Multimodality Management of Localized Pancreatic Cancer

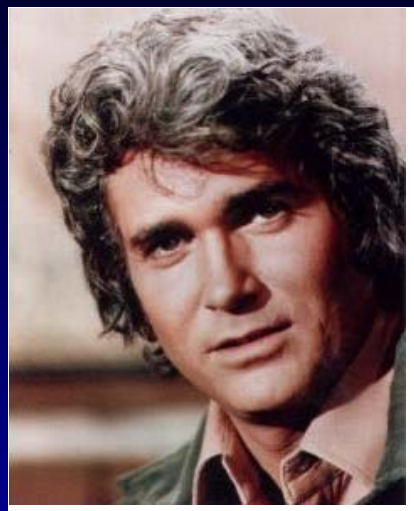
Department of Surgery

- Cardiothoracic Surgery
- Community Surgery
- Education
- Oral Maxillofacial Surgery
- General Surgery
- Pediatric Surgery
- Surgical Oncology
- Transplantation
- Trauma, Critical Care
- Vascular Surgery

Douglas B. Evans
Medical College of Wisconsin
MCW/Froedtert Cancer Center
devans@mcw.edu

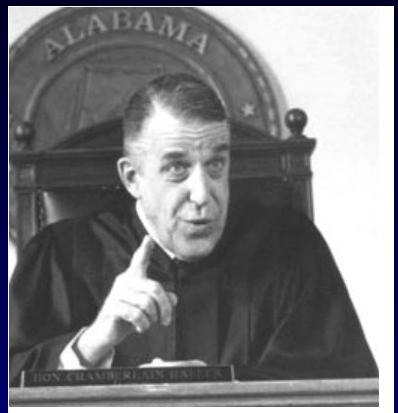
Milwaukee late Jan 2009 – July 2011

- Laurie Andrzejewski
- Elaine Babel
- Peter Bapes
- Judith Berndt
- Ze'ev Boim
- Eugene Bojarski
- Charlotte Bouchard
- Richard Broder
- Cassandra Brown
- Thomas Carlisle
- Donald Claesges
- James Cunningham
- Kathleen Daily
- Mildred Donahue
- Richard Drallmeier
- Billie Drath
- Jean Fricke
- Jay Fry
- H. B. Gay
- Cheryl Green
- Donnie Hand
- David Hanschke
- Paul Helgeson
- Jane Hollander
- Rosemary Jacobson
- Harold Kaminski
- James Klein
- Nancy Labott
- Sarah Levin
- Susan Lineberger
- Sharon Lousier
- Donald Macrae
- Earleen McGhee
- Robert Morris
- Thomas Murphy
- Terrance Neary
- Mowaffaq Ousachi
- Donald Panuce
- Eileen Paquin
- Merrie Patch
- James Pauls
- Jay Peck
- Gerald Plost
- Joyce Pratt
- Peter Rillo
- Harriet Russell
- Lillian Rzentkowski
- Gerald Seymour
- Killian Schneider
- Thomas Sullivan
- Marjorie Thome
- Robert Troost
- Norbert Wickman
- Peter Wroblewski
- Ronald Wysocki
- Howard Veldhorst
- Robert Vescio
- Nancy Zabkowicz



Michael Landon

Judge Ruth Bader Ginsburg

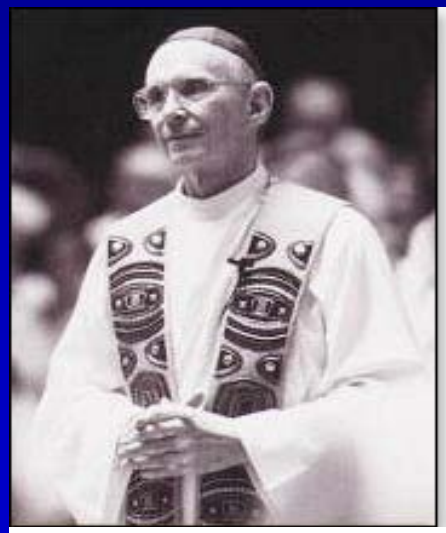


Fred Gwynne

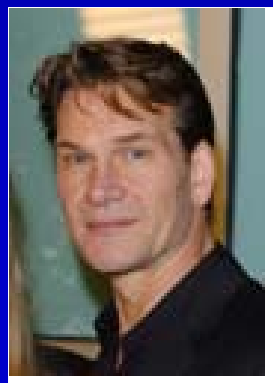
Sheikh Zayed

Gene Upshaw

Luciano Pavarotti



Joseph Cardinal Bernardin
Archbishop of Chicago



Patrick Swayze

Count Basie

49 y.o. woman executive

Dec 2005
- Jaundice
- Taken to surgery, unresectable (double bypass)
- Recovers
- Comes to Houston for another opinion

Can my tumor be removed

673729

Natural History of Pancreatic Cancer

	Months From Dx
All patients	9.3
Stage I, II (potentially resectable)	15.4
resected	24.1
not resected	10.3
Stage III (locally advanced)	9.9
borderline resectable	17.6
Stage IV (metastatic)	6.1

MDACC: Pancreatic Cancer Program Database 1991-2007, N = 4,395

Katz MHG, Hwang RF, et al. TNM staging of pancreatic adenocarcinoma. CA Cancer J Clin. 2008;58(2):111-25.

Postoperative Adjuvant Therapy

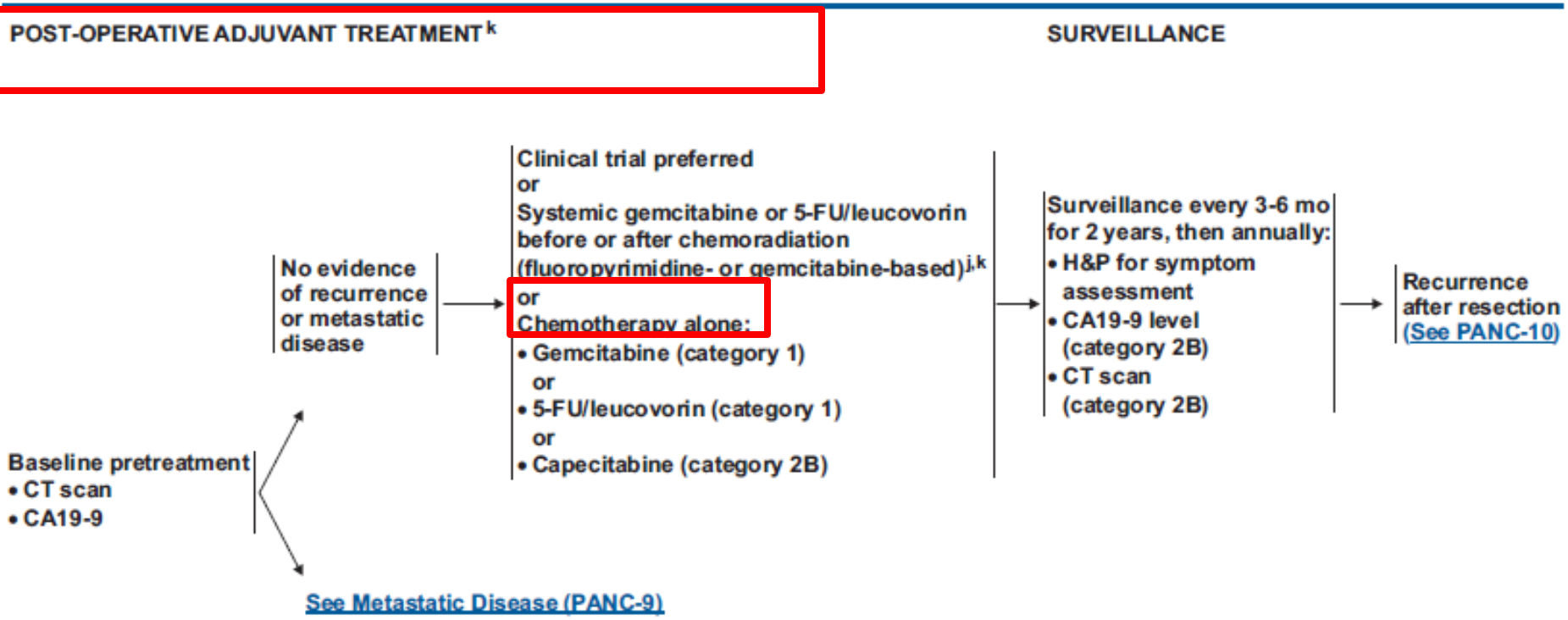
Author	No. Patients	Med. Survival	P-Valve
GITSG (1985) 5-FU/XRT	21	**20**	.03
Surgery alone	22	11	
EORTC (1999/2007) 5-FU/XRT			
Surgery alone			
ESPAC-1 (2001) 5-FU/LV	146	**20**	.011
No chemo	139	16	
CONKO (2008 ASCO) Gem	179	**23**	.005
Surgery alone	175	20	
RTOG (2010) 5-FU/XRT	187	**20**	.12
Gem vs 5-FU	201	17	
ACOSOG Z5031(2010)	89	**25**	
ESPAC-3 (JAMA 2010)	537	24	.39
Gem vs 5-FU/LV	551	23	
EORTC (JCO 2010)	45	24	
*Gem vs Gem/GemXRT	45	24	

*Treatment started within 8 wks of surgery

Surgery plus something is better than surgery alone

NCCN Guidelines™ Version 2.2011
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Pancreatic Table of Contents
Discussion



[j] See Principles of Radiation Therapy (PANC-D).

[k] Patients who have received neoadjuvant chemoradiation or chemotherapy are candidates for additional chemotherapy following surgery. Adjuvant treatment should be administered to patients who have not had neoadjuvant chemotherapy and who have adequately recovered from surgery; treatment should be initiated within 4-8 weeks. If systemic chemotherapy precedes chemoradiation, restaging with a CT scan should be done after each treatment modality.

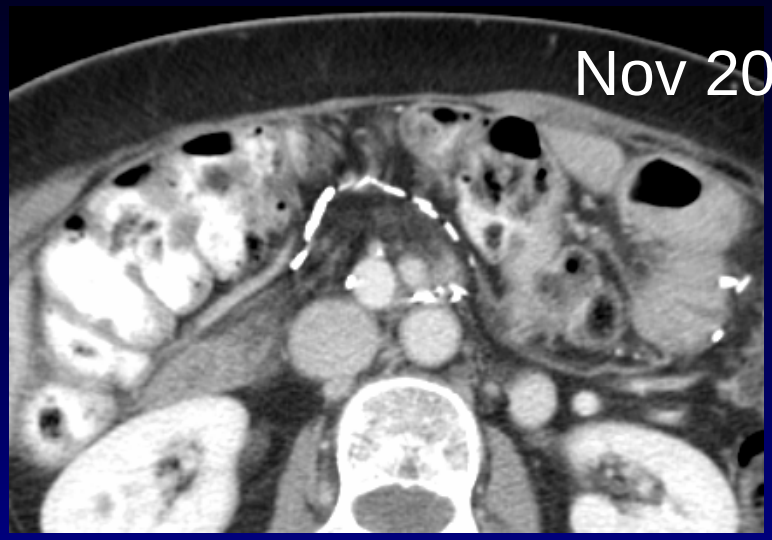
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

12/14/06: Pancreaticoduodenectomy

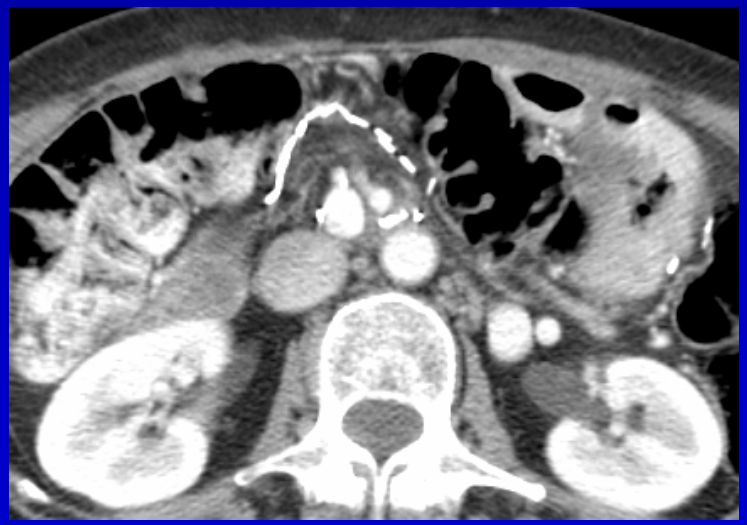
Surgical pathology:
ductal adenocarcinoma
2.5 x 2.3 x 2.3 cm
8 LN negative/ margins uninvolved

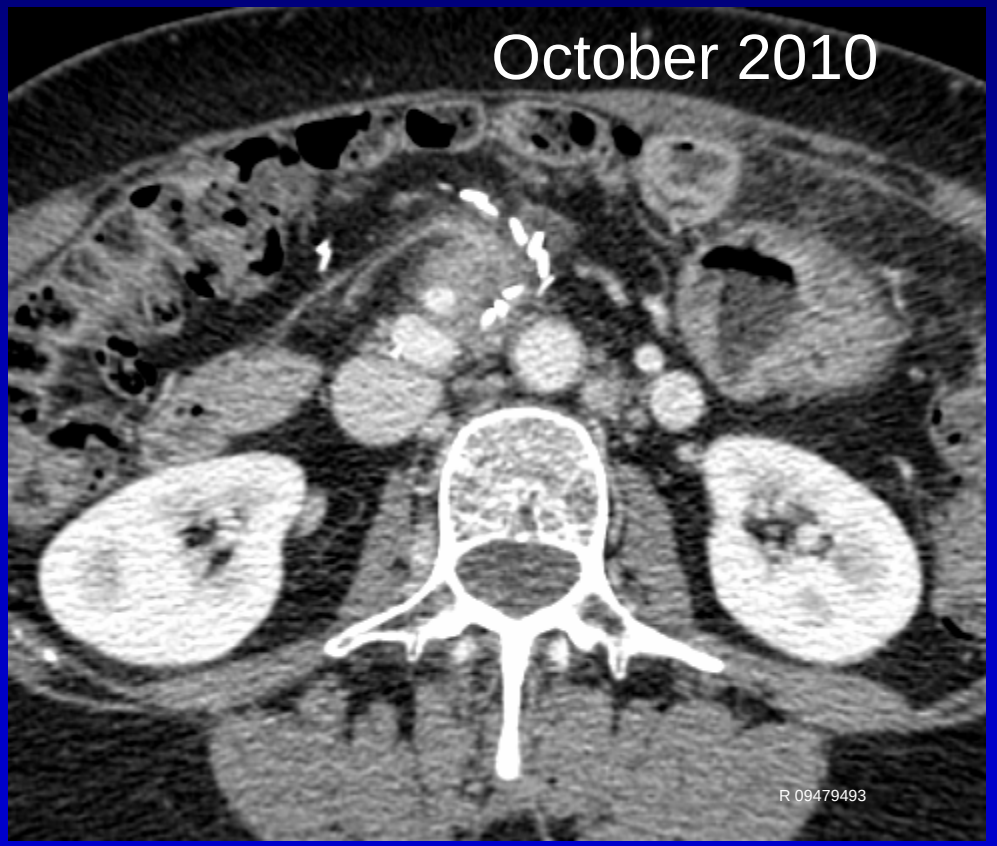
1/29/07: 6 cycles Gemcitabine - 3 weeks on and 1 week off

10/11/10: US guided biopsy - soft tissue near SMA - Pathology : adenocarcinoma



Oct 2007





329 consecutive pts / pancreatic resection / *min F/U 5 yrs*

Characteristic	Survival <5 years ($n = 241$)	Survival ≥5 years ($n = 88$)		
	n	n	Recurrence <5 years (n)	Recurrence ≥5 years (n)
No. of patients whose disease recurred	208	21	14	7
Site of first recurrence[a]				
Liver	104 (50)	3 (14)	3 (21)	0
Lung	37 (18)	13 (62)	7 (50)	6 (86)
Locoregional	38 (18)	2 (10)	2 (14)	0
Peritoneum	28 (13)	2 (10)	1 (7)	1 (14)
Abdominal wall/dermis	1 (1)	2 (10)	1 (7)	1 (14)
Brain	0	1 (5)	1 (7)	0
Bone	3 (1)	0	0	0
Other				

Total local-regional recurrence: 40/329 = 12%

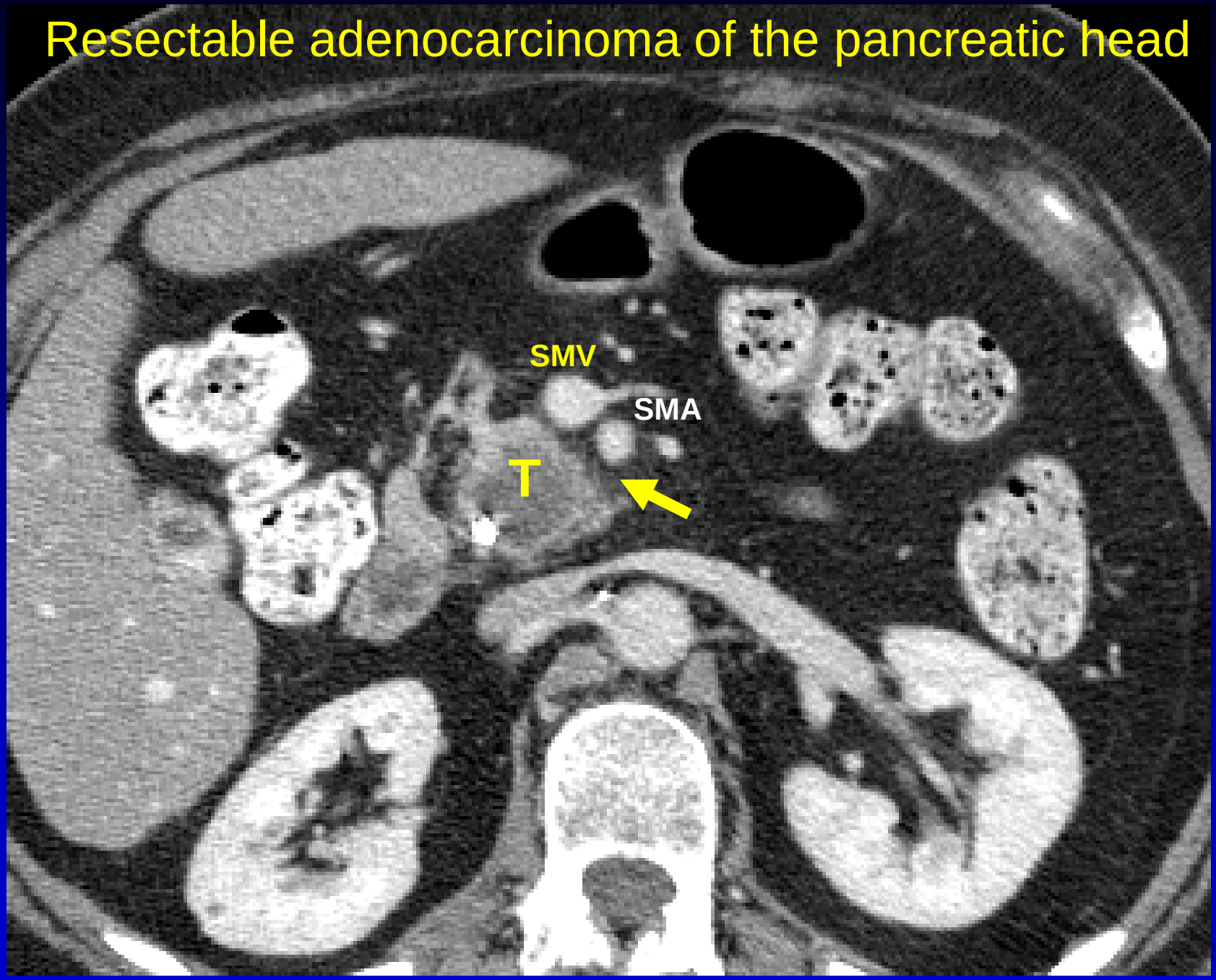
Katz MHG, Wang H, Fleming JB, Sun CC, Hwang RF, Wolff RA, Varadhachary G, Abbruzzese JL, Crane CH, Krishnan S, Vauthey JN, Abdalla EK, Lee JE, Pisters PWT, Evans DB. Long-term survival after multidisciplinary management of resected pancreatic adenocarcinoma. Ann Surg Oncol; 2009:16:836-47

