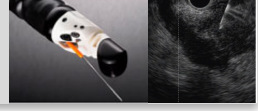
Semana Digestiva 2018

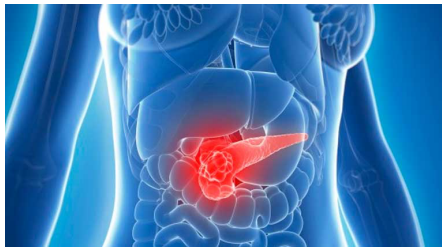
Endoscopic Management of Pain in Pancreatic Cancer

Pedro Moutinho-Ribeiro MD, MMed, FEBGH

Centro Hospitalar de São João - Faculdade de Medicina do Porto
Serviço de Gastrenterologia
Director: Guilherme Macedo MD, PhD



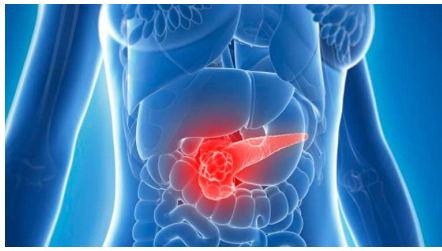
Introduction



- PDAC is the 4th leading cause of cancer related deaths in US.
- Aggressive tumor biology & late manifestations of the disease.
- Only 15-20% of patients amenable for surgical resection.
- Majority is treated with palliative Qt or BSC.
- Overall 5-year survival rate 5-7%.
- Palliation plays a critical role in the management of pts.

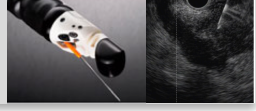
Jemal A et al. Cancer J Clin 2010
Mekaroonkamol et al. JOP 2015

PAIN in pancreatic cancer

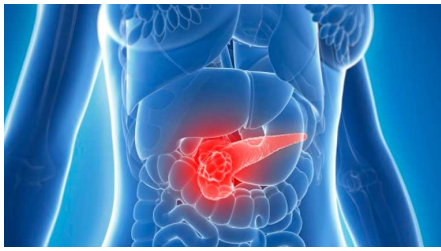


- Up to 80% of patients with PDAC report abdominal pain.
- 44-70% suffer from severe pain.
- Difficult-to-control in more than 90% of pts w/ advanced disease.
- May represent extrapancreatic perineural invasion and is associated with a higher recurrence rate and poorer prognosis.
- Critically impacts QoL.
- Pain management plays a central role in palliation.

Molinari et al. Surg Clin Am 2001
Arcidiacono et al. Cochrane DB Syst Rev. 2011
Ascunce et al. Gastrointest Endosc 2011



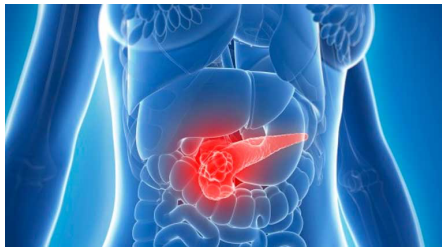
PAIN in pancreatic cancer



- NSAIDs and opioid agents are first line medications in pain management.
  -NCCN (2018) and ESMO (2017) guidelines.
- However, their use is limited by numerous adverse effects.
  (constipation, somnolence, nausea, pruritus, tolerance, and addiction)
- **Endoscopic therapy,** albeit more extensively studied in chronic pancreatitis, has an important role in pancreatic cancer patients, as both conditions share some common pathways for pain development.

Michaels et al. World J Gastroenterol 2007
Adler et al. Gastrointest Endosc 2006

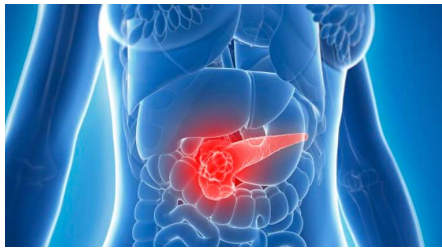
Pathophysiology of Pain in PC



- Multifactorial.
- Nociceptive signals generated by three main mechanisms:
  - Neurogenic inflammation
  - Pancreatic duct hypertension
  - Perineural invasion
- Biliary and duodenal obstruction (mechanism similar to non-malignant etiologies).

Michaels et al. World J Gastroenterol 2007
Tonozuka et al. Digest Endosc 2013

Clinical Manifestations of Pain



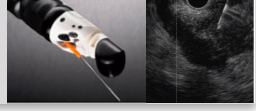
- **Neuropathic (visceral)**

  Fairly continuous, dull, epigastric or upper back pain that is not related to a meal (perineural invasion and neurogenic inflammation)

- **Obstructive**

  Episodic post-prandial epigastric or left hypochondrial pain that typically radiates to the back, similar to the pain in chronic pancreatitis (pancreatic ductal hypertension)

Tham et al. Am J Gastroenterol 2000
Costamagna et al. Dig Liver Dis 2004
Wehrmann et al. Eur J Gastroenterol Hepatol 2005

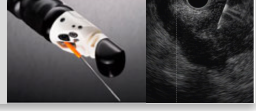


NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Adult Cancer Pain

Version 1.2018 — January 22, 2018



National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2018
Adult Cancer Pain

NCCN Guidelines Index
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Discussion

PAIN INTENSITY See Pain Intensity Rating (PAIN-A)

SUBSEQUENT PAIN MANAGEMENT[d]

GOALS OF TREATMENT

General Principles →
- For persistent pain, initiate regular schedule of opioid with rescue dose as needed
- Continue management of constipation (See PAIN-F) and other adverse effects
- Provide psychosocial support (See PAIN-H)
- Provide patient and family/caregiver education (See PAIN-I)
- Optimize integrative interventions (See PAIN-J)
- Consider adding/adjusting adjuvant analgesics (See PAIN-G)

