City of Hope®

Multidisciplinary Approaches to Cancer Symposium

Tumor Board:
Complex Cases of Pancreatic Adenocarcinoma

Moderator: Daneng Li, MD

Surgical Oncology: Gagandeep Singh, MD

Radiation Oncology: Heather McGee, MD, PhD

Medical Oncology: Richard T. Lee, MD

Panel & Disclosures

Daneng Li, MD
Associate Professor
Department of Medical Oncology
City of Hope

- *Grant/Research Support from AstraZeneca.*
- *Consultant for Adagene, AstraZeneca, Coherus, Delcath, Eisai, Exelixis, Genentech, Ipsen, Merck, Servier, and TerSera.*

Gagandeep Singh, MD
Hepatobiliary & Pancreatic Surgery
Professor of Clinical Surgery
City of Hope

- *No relevant financial relationships*

This presentation and/or comments will be free of any bias toward or promotion of the above referenced company or their product(s) and/or other business interests.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

This presentation has been peer-reviewed and no conflicts were noted.

Panel & Disclosures

Heather McGee, MD, PhD
Assistant Professor
Departments of Radiation Oncology and Immuno-Oncology
City of Hope

- *No relevant financial relationships*

Richard T. Lee, MD
Medical Director, Integrative Medicine Program
Department of Supportive Care Medicine and Medical Oncology
City of Hope

- *No relevant financial relationships*

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

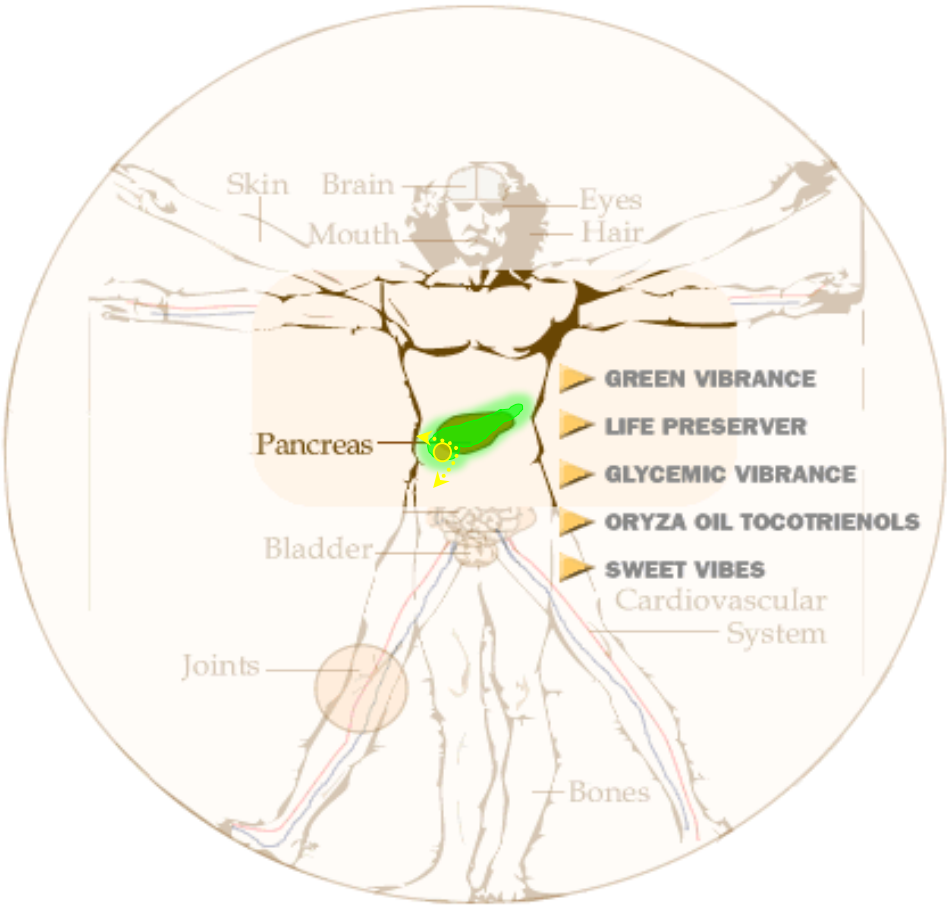
EXEMPTION:

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

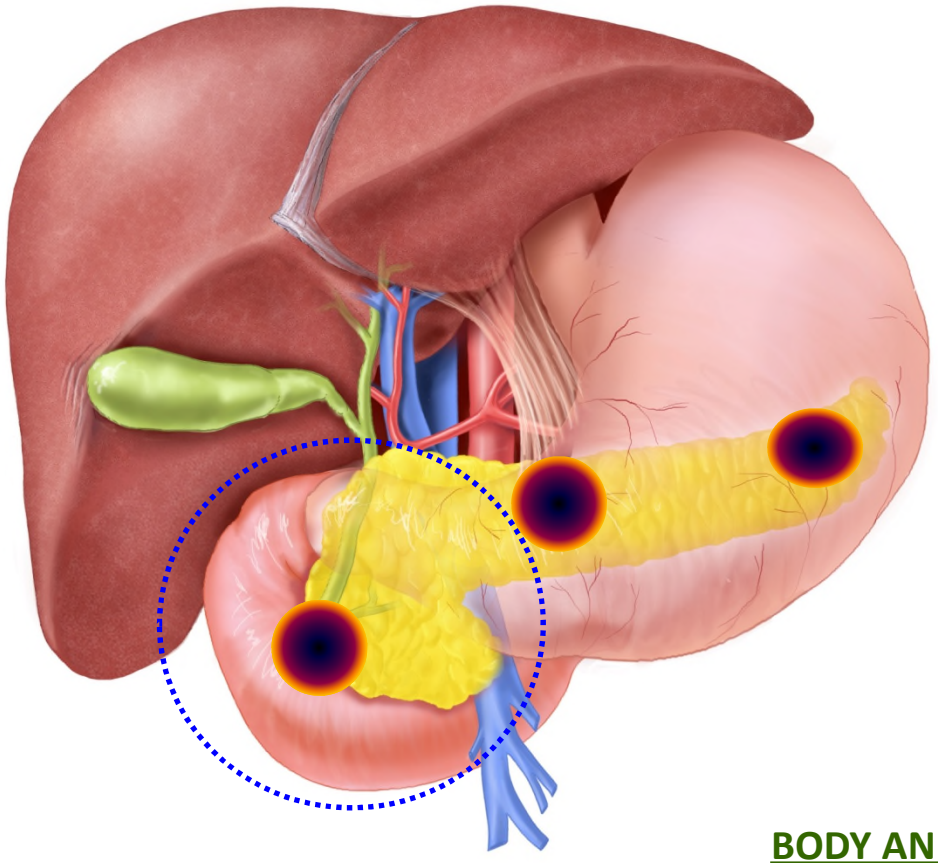
- *Any impact of age on treatment of pancreatic cancer*

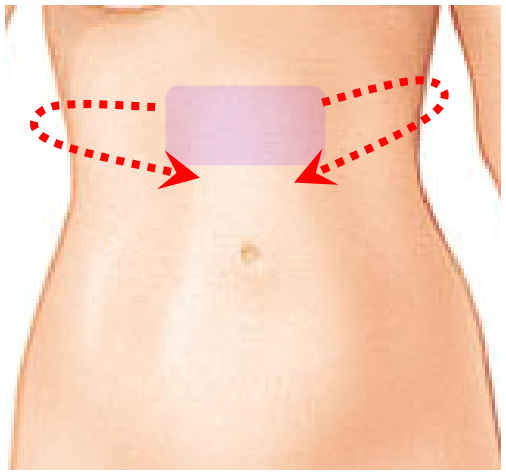
Surgical Interventions for the Spectrum of Pancreatic Tumors



Gagandeep Singh, MD, FACS

Clinical Presentation





Vague Gnawing Pain
Radiating to the back

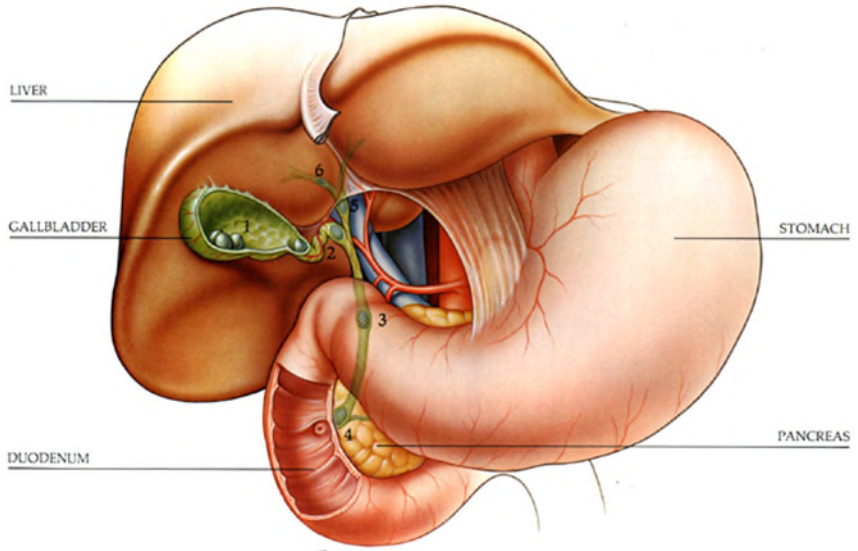
HEAD

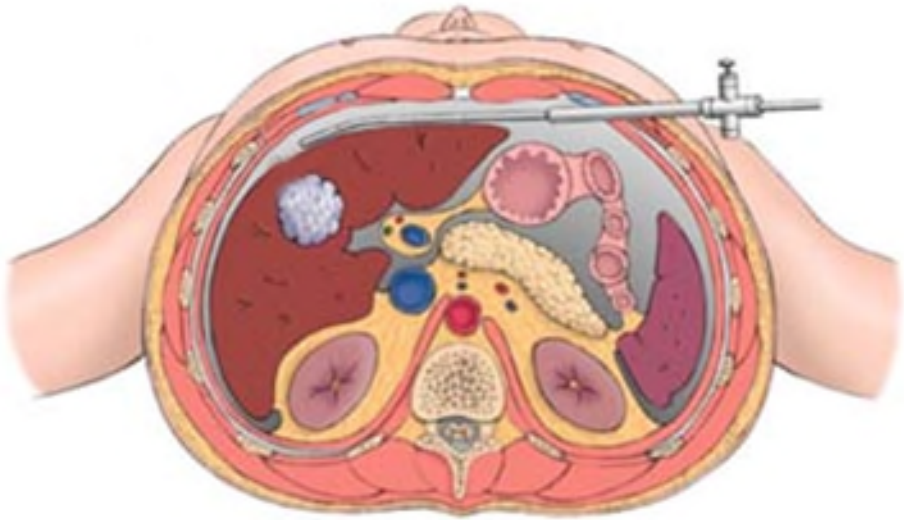
Weight loss	92%
Jaundice	82%
Pain	72%

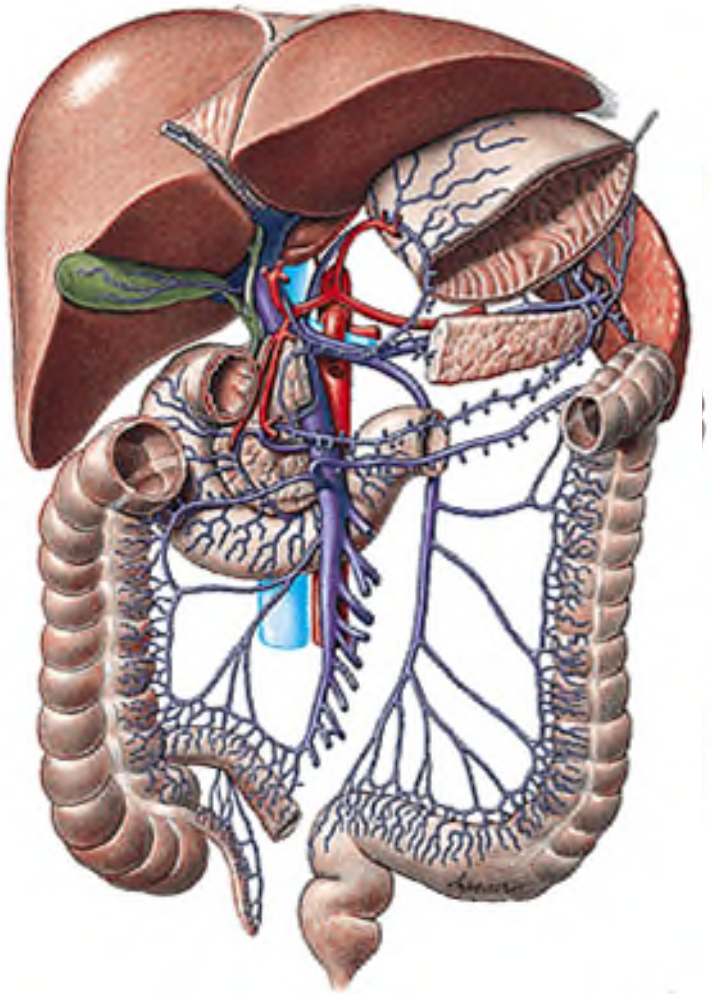
BODY AND TAIL

Weight loss	100%
Pain	87%

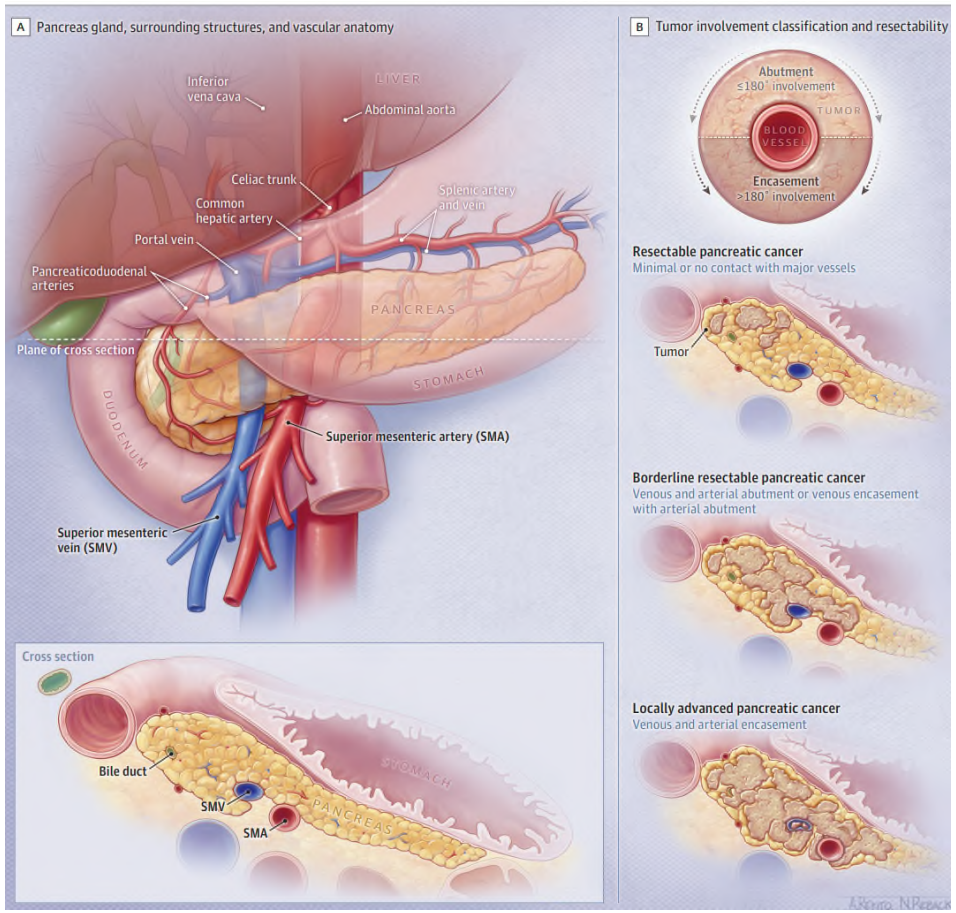
Anatomical Complexity

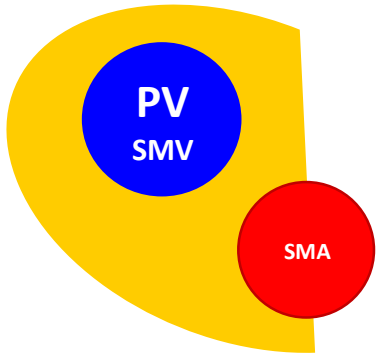






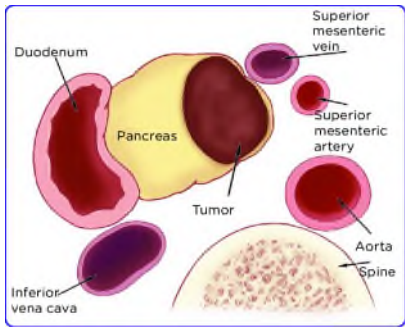
Borderline Resectable Vs Locally Advanced/ Unresectable

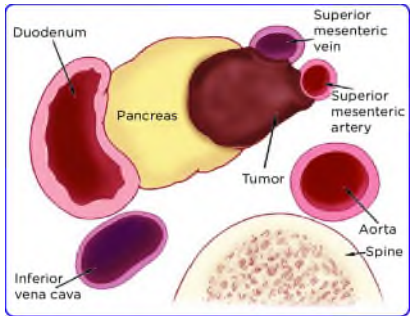




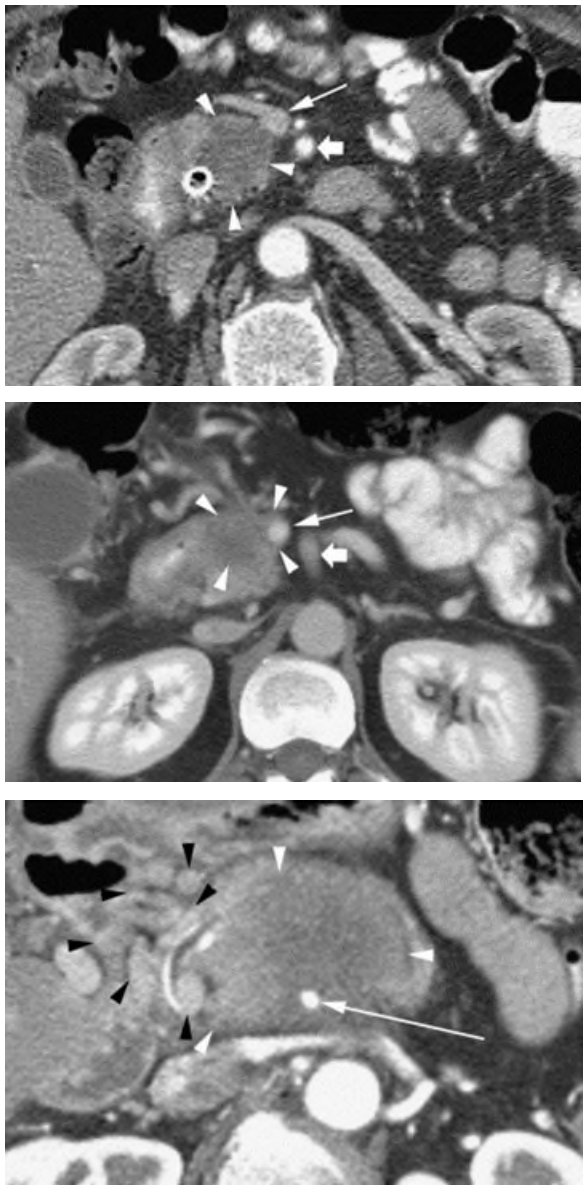
<180
Borderline

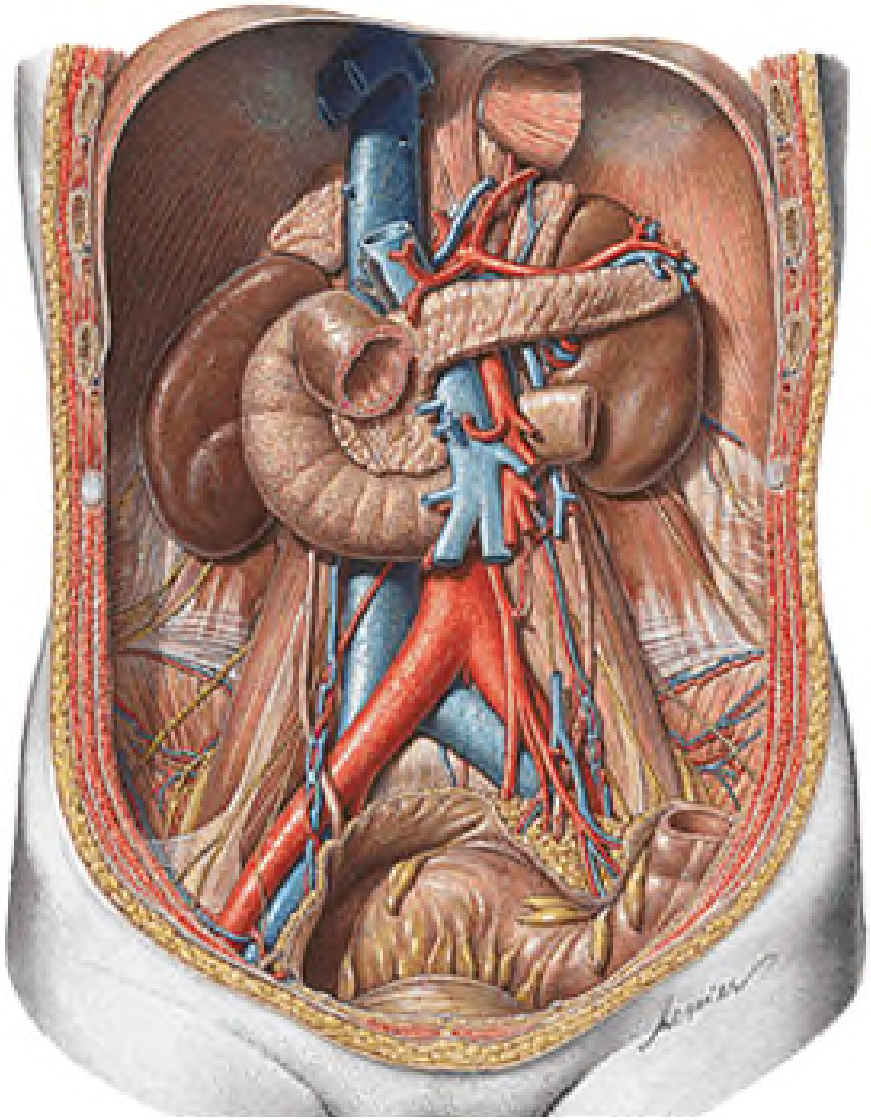
>180
Locally Advanced



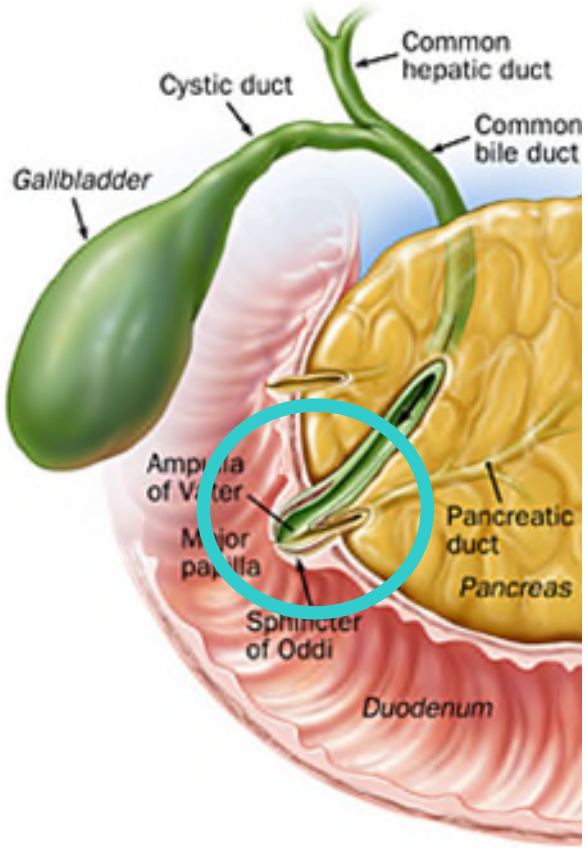


Vascular Involvement- PV, SMV, SMA





What is Periampullary Ca ?