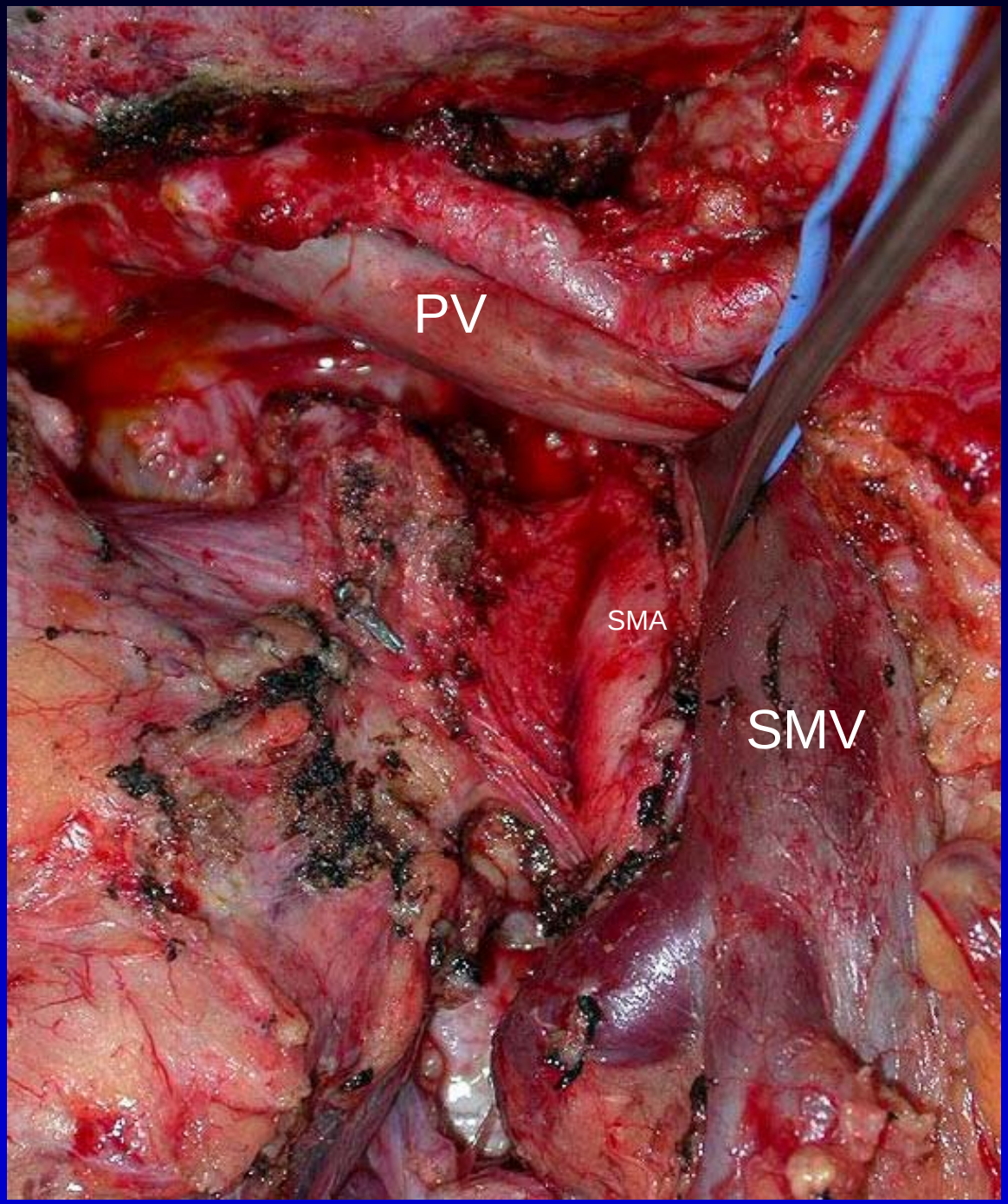
Hopkins Rapid Autopsy Patterns of Failure

Stage at dx	I/II n=20	III n=18
Local only	**15%**	28%
DM only	20%	-
LR + DM	65%	72%

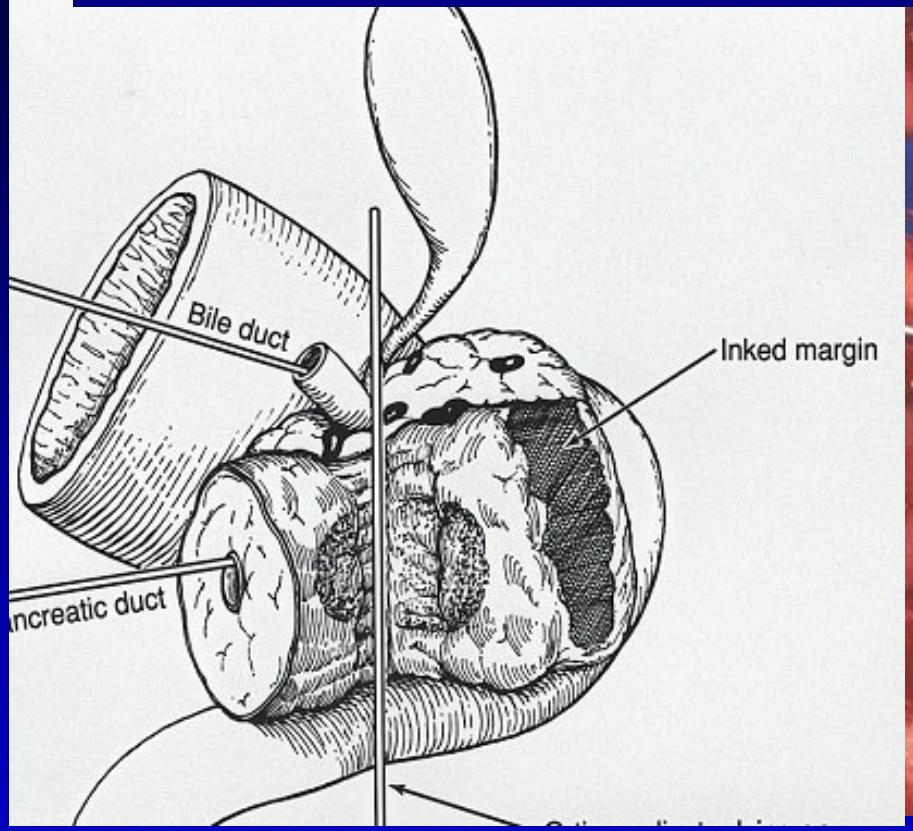
Iacobuzio-Donahue et al, JCO. 2009;27:1806

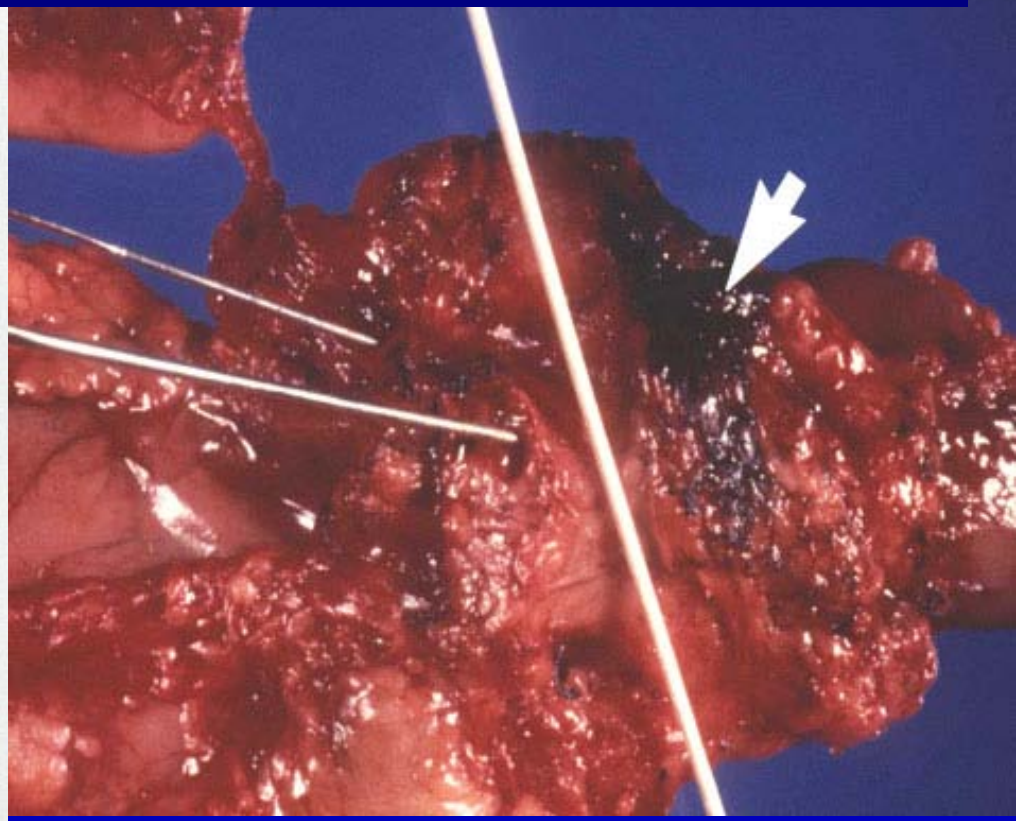
Resectable adenocarcinoma of the pancreatic head

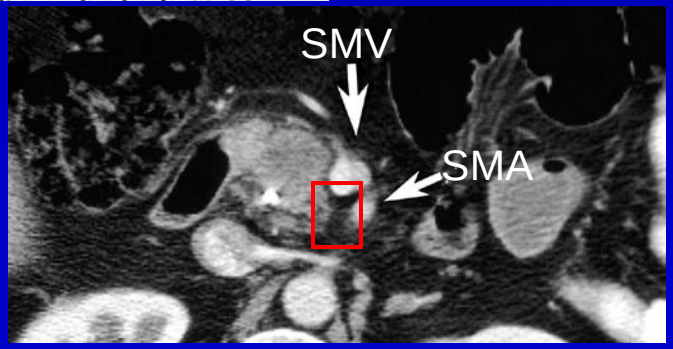



PV
SMA
SMV

SMA (Retroperitoneal) Margin
AJCC Cancer Staging Manual 7th Edition







Standardization of Surgical and Pathologic Variables is Needed in Multicenter Trials of Adjuvant Therapy for Pancreatic Cancer: Results from the ACOSOG Z5031 Trial

Matthew HG Katz MD, et al.
for the American College of Surgeons Oncology Group

TABLE 2. *Frequency with which surgical margins were evaluated prior to enrollment in as determined by critical review of the pathology reports (n=79)*

	No. of patients (%)			
Status	SMA	CBD	Panc	AJCC*
Evaluated	**37 (47)**	74 (94)	79 (100)	36 (46)
Positive	14 (38)	2 (3)	12 (15)	16 (44)
Negative	23 (62)	72 (97)	67 (85)	20 (56)

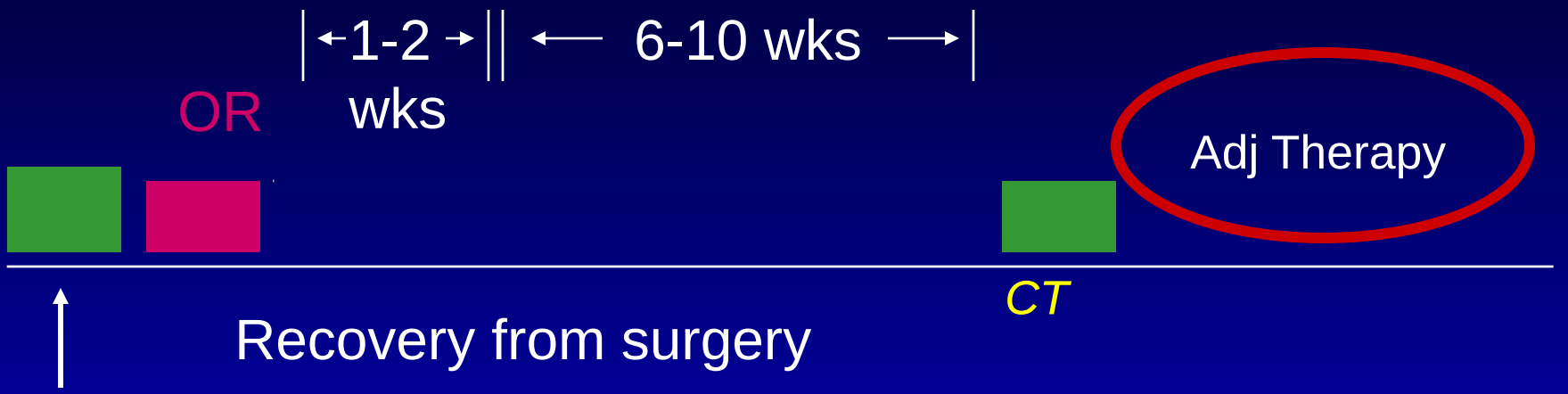
*Cases in which all three margins recommended by the AJCC (sixth edition[11])--SMA, CBD, and Panc--were evaluated. Positive indicates at least one margin of the three AJCC margins was positive; negative indicates all three margins were negative.

Katz, et al. Ann Surg Oncol. 2010;18:337-344

TABLE 3. Frequency with which critical surgical and pathologic factors were documented in operative and pathology reports of patients enrolled on ACOSOG Z5031.

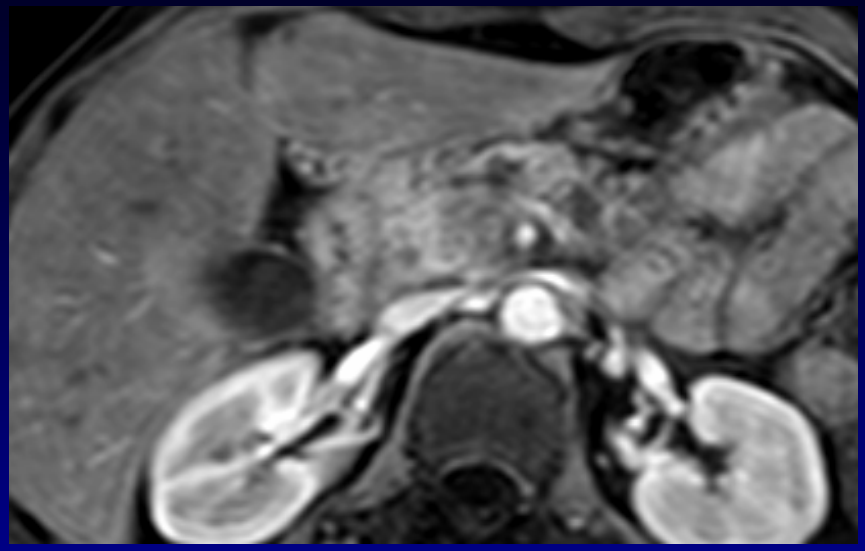
Clinical Factor	Reported, n (%)
Surgical Factors*	
Type of resection	80 (100)
Preoperative clinical stage	10 (13)
Transfusion requirement	14 (18)
Search for extrapancreatic disease	77 (96)
Description of liver	64 (80)
Description of peritoneum	54 (68)
Relationship of tumor to SMV	55 (69)
Technique of SMA dissection	**54 (68)**
Marking of SMA margin†	20 (25)
Absence of residual macroscopic disease	**19 (24)**
Pathologic Factors	
Histologic subtype	79 (100)
Inking performed	**52 (66)**
Evaluation of SMA margin	**37 (47)**
Examination of regional lymph nodes	79 (100)
Maximum tumor diameter	74 (94)
Tumor grade	79 (100)
Lymphovascular invasion	63 (80)
Perineural invasion	75 (95)
AJCC TNM stage	39 (49)
CAP guidelines observed	27 (34)

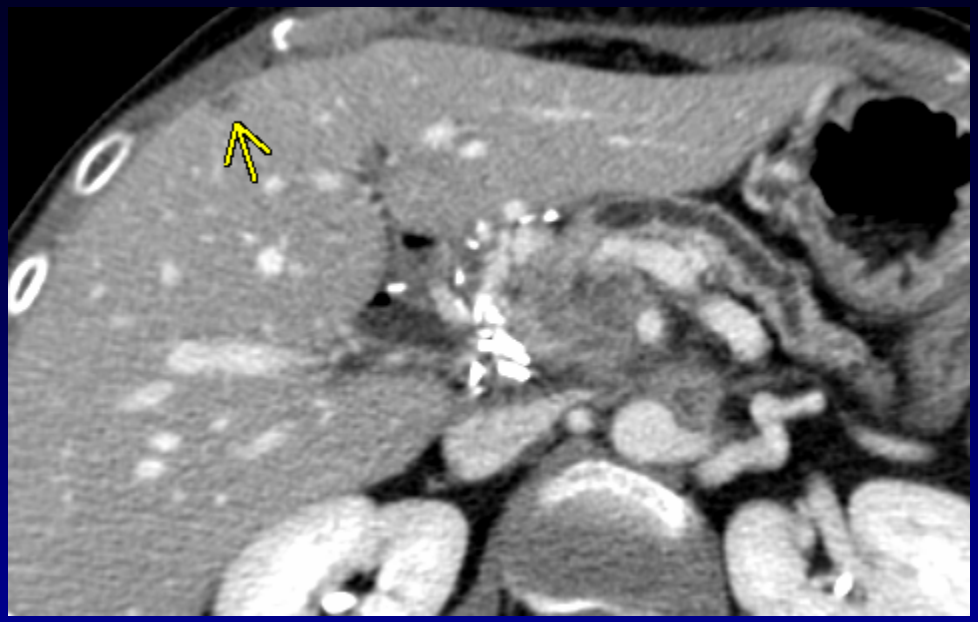
Surgery-first approach to localized pancreatic cancer

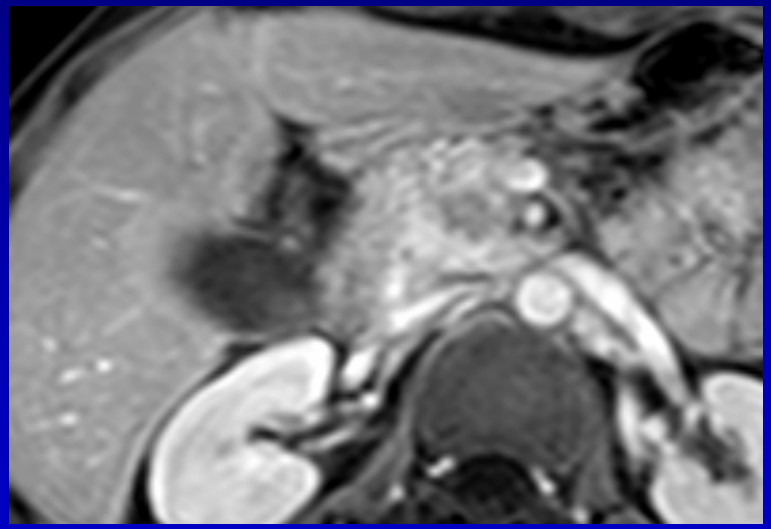


What we know:
Not everyone makes it to Adj Rx

What we do not know:
The biologic impact of surgery first







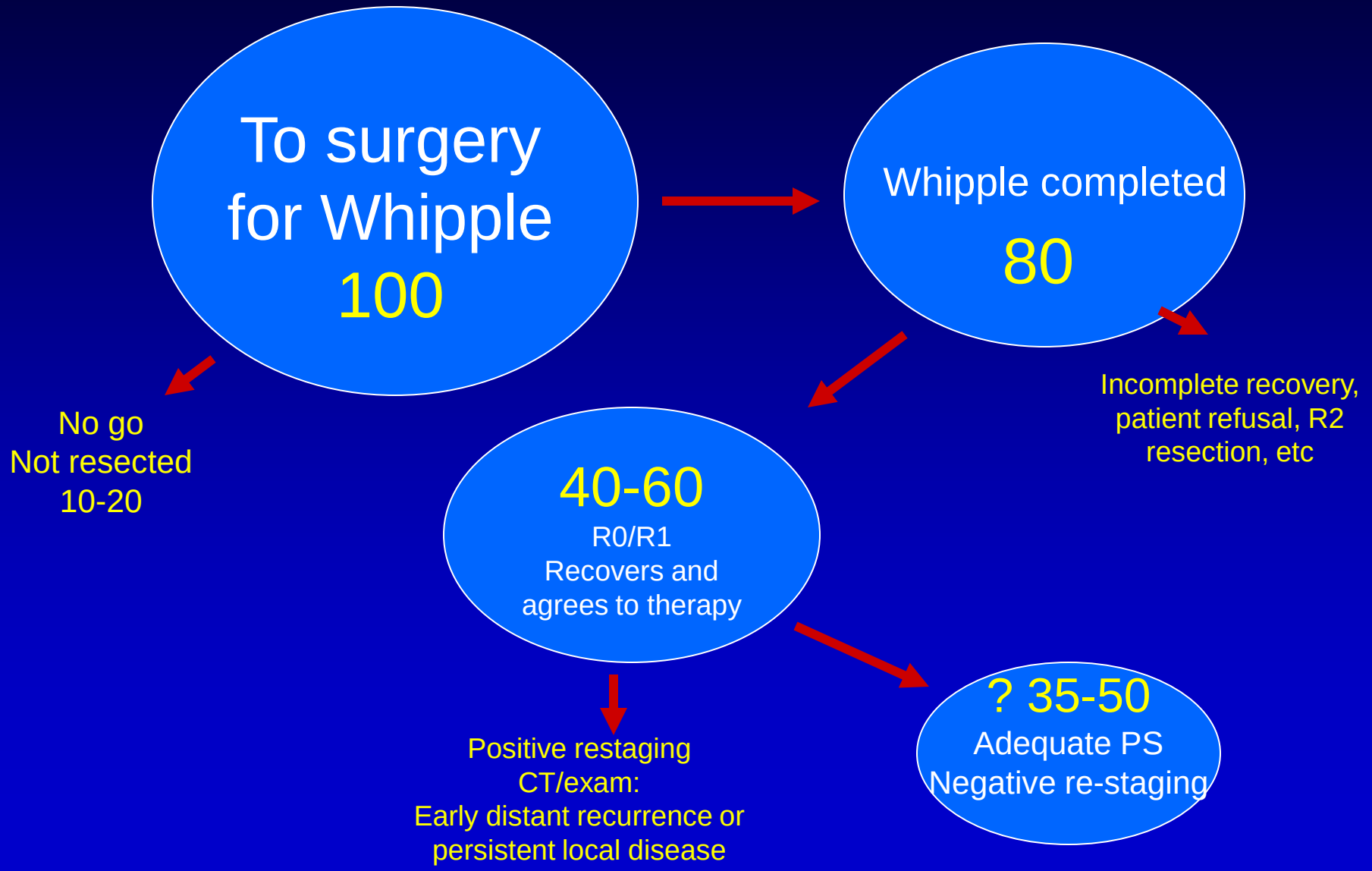
	12/7/2009	12/29/2009	1/5/2010	3/1/2010
BILI T	1.1 (H)			
CA19-9	1312.1 (H)	1726.0 (H)	2195.0 (H)	9083.0 (H)
CEA	2.4	8.3 (H)	9.8 (H)	17.1 (H)

Nov 18, 2009

Gem-cis

JH 00490103

Adjuvant Therapy for pancreatic cancer



All patients do not receive intended adjuvant therapy

Aloia, Pisters, et al. : J Amer Col Surg 2007;204(3):347-55

- Treatment related: surgery complications, delayed recovery
- Disease related: disease progression
- Patient related: age, preoperative PS, medical co-morbidities, patient refusal

---

35% did not receive adjuvant therapy: MDACC

Katz MH, et al. Survival and Quality of Life of Patients with Resected Pancreatic Adenocarcinoma Treated with Adjuvant Interferon-Based Chemoradiation: A Phase II Trial. Ann Surg Oncol. 2011 Jun 24. [Epub ahead of print].

