Pancreatic Cancer: Sequence of Therapy and Resectability

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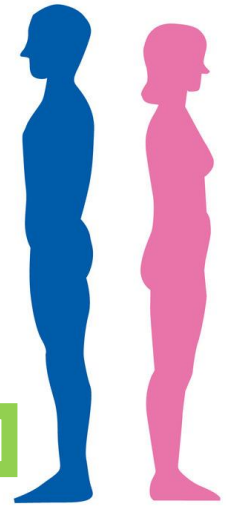
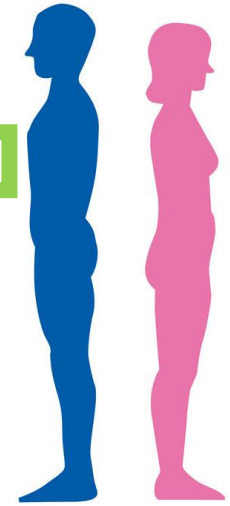
Estimated New Cases

Males			Females		
Prostate	191,930	21%	Breast	276,480	30%
Lung & bronchus	116,300	13%	Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%	Colon & rectum	69,650	8%
Urinary bladder	62,100	7%	Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%	Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%	Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%	Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%	Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%	Pancreas	27,200	3%
Pancreas	30,400	3%	Leukemia	25,060	3%
All Sites	**893,660**	**100%**	**All Sites**	**912,930**	**100%**

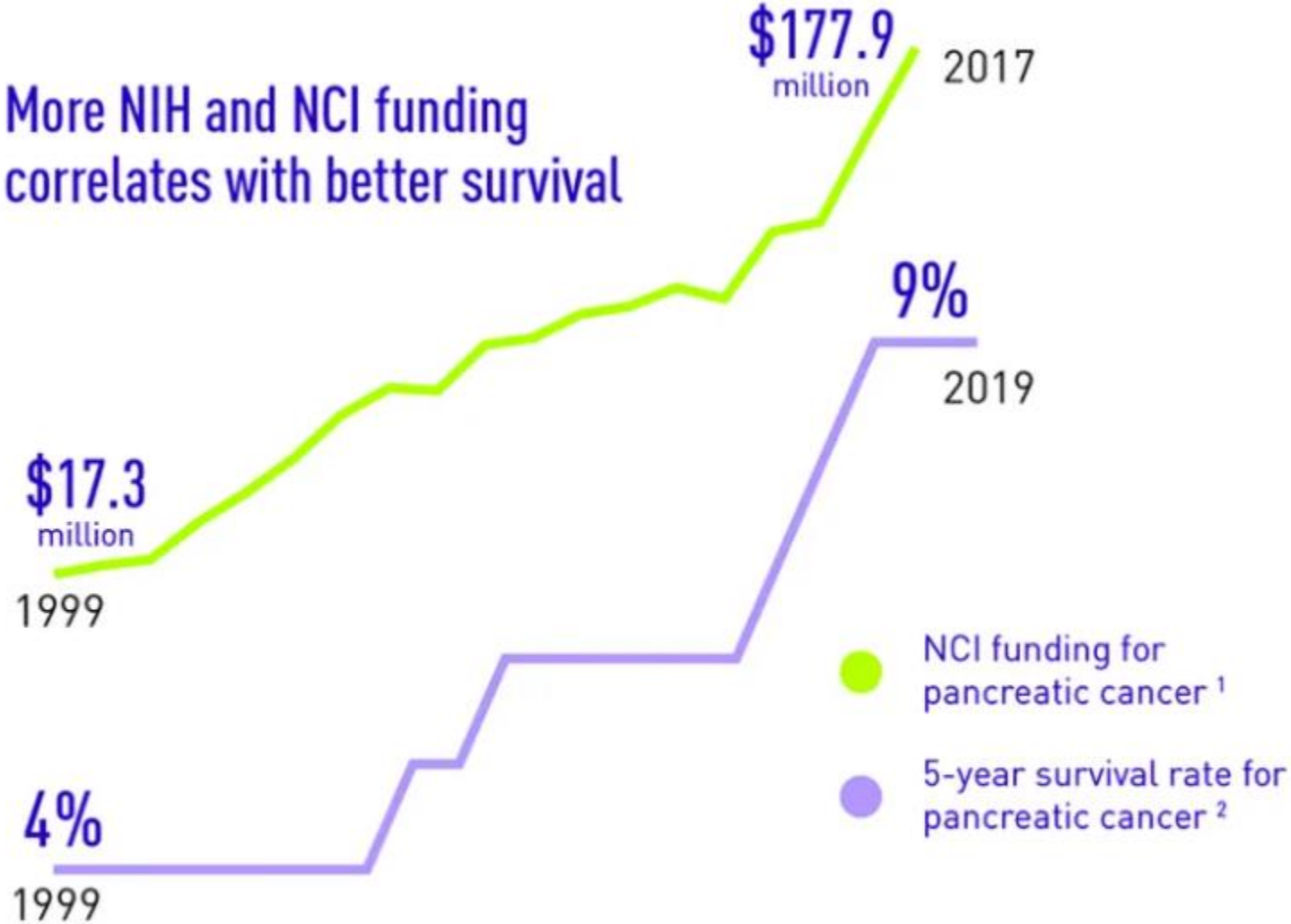


Estimated Deaths

Males			Females		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All Sites	**321,160**	**100%**	**All Sites**	**285,360**	**100%**



More NIH and NCI funding correlates with better survival



1. NCI Funded Research Portfolio – http://fundedresearch.cancer.gov/nciportfolio/ (accessed: May 2019).
2. American Cancer Society, Cancer Facts and Figures 1999-2019, SEER-9 database.

Multidisciplinary Management

- Weekly dedicated Upper GI / Hepatobiliary Tumor Board
  - Surgical Oncology
  - Medical Oncology
  - Gastroenterology
  - Radiation Oncology
  - Radiology
  - Pathology
- Multidisciplinary Appointments – Promotes communication, patient education/understanding
- Tracking of outcomes (NSQIP, clinical trials)

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Staging

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Staging

“All I want to know is, what stage am I?”

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Table 1. **Definitions for T, N, M**
American Joint Committee on Cancer (AJCC) TNM Staging of Pancreatic Cancer (8th ed., 2017)

T	**Primary Tumor**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ* This includes high-grade pancreatic intraepithelial neoplasia (PanIn-3), intraductal papillary mucinous neoplasm with high-grade dysplasia, intraductal tubulopapillary neoplasm with high-grade dysplasia, and mucinous cystic neoplasm with high-grade dysplasia
T1	Tumor ≤2 cm in greatest dimension
T1a	Tumor ≤0.5 cm in greatest dimension
T1b	Tumor >0.5 cm and <1 cm in greatest dimension
T1c	Tumor 1–2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension
T4	Tumor involves the celiac axis, superior mesenteric artery, and/or common hepatic artery, regardless of size

N	**Regional Lymph Nodes**
NX	Regional lymph nodes cannot be assesseds
N0	No regional lymph node metastases
N1	Metastasis in one to three regional lymph nodes
N2	Metastasis in four or more regional lymph nodes

M	**Distant Metastasis**
M0	No distant metastases
M1	Distant metastasis

Table 2. **AJCC Prognostic Groups**

	T	N	M
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2, T3	N1	M0
Stage III	T1, T2, T3	N2	M0
	T4	Any N	M0
Stage IV	Any T	Any N	M1

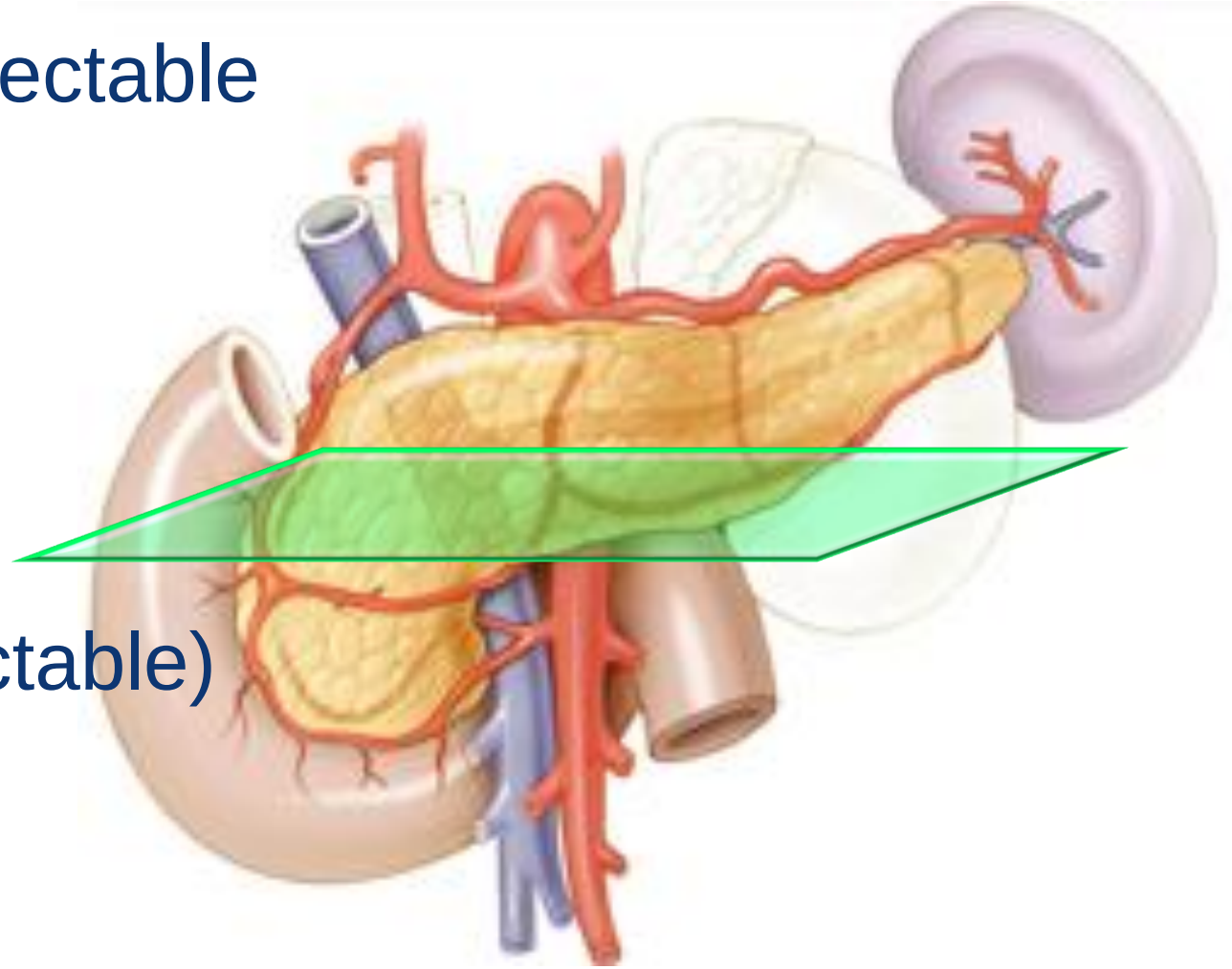
“Resectability” trumps TNM

Heterogeneity in Stage III patients

- Planning Resection←→ Unresectable

Standard Terminology

- Resectable
- Borderline Resectable
- Locally Advanced (ie unresectable)



