

# Pancreas cancer- an overview

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# Objectives

- Understand the burden of pancreas cancer
- Clinical evaluation of a pancreatic mass
- Role of screening
- Defining treatment goals and options
- Understand best treatment practices
- Research options

# Pancreas anatomy

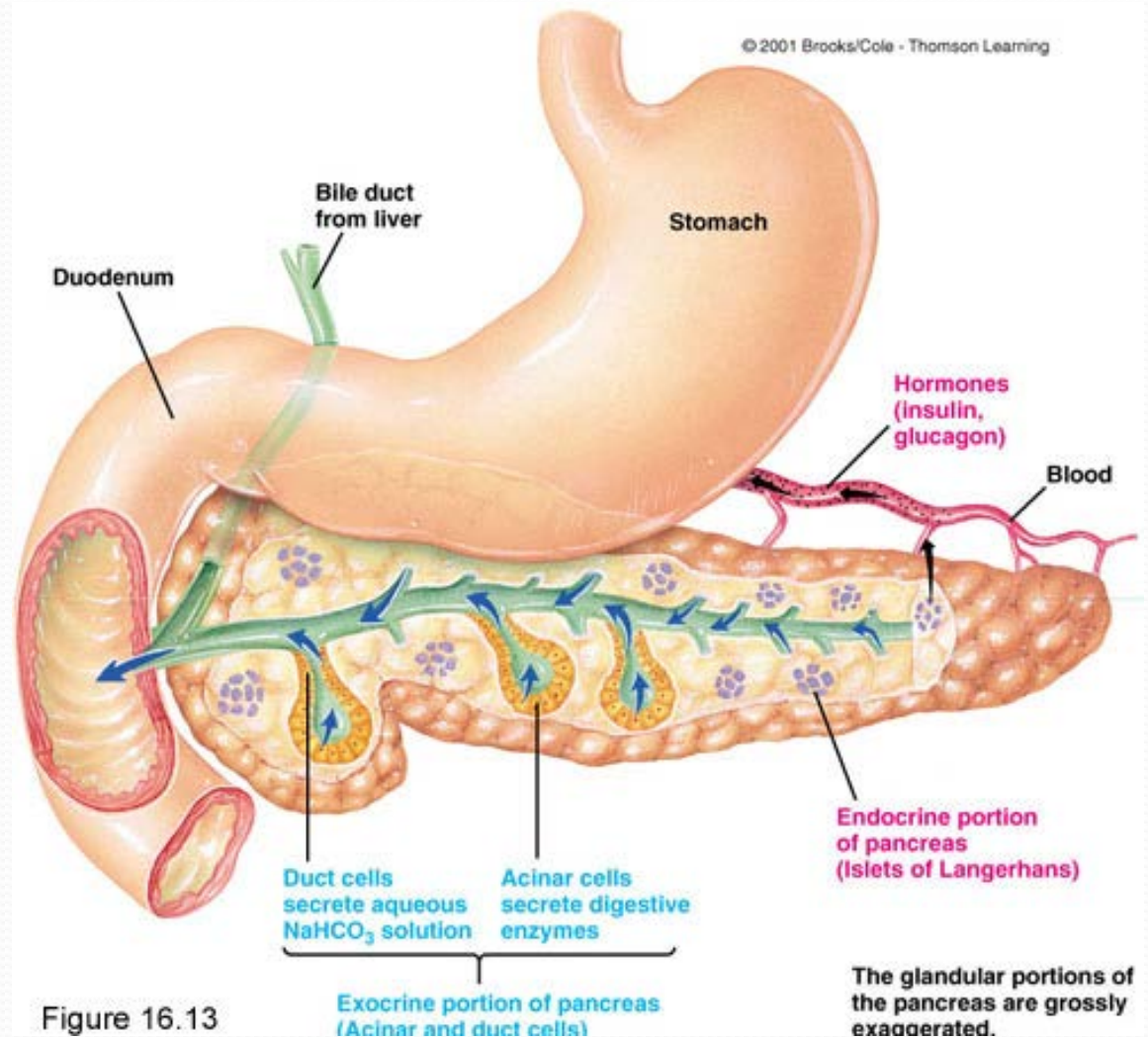
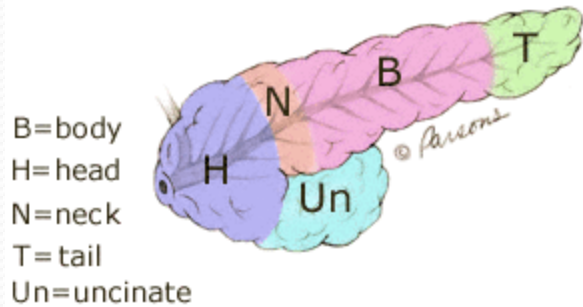


