Optimal Management of Localized Pancreatic Cancer: Sequence of Therapy and "Resectability"

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Ochsner Health System

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Department of General Surgery

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Disclosures:

- None!

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Topics at hand

- **Evolution of Systemic Therapy in Pancreatic Cancer**
- Staging and Resectability
- Sequence of Therapy

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Systemic Therapy

- Evolution of Systemic Therapy – This is not a long slide deck
  - Conko 01 – Gem -- 2008
  - ESPAC-4 - Gem-Cap -- 2017
  - FOLFIRINOX – Metastatic, LA, to resectable
  - Gem-Nab?
  - Gem-Cis-Nab?

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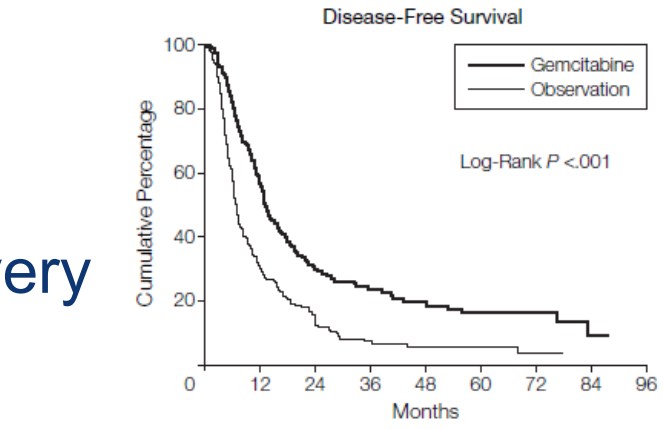
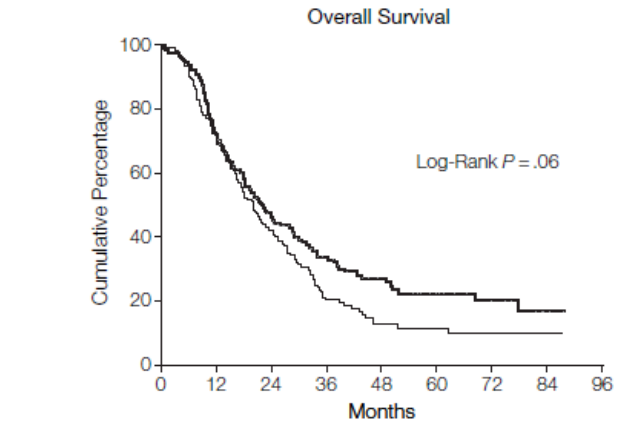
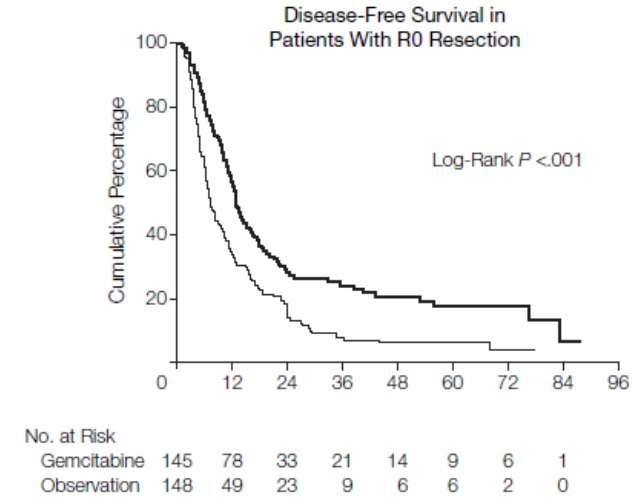
CONKO-001

- Published 2008
- Randomized post resection/recovery
- R0 and R1 patients
  - 19% R1 (gem) vs 15% (obs)







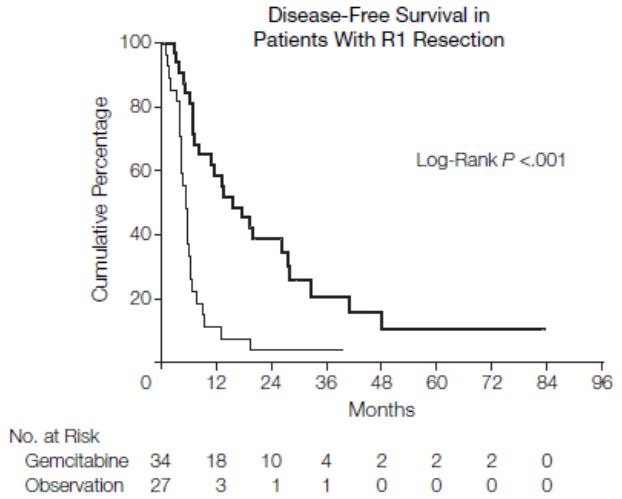


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Table 1
Overall survival data from older prospective, randomized trials of adjuvant therapy in resected pancreas cancer

Trial	N	Randomization	Overall Survival (mo)	*P*	Classification
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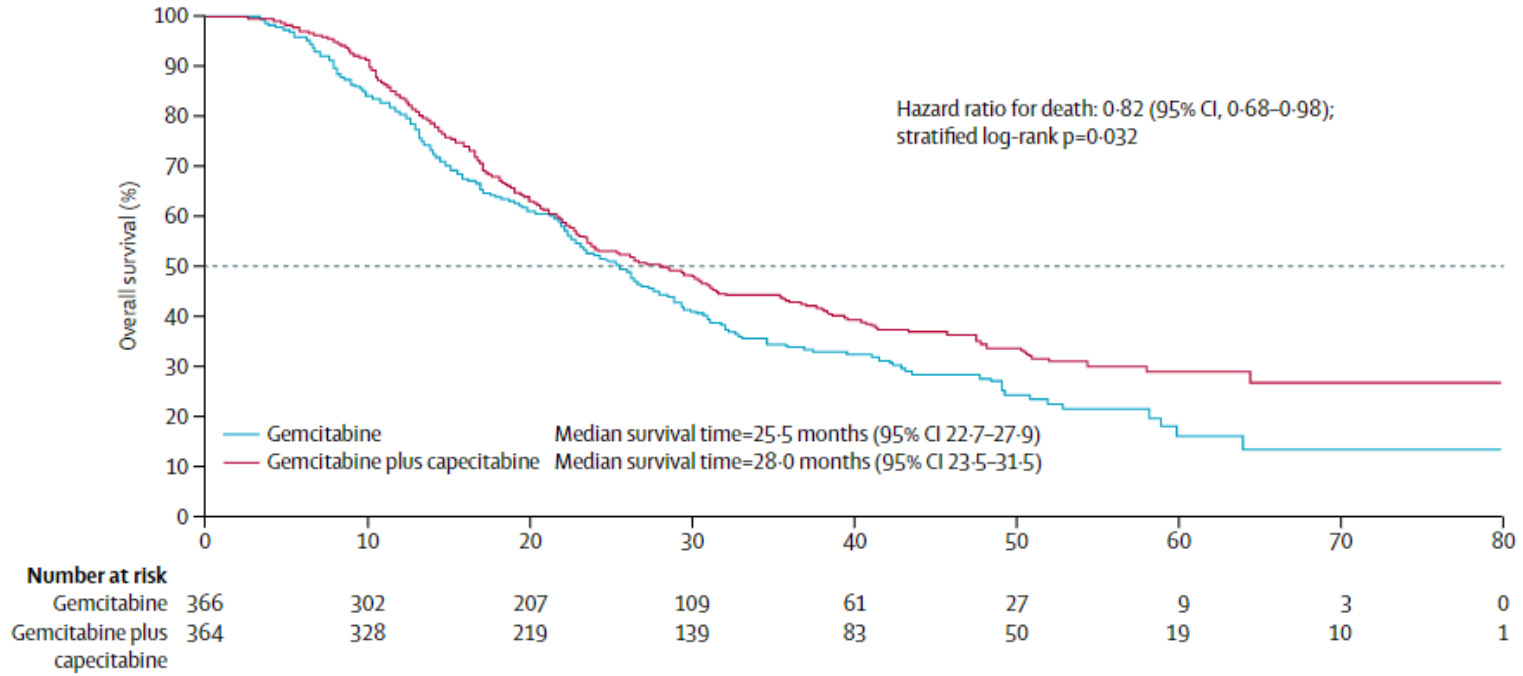
RTOG 9704	451	Gemcitabine and 5-FU 1 50.4 Gy EBRT vs 5-FU 1 50.4 Gy EBRT	20.5 vs 16.9	.05	1a

ESPAC-4

- Published 2017, European study → 10 year gap!
- Randomized post resection/recovery
- R0 and R1 patients → 60% R1!
  - 46% local recurrence rate!