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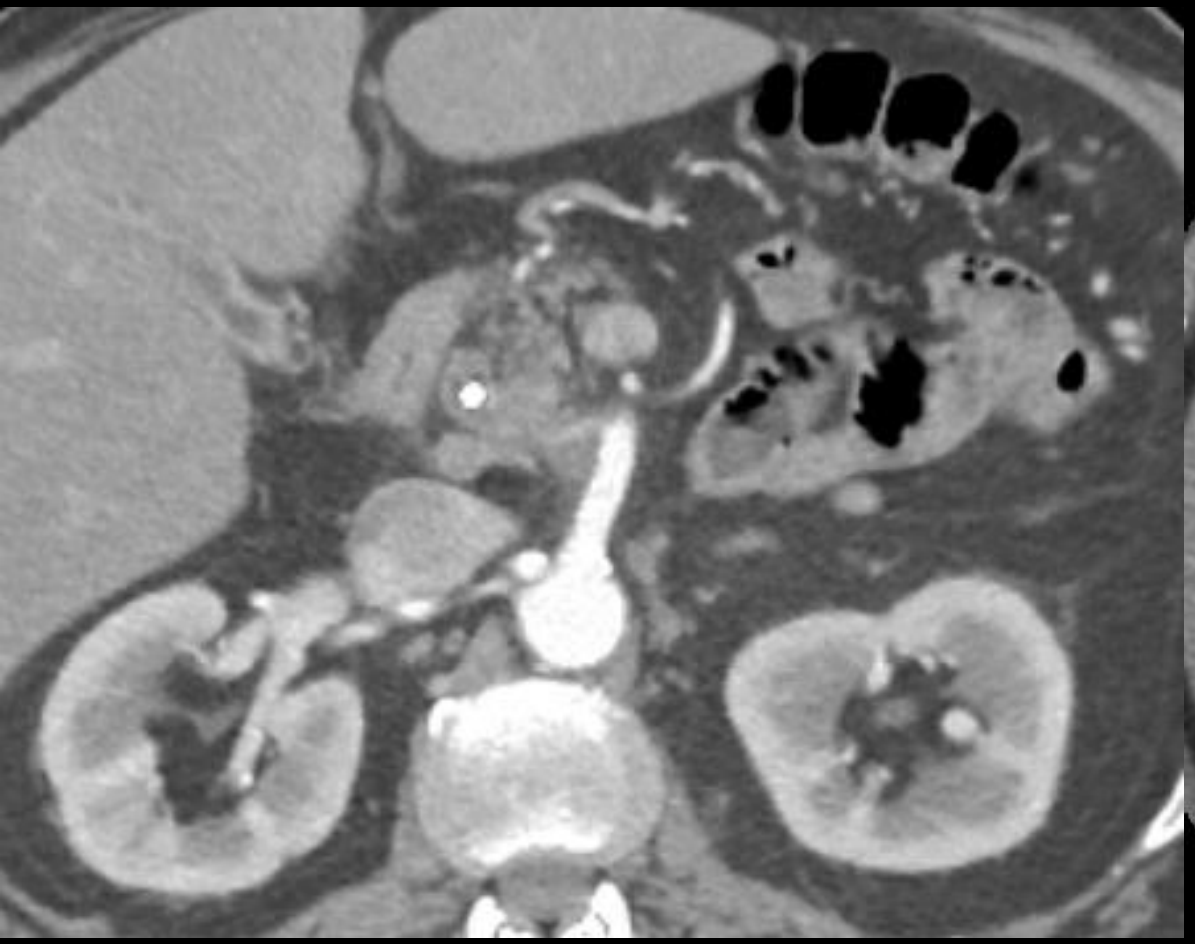
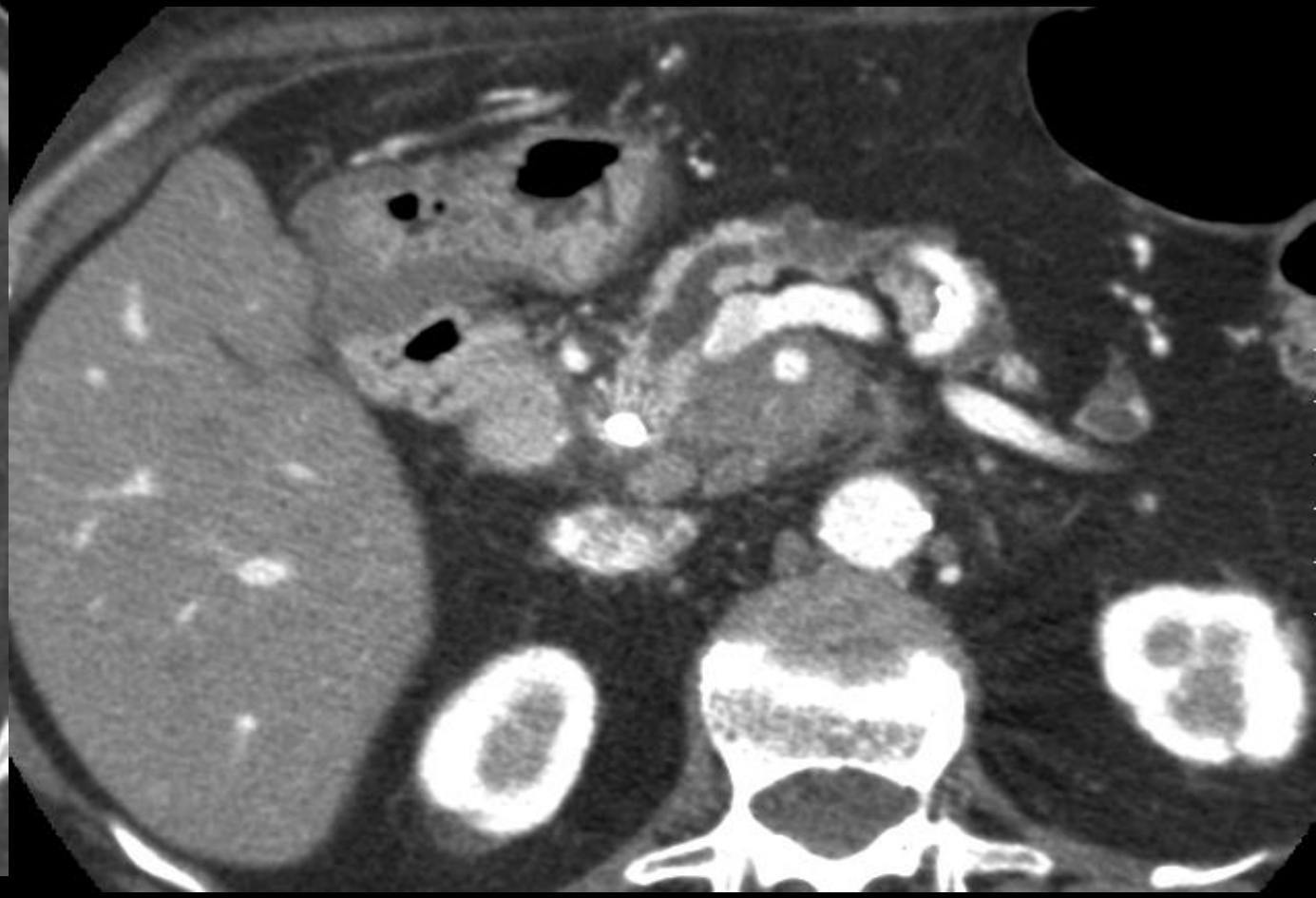
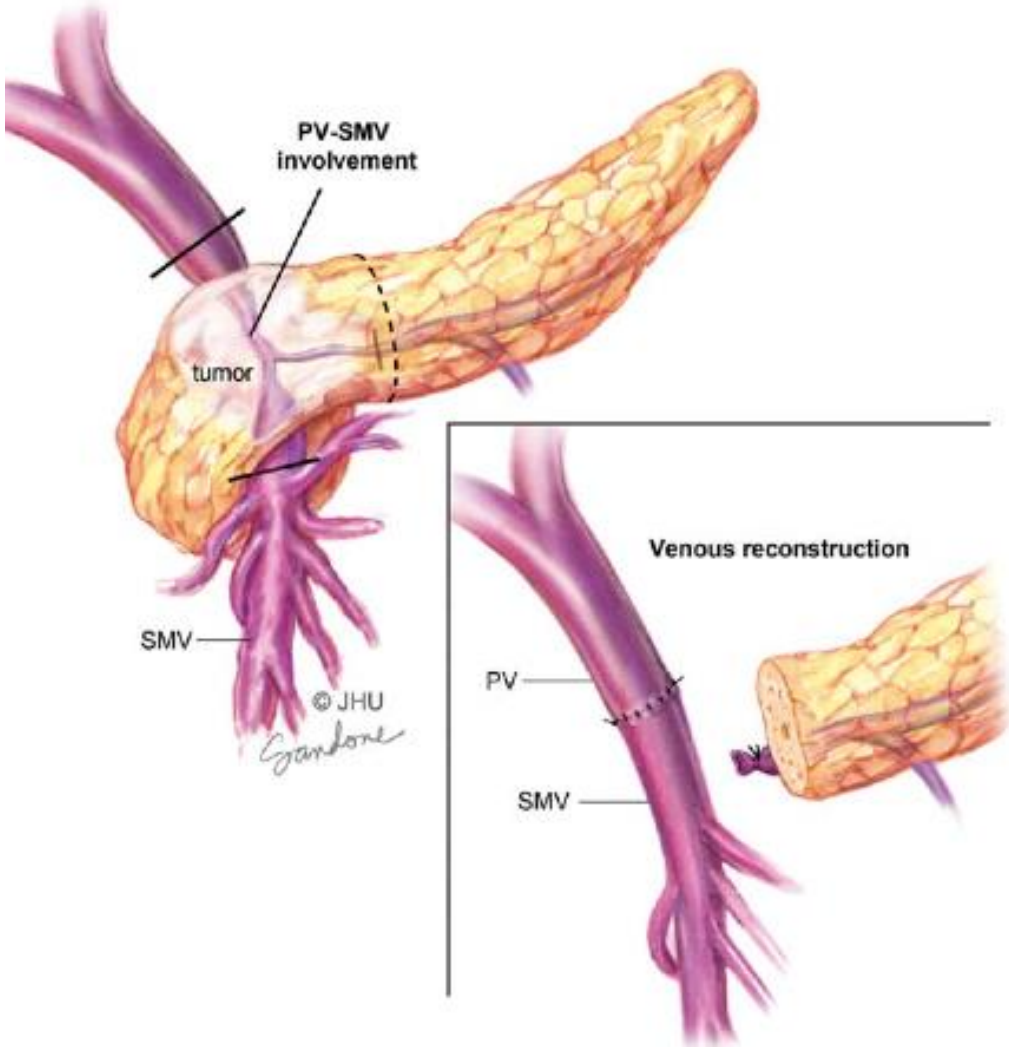
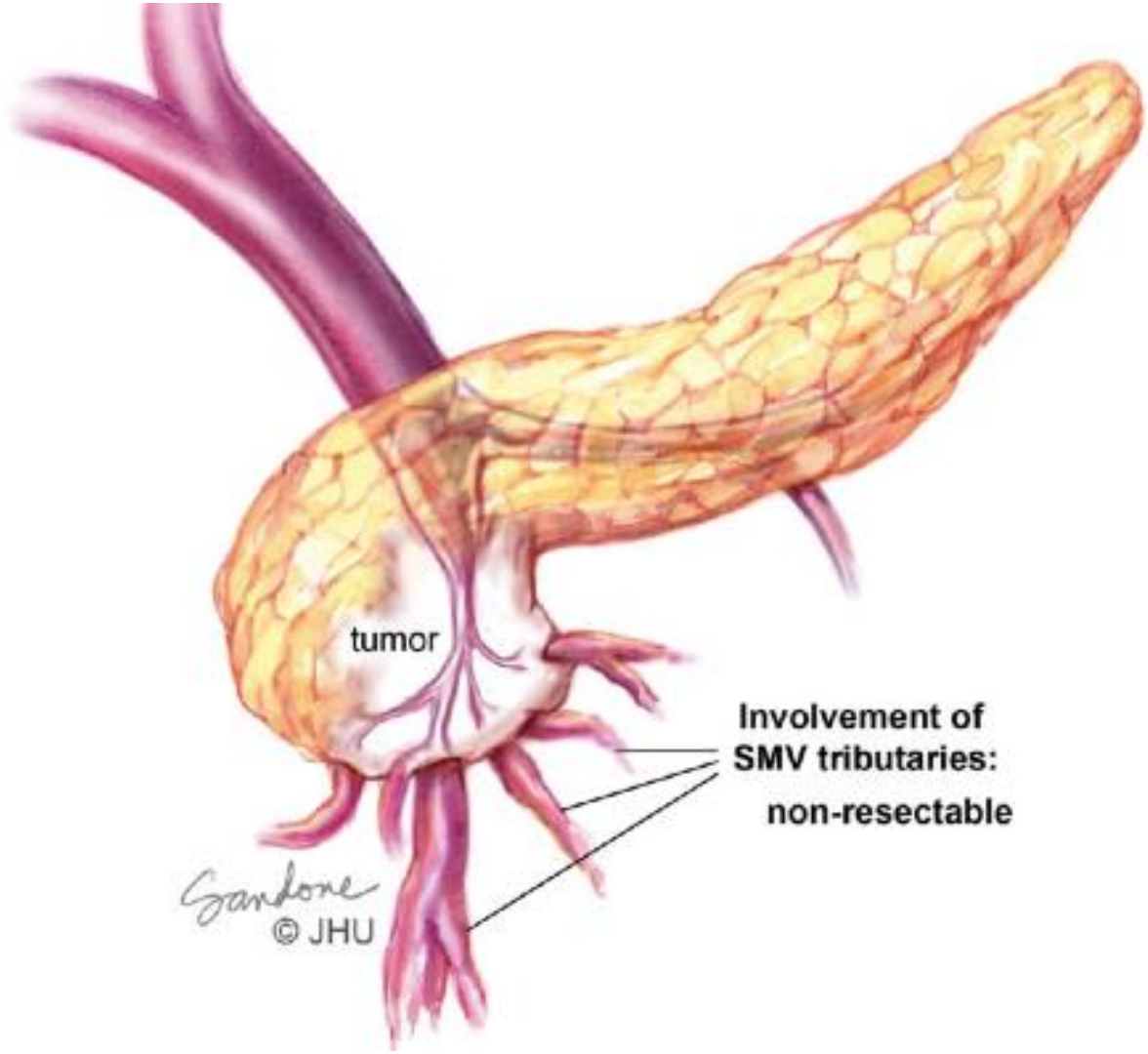