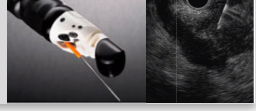
Moderate to Severe Pain ≥4 →
- See General Principles above AND
- If pain is inadequately controlled reevaluate opioid titration (See PAIN-E)
- If pain is inadequately controlled reevaluate working diagnosis with a comprehensive pain assessment (See PAIN-C)
- Consider specific pain syndrome problems (See PAIN-D)
- Consider pain specialty consultation (See PAIN-L)
- Consider opioid rotation if dose limiting adverse effects are noted

Mild Pain 0–3 →
- See General Principles above AND
- Reassess and modify regimen to minimize adverse effects; taper opioids and other treatments when no longer needed (See PAIN-E and See PAIN-F)

→ Routinely reevaluate pain at each contact and as needed to meet patient-specific goals for comfort, function, and safety

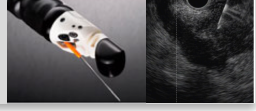
Achieved → See Ongoing Care (PAIN-7)

Not achieved →
- See Universal Screening and Assessment (PAIN-2)
- Consider pain management specialty consultation.
- Consider interventional strategies (PAIN-M) or other treatments
- Consider palliative care consultation (See NCCN Guidelines for Palliative Care)



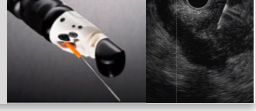
Endoscopic therapies for alleviating pain associated with pancreatic cancer

- **MULTIDISCIPLINARY TEAM**



Endoscopic therapies for alleviating pain associated with pancreatic cancer

- **EUS-guided celiac plexus interventions**
- **Pancreatic duct stent placement**
- **Peripancreatic luminal obstruction management** *(duodenal & biliary)*

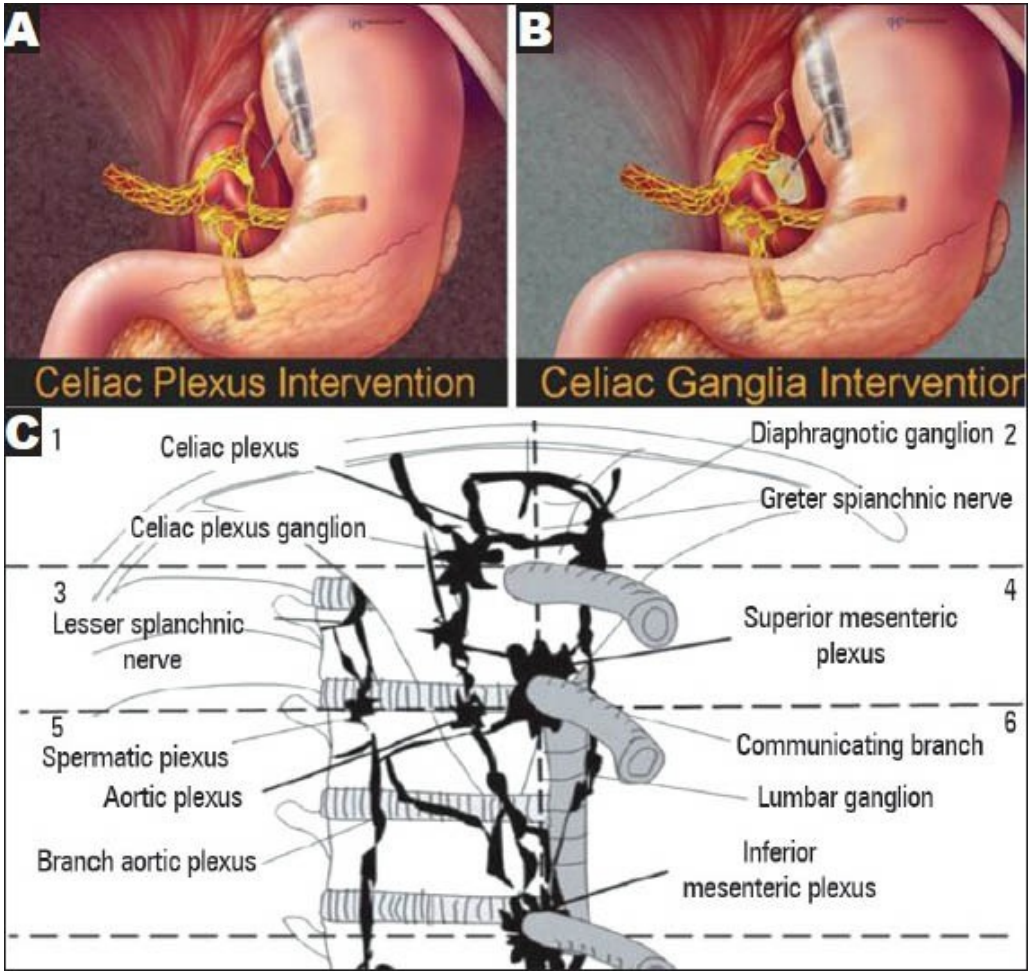


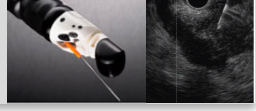
EUS-guided celiac plexus interventions

- Celiac plexus neurolysis (CPN) and celiac plexus block (CPB) are considered first line adjuvant therapies for the treatment of non controlled pain. *(NCCN Guidelines v.2018 & ESMO Guidelines 2017).*
- EUS-guided CP interventions show advantage over percutaneous route.
- Central *vs* bilateral injection (no difference)
- ***RCT and Meta-analysis***
    - Safe
    - Effective pain relief (60-70% after 1-4w; durable for 24w)
    - Reduction of analgesia use
    - Improves QoL