- Should Include all within 1 cm of the ampulla

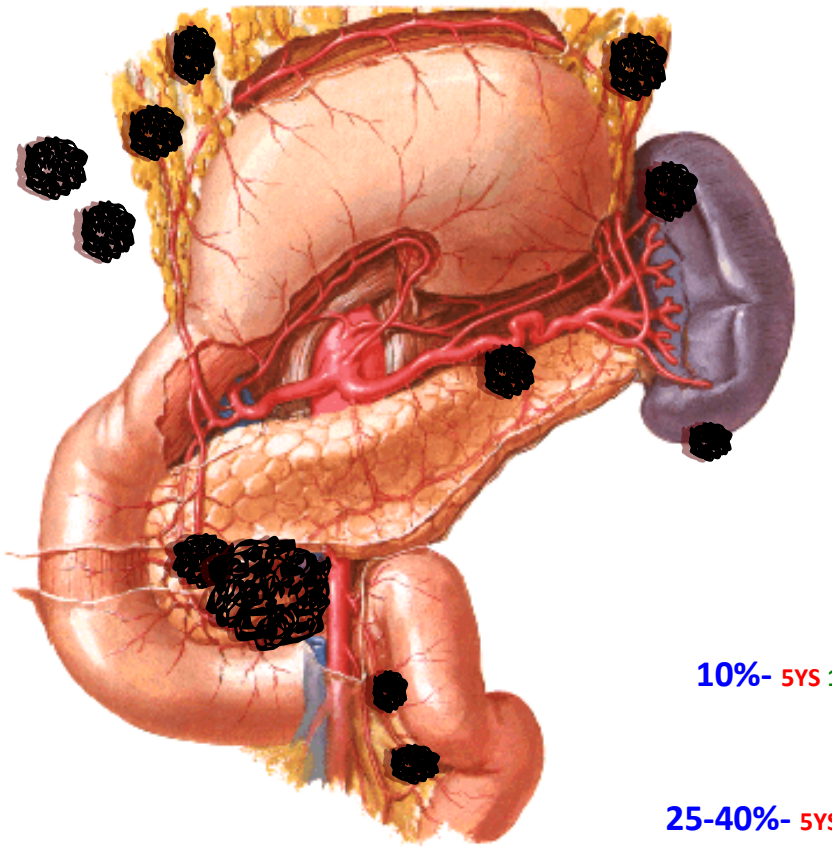
CANCERS OF:

- Ampulla
- Papilla
- Duodenum
- Distal CBD
- Small pancreatic head cancer which does not produce a mass lesion on imaging or surgery

ERROR:

BUT IN REALITY EVEN AMONG THESE THE SURVIVAL IS DIFFERENT- IT SHOULD BE BASED OFF OF TISSUE TYPE

Staging & Treatment



STAGE OF THE DISEASE

Stage I/ II Resectable

STAGE SPECIFIC THERAPY

10%- 5YS 18%

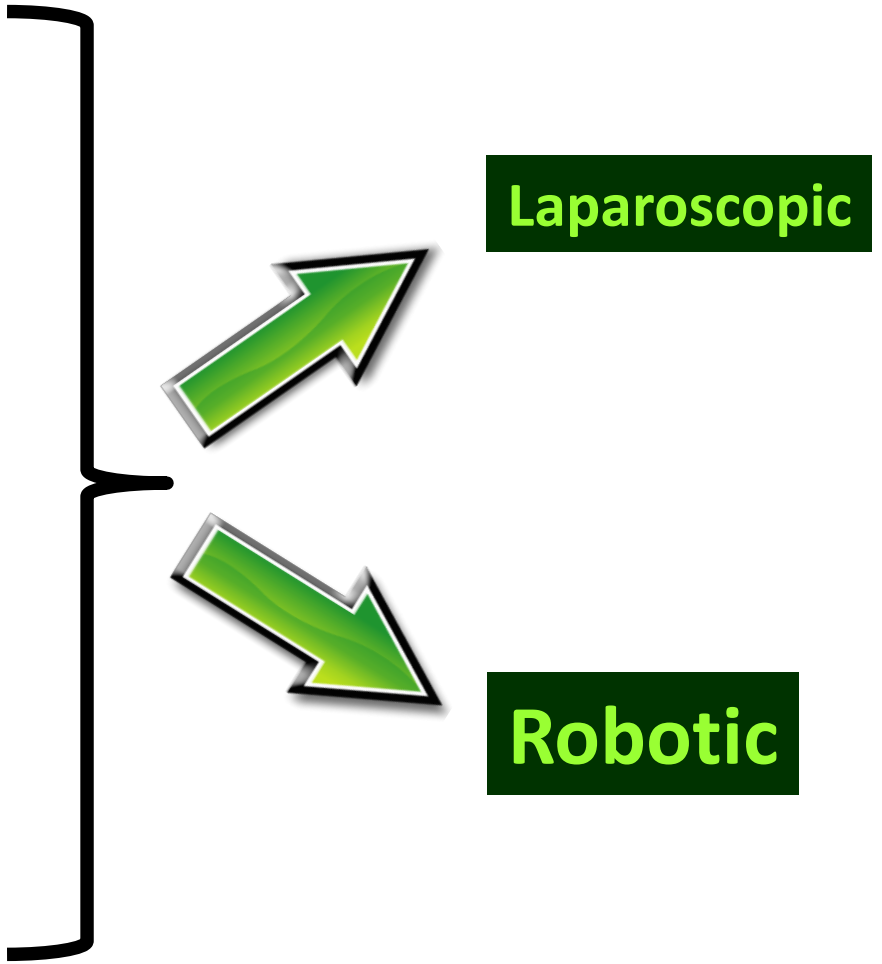
Stage I/ II Surgery -> Chemo/ XRT

25-40%- 5YS 7%

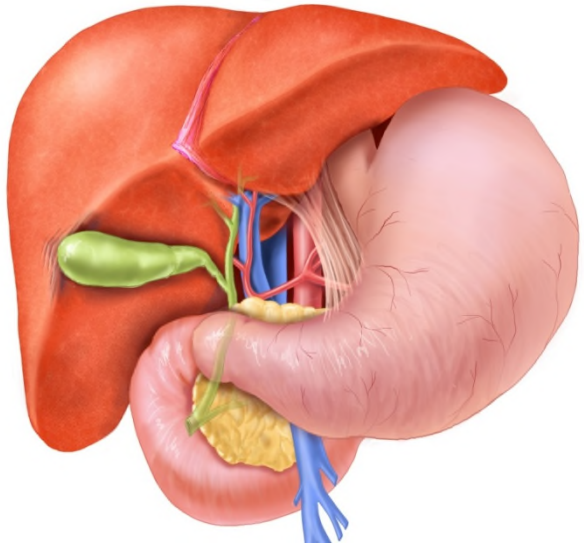
50%- 5YS 2%

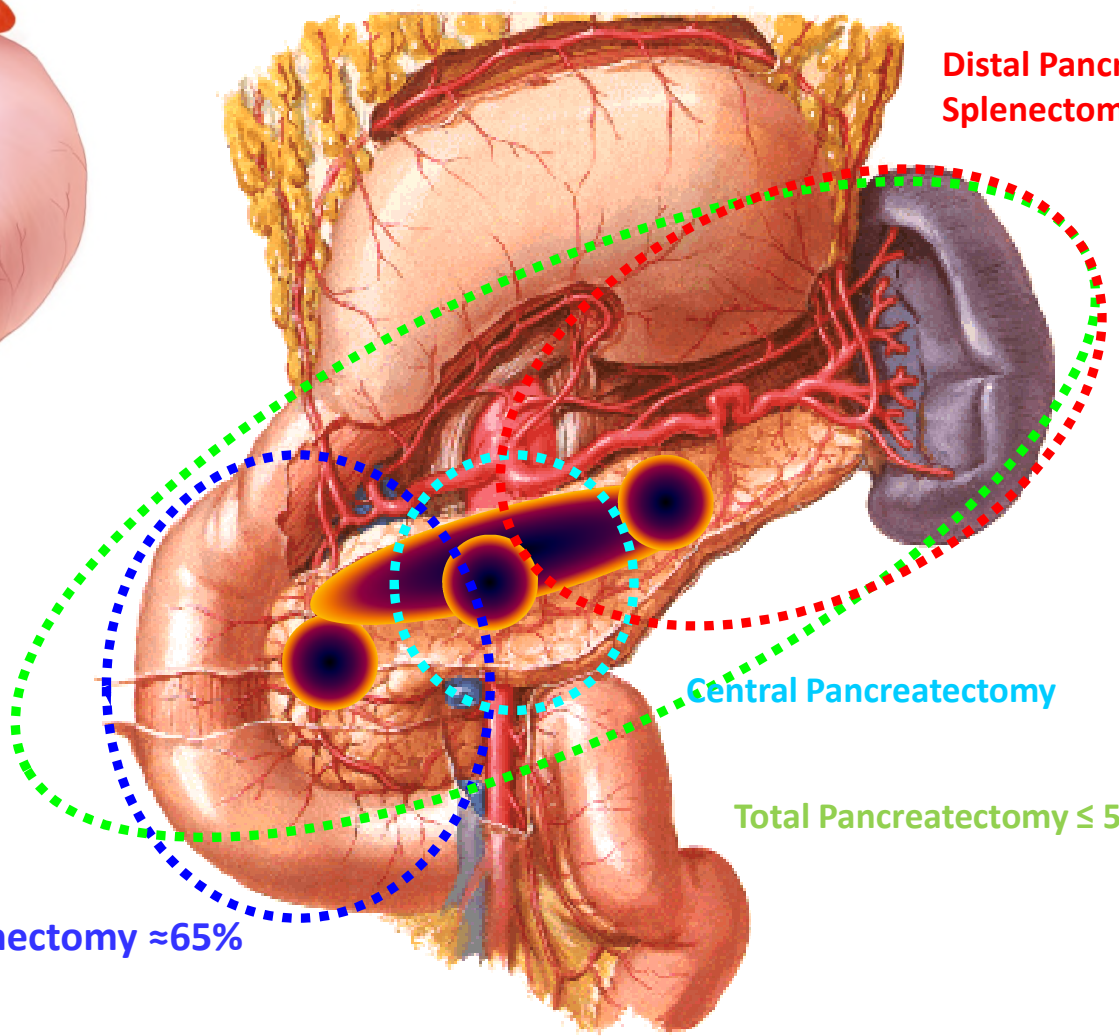
Surgery

- Whipple- Classic & PPPD
- Total Pancreatectomy
- Distal Pancreatectomy
- Palliative Procedures
- PUSHING THE LIMITS



Operations for Pancreatic Cancer





Distal Pancreatectomy with Splenectomy ≈30%

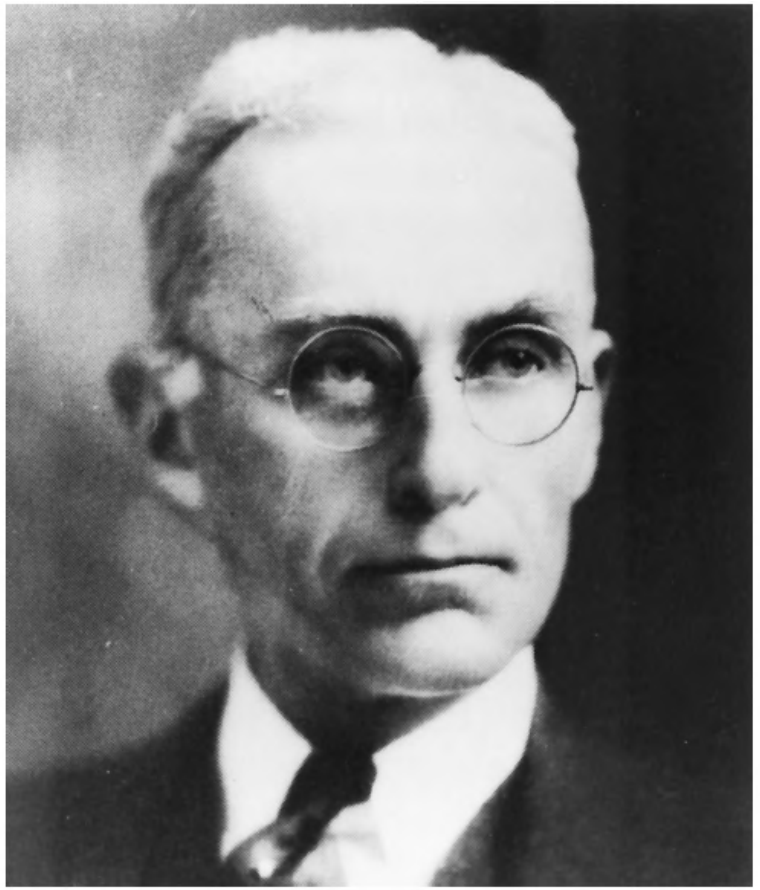
Central Pancreatectomy

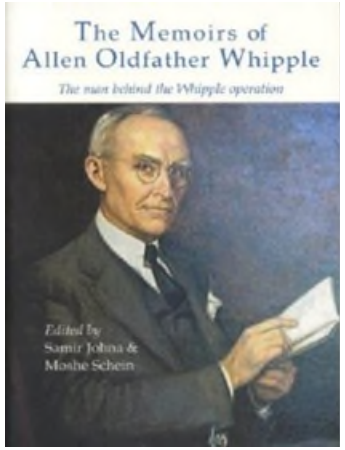
Total Pancreatectomy ≤ 5%

Whipple Pancreatoduodenectomy ≈65%

- Classic
- Pylorus Preserving

Allen Oldfather Whipple (1881- 1963)





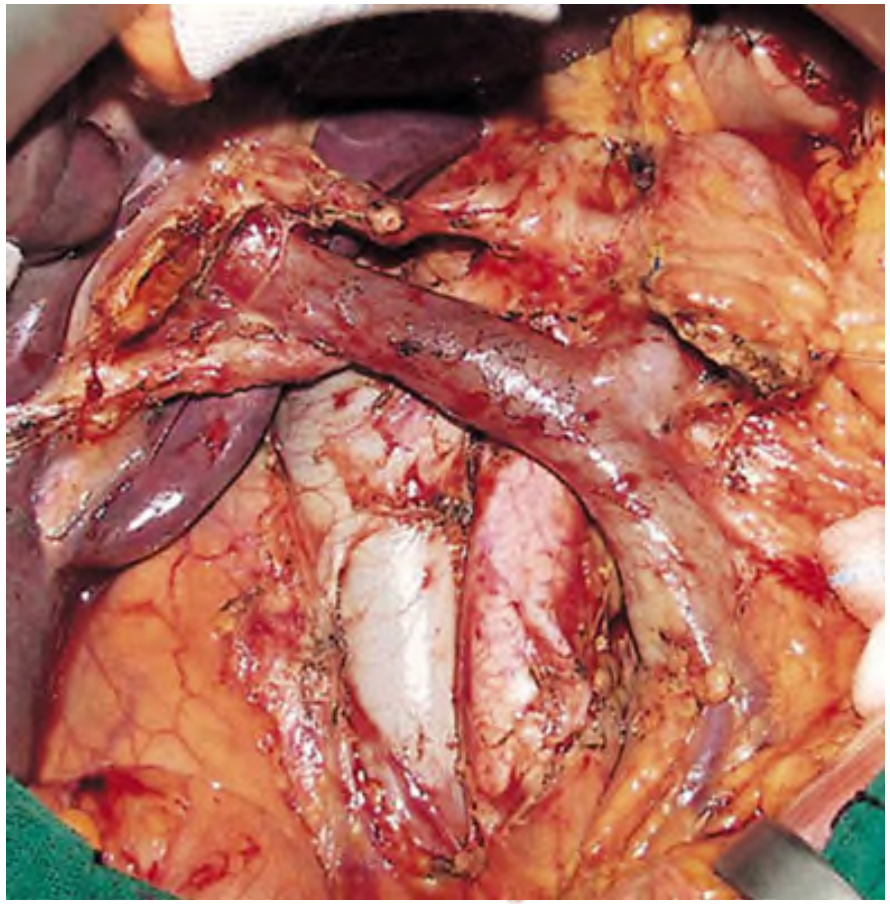
- **1935, Surgeon in Chief,** Columbia College of Physicians and Surgeons and the Presbyterian
- 2 Stage Resection: Pancreatoduodenectomy

Reason For The CREDIT:

- Classic account with clarity
- The prose was clear and instructive
- Provided an analysis of failures

Whipple AO, Parsons WB, Mullins CR. Ann Surg 1935; 102: 763.

