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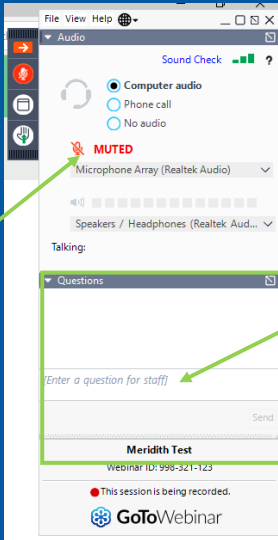
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Faculty: Andres J. Yarur, MD, FACP
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SPECIAL EDITION – GIQuIC Bite Webinar – September 28, 2022
Screening Colonoscopy Updates: What They Mean for Your Practice
Wednesday, September 28, 2022 at 8:00 PM Eastern

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Disclosures



Nalini M. Guda, MD, FACP

Boston Scientific Corporation: Consultant
 Hemostasis LLC: Consultant
 Lupin India: Honorarium for non-product-related educational talks
 Zydus India: Honorarium for non-product-related educational talks



Prabhleen Chahal, MD, FACP

BSCI: Consultant, advisory council
 Medtronic: Consultant, advisory council

*All of the relevant financial relationships listed for these individuals have been mitigated

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Palliation in Pancreatic Cancer

Nalini M Guda MD, FCG

Aurora St. Luke's Medical Center, Milwaukee, WI

Clinical Adjunct Professor of Medicine
University of Wisconsin School of Medicine & Public Health

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Current Problem

- 7th highest mortality in the world and 4th in US – likely 2nd by 2030 in US
- Resectability at the time of diagnosis 20%
- 5-year survival approximately 5%
- Most common problems : Gastric outlet obstruction, Biliary obstruction, Pain control and local tumor sensitization/treatment

Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. *CA Cancer J Clin* 2019; **69**: 7-34

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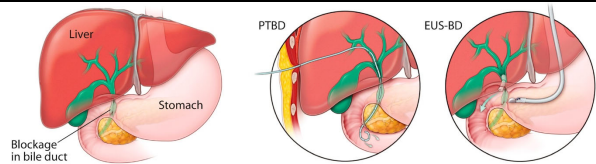
Palliation in Pancreatic Cancer –Endoscopist’s role

Objectives: Explain endoscopic palliation options

1. Biliary drainage – ERCP stent/EUS guided drainage
2. Gastric outlet obstruction (GOO) – Stents/Surgery/EUS guided bypass
3. Tumor localization – fiducial placement
4. Pain management
5. Local therapies- tumor regression/sensitization

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Biliary drainage



- Lesions in the head of pancreas likely cause biliary obstruction – jaundice, pruritus, cholangitis
- Current concept is for upfront stenting prior to neoadjuvant therapy
- Options: Surgical, Percutaneous, Endoscopic
- Surgical – Increased recovery time, long recovery time – rarely done
- Percutaneous drainage – Not desirable – external bag, leakage, infection – last resort!!

Speer A.G. et al. *Lancet* 1987; 2: pp. 57-62.

Smith A.C et al. *Lancet* 1994; 344: pp. 1655-1660

Sharaiha et al. *Gastrointestinal Endoscopy* Vol. 85 Issue 5p904–914

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Endoscopic Biliary drainage – should it be routine?

- Not everyone needs drainage
- Indications: HOP lesions, biliary obstruction, surgery >2 weeks, GOO needing stenting
- ERCP even with experts – 5-8% risk of complications
- For upfront surgery – No Routine preop ERCP :higher complications, delay in surgery
- Limitations: High failure rates of ERCP, high complication rates, no data on EUS intervention

Wang P et al. Am J Gastroenterol 2009;104(1):31-40
 Van derGaag N Engl J Med 2010
 Lee J, Ahmed Surg Oncol Clin N Am 28 (2019) 147-159
 Lee PJ, et al. HPB (Oxford). 2018 Jun;20(6):477-486.