LeBlanc JK et al. Gastrointest Endosc 2011
Puli Sr et al. Dig Dis Sci 2009
Arcidiacono PG et al. Cochrane Database Syst Rev 2011
Levy MJ et al. Gastrointest Endoscopy Clin N Am 2012

EUS-guided celiac plexus interventions



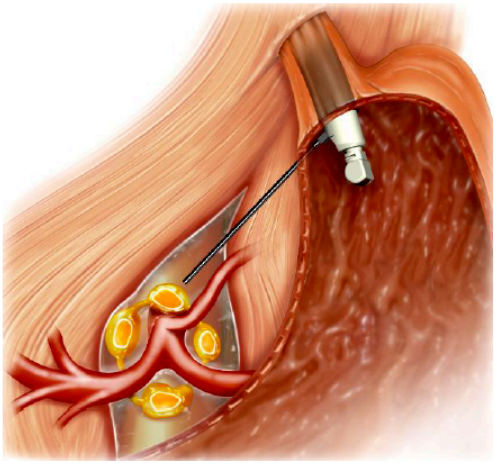


EUS-guided celiac plexus interventions

- **Modalities:**
  - **Celiac plexus neurolysis (CPN)**
    First reported in 1996[1]
  - **Celiac ganglia neurolysis (CGN)**
    Visible in 70-80%; seems to be more effective[2,3]
  - **Broad plexus neurolysis (BPN)**
    Extended to SMA & IMA; Japanese group[4]; needs validation

[1]Wiersena MJ et al. Gastrointestinal Endosco 1996
[2]Levy MJ et al. Am J Gastroenterol 2008
[3]Doi S et al. Endoscopy 2013
[4]Sakamoto H et al. J Gastroenterl 2010

EUS-guided celiac plexus neurolysis (EUS-CPN)



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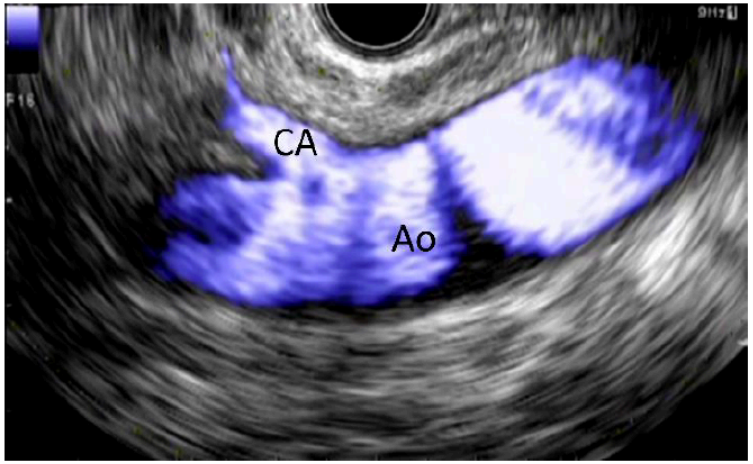

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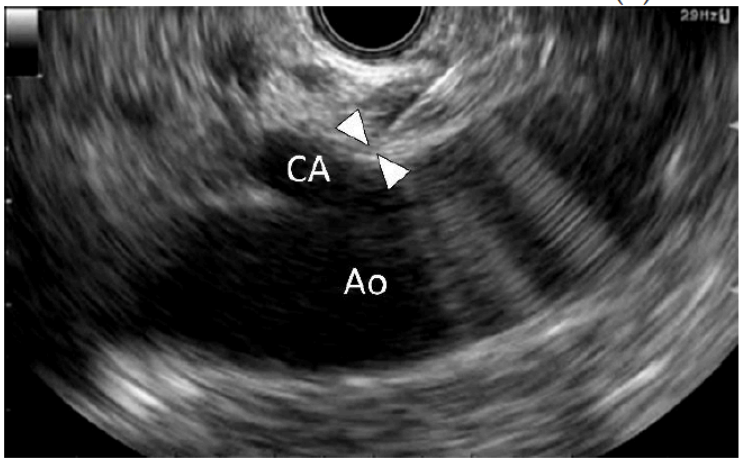

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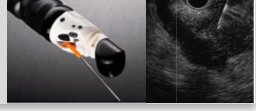
Minaga K. *et al*. Cancers 2018



EUS-guided celiac plexus neurolysis (EUS-CPN)

- Permanent ablation of nervous tissue using sclerosing or neurolytic agents. (5% phenol, absolute alcohol).
- Only in unresectable disease, as retroperitoneal fibrosis may preclude future surgery.
- Single or double-puncture (cephalad, or left and right to the celiac trunk).
- Improves pain, narcotic usage, and constipation in ≈ 80% of patients (up to 4mo).
- Involvement of the pancreatic head and a locally advanced presentation are known to have less response to the intervention.

Minaga K. *et al*. Cancers 2018
Mekaroonkamol P. *et al.* JOP 2015
Kaufman M eta al. J Clin Gastroenterol 2010

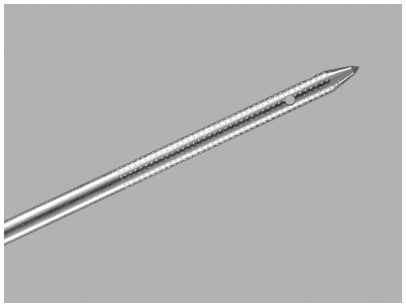
EUS-guided CPN: Technical aspects

- Pretreatment hydration (saline solution 500-1000ml)
- Sedation
- Continuous monitoring of vital signs

- Local anesthetic (bupivacaine or lidocaine) – 2-3ml
- Neurolytic agent (absolute alcohol or phenol) – 10-20ml

