Management of Chronic Pancreatitis

CDDW 2016

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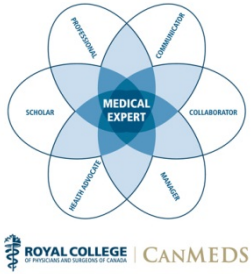
Financial Interest Disclosure

(over the past 24 months)

No relevant financial relationships with any commercial interests



CDDW/CASL Meeting Session: *Chronic Pancreatitis*

CanMEDS Roles Covered in this Session:

✓	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS framework.)
	Communicator (as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)
	Collaborator (as *Collaborators*, physicians effectively work within a healthcare team to achieve optimal patient care.)
	Manager (as *Managers*, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)
	Health Advocate (as *Health Advocates*, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)
	Scholar (as *Scholars*, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)

Objectives

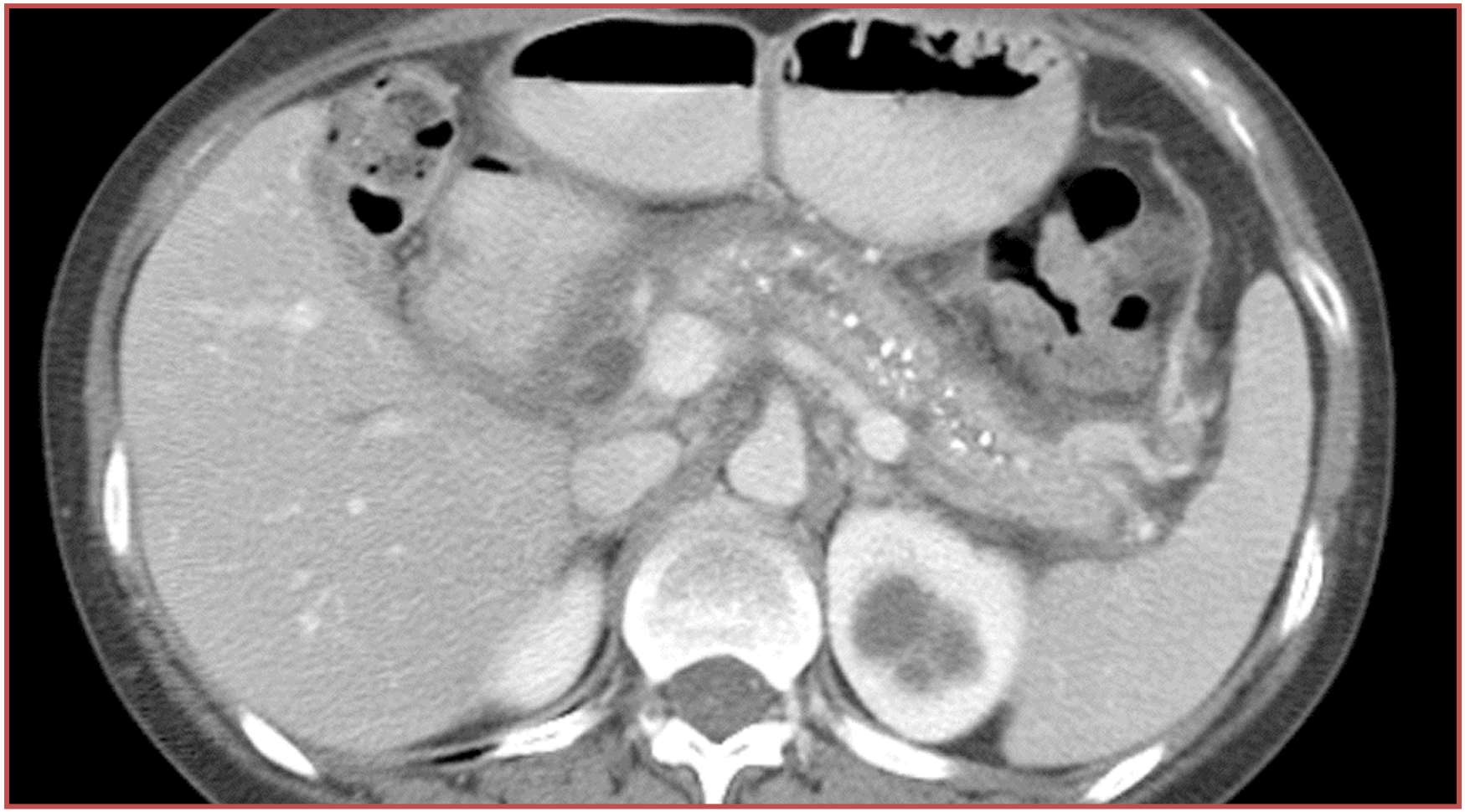
At the end of this session, the participant will:

1) Know the medical management of chronic pancreatitis
2) Know the data on celiac plexus block in the management of chronic pancreatitis
3) Understand which patients to refer for endoscopic management
4) Understand which patients to refer for surgical management

Case 1

- A 52 year old male presents to the GI clinic with a 6 month history of epigastric pain with radiation to the back. He has pain most days; the pain has progressively increased – interfering with his quality of life. He has been using ibuprofen to deal with the pain – ineffective. Denies jaundice, weight loss nausea or vomiting. 1 formed BM/d.
- PMHx hypercholesterolemia. No ORs.
- Meds: Statin
- Social: 20 Pack Year smoker; drinks 4-6 beers per day and may binge on weekends
- Px: epigastric tenderness; no mass
- CBC / Lytes/ albumin/LFTs normal
- EGD Normal

CT



Case #1

- As a first step you advise the patient to stop alcohol consumption and smoking.
- Is there evidence to support that recommendation?