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Biliary stenting – ERCP

- Metal stents favored over plastic stents*
- Metal stents: longer patency, fewer complications
- Covered: less tumor ingrowth but more migration, >risk of PEP, cholecystitis
- No clear consensus for covered vs Uncovered – both can be used for neoadjuvant therapy**
- Reasons for failure of stenting: Stricture, Mass effect and angulation
- Stent PD if even unintentional cannulation
- Biliary and GOO may be synchronous/asynchronous –evaluate and proceed – double stenting when needed
- Endoscopic decompression improves QoL

Davids P.H. et al. Lancet 1992; 340: pp. 1488-1492 * Lee JH et al. Gastrointest Endosc. 2013 78(2):312-24
 Moole et al. Indian J Gastroenterol (Sept-Oct 2016) 35(5):323-330
 Seo D.W, et al. Gastrointest Endosc 2019; 90: pp. 602-612.e4** Fogel EL, et al. Am J Gastroenterol. 2017 Apr;112(4):537-554

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Drug Eluting Stents

- Likely increase stent patency
- Improve local drug penetration without increasing systemic toxicity
- Increased patency but no survival benefit (429 vs 148 (covered)/143 (uncovered) days)

Lee et al. Gastrointest Endosc 2005;61(2):296-301
Suk et al. Gastrointest Endosc 2007;66(4):798-803

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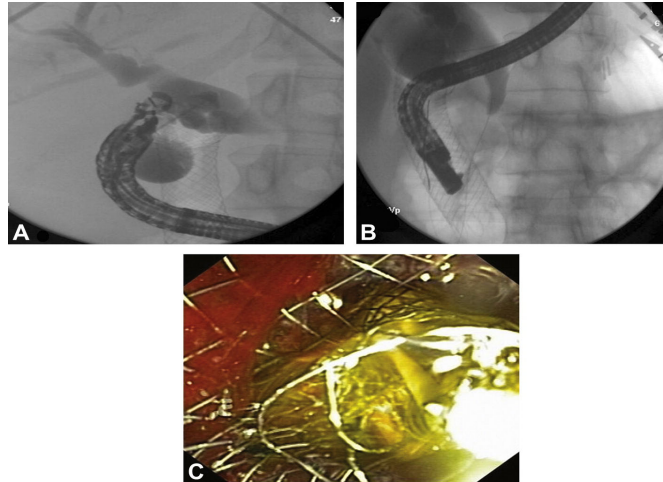
EUS guided Biliary drainage

- Failure rate of ERCP 5-7%
- Three options:
 1. Biliary Rendezvous
 2. Direct Access: Choledochoduodenostomy/Hepaticogastrostomy – puncture LHD/CHD from stomach or duodenum
 3. Antegrade drainage – Stent through the liver across the ampulla
- Clinical success for EUS- biliary drainage: 94% with AE of 17%
- Data suggest primary EUS guided biliary drainage to minimize complications

Coté GA et al. Clin Gastroenterol Hepatol 2012; 10: 920-924
Giovannini M et al. Endoscopy 2001; 33: 898-900
Khan S et al. Dig Dis Sci 2016; 61: 684-703
Han SY et al. Sci Rep 2019; 9: 16551

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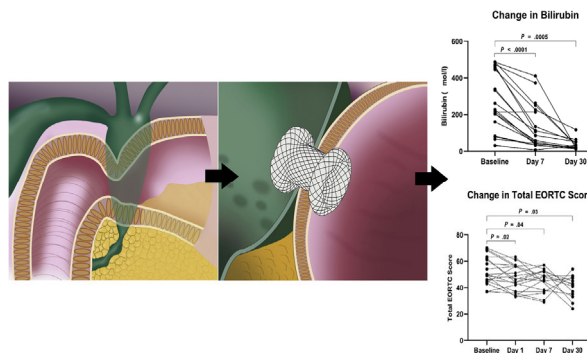
Biliary Rendezvous. EUS guided biliary access followed by ERCP



Mallery, Shawn et al. *Gastrointestinal Endoscopy*, Volume 59, Issue 1, 100 - 107
Khasab et al. *Gastrointestinal Endoscopy* Volume 78 Issue 5 Pages 734-741