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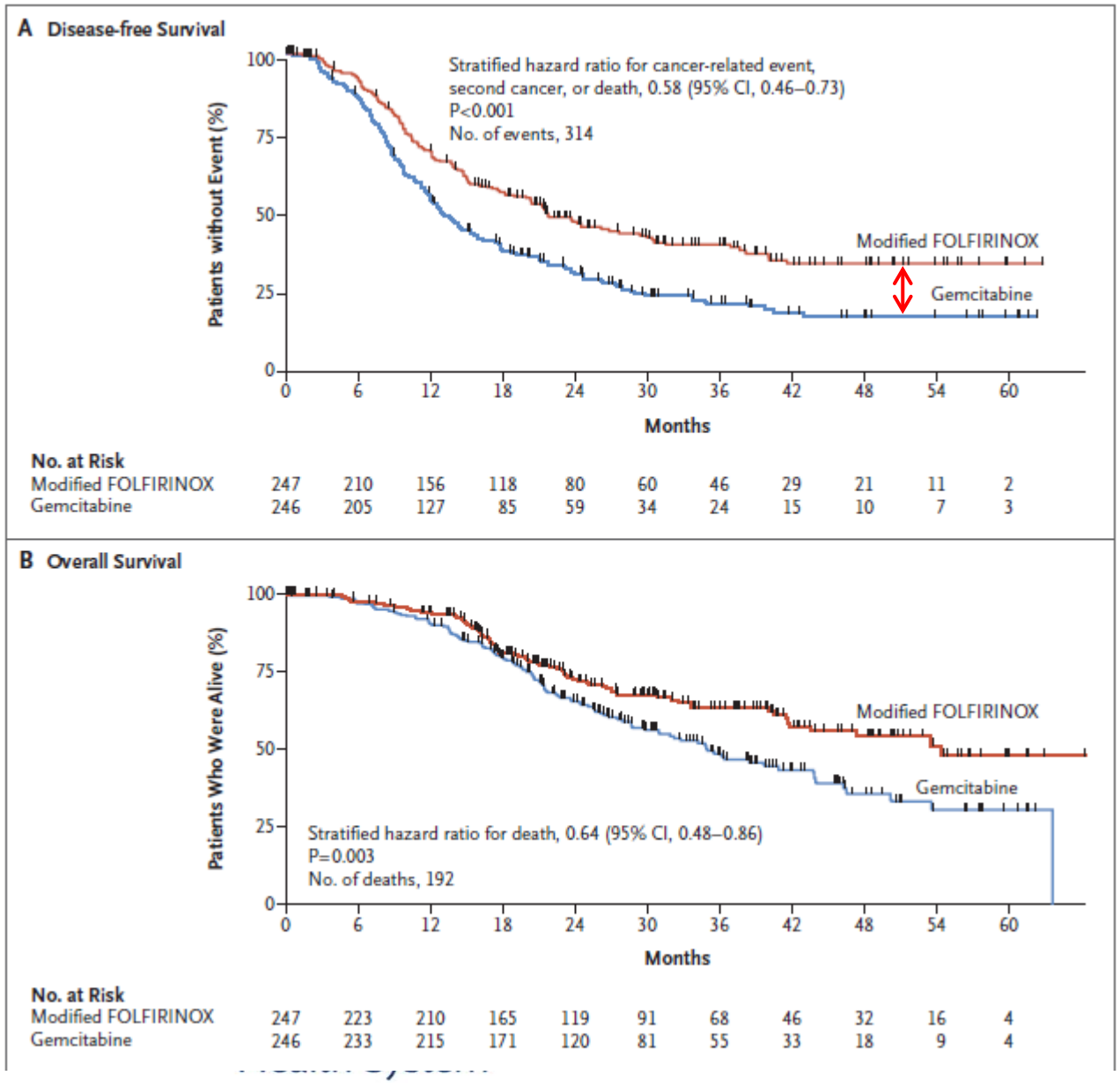
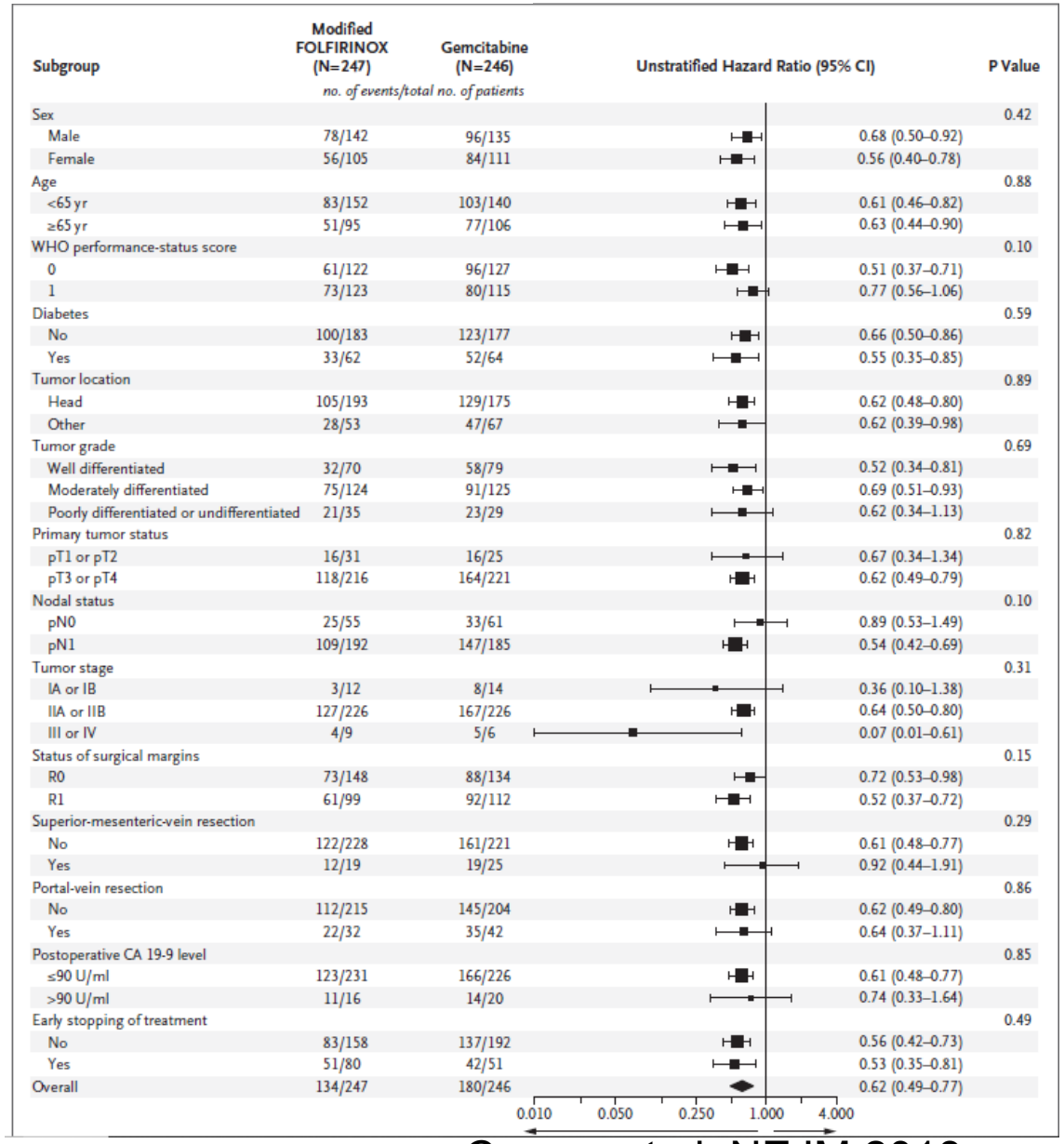
FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer





Conroy et al, NEJM 2018

FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer

- Extraordinarily well selected population
- Randomized after recovery from surgery
- CA 19-9 <180

- Are we really achieving mOS 54 months in the adjuvant setting in the real world?

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What else?

- Gem-Nab – works metastatic, no strong data for adjuvant/periop
  - APACT – adjuvant Gem-Nab, equally well selected patients – no OS benefit
  - AGITG GAP – periop Gem-Nab – mOS 23 months, consistent with earlier trials
- CONKO-005 – adjuvant Gem-Erlotinib – no OS benefit
- Gem-Cis-Nab – active in biliary tract cancers, 70+% response in metastatic disease.

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Topics at hand

- Evolution of Systemic Therapy in Pancreatic Cancer
- **Staging and Resectability**
- Sequence of Therapy

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

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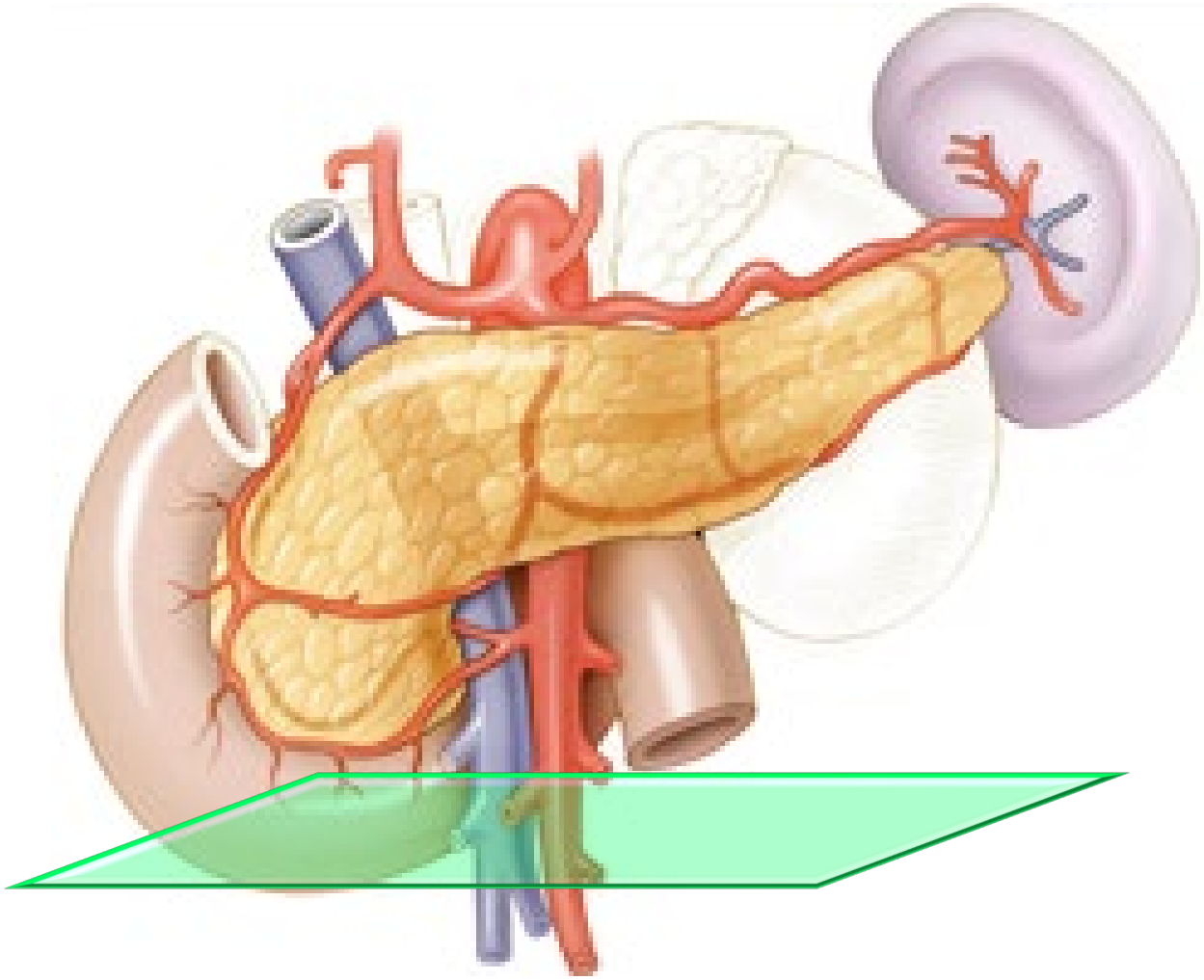
“Resectability” trumps TNM