Smoking

- Independent association between smoking and chronic pancreatitis established (Case control and Population based data)
  - Smoking is estimated to account for 25% risk of CP
  - Average OR ~ 2
- Risk of developing chronic pancreatitis among smokers is dose dependent (> 12 Pack-Years)
  - Alcohol use synergistic
  - Onset of CP among smokers with chronic alcoholic pancreatitis is at least 5 years earlier compared to nonsmokers

Yadav and Whitcomb Nat Rev. Gastroenterol Hepatol 2010; Brock et al. World J Gastronenterol 2014

Smoking

- Smoking is associated with the progression of established chronic pancreatitis
  - Calcification; DM
- Smoking cessation may reduce the progression of chronic pancreatitis
  - the risk of developing pancreatic calcifications in patients who stopped smoking was similar to that of nonsmokers

Yadav and Whitcomb Nat Rev. Gastroenterol Hepatol 2010

Alcohol

- Threshold
  - Minimum consumption ≥ 5 drinks / d
- Ongoing heavy consumption significantly enhances risk of progression to CP and diabetes after a single episode of AP
- Counseling + ETOH cessation decreased risk of ETOH-related RAP

Takeyama et al. Clin Gastroenterol and Hepatol 2009; Yadav et al. Gastroenterology 2013; Muniraj et al. Dis Month 2014

Alcohol

- CP + ↓ETOH: Abdominal pain decreases, exocrine insufficiency occurs at a slower pace and mortality rate decreases (compared to patients who continue to drink)
  - Small retrospective series
- Only 5-10% of heavy consumers develop chronic pancreatitis
  - other cofactors: genetic, nutritional deficiency

Strum, AB. J Clin Gastroenterol. 1995

Lifestyle Modification

- Important to recommend **both** alcohol and smoking cessation to all patients

- With regards to the case, smoking and ETOH related cessation strategies are introduced.
- He expresses an interest in “natural remedies” and has read on the Internet that antioxidants could be of benefit in terms of treating his pain.
- What is the rationale for using antioxidants in the treatment of pain associated with chronic pancreatitis? What would your recommendation be?

Antioxidants

- Theory
  - Patients with chronic pancreatitis may be nutritionally compromised
    - Chronic ETOH
  - Oxidative stress may increase pain in CP
    - Results from an imbalance between the generation of reactive oxygen species (increased in CP) and an inadequate antioxidant defense mechanism (deficiency)
    - Results in cellular injury via increased free radical formation (lipid peroxidation, cellular impairment) and inflammation
  - Studies conflicting results: small numbers and high drop out rates, different patient populations, different formulations

Forsmark and Liddle, Gastroenterol 2012

GASTROENTEROLOGY 2009;136:149–159

A Randomized Controlled Trial of Antioxidant Supplementation for Pain Relief in Patients With Chronic Pancreatitis

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- Antioxidant supplementation: Selenium/ Ascorbic acid/Carotene/Tocopherol/ Methionine
- Significant reductions in # painful days per month/use of analgesic tablets and increased number of pain free patients in antioxidant group

- Idiopathic CP >> ETOH CP (2:1)
- Post-randomization drop out higher in placebo arm than treatment arm

Gastroenterology 2012; 143:655–663

Antioxidant Therapy Does Not Reduce Pain in Patients With Chronic Pancreatitis: The ANTICIPATE Study

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Antioxidant supplementation: (Selenium/Tocopherol/Ascorbic acid/methionine)

- No benefit
- Different population (ETOH); more smokers

Antioxidants

- Overall, studies show conflicting results: small numbers and high drop out rates, different patient populations, different formulations

- Cochrane Review:
  - Reduced pain in the antioxidant group than in the control group
    - » MD = -0.33, 95% (CI) -0.64 to -0.02, P = 0.04
- Conclusion (mine):
  - Insufficient evidence to suggest routinely
  - Does not appear to be effective in ETOH/smokers (majority of patients)
  - Consider in truly idiopathic, early cases

Ahemed Ali et al. Cochrane Databse Syst Rev, 2014

Case #1

- Upon reviewing the evidence you decide against trialing antioxidant therapy. You recall that pancreatic enzyme replacement therapy (PERT) may be considered.
- What is the rationale for this form of treatment? Effective?

PERT

Pancreatic Enzyme Replacement Therapy

Non-Enteric Coated

- **Non-Enteric coated**
  - **Immediately released**
  - **Pancreatic enzymes (lipase) acid sensitive**
    - **Denatured pH < 4**
      - **Deactivated in stomach**
    - **Add PPI to enhance bioavailability**

Enteric Coated

- **Enteric coating of microspheres (< 2 mm) ensures delivery to the SI**
  - **Dissolves over a variable period of time @ pH > 5.5.**
  - **Due to erratic $HC0_3^-$ secretion in CP, release may not occur until jejunum/ileum**

Adverse effects (with higher doses): Nausea, vomiting, bloating, diarrhea; hyperuricemia (purine content) thus gout exacerbation and kidney stones

Sikkens et al. Best Pract Res Clin Gastroenterol 2010

- Plumbing Theory
  - Increased pressure within the pancreas from ductal obstruction (stricture/stones)
  - Pancreatic ischemia
    - Compartment Syndrome
  - Pancreatic enzymes may enable “Pancreatic rest”
    - Limit pancreatic secretion

Pasricha PJ. Nat Rev Gastroenterol and Hepatol 2012

PERT

Pancreatic Enzyme Replacement Therapy

- Low quality data
  - Meta-Analysis (1997)[1]
    - 6 RDBCTs
      - No significant benefit vs. placebo
  - Cochrane Review (2009)[2]
    - Results from individual studies could not be pooled due to study heterogeneity
  - 2 small studies showed benefit with non-enteric coated pancreatic enzymes[3,4]
    - Small numbers/data collected in the 80's

[1]Brown et al. Am J Gastroenterol; [2]Shafiq et al. Cochrane Database Syst Reviews, 2009; [3]Isaksson et al. Dig Dis Sci, 1983; [4]Slaff et al.Gastroenterol 1984