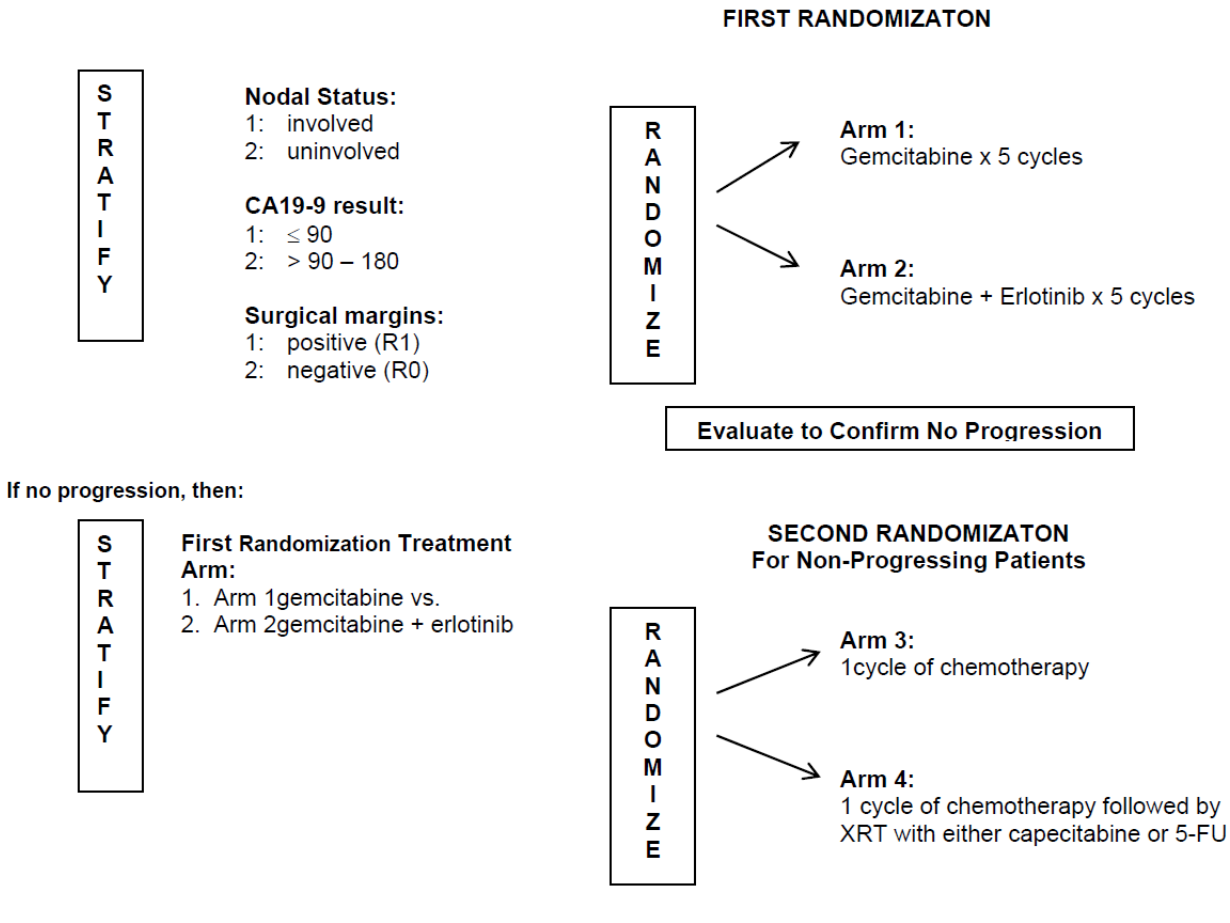
Received intended adjuvant therapy

Corsini, JCO 2008;26:3511-3516-3502 (Mayo)	60%
Herman JCO 2008;26:3503-3510 (Hopkins)	44%
Simons Cancer 2010;116:1681-90 (SEER)	48%
Merchant J Am Coll Surg 2009:208:829-841	50%

RADIATION THERAPY ONCOLOGY GROUP

RTOG 0848
A Phase III Trial Evaluating Both Erlotinib and Chemoradiation as Adjuvant Treatment for Patients with Resected Head of Pancreas Adenocarcinoma

SCHEMA



The operating surgeon must document in the operative note that a complete gross excision of the primary tumor was achieved. The pathology report must include documentation of the margin status and the size of the tumor.

Abdominal/pelvic CT scan with contrast and chest CT/x-ray (CT of chest preferred) within 31 days of registration on study.

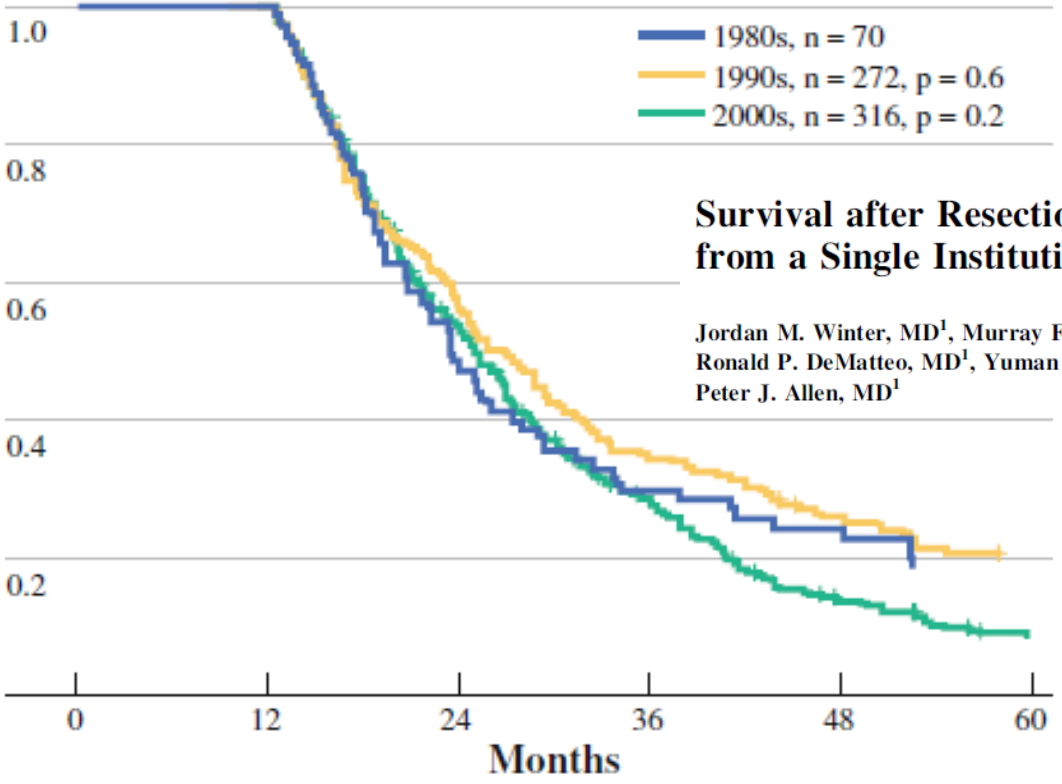


FIG. 3 Long-term survival after pancreatectomy for pancreatic cancer (1-year survivors). 1980s, median = 23.2 months; 1990s, median = 25.6 months; 2000s, median = 24.5 months. *P* values compare the specified decade to the 1980s

Survival after Resection of Pancreatic Adenocarcinoma: Results from a Single Institution over Three Decades

Jordan M. Winter, MD[1], Murray F. Brennan, MD[1], Laura H. Tang, MD[2], Michael I. D'Angelica, MD[1], Ronald P. DeMatteo, MD[1], Yuman Fong, MD[1], David S. Klimstra, MD[2], William R. Jarnagin, MD[1], and Peter J. Allen, MD[1]

Ann Surg Oncol
DOI 10.1245/s10434-011-1900-3

trial. The lack of improvement in long-term survival observed in this study in patients with resected pancreatic cancer underscores the need for improved early detection and novel treatment strategies for this aggressive disease.

Advantages of the neoadjuvant approach

- Provides early treatment of micrometastatic disease (80-90% of “resectable” patients))
- Patients with rapidly progressive disease will not be subjected to surgery
- A logical strategy for the high incidence of positive margins
- Delayed recovery not an issue as the patient is preop

Development of a Clinical Protocol neoadjuvant therapy for pancreatic cancer

1. Write the eligibility section
Objective definition of resectability

↓

Confirmation the diagnosis of cancer:
FNA (CT evolved to EUS)
Endobiliary stents (plastic evolved to metal)

↓

Review patient eligibility
Multidisciplinary Conference

Definitions

Resectable:

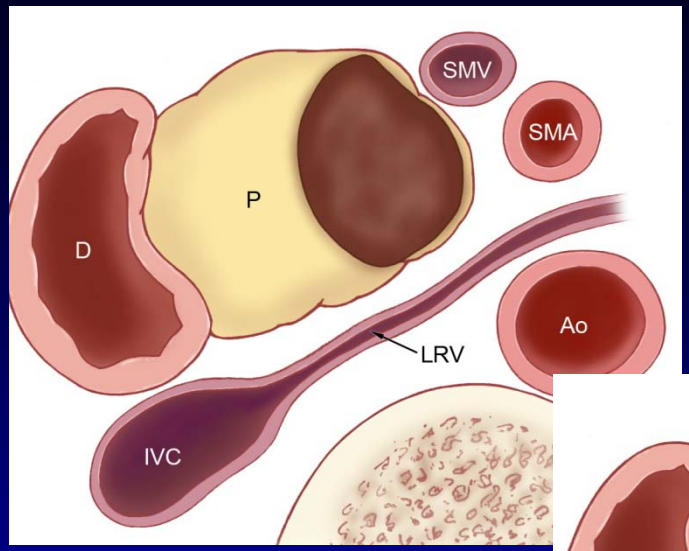
- no extension to celiac, CHA, SMA
- patent SMV-PV confluence
- stage I, II (T1-3, Nx, M0)

Locally Advanced:

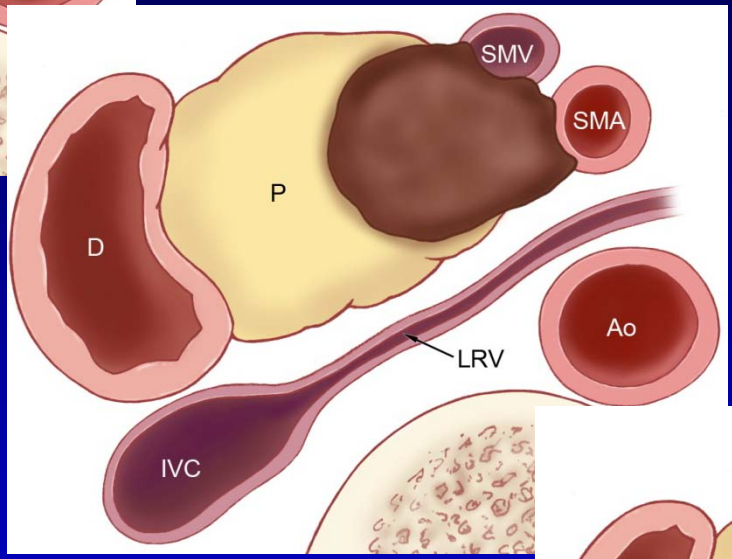
- celiac, SMA encasement ($> 180^0$)
- stage III (T4, Nx, M0)

Borderline:

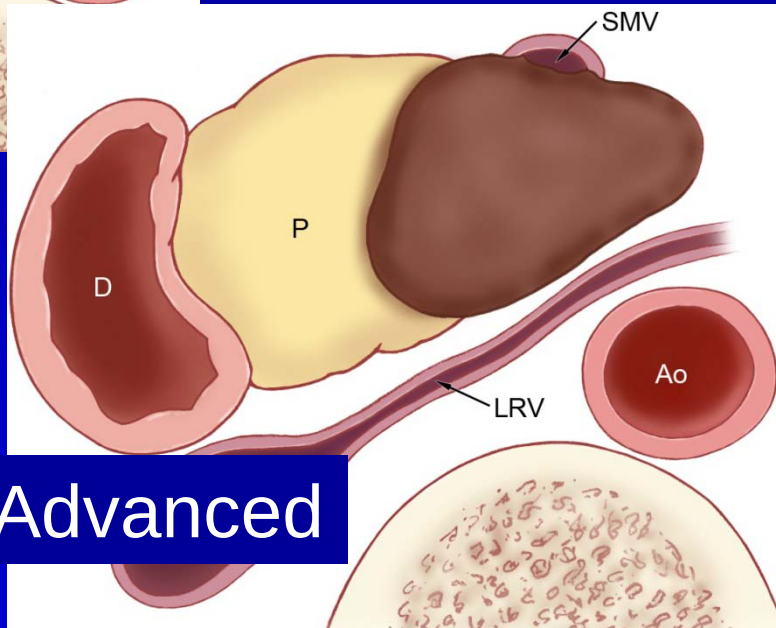
- arterial abutment ($\leq 180^0$)
- stage III (minimal T4)



Resectable

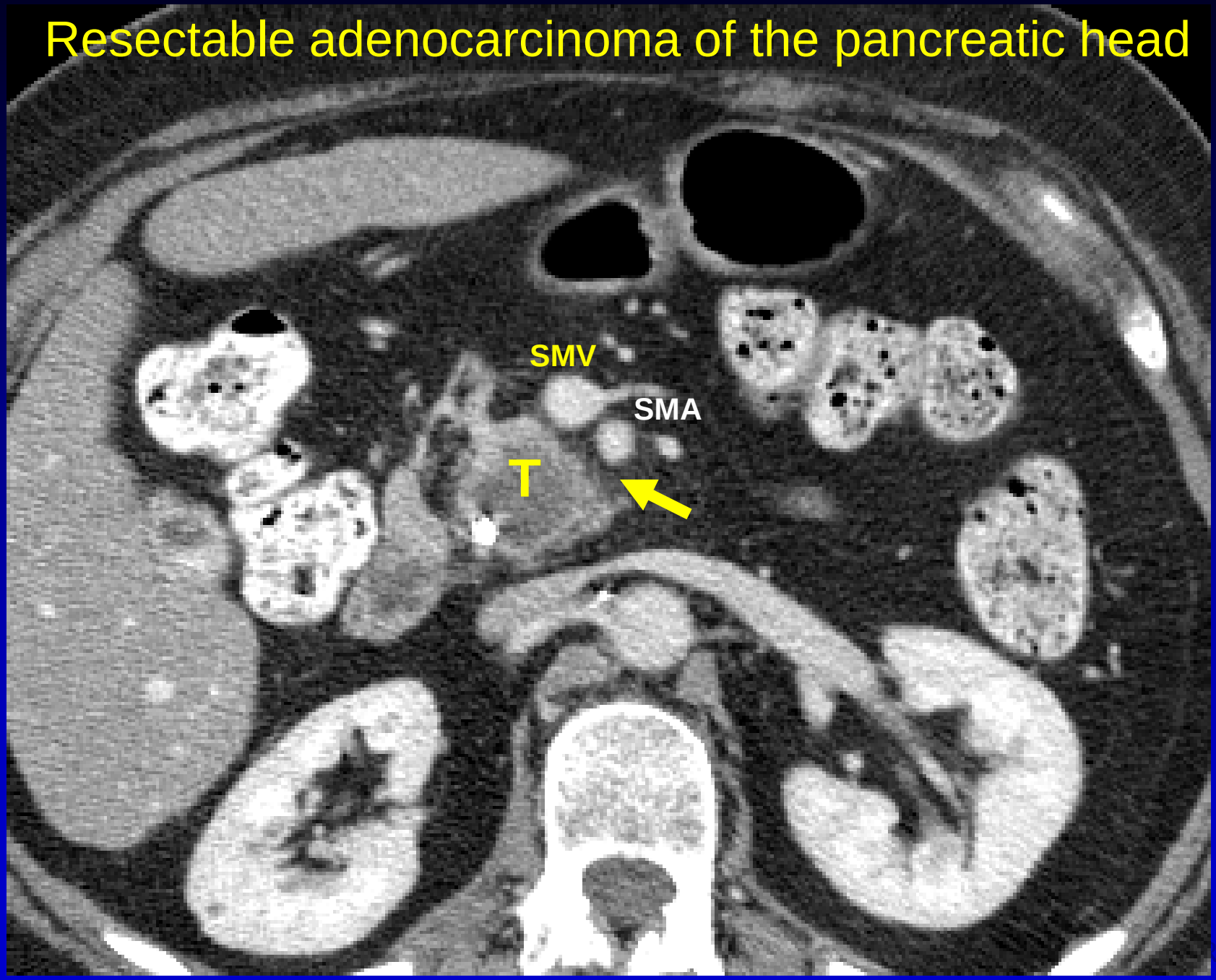


Borderline Resectable

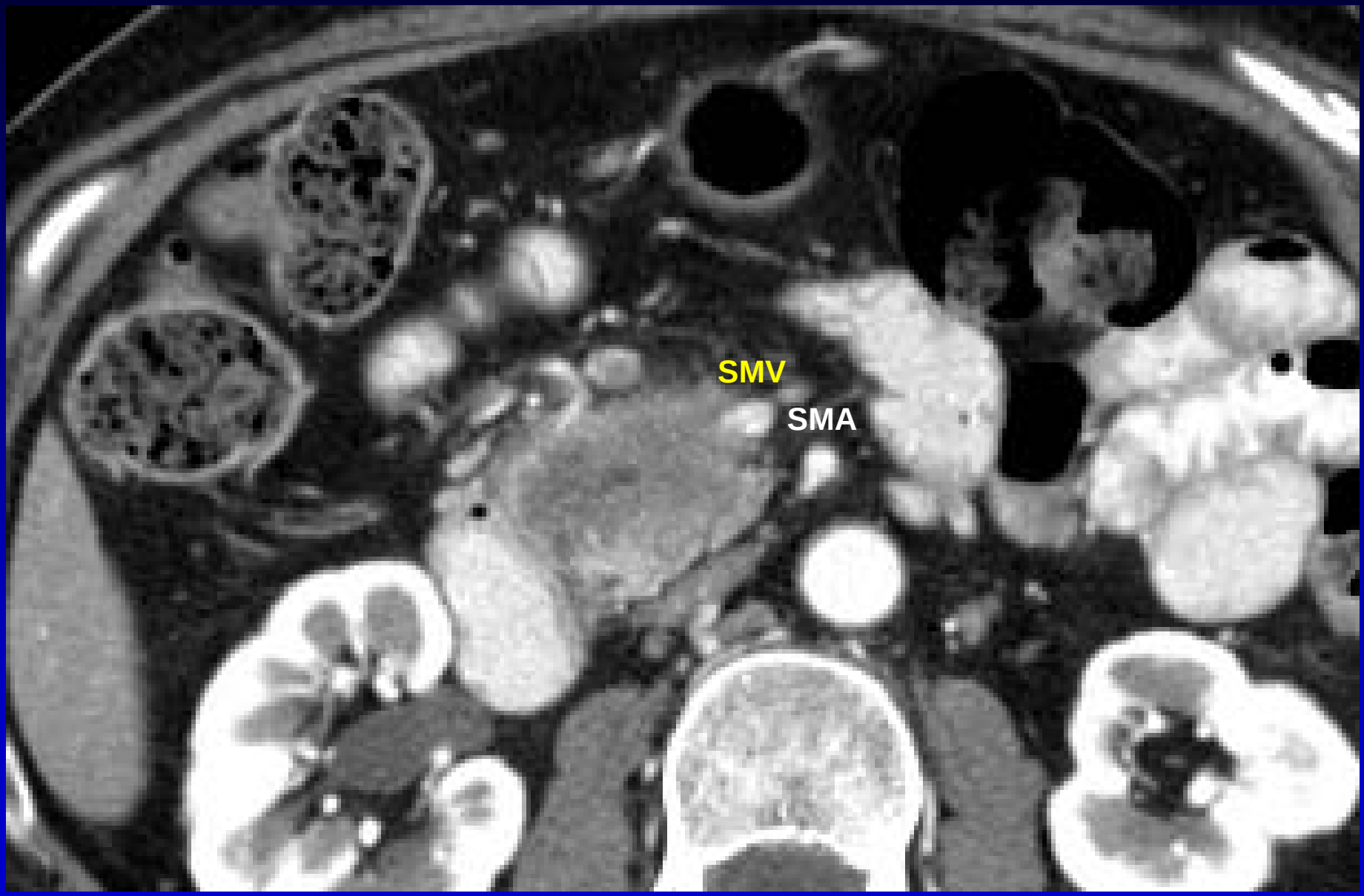


Locally Advanced

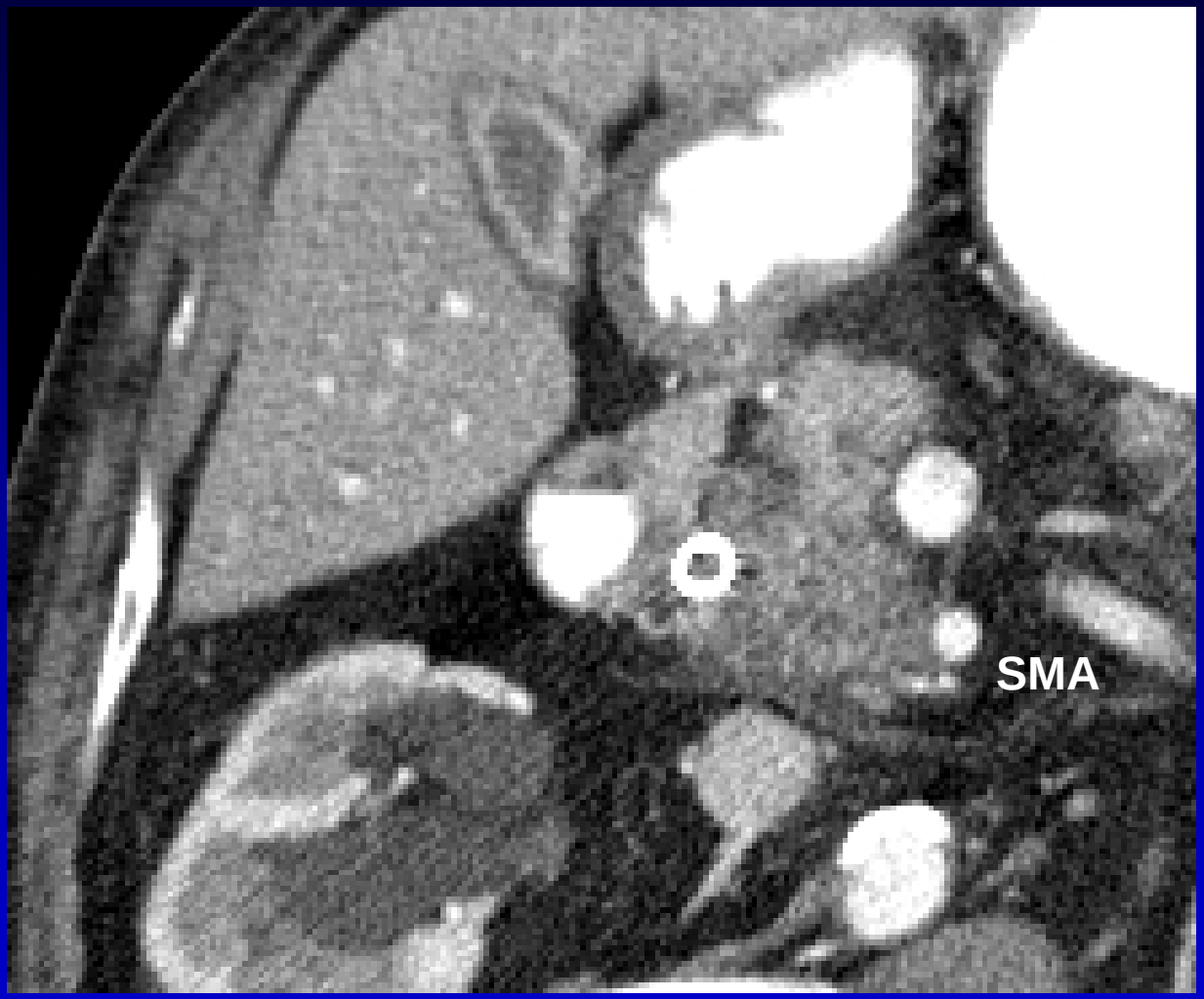
Resectable adenocarcinoma of the pancreatic head