PV-SMV
involvement
tumor
SMV
© JHU
Gandone
Venous reconstruction
PV
SMV


tumor
Involvement of
SMV tributaries:
non-resectable
Gandone
© JHU

Resectability, NCCN 2018

Resectability Status	Arterial	Venous
Resectable	No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).	No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ≤180° contact without vein contour irregularity.
Borderline Resectable[b]	Pancreatic head/uncinate process: • Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction. • Solid tumor contact with the SMA of ≤180° • Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning. Pancreatic body/tail: • Solid tumor contact with the CA of ≤180° • Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some panel members prefer these criteria to be in the unresectable category].	• Solid tumor contact with the SMV or PV of >180°, contact of ≤180° 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 (IVC).
Unresectable[b]	• Distant metastasis (including non-regional lymph node metastasis) Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° Body and tail: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	Head/uncinate process: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) • Contact with most proximal draining jejunal branch into SMV Body and tail: • Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

TABLE 1. Classification of Locally Advanced Pancreatic Adenocarcinoma Into Type A and B and Comparison With Definitions Used for Resectable and Borderline Resectable Disease

Vascular Structures That Determine Stage of Disease for Localized Pancreatic Cancer	Resectable	Borderline Resectable	Locally Advanced	
			Type A	Type B
Tumor-artery anatomy				
SMA (usually pertains to tumor of head or uncinate process)	No radiographic evidence of abutment or encasement	≤ 180° (abutment)	> 180° (encasement) but ≤ 270°	> 270° encasement
Celiac artery (usually pertains to tumor of pancreatic body)	No radiographic evidence of abutment or encasement	≤ 180° (abutment)	> 180° (encasement) but does not extend to aorta and amenable to celiac resection (with or without reconstruction)	> 180° and abutment/ encasement of aorta
Hepatic artery (usually pertains to tumor of pancreatic neck/head)	No radiographic evidence of abutment or encasement	Short-segment abutment/encasement without extension to celiac artery or hepatic artery bifurcation	> 180° encasement with extension to celiac artery and amenable to vascular reconstruction	> 180° encasement with extension beyond bifurcation of proper hepatic artery into right and left hepatic arteries
Tumor-vein anatomy				
SMV-PV	≤ 50% narrowing of SMV, PV, SMV-PV	> 50% narrowing of SMV, PV, SMV-PV **with** distal and proximal target for reconstruction	Occlusion **without** obvious option for reconstruction	
Traditionally considered for resection after neoadjuvant therapy	Yes	Yes	No	No

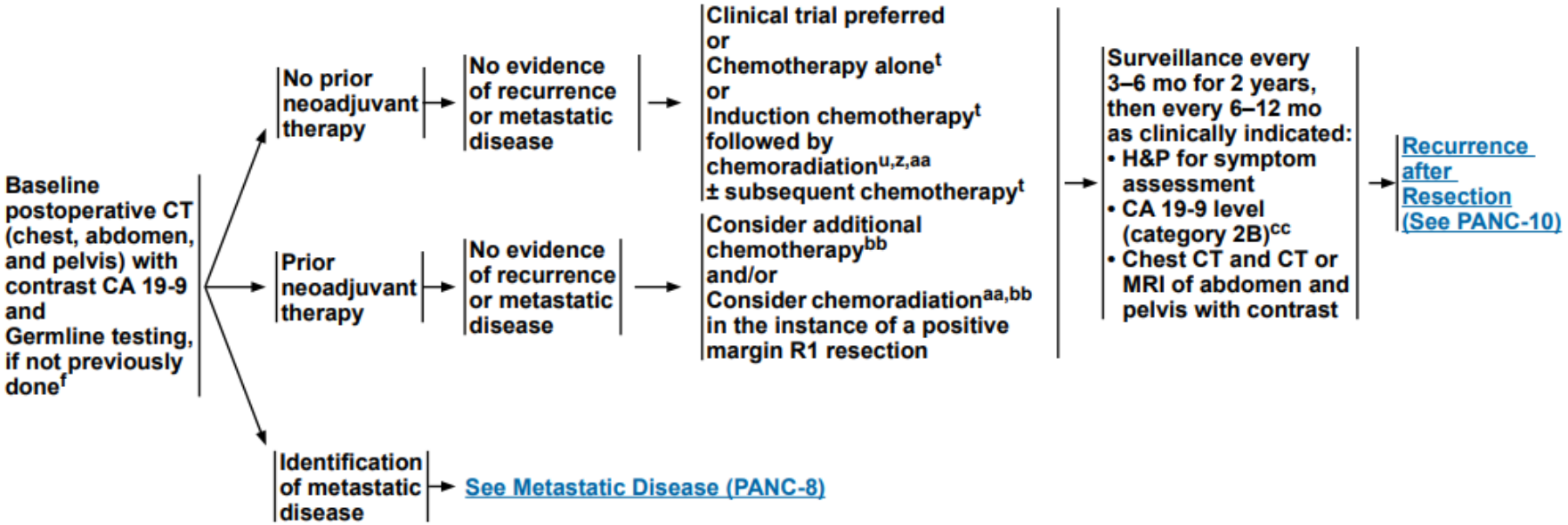
Does resectability influence sequence of therapy?

National Comprehensive Cancer Network®

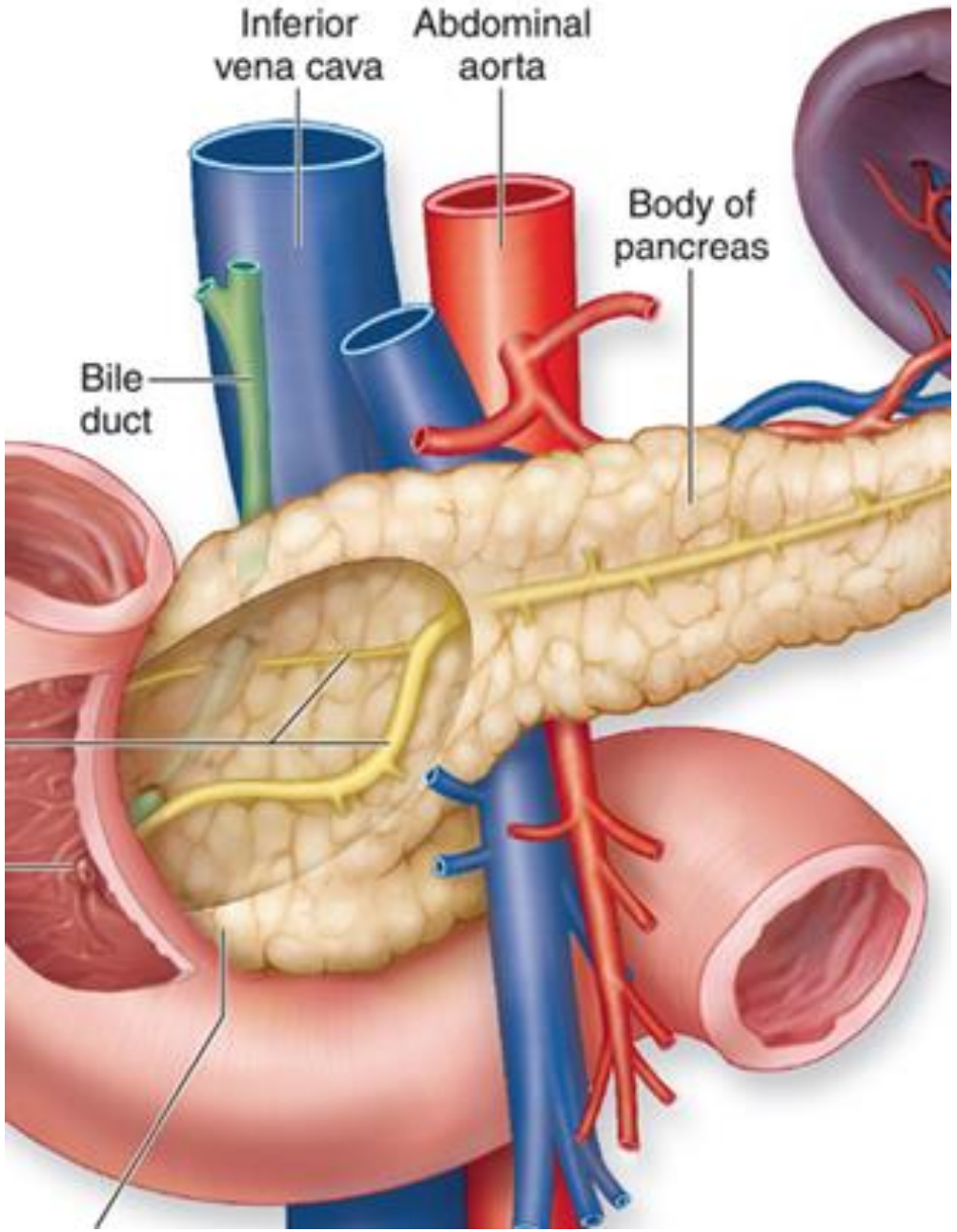
NCCN Guidelines Version 1.2021
Pancreatic Adenocarcinoma