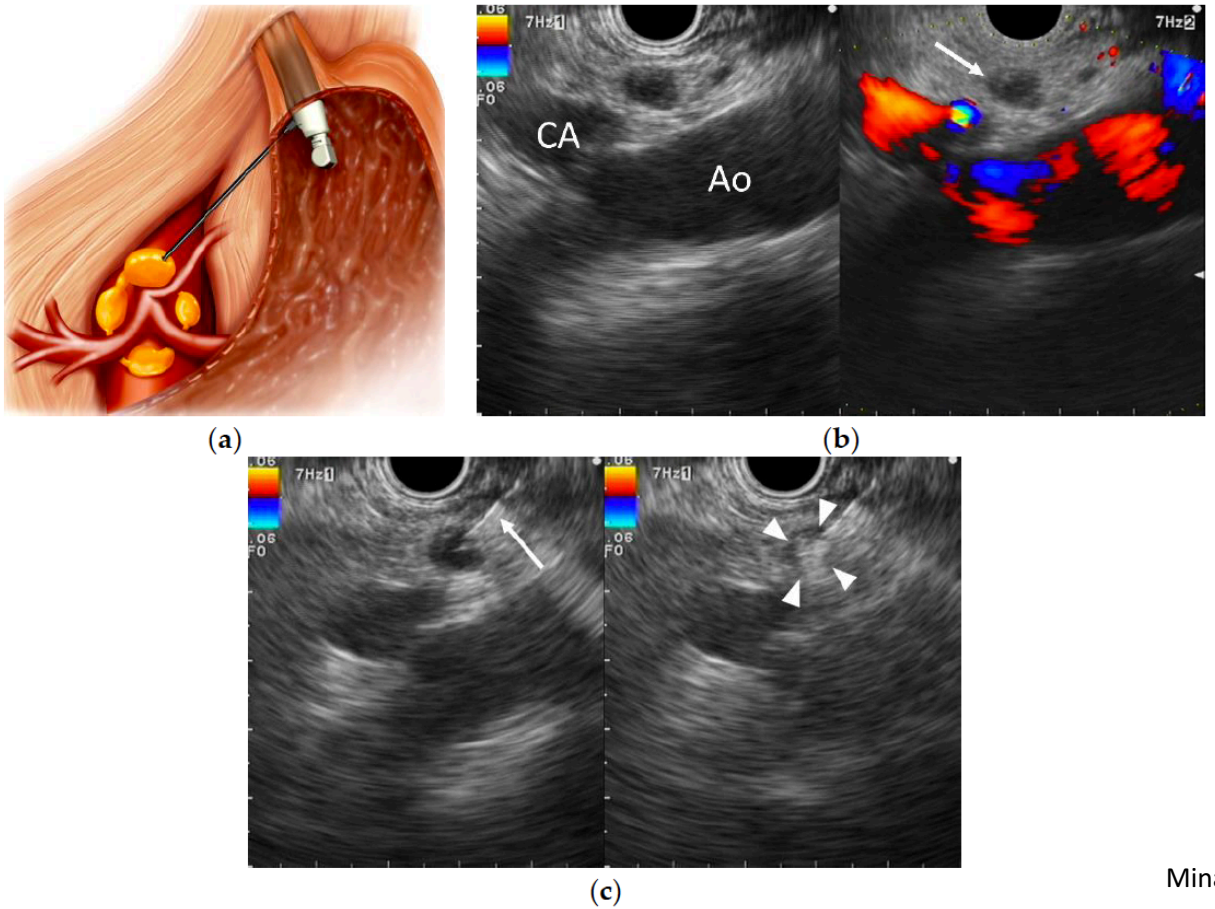
- 19- or 22-gauge aspiration needle
- 20-gauge “spray” needle (EchoTip® Ultra CPN Needle)

- Unilateral: cephalic to the CT
- Bilateral: both sides of the CT

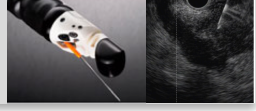


Minaga K. *et al*. Cancers 2018

EUS-guided celiac ganglia neurolysis (EUS-CGN)



Minaga K. *et al*. Cancers 2018



EUS-guided celiac ganglia neurolysis (EUS-CGN)

- One to five small (0.5-4.5 mm) elongated hypoechoic structures with hyperechoic central foci, anterolateral to the aorta, just distal to the take-off of celiac artery.
- Each ganglion is punctured with a 19- or 22-gauge aspiration needle and absolute alcohol is injected (1-2ml) until the entire ganglion becomes hyperechoic.
- Puncture of as many visualized ganglia as possible, to maximize efficacy.
- Believed to be the most accurate and most effective technique, yielding a 5-fold higher chance of clinical response compared to blind injection.

Minaga K. *et al*. Cancers 2018
Ascune G et al. Gastrointest Endosc 2011

PROSPECTIVE, RANDOMIZED, DOUBLE BLIND CLINICAL TRIAL OF CELIAC PLEXUS NEUROLYSIS AND CELIAC GANGLIA NEUROLYSIS: IMPACT ON PANCREATIC CANCER PAIN, QUALITY OF LIFE, AND SURVIVAL

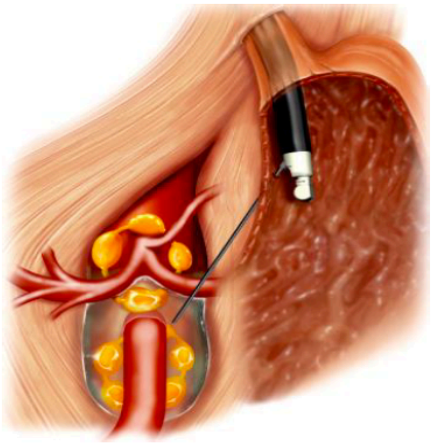
M Levy, FC. Gleeson, M Topazian, LL Fujii-Lau, F Enders, JJ. Larsn, K Mara, BK Abu Dayyeh, SR Alberts, C Hallemeier, PG Iyer, ML. Kendrick, W Mauck, RK. Pearson, Bret BT Petersen, E Rajan, N Takahashi, SS Vege, KK. Wang, ST Chari.
Mayo Clinic, Rochester, Minnesota, United States;

- 110 patients: 53 randomized to CPN and 57 to CGN .
- Hypothesis: when compared to EUS-CPN, EUS-CGN improves pain control, QOL and survival.