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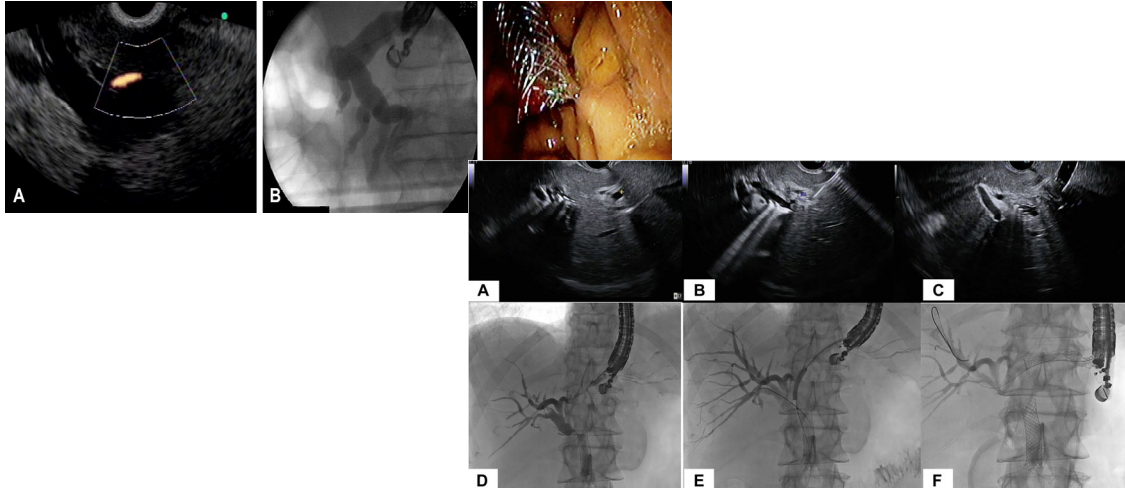
Direct Access Choledochoduodenostomy or Hepaticogastrostomy



Suresh Vasan Venkatachalapathy et al. *Gastrointestinal Endoscopy* Volume 94 Issue 2 Pages 321-328

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Antegrade drainage – Stent through the liver across the ampulla



Khasab et al. Gastrointestinal Endoscopy Volume 82 Issue 6 Pages 993-1001
Hathorn et al. Gastrointestinal Endoscopy Vol. 95 Issue 3 p443-451

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Will or should EUS- BD be preferred over ERCP- BD

- Three RCTs done – SEMS used
- EUS-BD comparable to ERCP – safety and patency
- No pancreatitis, reduced stent occlusion, re intervention rates
- Potential for same setting diagnosis, relief of obstruction, fiducial placement

Bang JY, et al. *Gastrointest Endosc.* 2016 Nov;84(5):773-779
 Paik W.H., et al. *Am J Gastroenterol* 2018; 113: pp. 987-997.
 Park J.K *Gastrointest Endosc* 2018; 88: pp. 277-282

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Gastric outlet obstruction

- Tumor growth, related inflammation -15-25%
- Nausea, vomiting, poor oral intake
- Surrogate marker for poor survival
- Options:
 - Surgical Bypass
 - Endoscopic stenting of the duodenum
 - EUS guided gastro jejunostomy

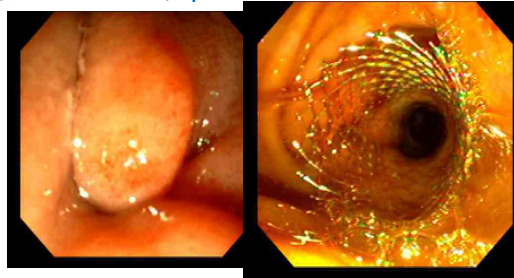
Tendler DA. *Am J Gastroenterol* 2002;**97**: 4-6

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Endoscopic stenting for GOO

- Seen in up to 15% of patients with pancreatic cancer
- Symptoms: Abdominal pain, early satiety, fullness, nausea, vomiting, GERD
- High technical success once you pass the wire
- Easier to deploy, good palliation, shorter LOS but HIGH recurrence of symptoms
- Compared to surgery fewer complications, shorter LOS, quicker PO intake
- Common problems:
 - Perforation
 - Bleeding
 - Tumor ingrowth
 - Difficulty in subsequent ERCP