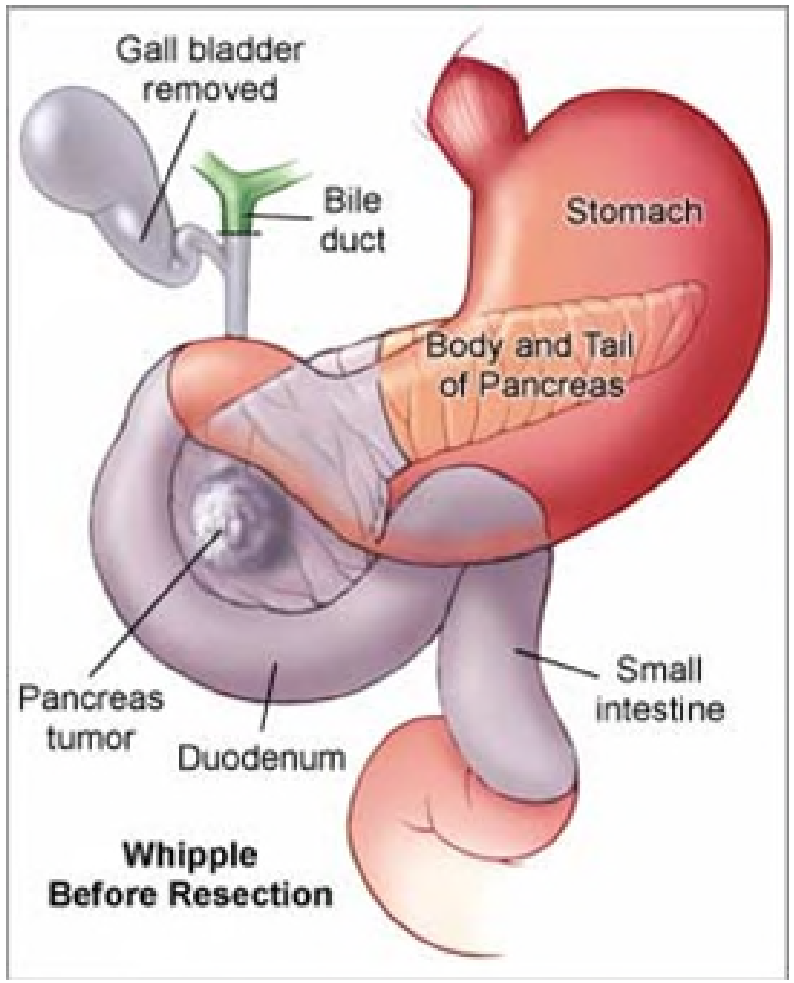
Good Clearence

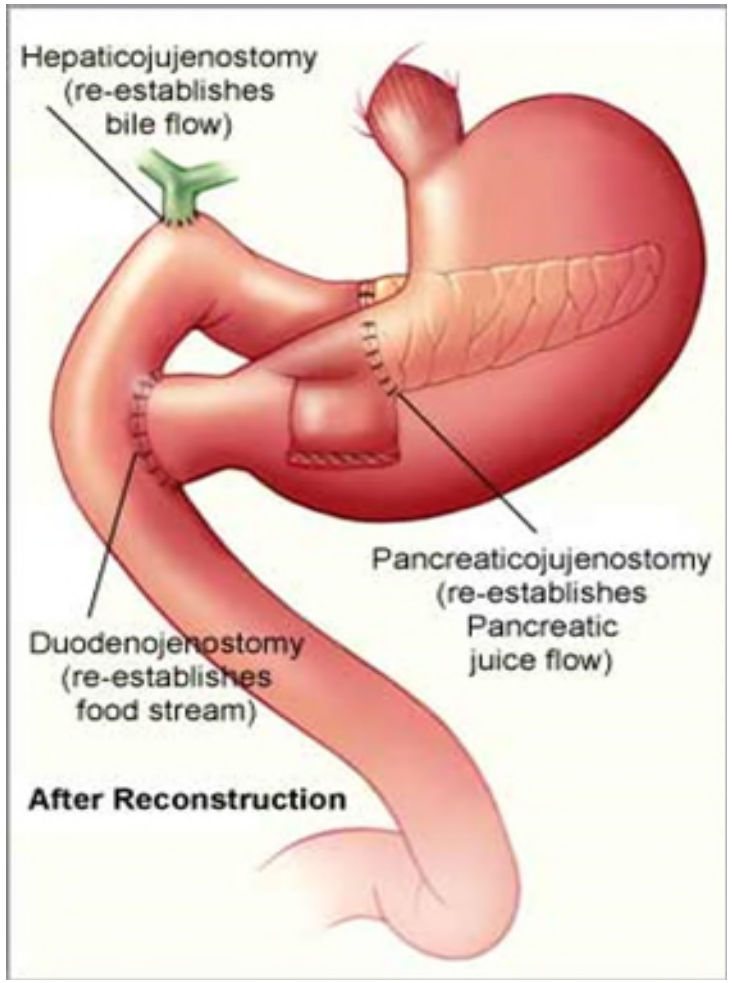


3 Steps to Reconstruction

Isaac Trimble- 1941- PPPD

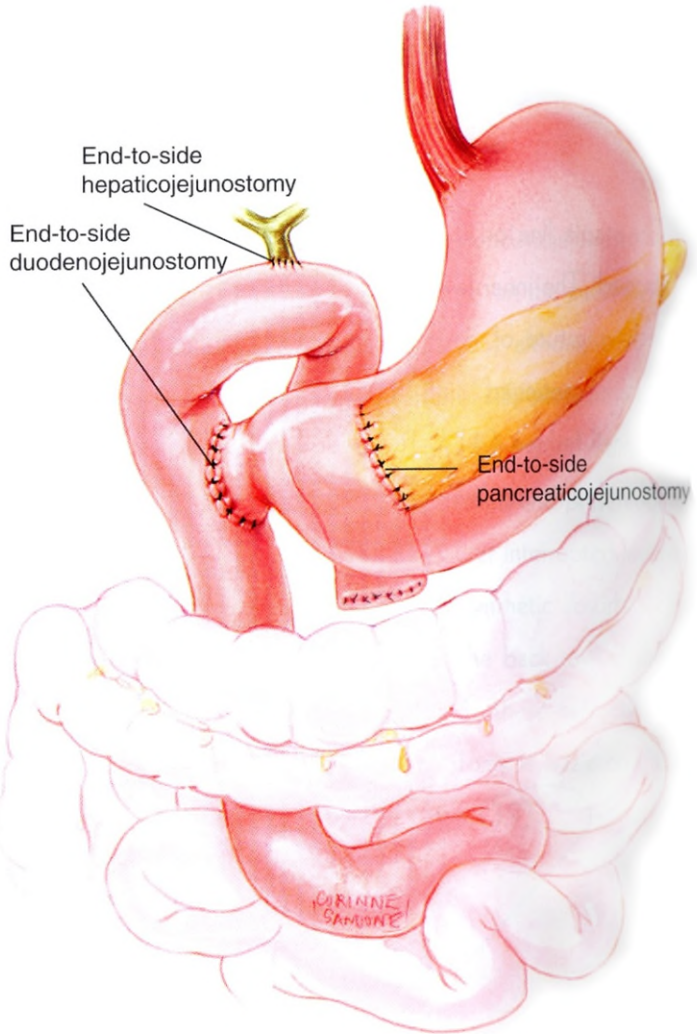
Traverso & Longmire: Rebirth of PPPD in 1978

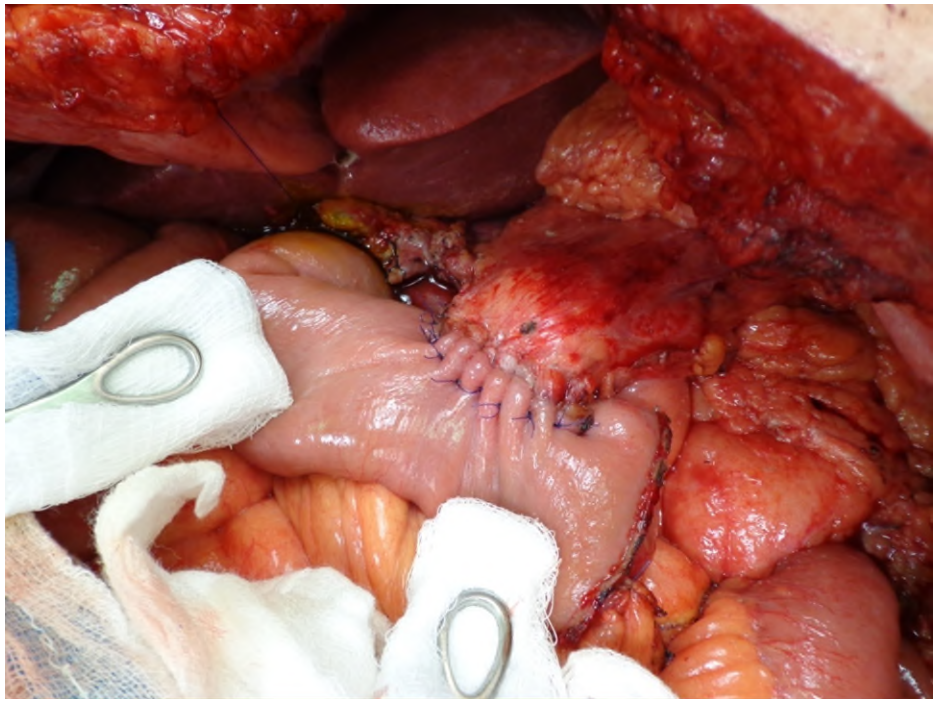




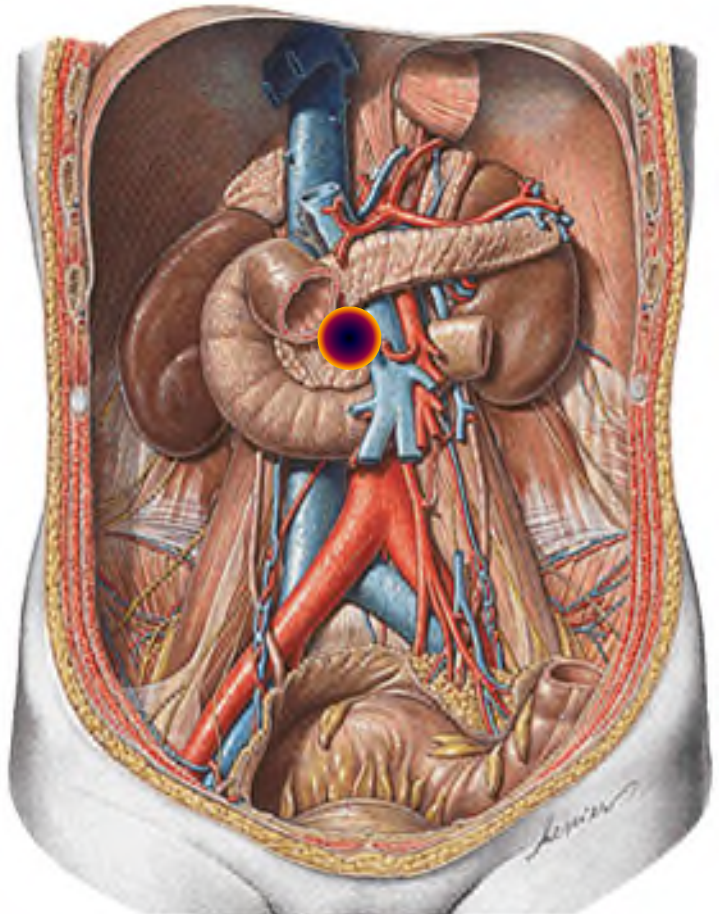
Trimble IR, Parsons WB, Sherman CP. Surg. Gynecol. Obstet. 1941; 73: 711

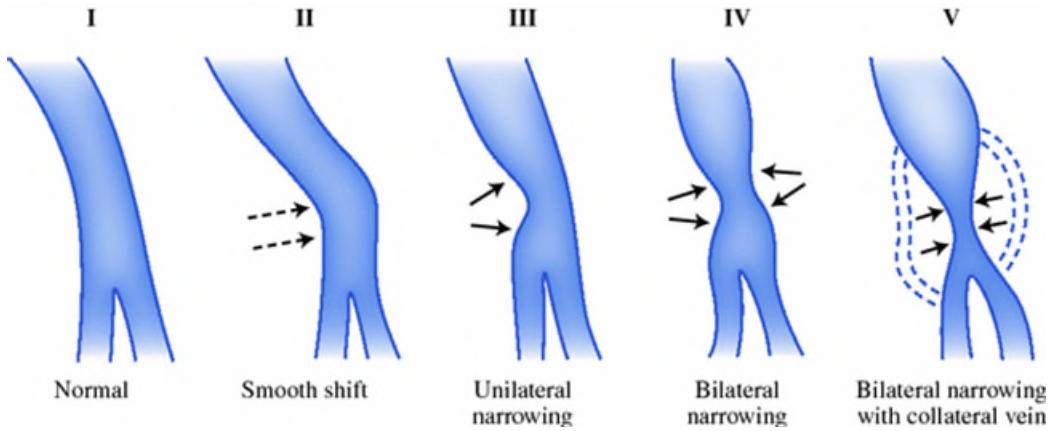
Pancreatico-Jejunostomy

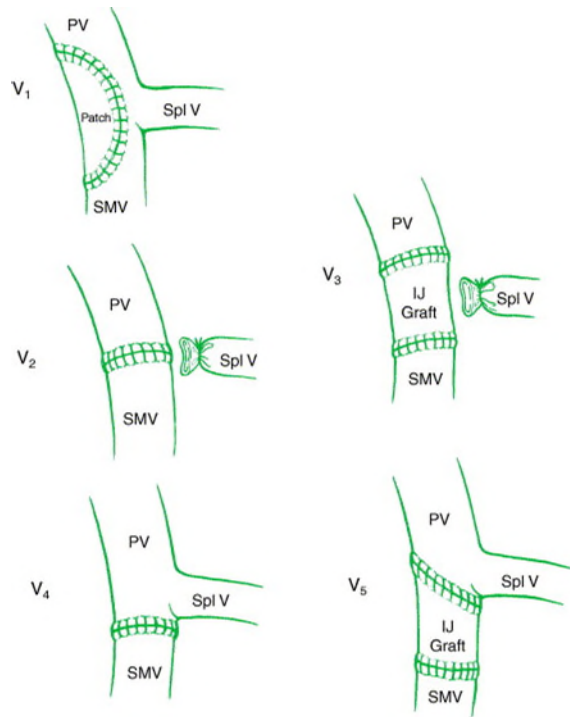




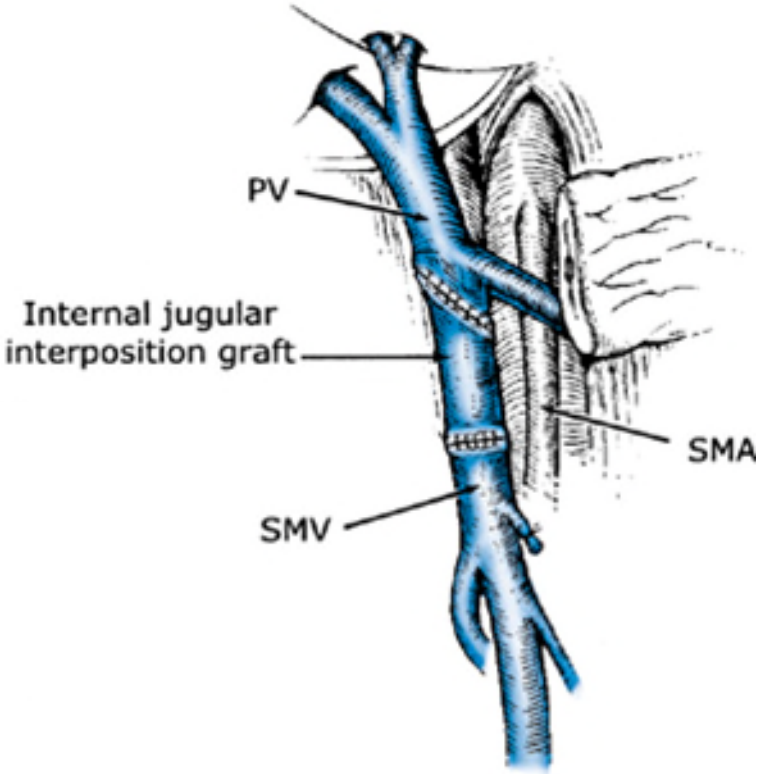
Portal Vein Involvement by the Cancer

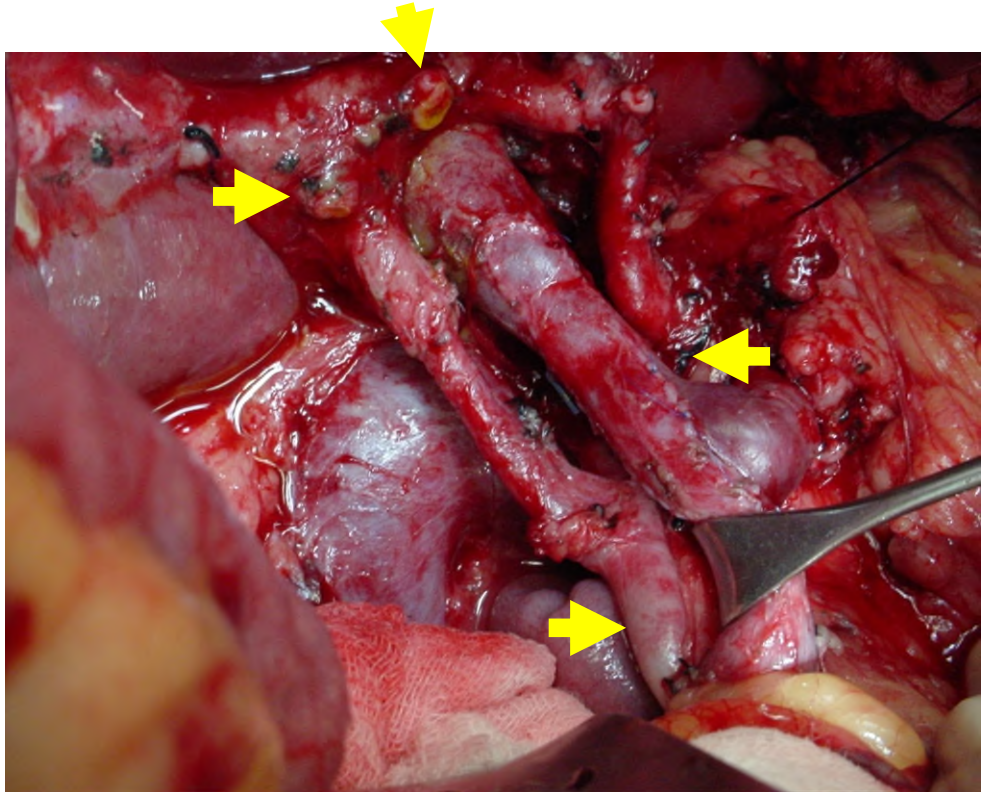


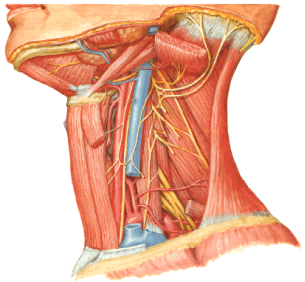


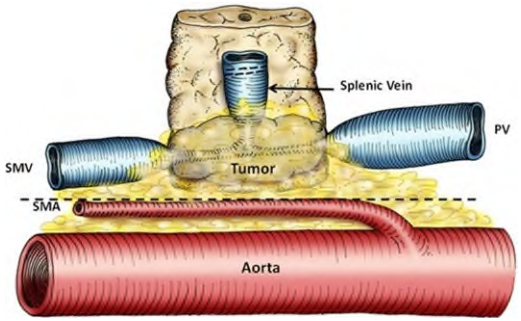


Extended Pancreatectomy









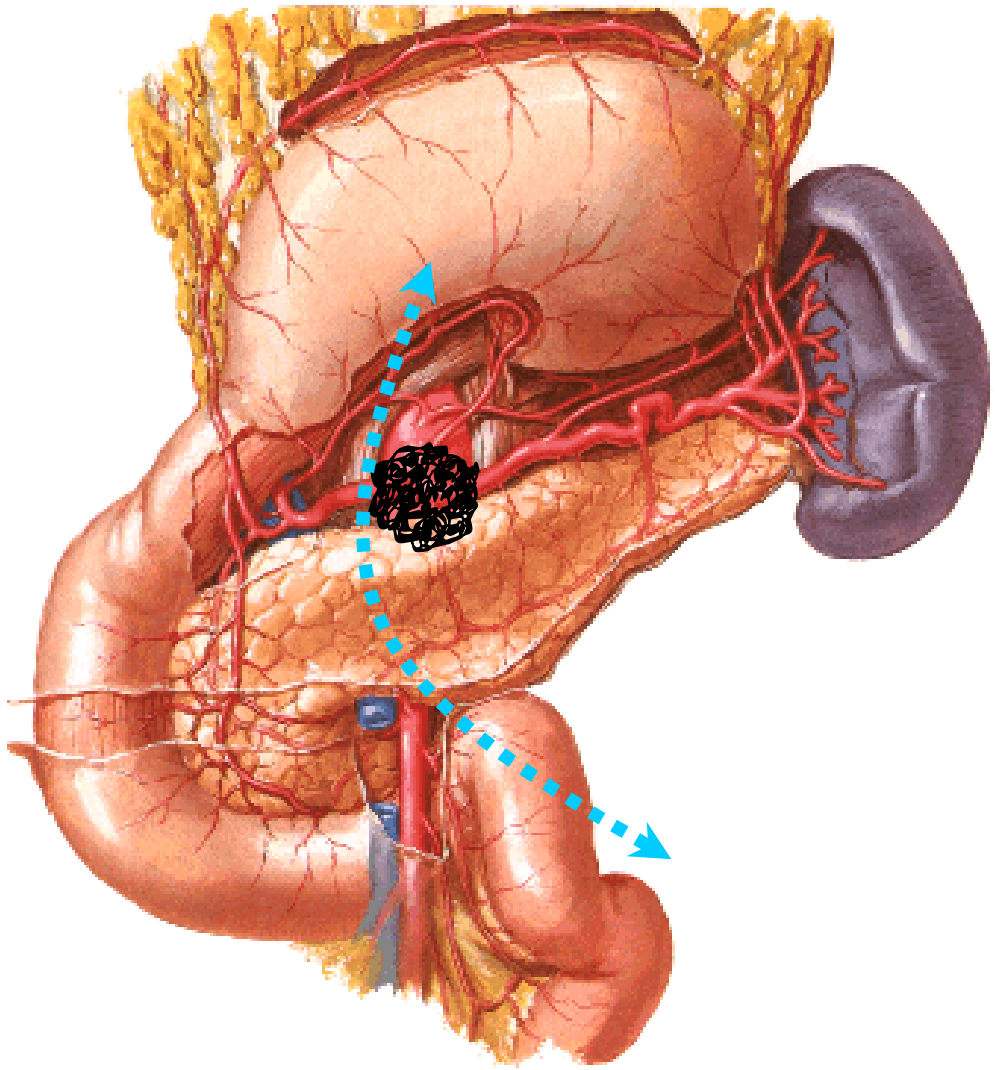
What is the next surgical challenge in pancreatic surgery ?