CONCLUSIONS:

- In contrast to the hypothesis, we found that CGN shortens survival without improving pain, AE rate, or QOL when compared to conventional CPN.
- These findings cast doubt on the clinical role of CGN.
- Although fewer than 50%** of PDAC patients experience pain relief with CPN, it continues to have a clinical role.

EUS-guided broad plexus neurolysis (EUS-BPN)



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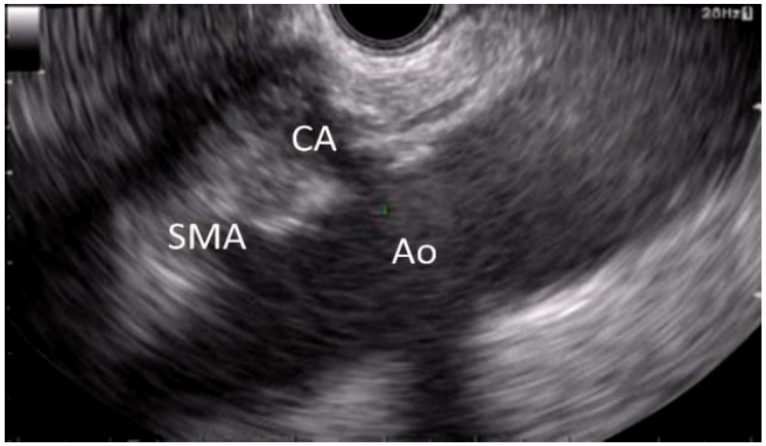

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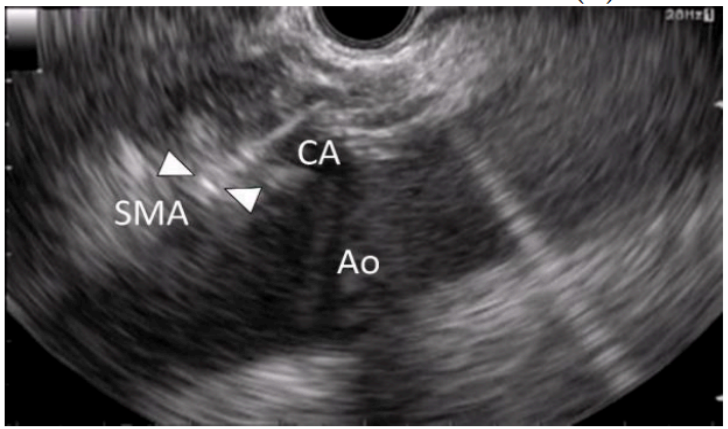

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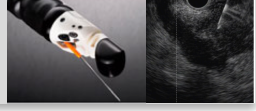
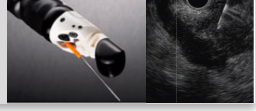
Minaga K. *et al*. Cancers 2018



EUS-guided broad plexus neurolysis (EUS-BPN)

- First described in 2010, a neurolytic agent is injected around the origin of the SMA to produce a wider distribution.
- Bilateral injection anesthetic (2-3ml), followed by neurolytic agent (up to a 10 ml).
- A 25-gauge needle should be used to provide safety and flexibility during needle advancement into the target area (deeper than in CPN).
- The initial study suggested that EUS-BPN was more effective than EUS-CPN, especially in patients with extensive spread of cancer within the abdominal cavity beyond the distribution of the CP, without serious complications.
- In a recent study, a multivariable analysis revealed that EUS-BPN in combination with EUS-CGN was a significant determinant of pain-relief response.

Sakamoto H et al. J Gastroenterl 2010
Minaga K. *et al*. Therap Adv Gastroenterol 2016



EUS-guided celiac plexus interventions

- **Recent Modalities:**
  - **EUS-guided implantation of ^{125}I seeds**

    into the celiac ganglia was recently believed to offer enhanced pain relief with acceptable feasibility and safety.

    Wang KX *et a*l. Gastrointest Endosc. 2012
  - **EUS-guided Radiofrequency ablation**

    in a randomized trial, EUS-guided RFA of celiac ganglia seemed to be superior over CPN.

    Bang JY *et al*. DDW 2018
  - **EUS-guided ethanol tumor ablation**

    EUS-guided tumor ablation combined with CPN appeared to be superior to CPN alone with respect to pain relief and overall survival.

    Facciorusso A *et al*. J Gastroenterol Hepatol 2017

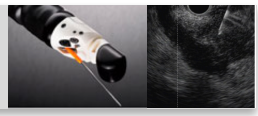
SUPERIORITY OF EUS-GUIDED RFA OVER EUS-GUIDED CPN FOR PALLIATION OF PAIN IN PANCREATIC CANCER IN A RANDOMIZED TRIAL

JY Bang, U Navaneethan, MK. Hasan, B Sutton, RH Hawes, S Varadarajulu.
Florida Hospital, Orlando, Florida, USA

- single-blind, randomized trial: EUS-CPN (n=14) or EUS-RFA (n=12)
- RFA: Habib EndoHPB probe, via 19G-FNA needle and by targeting the area of celiac plexus or visualized ganglia.
- Primary endpoint: QoL at 2 and 4-weeks, evaluated by EORTC core cancer (QLQ-C30) and pancreatic cancer-specific (QLQ-PAN26) questionnaires.
- In EUS RFA group:
  - less pain ($P<0.001$), less alteration in bowel habits ($p=0,03$), less indigestion($P<0.001$), less fear of future health ($P=0,001$) and better ability to plan future ($p=0,003$) .