Resectable : likely to require venous resection



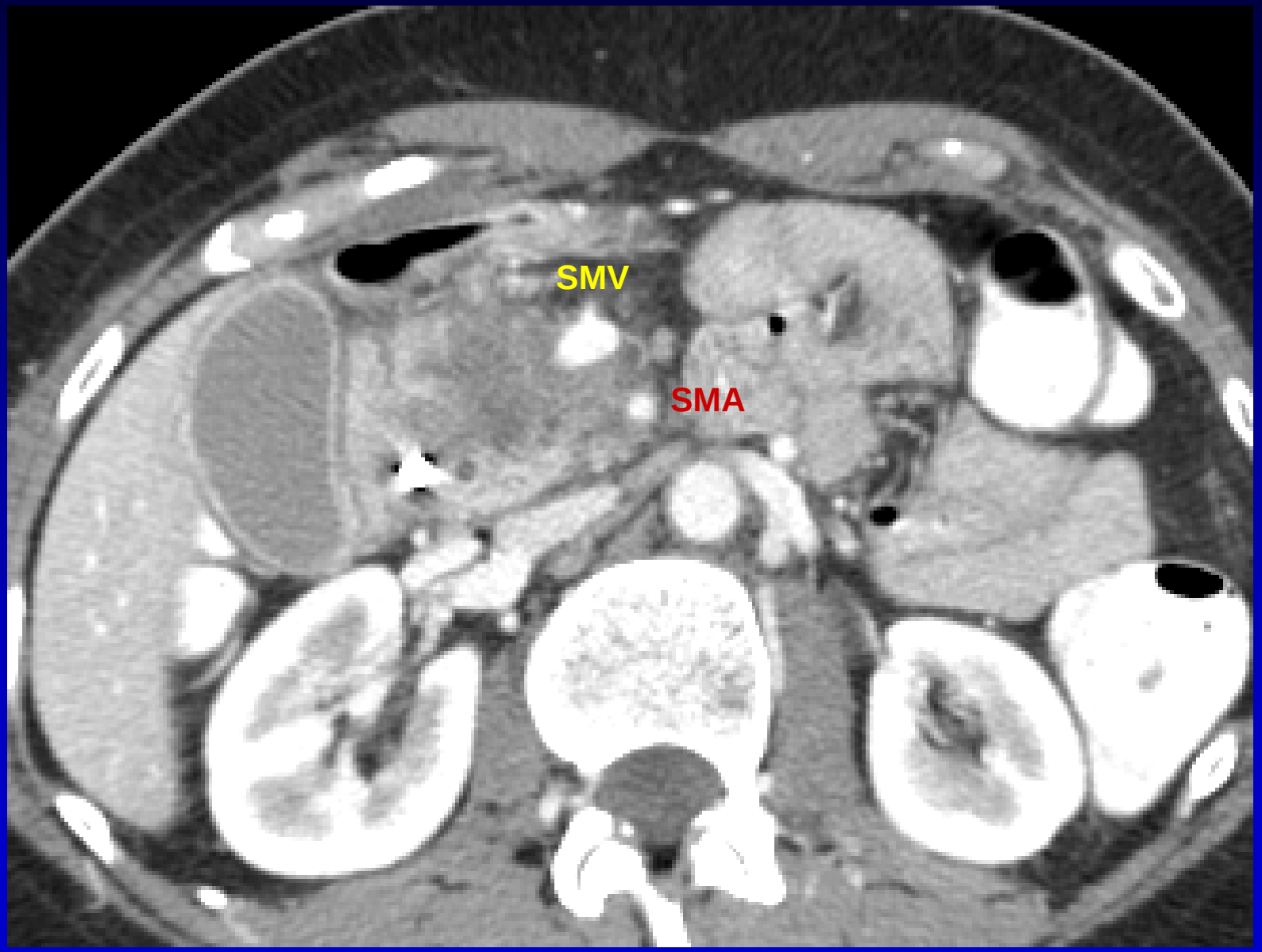
Borderline Resectable



Varadhachary GR, et al. Ann Surg Oncol. 2006;13(8):1035-46

Katz MHG, et al. J Am Coll Surg. 2008;206(5):833-46

Locally Advanced (Stage III)



Imaging Template for Pancreatic Cancer

- Tumor size and location
- Tumor - vein relationship: SMV, portal vein and splenic vein
- Tumor - artery relationship: SMA, celiac axis, common hepatic artery
- Presence or absence of distant metastases: liver, lung, peritoneum

NCCN Guidelines™ Version 2.2011
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Pancreatic Table of Contents
Discussion

CRITERIA DEFINING RESECTABILITY STATUS

Tumors considered localized and resectable should demonstrate the following:

- No distant metastases
- No radiographic evidence of superior mesenteric vein (SMV) and portal vein abutment, distortion, tumor thrombus, or venous encasement
- Clear fat planes around the celiac axis, hepatic artery, and SMA.

Tumors considered borderline resectable include the following:

- No distant metastases
- Venous involvement of the SMV/portal vein demonstrating tumor abutment with impingement and narrowing of the lumen, encasement of the SMV/portal vein but without encasement of the nearby arteries, or short segment venous occlusion resulting from either tumor thrombus or encasement but with suitable vessel proximal and distal to the area of vessel involvement, allowing for safe resection and reconstruction.
- Gastroduodenal artery encasement up to the hepatic artery with either short segment encasement or direct abutment of the hepatic artery, without extension to the celiac axis.
- Tumor abutment of the SMA not to exceed greater than 180 degrees of the circumference of the vessel wall.

Adapted from: Callery MP, Chang KJ, Fishman EK, et al. Pretreatment Assessment of Resectable and Borderline Resectable Pancreatic Cancer: Expert Consensus Statement. Ann Surg Oncol 2009;16:1727-1733.

Tumors considered to be unresectable demonstrate the following:

- **HEAD**
  - Distant metastases
  - Greater than 180 degrees SMA encasement, any celiac abutment
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion or encasement
- **BODY**
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
  - Unreconstructible SMV/portal occlusion
  - Aortic invasion
- **TAIL**
  - Distant metastases
  - SMA or celiac encasement greater than 180 degrees
- **Nodal status**
  - Metastases to lymph nodes beyond the field of resection should be considered unresectable.

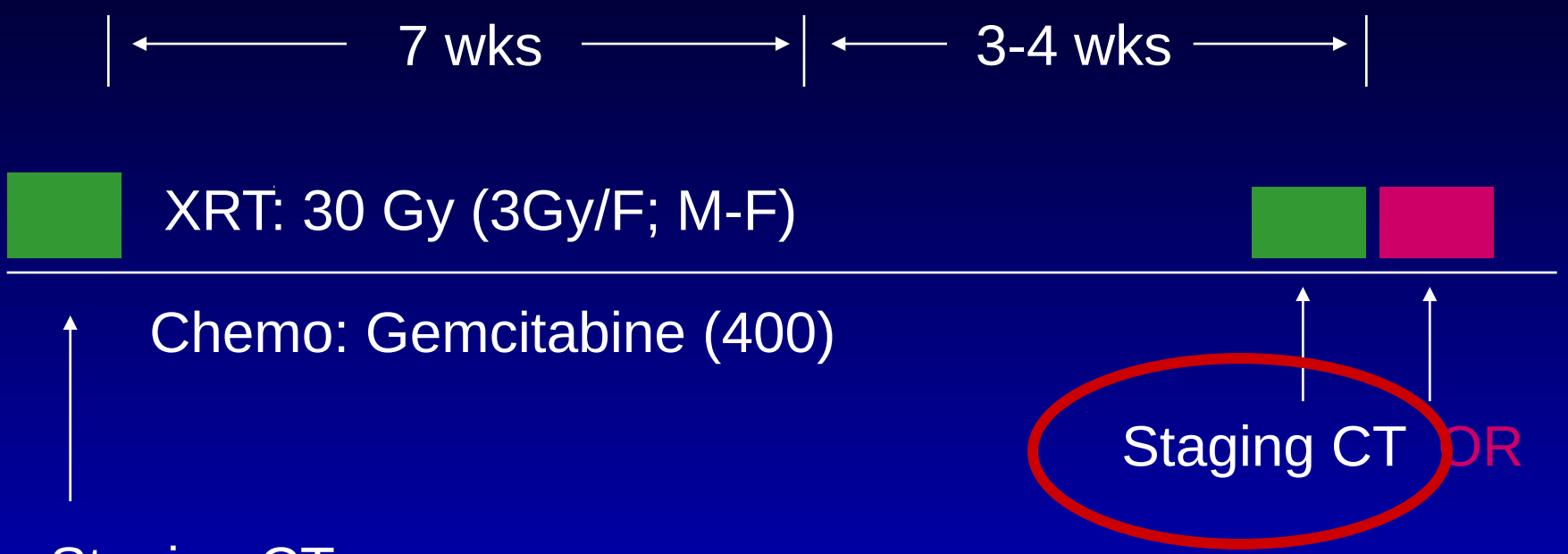
Preop Clinical Trials

investigator initiated – industry supported

Protocol-based preop chemoradiation

- 88-004 50.4 Gy/ 5-FU 300mg/m^2
- 92-002 wide field liver irradiation
- 93-007 30 Gy/ 5-FU 300mg/m^2
- 95-224 30 Gy/paclitaxel 60mg/m^2/wk
- 98-020 30 Gy/Gem 400mg/m^2/wk
- 01-341 Gem/Cis, 30 Gy/Gem
- 05-0784 Gem/Bev, 50.4 Gy
- 08-0459 Gem/Erlotinib +/- XRT

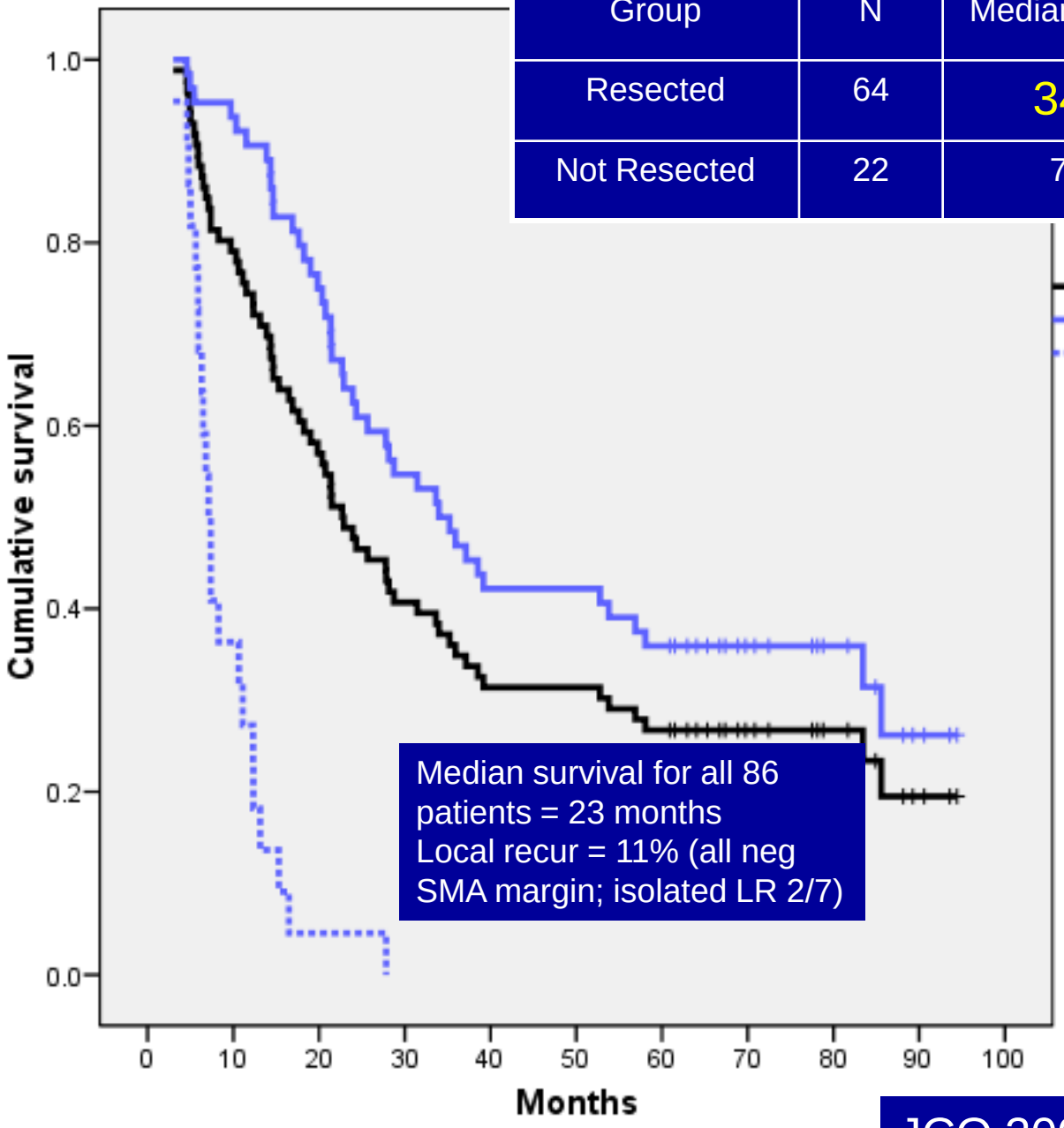
Gem-XRT



3 months

JCO 2008;26:3496-3502

Group	N	Median Survival	5-yr surv
Resected	64	34 mo	21/64
Not Resected	22	7 mo	0



Median survival for all 86 patients = 23 months
Local recur = 11% (all neg SMA margin; isolated LR 2/7)

98-020 GemXRT

JCO 2008;26:3496-3502

Is a window of opportunity lost with the neoadjuvant approach?

- Local progression during neoadjuvant therapy
  - No (but chemo alone without postop chemoXRT untested)

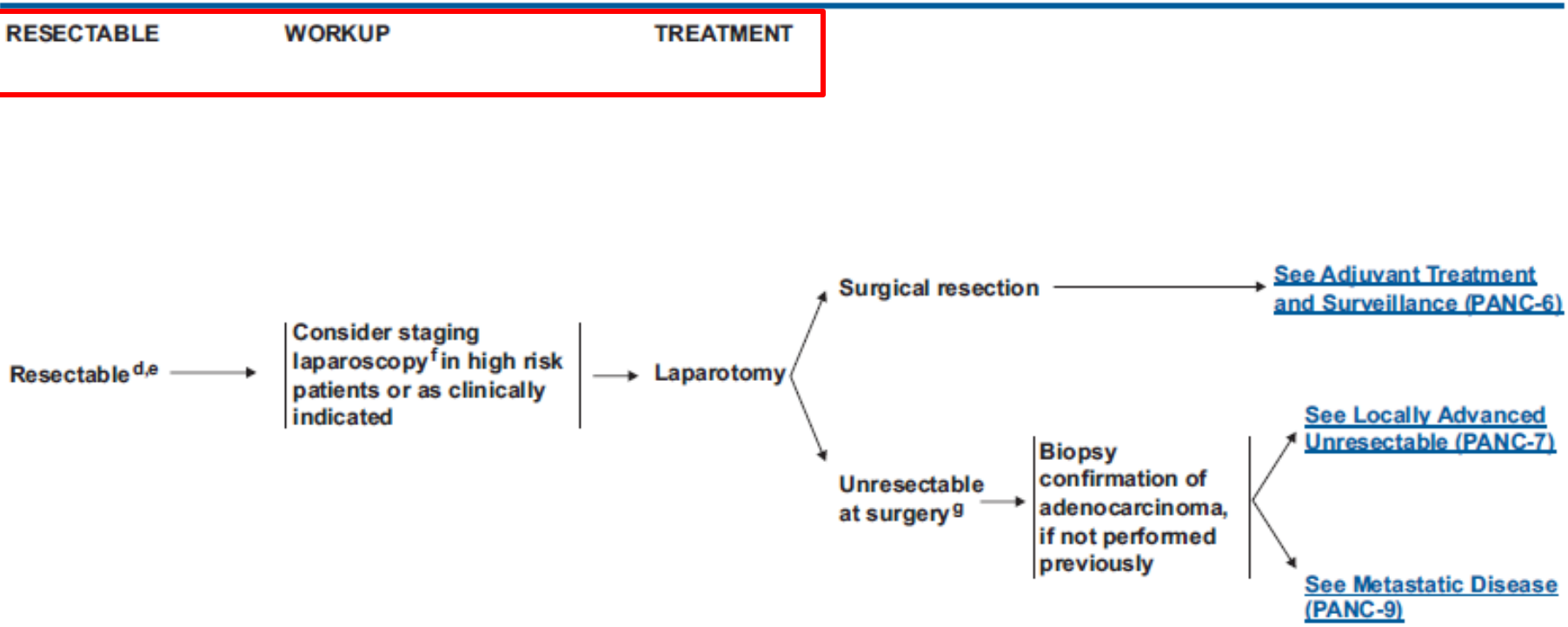
  JCO 2008;26:3496-3502

  JCO 2008;26:3487-3495

  (1/176 patients (0.6%)

- Distant metastases develop during neoadjuvant therapy?
  - Already there in the majority of patients
  - Small volume disease may be more responsive to systemic therapy (improved survival in resected patients)

NCCN Guidelines™ Version 2.2011
Pancreatic Adenocarcinoma



[d] See Criteria Defining Resectability Status (PANC-B).
[e] Consider neoadjuvant therapy on clinical trial. This requires biopsy confirmation of adenocarcinoma, and for patients with biliary obstruction, durable biliary decompression.
[f] See Principles of Diagnosis and Staging (PANC-A).
[g] See Principles of Palliation and Supportive Care (PANC-C).