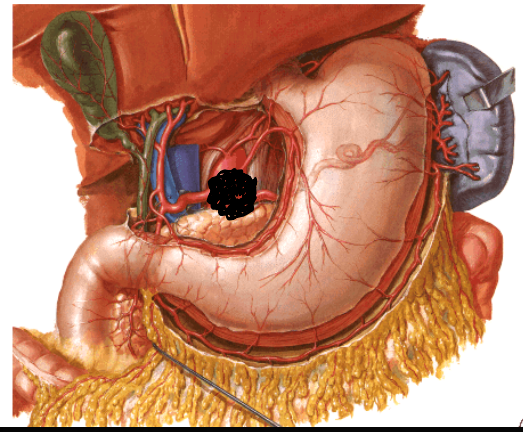
- Have we Maxed Out? What more can we resect?
- Do we need to resect anything more?
- Extended Lymphadenectomy → DONE
- Portal Vein Resection → DONE

- Can we resect Arteries?
  - **Hepatic Artery**
  - **Celiac Axis**
  - **Superior Mesenteric Artery**
- The obvious answer is “NO”- Does it belie logic?
- At best Level 5 evidence- and started before the era of FOLFIRINOX

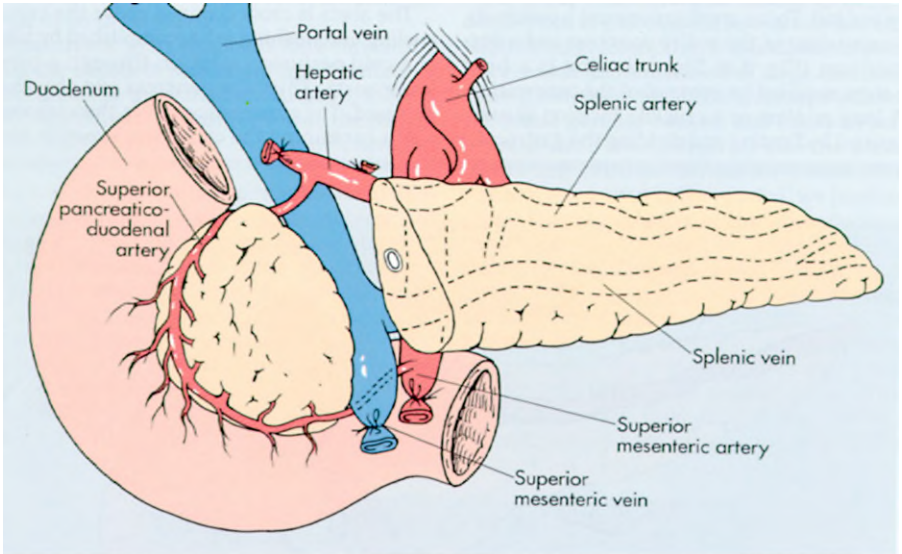
Arterial Knockout- Celiac Axis

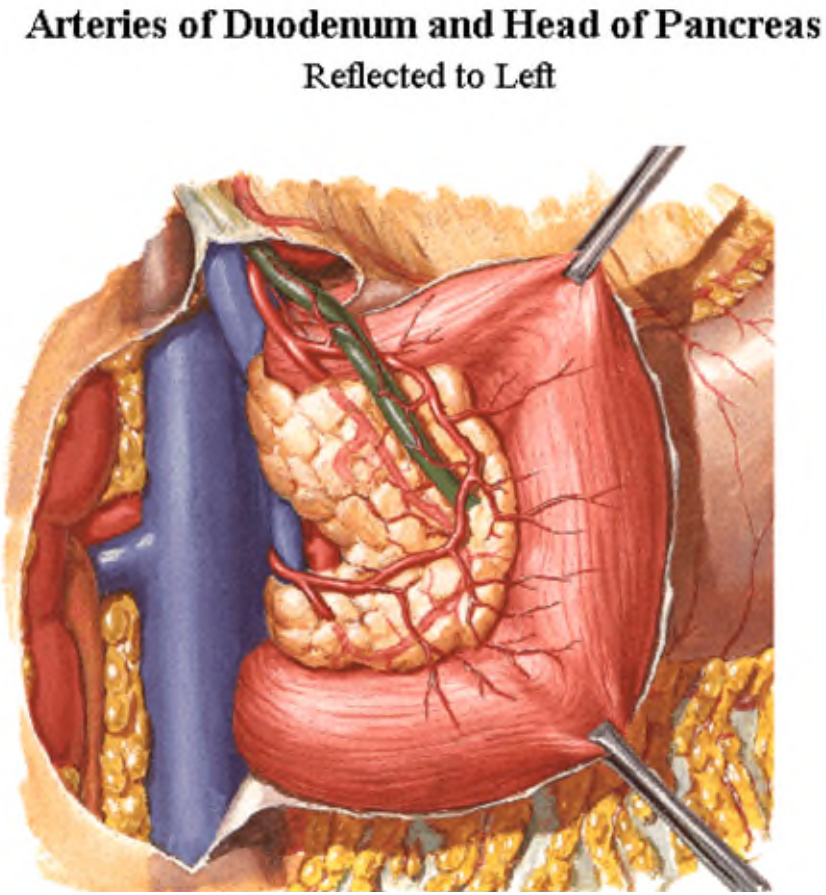
Pushing the limit- The Modified Appleby Operation





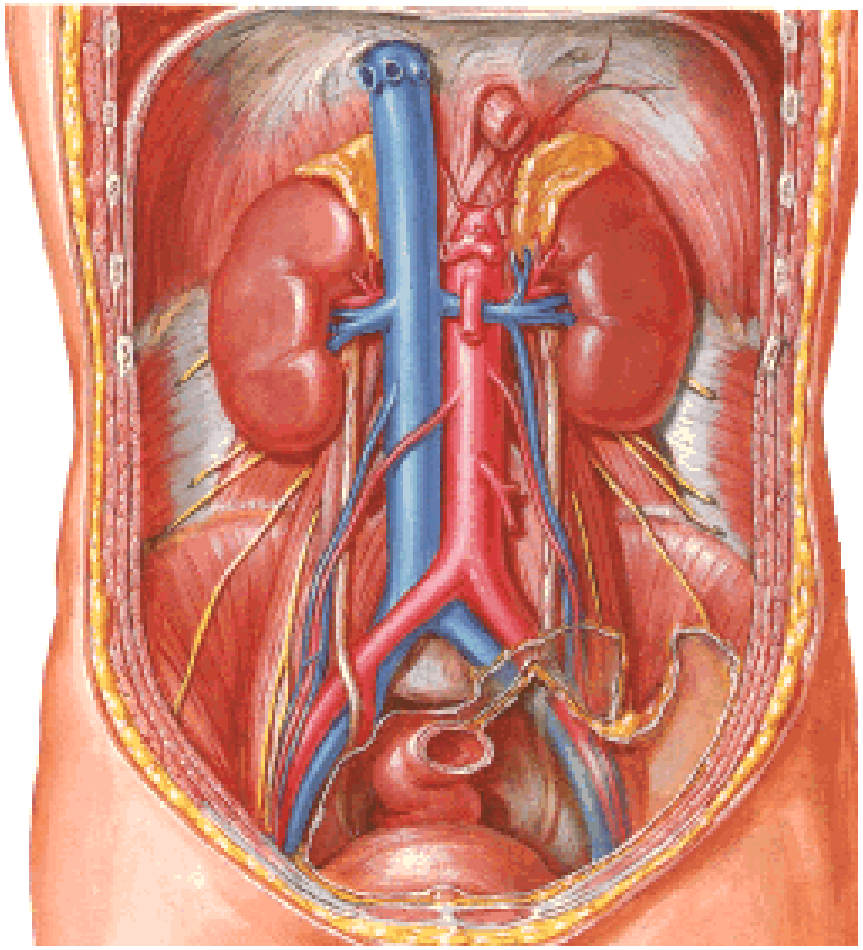
Well preserved pancreatoduodenal arcade

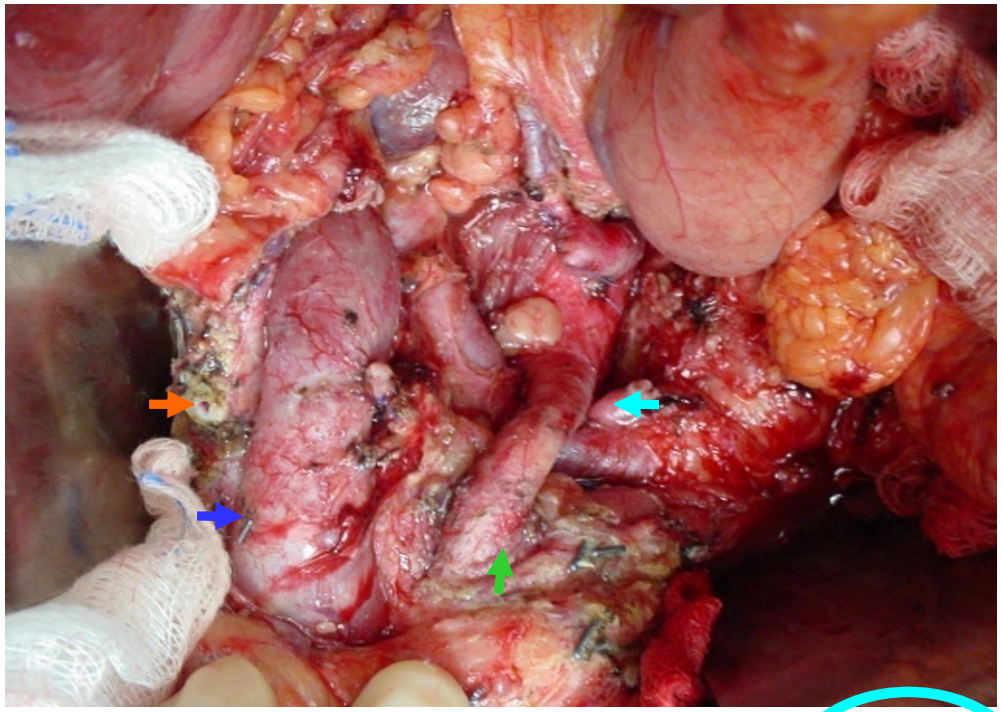




SMA Angiogram

Modified Appleby Operation





Excerpta Medica

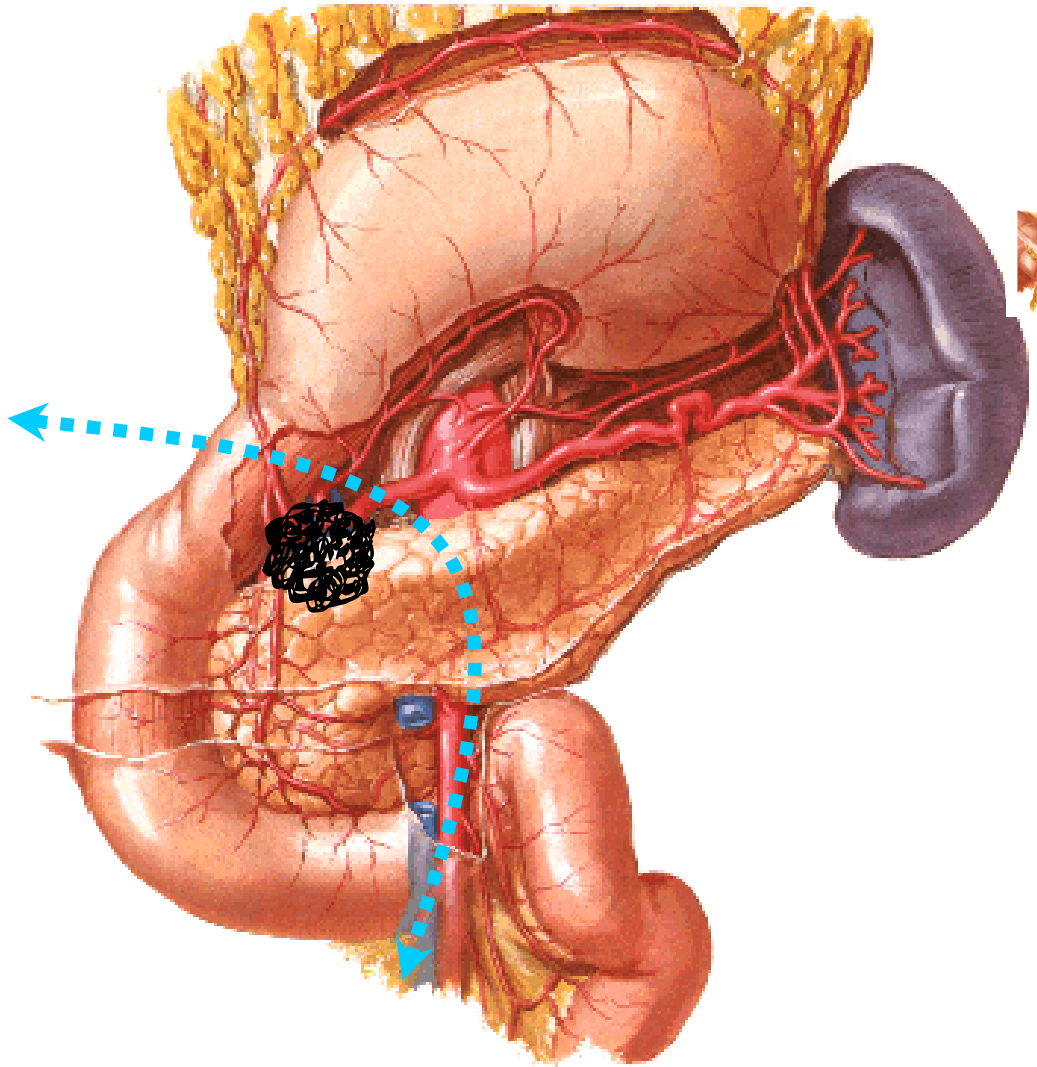
The American Journal of Surgery

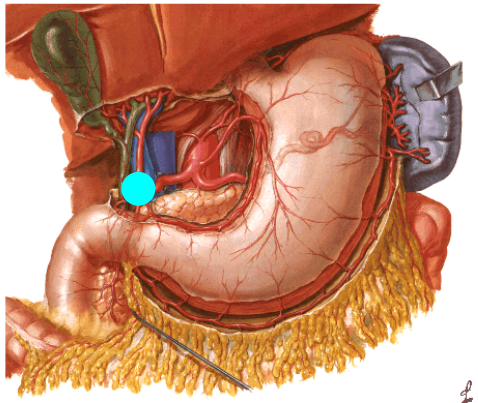
The American Journal of Surgery 192 (2006) 330–335
Clinical surgery–American

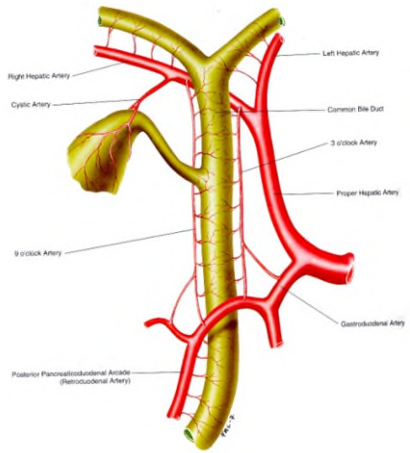
Extended pancreatectomy with resection of the celiac axis: the modified Appleby operation

Singh Gagandeep, M.D.[a,b], Avo Artinyan, M.D.[a,b], Nicolas Jabbour, M.D.[a,b], Rodrigo Mateo, M.D.[a,b], Lea Matsuoka, M.D.[a,b], Linda Sher, M.D.[a,b], Yuri Genyk, M.D.[a,b],