PERT

- Problems with our understanding of pain pathophysiology in CP
  - (1) Intraductal pressure does not reliably correlate with pain; patients have incomplete response to ductal decompression Rx
  - (2) Morphologic changes of chronic pancreatitis (stones, strictures, PD dilation) occur in asx and sx patients; no association with severity of pain
  - Shift in focus from structural (plumbing) to neurobiological etiologies (wiring)

Wilcox et al. Clin Gastroenterol and Hepatol 2015

Pathophysiology

Pancreatic nerves (autonomic) undergo changes in CP

- Infiltration of peri-neural space by inflammatory cells
- Micro-disruptions in peri-neural sheath leaves nerves exposed
- Increased number of peri-pancreatic nerves
- Increased size of peri-pancreatic nerves

Anderson et al. Pancreatology 2016

Pathophysiology of Pain in CP

- Nociception
  - The sensing of noxious stimuli (pain)
  - Begins with the primary afferent nociceptor (a nerve)
    - 2 branches – target tissue (pancreas) and dorsal horn spinal cord
    - Ascending pathways relay "information" to the brain
      - Perceive and emotionally respond to the pain

Vardanyan M.Disc Med 2010; Pasricha PJ. Nat Rev Gastroenterol and Hepatol 2012

Pathophysiology of Pain in CP

- Sensitization
  - tissue injury triggers nociceptor activation
    - Over time can increase the gain of the entire system
    - A sensitized system can lead to:
      - enhanced nerve responses which generate significantly more pain (hyperalgesia)
      - Sensation of pain with normal physiologic stimuli (allodynia)

Vardanyan M.Disc Med 2010; Pasricha PJ. Nat Rev Gastroenterol and Hepatol 2012

Managing Pain in CP

- You give the patient a 2 month trial of uncoated pancreatic enzymes in conjunction with a PPI
- The patient fails to respond
- In the interim, the patient sees their family MD and is prescribed hydromorphone

Narcotic Analgesia

- Lowest possible dose, last resort
  - Tramadol less incidence of gut hypo-motility
- Undesirable side effects (e.g. narcotic bowel syndrome)
- May lead to increased sensitization of peripheral nerves and hyperalgesia – increasing pain
- Should combine with “adjunctive agents”
  - Low dose TCA (amitriptyline)
  - No direct evidence in CP
- ? Other options to consider (neuro-biologic theory) “wiring”

Wilder-Smith et al. Dig Dis Sci 1999

Pregabalin and CP

- Pregabalin
  - Abnormal pain processing evident in CP – similar to neuropathic pain
  - Gabapentinoids have been used to treat chronic neuropthaic pain (e.g. DM neuropathy)

GASTROENTEROLOGY 2011;141:536–543

Pregabalin Reduces Pain in Patients With Chronic Pancreatitis in a Randomized, Controlled Trial

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- Pregabalin group: Significant reduction in pain and adjunct narcotic use

Pregabalin and CP

- Titration Method:
  - Pregabalin 75 mg po bid x 3 days ➔150 mg po bid x 1 week➔300 mg po bid
- Adverse effects: CNS
  - More common in pregablin group
  - Lightheadedness, feeling drunk;depression
  - Cochrane Review: only above trial met inclusion criteria – low to moderate evidence to support use but also noted increased adverse effects

Gurusamy and Davidson. Cochrane Database Syst Rev. 2016

Case #1

- The patient does have an improvement in his pain with the addition of pregabalin and tolerates 150 mg po bid.
- The EUS fellow sees the patient in follow up and puts forward the option of celiac plexus block as an additive potential benefit
- Should this be considered in this case?

Celiac Plexus Block and CP

- Bupivicaine + triamcinolone
- Celiac plexus block does not provide effective long term pain relief
- Response rate 55%
  - 26% @ 12 weeks
  - 10% @ 24 weeks

Gress et al. Am J Gastroenterol 2001

Thoracic Splanchnicectomy

- Rationale
  - Nociceptive input of the pancreas starts at the celiac plexus and runs to the sympathetic trunci on both sides of the spine and onto the CNS
  - Splanchnic nerves arise from the thoracic sympathetic ganglia
  - Splanchnic nerves easily identified at thoracocopy (greater, lesser and least) at the level of the thorax before entering the spinal cord T6-T9 (greater), T10-11 (lesser) and T11-12 (least)
    - Thoracic splanchnicectomy provides pain relief in up to 80% of patients immediately (variable)
    - Long-term pain relief falls to less than ~30%
  - Not routinely recommended