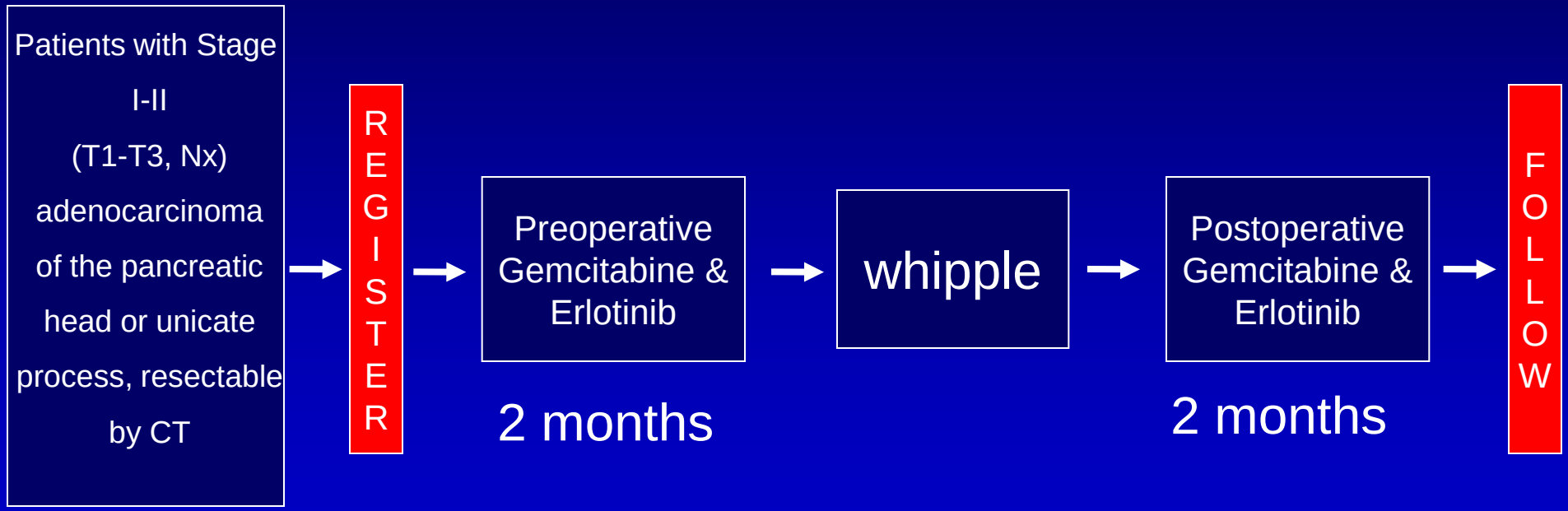
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ACOSOG Z5041: phase II (operable pancreatic adenocarcinoma)

2008

preop / postop Gem / Tarceva

surgery



Accrual goal = 91
Central review of CT / path
Protocol-specific operative summary

Pisters PWT, et al

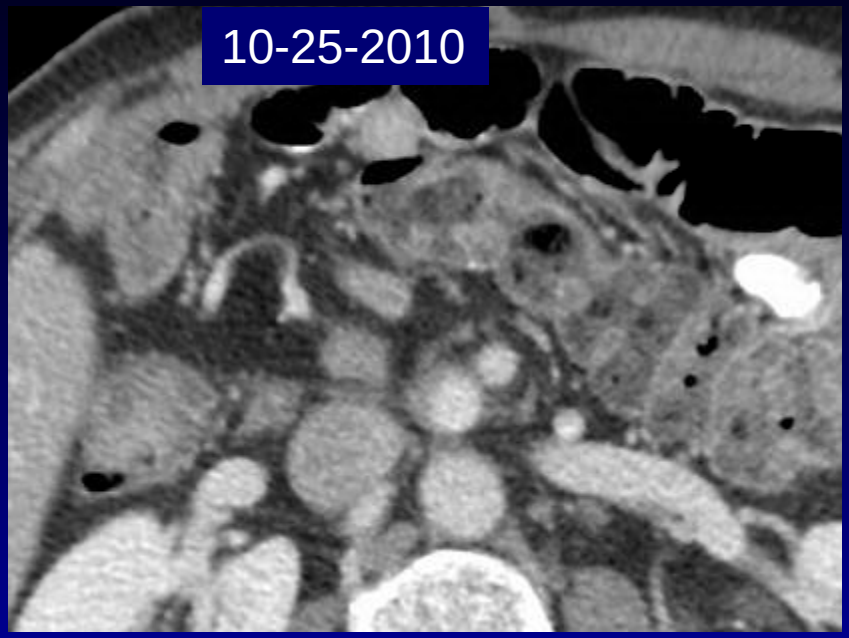
ACOSOG Z5041

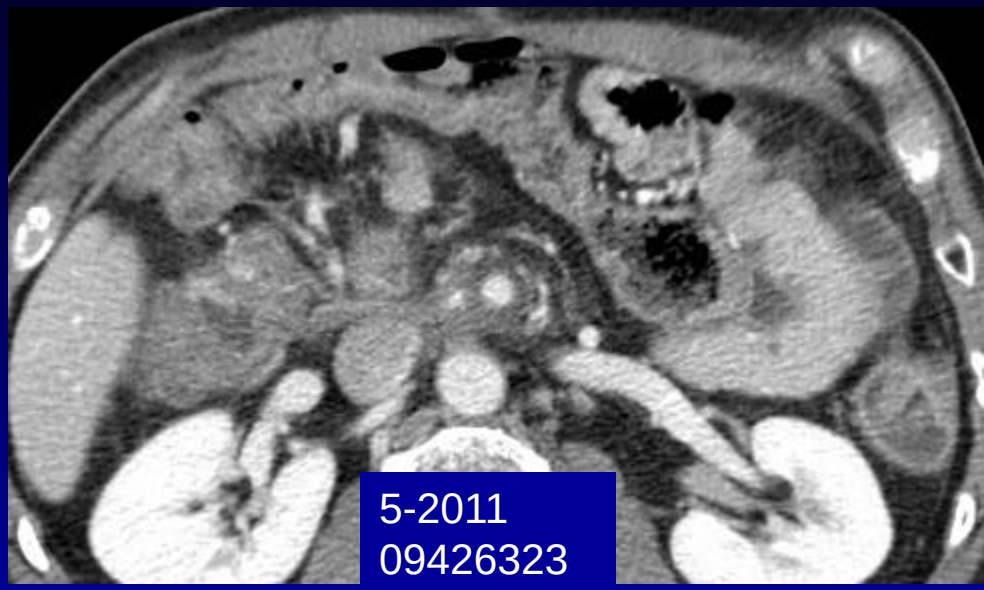
10-22-2009
JC 09426323

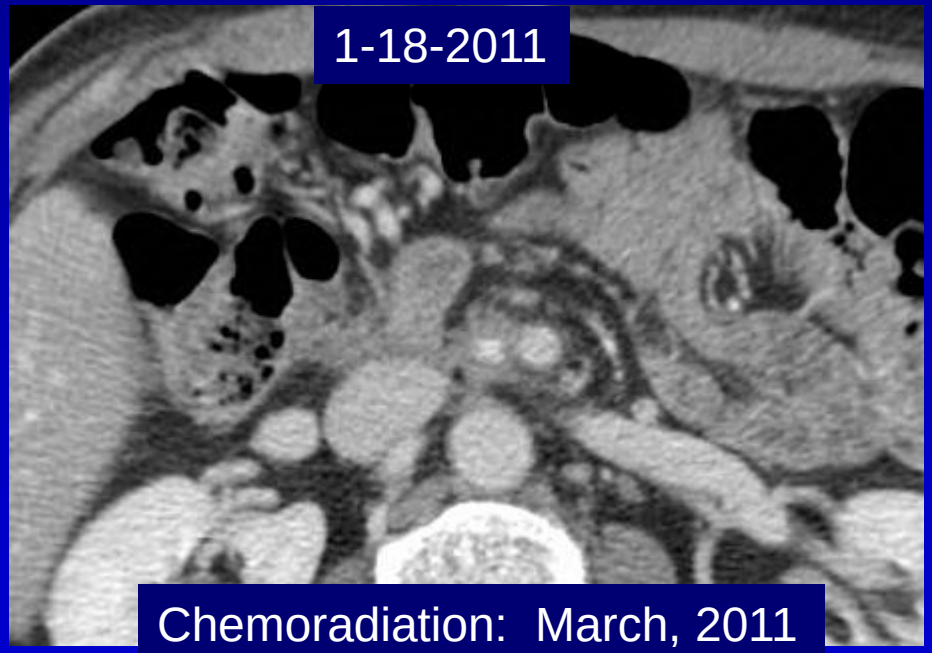
4-2010

SURGICAL MARGINS:
All negative
Superior mesenteric artery margin - Negative, tumor distance from bed margin 0.6 cm (Slide G4)
PRIMARY TUMOR (pT): pT3:
LYMPH NODES:
Total number of lymph nodes involved: 0
Total number of lymph nodes examined: 43

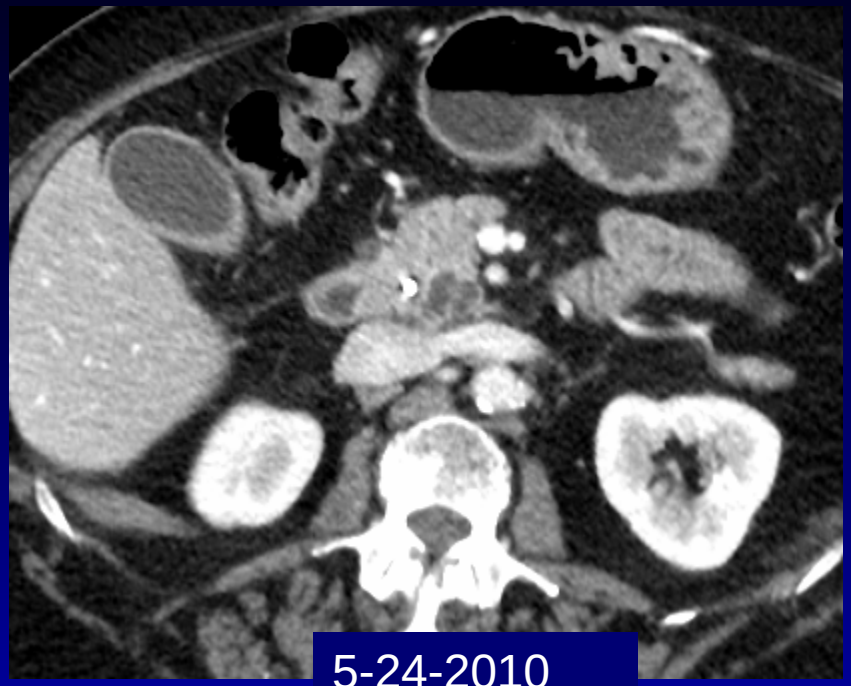
ACOSOG Z5041



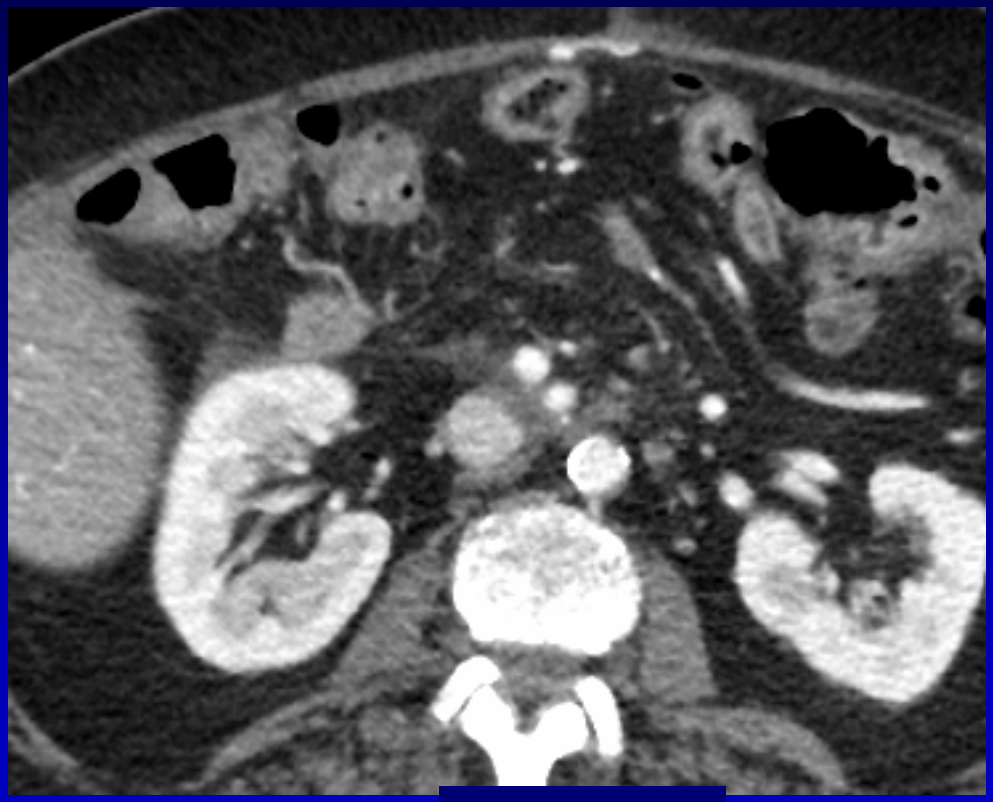




ACOSOG Z5041



5-24-2010
JB 09456340



10-10-2010

SURGICAL MARGINS:
All surgical margins are free of tumor
Distance of invasive carcinoma from SMA margin: 10.0 mm
PRIMARY TUMOR (pT): pT3
LYMPH NODES:
Total number of lymph nodes involved: 0
Total number of lymph nodes examined: 22

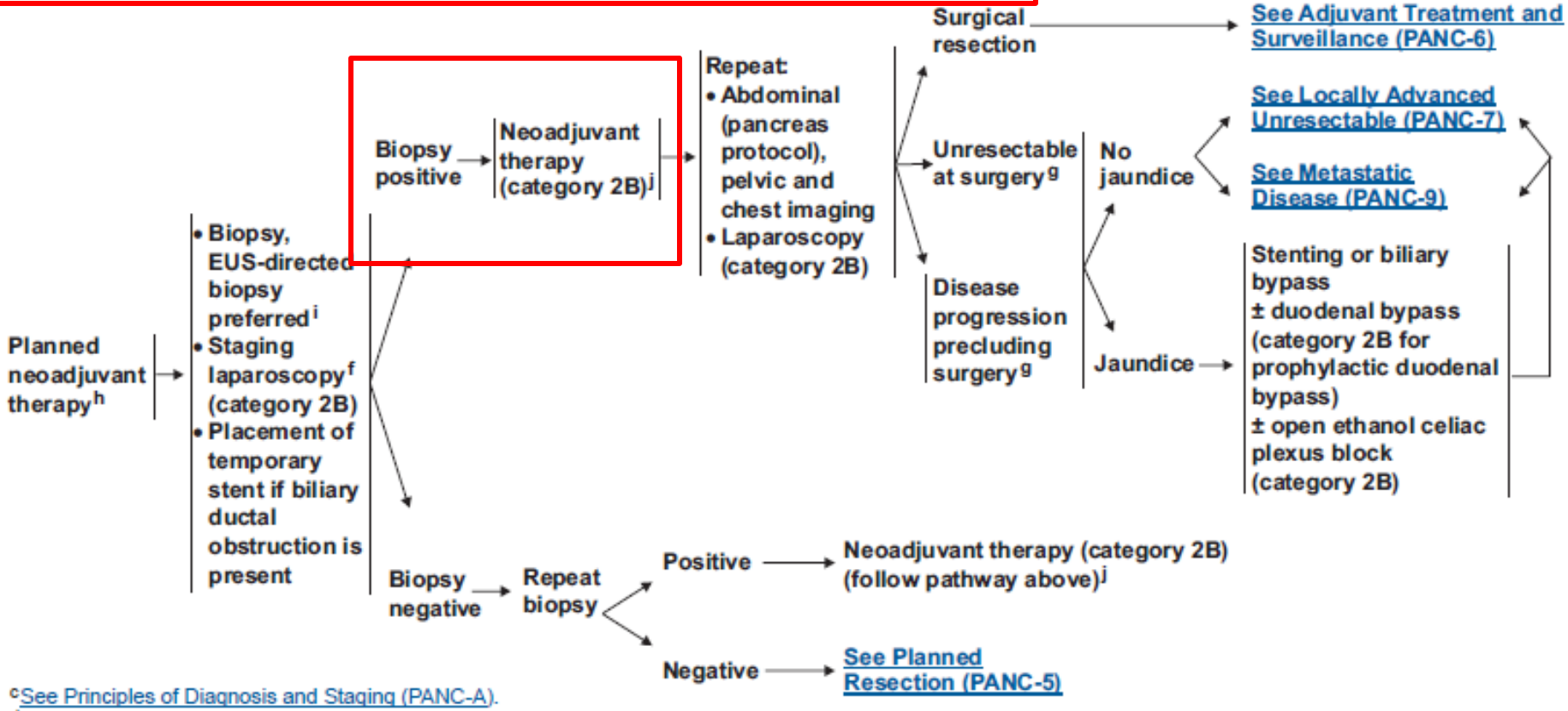
3-14-2011
09456340

6-10-2011

NCCN Guidelines™ Version 2.2011
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Pancreatic Table of Contents
Discussion

BORDERLINE RESECTABLE[c,d] NO METASTASES, PLANNED NEOADJUVANT THERAPY



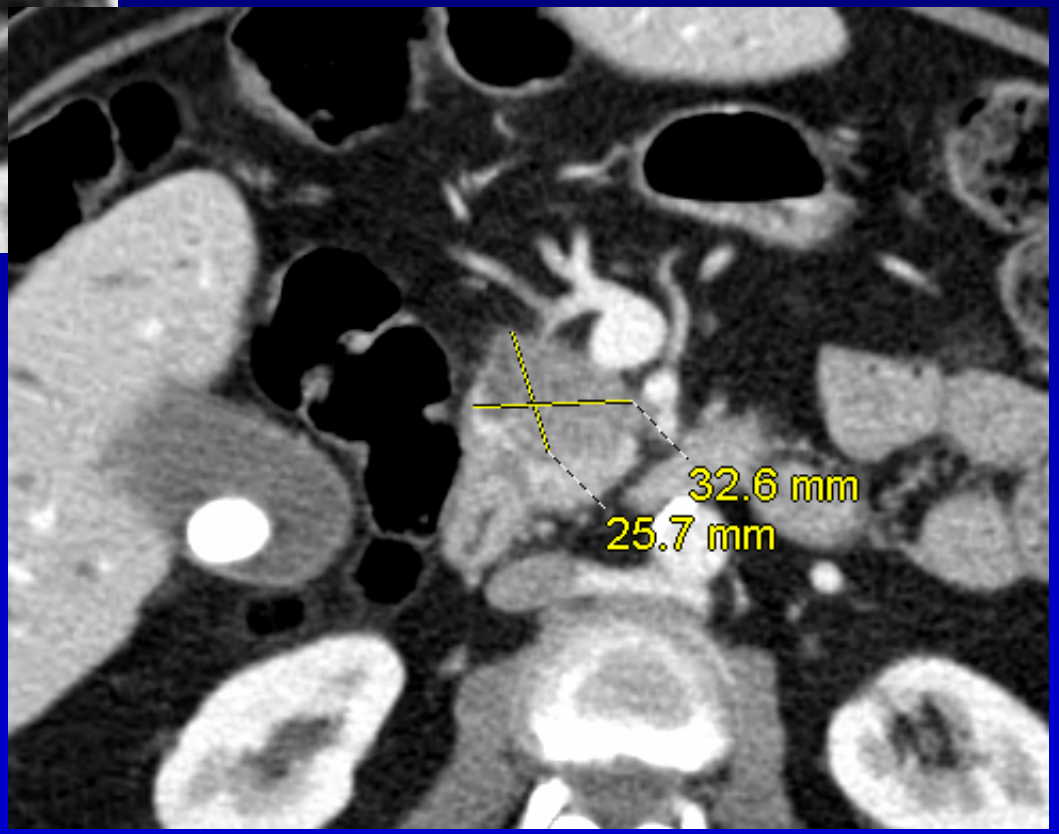
[c] See Principles of Diagnosis and Staging (PANC-A).
[d] See Criteria Defining Resectability Status (PANC-B).
[f] See Principles of Diagnosis and Staging #6 (PANC-A).
[g] See Principles of Palliation and Supportive Care (PANC-C).
[h] Most NCCN institutions prefer neoadjuvant therapy in the setting of borderline resectable disease at a high volume center. Performing surgery with a high likelihood of a positive margin is not recommended.
[i] See Principles of Diagnosis and Staging #1 and #5 (PANC-A).
[j] See Principles of Radiation Therapy (PANC-D).

KM 09463789

67 woman

Presented with painless jaundice

Initial CT: July 12, 2010

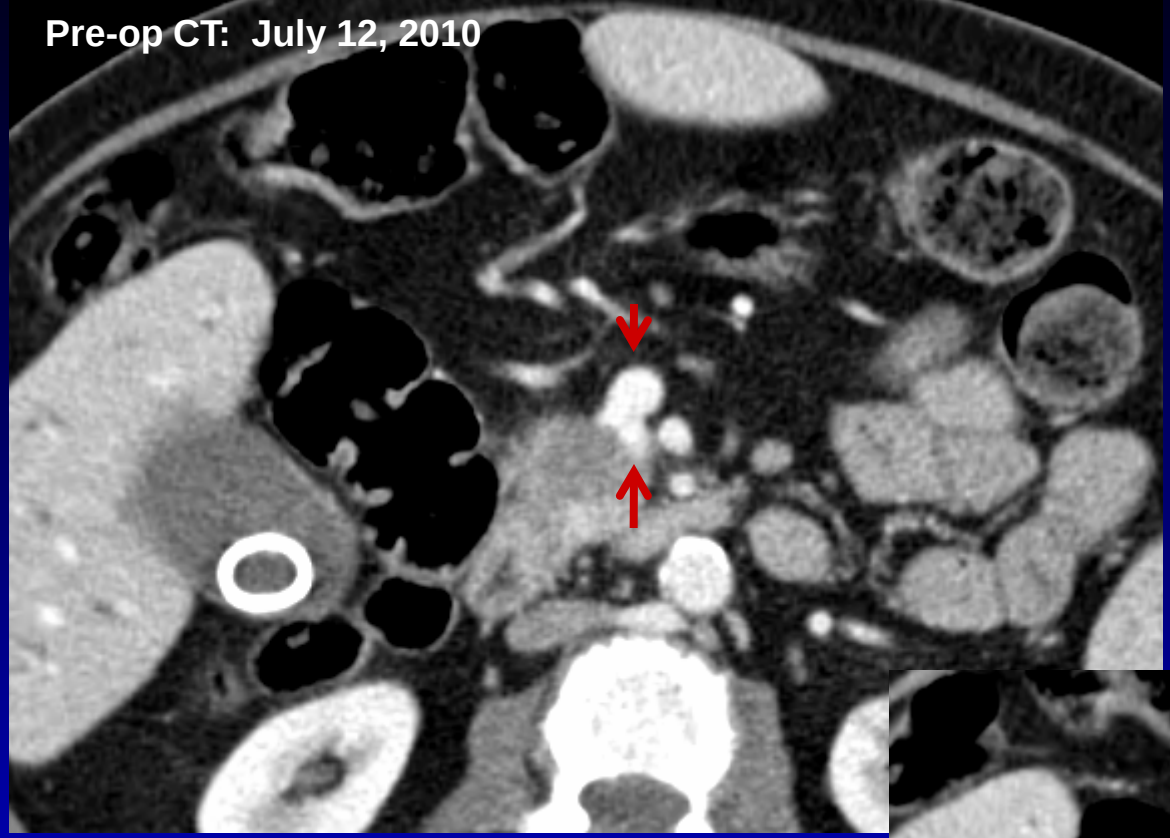


A preoperative CT scan had documented several enlarged lymph nodes.