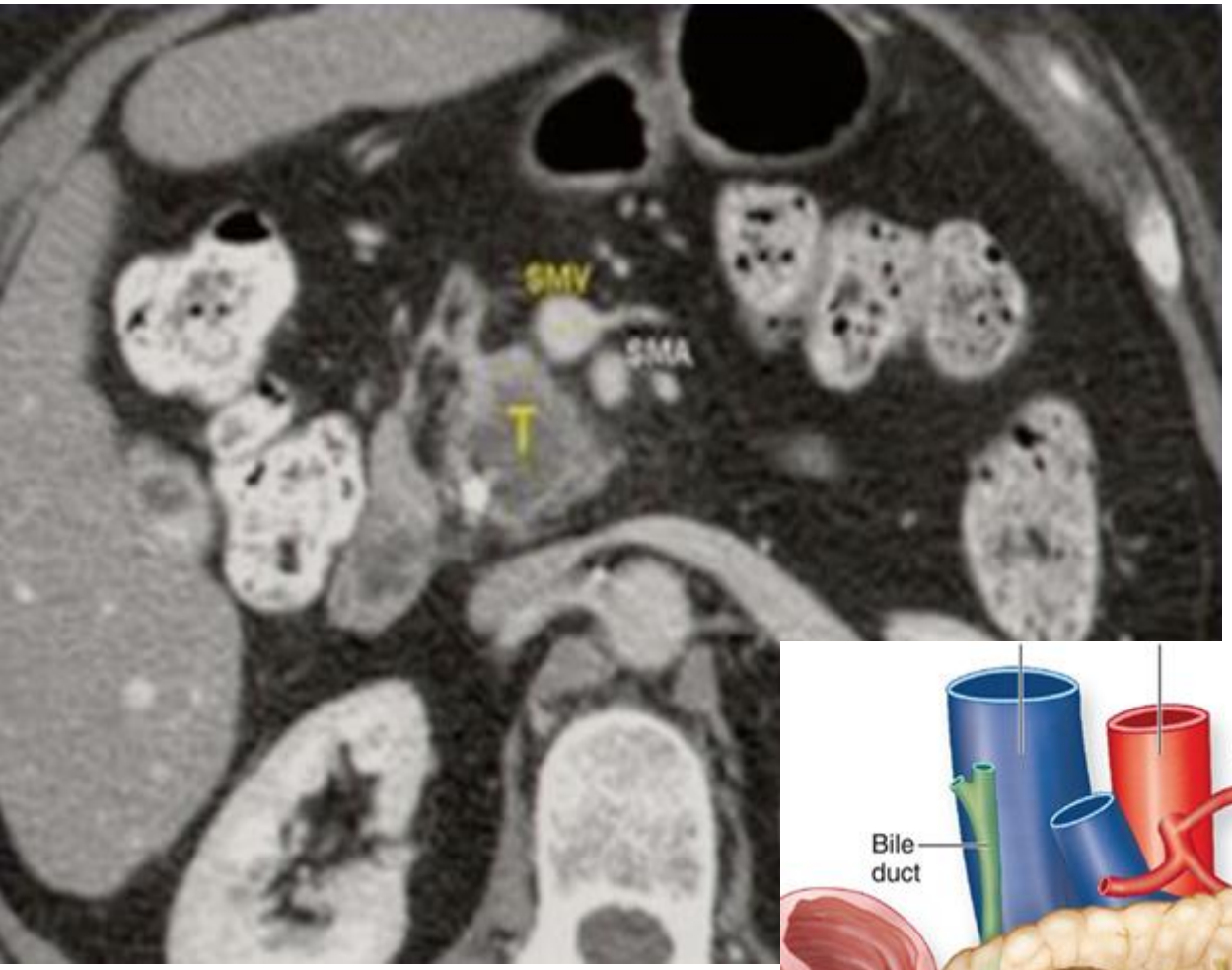
NCCN Guidelines Index
Table of Contents
Discussion

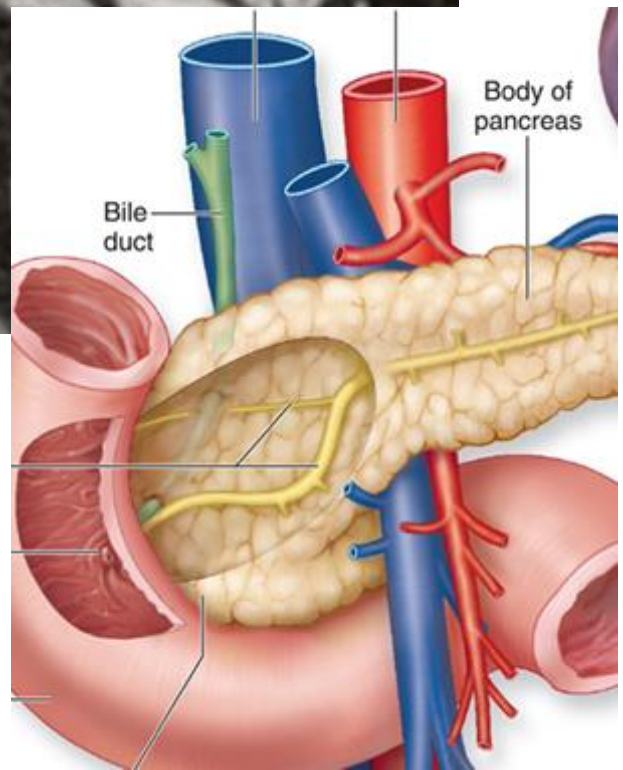
POSTOPERATIVE ADJUVANT TREATMENT | **SURVEILLANCE**



- Resectable
  - Tumor is not touching important vessels
  - Neoadj or Upfront Surgery?
- Borderline resectable
  - Tumor is touching PV/SMV/HA/CA/SMA
  - No SMA encasement
  - Neoadjuvant approach







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NCCN Guidelines Version 2.2018
Pancreatic Adenocarcinoma

RESECTABLE **TREATMENT**

Resectable[h,i,j,k] → Consider staging laparoscopy in high-risk[l] patients or as clinically indicated[m]

- Proceed to surgery (without neoadjuvant therapy)
- or
- Consider neoadjuvant therapy in high-risk patients,[l] clinical trial preferred[n]

- Repeat pancreatic protocol CT or MRI
- Repeat chest/pelvic CT[c]
- Post-treatment CA 19-9[o]
- Consider stent if clinically indicated[e,k]

→ Surgery (laparotomy or minimally invasive surgery)[j]

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done

Neoadjuvant therapy

- Giving chemotherapy or radiation prior to resection for patients with local / regional disease
- Merits
  - Front-loading therapy allows for
    - Receipt of therapy
    - Less toxicity
    - In vivo evaluation of response
    - Identification of early metastatic disease
    - Trial opportunities, measurable disease
    - Improvement in patient performance status (Prehabilitation)

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Criticisms of Neoadjuvant Therapy for Resectable Pancreatic Cancer

- Only real chance for cure
- Treatment sequencing does not matter – can give adjuvant therapy
- Window of resectability may be lost
- Other therapies largely ineffective

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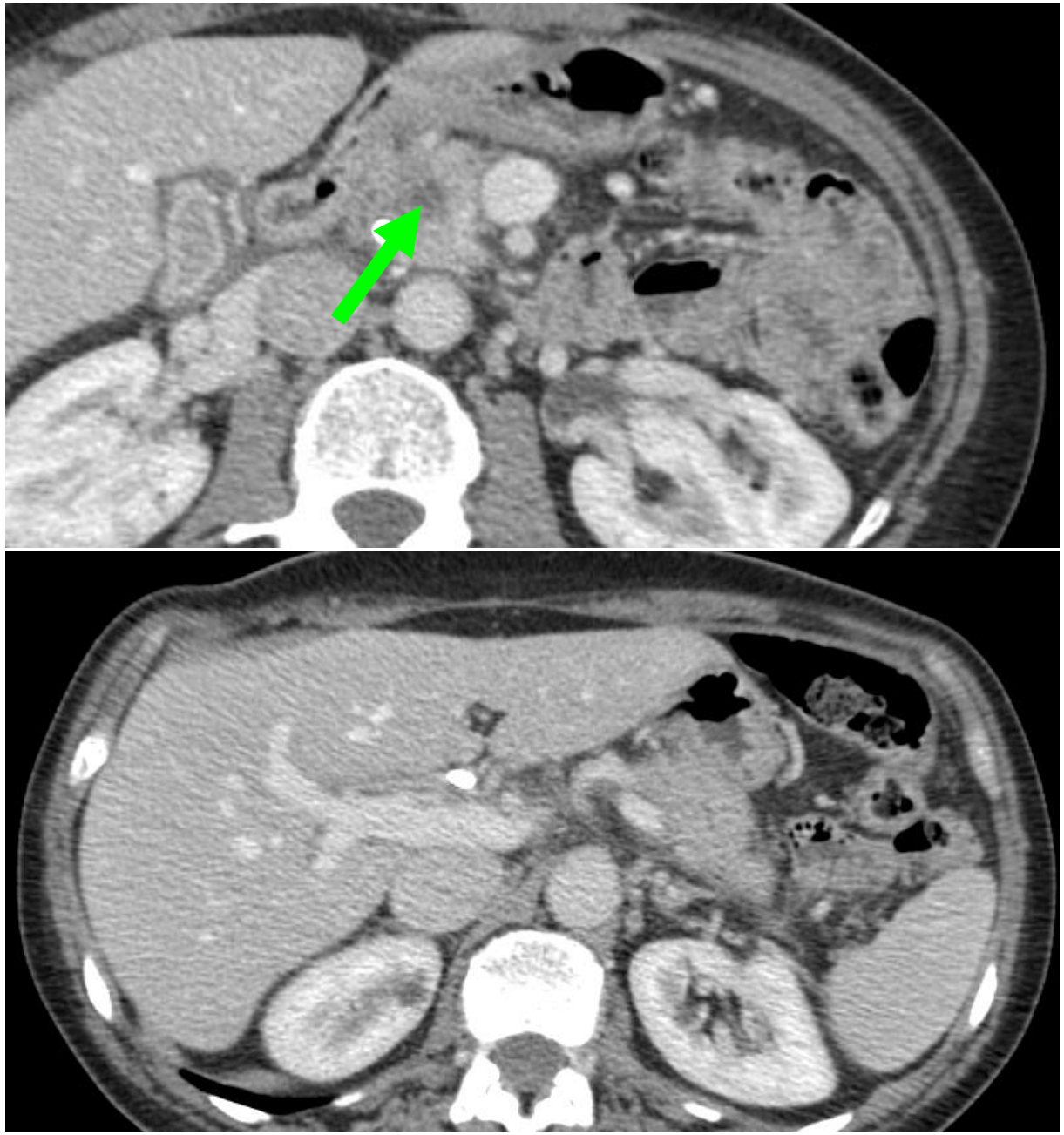
- Healthy 52 y/o female with painless jaundice

