - advancing a guide wire into the MPD to proceed with :
    - ✓ **transpapillary** (rendezvous technique)
    - ✓ **transmural** drainage
- morbidity (ie, perforation, bleeding, infection)

EUS-GUIDED CELIAC BLOCK

- 1 to 5 ganglia , diameter(0.5 cm to 4.5 cm) , location under diaphragm, surrounds celiac artery, from T12 to L2
- Celiac block may be performed endoscopically.
- more effective, less expensive
- anesthetic agent, combination with a steroid
- Relief pain **temporary** (<24 WK)
- SE: transient diarrhea, orthostasis, transient increase in pain, retroperitoneal abscess formation, and spinal cord infarction with paralysis
- offered to hospitalized patients with refractory pain, or patients with severe pain that markedly impairs their quality of life after failing aggressive pharmacologic therapy.

CHRONIC PANCREATITIS-RELATED BILIARY STRICTURES

- (3-23)% of CP
- Endoscopic or surgical treatment depend on
  - ✓ local **expertise**,
  - ✓ local or systemic patient **co-morbidities**
- Temporary placement of simultaneous multiple plastic stents is feasible in >90% of patients with benign CBD strictures;
- Long-term biliary patency rate in chronic pancreatitis-related biliary strictures (65 %);

SURGICAL INTERVENTION

- malignancy cannot be excluded
- coexisting pathology (eg, inflammatory mass, biliary or duodenal obstruction)
- types of strictures (long, complex, or multiple),
- types of stones (large, location in the pancreatic tail, or complex)
- When endotherapy fails.

SUMMARY

COMPARING ET /SURGICAL IN CP :

- **surgical drainage**
  - more effective obstruction and pain relief
  - more cost-effective

- most centers attempt endoscopic therapy prior to surgery (unless sus cancer)