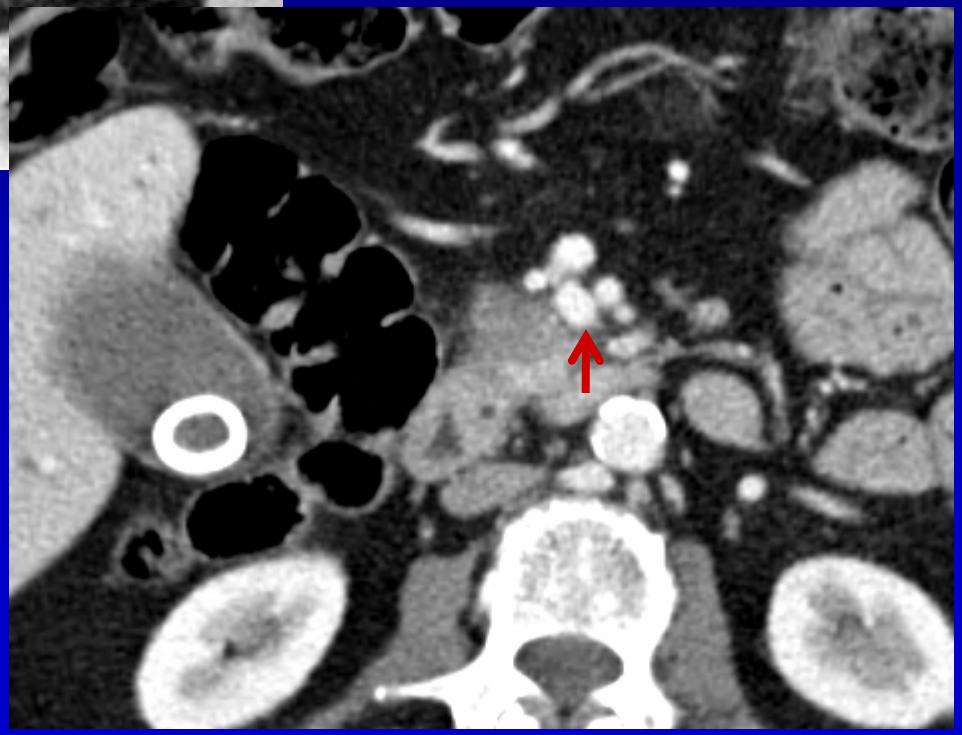
Further exploration of the porta hepatis and hepatoduodenal ligament identified a enlarged lymph node. A biopsy of this lymph node documented metastatic adenocarcinoma consistent with a pancreatic primary. This lymph node was outside the margins of a pancreatoduodenectomy and, therefore, a Whipple procedure was not performed.

Date of operation: 7-18-2010 (dictated 7-26-2010)

KM 09463789

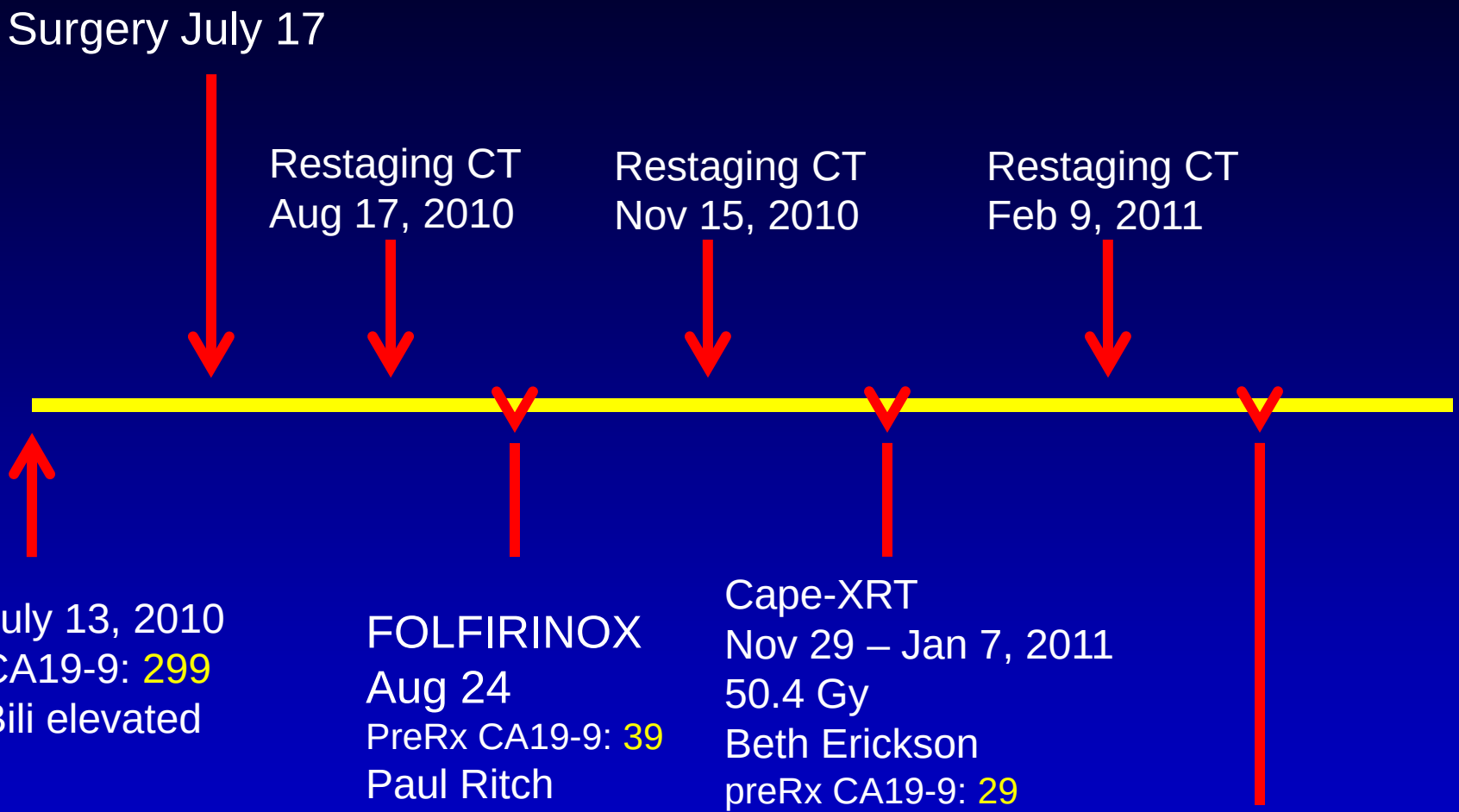


Referred to MCW medical oncology (Dr. Ritch)
Aug 10, 2010



Postop / Pre-chemo CT, Aug 17, 2010:

Mesenteric venous anatomy and tumor involvement: Tumor abuts the proximal anterior/lateral aspect of the main SMV trunk without encasement. The first jejunal branch courses normally under the SMA and there is tumor abutment with mild narrowing at the origin of the first jejunal branch (series 5, image 185; series 457, image 23). The ileal branches are free of disease.


Surgery July 17
Restaging CT
Aug 17, 2010
Restaging CT
Nov 15, 2010
Restaging CT
Feb 9, 2011
July 13, 2010
CA19-9: 299
Bili elevated
FOLFIRINOX
Aug 24
PreRx CA19-9: 39
Paul Ritch
Cape-XRT
Nov 29 – Jan 7, 2011
50.4 Gy
Beth Erickson
preRx CA19-9: 29
Reoperative Whipple
March 9, 2011
Preop CA19-9: 16

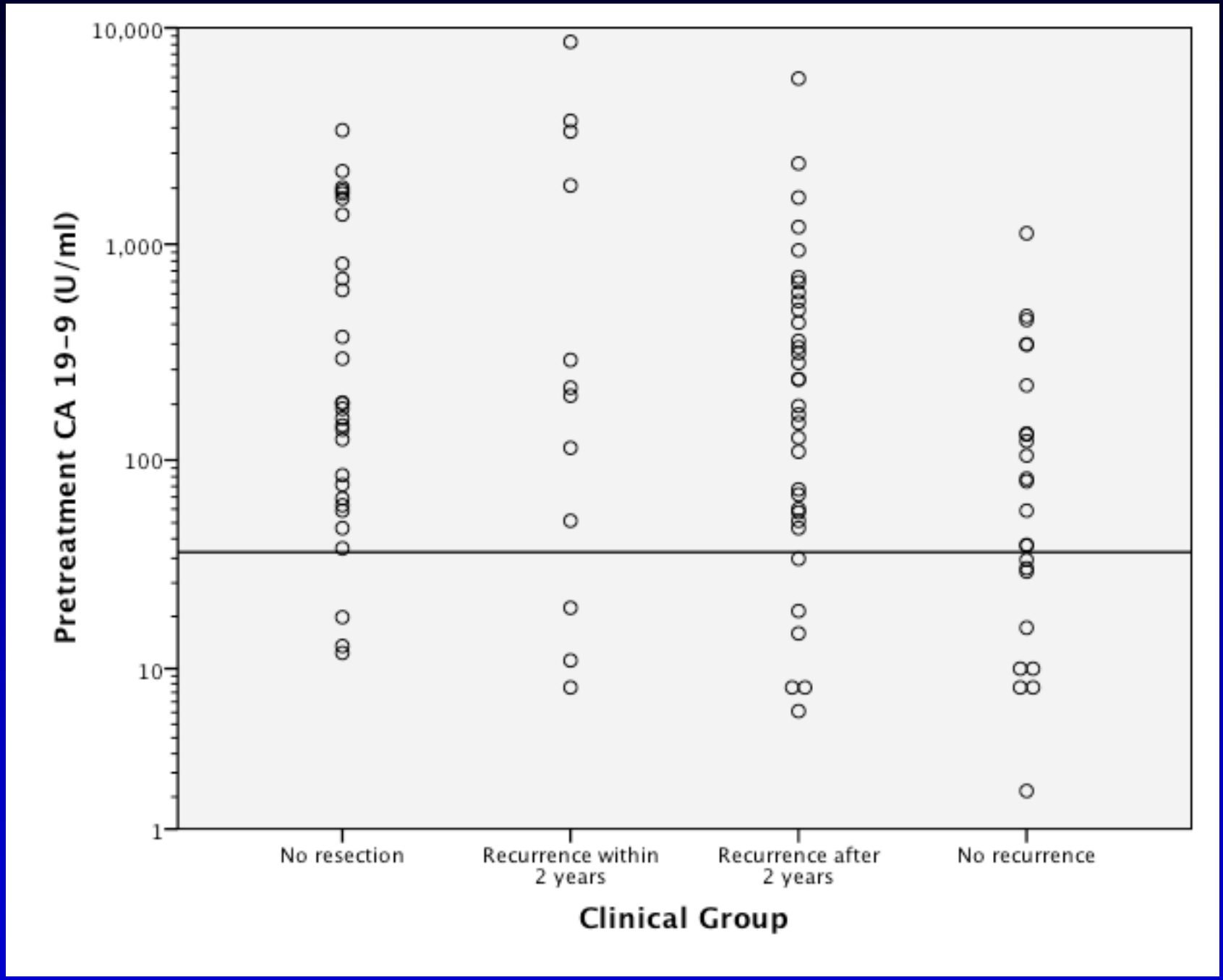
Tumor Characteristics:
G: Whipple Resection, Pancreas (Exocrine)

TUMOR SITE: Pancreatic head
TUMOR SIZE: Greatest dimension: 3.2 cm
HISTOLOGIC TYPE: Ductal adenocarcinoma
HISTOLOGIC GRADE: Moderately differentiated
MITOTIC ACTIVITY: Absent
IN SITU CARCINOMA: In situ carcinoma is also present
EXTRAPANCREATIC EXTENSION: No extrapancreatic extension is identified
DIRECT EXTENSION: The tumor does not extend into the adjacent structures
VASCULAR INVASION: Absent
PERINEURAL INVASION: Absent
SURGICAL MARGINS: All surgical margins are free of tumor
Distance of invasive carcinoma from closest margin: 4mm (SMA)

PRIMARY TUMOR (pT):
pT2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
LYMPH NODES:
Total number of lymph nodes involved: 0
Total number of lymph nodes examined: 16

Figure 2A

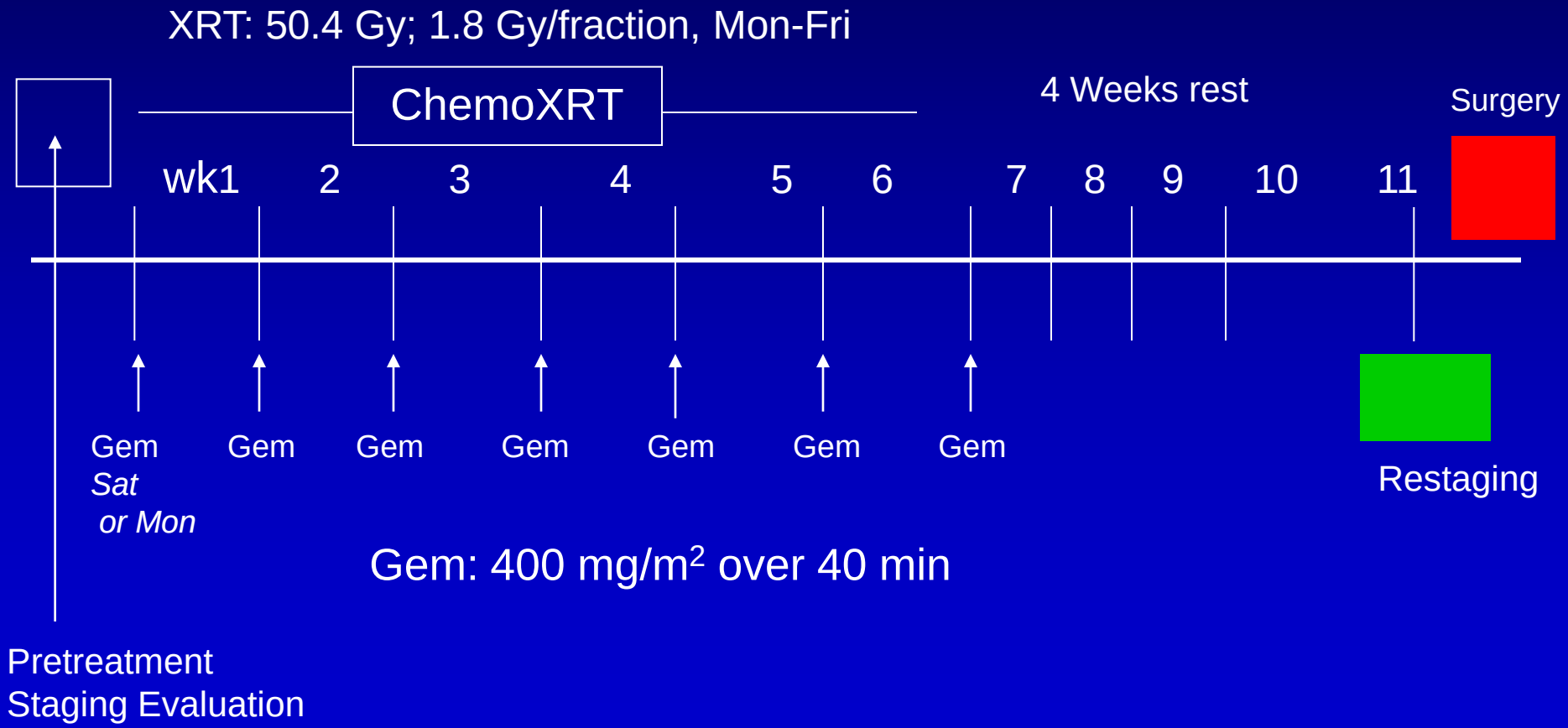
Katz M, et al: Ann Surg Oncol 2010:17;1794-1801

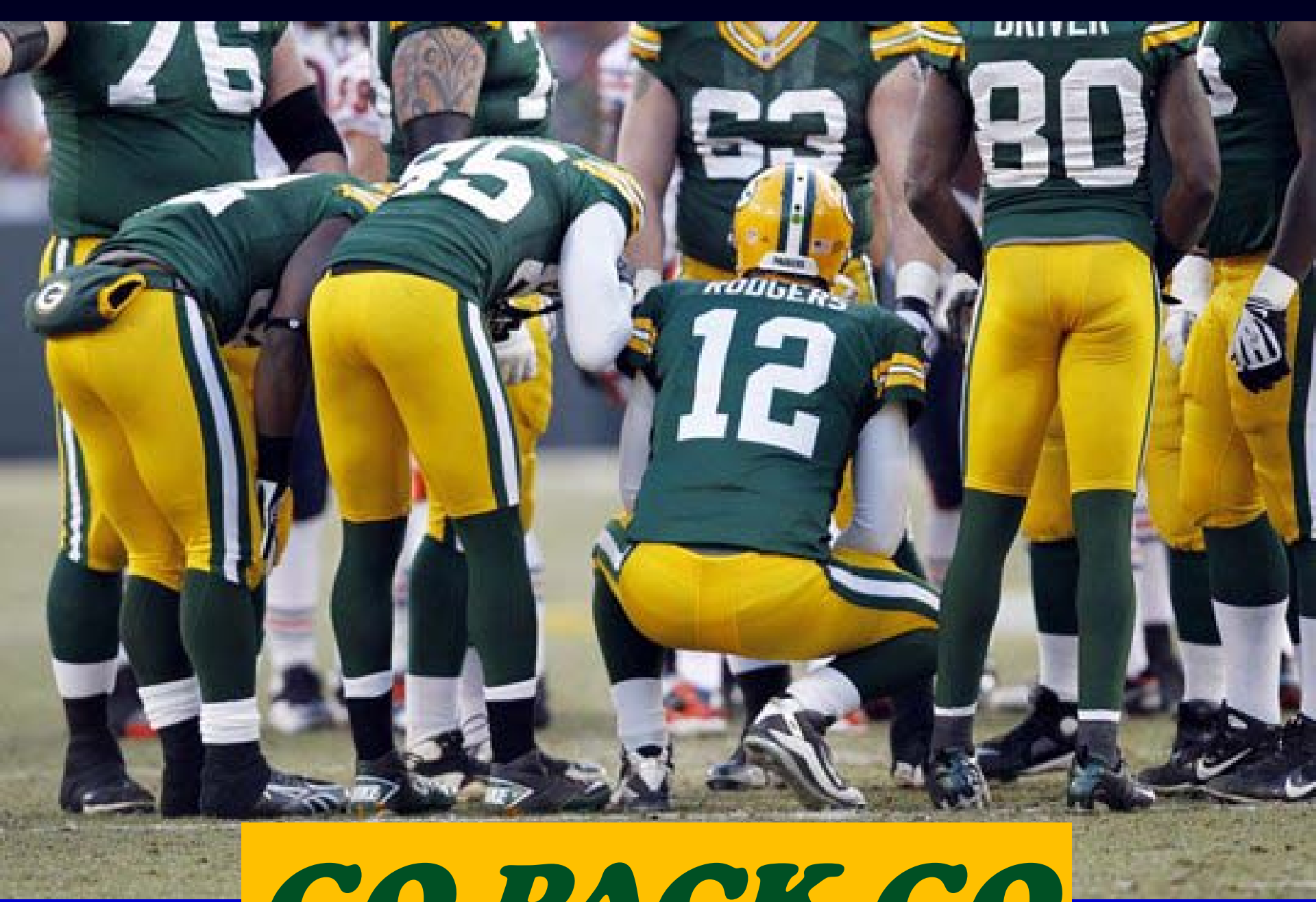


Medical College of Wisconsin

Pancreatic Cancer Program: off-protocol therapy of resectable pancreatic cancer

TREATMENT SCHEMA: Pre-op Gem-XRT





GO PACK GO

Extra-hepatic obstruction of the bile duct on CT *with a pancreatic mass*

Metal stent regardless of stage of disease / resectability status (as surgery will not be the first treatment)

↓ EUS

Be sure this is a good quality CT!!