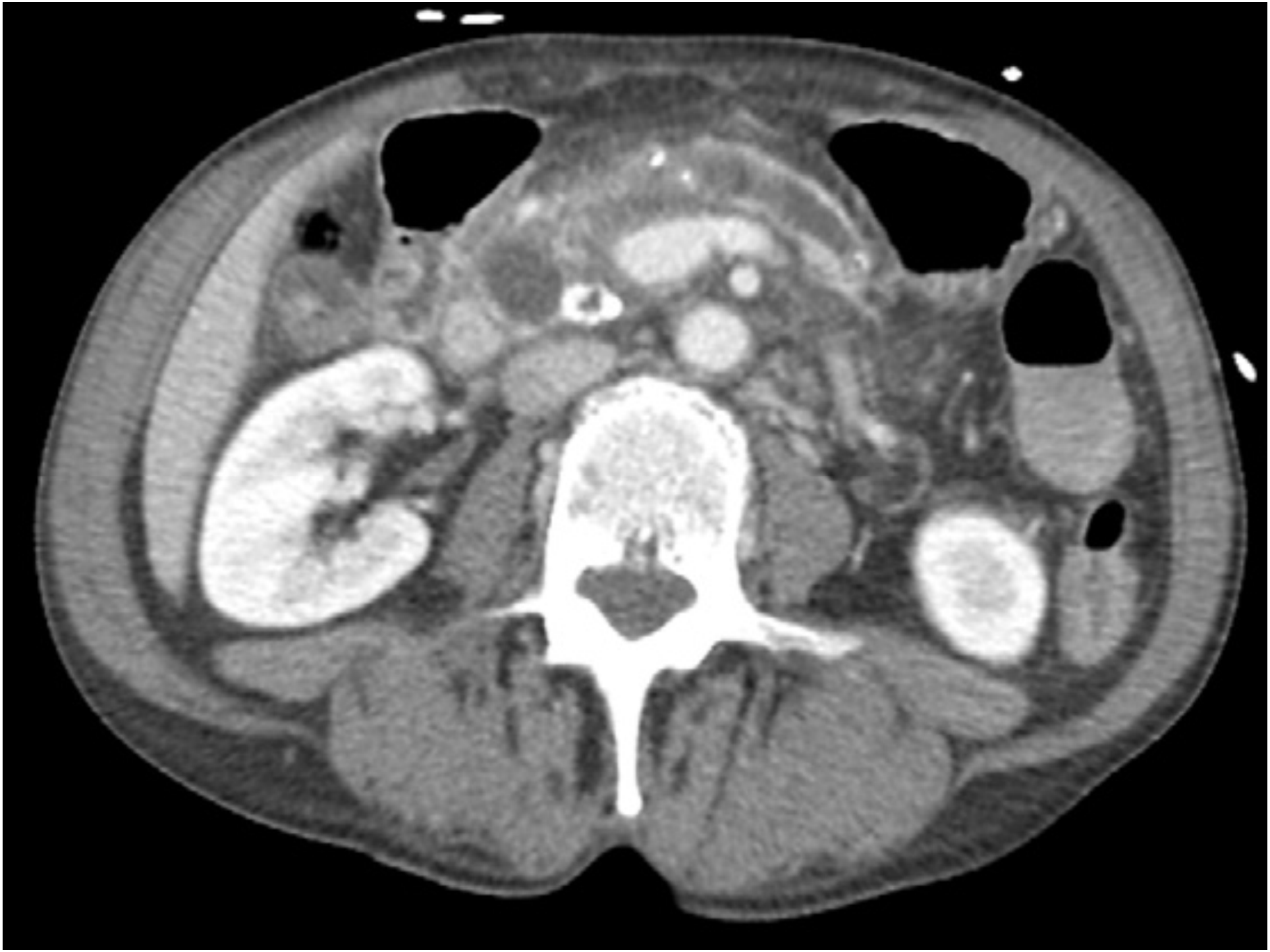
Baghdadi et al. Surg Endosc 2008

Endoscopic management of chronic pancreatitis

- Indications
  - Pancreatic duct obstruction + pain
  - Pancreatic fluid collections + symptoms
  - Pancreatic duct disruption + symptoms
  - Common bile duct stricture

Case #2

- 56 year old male
  - Non-smoker, remote alcohol abuse
  - Previous cholecystectomy for cholelithiasis
- Presents with acute pancreatitis
  - Abdominal pain and nausea
  - Elevated lipase ~1500
  - Elevated WBC
  - Normal liver enzymes
- Abdominal ultrasound
  - Normal biliary system
  - Calcification in pancreas



Case #2

- Responds to medical therapy
- Residual daily post-prandial pain
- Readmitted 2 months later with acute pancreatitis

- What would you do next?

Pain caused by duct obstruction

- PD obstruction and increased pressure within the ductal system
  - PD stricture
  - PD stones

Endoscopic PD decompression

Rösch et al. Endoscopy 2002

- Cohort 1018 patients with 5 yrs (2-12 yrs) follow-up
  - 47% strictures
  - 18% stones
  - 32% strictures + stones
  - 3% complex disease involving body/tail
- 60% endoscopic therapy alone
  - Additional 16% in progress
  - Pancreatic sphincterotomy 92%
  - Dilation 19%
  - ESWL 61% with stones alone, 49% stones + stricture
  - Stent > 2 weeks 72%