Standard Terminology

- Resectable
- Borderline Resectable
- ~~Locally Advanced~~



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Resectability, NCCN

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Pancreatic Adenocarcinoma

NCCN Guidelines Index
Table of Contents
Discussion

CRITERIA DEFINING RESECTABILITY STATUS AT DIAGNOSIS[a]

- Decisions about resectability status should be made in consensus at multidisciplinary meetings/discussions.

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 locally advanced 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).
Locally Advanced[b,c]	Head/uncinate process: • Solid tumor contact with SMA >180° • Solid tumor contact with the CA >180° Pancreatic body/tail: • Solid tumor contact of >180° with the SMA or CA • Solid tumor contact with the CA and aortic involvement	• Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)

“Resectability” trumps TNM

Standard Terminology

- Resectable
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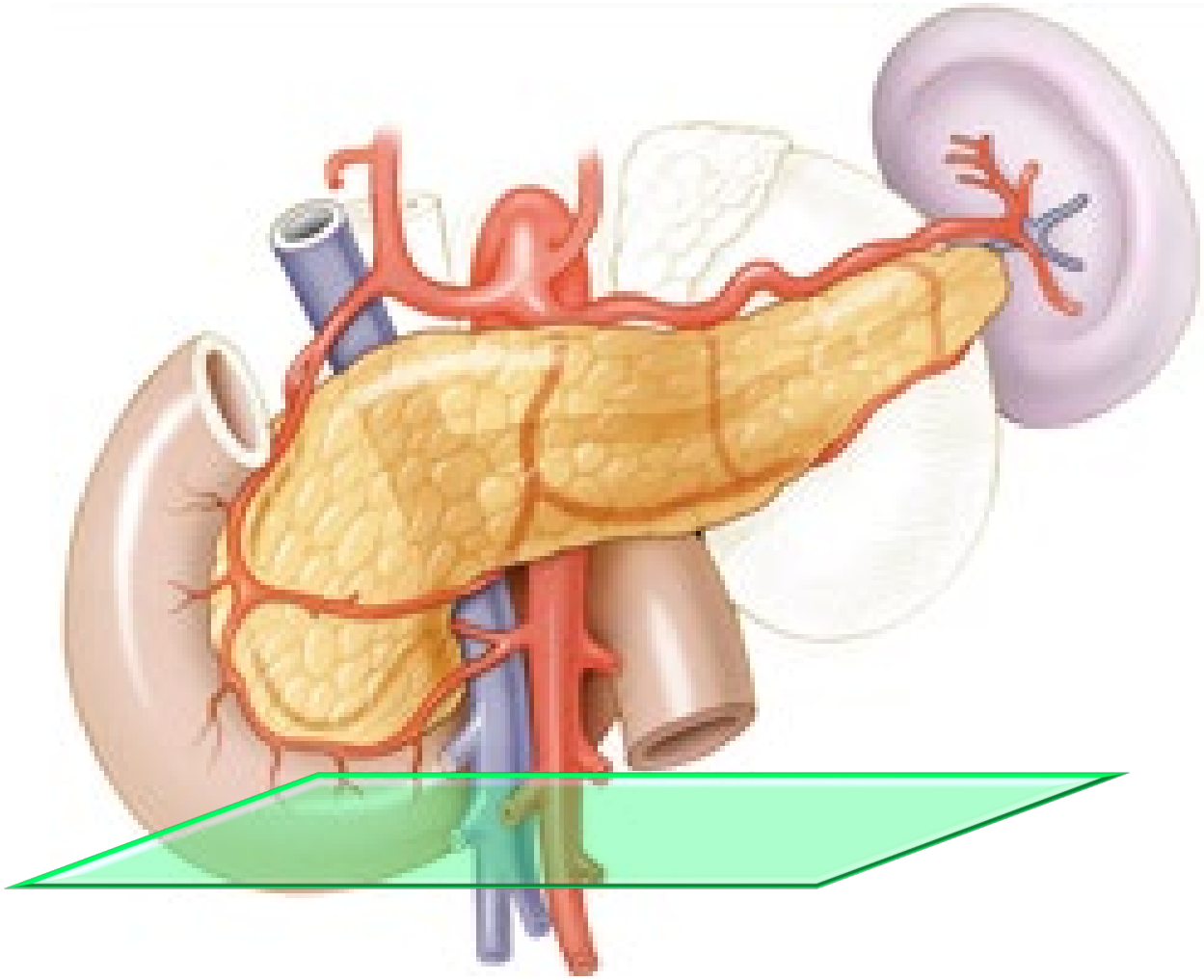
- ~~Locally Advanced~~



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Resectability, NCCN

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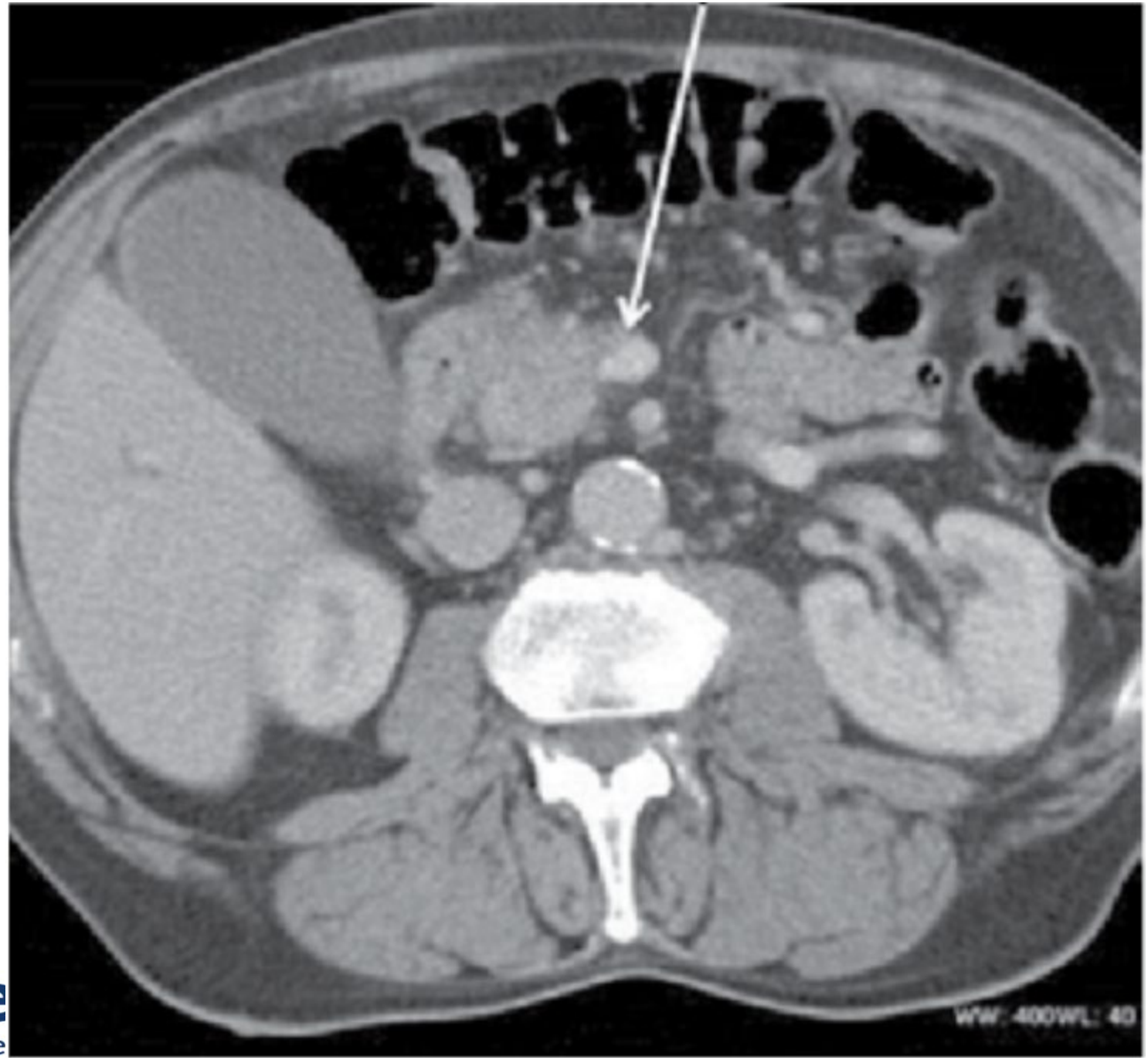