CONCLUSIONS:

Compared to EUS-CPN, EUS-guided RFA provided more pain relief and improved QoL.



Complications of EUS-guided neurolysis

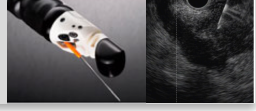
- **Sympatholytic reactions**
  - Transient hypotension (1-38%)
  - Diarrhea (4-44%)

  (post-procedure, usually self-limited to 48 hours)

- **Paradoxical increase in pain** (9%), that can last 2 days

- **Major complications** (rare)
  - Peripancreatic abscess
  - Retroperitoneal bleeding
  - Hepatic, kidney, splenic infarction
  - Celiac artery thrombosis / bowel ischemia
  - Impotence
  - Paraplegia

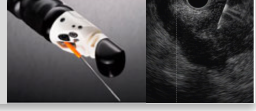
Mekaroonkamol P. *et al.* JOP 2015
Minaga K. *et al*. Cancers 2018



Pancreatic duct stent placement

- Effectively decompresses the pancreatic duct and is known to be an effective treatment for pain in chronic obstructive pancreatitis.
- The role in pancreatic cancer is less well established.
- Particularly suited to pancreatic head tumors causing ductal obstruction and obstructive pain, which may be less likely to respond to CPN.
- Plastic stents and metallic stents have been employed

Adler et al. Gastrointest Endosc 2006
Catalano et al. Gastrointest Endosc 2005



Pancreatic duct stent placement

European Journal of Gastroenterology & Hepatology 2005

Endoscopic pancreatic duct stenting for relief of pancreatic cancer pain

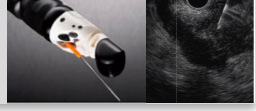
Wehrmann, Till; Riphaus, Andrea; Frenz, Markus B.; Martchenko, Ksenia; Stergiou, Nikos

- Prospective study: 20 pts with pancreatic head cancer
  PD obstruction & Postprandial epigastric pain

- Plastic stents: 7 and 10Fr
- Mean F-Up 16w: pain, opioid doses, QoL

- Response rate: 82%; Long-lasting effect up to 12w in 62% (irrespective of stent diameter).

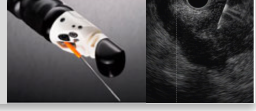
- Significant improvement in pain relief and QoL.



Pancreatic duct stent placement

Gut 2005 Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas

- British Society of Gastroenterology has endorsed PDSP as an adjunctive approach for palliation of obstructive pain in patients with pancreatic ductal stenosis.
- However, the available studies are small with a non-randomized design
- Larger high-quality controlled studies are needed to evaluate PDSP and EUS-CPN, given the different pain relieving mechanisms these two procedures can offer.



Pancreatic duct stent placement

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

Endoscopic Pancreatic Duct Stenting for Relief of Obstructive Pain in Patients With Pancreatic Cancer

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT01895790

Recruitment Status: Withdrawn (We could not find any candidate eligible for recruitment)
First Posted: July 11, 2013
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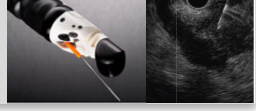
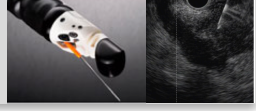
Sponsor:
Johns Hopkins University



Peripancreatic *(duodenal & biliary)* **luminal obstruction management**

- Approximately 70% of PDAC involves the pancreatic head, predisposing patients to biliary and gastroduodenal obstruction.
- Pain, jaundice, pruritus, nausea and vomiting are common presenting obstructive symptoms.



