Multidisciplinary Treatment of Pancreatic Cancer: Are we still rolling the rock uphill?

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Chief, Division of Surgical Oncology

James Comprehensive Cancer Center

The Ohio State University
Wexner Medical Center

The myth of Sisyphus

Pancreatic Cancer: Epidemiology

Estimated Deaths

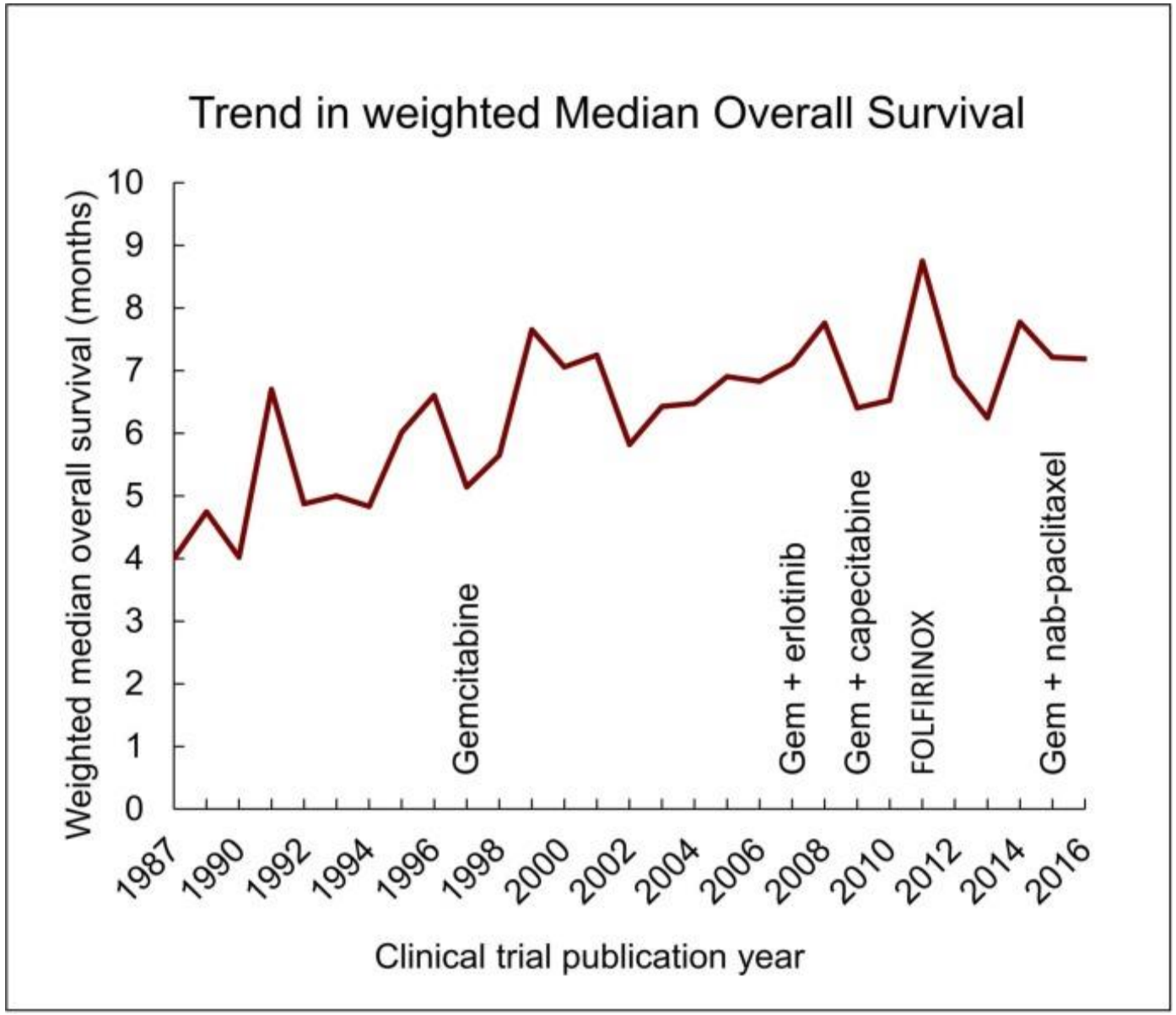
Males			Females		
Lung & bronchus	84,590	27%	Lung & bronchus	71,280	25%
Colon & rectum	27,150	9%	[illegible]	40,610	14%
Prostate	26,730	8%	[illegible]olon & rect	23,110	8%
Pancreas	22,300	7%	[illegible]ncreas	20,790	7%
Liver & intrahepatic bile duct	19,610	6%	[illegible]ary	14,080	5%
Leukemia	14,300	4%	Uterine corpus	10,920	4%
Esophagus	12,720	4%	Leukemia	10,200	4%
Urinary bladder	12,240	4%	Liver & intrahepatic bile duct	9,310	3%
Non-Hodgkin lymphoma	11,450	3%	Non-Hodgkin lymphoma	8,690	3%
Brain & other nervous system	9,620	3%	Brain & other nervous system	7,080	3%
All Sites	**318,420**	**100%**	**All Sites**	**282,500**	**100%**

FIGURE 1. Ten Leading Cancer Types for the Estimated New Cancer Cases and Deaths by Sex, United States, 2017.
Estimates are rounded to the nearest 10 and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

3rd Leading cause of Cancer Death in the United States

CA Cancer J Clin 2017;67:7-30

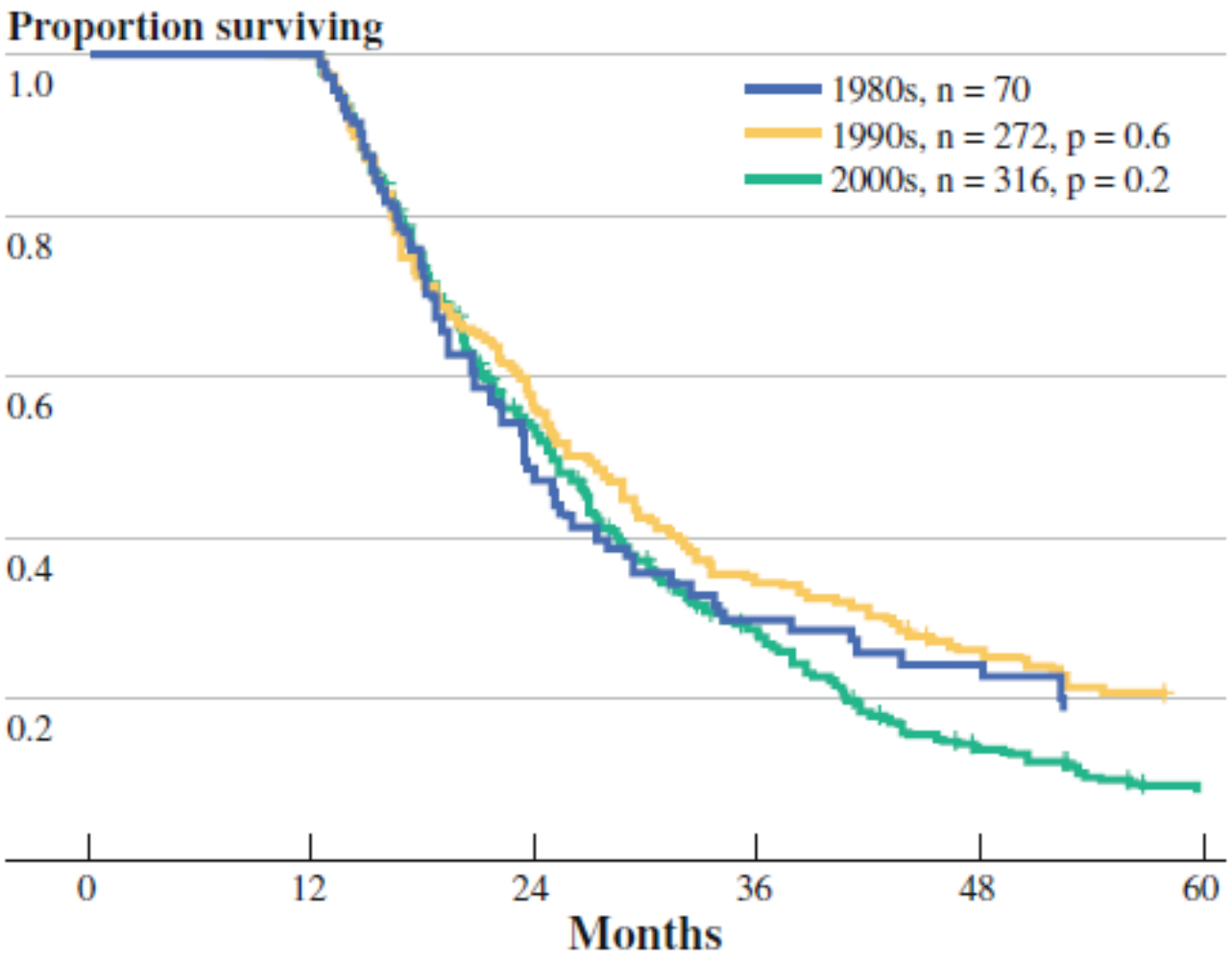
Have we made a difference?



5-year survival ~ 8.5%

Hall BR et al. Oncotarget 2018

Survival after Surgery



Winter, *Annals Surg Onc* 2012

Pancreas Cancer: Survival by Stage

	Survival		
	Unresected	Resected	All Pts
IA	6.8%	24.1%	10%
IB	6.1%	20.6%	9.1%
IIA	6.2%	15.4%	8.1%
IIB	6.7%	12.7%	9.7%
III	7.2%	10.6%	7.7%
IV	2.5%	4.5%	2.5%

Take home message

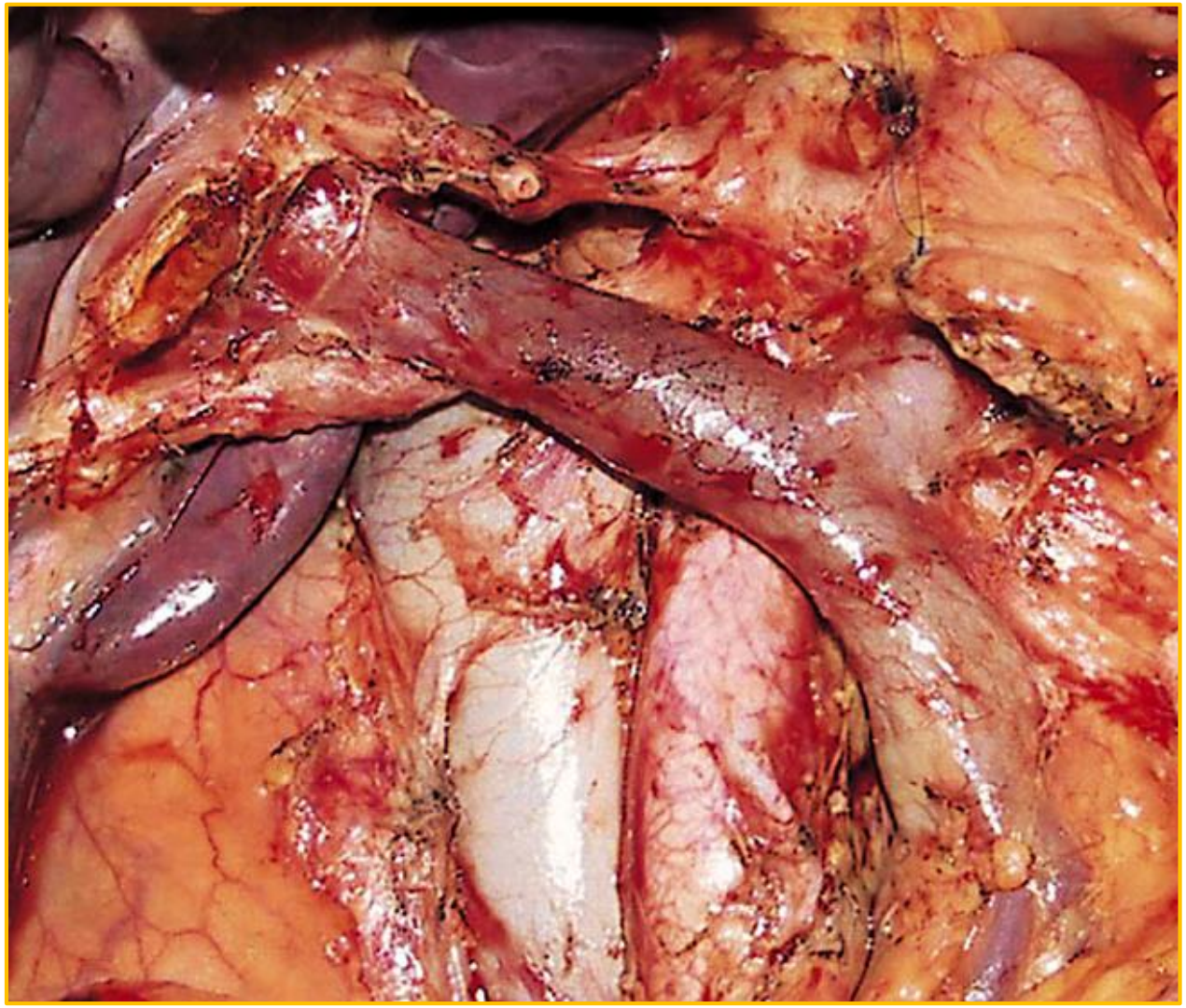
In the absence of better options, surgical resection has played an outsized role in the management of PDAC

As newer and more effective treatments emerge,
the role of surgical resection may be evolving - **and expanding**