Positive for adenocarcinoma

↓ ERCP – stent (metal)

Discuss at multidisciplinary conference

Resectable

Borderline Resectable
Locally Advanced

Metastatic

Clinical Trial when possible
Neoadjuvant therapy favored

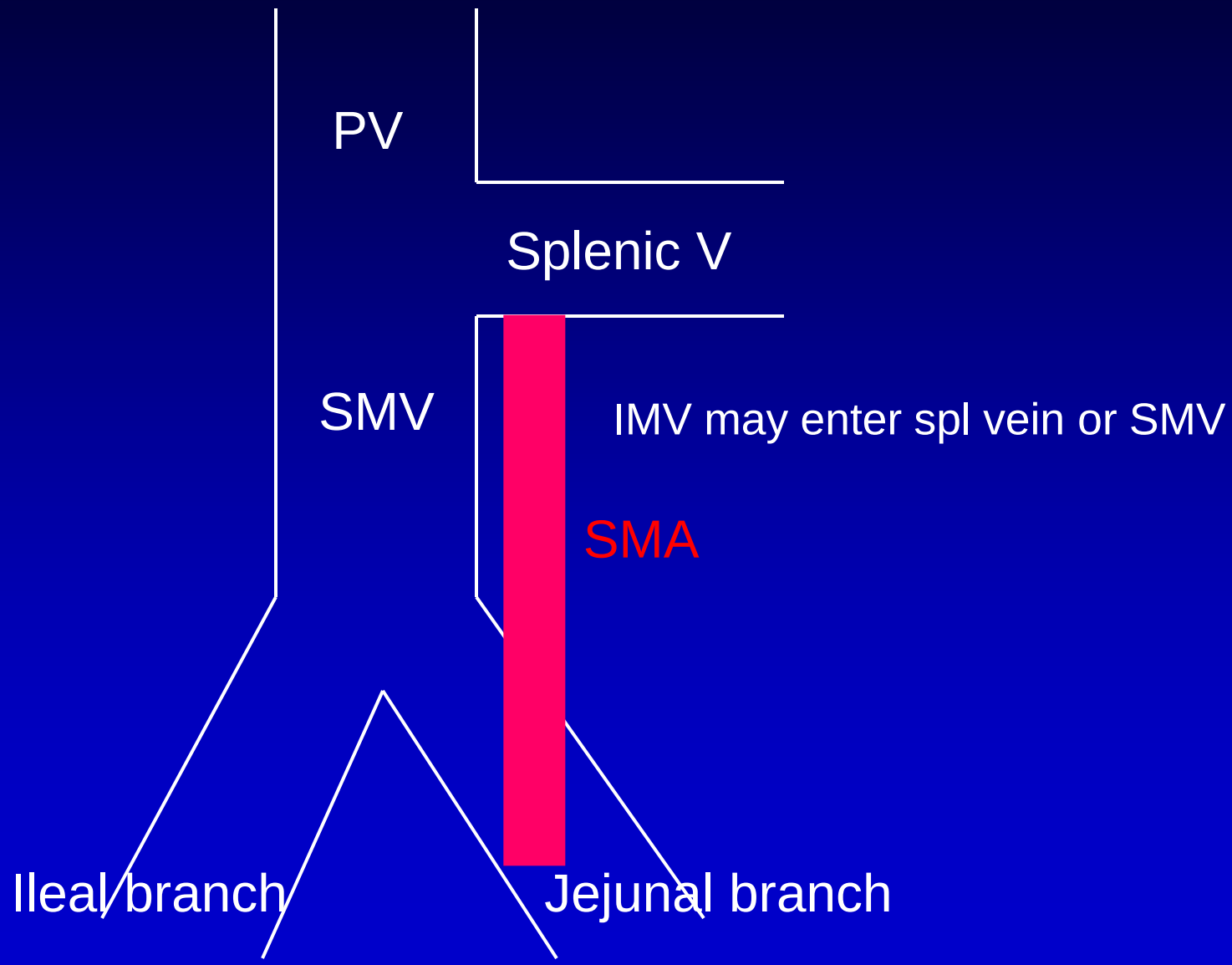
Criticisms of Neoadjuvant Therapy for Resectable Pancreatic Cancer

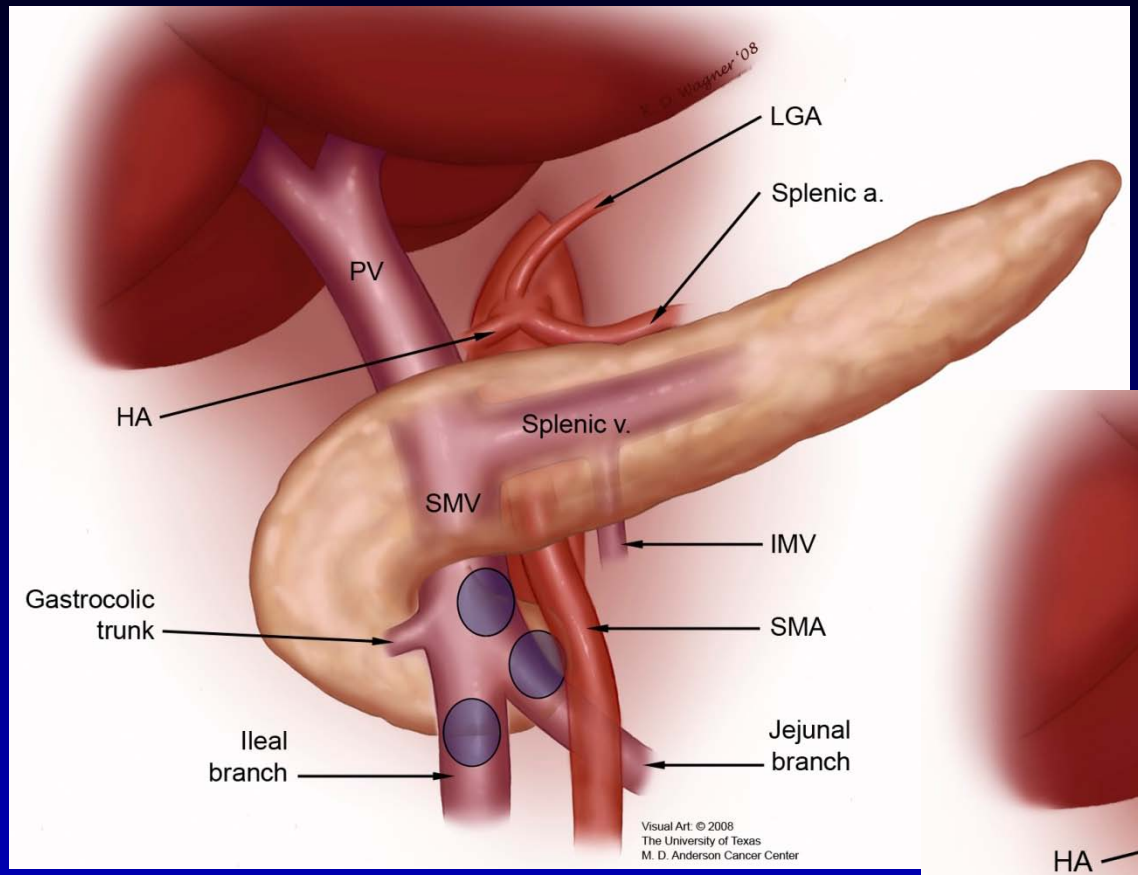
Only real “shot” for the patient is surgery – other therapies largely ineffective

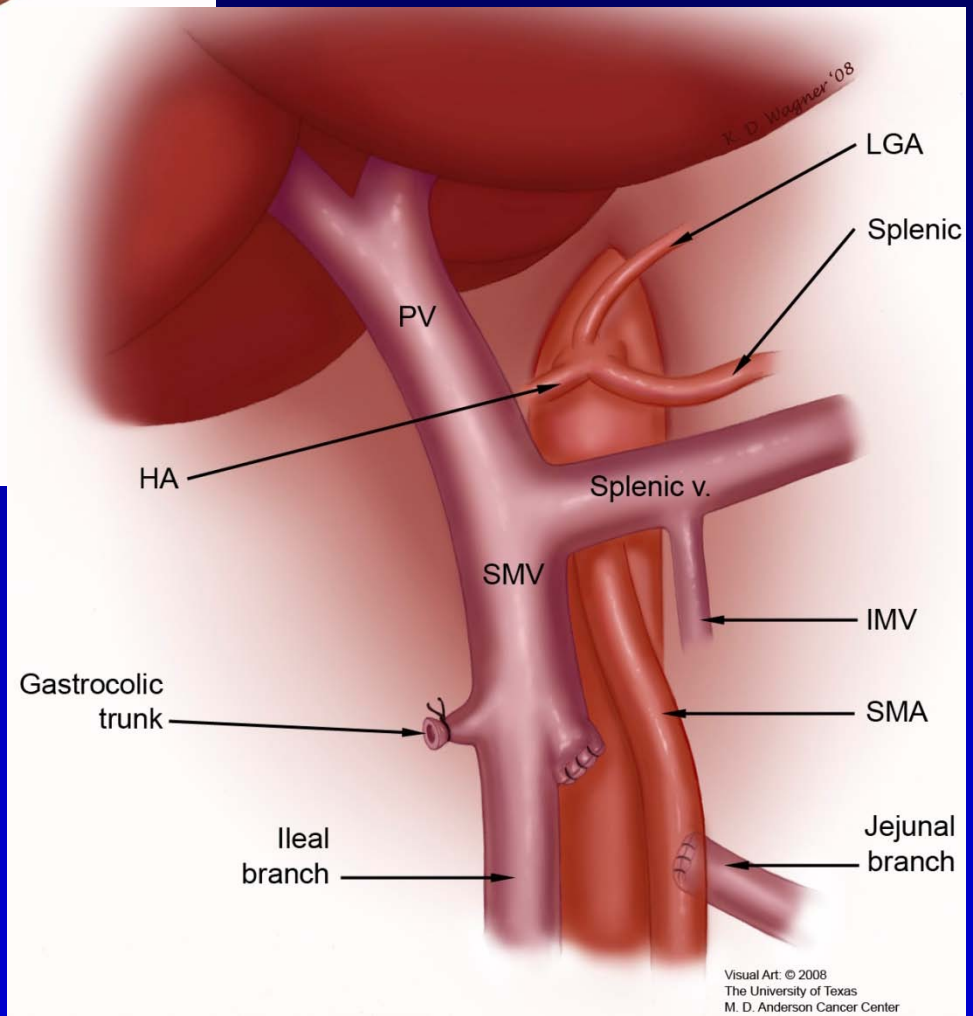
Treatment sequencing does not matter – can reliably give chemotherapy and radiation after surgery (at which time one has a tissue dx and stent not an issue)

Window of resectability may be lost (local and distant)

SMV Anatomy

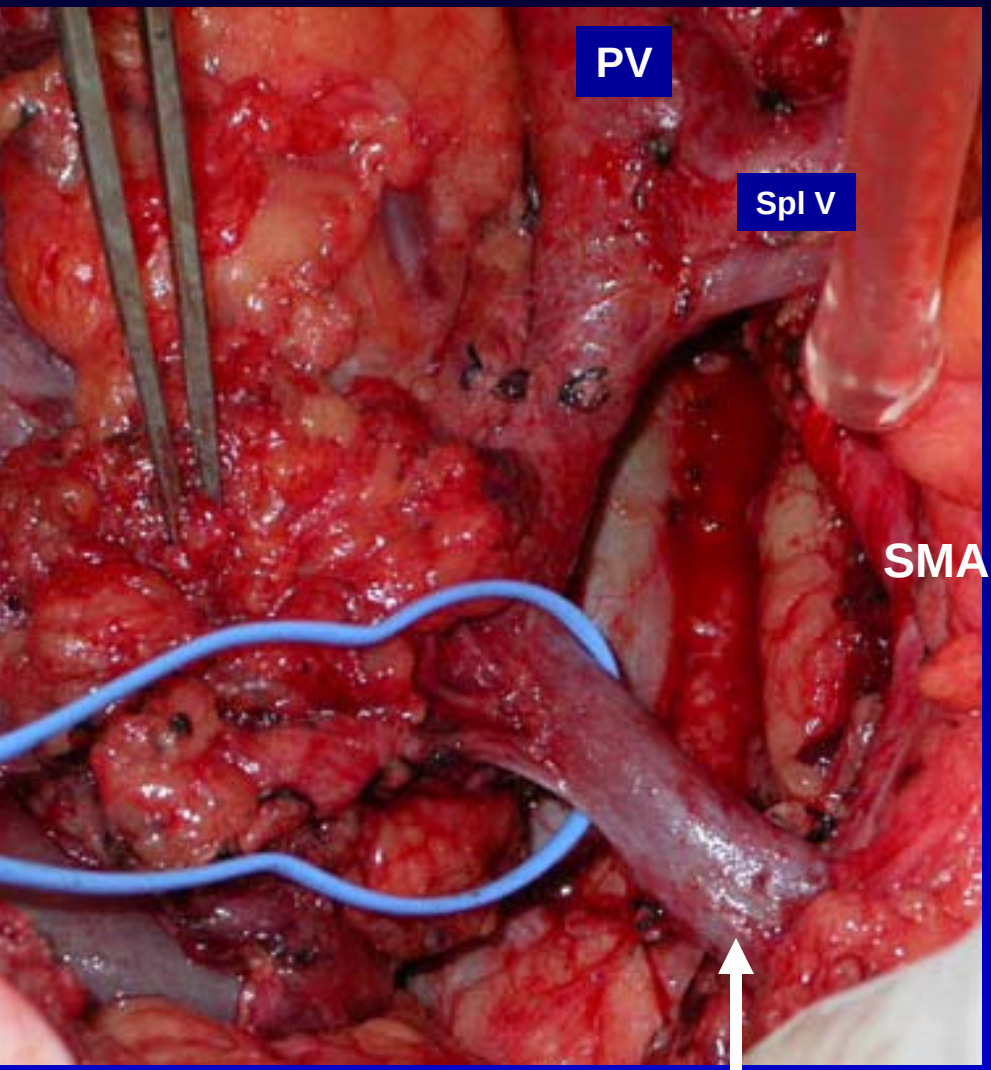

PV
Splenic V
SMV
IMV may enter spl vein or SMV
SMA
Ileal branch
Jejunal branch

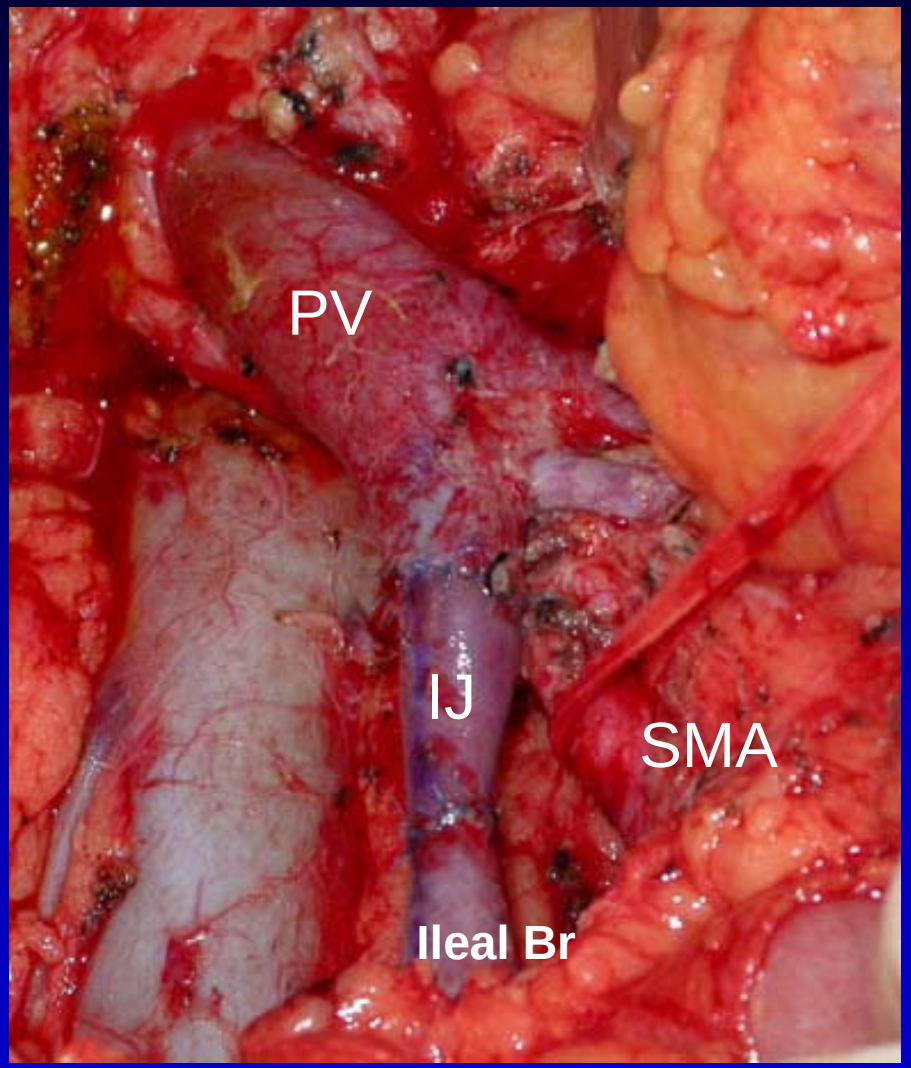




Katz MHG, Fleming JB, Pisters PWT, Lee JE, Evans DB. Anatomy of the superior mesenteric vein with special reference to the surgical management of first-order branch involvement at pancreaticoduodenectomy. Ann Surg. 2008;248(6):1098-102.

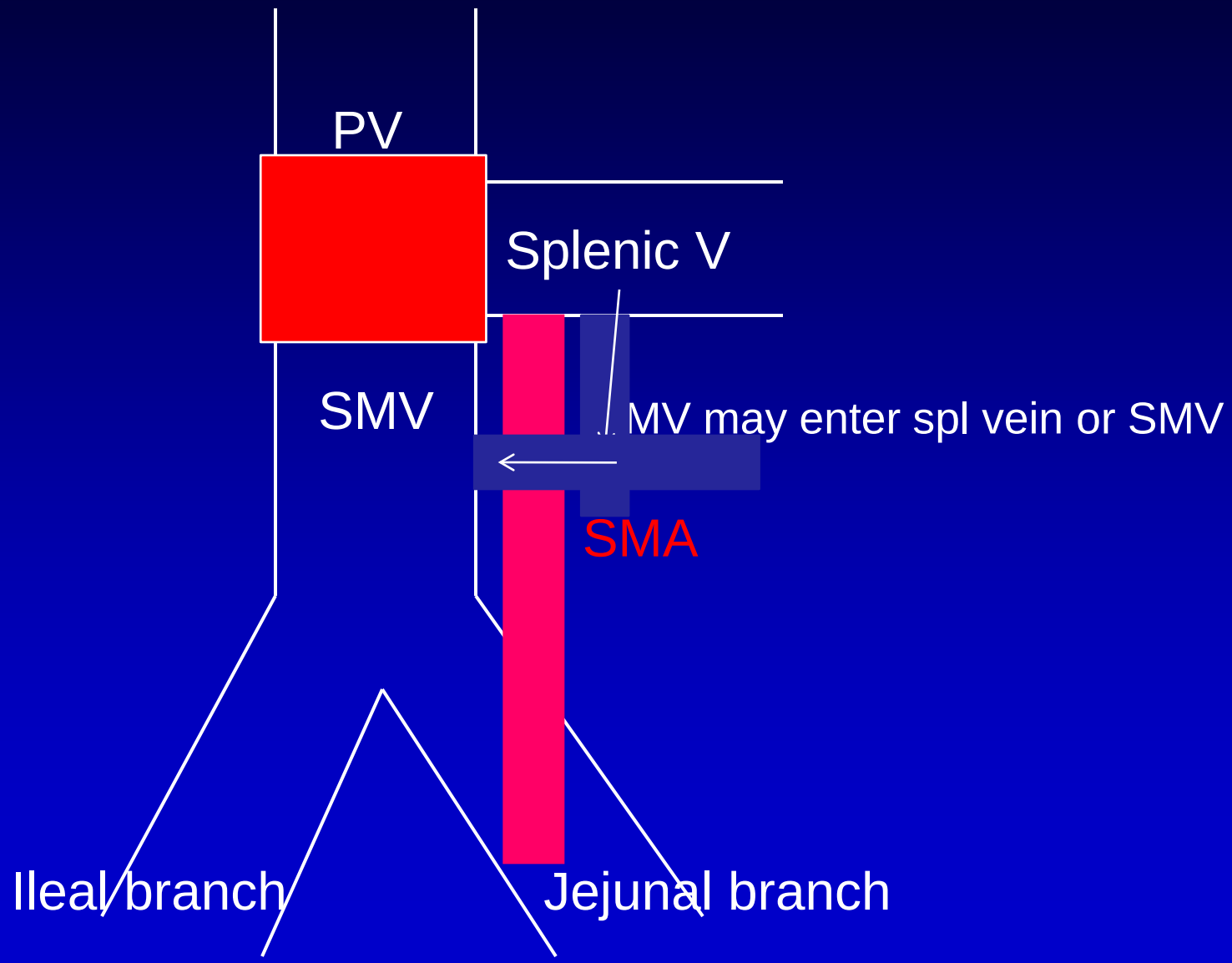
Jejunal branch of the SMV has been divided and the involved segment of the ileal branch is resected and an IJ interposition graft used to reconstruct the SMV