Wong Y.T., et al. *Surg Endosc* 2002; 16: pp. 310-312
 Nagaraja V, et al. *J Gastrointest Oncol.* 2014;5:92-8

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Surgical GJ vs Endoscopic stenting

- Multicenter RCT 18 in GJ and 21 to stent
- Stent placement: less time to PO intake, <LOS, lower costs
- GJ had higher patency rates
- If survival is > 2 months GJ recommended
- Similar conclusions from a retrospective propensity score matched study
- GJ probably favored with neoadjuvant therapy and improved survival

Jeurnink SM, et al. *Gastrointest Endosc.* 2010 Mar;71(3):490-9
 Jang S., et. al. *Clin Gastroenterol Hepatol* 2019; 17: pp. 1295-1302.e1

23

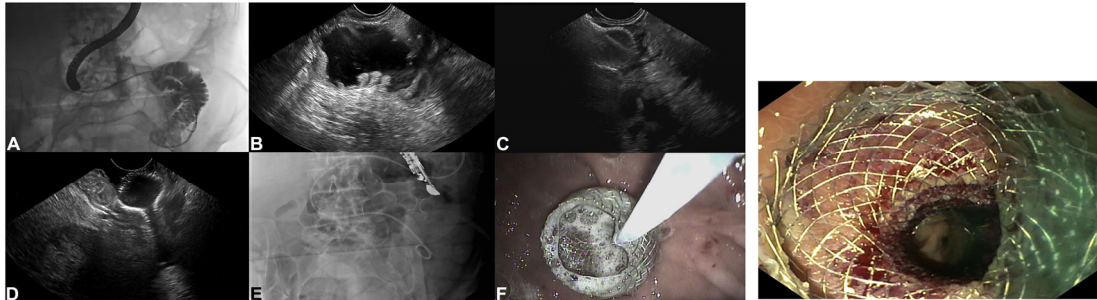
Endoscopic Ultrasound guided GJ

- EUS guided GJ alternative to stenting and surgery
- LAMS used to create connection between stomach and small bowel distal to obstruction
- Technical success rates: 92%, Clinical Success 90% and pooled AE: 12%, Reintervention rate 9%
- Impact of EUS-GJ on subsequent pancreaticoduodenectomy unclear

Khashab M.A., et. al. *Gastrointest Endosc* 2015; 82: pp. 932-938
 Tyberg A et al. *Endosc Int Open* 2016; 4: E276-E281
 Iqbal U et al. *Endosc Ultrasound* 2020; 9: 16-23
 Sánchez-Aldehuelo, Rubén et al. *Gastrointestinal Endoscopy*, Volume 0, Issue 0. In Press

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EUS- GJ



*Michiel Bronswijk, et al. Gastrointestinal Endoscopy Volume 94 Issue 3 Pages 526-536**
 EUS GJ better than Lap GJ

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EUS-GJ VS SURGICAL GJ vs ENTERAL STENT

N=463	EUS GJ N=241	ES N=142	Surgical GJ N=80	
Technical success	98.3%	98.9%	100%	P=0.58
Clinical success	97.5%	90.1%	85.0%	P<0.0001
Re-intervention	1.7%	14.1%	15%	P<0.0001
LOS days	2	4	5	P<0.0001
AE	9.1%	39.3%	28.7%	P<0.0001

Conclusion: This large cohort study demonstrates the long-term durability and safety of EUS-GJ as an alternative strategy for GOO palliation

Jaruvongvanich, Veeravich et al. Gastrointestinal Endoscopy, Volume 95, Issue 6, AB508 - AB509

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EUS GJ vs SURGICAL GJ

	EUS GE (N=97)	Surgical GE (N=64)	
Technical Success	96.9%	100%	p=0.156
Clinical Success	93.8%	96.9%	p=0.382
Resumption of chemotherapy	23.1 days	41.1 days	p<0.001
Pre procedure Albumin	2.9	3.7	p<0.001
AE	16.5%	32.8%	p=0.016