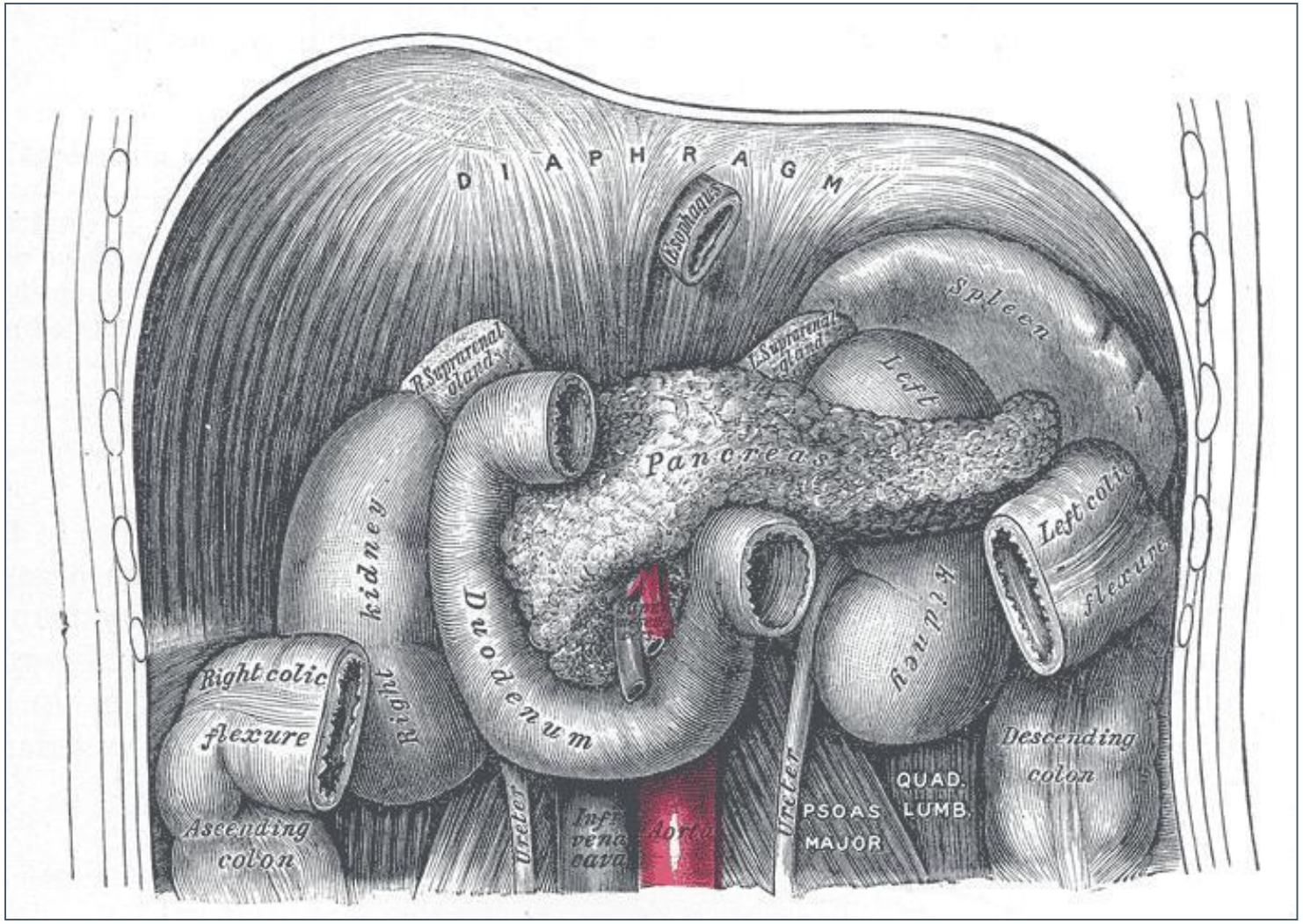
The Issue

Operative resection is still:

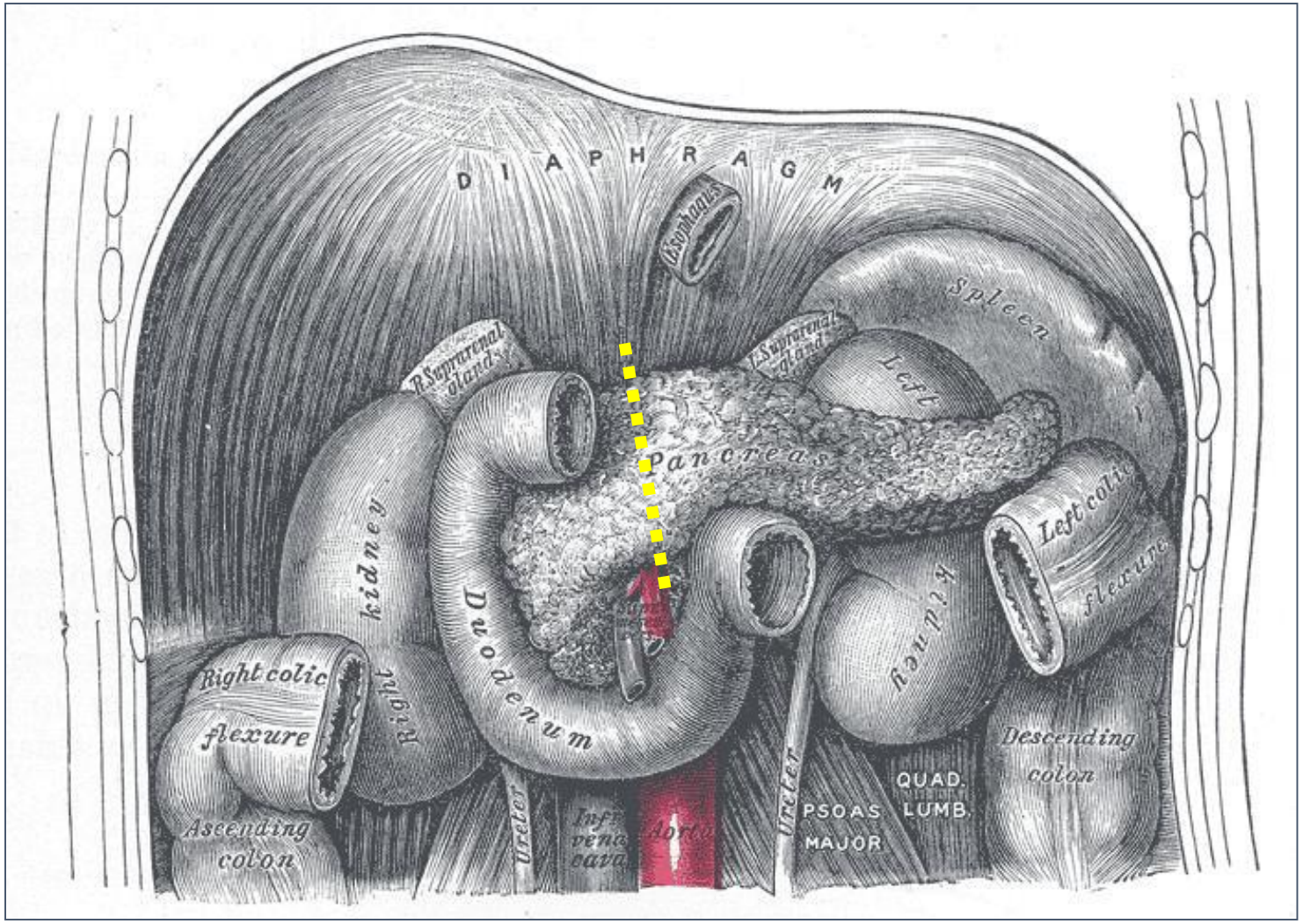
- The only pathway to cure
- Available to so few
- A risky undertaking



What do we do?


DIAPHRAGM
Œsophagus
Spleen
R. Suprarenal gland
L. Suprarenal gland
Left
Pancreas
kidney
Duodenum
Left colic
flexure
kidney
Right colic
flexure
Right
Descending colon
Ascending colon
Ureter
Inf. vena cava
Aorta
Ureter
QUAD. LUMB.
PSOAS MAJOR

What do we do?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Ureter
Inf. vena cava
Aorta
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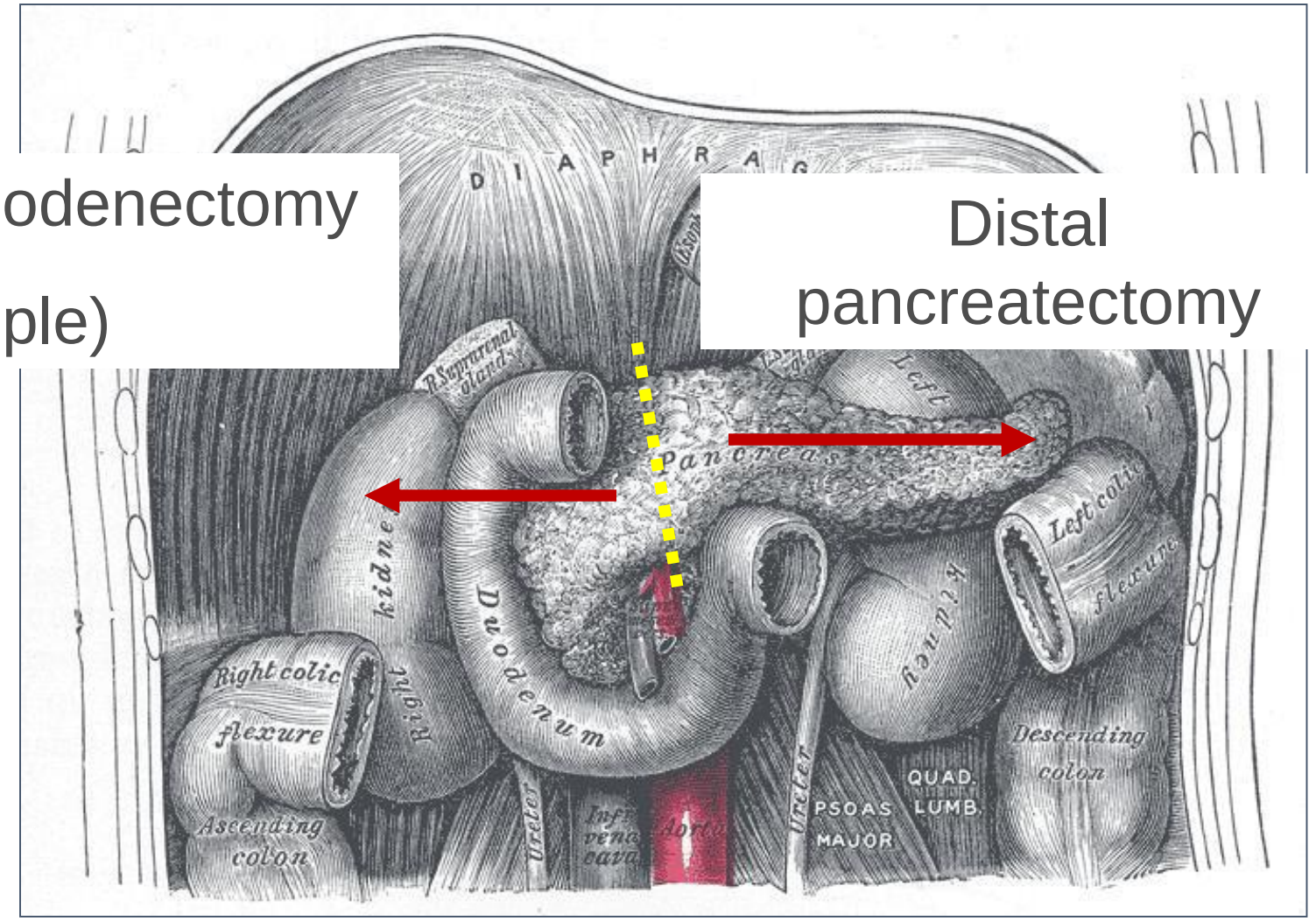
PSOAS MAJOR
QUAD. LUMB.

What do we do?
Simple! Only Two Things

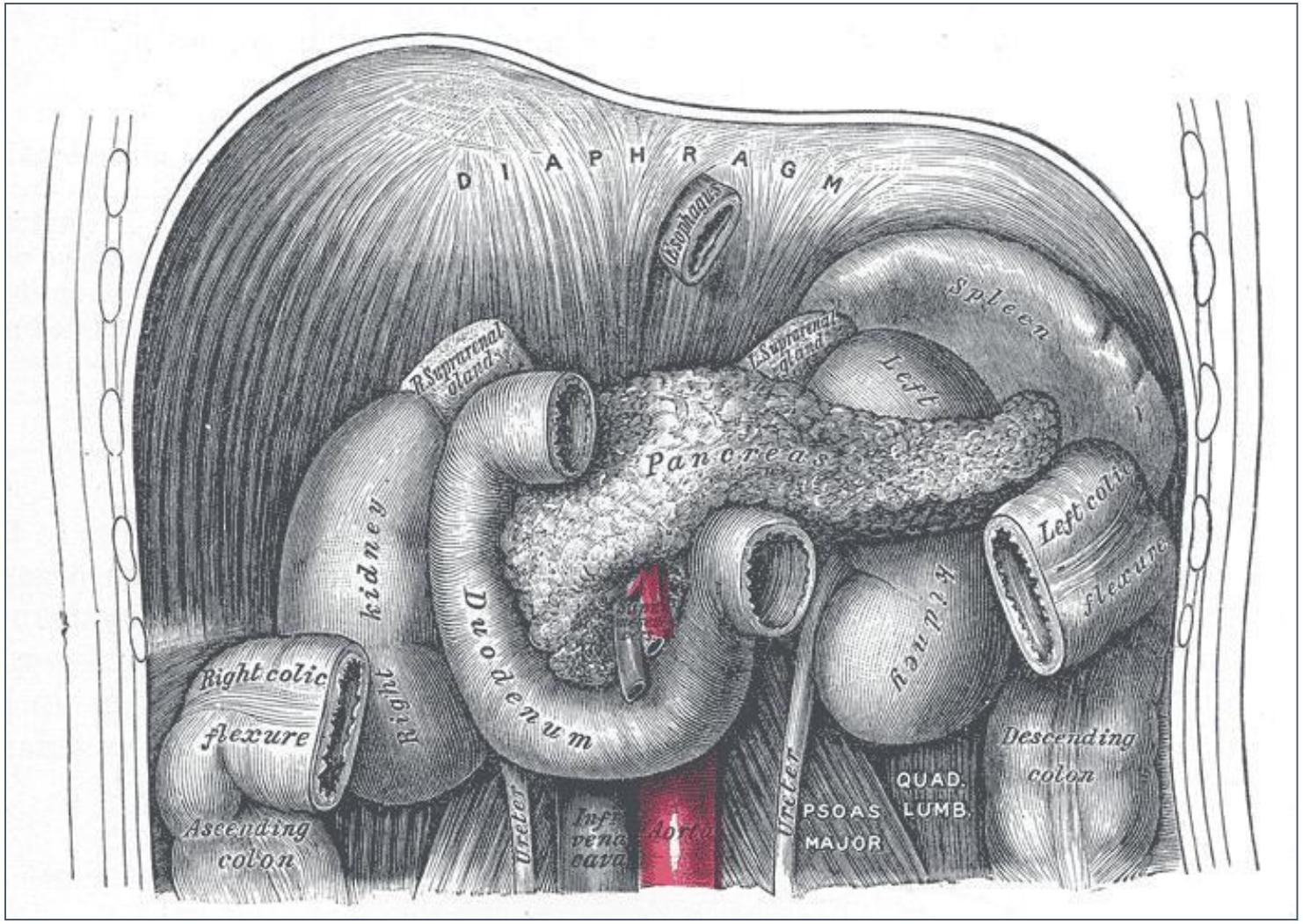
Pancreaticoduodenectomy

(Whipple)