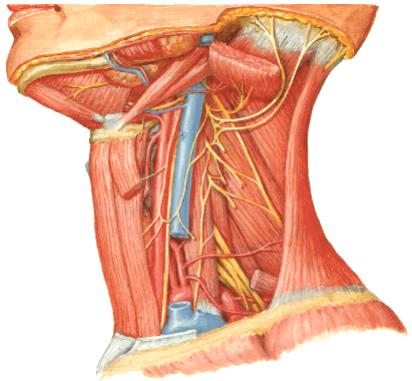
Arterial Knockout- Hepatic Artery

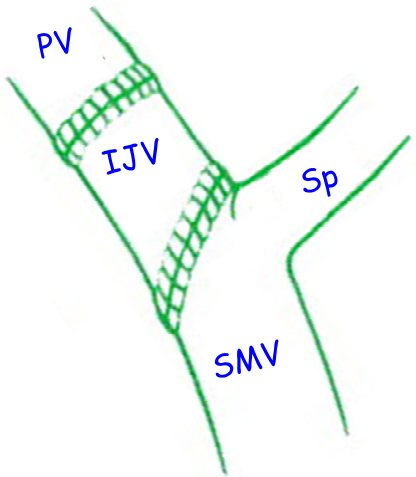


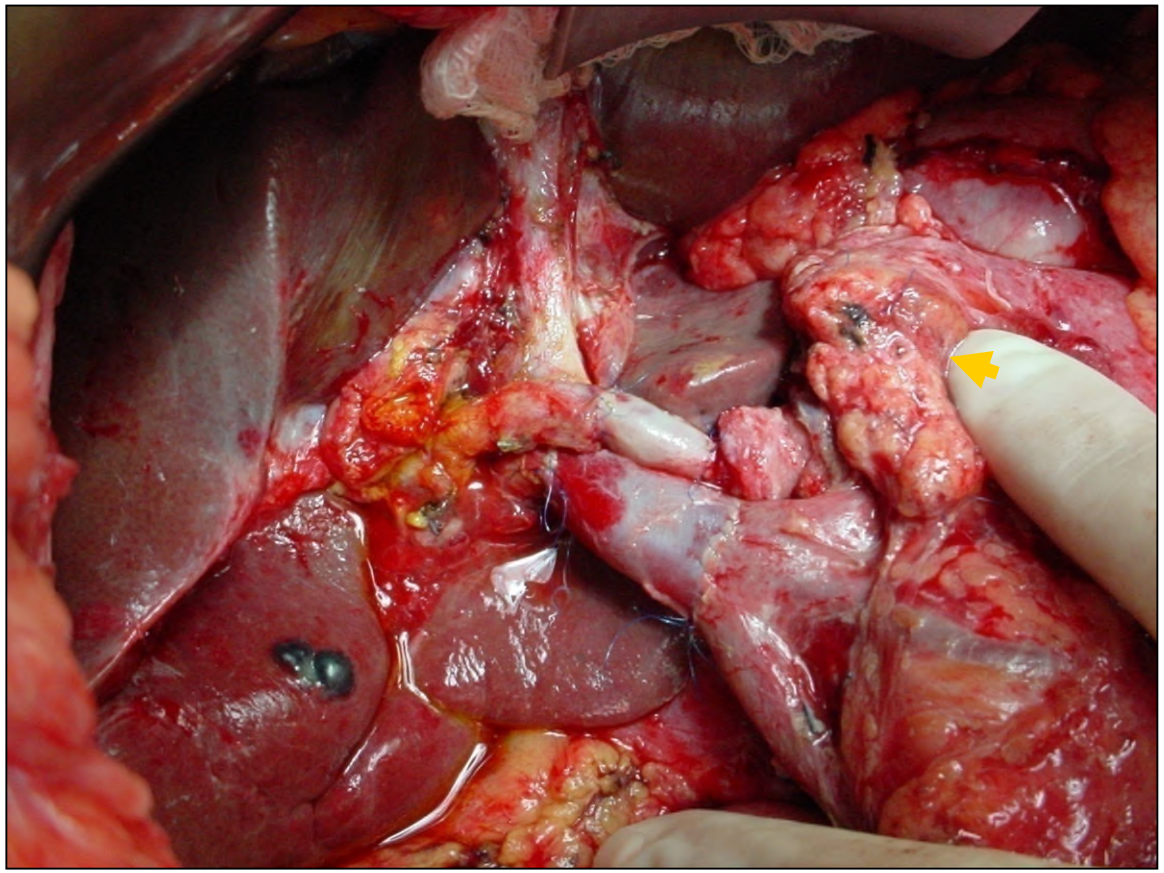




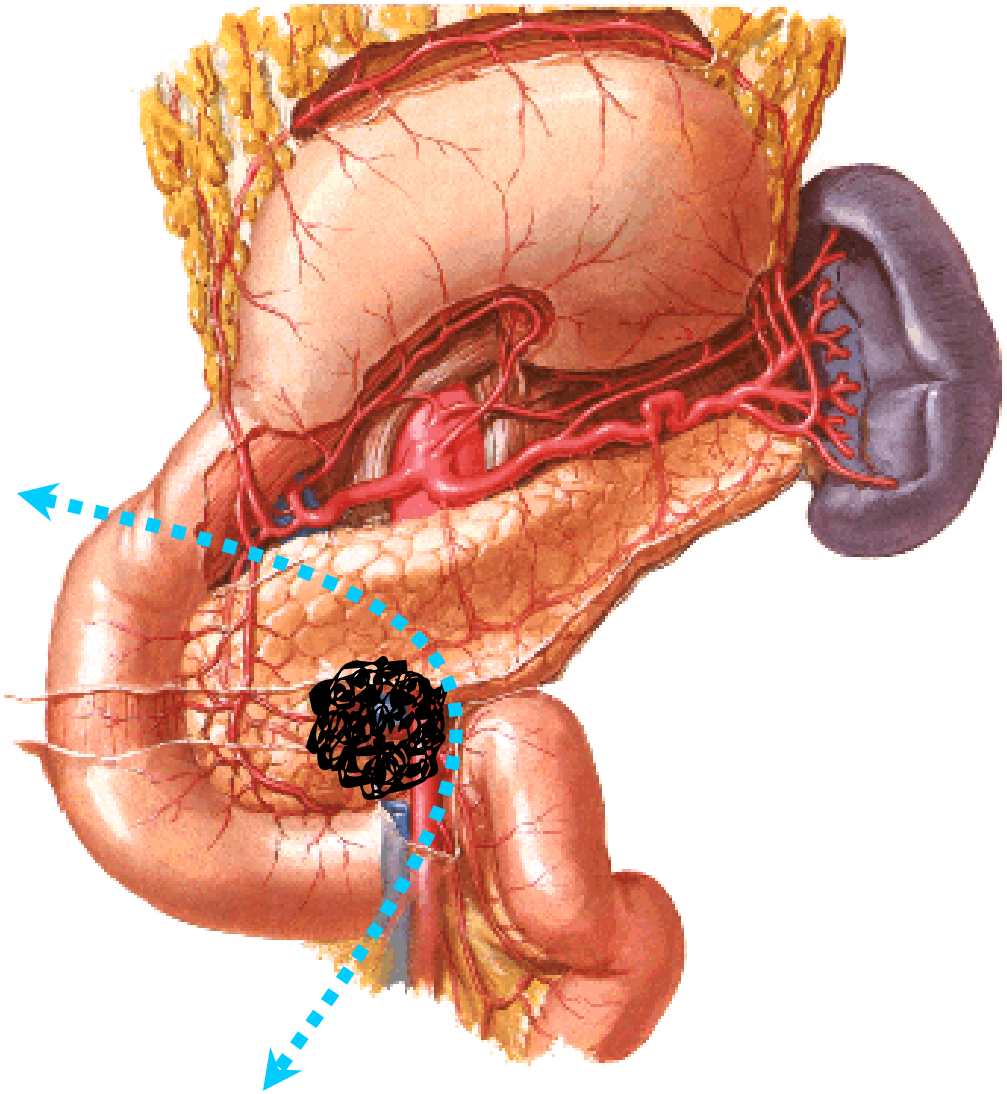
Hepatic Ar and PV Reconstruction

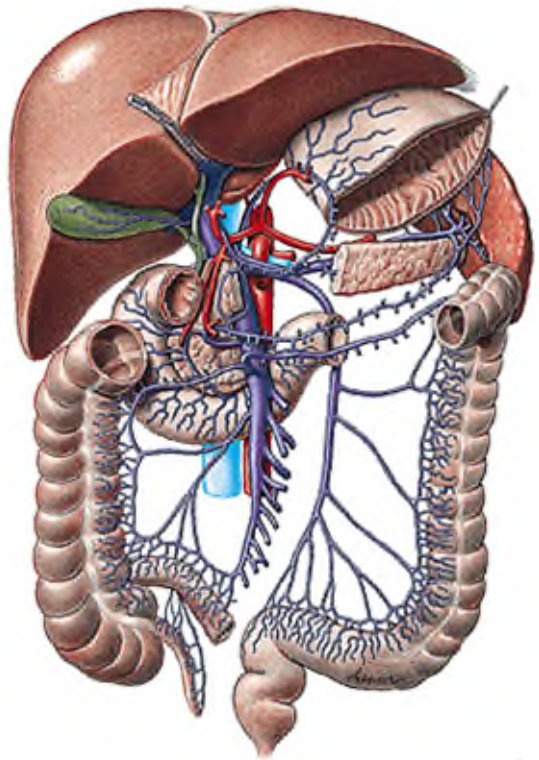






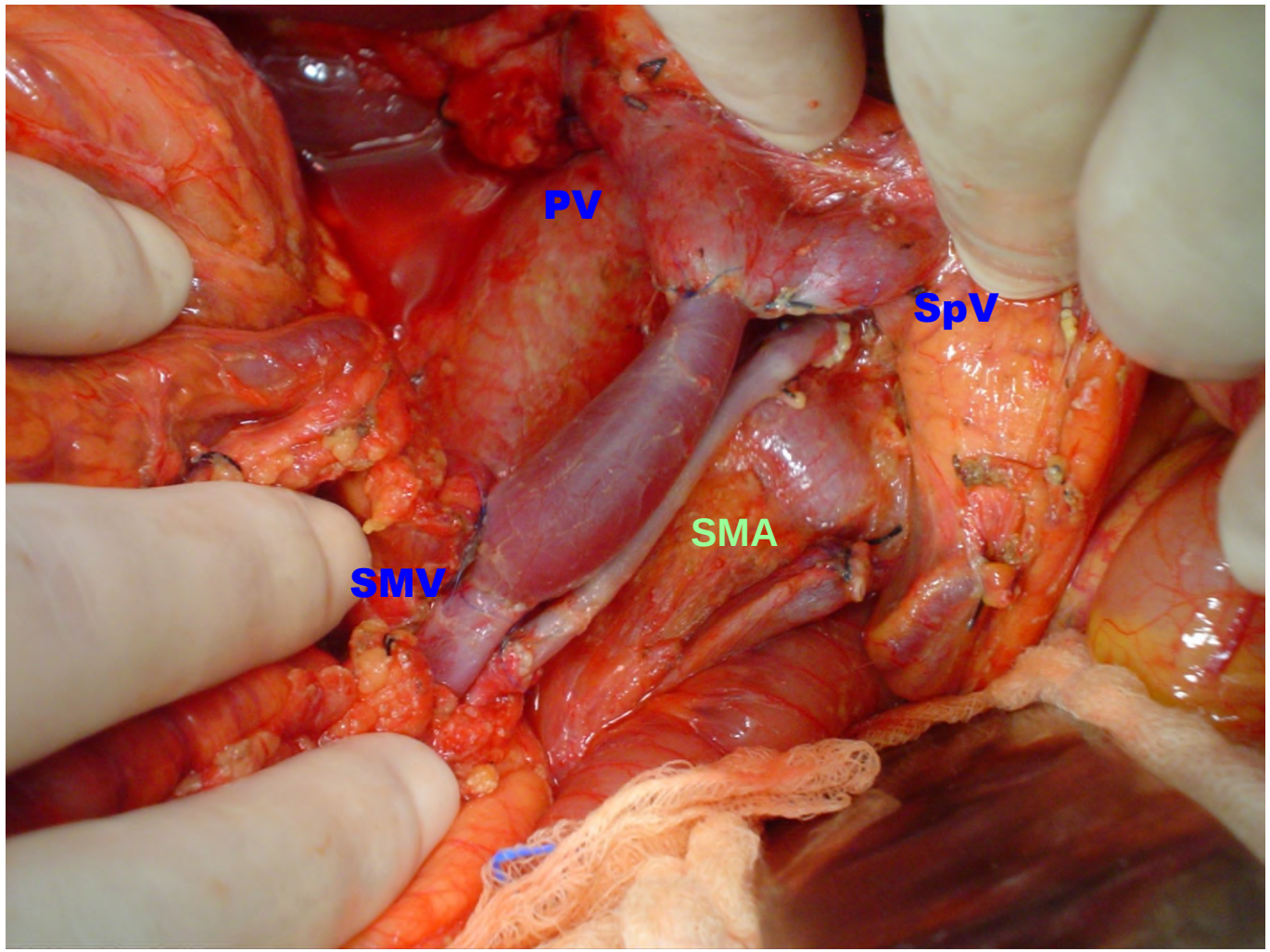
Arterial Knockout- Superior Mesenteric Artery

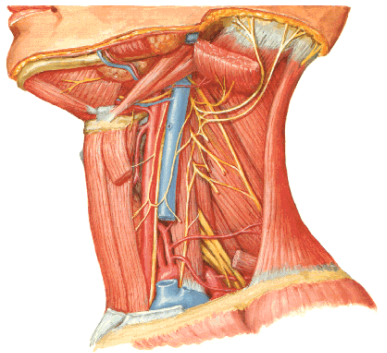


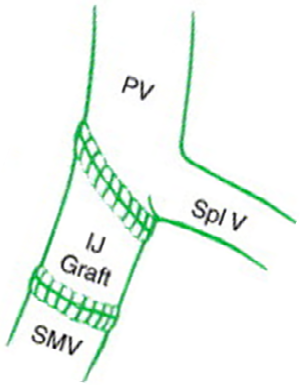


CT Scan with SMA Involvement

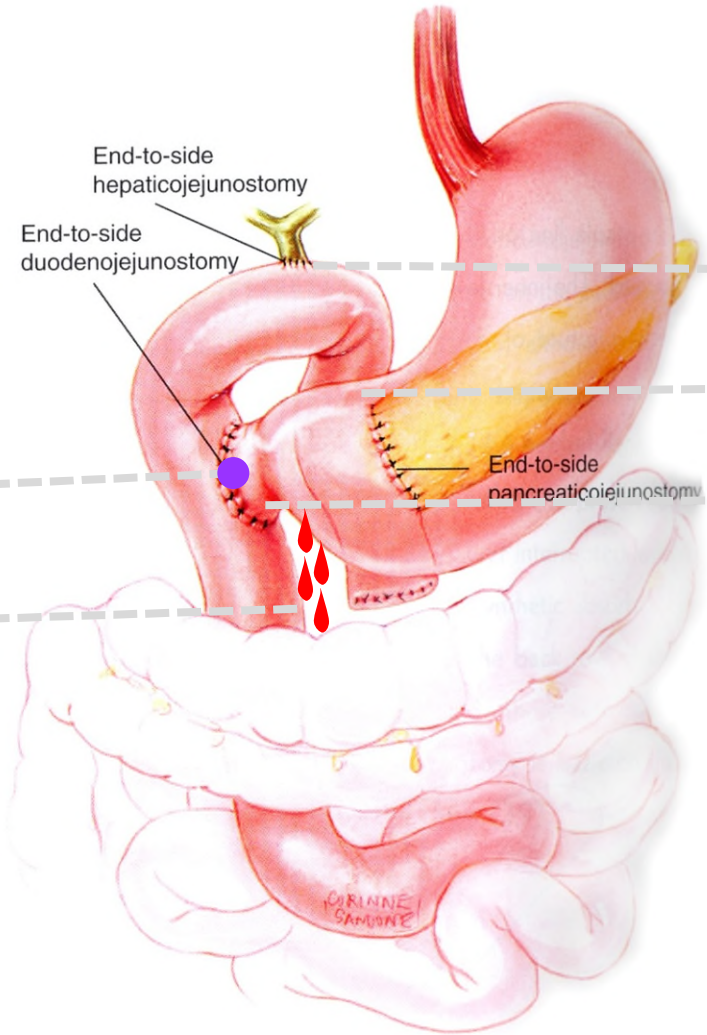
Reconstruction of the SMA and SMV







Complications from a Whipple Operation



Delayed Emptying

Biliary Leak

Pancreatic Leak

Stomach Leak

Infections

Ulcers

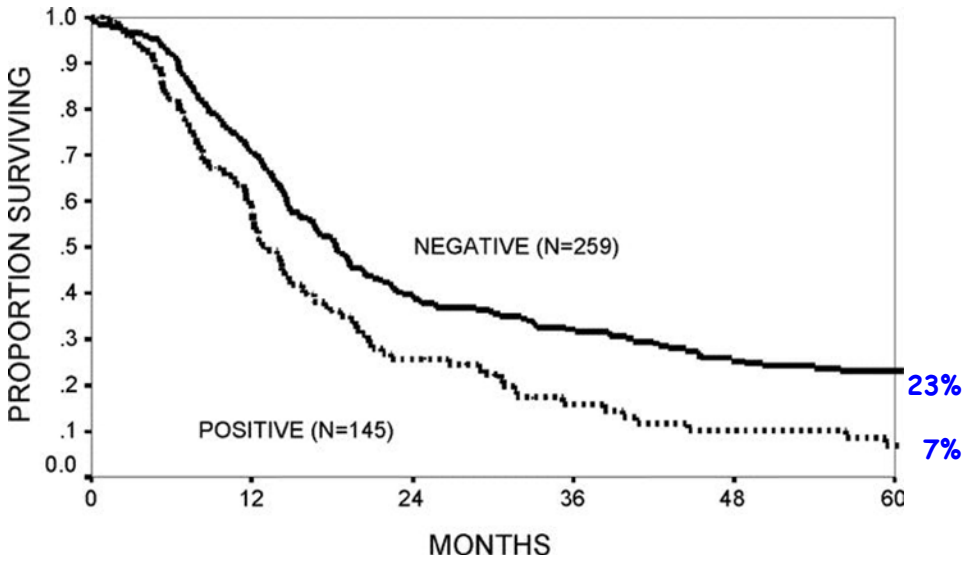
Bleeding

Mortality should be <3-5%

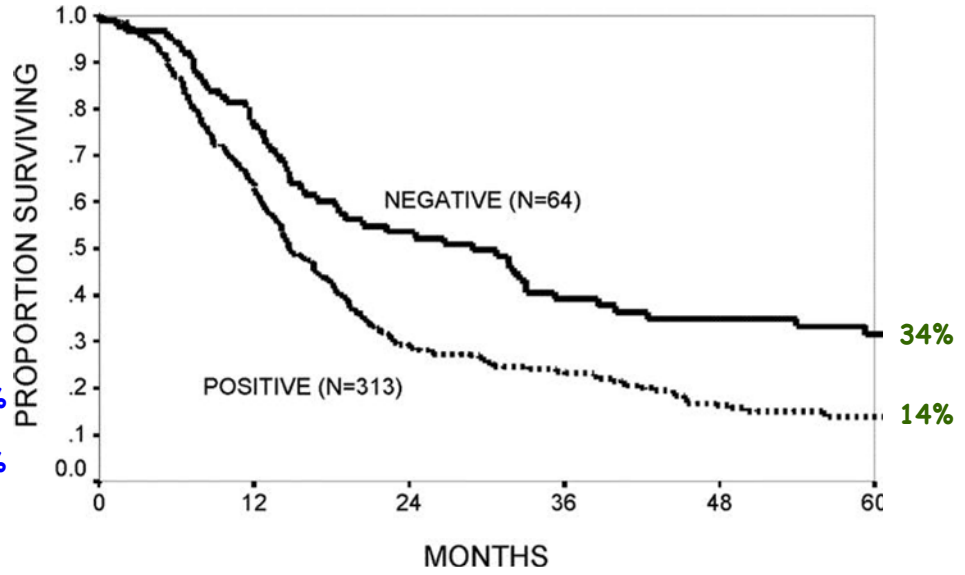
Negative Margins & Negative Nodes

Results

Margins



Nodes



Actuarial 5-year survival for margin-negative and margin-positive patients with adenocarcinoma of the pancreas undergoing a pancreaticoduodenectomy.

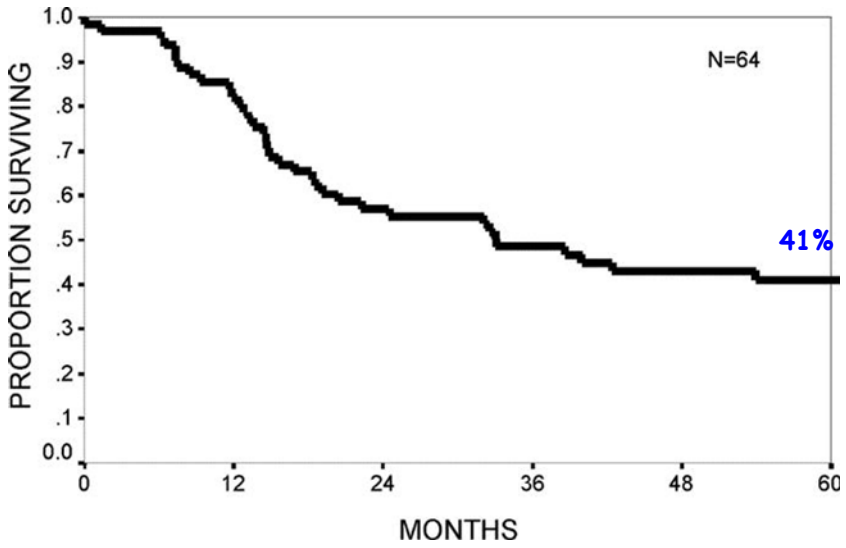
Actuarial 5-year survival for node-negative and node-positive patients with adenocarcinoma of the pancreas undergoing a pancreaticoduodenectomy.

Cameron: Ann Surg, Volume 244(1).July 2006.10-15

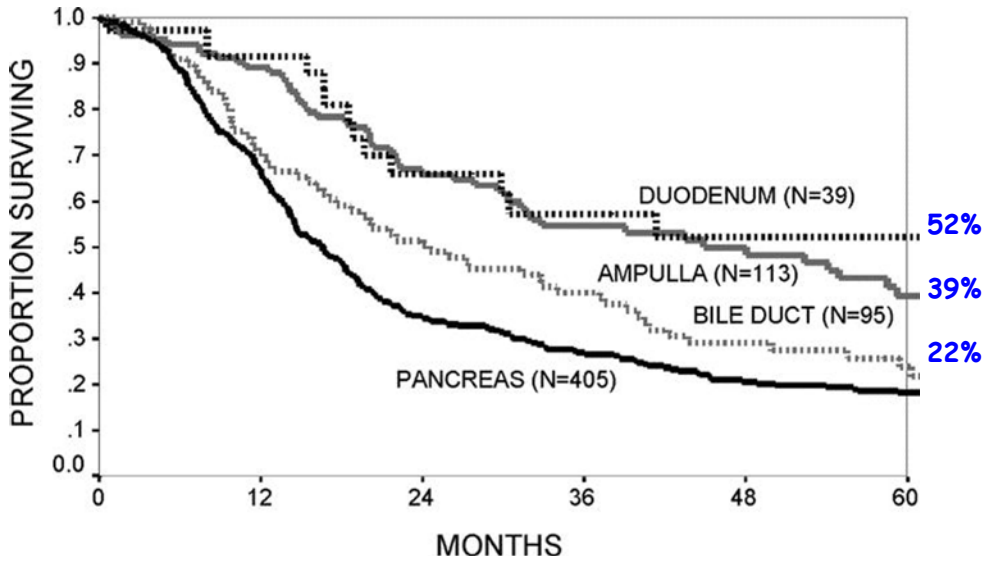
Favorable Factors

Results

Margin & Node Negative



Region

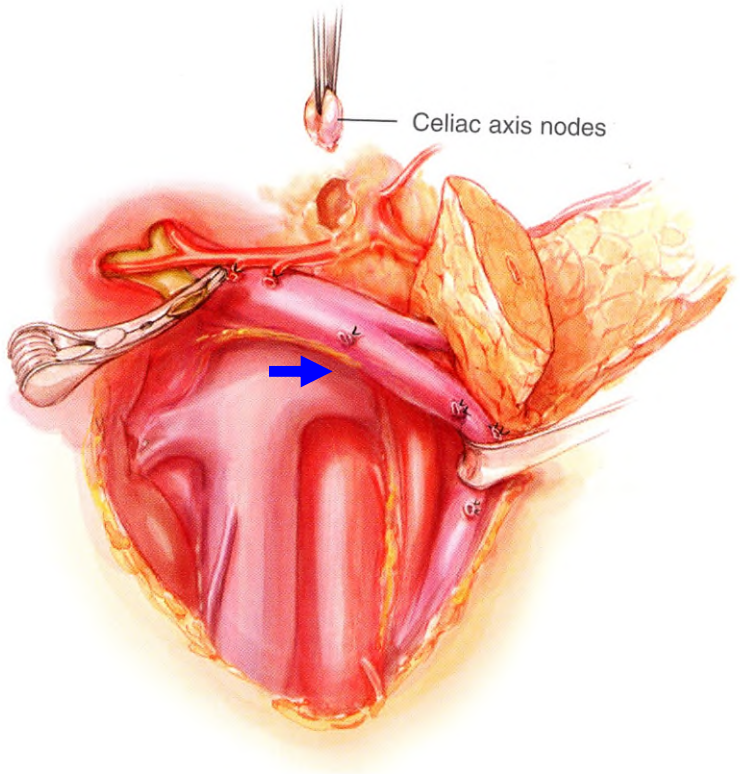


Actuarial 5-year survival for patients who were both node negative and margin negative with adenocarcinoma of the pancreas.

Actuarial 5-year survival for patients with adenocarcinoma of the duodenum, ampulla, distal bile duct, and pancreas undergoing a pancreaticoduodenectomy.