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Topics at hand

- Evolution of Systemic Therapy in Pancreatic Cancer
- Staging and Resectability
- **Sequence of Therapy**

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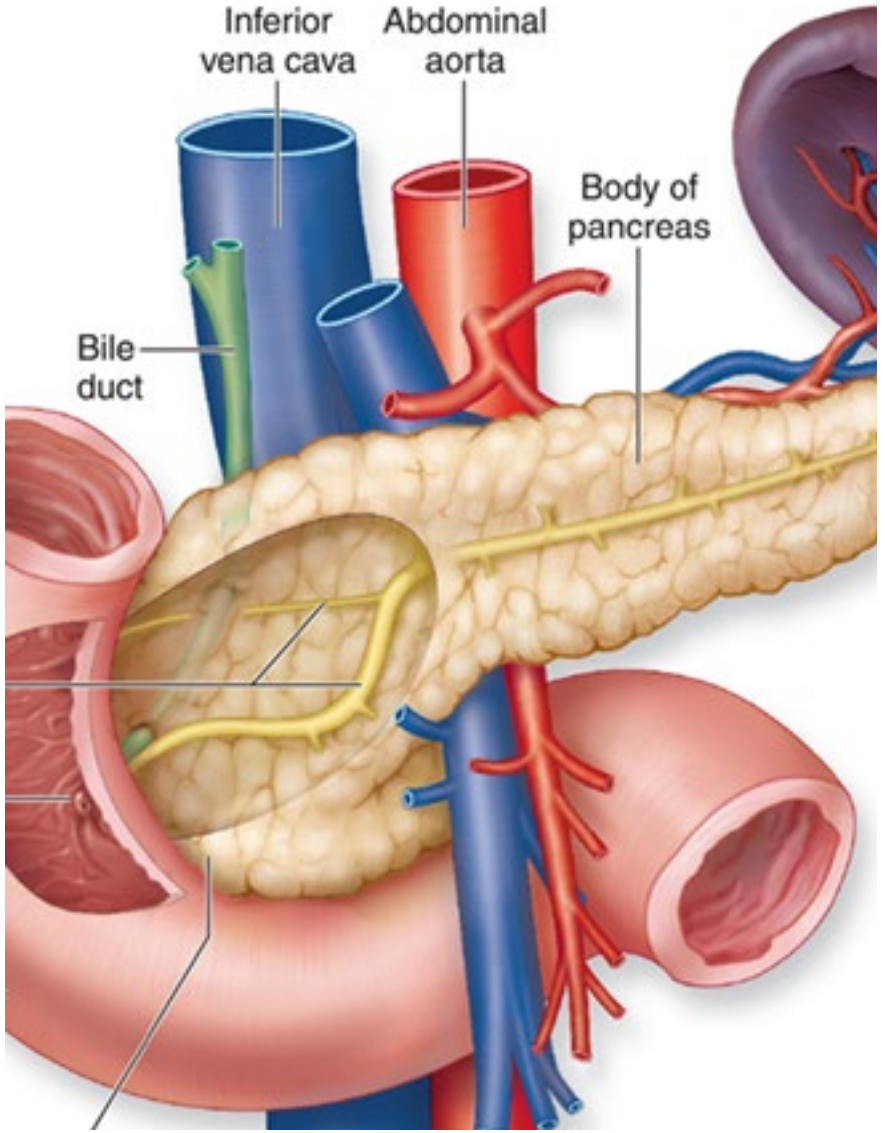
Does resectability influence sequence of therapy?

- Resectable
  - Tumor is not touching important vessels
  - Neoadj or Upfront Surgery?

- Borderline resectable
  - Tumor is touching PV/SMV/HA/CA/SMA
  - Neoadjuvant approach widely accepted



Neoadjuvant Therapy for **Resectable** Pancreatic Cancer

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Pancreatic Adenocarcinoma

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Table of Contents
Discussion

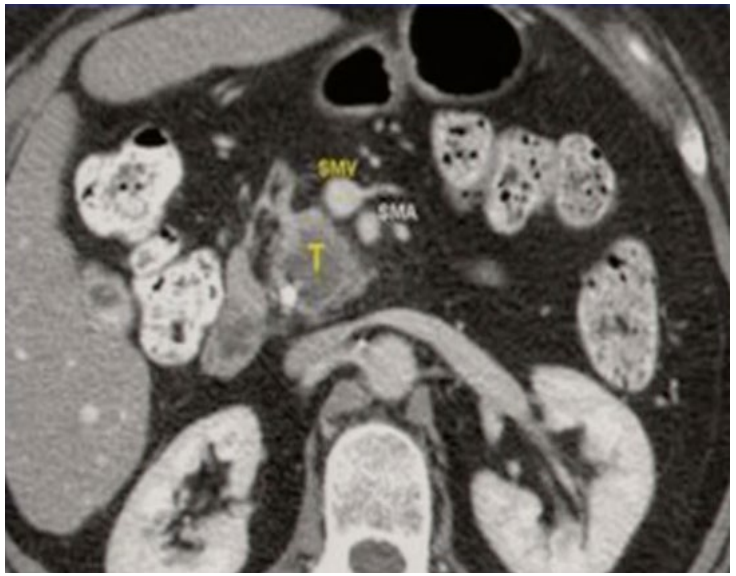
POSTOPERATIVE ADJUVANT TREATMENT | **SURVEILLANCE**

Baseline postoperative CT (chest, abdomen, and pelvis) with contrast CA 19-9 and Germline testing, if not previously done[f]

- No prior neoadjuvant therapy → No evidence of recurrence or metastatic disease → Clinical trial preferred or Chemotherapy alone[t] or Induction chemotherapy[t] followed by chemoradiation[u,z,aa] ± subsequent chemotherapy[t]
- Prior neoadjuvant therapy → No evidence of recurrence or metastatic disease → chemotherapy[bb] and/or Consider chemoradiation[aa,bb] in the instance of a positive margin R1 resection
- Identification of metastatic disease → See Metastatic Disease (PANC-8)

Surveillance every 3–6 mo for 2 years, then every 6–12 mo as clinically indicated:
- H&P for symptom assessment
- CA 19-9 level (category 2B)[cc]
- Chest CT and CT or MRI of abdomen and pelvis with contrast

→ Recurrence after Resection (See PANC-10)



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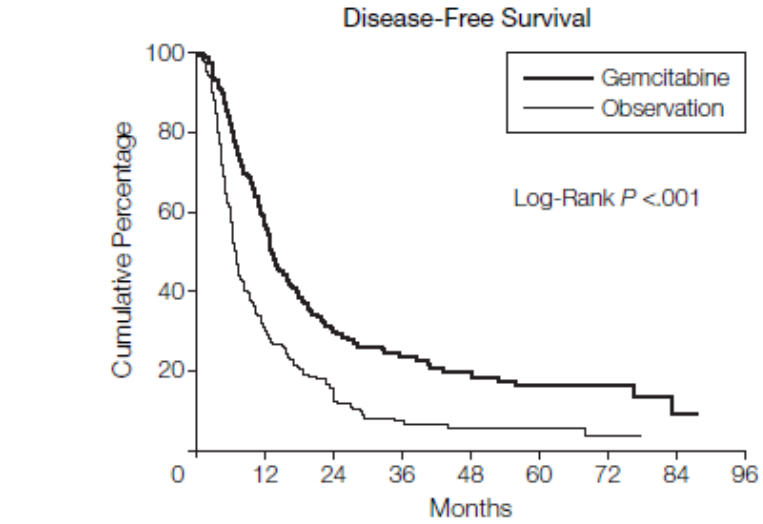
Pancreatic Adenocarcinoma

RESECTABLE DISEASE | **TREATMENT**

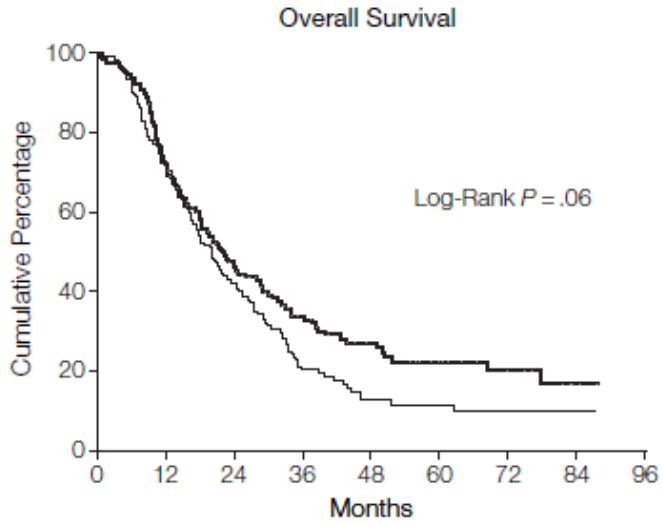
Resectable disease[e,f,h,i] → Consider staging laparoscopy, in high-risk[j] patients or as clinically indicated[k]

- Proceed to surgery (without neoadjuvant therapy)
- or
- EUS-guided biopsy[k,l] if considering neoadjuvant therapy and Consider stent if clinically indicated[e] → Consider neoadjuvant therapy, particularly in high-risk patients[j,m] → Repeat pancreatic protocol CT or MRI; Repeat chest/pelvic CT[b]; Post-treatment CA 19-9[n]