Conclusions: EUS-GE can be performed among nutritionally deficient patients and allows earlier resumption of chemotherapy

de Gooyer, Peter et al. *Gastrointestinal Endoscopy*, Volume 95, Issue 6, AB493

Sánchez-Aldehuelo, Rubén et al. *Gastrointestinal Endoscopy*, Volume 0, Issue 0 In Press*

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Tumor Localization – Fiducial placement

- Image guided radiotherapy – precise deliver of radiation to target lesion
- Allows local tumor control with decreased radiation toxicity
- Placement of gold radio opaque markers by EUS to delineate the tumor
- Technical success 96%, AE 5%

Tchelebi et al. Cancer 2020; **126**: 2120-2131

Patel et al. World J Gastrointest Endosc 2020; **12**: 231-240

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EUS – Injection therapies

- Small studies – animal/human
- Mostly feasibility studies
- No definite data on outcomes/survival advantage
- Studies include concomitant therapy – radiation/chemo and not local injection as standalone – unlikely
- Likely tumor sensitizing agents – minimize toxicity and increase response to systemic therapies

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Injectable therapies

Author, Year	Study Type	Malignancy	Injection Therapy
Chang et al, ³⁷ 2000	Phase I trial	Pancreatic adenocarcinoma	Cytoimplant
Hecht et al, ³⁸ 2003	Phase I/II trial	Pancreatic adenocarcinoma	ONYX-015
Gan et al, ³⁹ 2005	Pilot study	Cystic pancreatic lesions	Ethanol lavage
Meenan et al, ⁴⁰ 2007	Early phase clinical trial	Pancreatic cancer	32P Biosilicon
DeWitt et al, ⁴¹ 2009	Randomized, double-blind study	Cystic lesions	Ethanol lavage + paclitaxel
Yang et al, ⁴² 2009	Prospective study	Pancreatic cancer	Ethanol
Oh et al, ⁴³ 2011	Prospective study	Cystic lesions	Ethanol lavage + paclitaxel
Levy et al, ⁴⁴ 2011	Prospective study	Pancreatic cancer	Gemcitabine
Hecht et al, ⁴⁵ 2012	Phase I/II trial	Pancreatic adenocarcinoma	TNF- α
Levy et al, ⁴⁶ 2012	Prospective study	PNET	Ethanol lavage
Herman et al, ⁴⁷ 2013	Phase III trial	Pancreatic adenocarcinoma	TNF- α
Levy et al, ⁴⁸ 2017	Prospective study	Pancreatic cancer	Gemcitabine
Nishimura et al, ⁴⁹ 2017	Open-label study	Pancreatic cancer	STNM01 (double-stranded RNA oligonucleotide)

Lee, Ahmed. *Surg Oncol Clin N Am.* 2019 Jan;28(1):147-159.

Hirooka et al. *BMC Cancer.* 2018 May 25;18(1):596

Jong-chan Lee, DOI: <https://doi.org/10.1016/j.gie.2020.02.012> (in press)

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Brachytherapy

- Seeds/microparticles/liquids placed directly into or adjacent to the tumor
- Steady exposure of target tissue to low-energy gamma, Xrays/ Beta particles
- Leads to localized tissue injury and ablation
- EUS to delivery the radioactive seeds – phosphorus 32, iodine, gold, iridium and yttrium
- Goal is to downstage tumor for resection

Bhutani MS, et al. *VideoGIE*. 2019;4(5):223–5

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Radiofrequency ablation

- RFA generates high temperatures and causes local coagulative necrosis
- Possible stimulation of immune response – Abscopal effect
- Potential complications: Pancreatitis, PD strictures, bowel perforation, peritonitis, bleeding