Cameron: Ann Surg, Volume 244(1).July 2006.10-15

Patterns of Recurrence



- **Local recurrence → 80%**
- Peritoneal → 25%
- Liver Mets → 50%
- Locoregional control can be maximized by: Chemo ± Radiation

The TEAM

Surgical Oncologist

Medical Oncologist

Radiation Oncologist
Gene Therapist
Immune Therapist

Gastroenterologist
Radiologist, IR

Endocrinologist
Pathologist
Nutritionist
Social Worker

City of Hope

October 28, 2023 - MULTIDISCIPLINARY APPROACHES TO CANCER SYMPOSIUM

Systemic Therapy Challenges for Treatment of Pancreatic Cancer

Richard T. Lee, MD, FASCO

Clinical Professor

Cherng Family Director's Chair for the Center for Integrative Oncology

Medical Director, Supportive and Integrative Oncology Program, Orange County

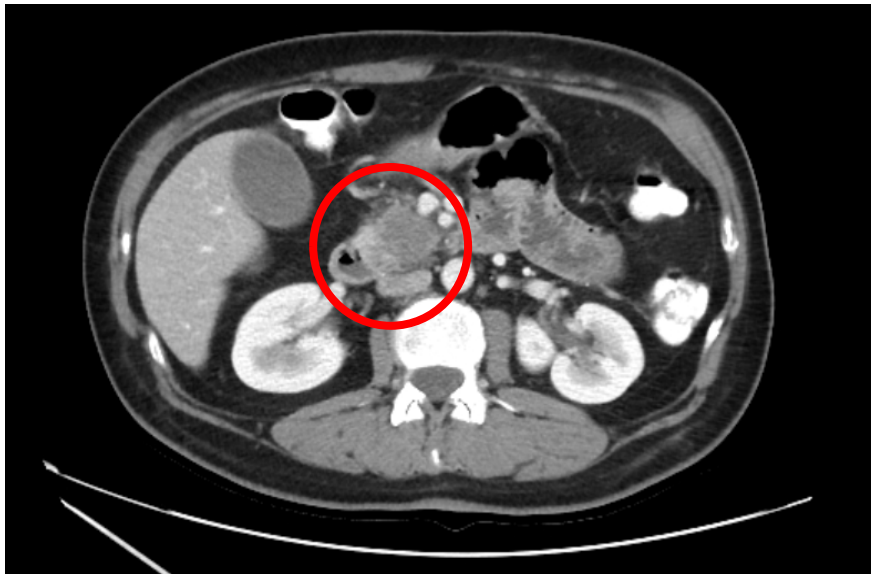
Departments of Supportive Care Medicine and Medical Oncology

Cherng Family Center for Integrative Oncology

City of Hope Comprehensive Cancer Center

Case 1 – Jane Doe

- Jane Doe is a 65 y/o woman presents with GI discomfort and light-colored diarrhea
- CT demonstrates a 2.5 cm pancreatic head mass with dilation of the pancreatic duct and the CBD up to 11 mm. Contact of the tumor with the SMV (<90 degrees) which is patent and presence of fat place between the tumor and SMA.
- EGD and EUS with FNA biopsy on 10/12/22 with findings of a 27 x 24 mm pancreatic head mass with noted visible tissue plane between the mass portal vein and SMV. Pancreatic duct and CBD dilation noted up to 7 mm.
- CA 19-9 = 335



Borderline Line Resectable Pancreatic Cancer

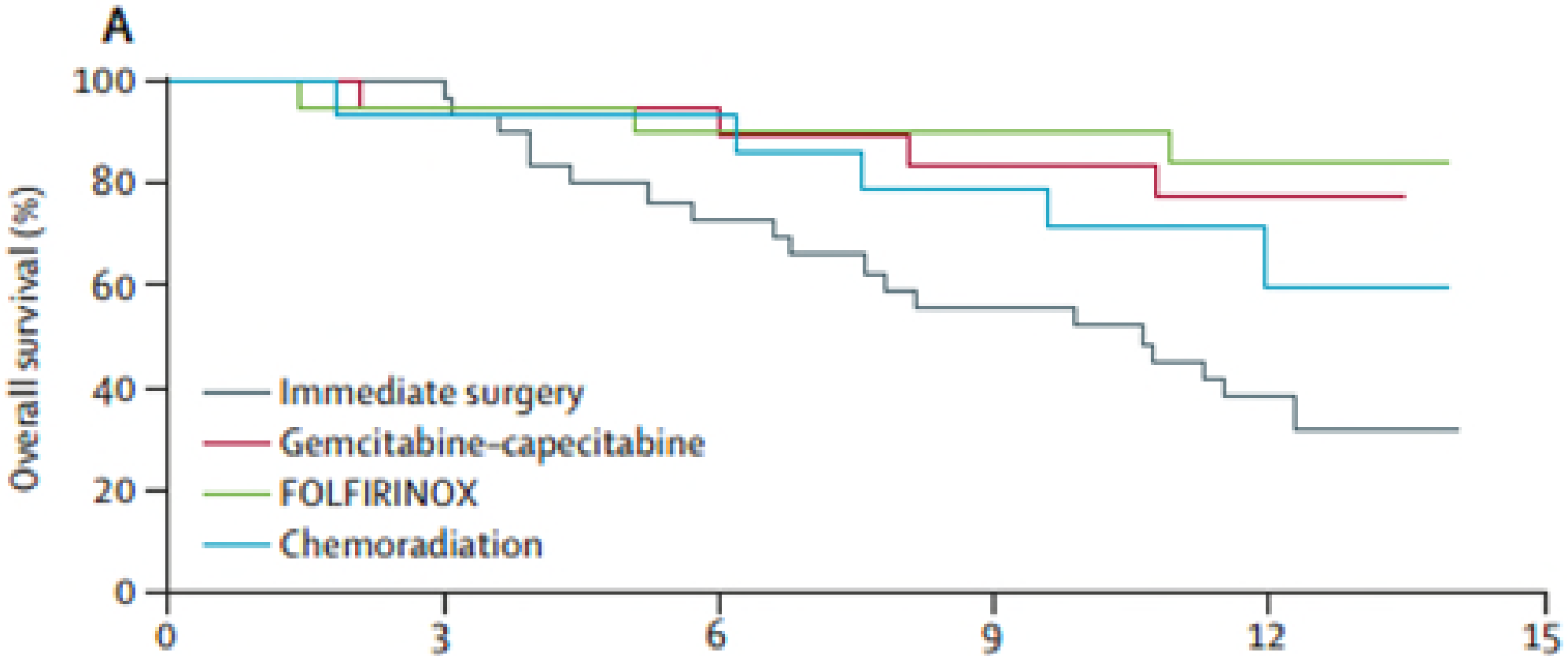
- Solid tumor contact with the SMA ≤180 degrees.
- Solid tumor contact with the SMV or portal vein of >180 degrees with contour irregularity of the vein or thrombosis of the vein, but with suitable vessel proximal and distal to the site of involvement, allowing for safe and complete resection and vein reconstruction.
- Solid tumor contact with the inferior vena cava.
- Solid tumor contact with the common hepatic artery without extension to the celiac axis or hepatic artery bifurcation, allowing for safe and complete resection and reconstruction.

Immediate surgery compared with short-course neoadjuvant gemcitabine plus capecitabine, FOLFIRINOX, or chemoradiotherapy in patients with borderline resectable pancreatic cancer (ESPAC5): a four-arm, multicentre, randomised, phase 2 trial

- 90 Patients with borderline resectable pancreatic cancer
- Randomized to 4 –arms
  - Immediate surgery (33)
  - Gemcitabine+capecitabine (20)
  - FOLFIRINOX (20)
  - Chemoradiotherapy (17)
- Neoadjuvant therapy was 2 months of treatment and chemoradiotherapy was 5.5 wks

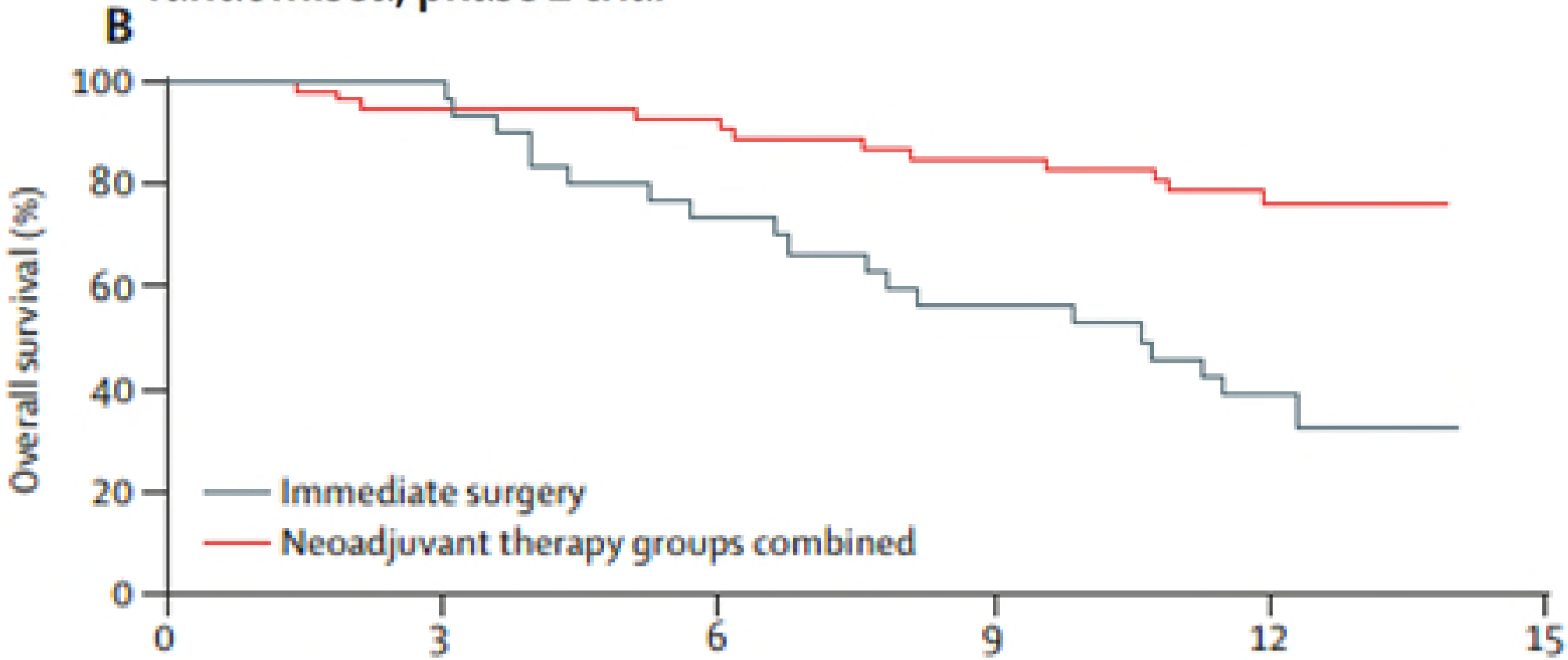
Lancet Gastroenterol Hepatol
2023; 8: 157-68

Immediate surgery compared with short-course neoadjuvant gemcitabine plus capecitabine, FOLFIRINOX, or chemoradiotherapy in patients with borderline resectable pancreatic cancer (ESPAC5): a four-arm, multicentre, randomised, phase 2 trial



Lancet Gastroenterol Hepatol 2023; 8: 157-68

Immediate surgery compared with short-course neoadjuvant gemcitabine plus capecitabine, FOLFIRINOX, or chemoradiotherapy in patients with borderline resectable pancreatic cancer (ESPAC5): a four-arm, multicentre, randomised, phase 2 trial

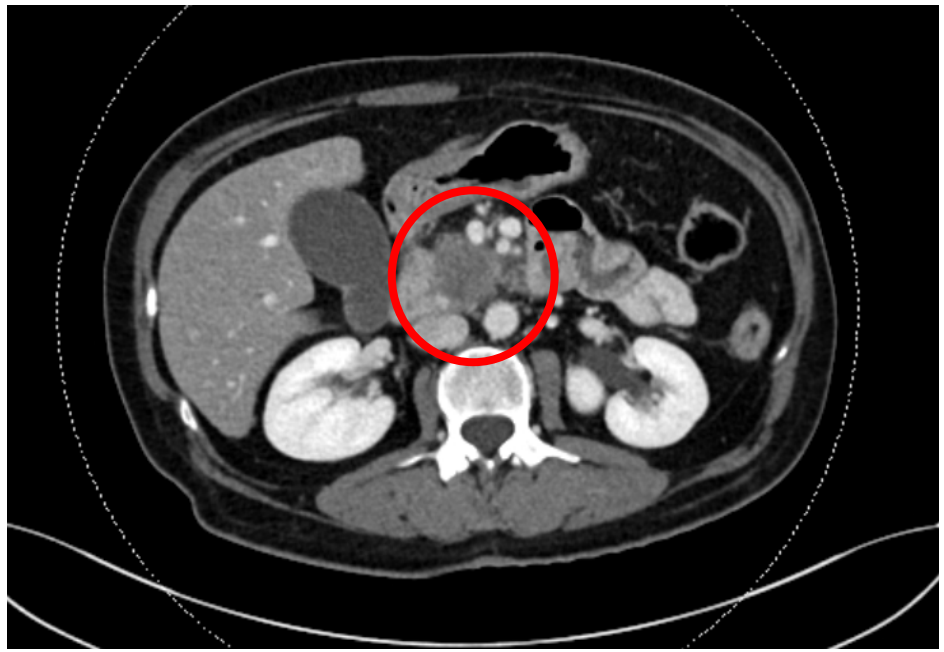


Lancet Gastroenterol Hepatol
2023; 8: 157-68

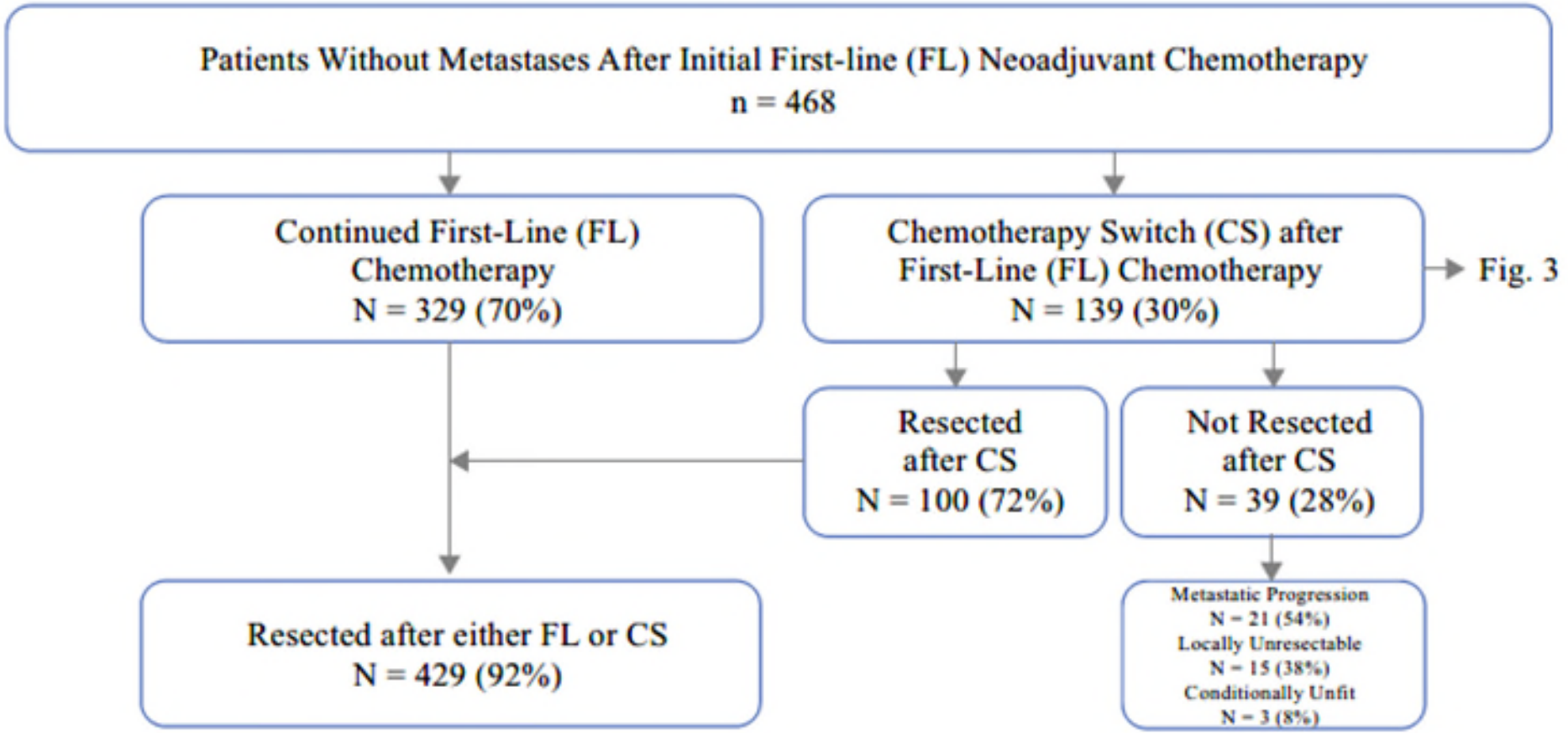
Case 1 – Borderline Resectable Pancreatic Cancer

- Patient is tolerating FOLFIRINOX well with some fatigue
- CT is repeated after 4 cycles: 3.1 cm mass in the head of the pancreas which measures larger than when seen on prior examination. The tumor is abutting the superior mesenteric artery and vein less than 180 degrees
- CA19-9 = 462=> 800 => 741

- What to do next?
    - o Continue FOLFIRINOX
    - o Change to surgery
    - o Change to Gemcitabine/Abraxane
    - o Change to chemoradiotherapy

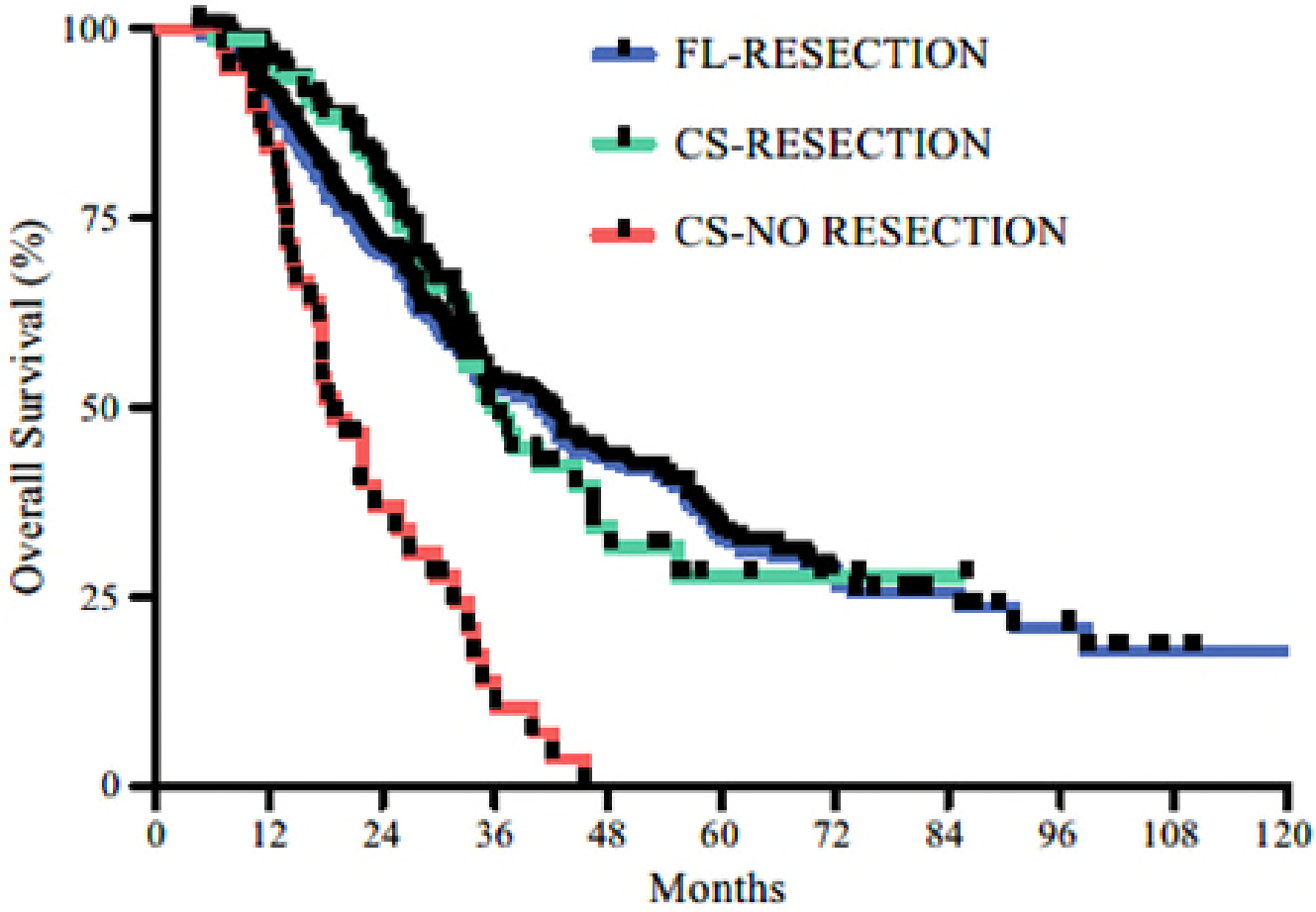


Neoadjuvant Chemotherapy Switch in Borderline Resectable/ Locally Advanced Pancreatic Cancer



Ann Surg Oncol (2022) 29:1579–1591

Neoadjuvant Chemotherapy Switch in Borderline Resectable/ Locally Advanced Pancreatic Cancer

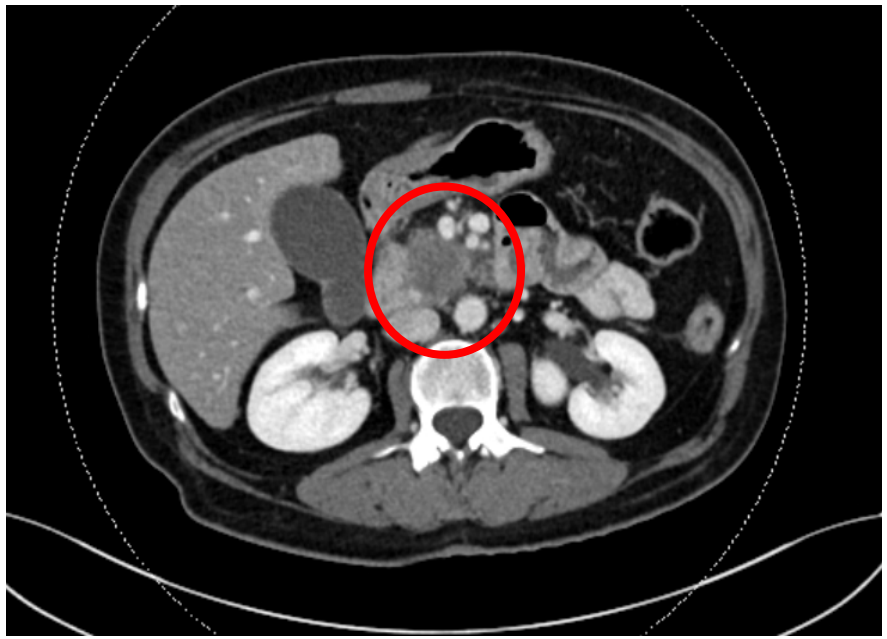


Ann Surg Oncol (2022) 29:1579–1591

Case 1 – Borderline Resectable Pancreatic Cancer

- GI Tumor Board suggests continuing treatment with FOLFIRINOX
- Patient continues to tolerate chemotherapy well
- CT is repeated after 8 cycles: Pancreatic mass is 3.4 x 3.1 cm hypodense mass which previously measured 3.1 x 3.0 cm. The mass is inseparable from the superior mesenteric artery and vein.
- CA19-9 = 462=> 800 => 741 => 284

- What to do next?