- 24% surgery

Endoscopic PD Decompression

Rösch et al. Endoscopy 2002

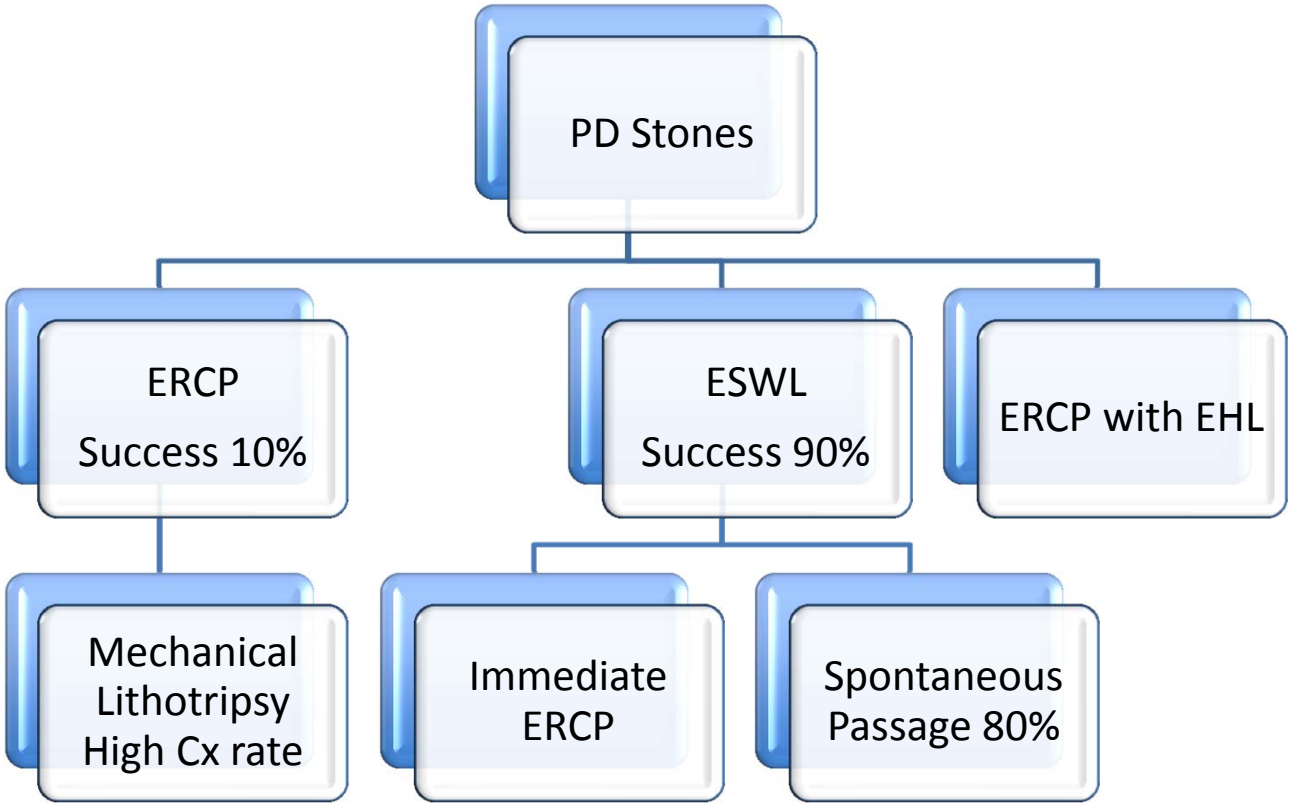
- Complications 13%
- Relief of pain
  - 65% in ITT analysis
  - 86% entire group
- No relieve in pancreatic function
  - Weight gain, diarrhea, diabetes

Endotherapy vs Surgery

Cahen et al. NEJM 2007

- 39 patients with symptomatic chronic pancreatitis and distal PD obstruction
- Randomized to endoscopic vs surgical therapy
  - Surgery = pancreaticojejunostomy
  - ERCP with pancreatic sphincterotomy, stricture dilation and stone removal (+/- ESWL)
- Compared morbidity, mortality, pain scores and SF-36

Endoscopic therapy of PD Stones



PD Stones

- ESGE Guidelines, Endoscopy 2012
  - ESWL followed by ERCP with fragment removal
  - ESWL alone can be considered
  - ERCP without ESWL only for stones < 5 mm, few in number and in the head of the pancreas
  - Intraductal EHL only for failed ESWL

PD Stricture

- ESGE Guidelines, Endoscopy 2012
  - Pancreatic stent placement across a dominant main PD stricture for 12 months
    - Usually with pancreatic sphincterotomy
  - Dilation may be performed prior to stent placement but not alone
    - Step-dilator, balloon, Soehendra stent retriever
  - Consider multiple plastic stents for persistent strictures at 12 months

PD Stricture

- ESGE Guidelines, Endoscopy 2012
  - Fully covered SEMS only in the setting of clinical trials
    - No randomized trials
    - No long-term follow-up
    - Available series leave SEMS in for 2-3 months
      - Migration in a third

Endoscopic PD decompression

- Factors independently associated with success
  - Stone disease in the pancreatic head without a stricture
  - Short duration of disease
  - No (ongoing) exposure to alcohol or cigarettes

EUS-guided access and drainage (ESGAD) of the PD

- Trans-gastric or –duodenal puncture of the PD with guidewire placement
  - Advancement across papilla with rendez-vous procedure
  - Transmural stent placement
- No direct comparisons, case series
  - Failed trans-papillary drainage, need PD > 6 mm for access
  - Similar reports of pain relief to other methods of PD decompression
  - Technically challenging - 8% failure
  - Stent dysfunction in 55%
  - High rate of pancreatic cancer at follow-up

Tessier GIE 2007, Kahaleh GIE 2007

Surgical Management

- Consider in patients with…
  - Distal PD obstruction and failed attempt at endoscopic therapy
    - Lateral pancreaticojejunostomy
  - Isolated body/tail disease
    - Pancreatic resection

Pancreatic Pseudocyst

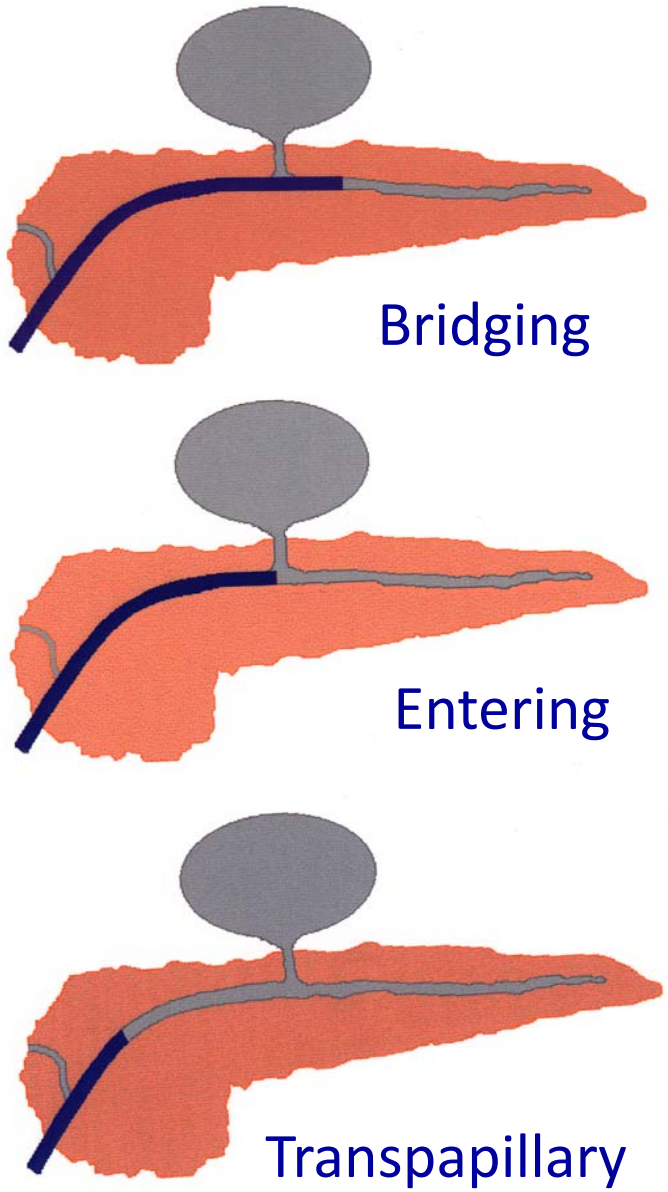
- Approximately 1/3 chronic pancreatitis patients will develop a pseudocyst but few need drainage
- Consider drainage for:
  - Infected
  - Mass effect with symptoms – CBD obstruction, early satiety, gastric outlet obstruction
  - Enlarging?
- Transpapillary
  - Communication with main PD
- Transmural
  - EUS-guided