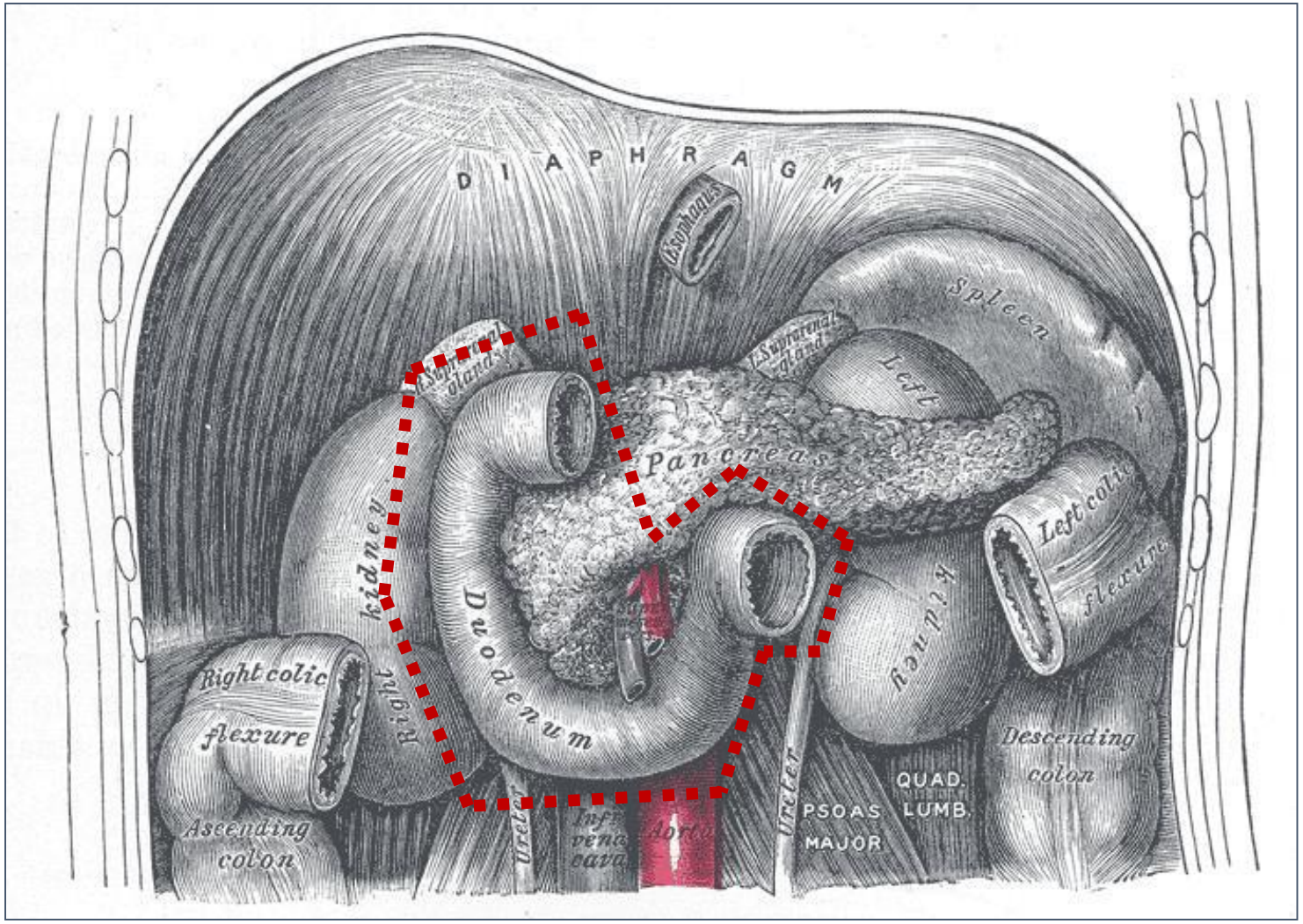
Distal pancreatectomy



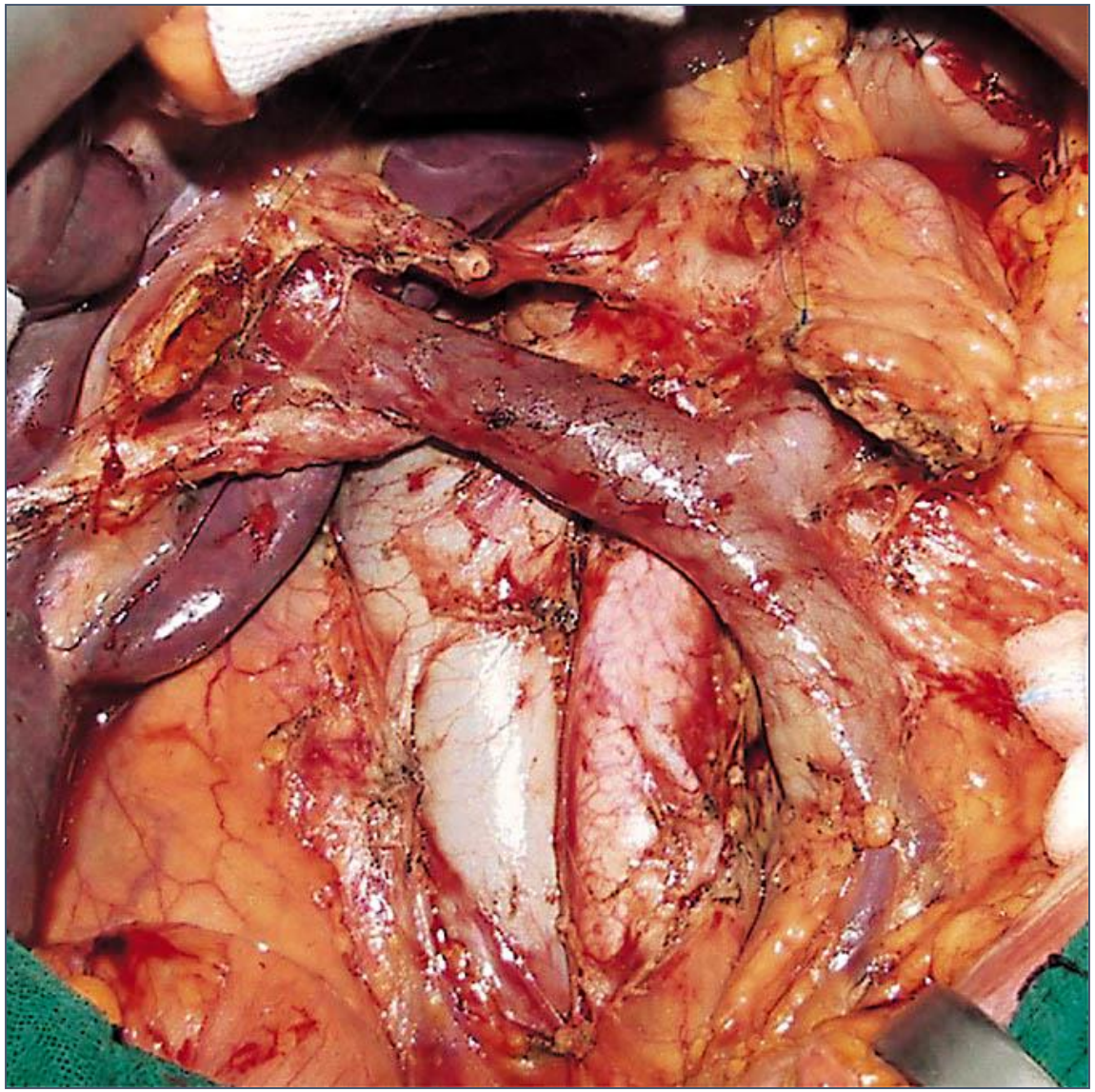
What you start with



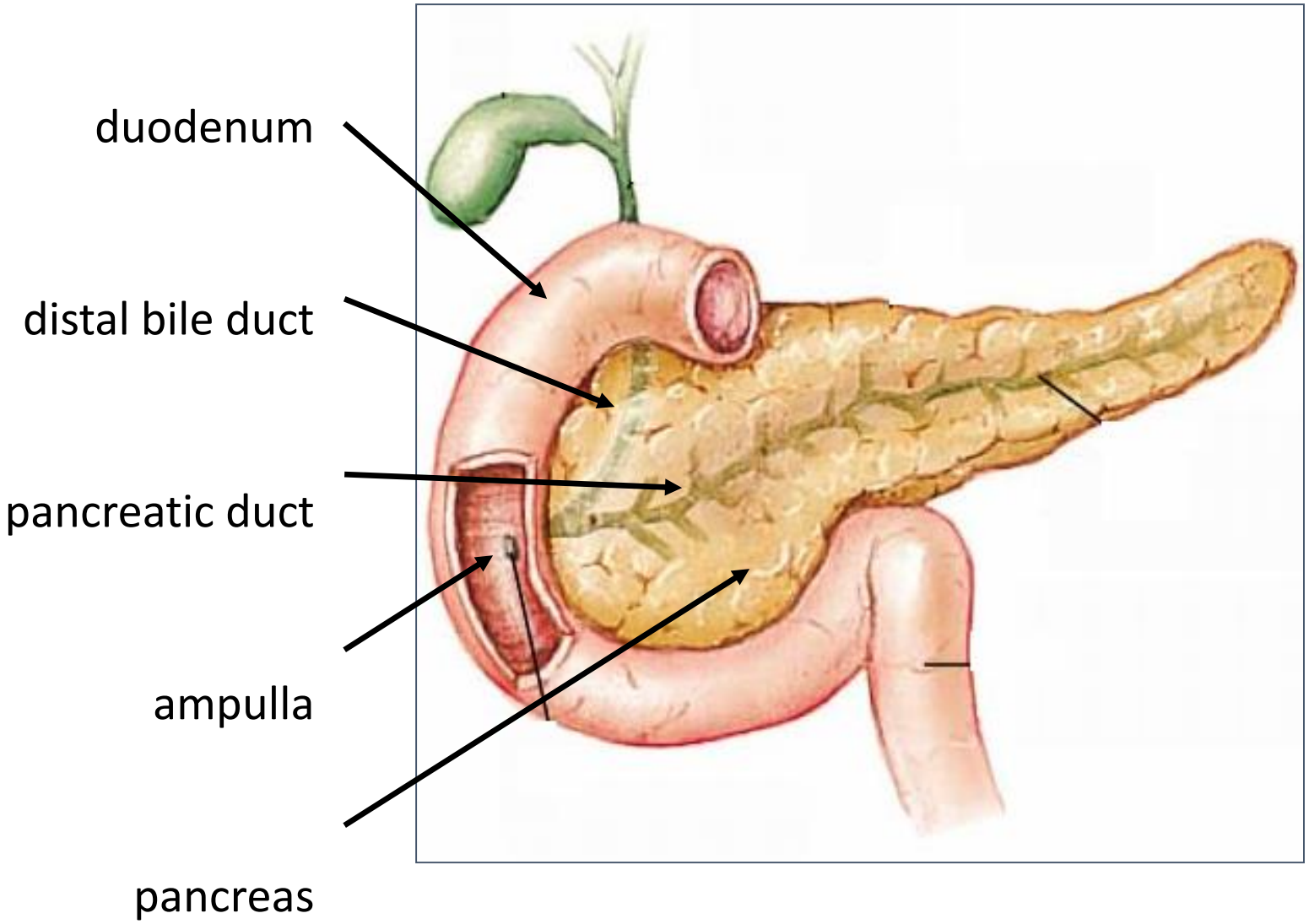
What we resect



What it looks like after we resect



The relevant anatomy



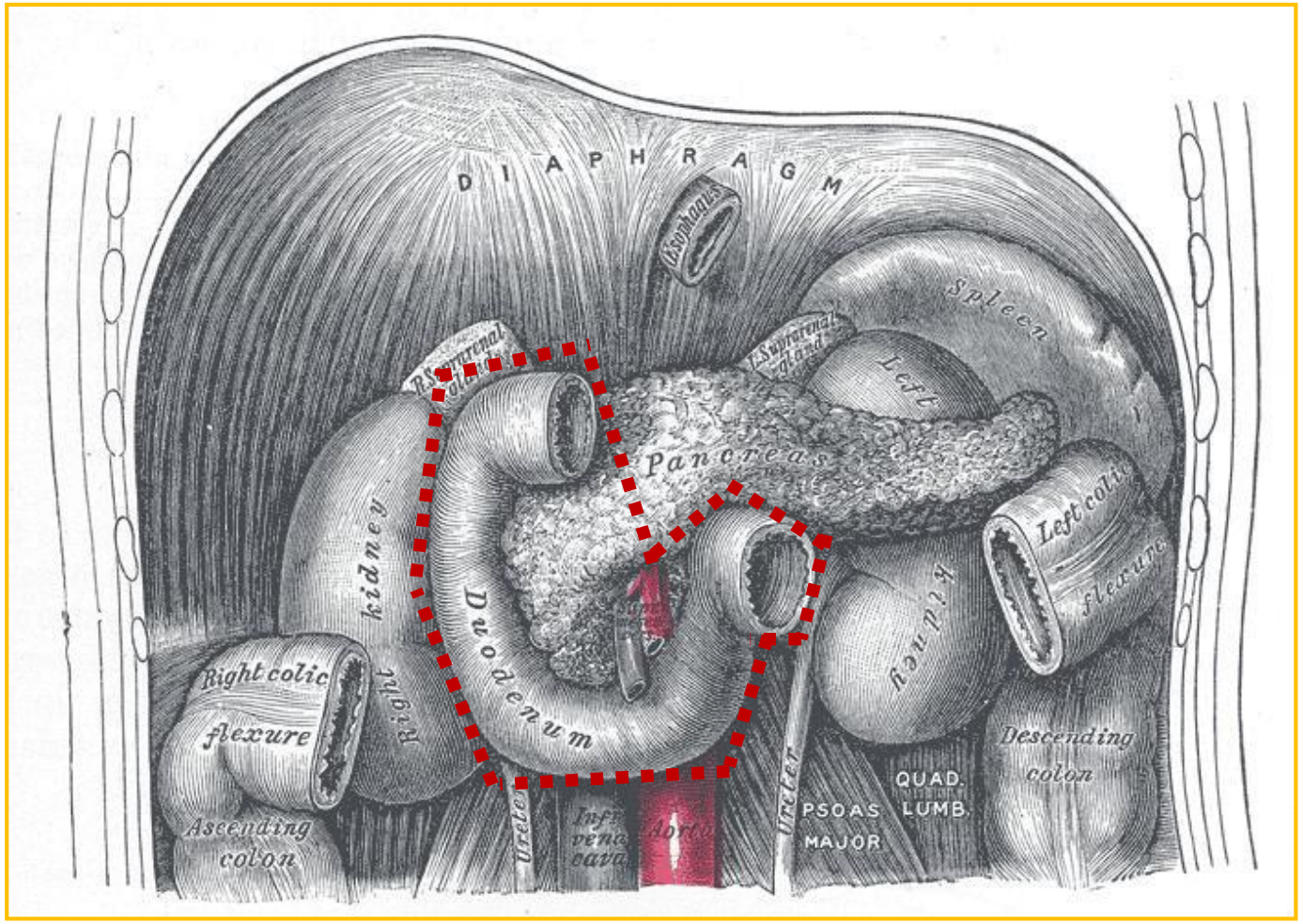
Paradigm

Potentially resectable

Borderline resectable

Locally advanced

Metastatic

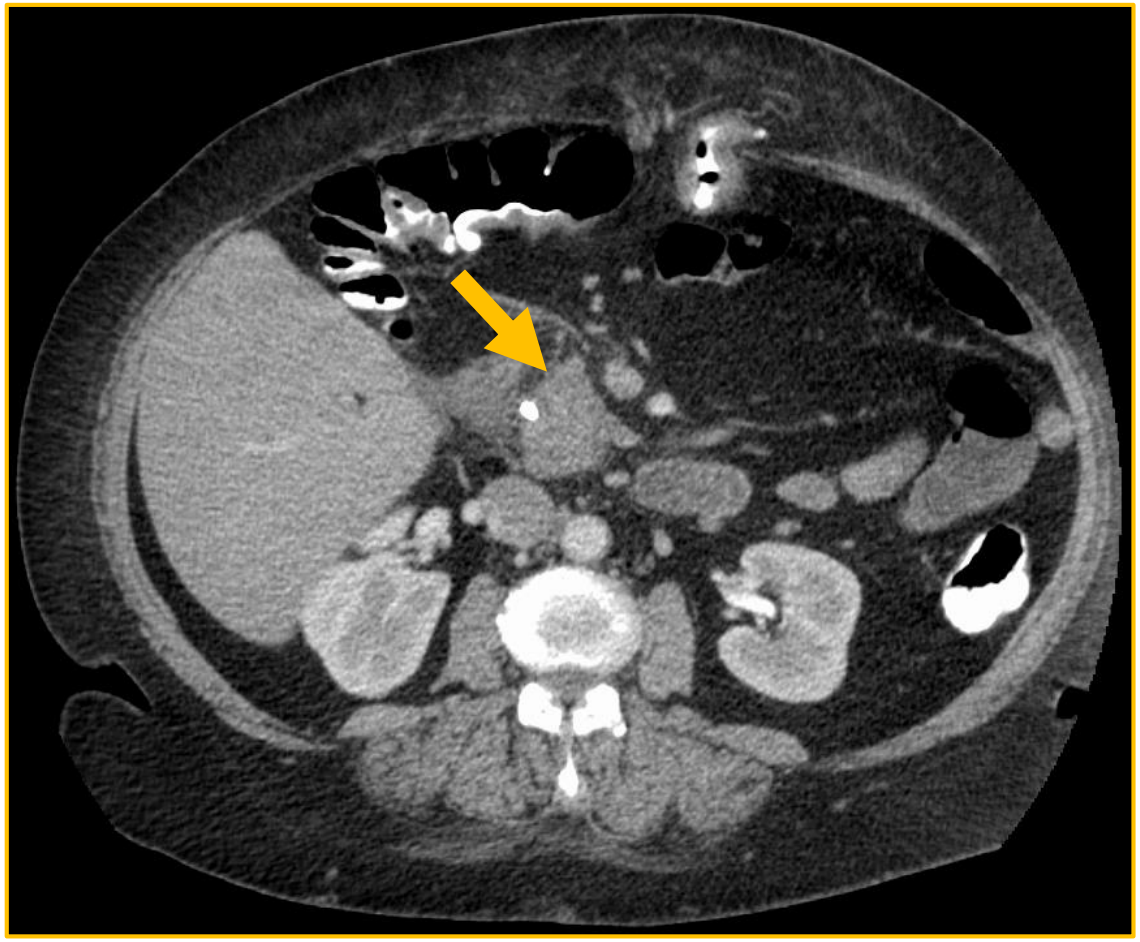


Potentially Resectable (10-20%)

no/minimal vascular involvement

(10-20% ultimately not resectable)