Tatli S et al. *Diagn Interv Radiol* 2012; **18**: 508-516

Kaminski JM et al. *Cancer Treat Rev* 2005; **31**: 159-172

Salom, Prat. *World J Gastrointest Endosc* 2022 January 16; **14(1)**: 35-48

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Pain Control

- Pain/analgesia ladder – escalation based on symptoms
- Mild: Acetaminophen, NSAIDs
 - Complementary approaches – acupuncture, massage, mindfulness etc.,
- Moderate: Adjuvant meds – Duloxetine, amitriptyline, gabapentin, tizanidine, baclofen etc..
 - Mild/Moderate opioids
- Severe: Stronger opioids (morphine, oxycodone, hydromorphone etc.,)
 - EUS- CPB
 - EUS – CPN
 - video-thoracoscopic splanchnicectomy (VSPL)
 - intrathecal drug delivery systems (IDDS)

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Celiac Plexus block & Neurolysis

- CPN used in treatment of pain
- Injection : central location, bilateral or into the celiac ganglion
- Overall response rates 68% (CI 61-74%) at week 2 and 53 % (95% CI 45-62%) at week 4
- No difference in injection techniques
- Complications higher in central injection

Koulouris AI, et al. .Pancreatology. 2021 Mar;21(2):434-442

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Celiac Plexus neurolysis with RFA

- RFA: Proven efficacy in splanchnic nerve blockade in chronic abdominal pain due to chronic pancreatitis/malignancies
- RCT of 28 patients CPN (14) RFA (12)
- At 4 weeks pain scores lower in RFA group
- No difference in opiate use
- Preliminary data favor RFA over CPN

Bang et al. *Gastrointest Endosc* 2019;89:58-66.

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Non endoscopic options

- Nausea
 - Serotonin receptor antagonists +/- dopamine-receptor antagonists
 - Antipsychotics
- Dyspnea
 - Opiates
- Abdominal distension (peritoneal metastases + Ascites)
 - Paracentesis (drain placement)/diuretics/Peritoneovenous shunt
- Constipation
 - Multiple drug regimens (different mechanism of action)
- Behavioral health
 - Pain control, anxiolytics, anti depressants, psychological support

Moffat GT et al. *Cancer*. 2019 Nov 15;125(22):3927-3935

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Thromboembolic disease

- >27%. 4 times > other cancers and >50 times to average individuals
- VTE poor prognostic factor for mortality
- PE and VTE second leading cause of death in PDAC
- Consider LMWH, DOACs

Yousuke Nakai et al. *Surgical Oncology Clinics of North America*, 2021-10-01, Volume 30, Issue 4, Pages 639-65

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Nutrition in Pancreatic Cancer

- Weight loss and cachexia seen in up to 80%
- Leads to decrease QOL
- Frequent small meals, well balanced, low fat, simple carbs
- Avoid excess alcohol
- Panc Enzyme Replacement Therapy (PERT) – improves malabsorption, pain, steatorrhea and QoL. Symptom correlation is poor.
- Consider appetite stimulants : Megestrol, synthetic tetrahydrocannabinol

Landers A et al. *Palliative care* 2019;12:1178224218825270
 Moffat GT et al. *Cancer*. 2019 Nov 15;125(22):3927-3935
 Bartel MJ, et al. *Dig Liver Dis*. 2015;47:1013-20

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Malignant Afferent Limb Syndrome

- Seen post pancreaticoduodenectomy
- Complete or partial obstruction of the afferent (pancreaticobiliary) limb
- Common causes: Radiation enteropathy, tumor recurrence
- Incidence: up to 13% in one year
- Treatment options: Surgical bypass or EUS –GE/enteral stent
- EUS-GE – technically feasible, natural way for biliary and pancreatic drainage

Yousuke Nakai et al. *Surgical Oncology Clinics of North America*, 2021-10-01, Volume 30, Issue 4, Pages 639-65

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In summary:

1. Endoscopic biliary drainage superior and favorable to surgical or percutaneous approaches
2. If ERCP drainage not feasible consider EUS drainage or EUS first approach is preferable as well.
3. Consider Biliary drainage at the time of stenting of GOO
4. EUS- GJ preferable over surgical approach and maybe superior to transpyloric stenting
5. Early Celiac plexus neurolysis may be beneficial in pain control
6. Local injection therapies, brachytherapy, RFA are still experimental in treatment of pancreatic cancer
7. Consider prophylaxis for VTE, nutrition and enzyme replacement

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Questions and Answers



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Prabhleen Chahal, MD, FACP

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