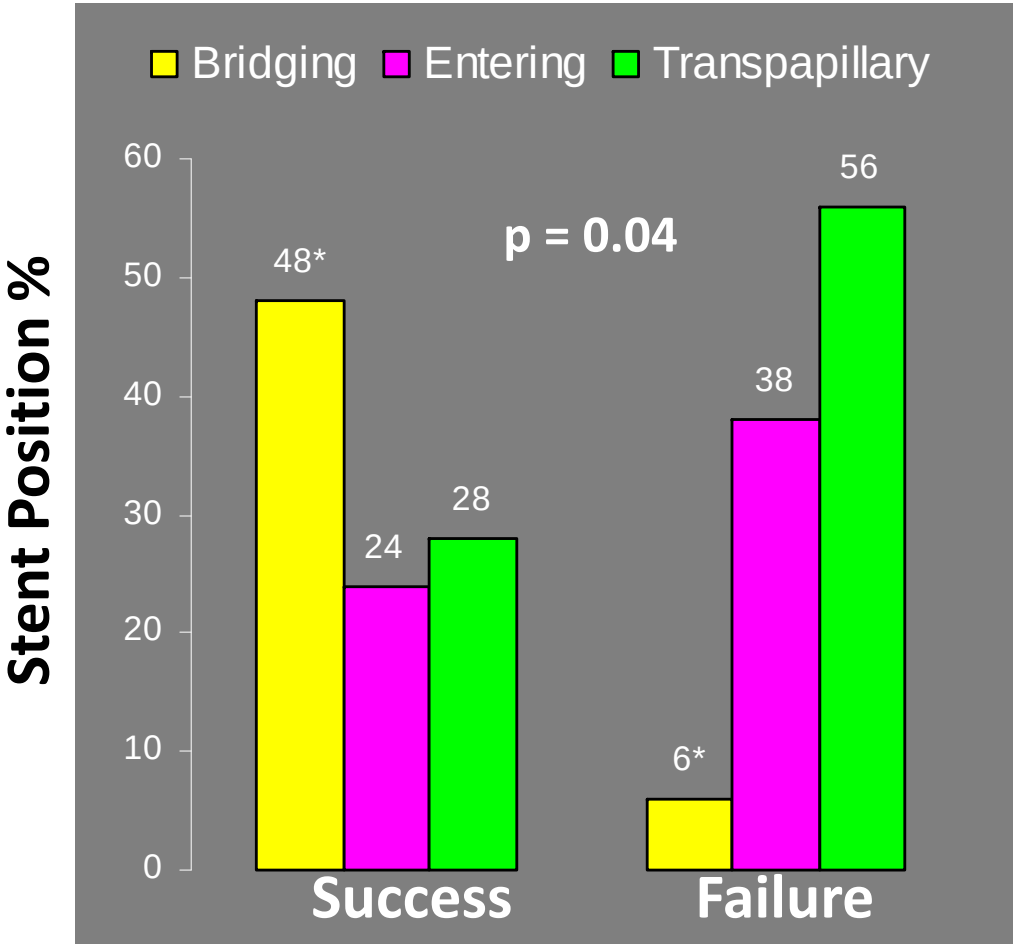
Transpapillary pseudocyst drainage

- Successful drainage associated with:
  - Bridging stent position
  - Longer duration of stent therapy (> 2 weeks)
  - Partial (vs complete) PD disruption