No. at Risk

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



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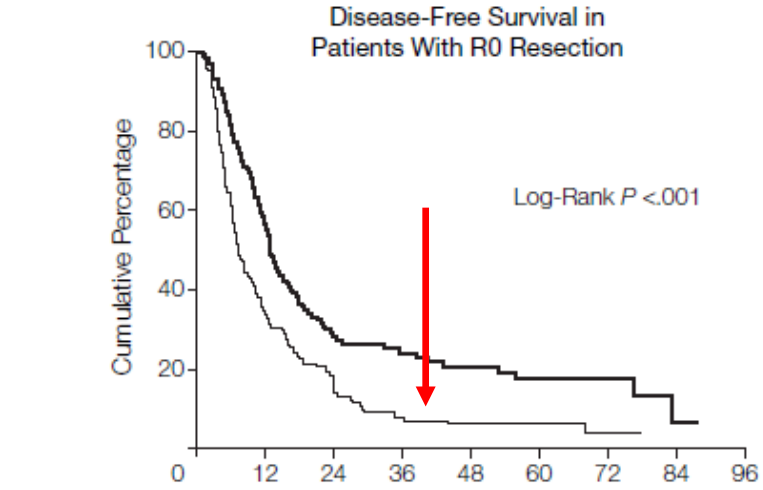
Gemcitabine	179	128	73	36	23	14	9	2
Observation	175	126	64	25	12	8	4	1



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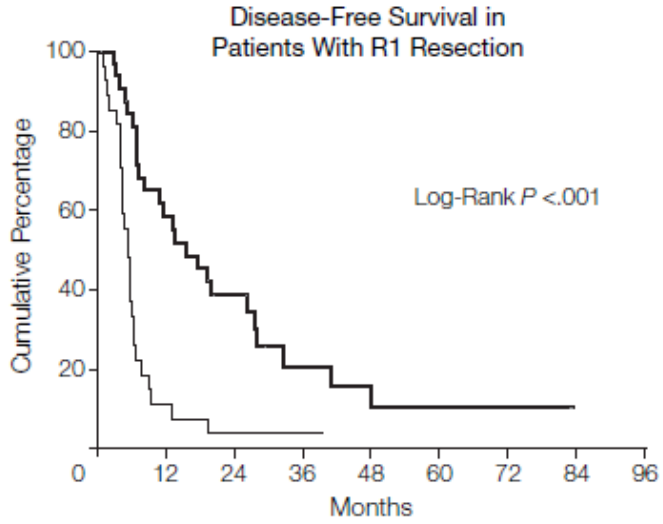

No. at Risk

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

Neoadjuvant therapy – Standard of Care?

- 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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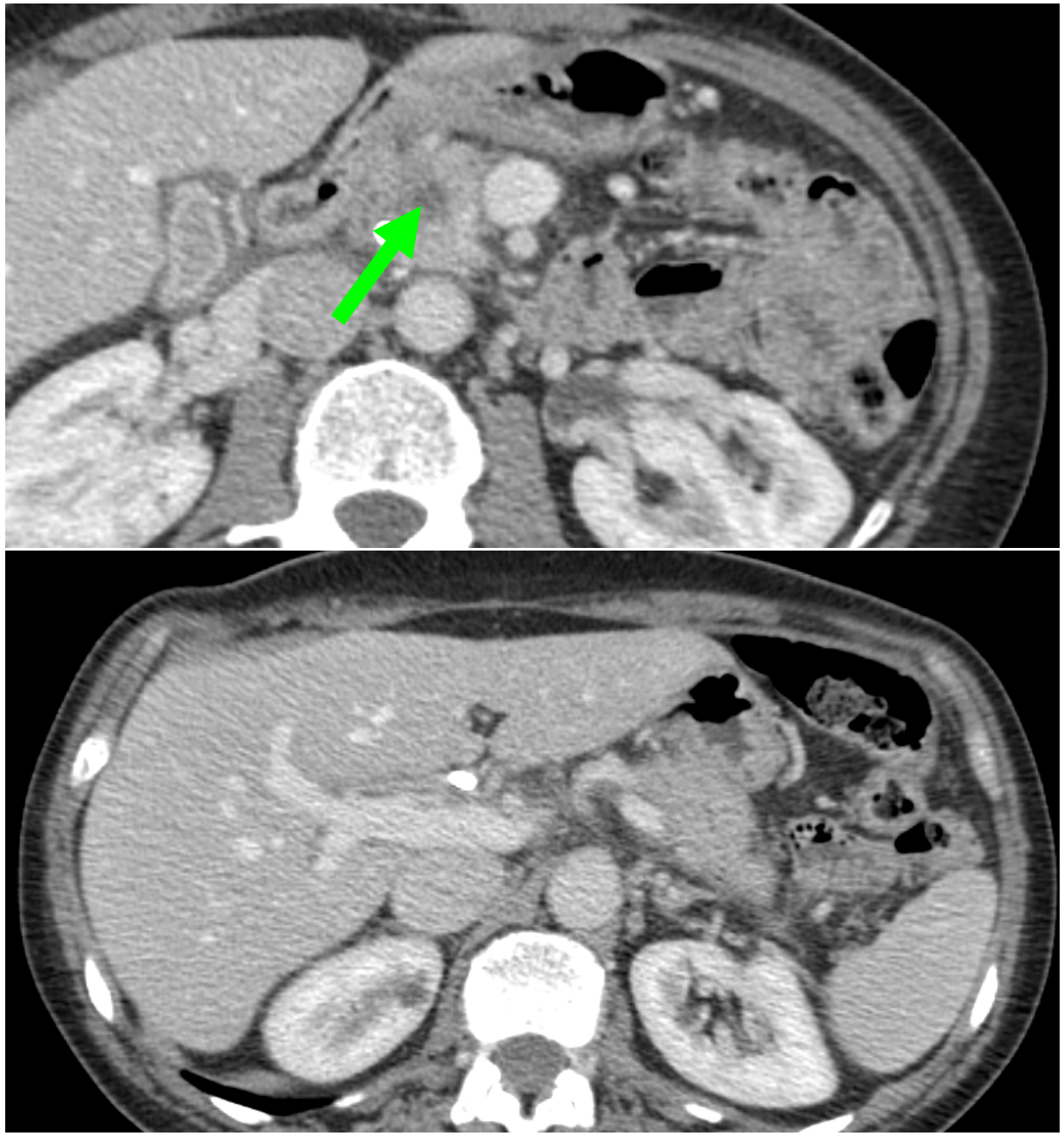
- Healthy 52 y/o female with painless jaundice

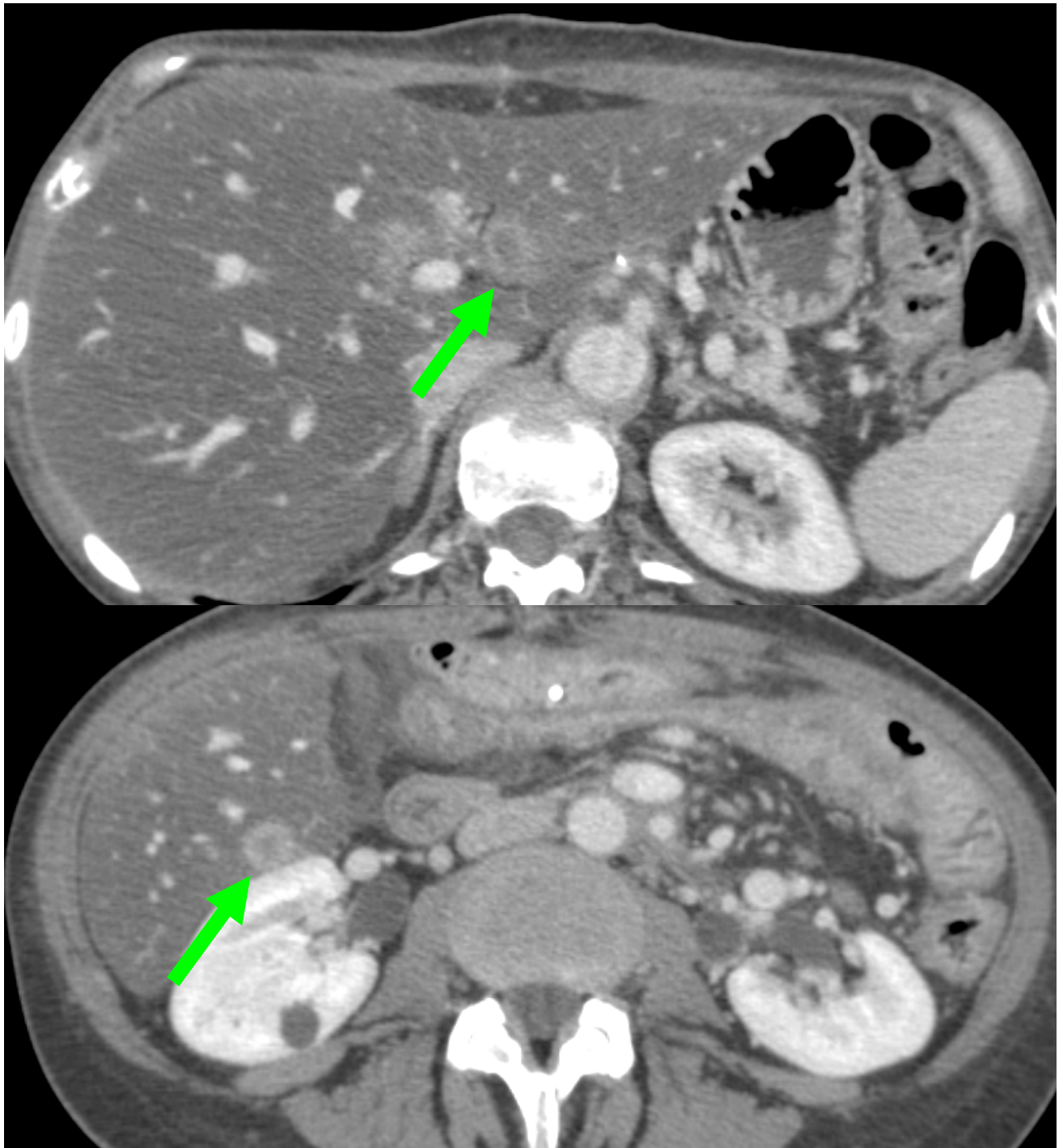
- Whipple
  - Uneventful recovery
  - Adenocarcinoma, node (+)