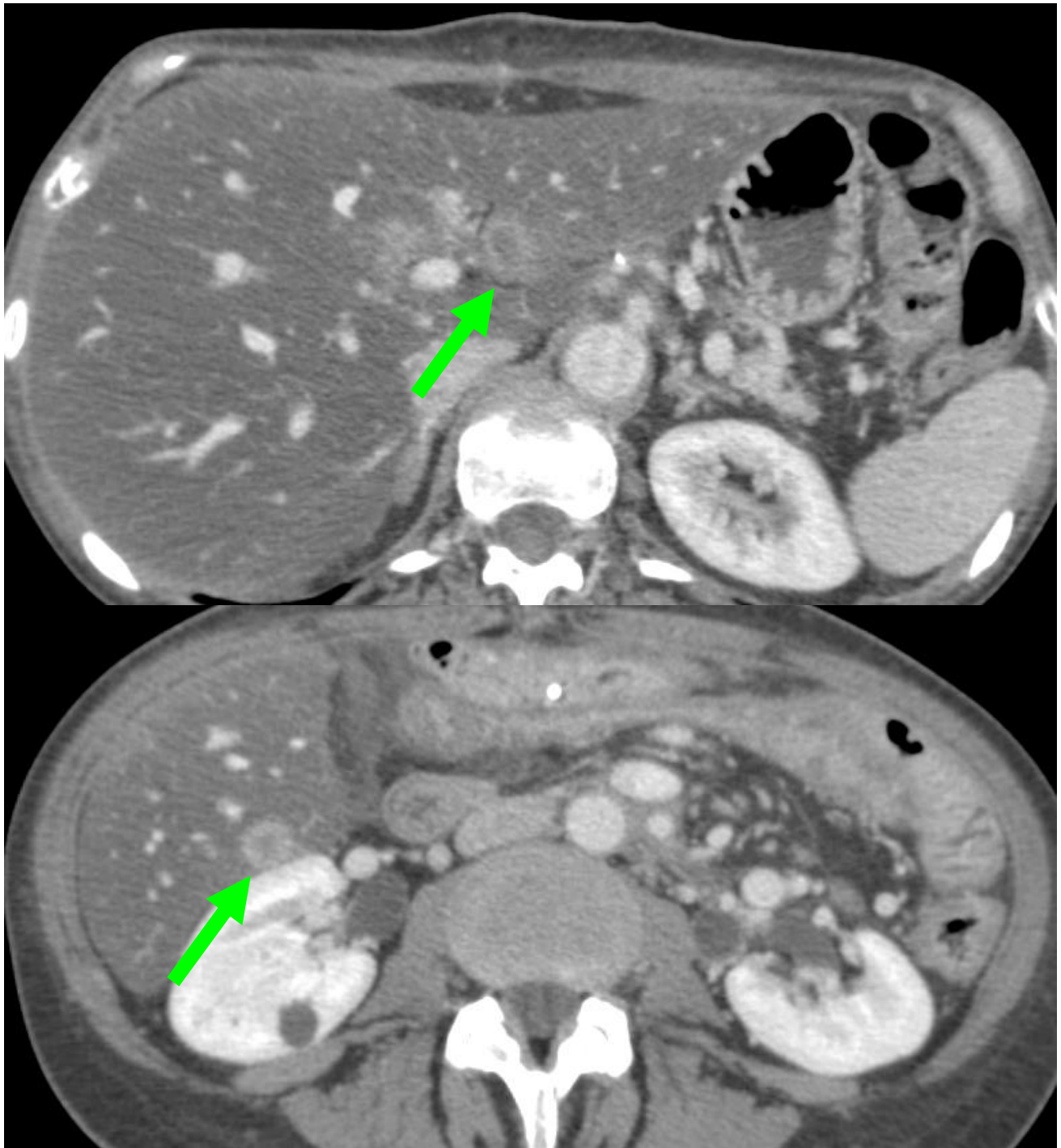
- Whipple
  - Uneventful recovery
  - Adenocarcinoma, node (+)



3 Months Later

Biopsy proven liver mets

- Zero benefit from major surgery



~~Only Real Chance for Cure~~

- Radiographically occult metastatic disease in >90% resectable pancreatic cancer
- Consensus now that multimodality therapy is better than surgery alone
- “How can we get this patient all the treatments that work” not “How can I get this patient surgery”

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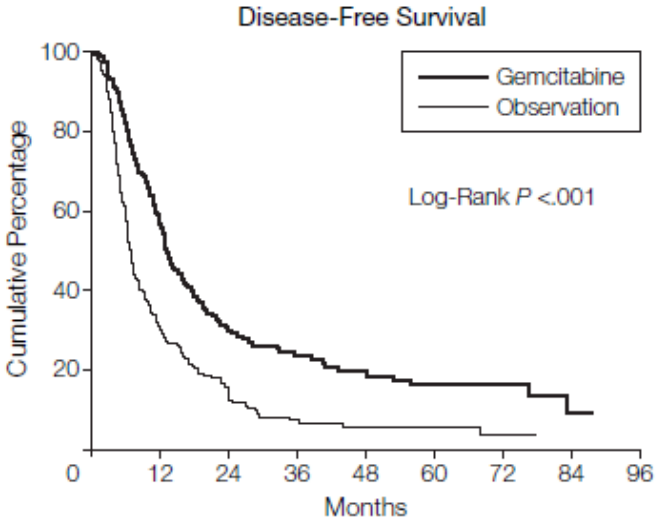
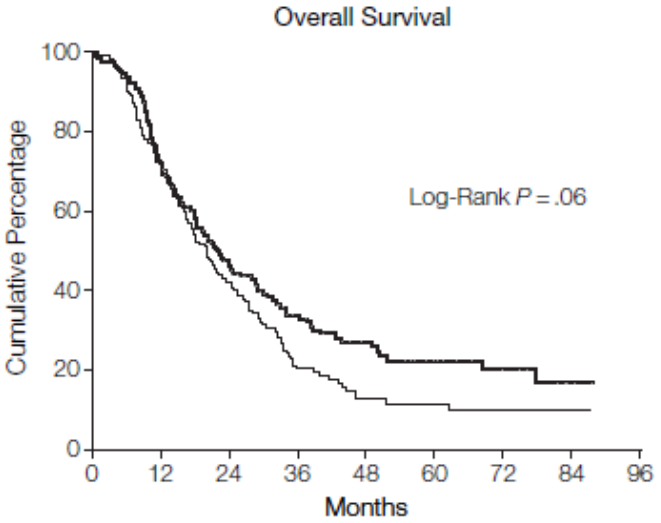


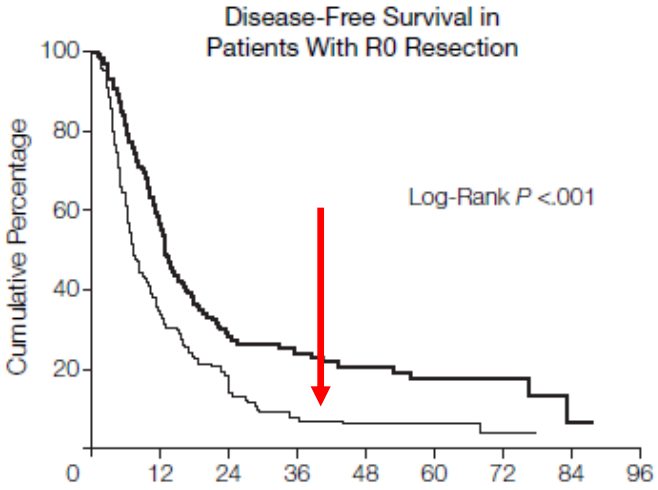
No. at Risk

Gemcitabine	179	96	43	25	17	11	8	1
Observation	175	52	24	10	6	6	2	0



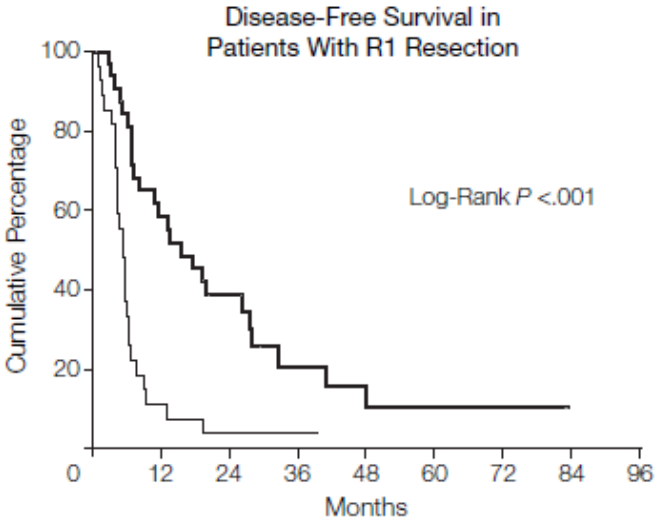
No. at Risk

Gemcitabine	179	128	73	36	23	14	9	2
Observation	175	126	64	25	12	8	4	1



No. at Risk

Gemcitabine	145	78	33	21	14	9	6	1
Observation	148	49	23	9	6	6	2	0



No. at Risk

Gemcitabine	34	18	10	4	2	2	2	0
Observation	27	3	1	1	0	0	0	0

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Criticisms of Neoadjuvant Therapy for Resectable Pacreatic Cancer

- Only real chance for cure - other therapies are largely ineffective
- Treatment sequencing does not matter – can give adjuvant therapy
- Window of resectability may be lost
- Other therapies largely ineffective

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~~Treatment Sequencing Does Not Matter~~

- Surgery has toxicity

How many pts actually receive all planned adjuvant therapy?	
Simons, Cancer 2010 (SEER)	48%
Corsini, JCO 2008 (Mayo)	60%
Herman, JCO 2008 (Hopkins)	44%
Merchant, JACS 2009 (Vanderbilt)	50%
Winter, Ann Surg Onc, 2012 (MSKCC)	60%