Biliary obstruction

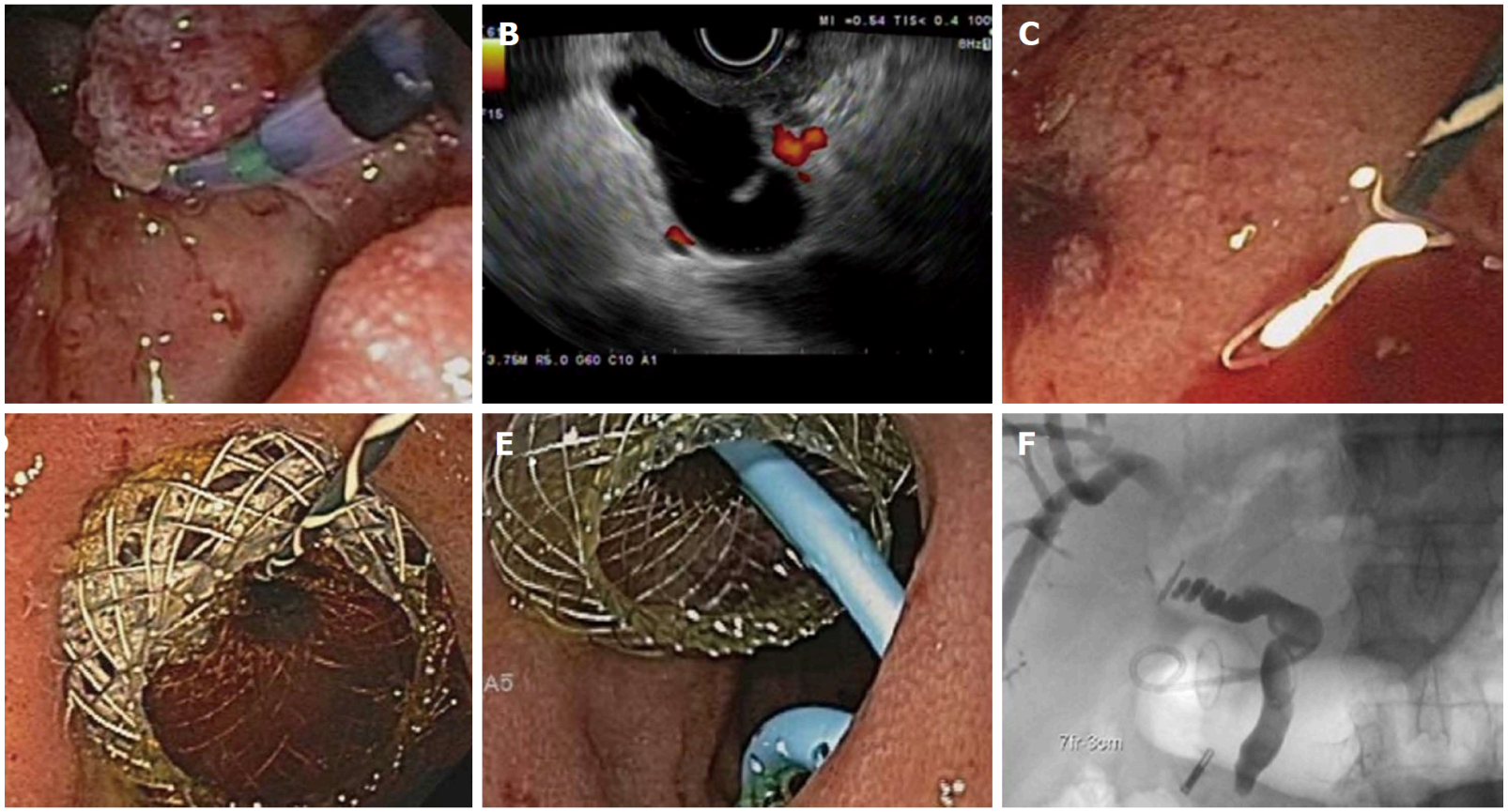
- **ERCP** is the procedure of choice for drainage.
- SEMS are preferred when life expectancy is greater than a few months.

- However, **failure occurs in 3-10 %**
  Anatomic variants; Prior surgery; Gastric outlet obstruction;
  Tumor extension; Operator inability.

- **RESCUE options**:
  Percutaneous transhepatic drainage
  Surgical interventions
  EUS-guided biliary drainage

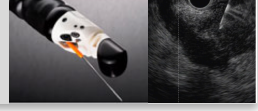
Kahalenh et al. World J Gastroenterol. 2015

EUS-guided biliary drainage



EUS-guided choledochoduodenostomy following unsuccessful ERCP.

Oh S, et al. World J Gastrointest Endosc 2016

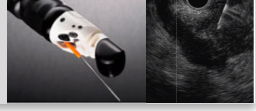


- **EUS-guided drainage *vs* percutaneous drainage**

SYSTEMATIC REVIEW AND META-ANALYSIS

- similar technical success
- better clinical success
- fewer procedure-related adverse events
- fewer unscheduled re-interventions

-**EUS-guided interventions may be preferred** over PTBD,
if adequate advanced endoscopy expertise and logistics are available.



Duodenal obstruction

- Usually occurs at the peripyloric and duodenal regions, late in the course of the disease (20% are in the terminal stage).
- Endoscopic gastroduodenal stenting has proven to be a safe and effective non-surgical minimally-invasive option.
- When concomitant biliary obstruction (23-61% of the cases), biliary stents can be placed before, simultaneously, or after the placement of the duodenal stent.

Moon et al. Gastointest Endosc. 2009
Dormann et al. Endoscopy 2004

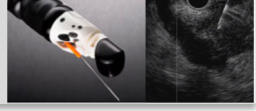
ENDOSCOPIC DUODENAL STENT *VERSUS* SURGICAL GASTROJEJUNOSTOMY FOR GASTRIC OUTLET OBSTRUCTION IN PATIENTS WITH ADVANCED PANCREATIC CANCER

S Uemura, T Iwashita, K Yoshida, N Mita, M Shimizu
Gifu University Hospital, Gifu, Japan

- 99 consecutive patients (2008 -2017)
- DS (n=64) or GJ (n=35)

- Technical success rates were 98% and 100% in DS and GJ.
- Clinical success rates were 92% and 94% in DS and GJ.
- Early and late adverse event rates did not differ.
- Median survival time did not differ.

- Length of hospital stay, time to resumption oral intake and time to start chemotherapy were significantly shorter following DS.



AJG The American Journal of GASTROENTEROLOGY 2006

Long-term Outcome of Biliary and Duodenal Stents in Palliative Treatment of Patients with Unresectable Adenocarcinoma of the Head of Pancreas

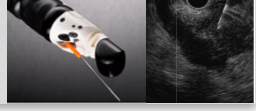
Frédérique Maire MD, Pascal Hammel MD ✉, Philippe Ponsot MD, Alain Aubert MD, Dermot O'Toole MD, Olivia Hentic MD, Philippe Levy MD & Philippe Ruszniewski MD

- Retrospective review of 100 patients

- Median metallic biliary stent patency of 7 months (0.4-21 months)
- Median metallic duodenal patency of 6 months (0.5-15 months).

- Clinical success rate: 96% for biliary and 92% for duodenal stenting.
- Combined stenting had technical success rate of 91%.