resection/adjuvant therapy or
neoadjuvant therapy/resection



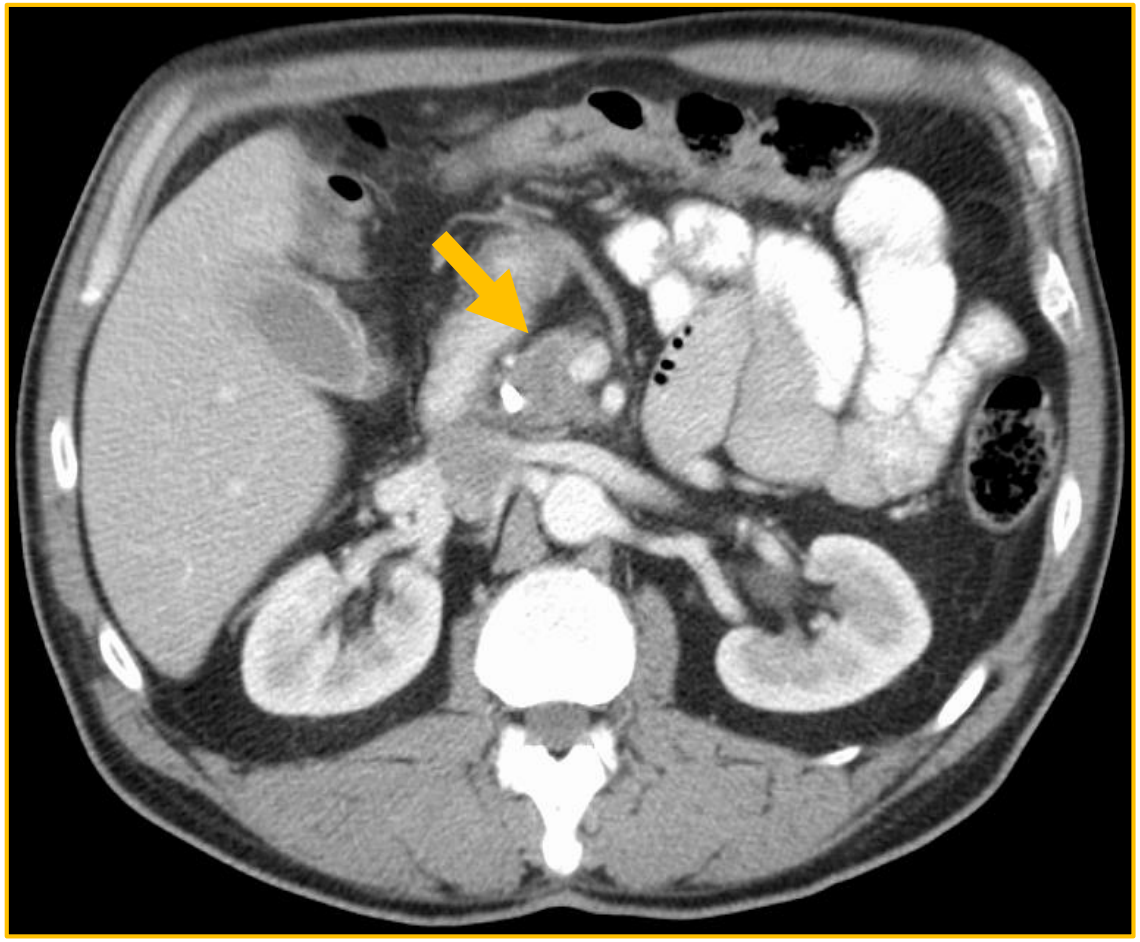
median survival 18-24 months

Borderline Resectable (10-20%)

reconstructable vascular involvement

30% ultimately not resectable

neoadjuvant therapy/resection

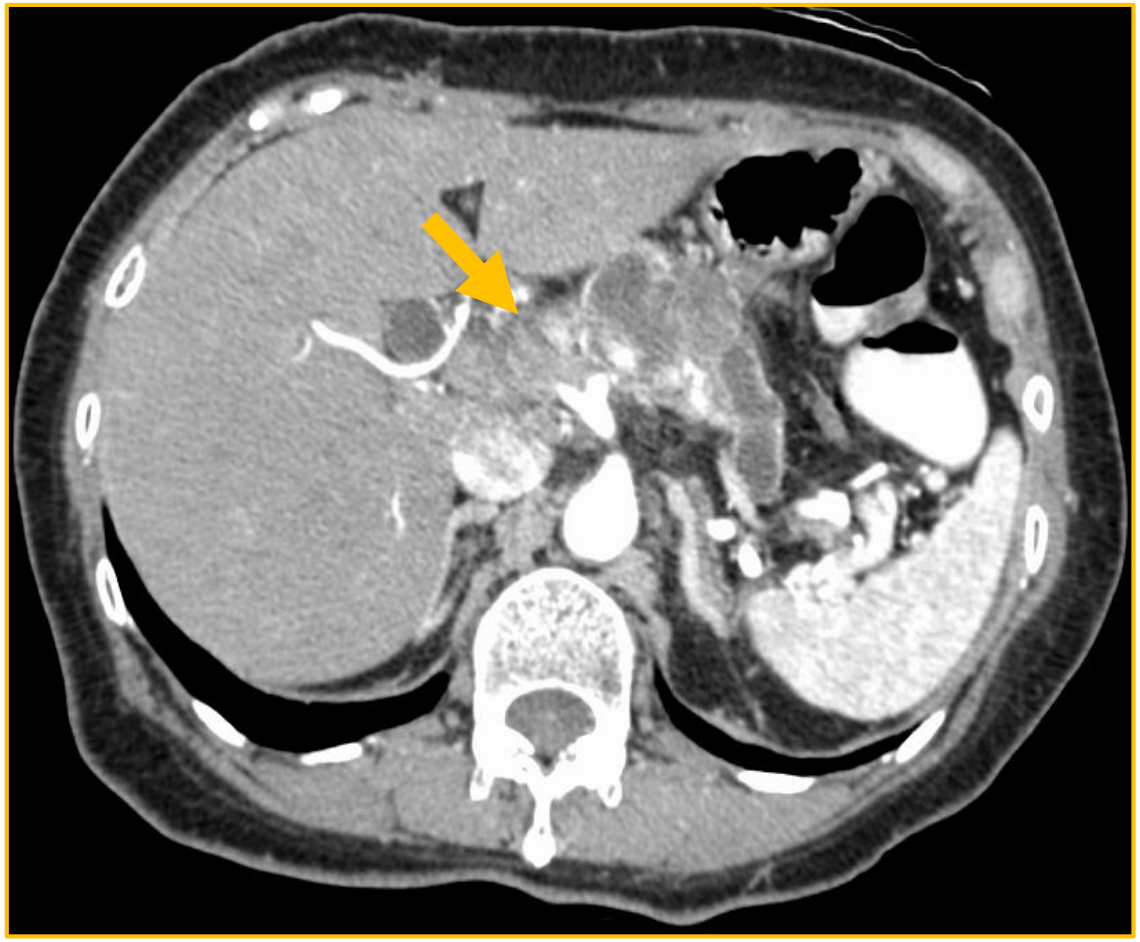


median survival 18-24 months

Locally Advanced (10-20%)

non-reconstructable vascular involvement

palliative chemotherapy/ radiation therapy

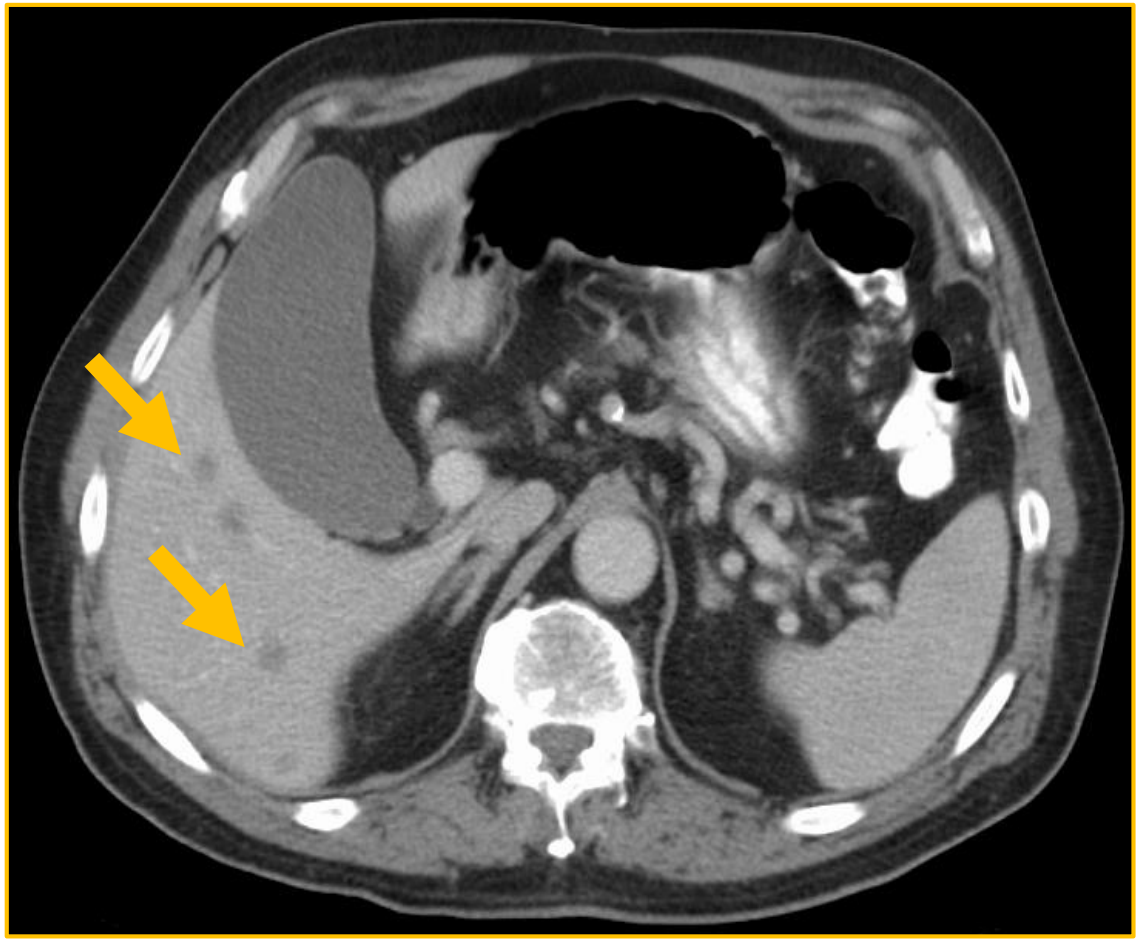


<u>median survival 8-12 months</u>

Metastatic (50-60%)