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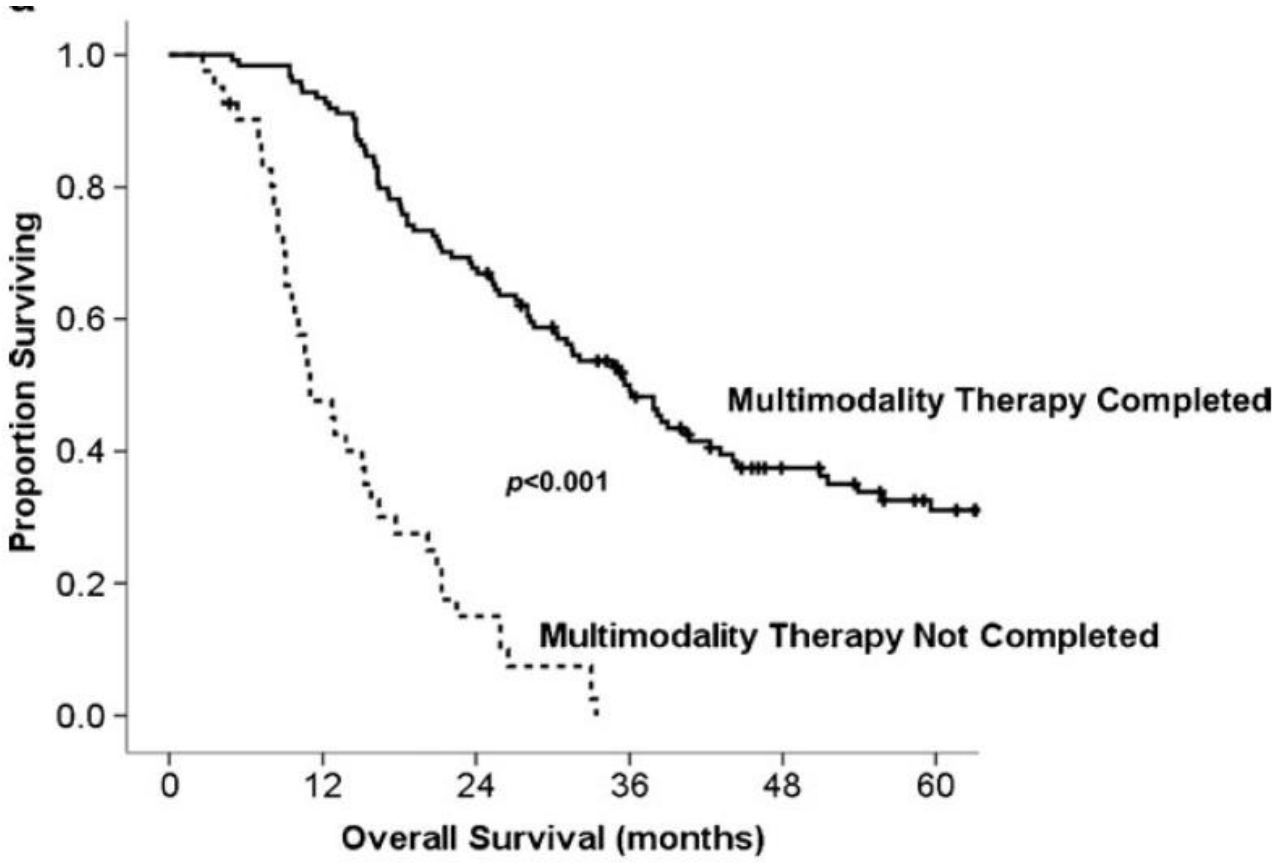
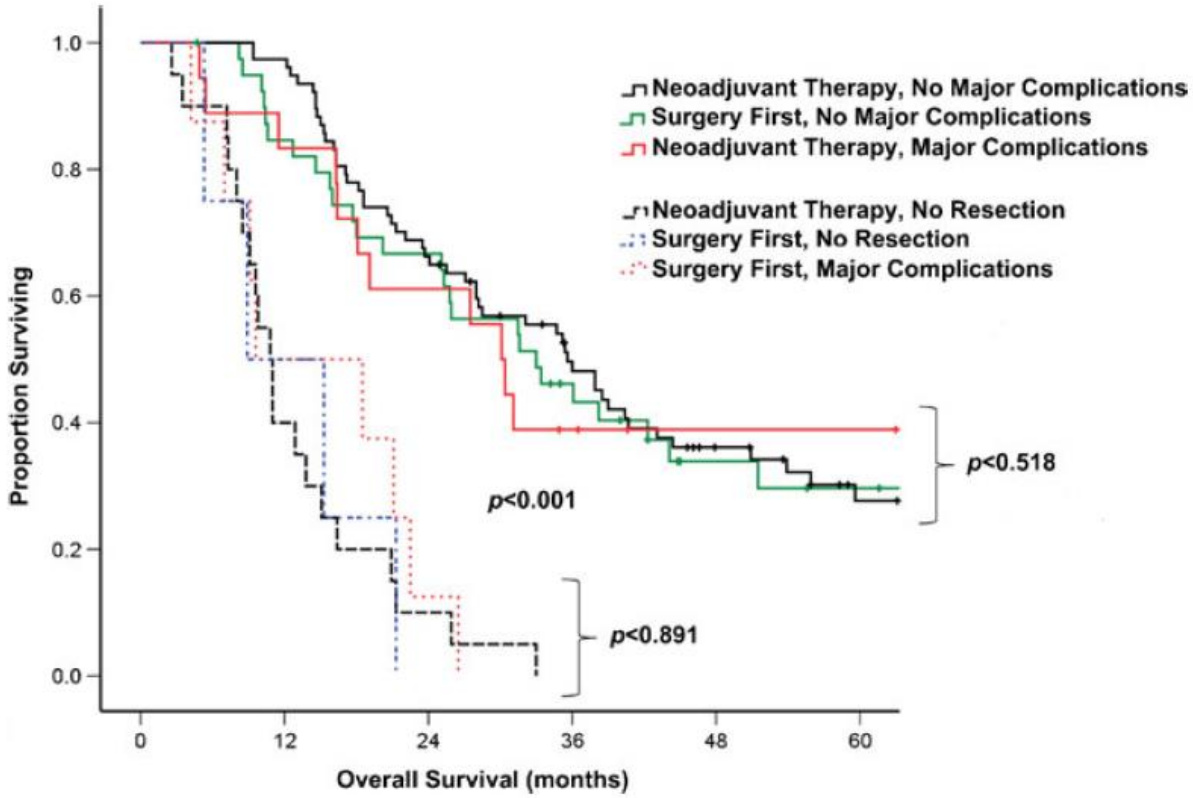
~~Treatment Sequencing Does Not Matter~~





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Tzeng et al, JOGS 2014

Criticisms of Neoadjuvant Therapy for Resectable Pancreatic Cancer

- Only real chance for cure - other therapies are largely ineffective
- Treatment sequencing does not matter – can give adjuvant therapy
- Window of resectability may be lost
- Other therapies largely ineffective

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~~Window of Resectability May Be Lost~~

- Local progression on NAT is rare
  - 1/176 patients (0.6%)
- Distant progression rate = 12-24%

VOLUME 26 · NUMBER 21 · JULY 20 2008

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Preoperative Gemcitabine and Cisplatin Followed by Gemcitabine-Based Chemoradiation for Resectable Adenocarcinoma of the Pancreatic Head

Gauri R. Varadhachary, Robert A. Wolff, Christopher H. Crane, Charlotte C. Sun, Jeffrey E. Lee, Peter W.T. Pisters, Jean-Nicolas Vauthey, Eddie Abdalla, Huamin Wang, Gregg A. Staerkel, Jeffrey H. Lee, William A. Ross, Eric P. Tamm, Priya R. Bhosale, Sunil Krishnan, Prajnan Das, Linus Ho, Henry Xiong, James L. Abbruzzese, and Douglas B. Evans

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Criticisms of Neoadjuvant Therapy for Resectable Pacreatic Cancer

- Only real chance for cure - other therapies are largely ineffective
- Treatment sequencing does not matter – can give adjuvant therapy and stent not an issue
- Window of resectability may be lost
- Other therapies largely ineffective

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Table 1
Overall survival data from older prospective, randomized trials of adjuvant therapy in resected pancreas cancer

Trial	N	Randomization	Overall Survival (mo)	*P*	Classification
CONKO-001	368	Chemotherapy (gemcitabine) vs observation	22.1 vs 20.1 Long follow-up: 22.8 vs 20.2	.06 .01	1a
GITSG	43	Observation or radiation/ bolus 5-FU	20 vs 11	Not reported	1a
ESPAC-1	541	Chemoradiation (5-FU, 20 Gy) vs no chemoradiation	15.5 vs 16.1	.24	1a
		Chemotherapy vs observation	19.7 vs 14.0	.0005	
EORTC 40,891	114	Chemoradiation (5-FU 1 40 Gy EBRT) vs observation	17.1 vs 12.6	.99	1a
RTOG 9704	451	Gemcitabine and 5-FU 1 50.4 Gy EBRT vs 5-FU 1 50.4 Gy EBRT	20.5 vs 16.9	.05	1a

They say laughter is the best medicine, unless you have cancer, in which case chemotherapy is more effective

yourecards
someecards.com

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Other Therapies Largely Ineffective