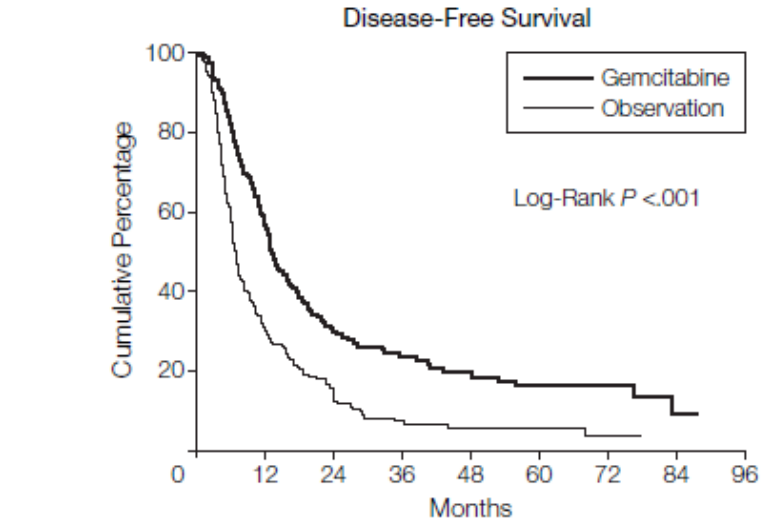


3 Months Later

Biopsy proven liver mets

- Zero benefit from major surgery





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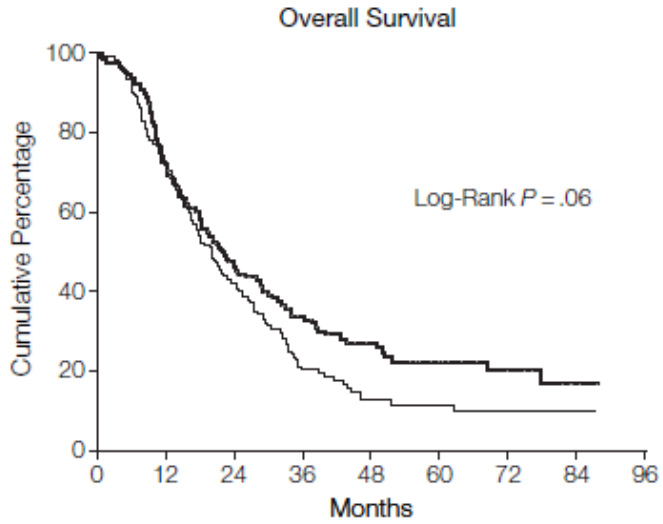

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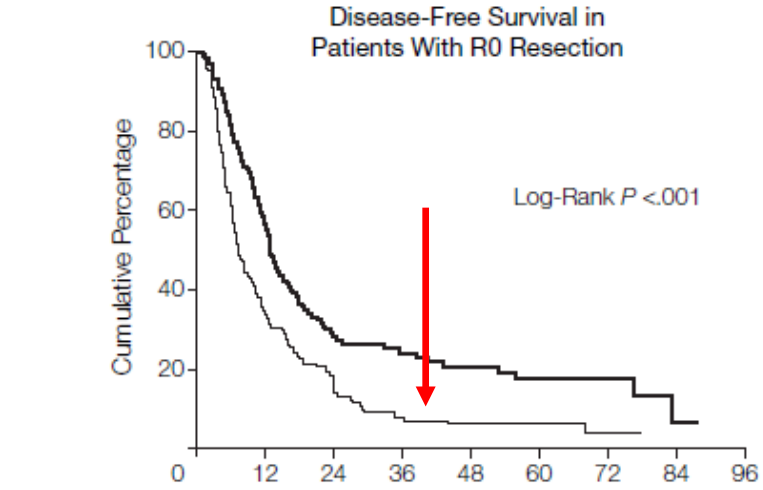

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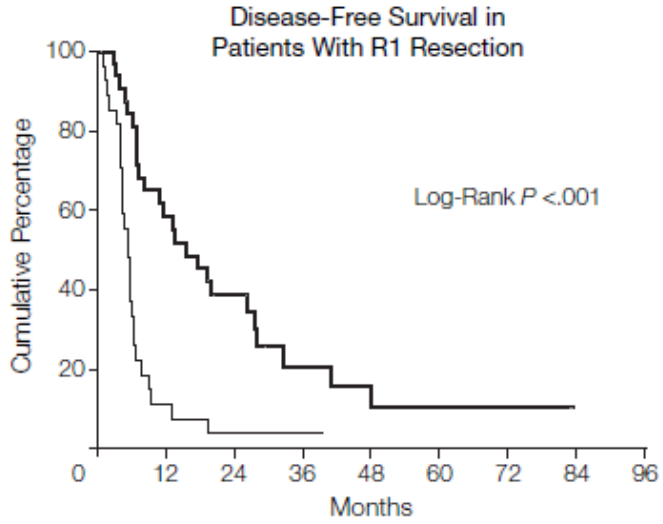

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~~Only Real Chance for Cure~~

- Radiographically occult metastatic disease in >90% resectable pancreatic cancer
- Consensus 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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Criticisms of Neoadjuvant Therapy for Resectable Pacreatic Cancer

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- Treatment sequencing does not matter – can give adjuvant therapy
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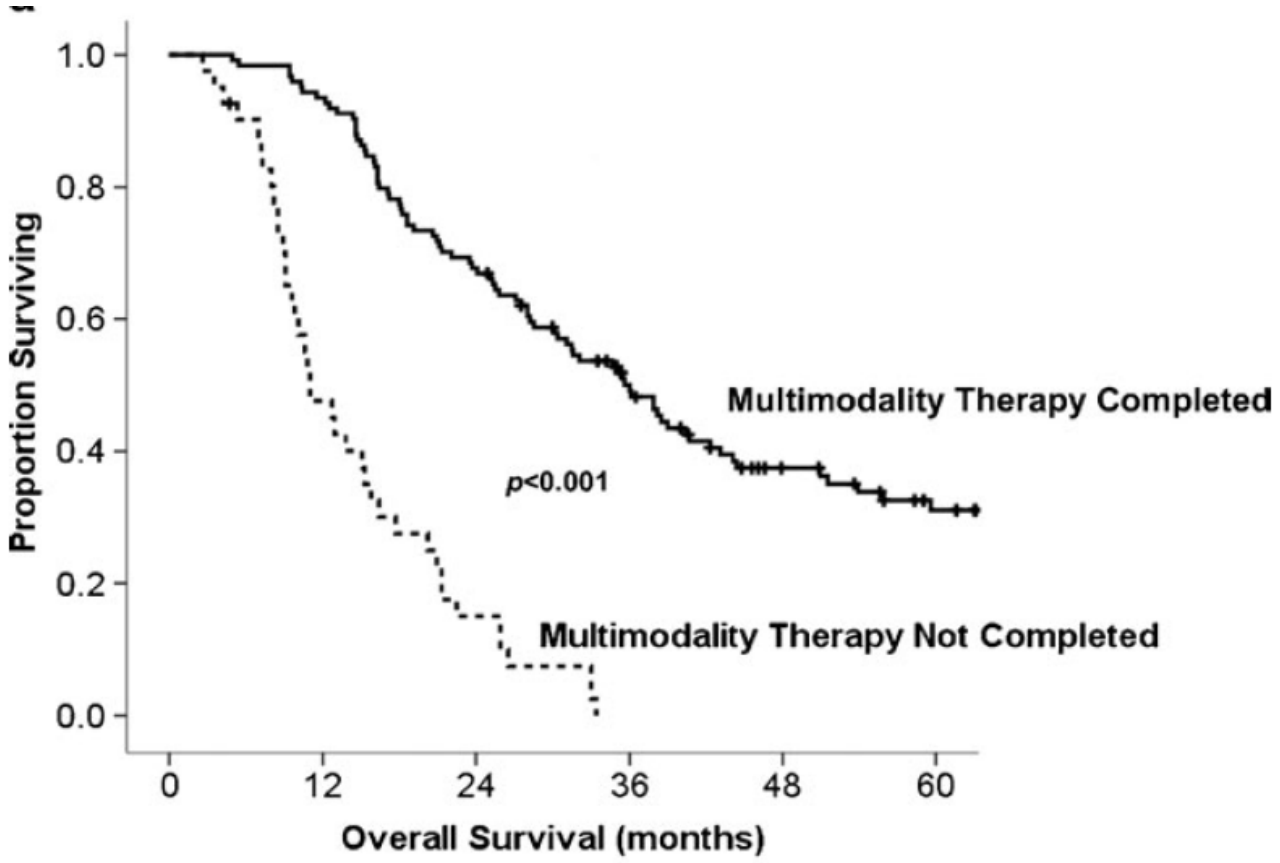
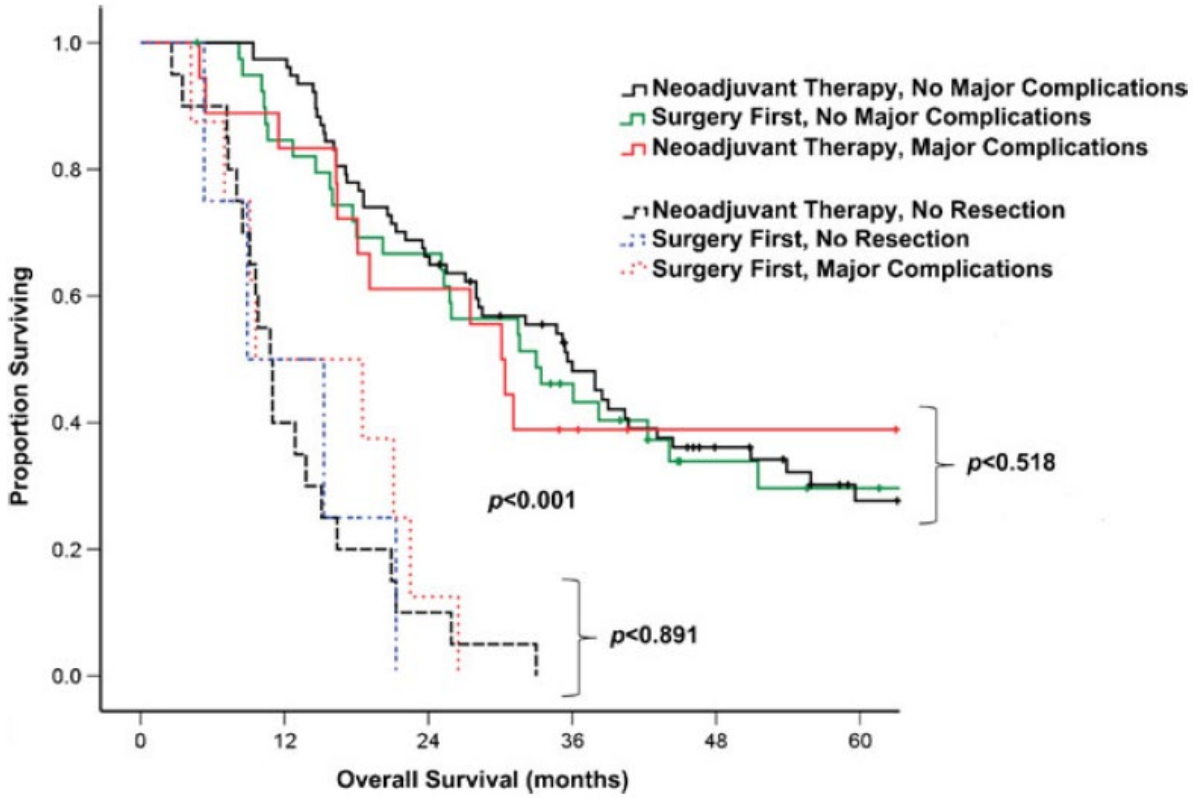
~~Treatment Sequencing Does Not Matter~~