Case 1 – Borderline Resectable Pancreatic Cancer

- Patient continues to tolerate chemotherapy but starting to have persistent neuropathy
- CT is repeated after 12 cycles: Pancreatic mass persistent 3.4 x 3.1 cm hypodense mass centered at the level of the head of the pancreas without significant change in size since prior examination. The mass is inseparable from the superior mesenteric artery and vein. The mass appears centrally hypodense.
- CA19-9 = 462=> 800 => 741 => 284 => 161

- What to do next?
    - Surgery
    - Chemoradiotherapy

Radiation for Borderline Resectable and Locally Advanced Pancreatic Cancer

Heather McGee, MD, PhD

Assistant Professor, Departments of Radiation Oncology and Immuno-Oncology

City of Hope

Treatment Paradigm Based on Resectability

Resectable:

- Surgery → adjuvant chemo alone (ESPAC-I study)
- Neoadjuvant chemo (for high risk) → Surgery
- Surgery → Chemoradiation (controversial) if positive margins

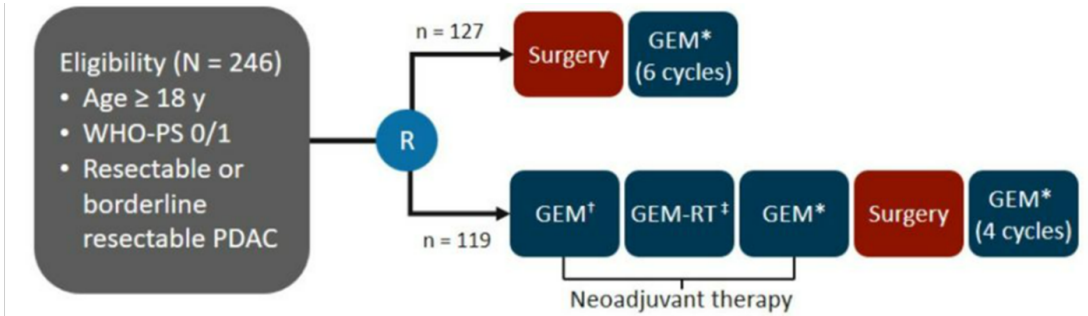
Borderline resectable:

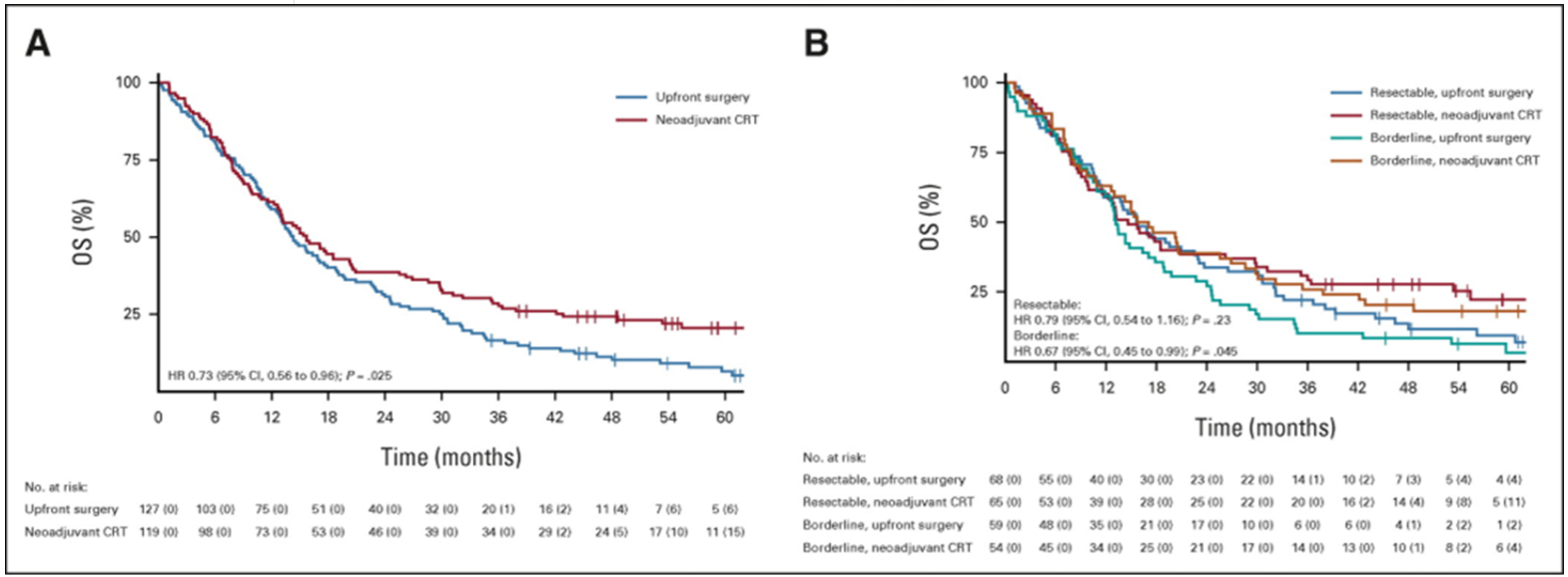
- Neoadjuvant chemo → Chemoradiation → surgery (TNT-like approach used at City of Hope)
- Neoadjuvant chemo alone → surgery
- Neoadjuvant chemoradiation alone → surgery
- NOTE: Do not give SBRT in the neoadjuvant setting (due to the negative ALLIANCE trial)

Locally advanced:

- Chemotherapy alone, as in metastatic disease
  - Often use FOLFIRINOX (ACCORD 11) or Gem-Abraxane (MPACT)
- Chemoradiation (controversial) = 50.4 Gy-54 Gy w/ Xeloda or 5-FU
  - Trials with mixed results, some trials positive (GITSG, EORTC 4201), some trials showing no difference (ECOG), some trials negative (FFCD/SFRO)
- Induction chemotherapy, then chemoradiation if no progression → this is a logical approach even though the LAP-07 trial was negative

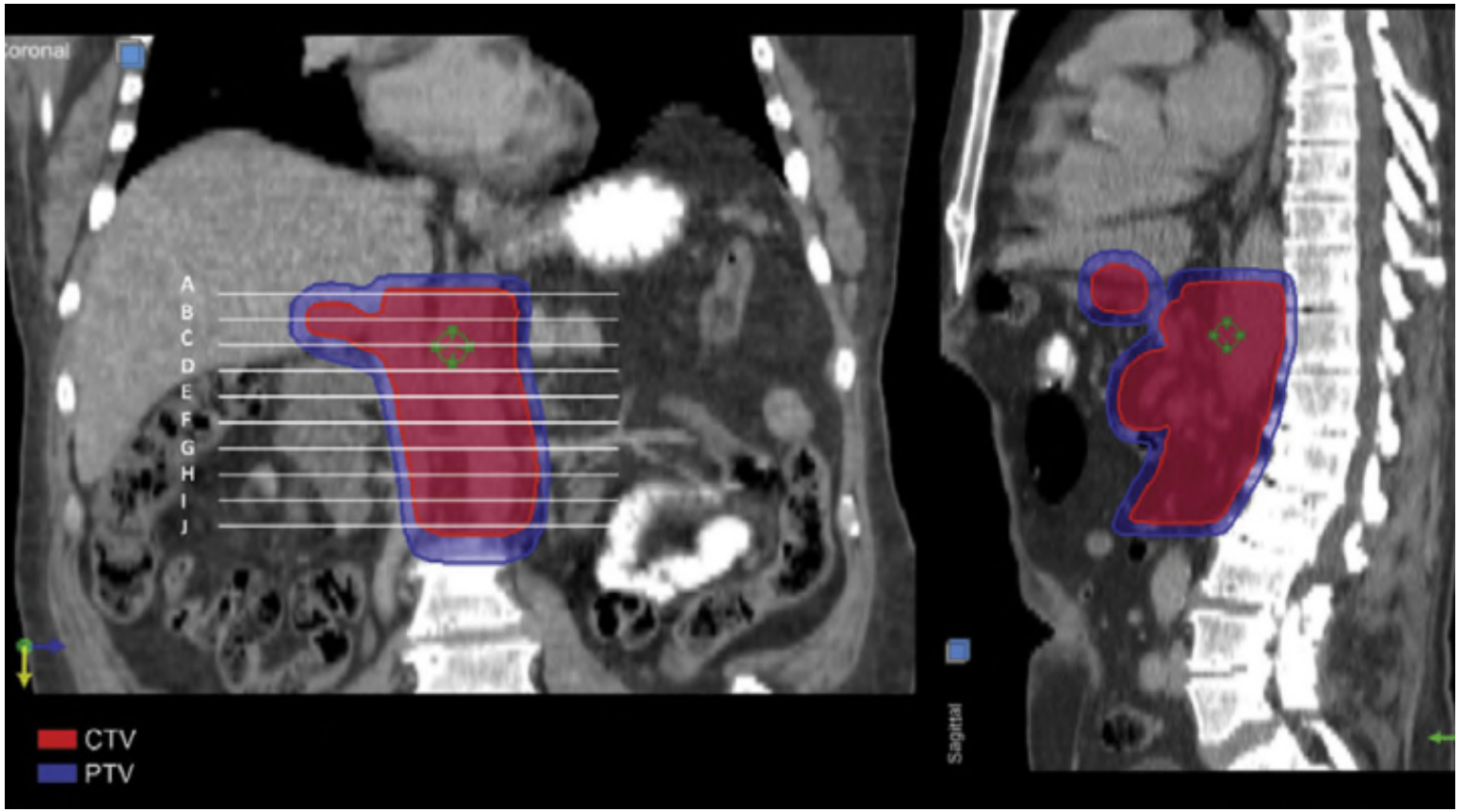
PREOPANC-1: A TNT-like Approach for Borderline Resectable Pancreatic Cancer





Verseteijne, et al, *J Clin Oncol*, 2020.

Radiation Volumes for Conventionally Fractionated RT



- Chemoradiation (45 Gy to the elective lymph nodes, 54 Gy to the primary lesion in 30 fractions delivered via simultaneous integrated boost or sequential boost)

- CTV includes:
  - Primary pancreatic tumor
  - SMA origin with 7mm margin
  - SMA and SMV vessels adjacent to the pancreatic head
  - Enlarged LN, +/- celiac axis depending on tumor location
  - Carve out bowel and bone.
  - *If the patient is definitely going to surgery, it is okay to leave out the elective nodal regions.*
  - *However, we often include elective nodes in case the patient does not go to surgery.*

- Daily IGRT with Respiratory gating (i.e. End expiration breath hold) if tumor motion > 1.0cm

Goodman, et al. *Int J Radiat Oncol Biol Phys.* 2012.

Near Complete Response to Chemoradiation

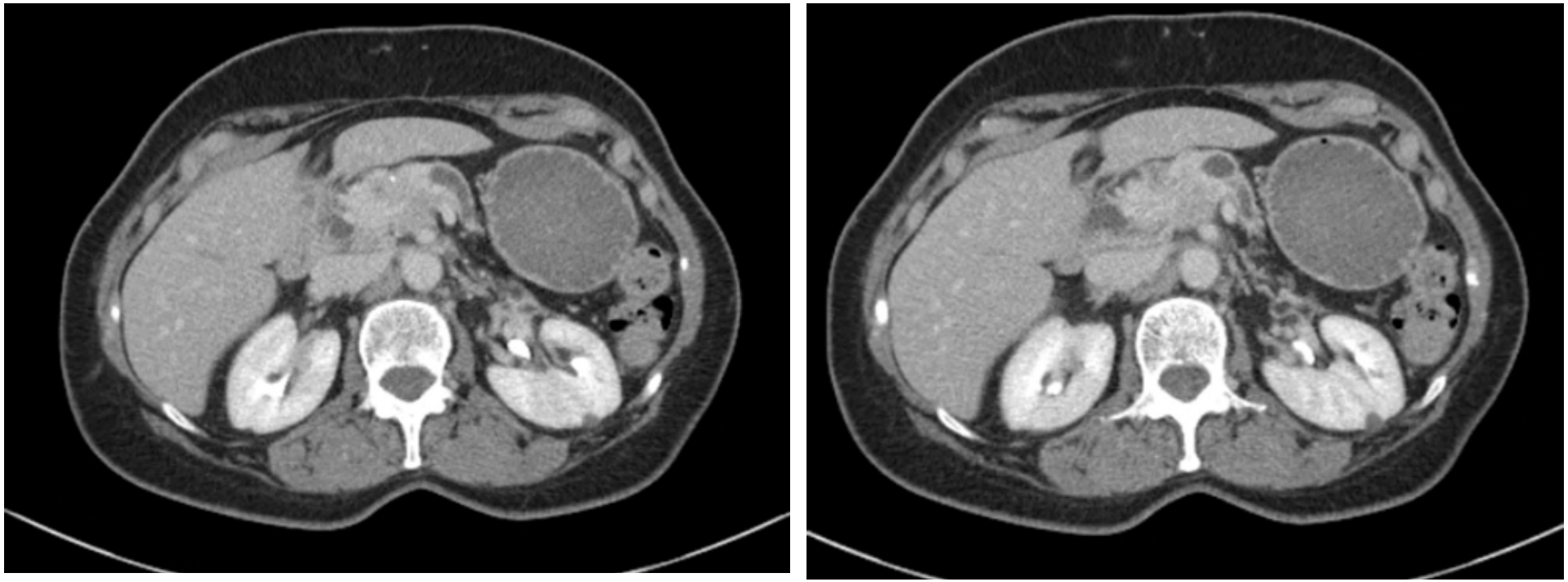
- After completing chemoradiation, she underwent a Whipple with Dr. Singh.
- Pathology demonstrated a near complete response!
    - 0.2cm tumor confined to the pancreas with a significant treatment response.
    - Negative margins
    - 0/25 LNs
    - ypT1aN0

Case 1 – Borderline Resectable Pancreatic Cancer

- Patient received concurrent radiotherapy (50.4 Gy, 28 fractions from April to June) and capecitabine treatment
- Whipple surgery in July
  - Extensive residual moderately differentiated ductal adenocarcinoma (3.9 centimeters) of the head of the pancreas with involvement of retroperitoneal surgical margin of resection (pR1).
  - Pathologic categories for staging: ypT2 ypN0 (one of thirteen lymph node involved by direct invasion)
- Patient now on active surveillance
  - October CA19-9 = 11.7

Case 2: Patient Mrs. B

- 72 yo W with locally advanced pancreatic cancer. CT showed a 3.1 cm hypoenhancing pancreatic head mass with involvement of the splenic vein, SMV and > 180 degree involvement of the SMA and celiac axis. Her CA 19-9 was 162.2. Endoscopic ultrasound was performed and biopsy showed pancreatic adenocarcinoma. She received 12 cycles of FOLFIRINOX and then underwent laparoscopy which showed no metastatic disease. She was referred to radiation oncology for definitive treatment.



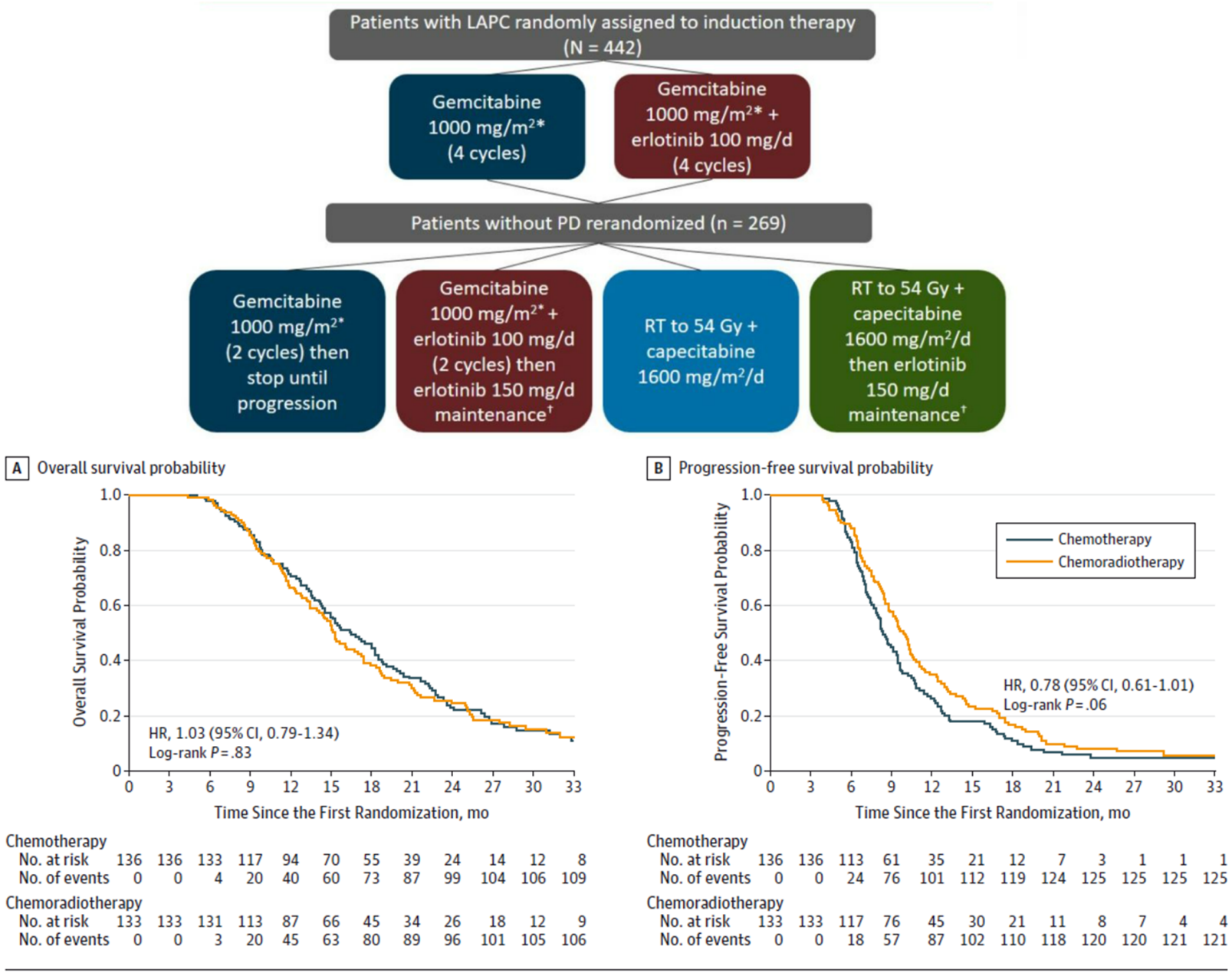
CT- October 2022

Randomized Trials of Conventionally Fractionated Radiation for Locally Advanced Pancreatic Cancer

Study	N	Treatment Arms	mOS (months)	2 year OS
FFCD-SFRO	119	60 Gy/30 fx + 5-FU + cisplatin → Gemcitabine	8.6	About 15%
		Gemcitabine	13, p = 0.03	About 21%
ECOG 4201	74	50.4 Gy/28 fx → Gemcitabine	11.1	12%
		Gemcitabine	9.2, p = 0.017	5%
LAP-07	269	Gemcitabine +/- Erlotinib → 54 Gy + Capecitabine	15.2	About 25%
		Gemcitabine	16.5, NS	

Reyngold et al, *Radiat Oncol*, 2019.