- This study suggests that, even in longer periods of survival, endoscopic stenting remains a viable palliative option for both biliary and duodenal obstructions.



EUS-guided gastrojejunal anastomosis

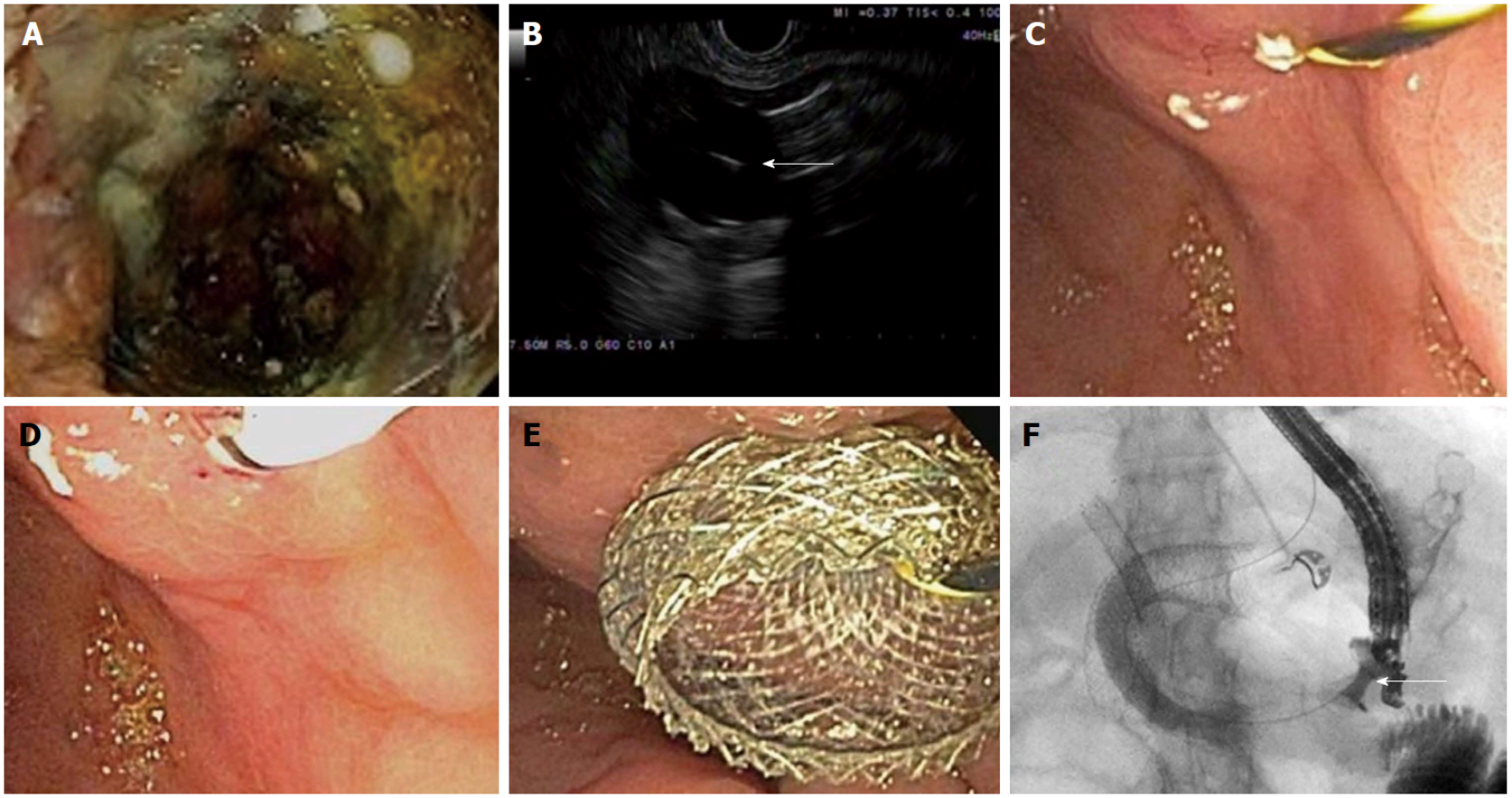
- When endoscopic gastroduodenal **stent placement** is unsuccessful, **bypass surgery** is an option.

- **In poor surgical candidates**, **EUS- guided approach** may be considered.

- A gastrojejunal fistula is created by obtaining an access to the jejunum via EUS-guided needle, followed by placement of a LAMS.

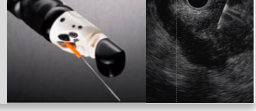
Tyberg A et al. Gastrointest Endosc 2015
Ikeuchi et al. Gastrointest Endosc 2015

EUS-guided gastrojejunal anastomosis



Gastric outlet obstruction undergoing endoscopic ultrasound-guided gastrojejunostomy.

Oh S, et al. World J Gastrointest Endosc 2016



Key notes

- EUS-CPN and pancreatic ductal decompression are useful endoscopic interventions for pain management and improvement of QoL in pancreatic cancer patients.
- They may spare terminal patients a laparotomy and the associated operative morbidity.
- RFA may represent an alternative in pain management in the near future
- When pain is associated with jaundice and gastric outlet obstruction, ERCP with biliary stenting, enteral stenting, or double stenting techniques can be offered.
- When conventional endoscopic procedures fail to provide decompression, EUS guided approaches may be considered.

- Pain is processed in some of the same areas of the brain as thoughts and emotions – ***structural damage or inflammation are not essential*** to experience pain.

- A ***personalized approach*** to pain requires understanding of its multidimensional components and looking beyond the traditional biomedical model, which focuses on the physical processes and structural causality, to a more ***holistic "biopsychosocial resilience" model*** (social, psychological and emotional well being).

pmoutinhoribeiro@gmail.com