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Tzeng et al, JOGS 2014

~~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%
Conroy, NEJM, 2018 (PRODIGE)	65%

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~~Window of Resectability May Be Lost~~

original reports

Preoperative Chemoradiotherapy Versus Immediate Surgery for Resectable and Borderline Resectable Pancreatic Cancer: Results of the Dutch Randomized Phase III PREOPANC Trial

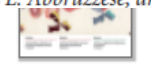
Eva Versteijne, MD[1]; Mustafa Suker, MD, PhD[2]; Karin Groothu
Marc G. Besselink, MD, PhD[4]; Bert A. Bonsing, MD, PhD[5]; Je
Geert-Jan M. Creemers, MD, PhD[7]; Ronald M. van Dam, MD,
Jan Willem B. de Groot, MD, PhD[11]; Bas Groot Koerkamp, MD,
Jeanin E. van Hooft, MD, PhD[13]; Emile D. Kerver, MD[14]; Sask
Joost Nuyttens, MD, PhD[17]; Gabriel M.R.M. Paardekooper, MD
Judith de Vos-Geelen, MD[21]; Johanna W. Wilmink, MD, PhD[22]
Casper H. van Eijck, MD, PhD[2]; and Geertjan van Tienhoven,

THE LANCET
Gastroenterology & Hepatology
Volume 3, Issue 6, June 2018, Pages 413-423

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



Articles

Safety and efficacy of preoperative or postoperative chemotherapy for resectable pancreatic adenocarcinoma (PACT-15): a randomised, open-label, phase 2–3 trial

Michele Reni MD [a], Gianpaolo Balzano MD [b, †], Silvia Zanon MD [a, †], Prof Alessandro Zerbi MD [e], Lorenza Rimassa MD [f], Renato Castoldi MD [b], Domenico Pinelli MD [g], Stefania Mosconi MD [h], Prof Claudio Doglioni MD [c, j], Marta Chiaravalli MD [a], Chiara Pircher MD [a], Paolo Giorgio Arcidiacono MD [d], Valter Torri MD Stat [k], Paola Maggiora MA [a], Domenica Ceraulo RN [a], Prof Massimo Falconi MD [b, i], Luca Gianni MD [a]

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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
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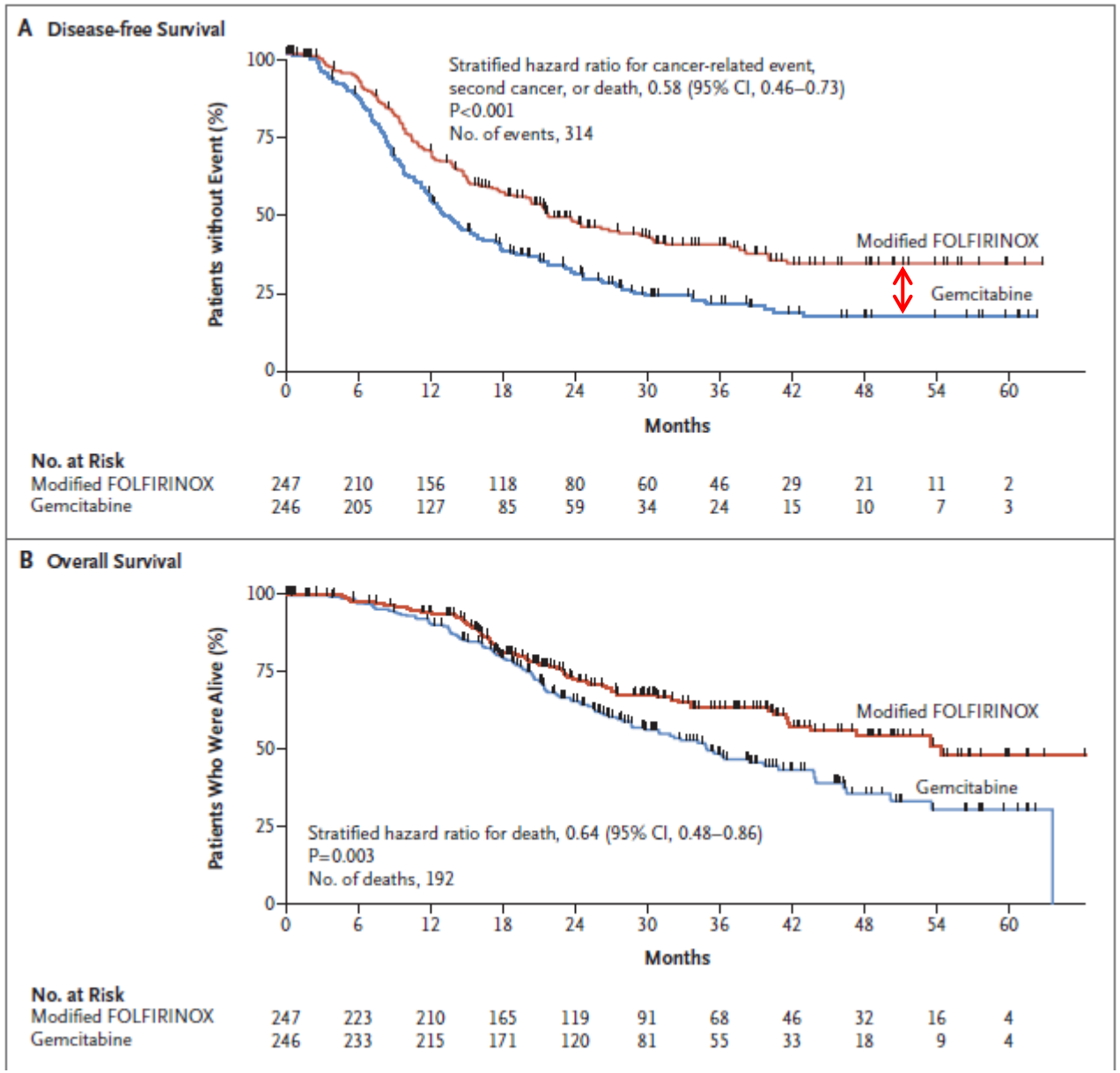
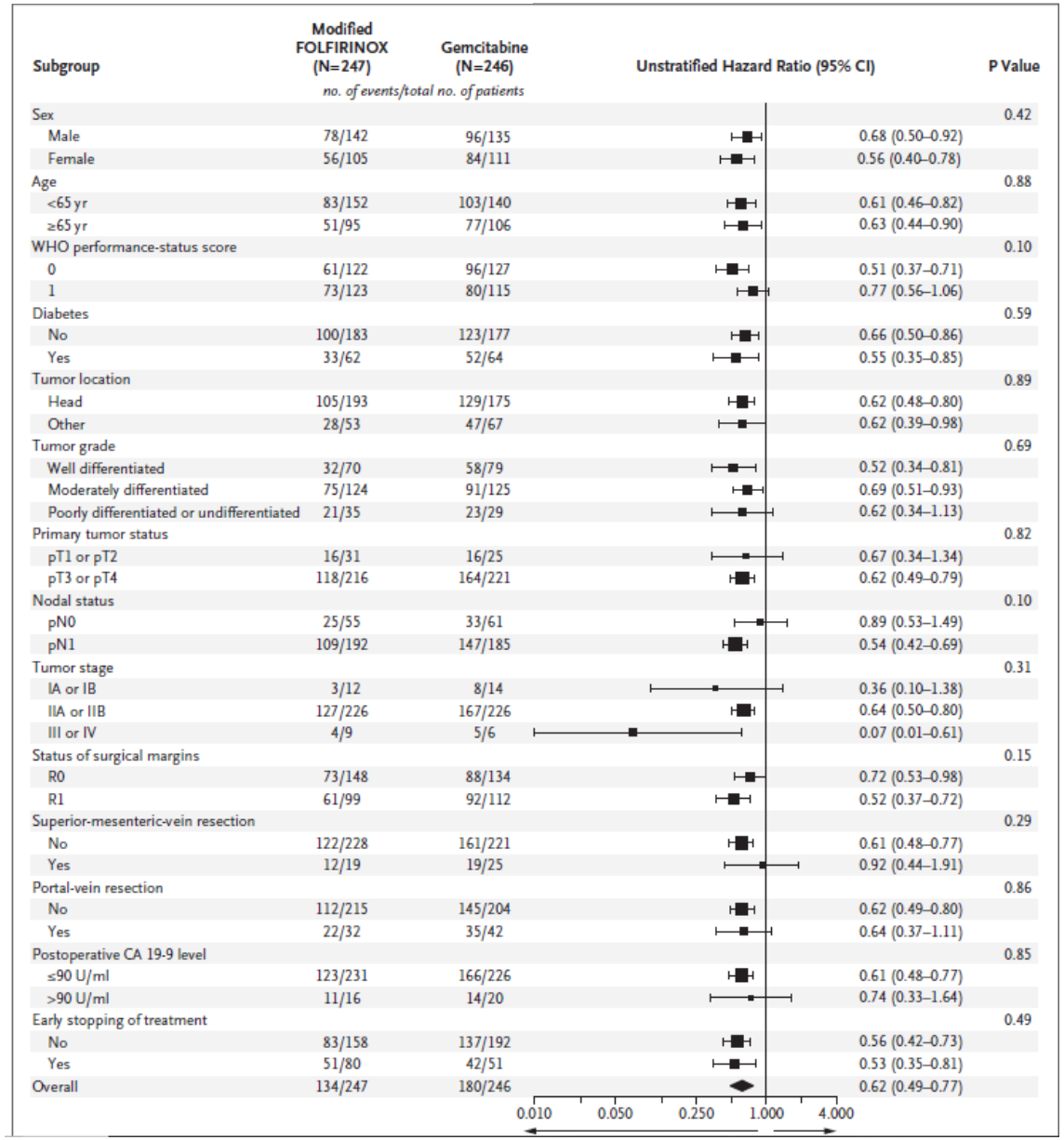
FOLFIRINOX or Gemcitabine as Adjuvant Therapy for Pancreatic Cancer