LAP-07



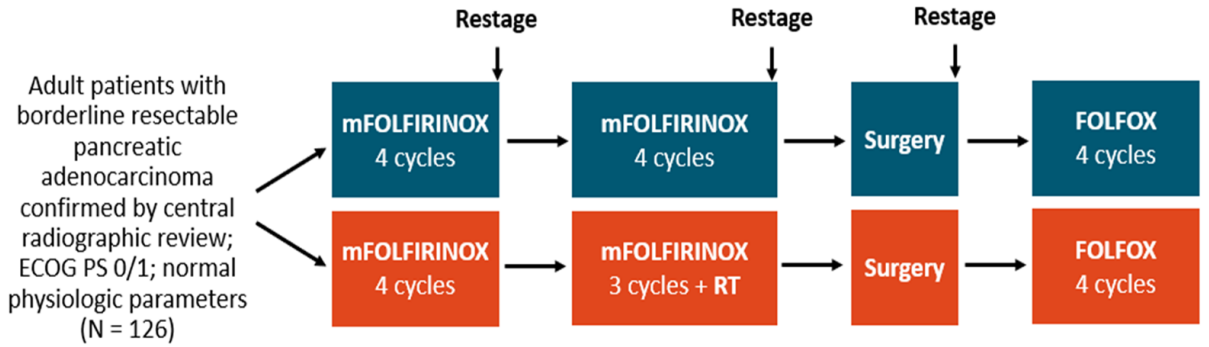
Hammel, et al, *JAMA*. 2017.

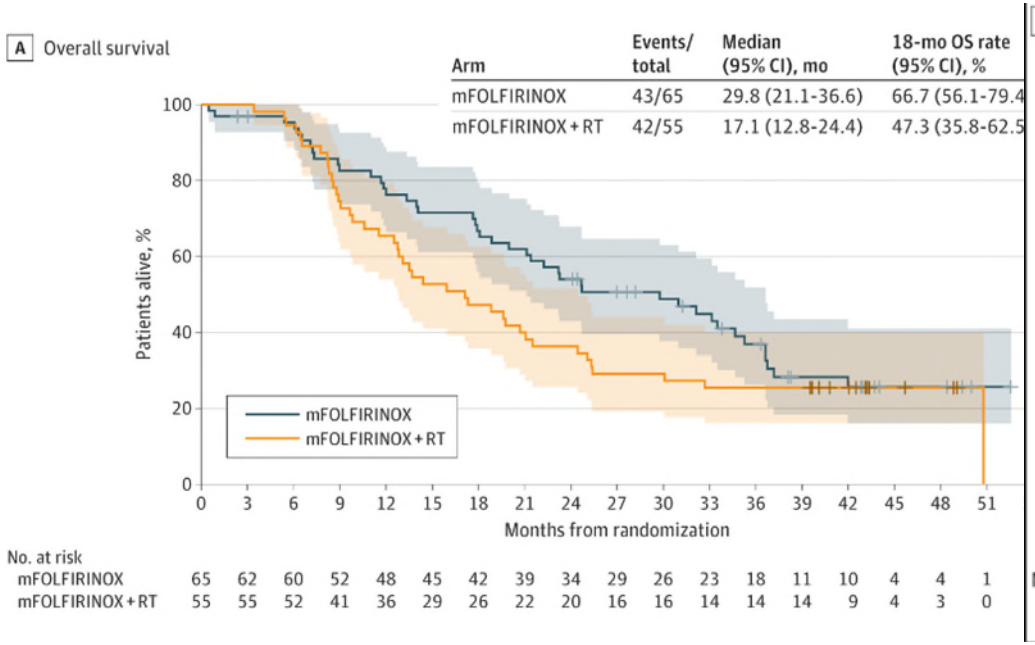
Why treat with SBRT for Pancreatic Cancer?

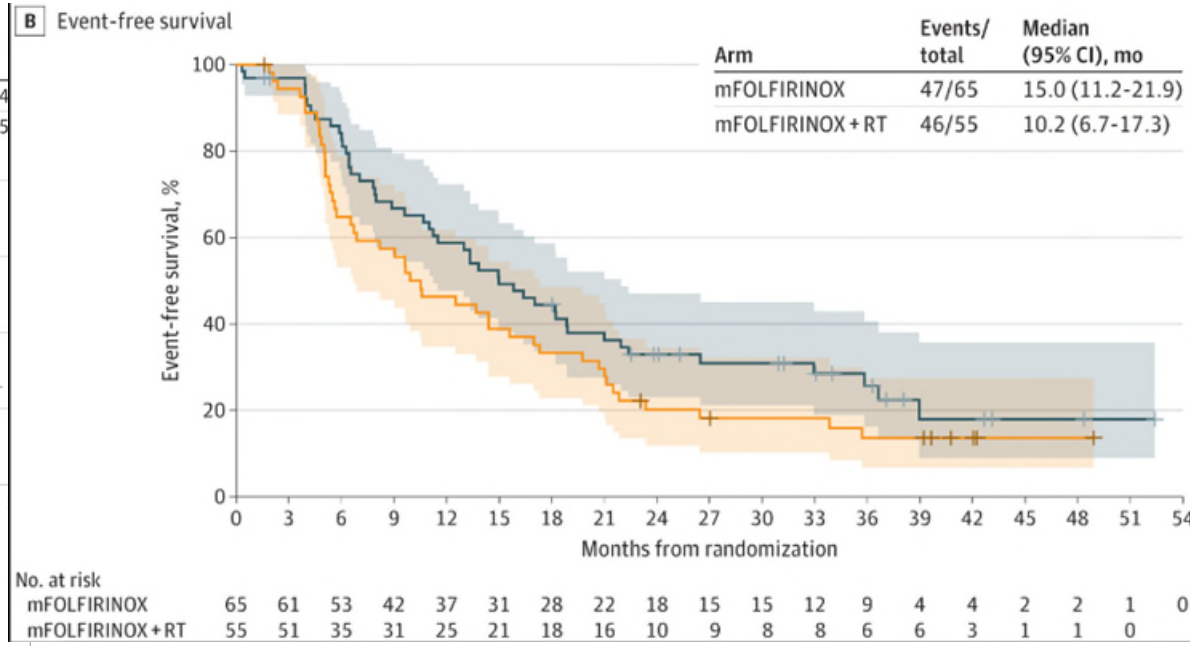
- Conventional chemoradiotherapy is hard to tolerate
  - 50-54 Gy over 6 weeks
  - Concurrent 5-FU or Capecitabine
  - Acute GI toxicities in up to 30% of patients

- Local control is important in advanced pancreatic cancer
  - To treat pain, bleeding, obstructive jaundice
  - Due to its higher BED (Biologically Effective Dose), SBRT can offer equal or better LC with less acute toxicity, and shorter treatment course

ALLIANCE A021501



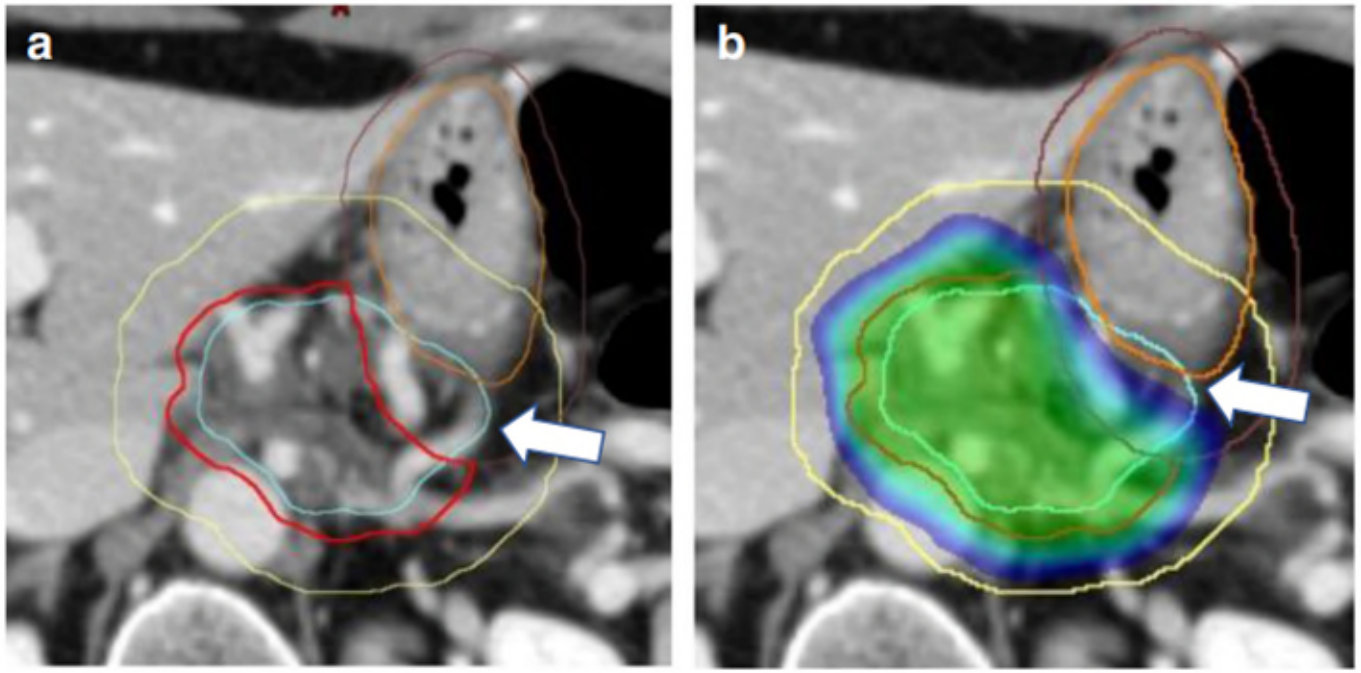




- **Chemoradiation (mFOLFIRINOX + SBRT) leads to worse OS and EFS**
- ****The dose of SBRT was too low to have a biologic effect.** A much higher biologically effective dose (BED) is needed to achieve tumor ablation.**

Katz et al, *JAMA Oncol*, 2022.

Hypofractionated Radiation



- Advanced organ motion management, cone beam CT (CBCT) image guidance, and adaptive planning techniques enable delivery of ablative doses of radiation (> = 100Gy BED)
- SIB approach (60 Gy in 15 fractions (4 Gy/fx) to the tumor with 0.5cm margin, and 37.5 Gy in 15 fractions (2.5 Gy/fx) to a larger volume which includes GTV + 1cm margin + celiac axis + SMA + portal vein
- **PRV (planning organ at risk volume) for bowel, duodenum and stomach** help ensure that the critical max point dose for these organs are achieved.

Reyngold et al, *Radiat Oncol*, 2019.

CLINICAL INVESTIGATION

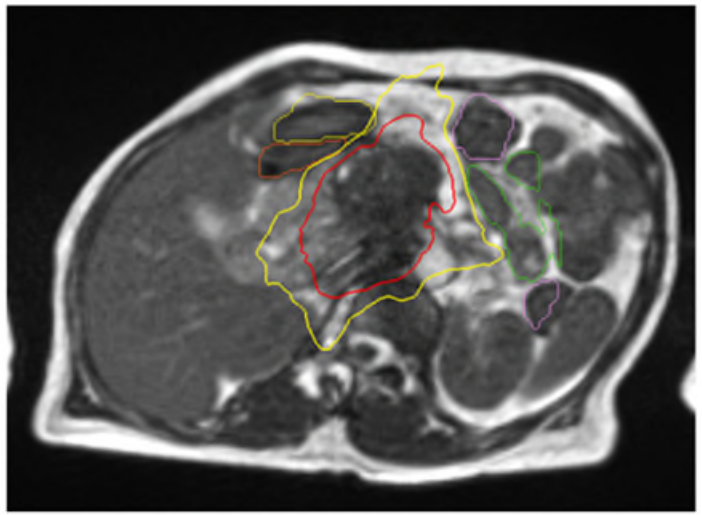
A Multi-Institutional Phase 2 Trial of Ablative 5-Fraction Stereotactic Magnetic Resonance—Guided On-Table Adaptive Radiation Therapy for Borderline Resectable and Locally Advanced Pancreatic Cancer

Parag Jitendra Parikh, BSE, MD,[*] Percy Lee, MD,[†] Daniel A. Low, PhD,[‡] Joshua Kim, PhD,[*] Kathryn E. Mittauer, PhD,[§] Michael F. Bassetti, MD, PhD,[‖] Carri K. Glide-Hurst, PhD,[‖] Ann C. Raldow, MD, MPH,[¶] Yingli Yang, PhD,[¶] Lorraine Portelance, MD,[#] Kyle R. Padgett, PhD,[#] Bassem Zaki, MD,[**] Rongxiao Zhang, PhD,[**] Hyun Kim, MD,[††] Lauren E. Henke, MD,[††] Alex T. Price, MS,[††] Joseph D. Mancias, MD, PhD,[‡‡] Christopher L. Williams, PhD,[‡‡] John Ng, MD,[§§] Ryan Pennell, PhD,[§§] M. Raphael Pfeffer, MD,[‖‖] Daphne Levin, PhD,[‖‖] Adam C. Mueller, MD, PhD,[¶¶] Karen E. Mooney, PhD,[¶¶] Patrick Kelly, MD, PhD,[##] Amish P. Shah, PhD,[##] Luca Boldrini, MD, PhD,[***] Lorenzo Placidi, PhD,[***] Martin Fuss, MD,[†††] and Michael D. Chuong, MD[§]

[*]*Henry Ford Health — Cancer, Detroit, Michigan;* [†]*City of Hope National Medical Center, Los Angeles, California;* [‡]*Department of Radiation Oncology, University of California, Los Angeles, California;* [§]*Miami Cancer Institute, Baptist Health South Florida, Miami,*

SMART Trial- Dr. Percy Lee and colleagues

- MRgRT in patients with locally advanced pancreatic cancer
- Prospective, Phase II Study, N=136
- Prescribed dose- 50Gy in 5 Fx
  - Real-time MRI imaging used through out treatment
  - On-table adaptive re-planning will be used when indicated



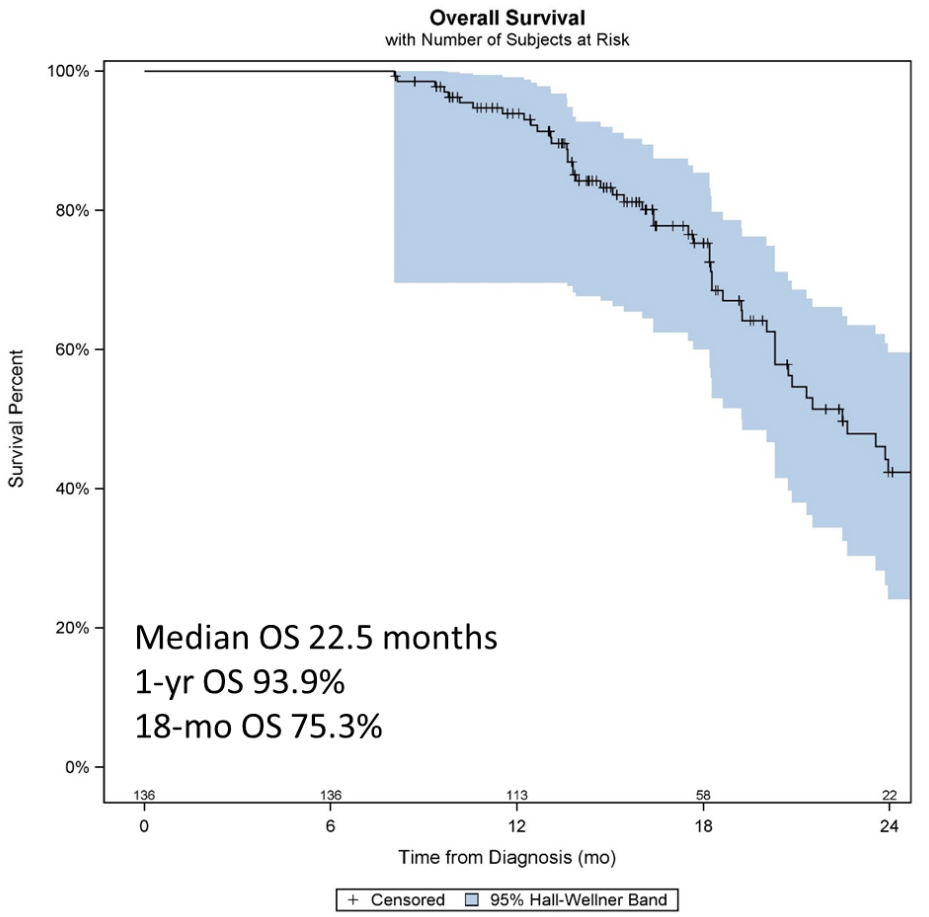
Red – 50 Gy isodose
Yellow – 33 Gy isodose
Light Yellow – Stomach
Orange – Duodenum
Purple – Colon
Green – Small Bowel

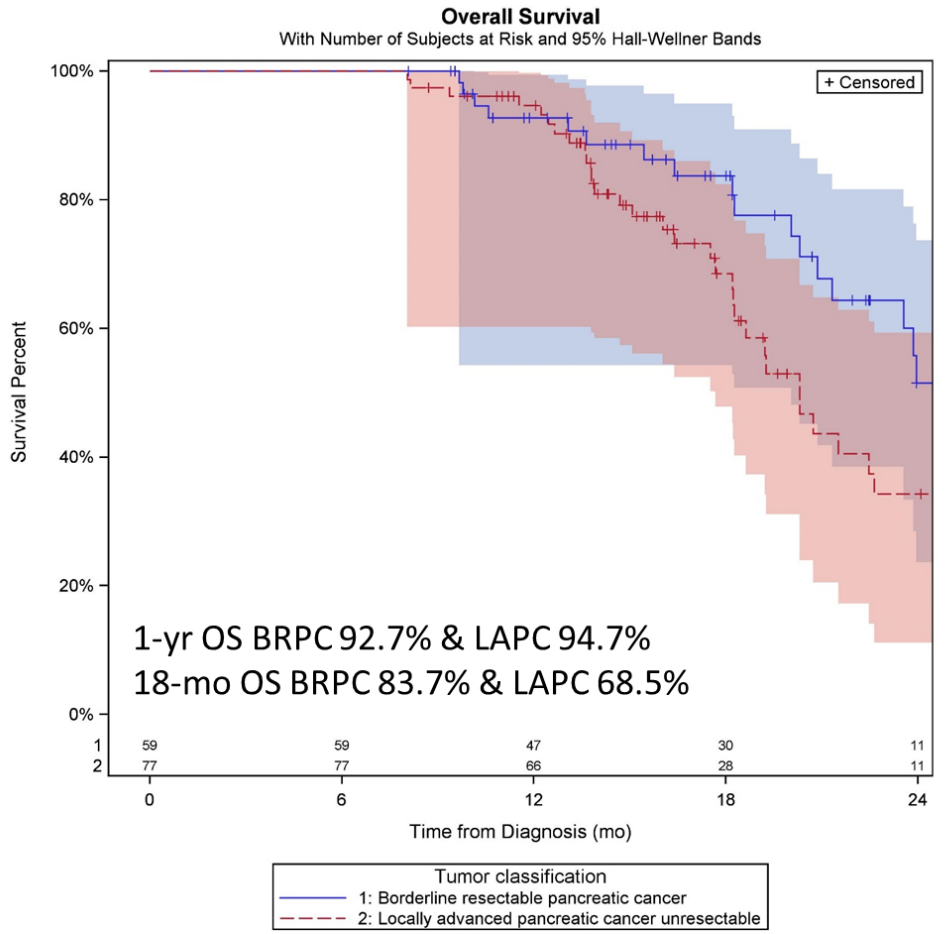
- **Primary Outcome-** GI toxicity (≥ grade 3) within 90 days (CTCAE criteria)

- **Secondary Outcomes**
  - Overall survival
  - Distant progression-free survival
  - Patient-reported QoL

https://clinicaltrials.gov/ct2/show/NCT03621644

SMART Trial - Outcomes





Gr 3+ GI Toxicity Definitely Related to SMART @ 90 Days	
0/136 patients	0%

90-day toxicity	Definitely	Probably	Possibly
Grade 3	0	Abdominal pain (3)	Abdominal pain (2)
			Bleed (1)
			Diarrhea (1)
			Chyle leak after Whipple (1)
Grade 4	0	0	Abdominal pain post surgery (1) Bleed (1)
Grade 5	0	0	Bleed after portal vein resection/reconstruction (2)*

Take-home points

- Most patients with borderline resectable pancreatic cancer receive chemotherapy followed by chemoradiation prior to surgery.
  - The concept of a TNT-like approach to pancreatic cancer is based on the PREOPANC-1 study.

- Many patients with locally advanced pancreatic cancer could benefit from hypofractionated radiation.
  - Dose escalation to 60-67.5 Gy in 15 fractions to the primary tumor in order to deliver a higher BED (biologic effective dose) than conventional fractionation.

- Dose escalation can be achieved safely with MR-guided radiation.
  - The safety of this approach for pancreatic cancer was demonstrated in the SMART trial.
  - MR-Linac will change the way we practice GI radiation oncology and an MR-Linac program is currently being developed at City of Hope by Dr. Percy Lee.

Case 1: Patient Mrs. G

- 60 yo W w/ Stage III (cT4 N0 M0) borderline resectable pancreatic cancer. CT showed a 2.1 x 3.1cm primary tumor with infiltrative soft tissue encasing < 180 degrees of the SMA. She received 8 cycles of FOLFIRINOX. Repeat imaging showed that the pancreatic mass abuts the posterior margin of the superior mesenteric artery with < 180 degrees of encasement. She is referred to Radiation Oncology for consultation. What treatment should she receive now?