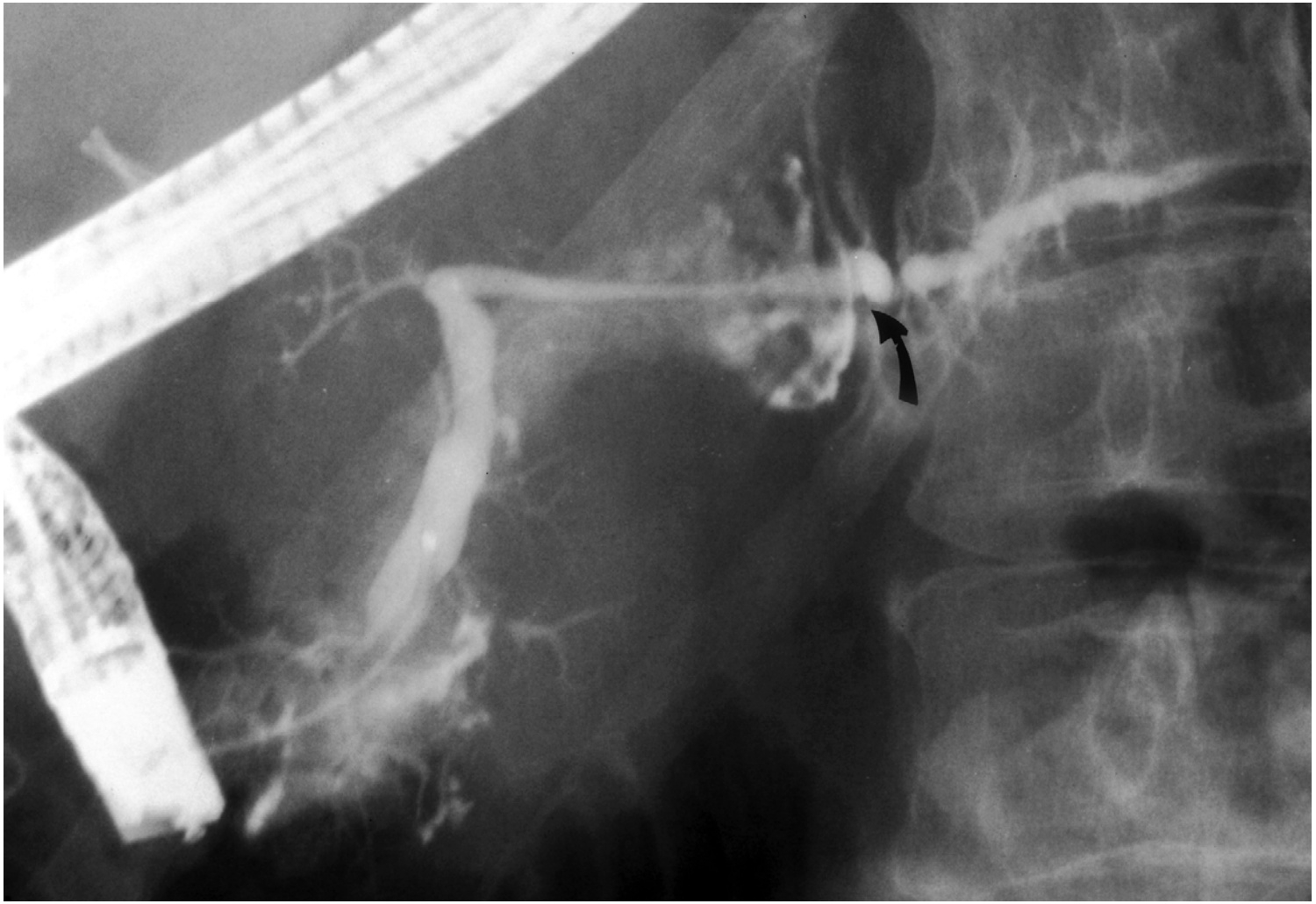
Telford et al GIE 2002
Varadarajulu et al GIE 2005