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
- Allows for assessment of response – tailoring systemic therapy, trial options
- Logical strategy for the high incidence of positive margins. (Katz JOGS 2012)
- Delayed recovery does not delay systemic treatment
- Tissue retrieval pre/post treatment for correlative studies

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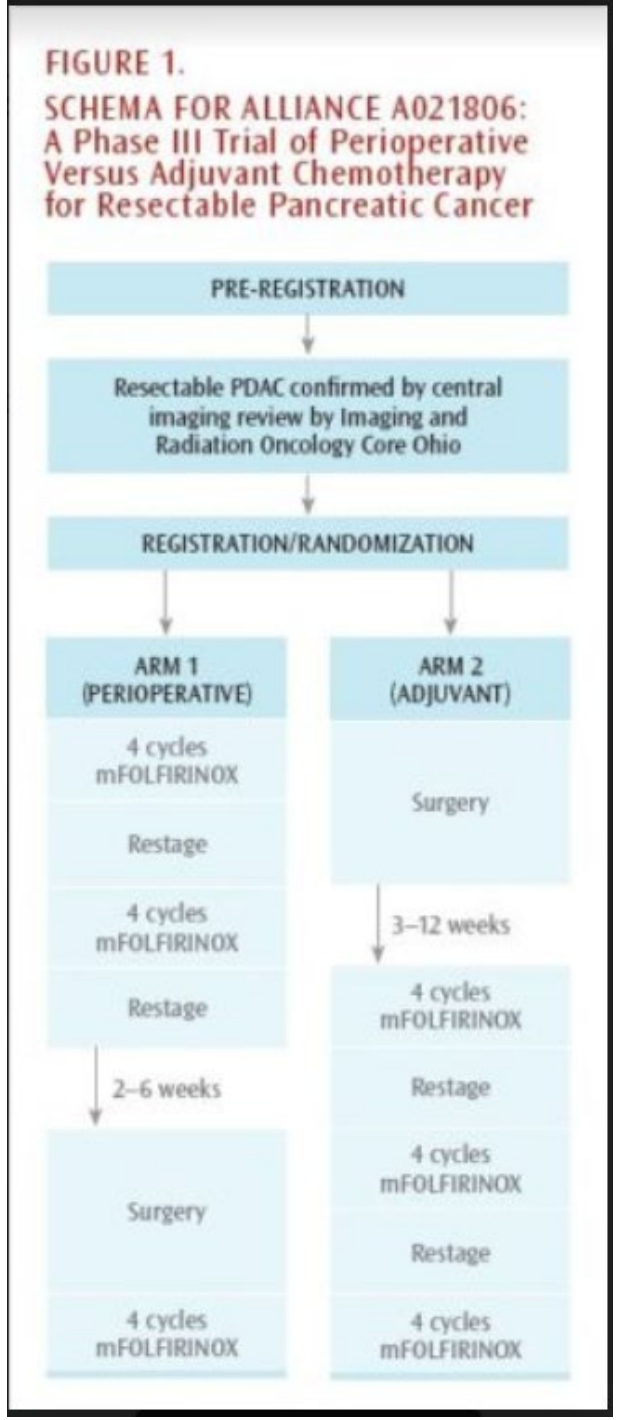
ALLIANCE A021806

- So lets answer the question!
  - Resectable cancer – randomized AT DIAGNOSIS
  - ECOG 0/1
  - Central rads review

  - Outcomes:
    - 2 year overall survival
    - DFS
    - Margin negative resection

  - Secondary analysis:
    - Chemotherapy tolerance/completion



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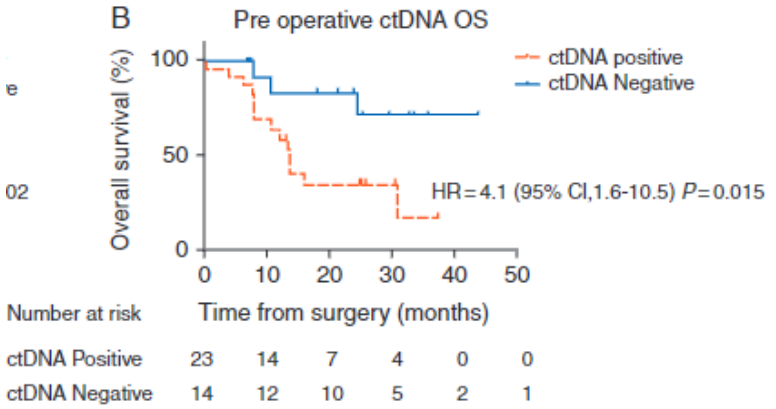
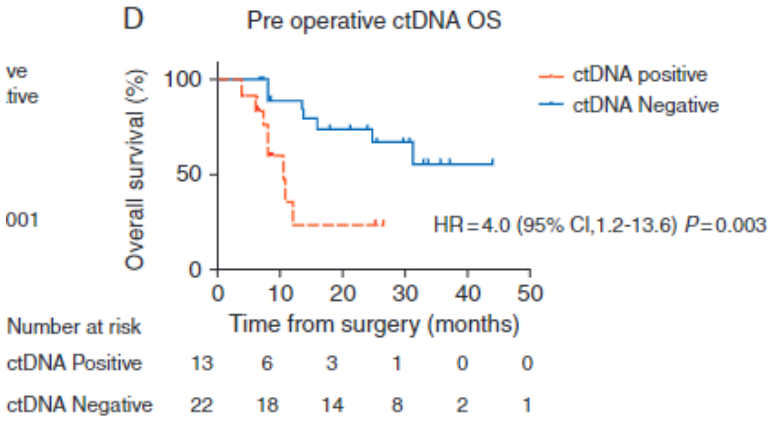
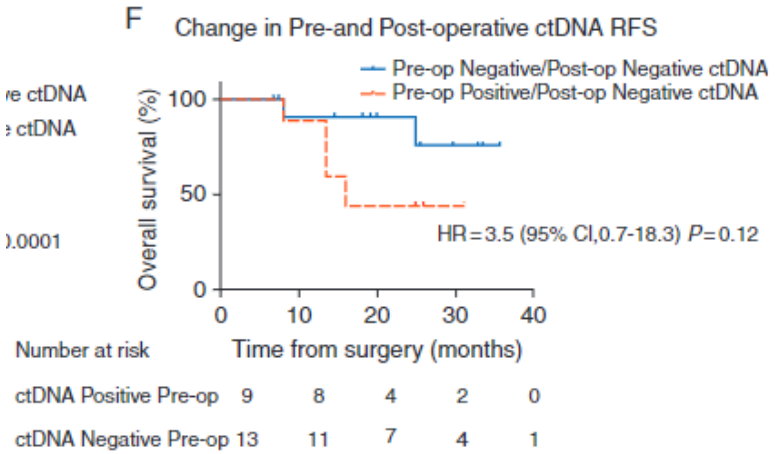
The Future

- Tailoring treatment to tumor biology
  - Varied response to platinum chemotherapy vs gem-abraxane – how do we predict this?
  - Markers of response – PET imaging, ctDNA clearance, biochemical response, miRNA
  - Duration of systemic therapy – total neoadjuvant? Tailored adjuvant?
  - New therapies – RAS targeting, novel immunotherapy pathways







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