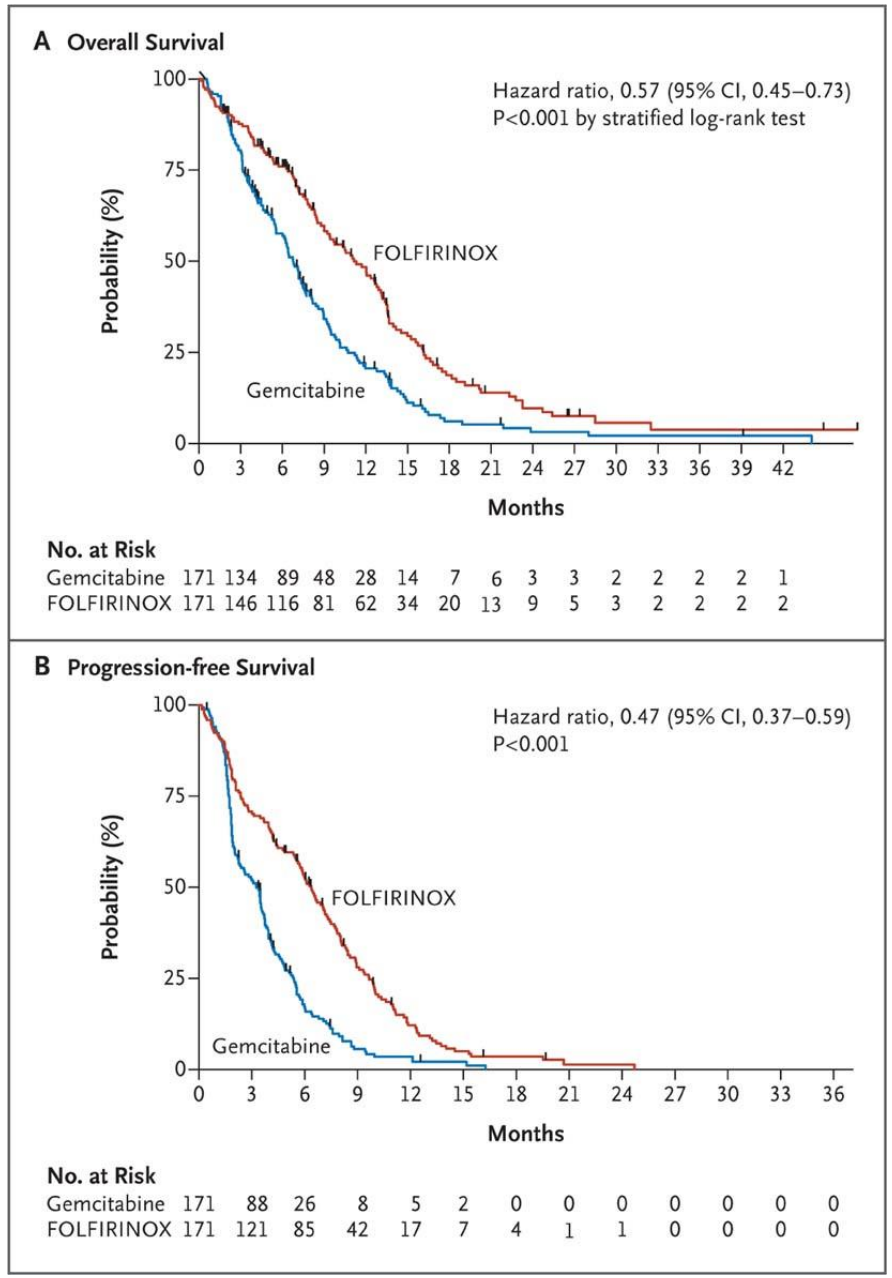


Table 2. Objective Responses in the Intention-to-Treat Population.*

Variable	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
Response — no. (%)			
Complete response	1 (0.6)	0	
Partial response	53 (31.0)	16 (9.4)	
Stable disease	66 (38.6)	71 (41.5)	
Progressive disease	26 (15.2)	59 (34.5)	
Could not be evaluated	25 (14.6)	25 (14.6)	
Rate of objective response†			<0.001
No. (%)	54 (31.6)	16 (9.4)	
95% CI	24.7–39.1	5.4–14.7	
Rate of disease control‡			<0.001
No. (%)	120 (70.2)	87 (50.9)	
95% CI	62.7–76.9	43.1–58.6	
Response duration — mo			0.57
Median	5.9	3.9	
95% CI	4.9–7.1	3.1–7.1	

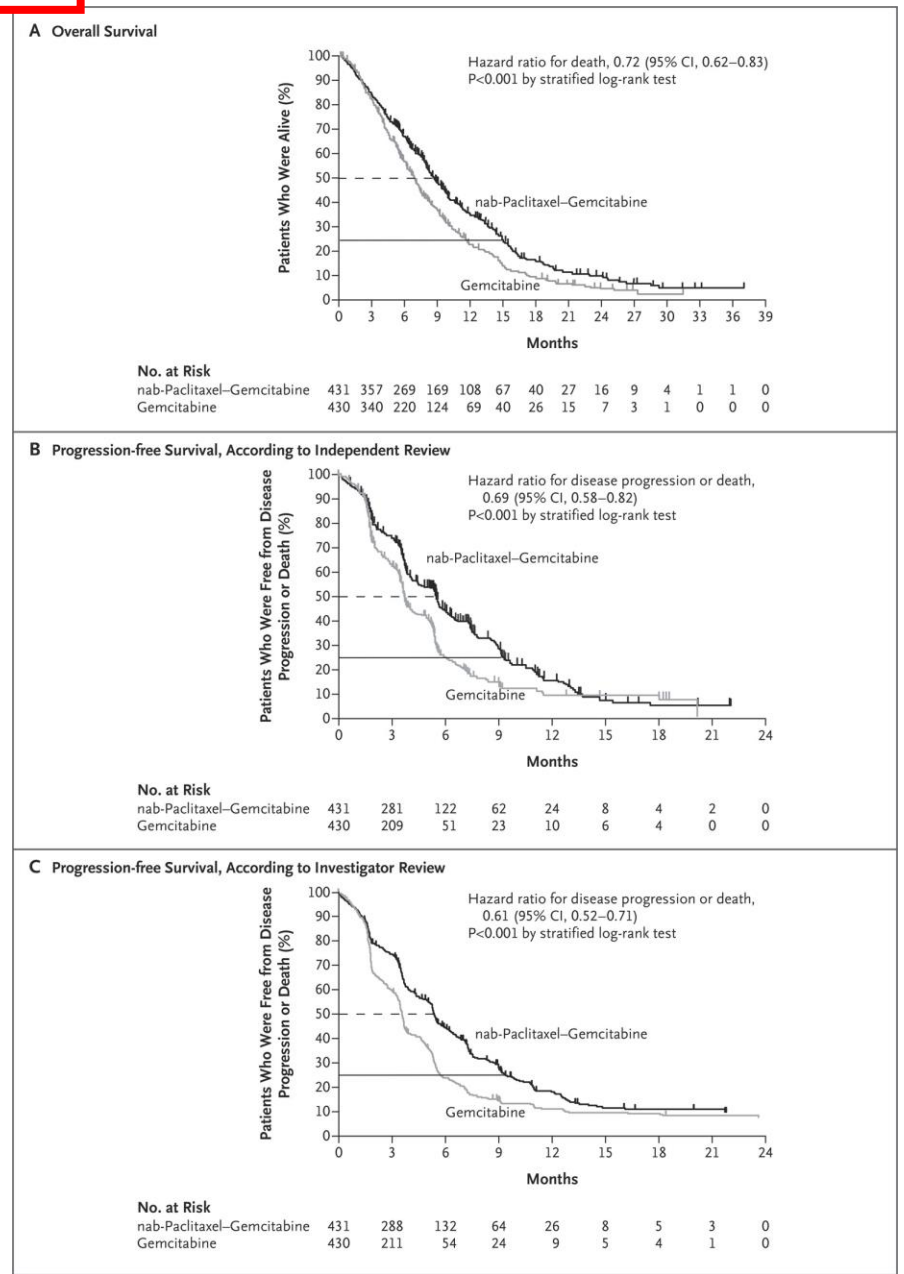
* CI denotes confidence interval, and FOLFIRINOX oxaliplatin, irinotecan, fluorouracil, and leucovorin.
† The rate of objective response was defined as the percentage of patients who had a complete response or partial response.
‡ The rate of disease control was defined as the percentage of patients who had a complete response, partial response, or stable disease.

Conroy, NEJM, 2011

Other Therapies Largely Ineffective

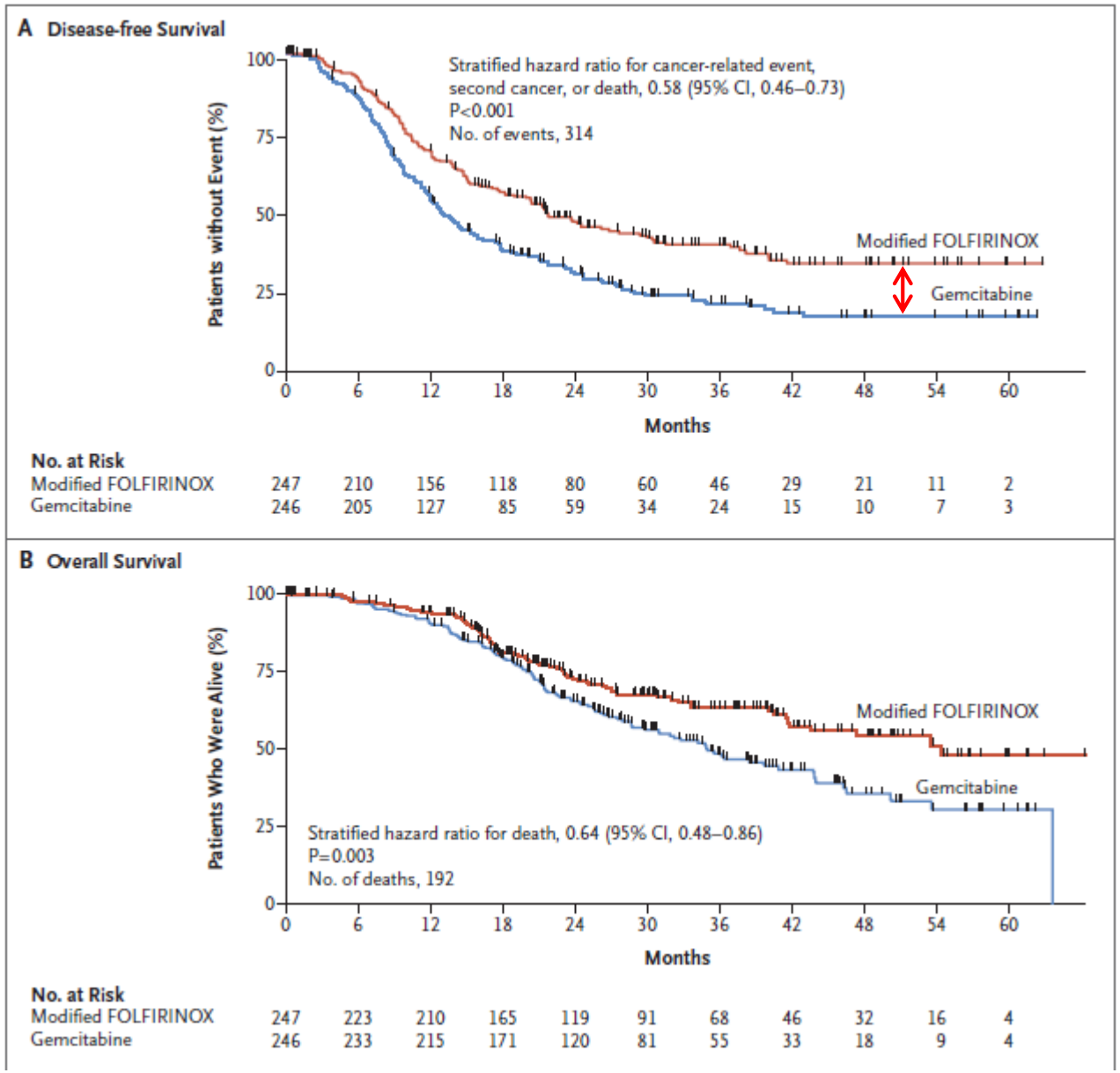
Table 2. Overall Survival, Progression-free Survival, and Response Rates in the Intention-to-Treat Population.