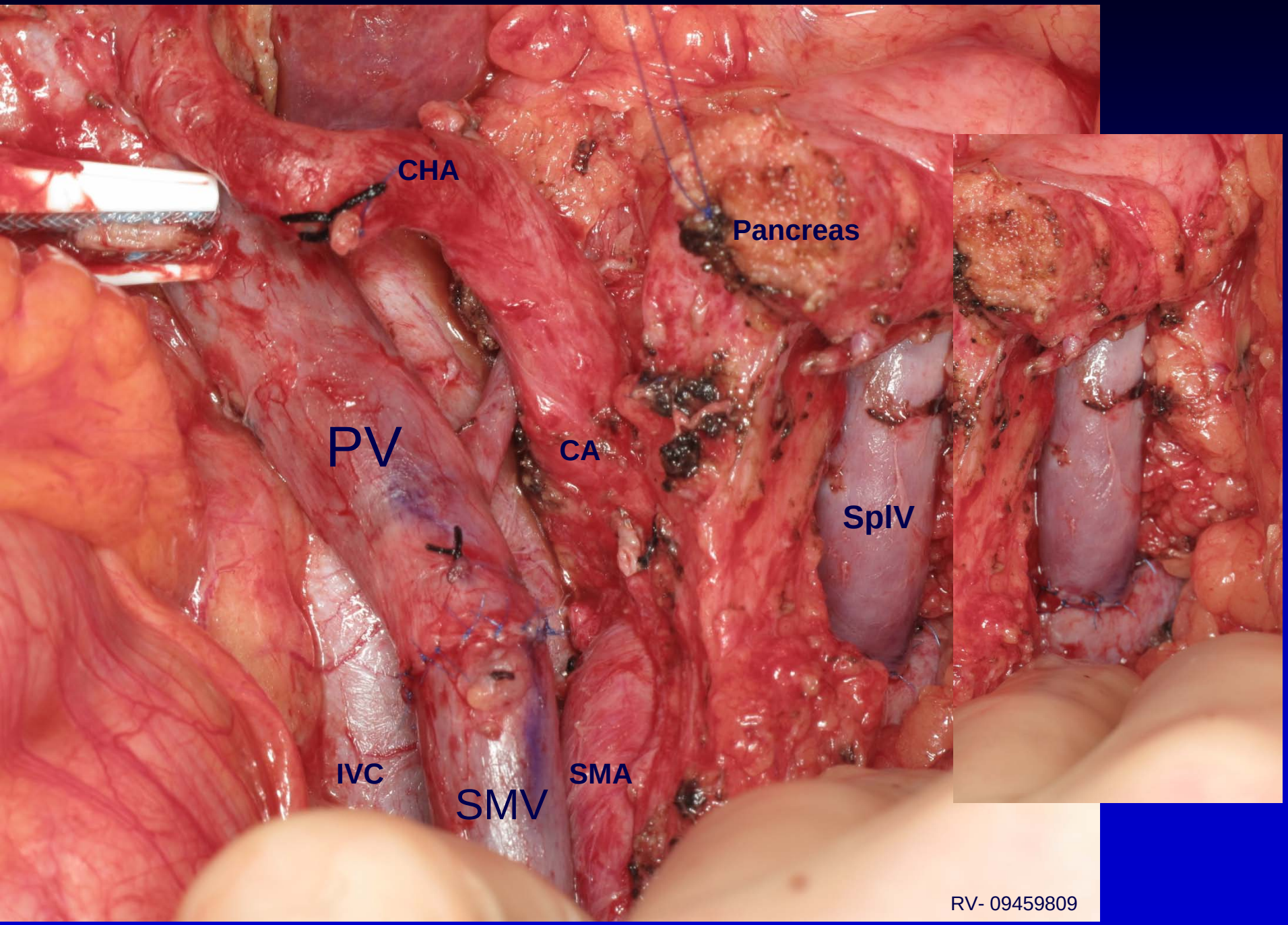




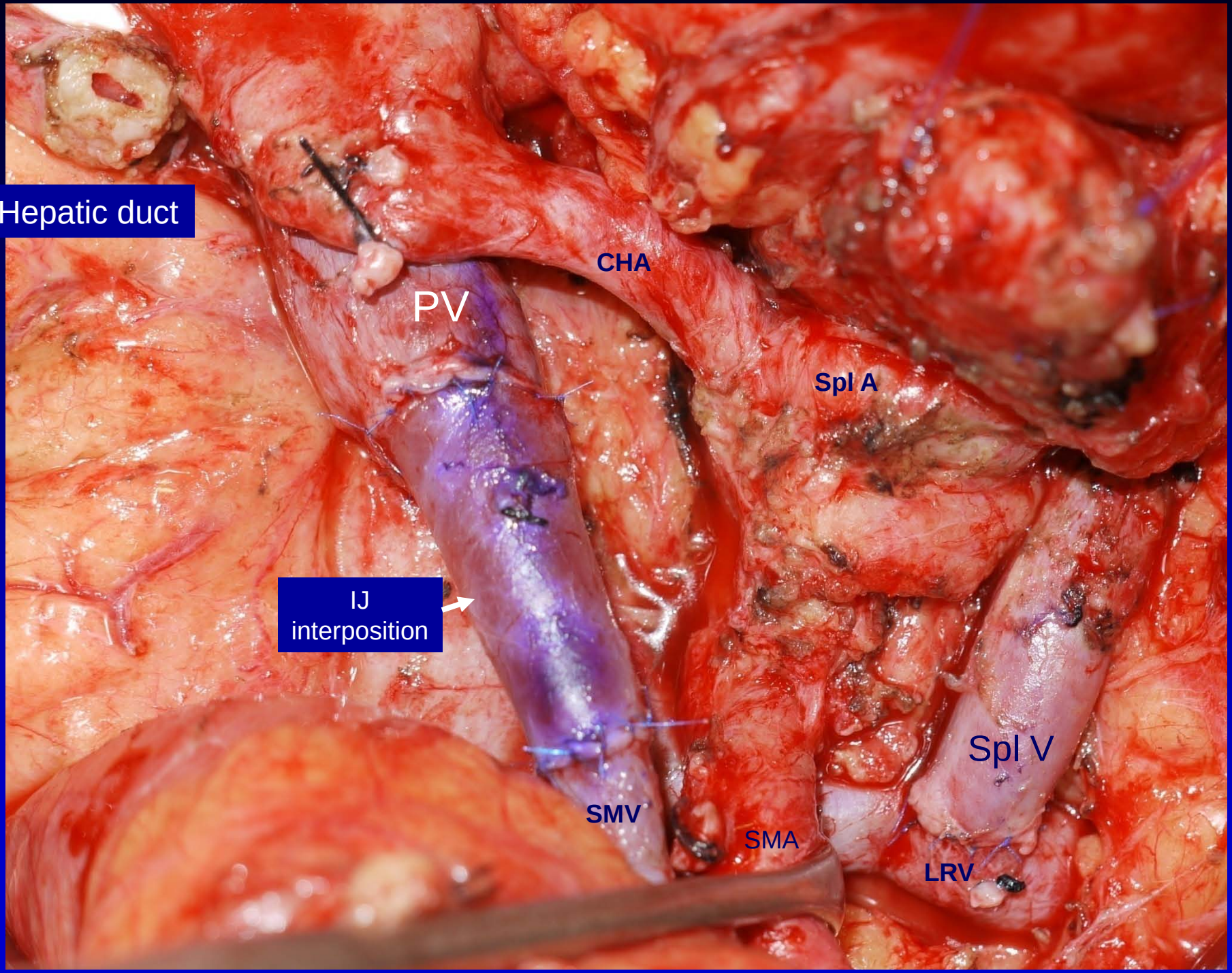
553869

SMV Anatomy

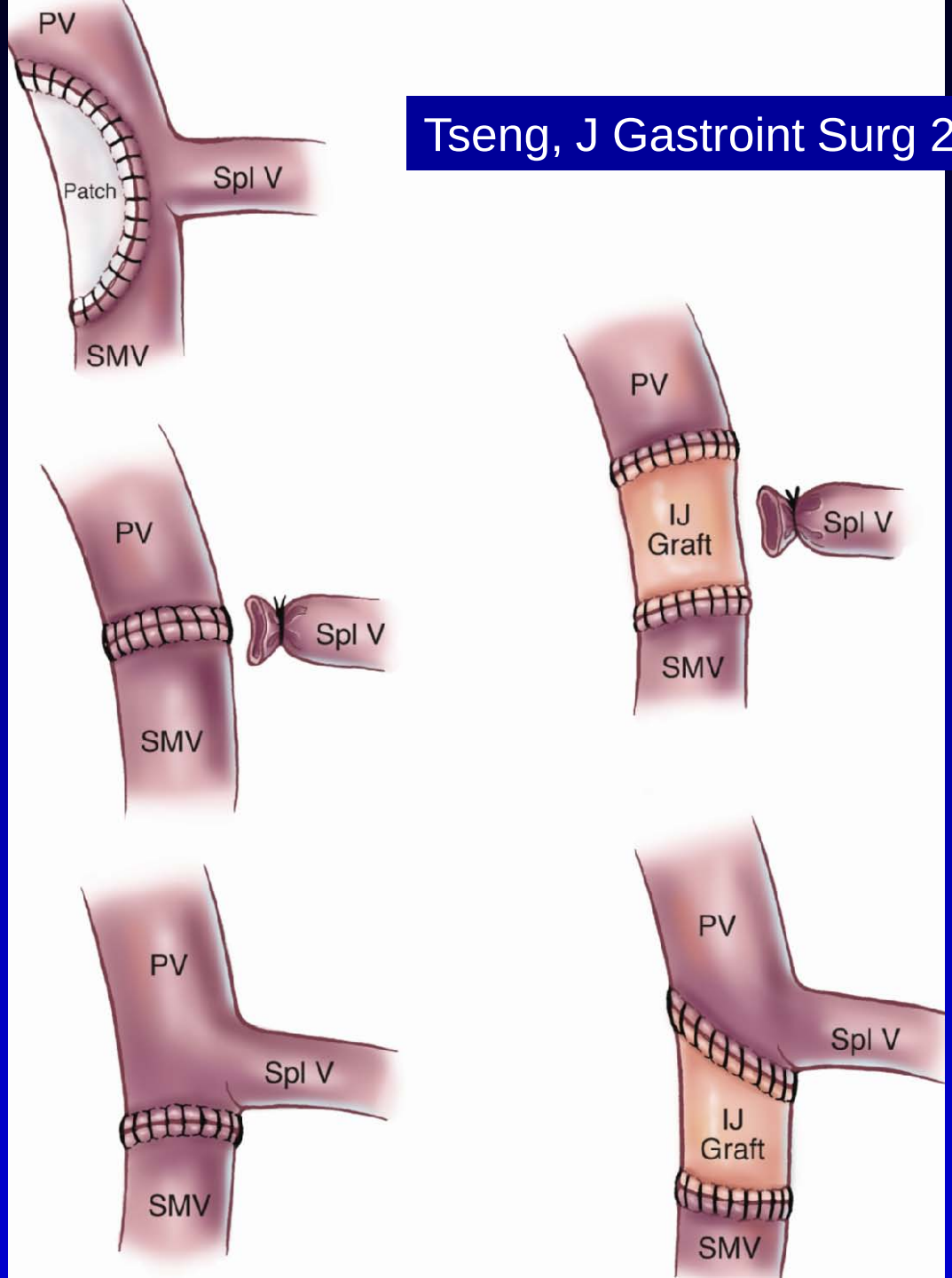

PV
Splenic V
SMV
MV may enter spl vein or SMV
SMA
Ileal branch
Jejunal branch



RV- 09459809


Hepatic duct
CHA
PV
Spl A
IJ
interposition
Spl V
SMV
SMA
LRV

Tseng, J Gastroint Surg 2004;8:935.



Pancreatic Adenocarcinoma

VR vs. standard PD (univariate analysis)

Variable	No. patients	Median survival (mo)	95% CI	P value
Overall	**291**	**24.9**	21.40-28.46	--
Male Female	175 116	23.1 27.0	19.05-27.15 22.43-31.50	.47
Standard PD PD with VR	181 110	**26.5** **23.4**	21.1-31.89 19.50-27.37	**.18**
T1 T2 T3	25 56 206	30.8 25.9 23.7	16.61-44.92 20.2-31.46 19.94-27.46	.22
N0 N1	146 145	**31.9** **21.1**	24.57-39.30 17.40-24.73	**.005**
R0 R1	246 45	26.5 21.4	22.29-30.71 17.05-25.68	**.14**
Adjuvant therapy No adjuvant therapy	209 29	25.1 18.5	21.42-28.85 9.48-27.52	.92

Tseng, J Gastroint Surg 2004;8:935.

Pancreatic Adenocarcinoma

VR vs. standard PD (multivariate analysis)

Covariate	HR	95% CI	P value
Female Gender	.925	.665-1.286	.642
Age (per year)	1.008	.991-1.026	.351
Reoperative PD	1.094	.722-1.66	.671
Vascular resection	1.132	.789-1.625	.499
Operative blood loss	1.0	1.0-1.0	.445
Tumor size	.953	.818-1.11	.537
RP margin positive	1.164	.772-1.755	.469
T stage (AJCC)			.730
Nodal metastasis	**1.502**	1.10-2.05	**.01**
Any adjuvant treatment	.962	.412-2.244	.929
Neoadjuvant treatment	1.176	.615-2.248	.623
Postop treatment	.946	.538-1.663	.846

Tseng, J Gastroint Surg 2004;8:935.

Treatment of Borderline Resectable Pancreatic Cancer
Underlying hypothesis / assumption

1. Neoadjuvant treatment sequencing used to:
   - select those with favorable biology for the larger, high risk operations
   - treat radiographically occult M1 disease
   - enhance the chance of a complete (R0, R1) resection

2. Outcome for R1 different than R2 (ie, <u>better</u>)

Borderline Resectable
Katz / M. D. Anderson Classification

- Type A: Anatomically *borderline* resectable tumor
- Type B: *Indeterminant* extrapancreatic metastasis
- Type C: Patient of *marginal* performance status

Katz MHG, et al. J Am Coll Surg. 2008;206(5):833-46

Evans DB, Erickson BA, Ritch P. Ann Surg Oncol. 2010;17(11):2803-5.

Stage Specific Therapy

Resectable: preop or postop chemo / chemoradiation

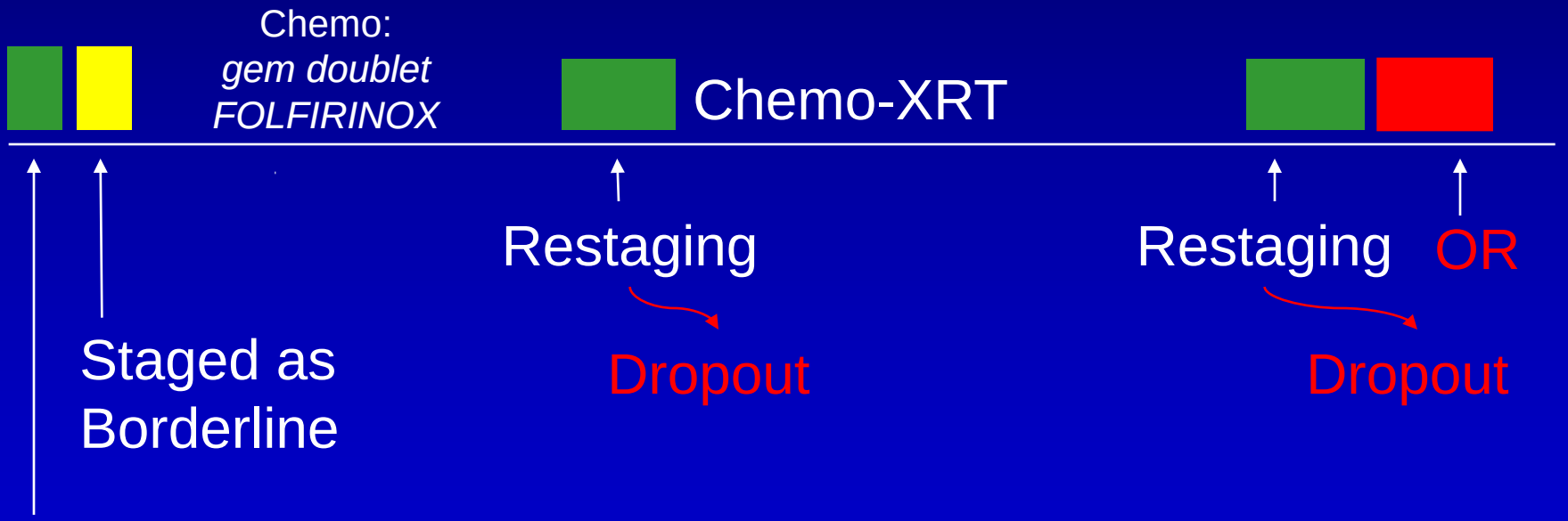
Borderline Resectable (A/B):
preop chemo (2 mon) – chemoradiation - surgery

Borderline Resectable (C):
preop chemo / chemoradiation - surgery

Locally Advanced: chemo (4-6 mon) - chemoradiation

Borderline Resectable Panc CA
Treatment Approach

Consider an additional 2 months of chemo only when a significant response occurs



Katz MHG, et al. J Am Coll Surg. 2008;206(5):833-46
Evans DB, et al. Ann Surg Oncol. 2010;17(11):2803-5

Borderline Resectable
Katz / M. D. Anderson Classification

- Type A: Anatomically *borderline* resectable tumor
- Type B: *Indeterminant* extrapancreatic metastasis
- Type C: Patient of *marginal* performance status

Katz MHG, et al. J Am Coll Surg. 2008;206(5):833-46

Evans DB, Erickson BA, Ritch P. Ann Surg Oncol. 2010;17(11):2803-5.

Treatment of Borderline Resectable Pancreatic Cancer
Underlying hypothesis / assumption

1. Neoadjuvant treatment sequencing used to:
   - select those with favorable biology
   - treat radiographically occult M1 disease
   - enhance the chance of a complete (R0, R1) resection

2. Outcome for R1 different than R2 (ie, <u>better</u>)

Accurate Pathology and Multimodality Therapy

Pancreaticoduodenectomy: Ductal Adenocarcinoma

M D Anderson (N = 360)

Variable	No. Pts	Med Sur	p value
Overall	360	25	
N0	174	32	
N1	186	22	
R0	300	28	
R1	60	22	
Maj Comp			
No	263	27	
Yes	93	22	

R0 17 mo
R1 11 mo

ESPAC-1
Ann Surg 2001

Raut, Ann Surg 2007;246:52-60
Local Failure (All pts) 8%

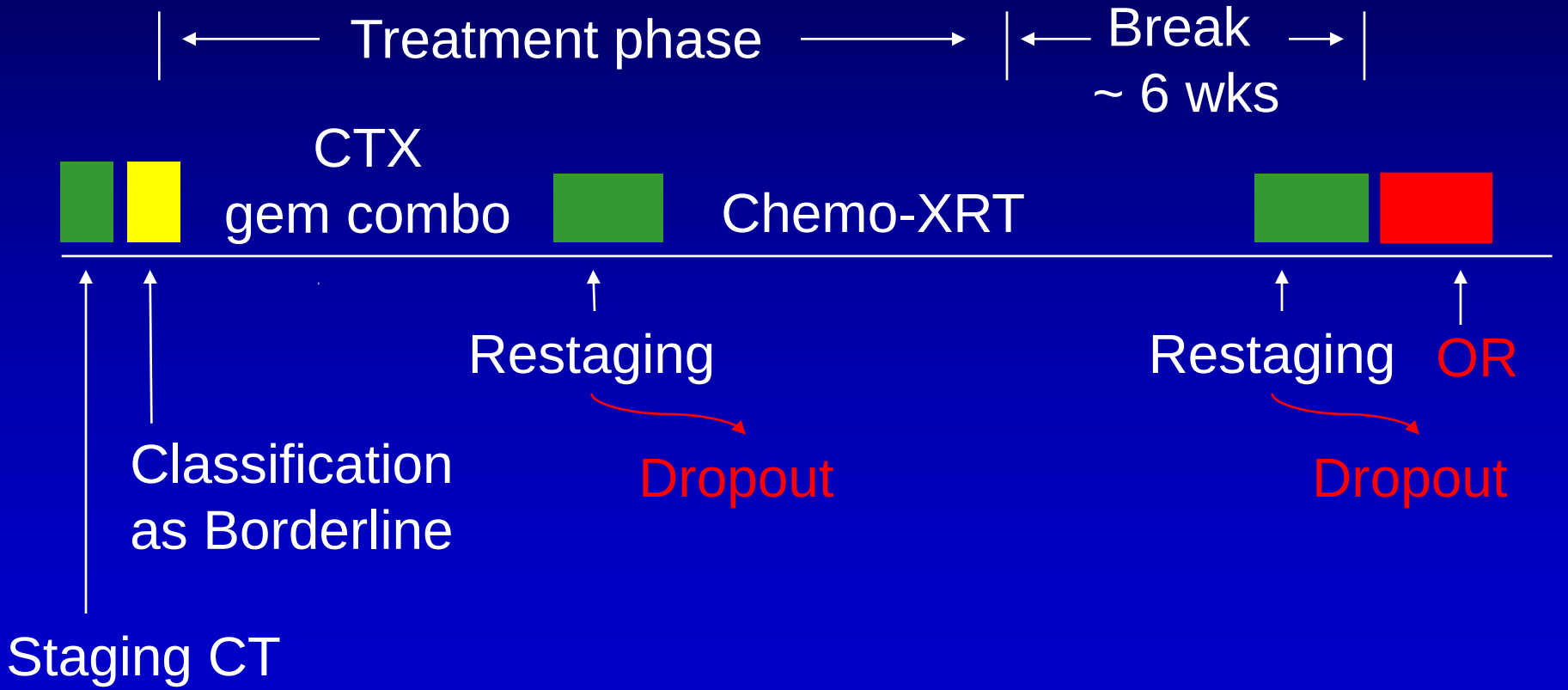
The Importance of Neoadjuvant Therapy

Pancreaticoduodenectomy: Ductal Adenocarcinoma
M D Anderson (N = 360)

Preoperative Therapy	R1 Resection
YES	13%
NO	19%

Raut, Ann Surg 2007;246:52-60
Local Failure (All pts) 8%

Borderline Resectable PC
Treatment Sequencing



Katz MHG, et al. J Am Coll Surg. 2008;206(5):833-46

Rates of Resection, Path Response, Survival

160 Patients with Borderline Resectable PC

MDACC Type	No. of Patients (%)			Median Survival (Mos)			p*
	Total	Resected	Path Resp. IIb, III, IV	All Pts	Resected	Unresected	
A	84 (53)	32 (38)	19 (59)	21	40	15	0.001
B	44 (28)	22 (50)	13 (59)	16	29	12	0.001
C	32 (20)	12 (38)	5 (42)	15	39	13	0.009
Total	**160**	**66 (41)**	**37 (56)**	**18**	**40**	**13**	**0.001**

*p: comparison of median survival between resected and unresected patients of each type

Katz MHG, et al. J Am Coll Surg. 2008;206(5):833-46

Definitions: AHPBA / SSO *2008*

Resectable (stage I, II (T1-3NxM0):
no extension to celiac, CHA, SMA, SMV-PV confluence

Borderline (*should not go straight to surgery*):
a) venous abutment or encasement (with option for reconstruction)
b) arterial abutment ($\leq 180^0$)

Locally Advanced (stage III (T4NxM0):
celiac, SMA encasement ($> 180^0$)

Callery, et al. Ann Surg Oncol 2009;16:1727-1733

	chemotherapy	Duration of chemotherapy	chemoradiation	No. Patients Assessed for Survival Analysis	Did not receive any of the intended treatment	Received slavage chemotherapy	Margin status pos or unknown	Overall Survival	Overall survival for panc head	Local Failure
RTOG 97-04	Infusional 5-FU before and after chemoradiation	3 weeks pre-, and 3 months post-chemoXRT	Infusional 5-FU and 50.4 Gy (28 fractions, 5 days per week)	230	0	95 (41%)	128 (56%)	Not provided	17.1	61 (27%)
	Gemcitabine before and after chemoradiation	3 weeks pre-, and 3 months post-chemoXRT	Infusional 5-FU and 50.4 Gy(28 fractions, 5 days per week)	221	0	77 (35%)	135 (61%)	Not provided	20.5	49 (22%)
EORTC	Gemcitabine then GemXRT	4 months	Gem (300 mg/m^2 weekly) 50.4 Gy	45	2 (Gem) 9 (XRT) (20%)	Not provided	0	24.3	***24.3	14 (31%)
	Gem	4 months	None	45	3 (7%)	Not provided	0	24.4	***24.4	17 (37%)
ESPC-3	Bolus 5-FU and Folinic Acid	6 months	None	551	65 (12%)	Not provided	195 (35%)	*23.0 From date of surg	Not provided	Not provided
	Gemcitabine	6 months	None	537	59 (11%)	Not provided	189 (35%)	*23.6	Not provided	Not provided
CONKO-001	Gemcitabine	6 months	None	179	18 (10%)	“Some patients”	34	22.1	Not provided	45 (25%)
	Control (surgery only)	None	None	175	NA	“Almost all patients”	27	20.2	Not provided	66 (38%)

General Consensus: Adj Rx Pancreas CA

- Positive margin resections are common (25%-50%) and confound the results of adjuvant therapy trials

- Chemoradiation delivered to persistent (macroscopic), incompletely resected disease (R2) is not adjuvant therapy

- Pathologists can not tell the difference between an R1 and an R2 resection

- Operative notes rarely contain information on the completeness of resection (ACOSOG Z5031: 24%)

- If adjuvant chemoradiation is delivered, it should follow systemic therapy