extrapancreatic involvement

palliative chemotherapy



<u>median survival 3-9 months</u>

Operative algorithm, until recently

potentially resectable

borderline resectable

} resection

locally advanced

metastatic

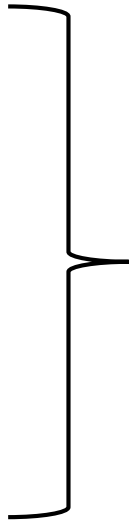
} **no resection**

Operative algorithm, recently

potentially resectable

borderline resectable

locally advanced



resection

metastatic

no resection

The reason for the shift

Survival benefit (11.1 vs. 6.8 mo) for FOLFIRINOX

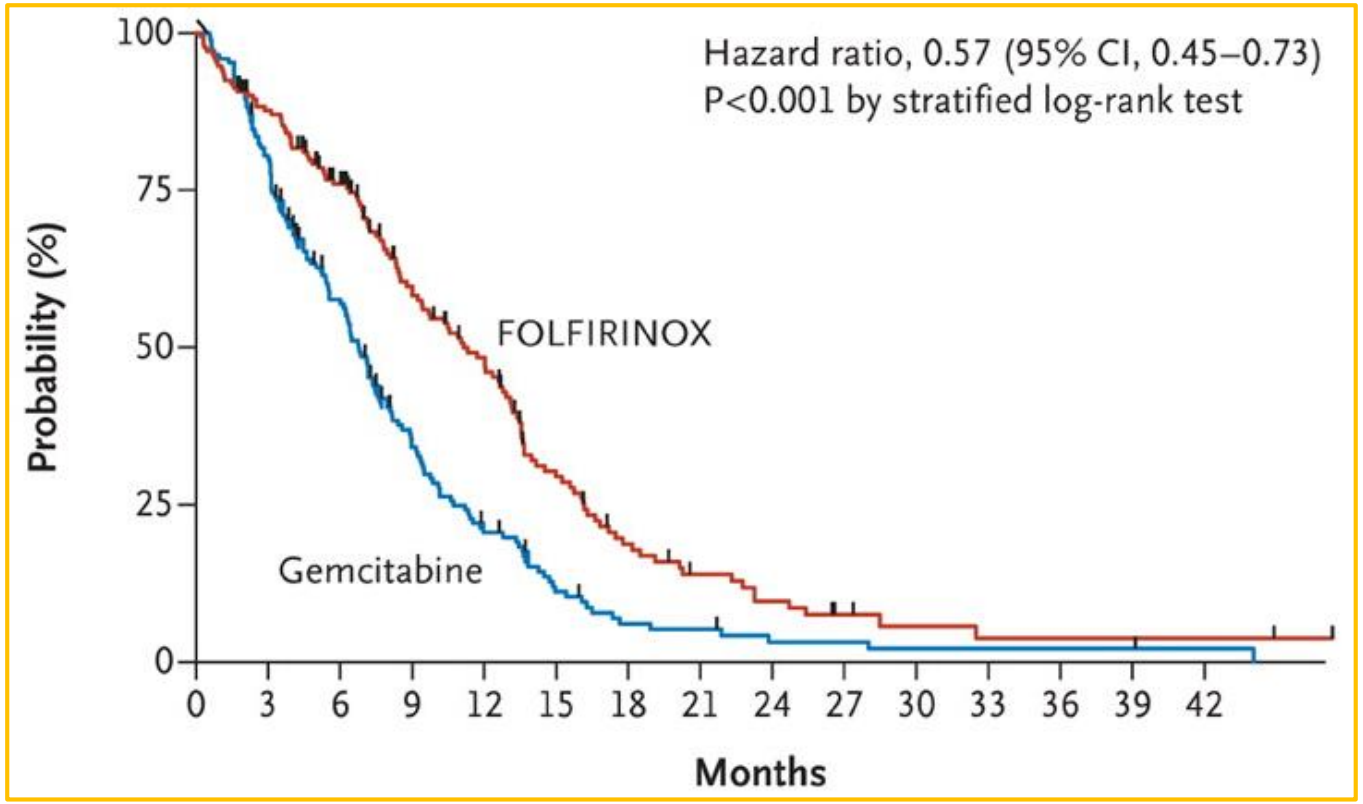
FOLFIRINOX

leucovorin (**FOL**inic acid)

5-**F**luorouracil

IRINotecan

OXaliplatin



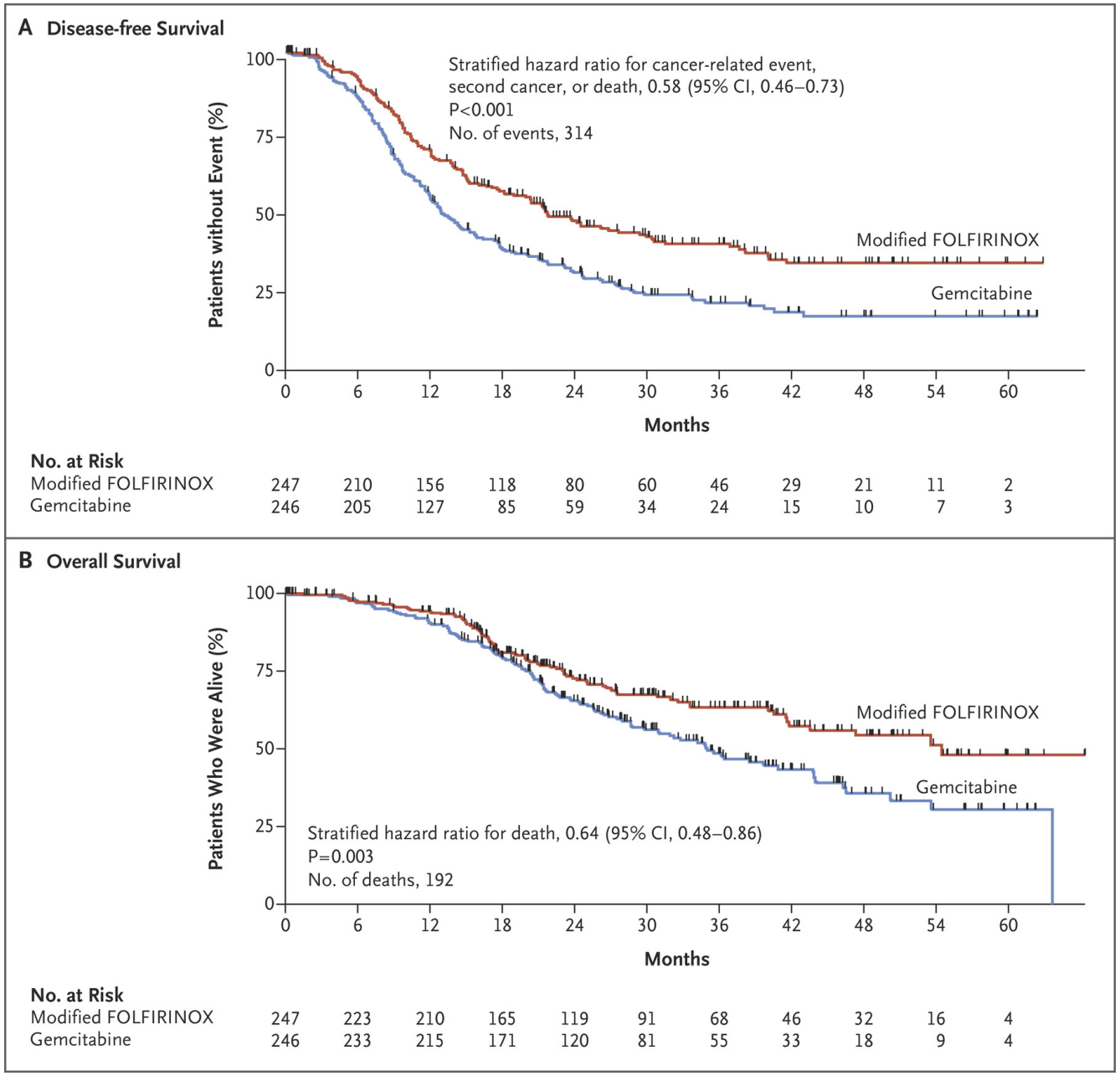
Conroy T, et al., *New Engl J Med* 2011

The NEW ENGLAND JOURNAL of MEDICINE

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

Conroy T et al., 2018

- Resected pancreatic cancer (R0/R1) treated with adjuvant FOLFIRINOX vs. Gemcitabine
- 3 year DFS - 39.7% vs. 21.4%
- **Overall Survival - 54.4 months vs. 35.0 months**
- **New Standard of Care**



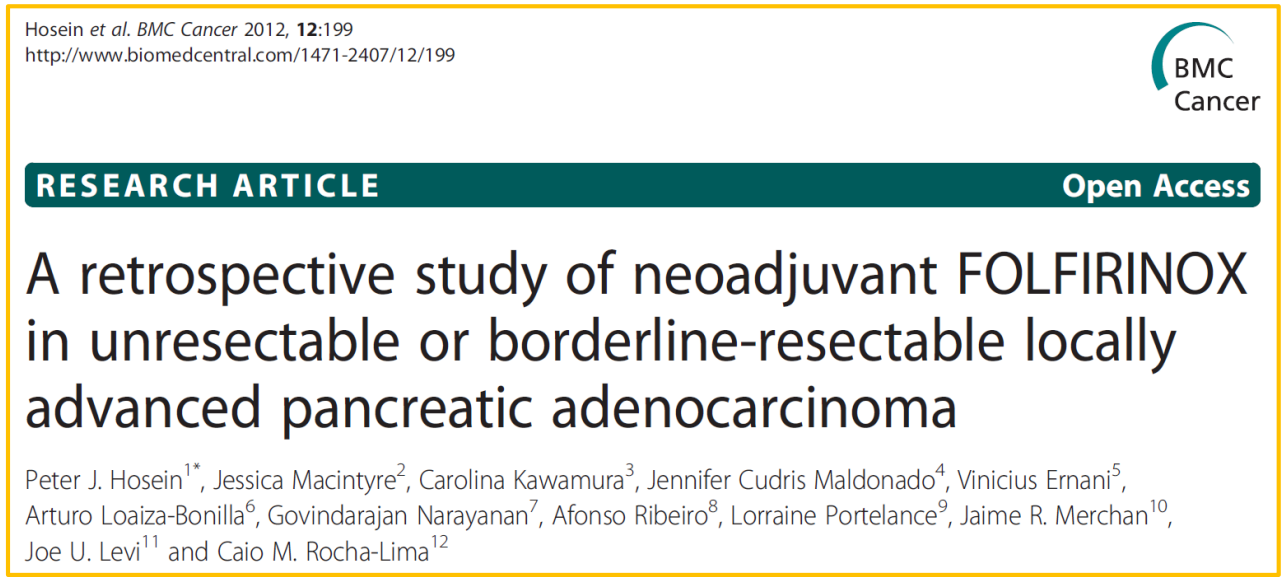
What about chemotherapy before surgery (Neoadjuvant)?

- To increase R0 resection rates by reducing tumor bulk and involvement of nearby structures.
- To ensure that all patients receive chemotherapy – **40-50% of patients do not receive chemotherapy in the adjuvant setting**
- To allow emergence of resistant, already present metastatic disease – allows for therapy switch
- To treat locally invasive disease before resection – “Downstage”
- To treat micrometastatic disease earlier, at the time of diagnosis.

Neoadjuvant FOLFIRINOX

7 of 14 patients with locally advanced PDAC were brought to operation (**50%**)

R0 resection performed in 5 (**36%**)



Hosein *et al. BMC Cancer* 2012, **12**:199
http://www.biomedcentral.com/1471-2407/12/199

BMC Cancer

RESEARCH ARTICLE Open Access

A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma

Peter J. Hosein[1*], Jessica Macintyre[2], Carolina Kawamura[3], Jennifer Cudris Maldonado[4], Vinicius Ernani[5], Arturo Loaiza-Bonilla[6], Govindarajan Narayanan[7], Afonso Ribeiro[8], Lorraine Portelance[9], Jaime R. Merchan[10], Joe U. Levi[11] and Caio M. Rocha-Lima[12]

Hosein PJ, et al., *BMC Cancer* 2012

Neoadjuvant FOLFIRINOX

4 of 14 patients with locally advanced PDAC were brought to operation (**29%**)

R0 resection performed in 3 **(21%)**

Ann Surg Oncol (2015) 22:S1212–S1220
DOI 10.1245/s10434-015-4851-2

Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

Resectability After First-Line FOLFIRINOX in Initially Unresectable Locally Advanced Pancreatic Cancer: A Single-Center Experience

Ulrich Nitsche, MD[1], Patrick Wenzel, MD[2], Jens T. Siveke, MD[2], Rickmer Braren, MD[3], Konstantin Holzapfel, MD[3], Anna M. Schlitter, MD[4], Christian Stöß[1], Bo Kong, MD[1], Irene Esposito, MD[5], Mert Erkan, MD[6], Christoph W. Michalski, MD[7], Helmut Friess, MD[1], and Jörg Kleeff, MD[1]

[1]Department of Surgery, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [2]Department of Internal Medicine II, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [3]Department of Diagnostic and Interventional Radiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany; [4]Institute of Pathology, Technische Universität München, Munich, Germany; [5]Institute of Pathology, Heinrich Heine University, Düsseldorf, Germany; [6]Department of Surgery, Koc University School of Medicine, Istanbul, Turkey; [7]Department of Surgery, University of Heidelberg, Heidelberg, Germany

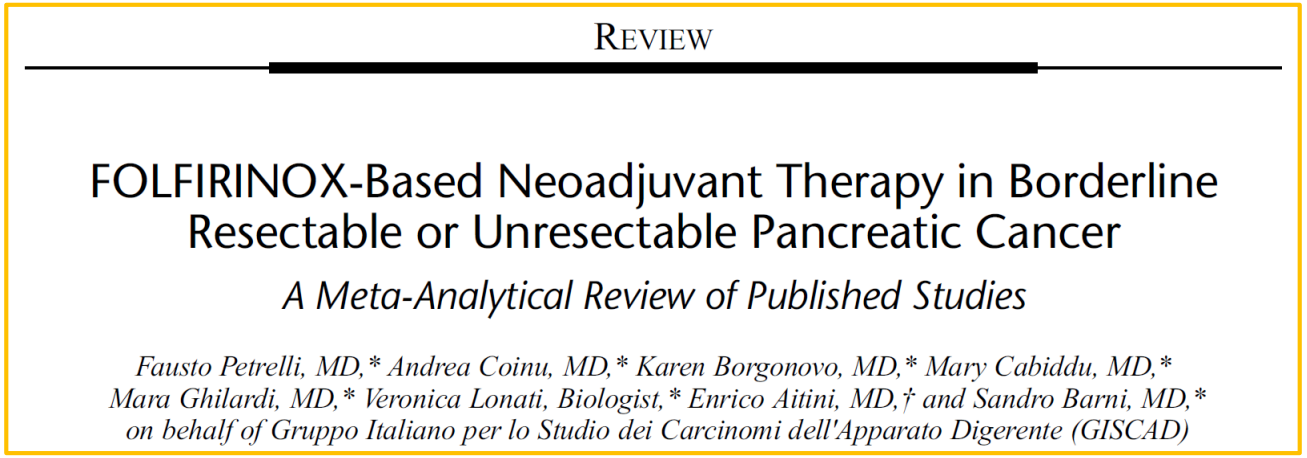
Nitsche U, et al., *Ann Surg Oncol* 2015