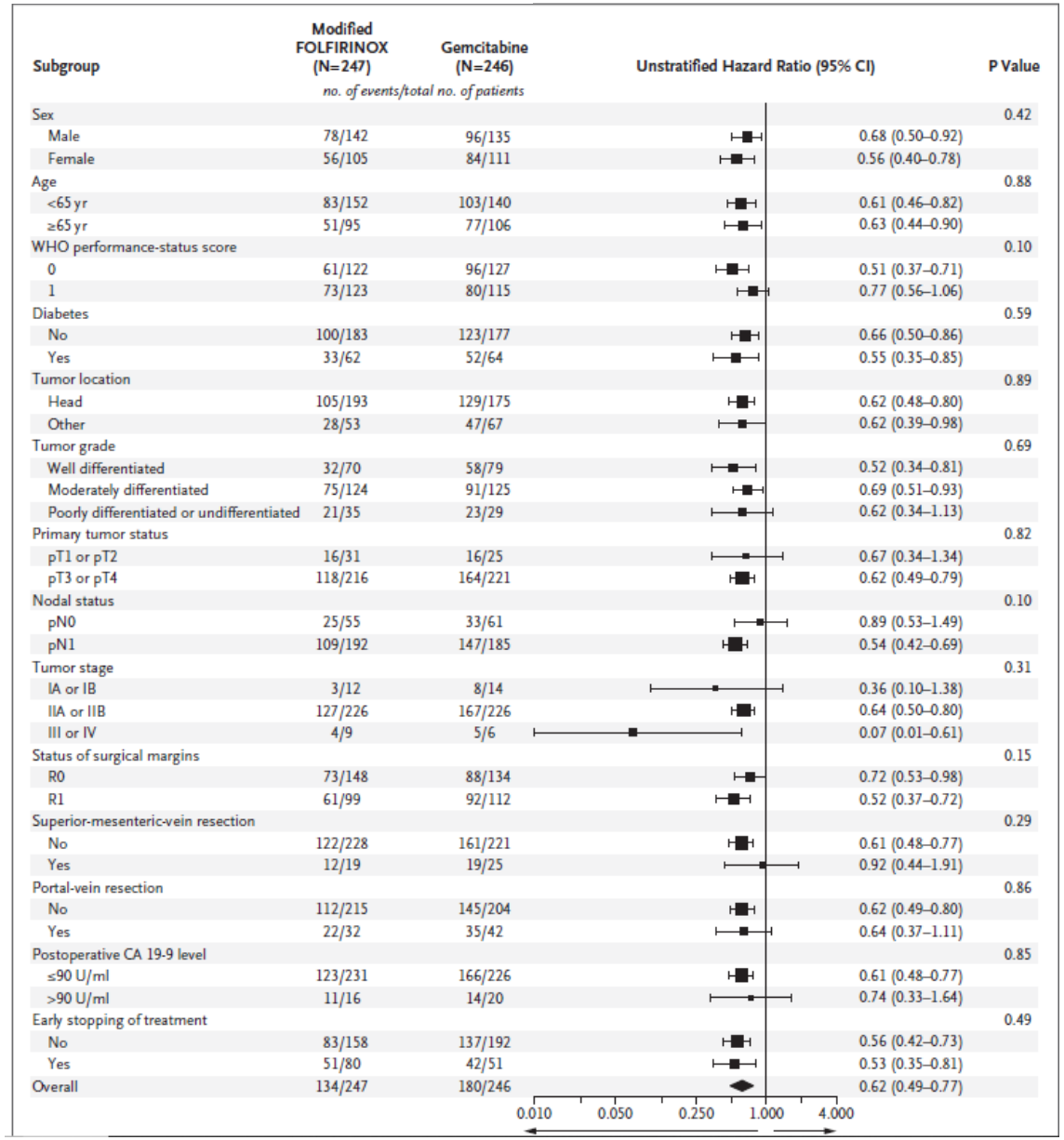
Efficacy Variable	nab-Paclitaxel plus Gemcitabine (N=431)	Gemcitabine Alone (N=430)	Hazard Ratio or Response-Rate Ratio (95% CI)*	P Value
Overall survival				
Median overall survival — mo (95% CI)	8.5 (7.9–9.5)	6.7 (6.0–7.2)	0.72 (0.62–0.83)	<0.001
Survival rate — % (95% CI)				
6 mo	67 (62–71)	55 (50–60)		<0.001
12 mo	35 (30–39)	22 (18–27)		<0.001
18 mo	16 (12–20)	9 (6–12)		0.008
24 mo	9 (6–13)	4 (2–7)		0.02
Progression-free survival				
Median progression-free survival — mo (95% CI)	5.5 (4.5–5.9)	3.7 (3.6–4.0)	0.69 (0.58–0.82)	<0.001
Rate of progression-free survival — % (95% CI)				
6 mo	44 (39–50)	25 (20–30)		
12 mo	16 (12–21)	9 (5–14)		
Response				
Rate of objective response				
Independent review				
No. of patients with a response	99	31	3.19 (2.18–4.66)	<0.001
% (95% CI)	23 (19–27)	7 (5–10)		
Investigator review				
No. of patients with a response	126	33	3.81 (2.66–5.46)	<0.001
% (95% CI)	29 (25–34)	8 (5–11)		
Rate of disease control†				
No. of patients	206	141	1.46 (1.23–1.72)	<0.001
% (95% CI)	48 (43–53)	33 (28–37)		
Best response according to independent review — no. (%)				
Complete response	1 (<1)	0		



Von Hoff DD et al. N Engl J Med 2013;369:1691-1703 GEM/Abrax vs. GEM

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer





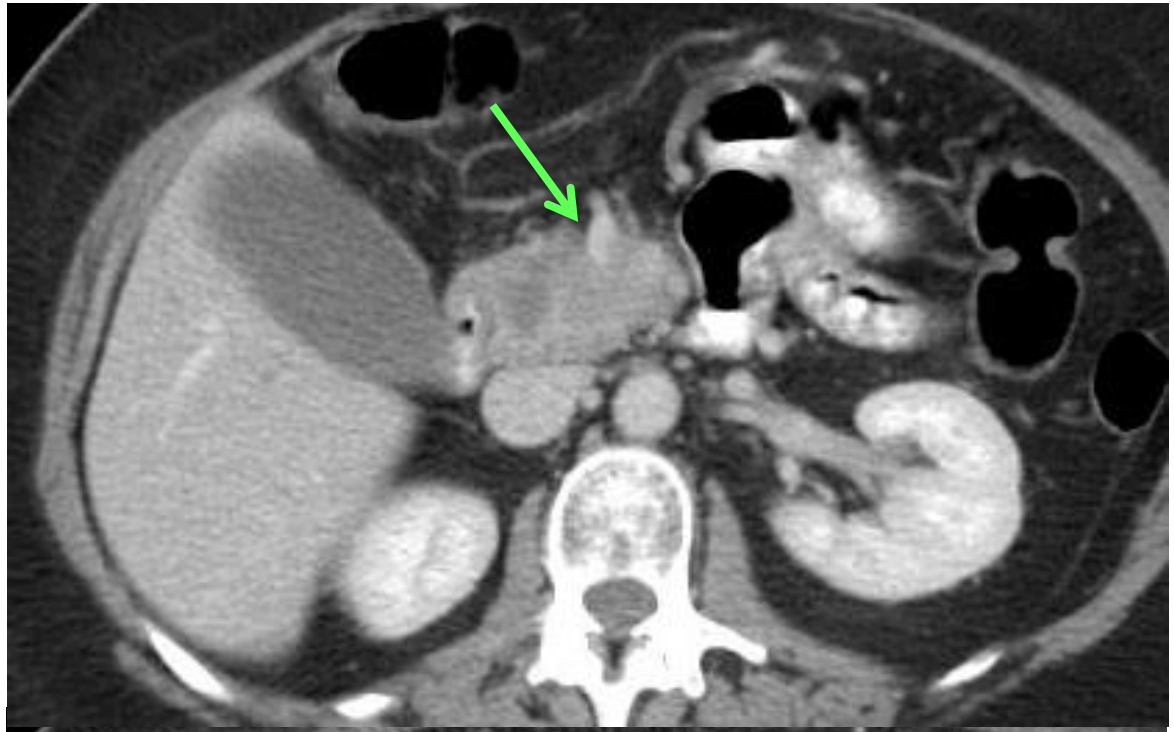
Conroy et al, NEJM 2018

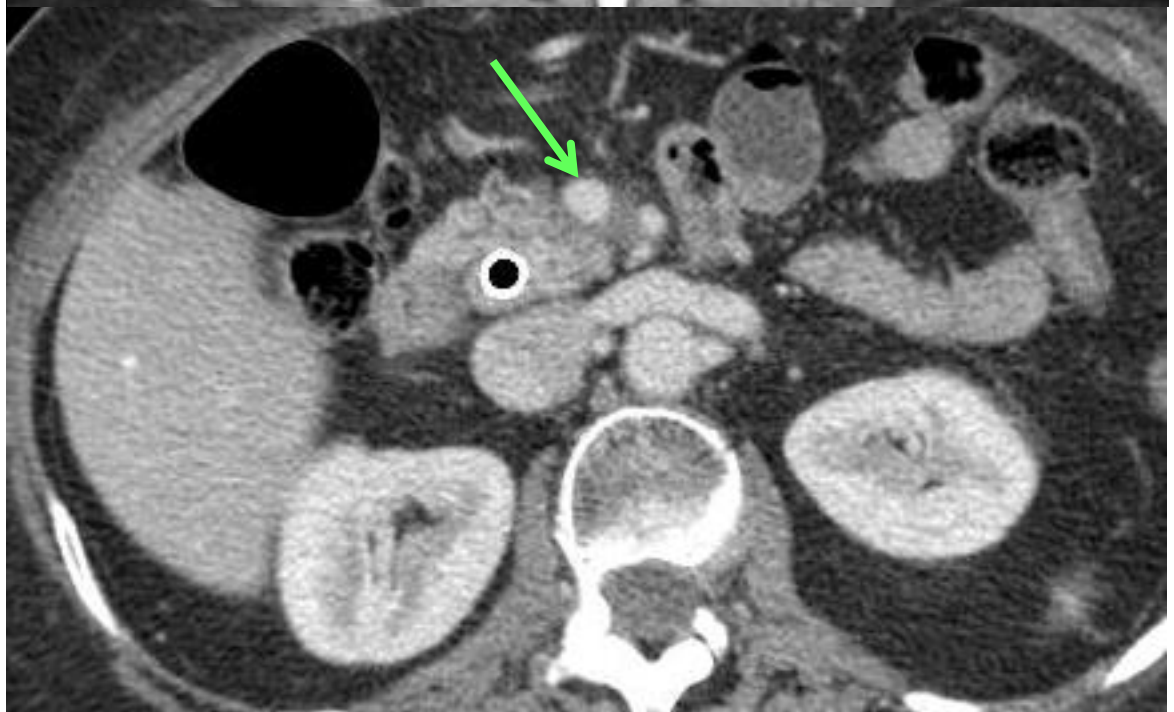
Neoadjuvant Approach

- Provides early treatment of micrometastatic disease
  (at least 90% of “resectable” patients)
- Patients with rapidly progressive disease will not be subjected to non-therapeutic operations
- Logical strategy for the high incidence of positive margins. (Katz JOGS 2012)
- Delayed recovery does not delay systemic treatment
  - Tzeng JOGS 2014: 83% vs. 58% completion
- Tissue retrieval pre/post treatment for correlative studies

Ochsner™ Health System

- 59 y/o female with abdominal pain and jaundice
- CA 19-9 1010
- 4 cycles FOLFIRINOX
- 5/FU + XRT
- CA 19-9 6
- Whipple
- Pathologic CR





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