Stent Position

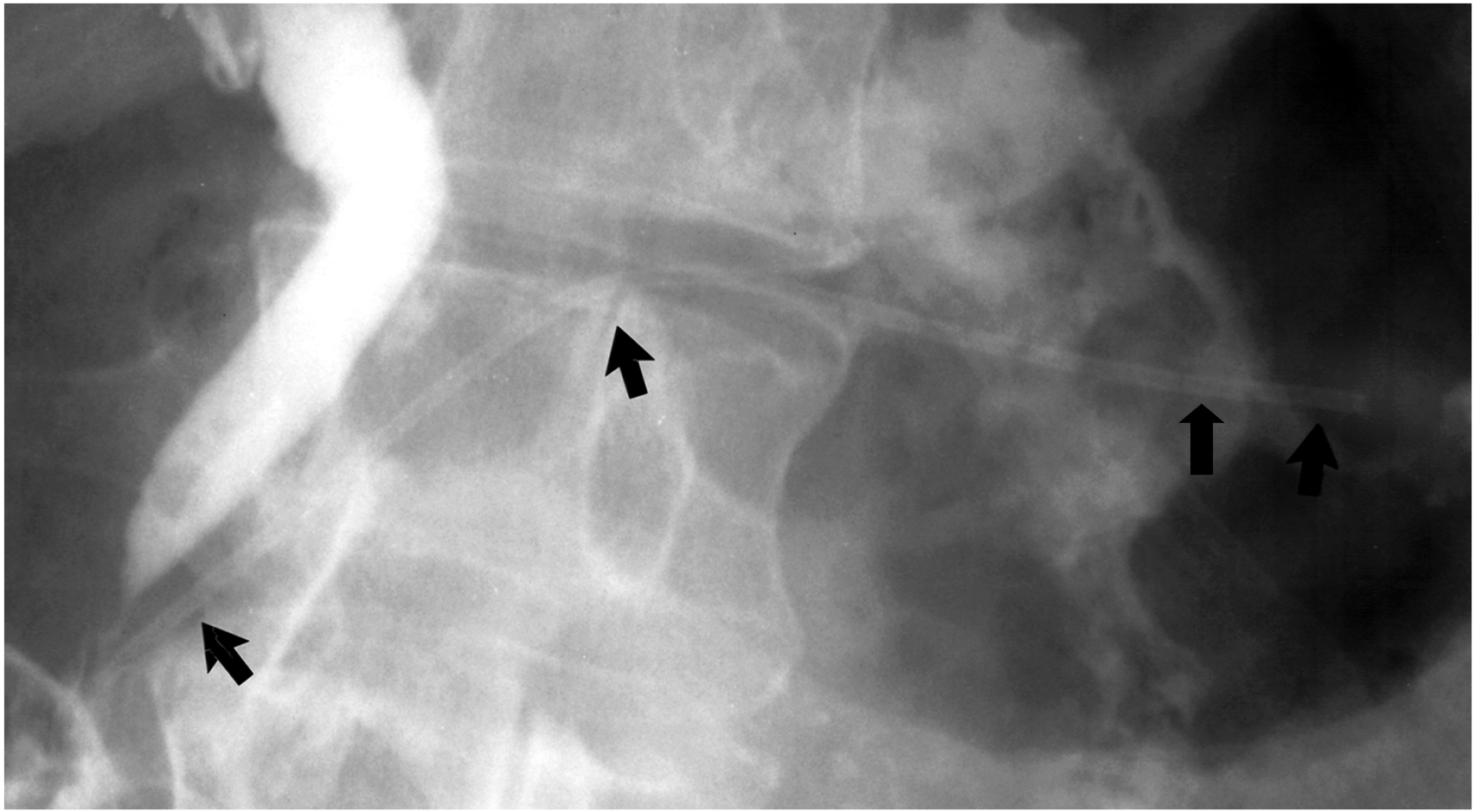




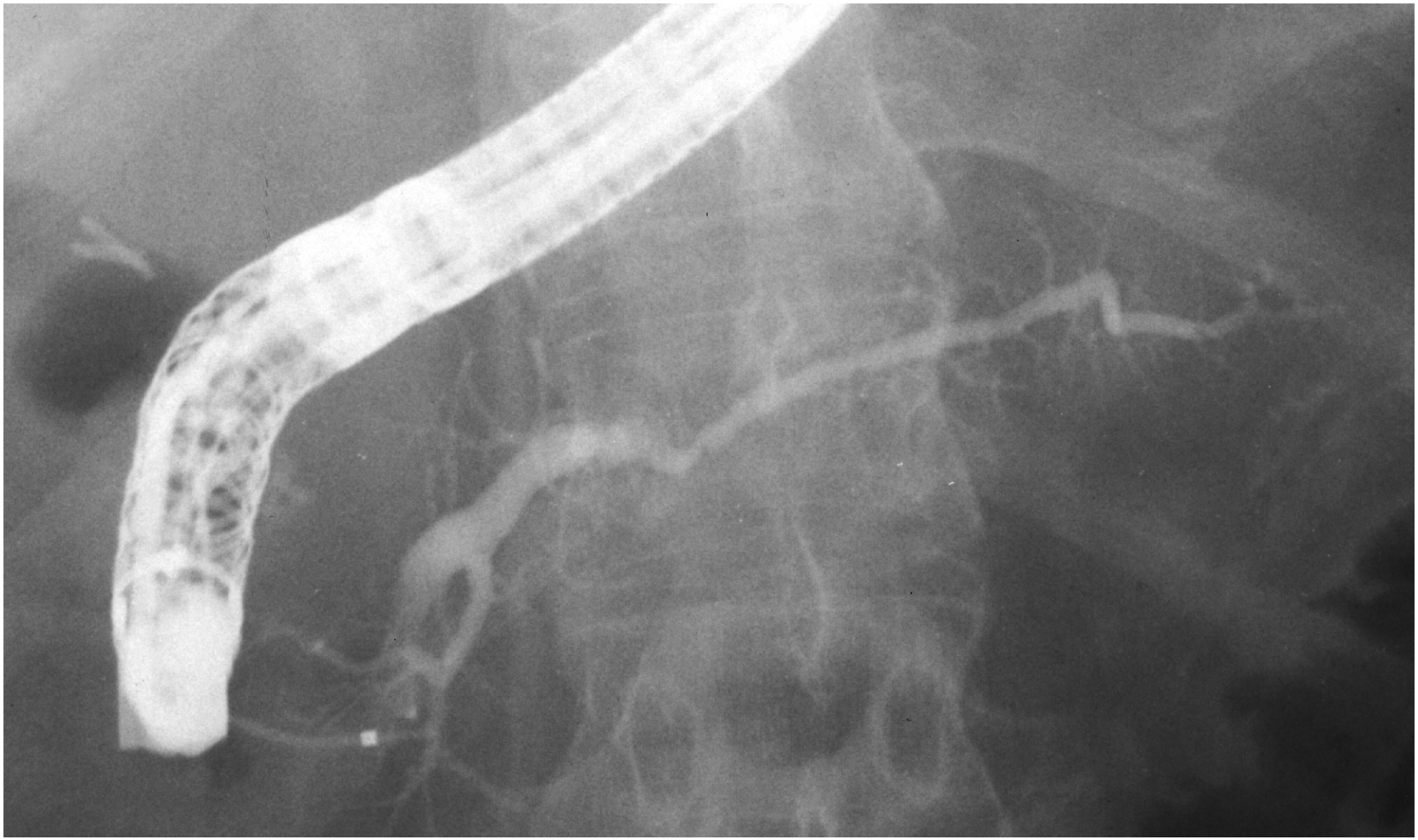
Duct Disruption



Bridging Stent Placed



Disruption Resolution



Transmural pseudocyst drainage

- EUS-guided
- Successful drainage associated with:
  - Double pigtail stents
    - Straight stents increase rates of bleeding, migration
  - Multiple stents
  - Long duration of therapy (forever?)
- Complications 13% (3-30%)
  - Antibiotic prophylaxis recommended

CBD stricture

- Chronic pancreatitis is associated with a CBD stricture in 3-23%
- Indications for stent placement:
  - Symptoms
  - Secondary biliary cirrhosis
  - Increase in alkaline phosphatase or bilirubin > 2x ULN

CBD stricture

- Rule out malignancy
- Long-term (12 months) therapy
- Multiple plastic vs single plastic
  - 92% vs 24% success[1]
- Fully covered SEMS
  - No direct comparison with plastic stents
  - Duration of therapy ~ 6 months

1) Catalano GIE 2004

Consider pancreatic cancer

- Pancreatic cancer
  - > 50 years of age
  - Female
  - Caucasian
  - Jaundice
  - Hereditary Pancreatitis

Summary

- PD decompression can relieve pain long term in ~60% patients
  - Stones – ESWL works best
  - Strictures – Rule out cancer, stent for a year

Thank you

- Questions?