Neoadjuvant FOLFIRINOX

meta-analysis of 13 studies

pooled rate of patients with
locally advanced PDAC
brought to operation = **26%**

pooled rate of R0 resection = **23%**


REVIEW

FOLFIRINOX-Based Neoadjuvant Therapy in Borderline Resectable or Unresectable Pancreatic Cancer

A Meta-Analytical Review of Published Studies

Fausto Petrelli, MD, Andrea Coinu, MD,* Karen Borgonovo, MD,* Mary Cabiddu, MD,* Mara Ghilardi, MD,* Veronica Lonati, Biologist,* Enrico Aitini, MD,† and Sandro Barni, MD,* on behalf of Gruppo Italiano per lo Studio dei Carcinomi dell'Apparato Digerente (GISCAD)*

Petrelli F, et al., *Pancreas* 2015

Case illustration

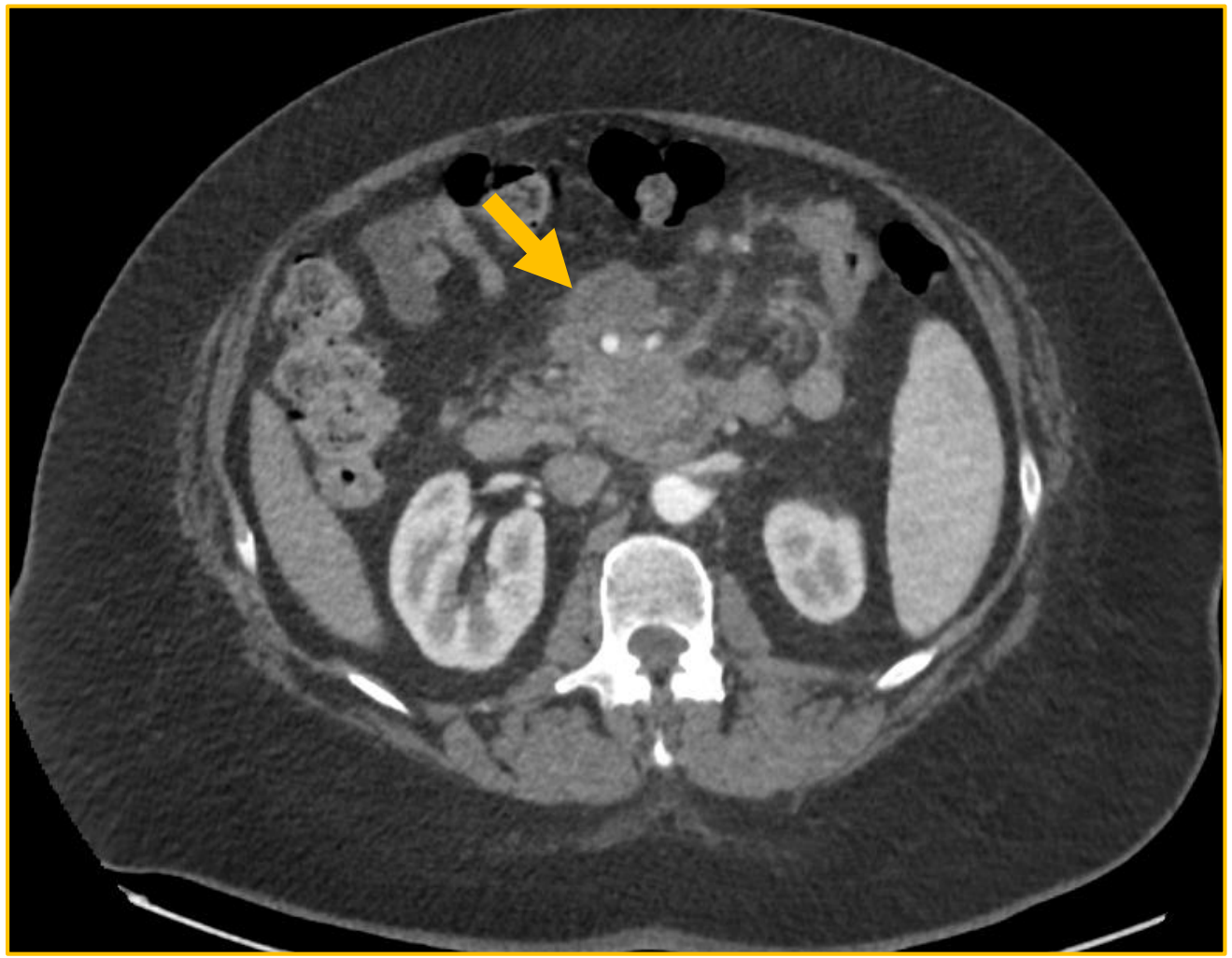
48F with morbid obesity presents with new onset DVT

returns with abdominal pain following initiation of anticoagulation

CT imaging identifies locally advanced pancreas mass

diagnosis of PDAC confirmed by EUS

Pre-treatment imaging



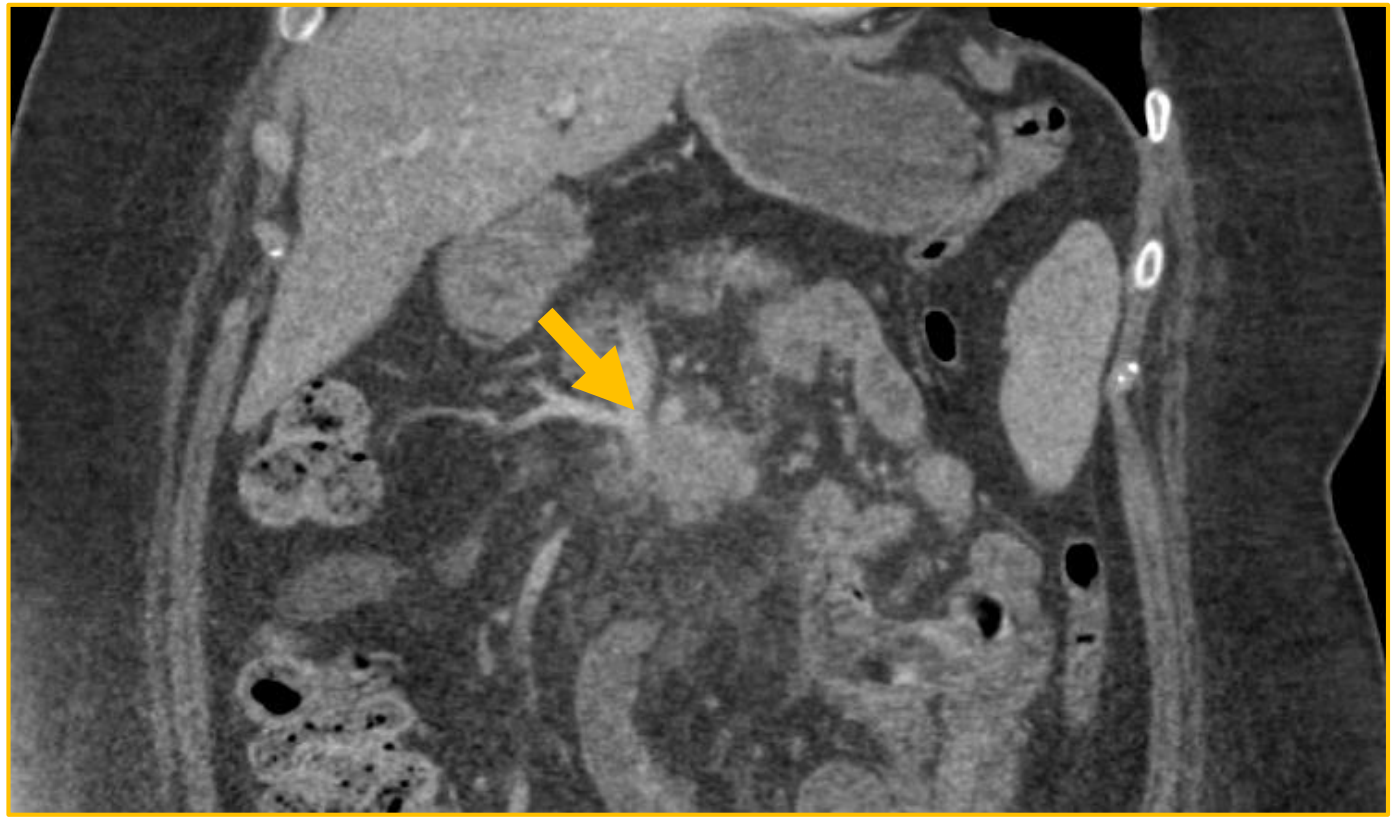
pre-treatment CT:

circumferential tumoral encasement of SMV, SMA

diagnosis:

locally advanced PDAC

Pre-treatment imaging



pre-treatment CT:

circumferential tumoral encasement of SMV, SMA

diagnosis:

locally advanced PDAC

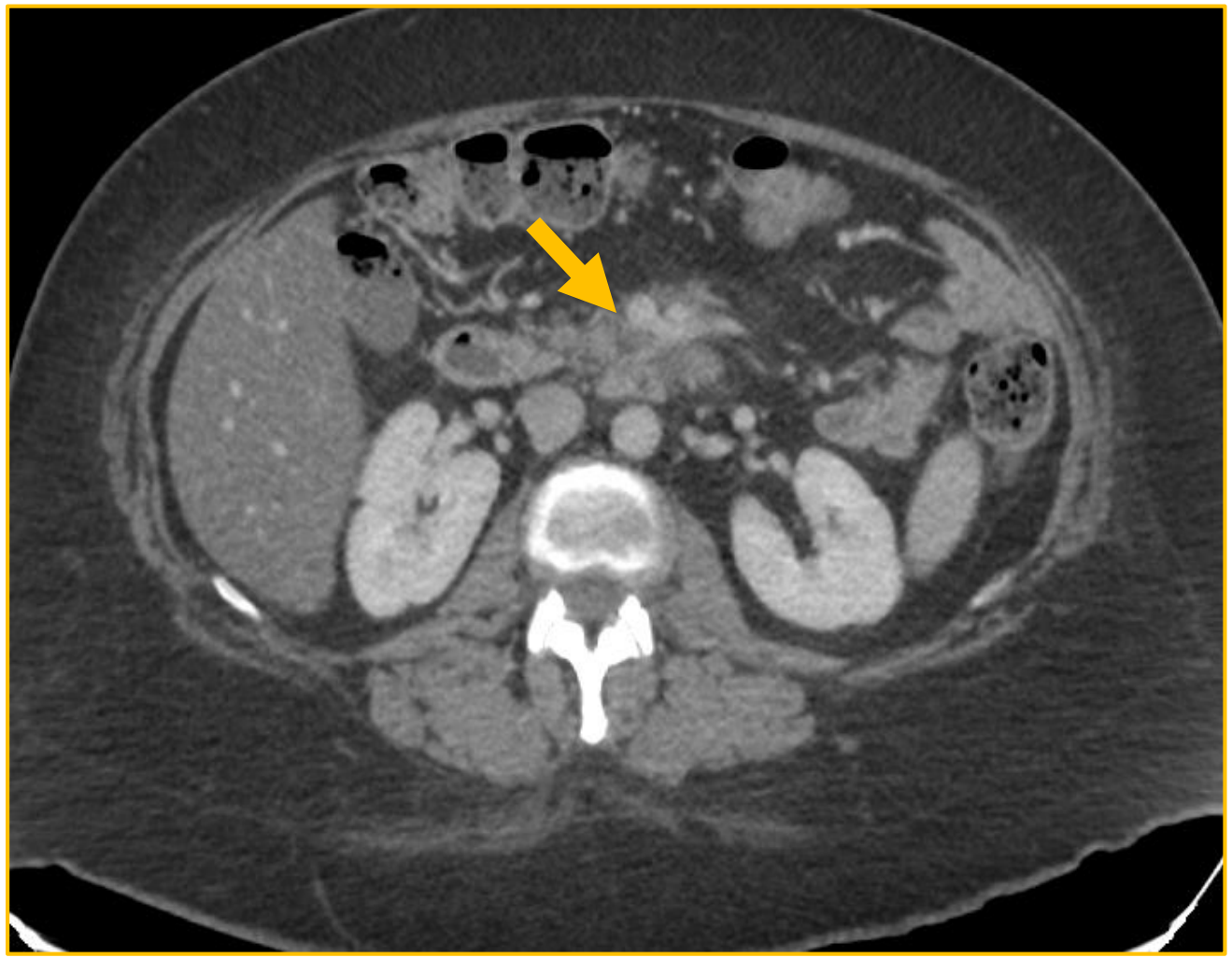
Neoadjuvant FOLFIRINOX

treatment sequencing initiated with FOLFIRINOX

developed irinotecan-induced GI toxicity

post-treatment CT imaging identified treatment response

Post-treatment imaging



post-treatment CT:

circumferential tumoral encasement of SMV, SMA

diagnosis:

locally advanced PDAC

Operative therapy

Operation:

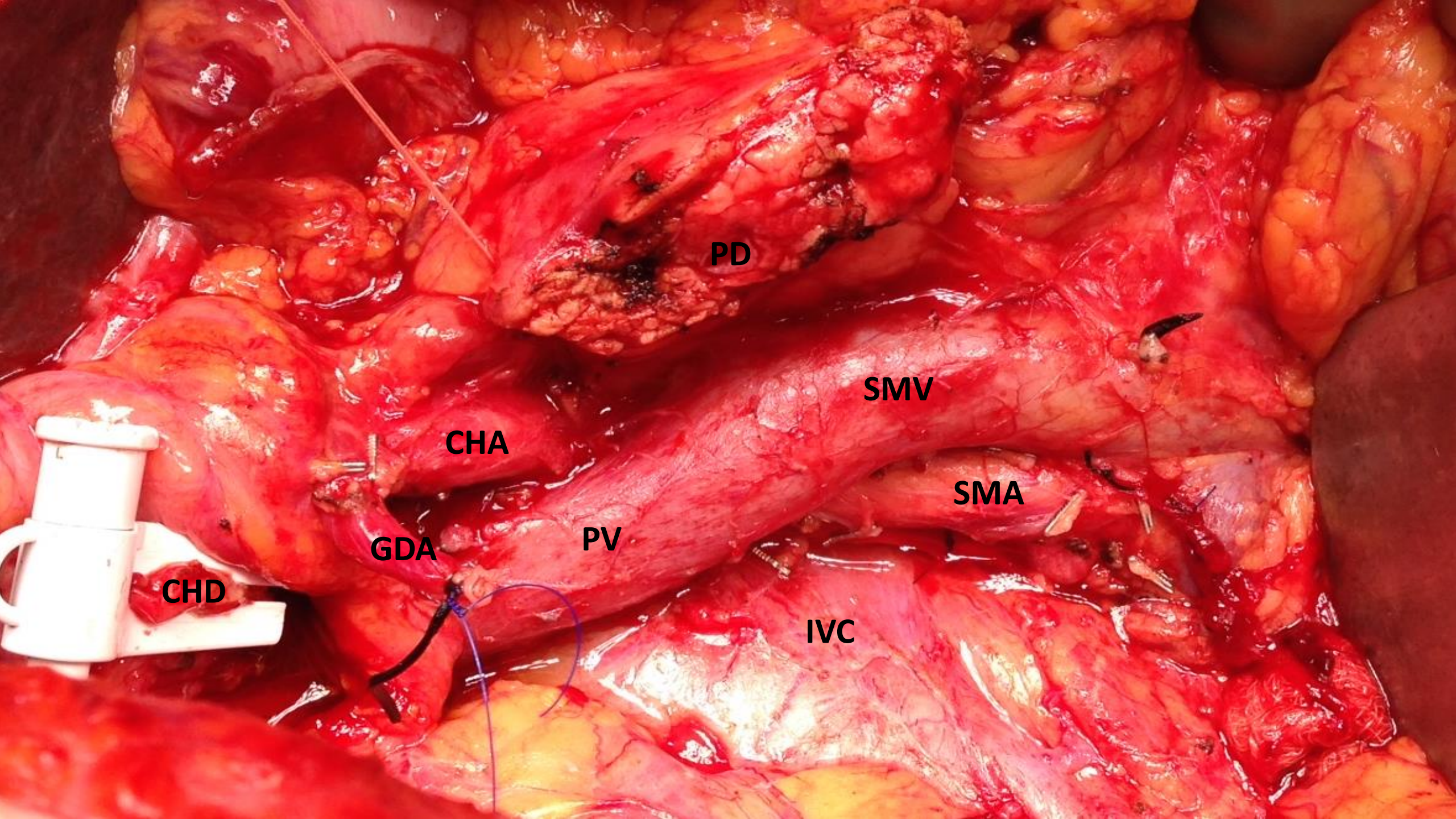
pancreaticoduodenectomy,

partial SMV resection, mesenteric lymphadenectomy

Pathology:

pT3N1 (3/24 LN) PDAC with treatment response,

no angiolymphatic/perineural invasion, negative margins

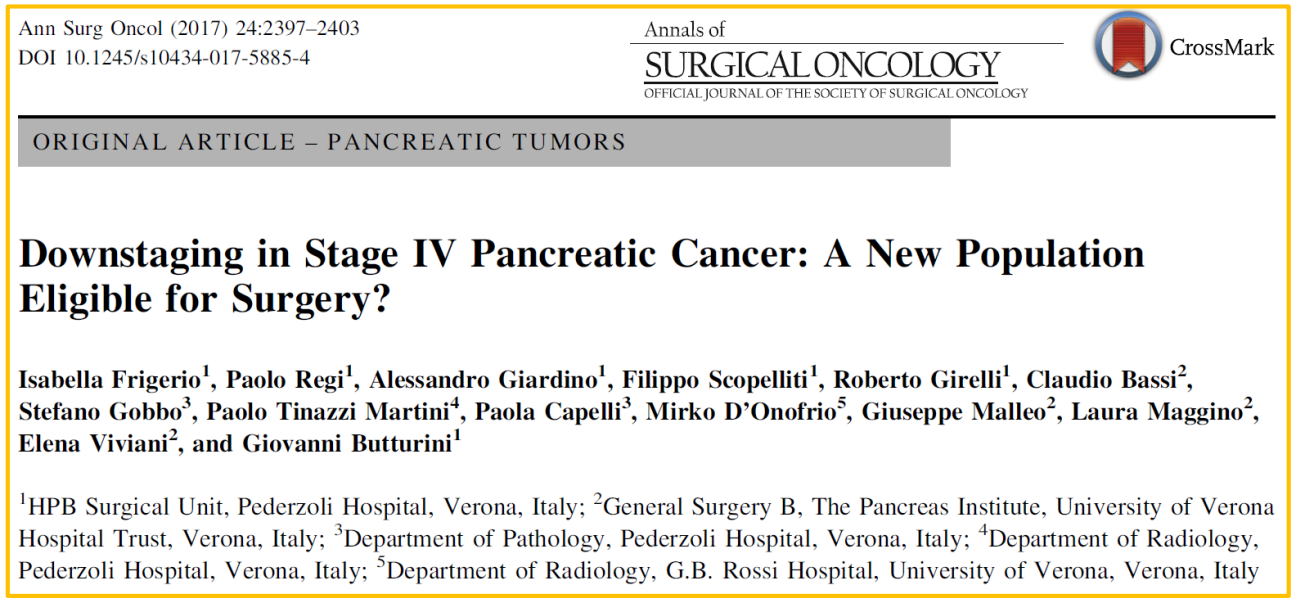

PD
SMV
CHA
SMA
GDA
PV
CHD
IVC

Taking things too far?

24 patients who demonstrated treatment response of metastatic PDAC underwent operative resection

median OS/DFS = **56/27 mos**

denominator of patients with metastatic disease = **535 (4.5%)**



Ann Surg Oncol (2017) 24:2397–2403
DOI 10.1245/s10434-017-5885-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

Downstaging in Stage IV Pancreatic Cancer: A New Population Eligible for Surgery?

Isabella Frigerio[1], Paolo Regi[1], Alessandro Giardino[1], Filippo Scopelliti[1], Roberto Girelli[1], Claudio Bassi[2], Stefano Gobbo[3], Paolo Tinazzi Martini[4], Paola Capelli[3], Mirko D'Onofrio[5], Giuseppe Malleo[2], Laura Maggino[2], Elena Viviani[2], and Giovanni Butturini[1]

[1]HPB Surgical Unit, Pederzoli Hospital, Verona, Italy; [2]General Surgery B, The Pancreas Institute, University of Verona Hospital Trust, Verona, Italy; [3]Department of Pathology, Pederzoli Hospital, Verona, Italy; [4]Department of Radiology, Pederzoli Hospital, Verona, Italy; [5]Department of Radiology, G.B. Rossi Hospital, University of Verona, Verona, Italy

Frigerio I, et al., *Ann Surg Oncol* 2017

Biology is King

'Biology is King,

Selection of cases is Queen,

And the technical details of surgical procedures are Princes and Princesses of the Realm who frequently try to overthrow the powerful forces of the King and Queen,

Usually to no long-term avail, although with some temporary apparent victories'

Blake Cady, Archives Surgical Oncology 1997; 132: 338-46

Have we made a difference?

We are beginning to expect treatment responses to FOLFIRINOX

A quarter of patients with locally advanced PDAC may be able to undergo resection after FOLFIRINOX

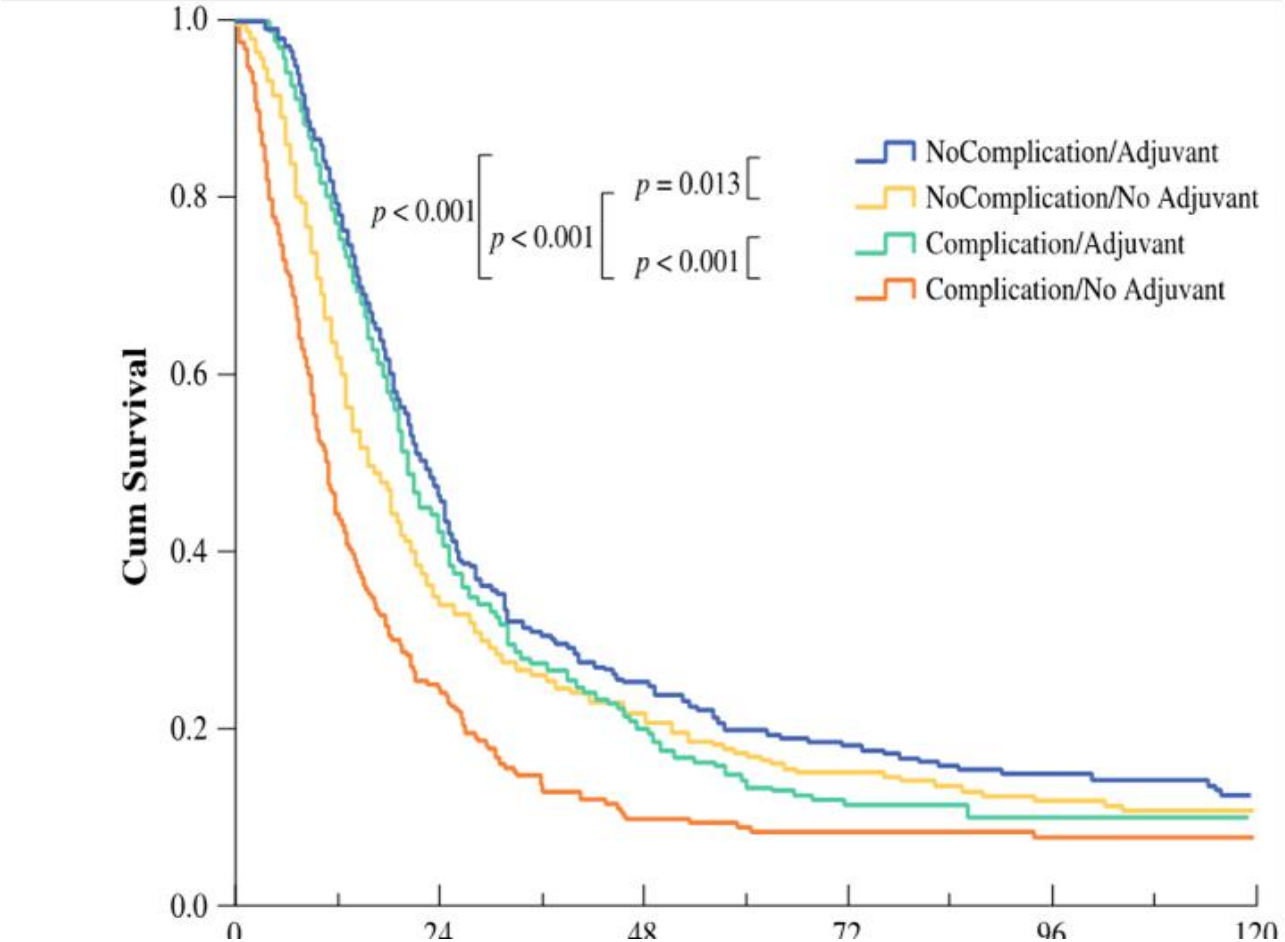
The long-term impact of this new opportunity has yet to be determined

How else have we evolved?

- Smaller incisions
  - Minimally invasive surgery
- Less blood loss
  - Better tools and techniques
- Better pain management
  - Blocks, PCA
- Faster recovery
  - ERAS protocols
  - Rehab/P.T.

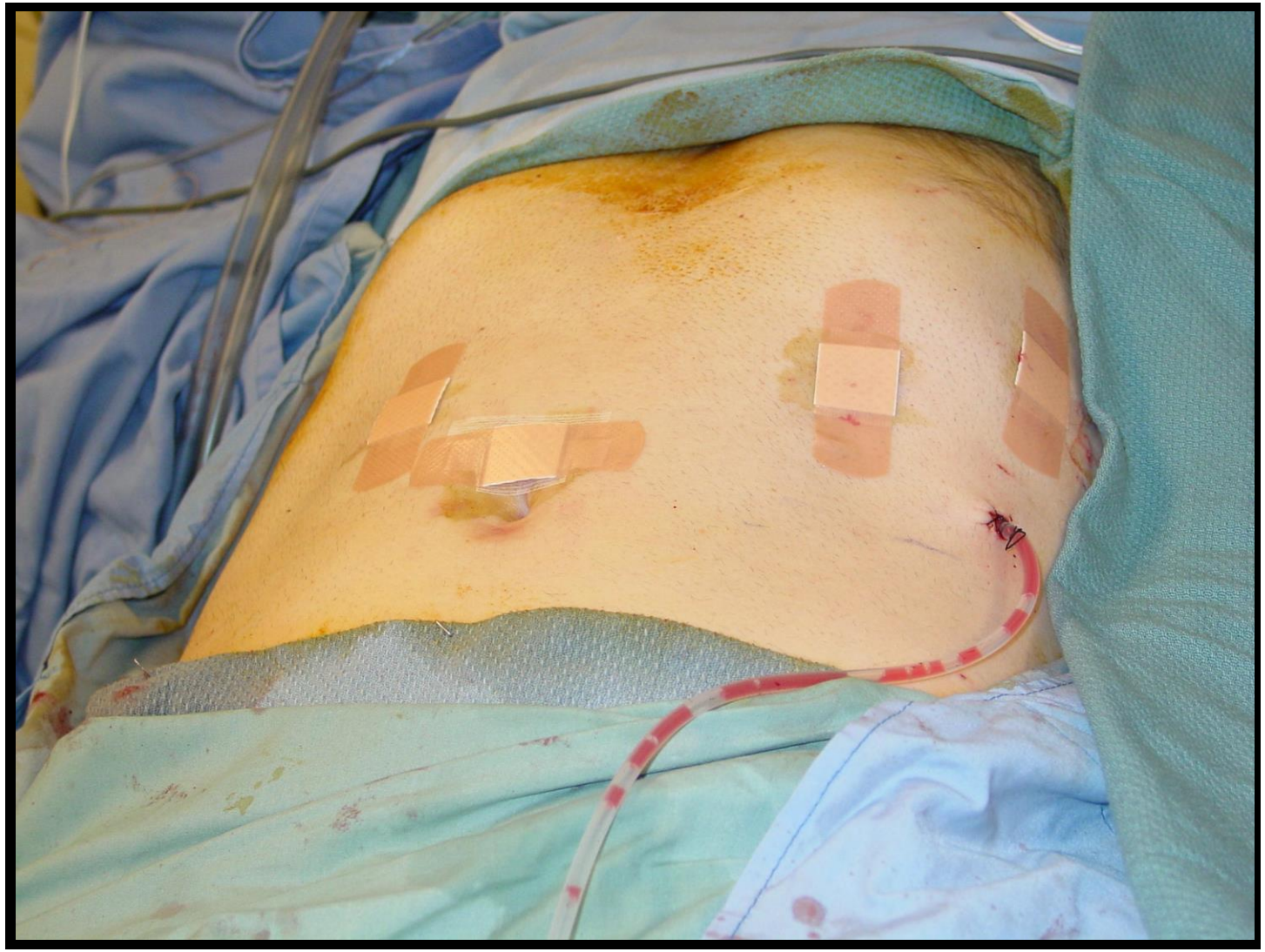
Rationale for improving surgical recovery

- Open pancreaticoduodenectomy (OPD)
  - low mortality <2%
  - significant morbidity up to 50%



Weiss et al., *ASO* 2014

Laparoscopic “Band-aid” Surgery



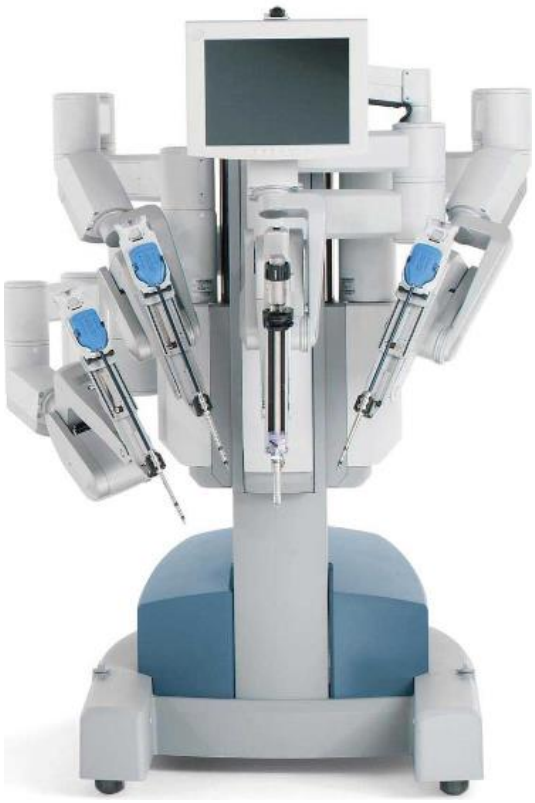
Its really hard!

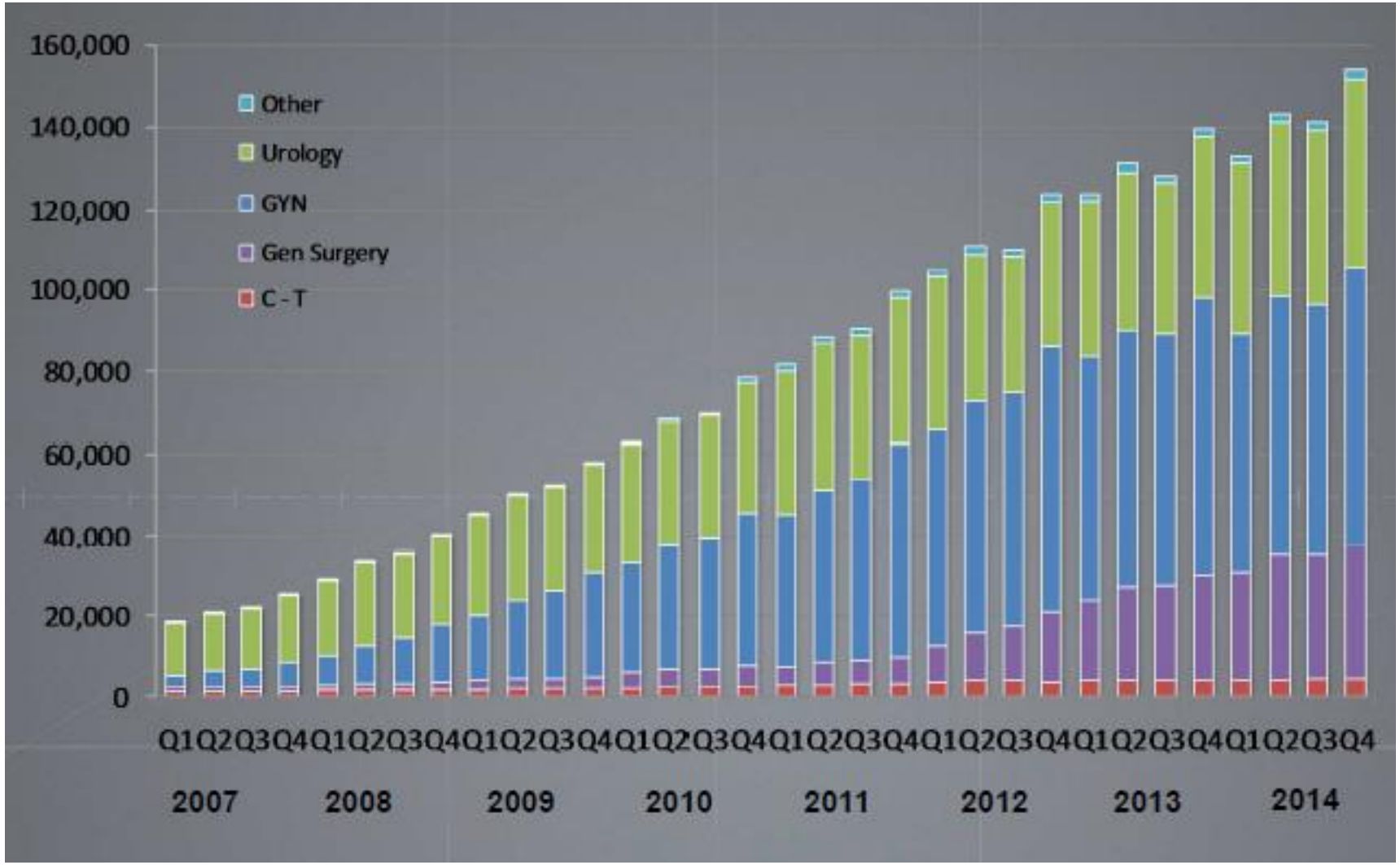
Difficulty

Laparoscopic abdominal procedures

- Laparoscopic cholecystectomy
- Laparoscopic appendectomy
- Laparoscopic antireflux surgery
- Laparoscopic splenectomy
- Laparoscopic colectomy
- Laparoscopic nephrectomy
- Laparoscopic gastrectomy/ pancreatectomy
- Laparoscopic bariatric surgery
- Laparoscopic esophagectomy
- Laparoscopic hepatectomy
- Laparoscopic pancreaticoduodenectomy

Growth of Robotics Worldwide

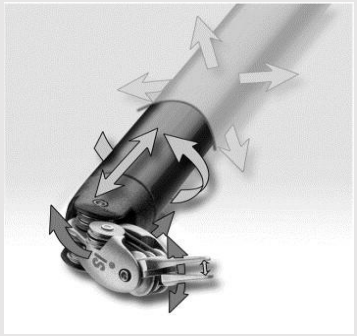




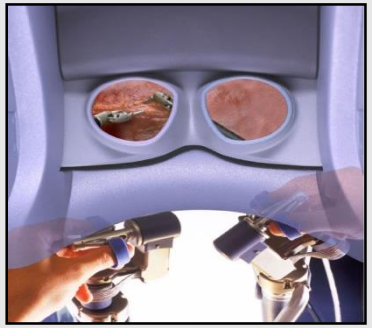
Robotic Pancreas Surgery

- Improved visualization-3D, Magnification
- Stable retraction (third arm)
- Dissection
- Suturing
- Decreased fatigue

Seven degree of freedom

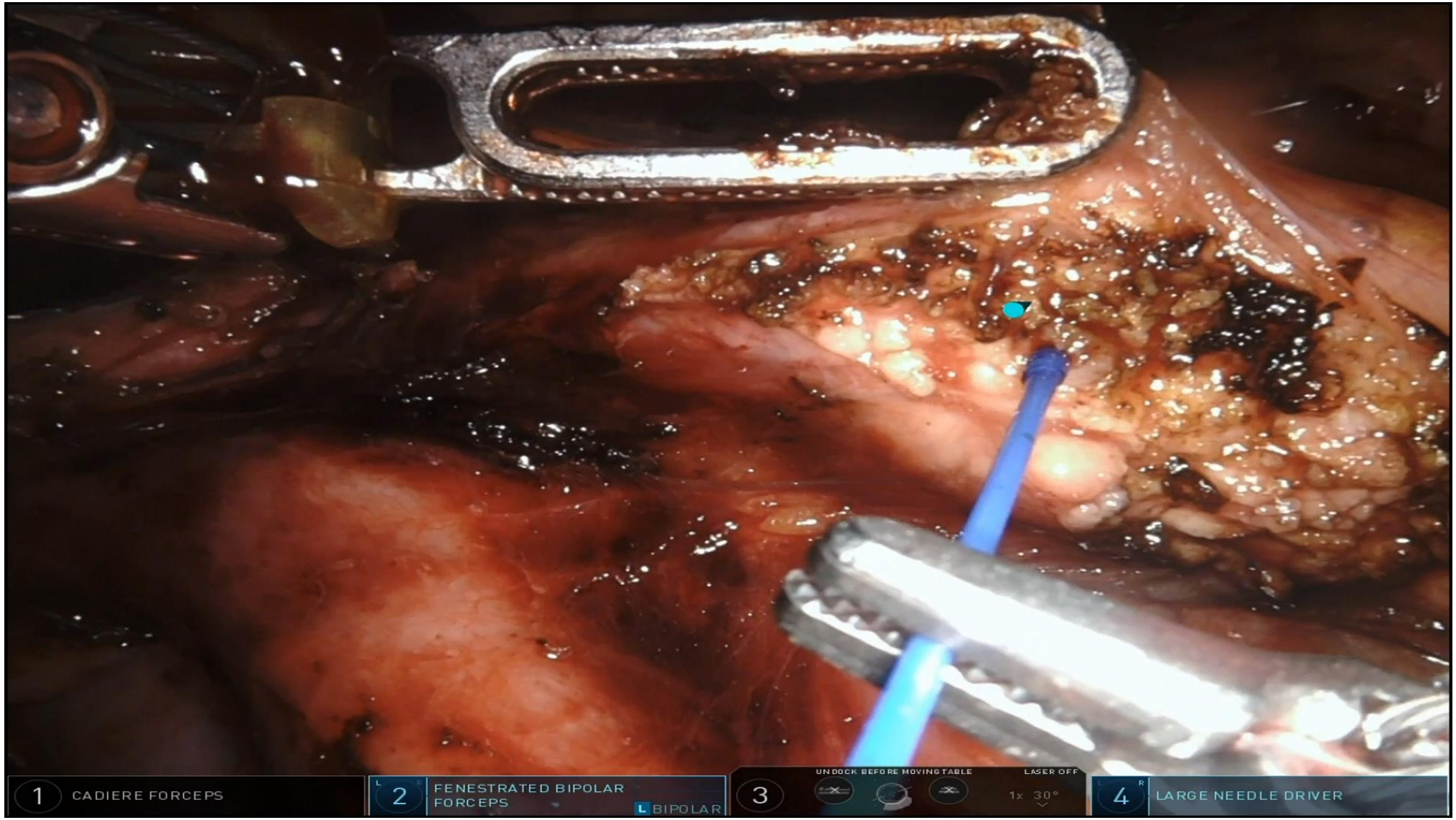


3-D image



Elimination of fulcrum effect

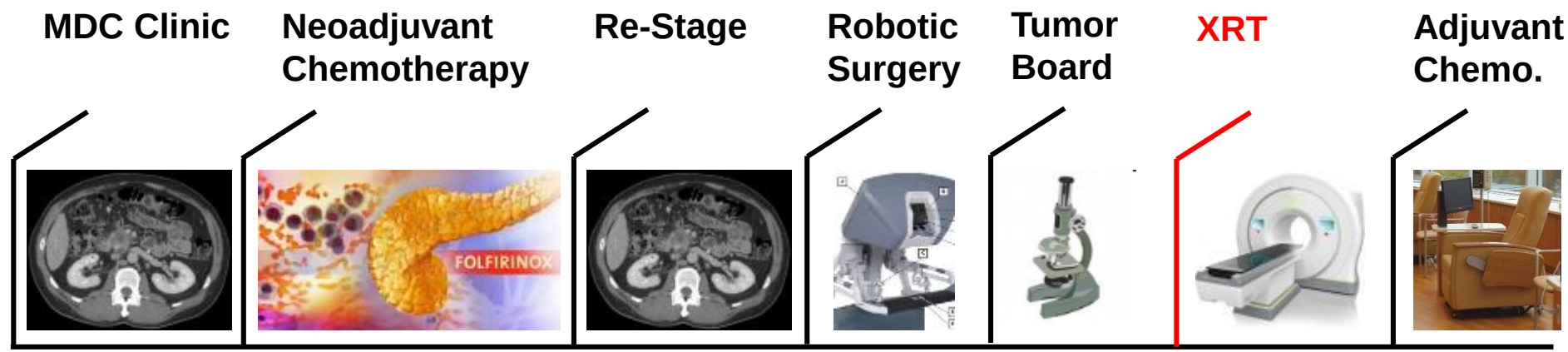
The Ohio State University: Robotic Pancreas Program



Robotic Pancreas Surgery

- The robotic platform is versatile, safe and feasible
- The learning curve for robotic pancreas surgery is now better defined; safe dissemination is possible
- When performed by high volume pancreatic surgeons at high volume centers
  - reductions in morbidity compared to open surgery
  - reduced conversions compared to laparoscopy
  - Improved outcomes can lead to cost benefits compared to open approach

Pancreas cancer: Our ideal timeline



1. Imaging
2. CA19-9

1. Gem/Abraxane
2. FOLFIRINOX

1. CT Scan
2. CA19-9

1. Whipple
2. Distal
3. Total
4. DP-CAR

1. Margins
2. Response

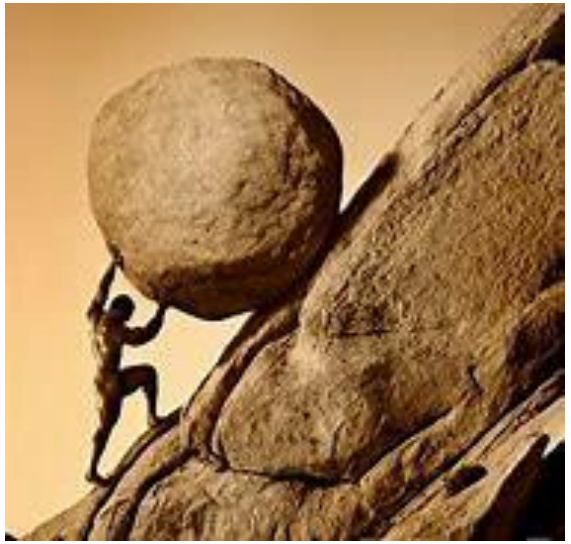
1. 6 cycles

Gem

Gem/Abraxane

Acknowledgements

- Surgeons
- Medical Oncologists
- Radiation Oncologists
- Gastroenterologists
- Radiologists
- Nurses/Hospital Staff
- **Our Patients and their Family Members**



Thank You

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