Figure 16.13

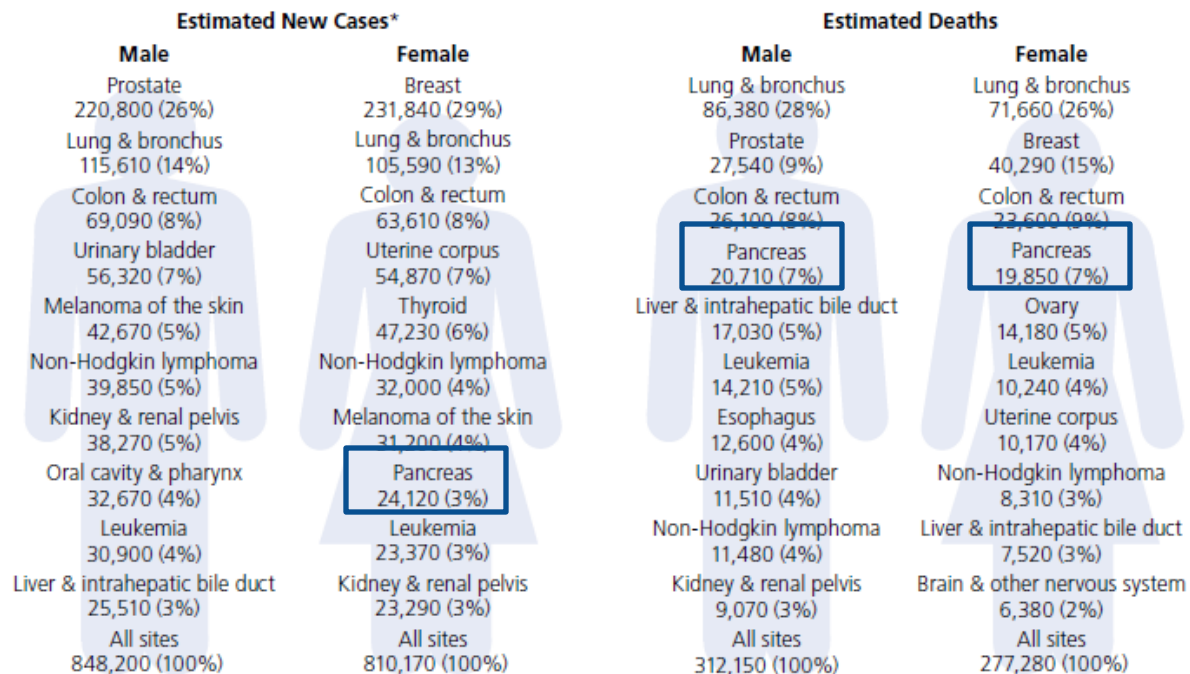
# Pancreatic cancer- stats

## 2015 Estimates (per ACS)

- Incidence: About 48,960 (24,840 men and 24,120 women)
- Death: About 40,560 people (20,710 men and 19,850 women)
- Pancreatic cancer accounts for about 3% of all cancers in the US, and accounts for about 7% of cancer deaths.
- The average lifetime risk of developing pancreatic cancer is about 1 in 67 (1.5%). A person's risk may be altered by certain risk factors

# The mortality from pancreas cancer is substantial

## Leading Sites of New Cancer Cases and Deaths – 2015 Estimates



\*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

# The five year survival is dismal

Five-year Relative Survival Rates\* (%) by Stage at Diagnosis, US, 2004-2010

	All Stages	Local	Regional	Distant		All Stages	Local	Regional	Distant
Breast (female)	89	99	85	25	Ovary	45	92	72	27
Colon & rectum	65	90	71	13	Pancreas	7	26	10	2
Esophagus	18	40	21	4	Prostate	99	>99	>99	28
Kidney†	72	92	65	12	Stomach	28	64	29	4
Larynx	60	75	43	35	Testis	95	99	96	73
Liver‡	17	30	11	3	Thyroid	98	>99	98	55
Lung & bronchus	17	54	27	4	Urinary bladder§	77	69	34	6
Melanoma of the skin	91	98	63	16	Uterine cervix	68	91	57	16
Oral cavity & pharynx	63	83	61	37	Uterine corpus	82	95	68	18

\*Rates are adjusted for normal life expectancy and are based on cases diagnosed in the SEER 18 areas from 2004-2010, all followed through 2011. †Includes renal pelvis. ‡Includes intrahepatic bile duct. §Rate for in situ cases is 96%.

**Local:** an invasive malignant cancer confined entirely to the organ of origin. **Regional:** a malignant cancer that 1) has extended beyond the limits of the organ of origin directly into surrounding organs or tissues; 2) involves regional lymph nodes; or 3) has both regional extension and involvement of regional lymph nodes. **Distant:** a malignant cancer that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis to distant organs, tissues, or via the lymphatic system to distant lymph nodes.

**Source:** Howlader N, Noone AM, Krapcho M, et al. (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute, Bethesda, MD, [http://seer.cancer.gov/csr/1975\\_2011/](http://seer.cancer.gov/csr/1975_2011/), based on November 2013 SEER data submission.

# Risk factors

- Modifiable:
  - Cigarette smoking: 20-30%
  - Obesity: 20%
  - Environmental toxins: pesticides, dyes, chemicals
- Non modifiable:
  - Age: median age at diagnosis: mid-late 60s
  - Sex: M>F by 30%
  - Diabetes (esp. type II)
  - H. pylori infection
  - Chronic pancreatitis, cirrhosis
  - Familial cancer syndromes (up to 10%)



# Hierarchical risk stratification

LOW RISK (<5x increase)	MODERATE RISK (5-10X)	HIGH RISK (>10x)
Alcohol use (>4 drinks/d)	BRCA2 carrier	3 or > relatives with pancreas ca (1->3 <sup>rd</sup> deg)
BMI >30	Chronic Pancreatitis	Hereditary pancreatitis
Diabetes-type II (> 5yrs)	Cystic Fibrosis	Peutz-Jeghers syndrome (Hereditary Intestinal Polyposis)
Tobacco use	2 or > first degree relatives with pancreas cancer	
HNPCC		
FAP		

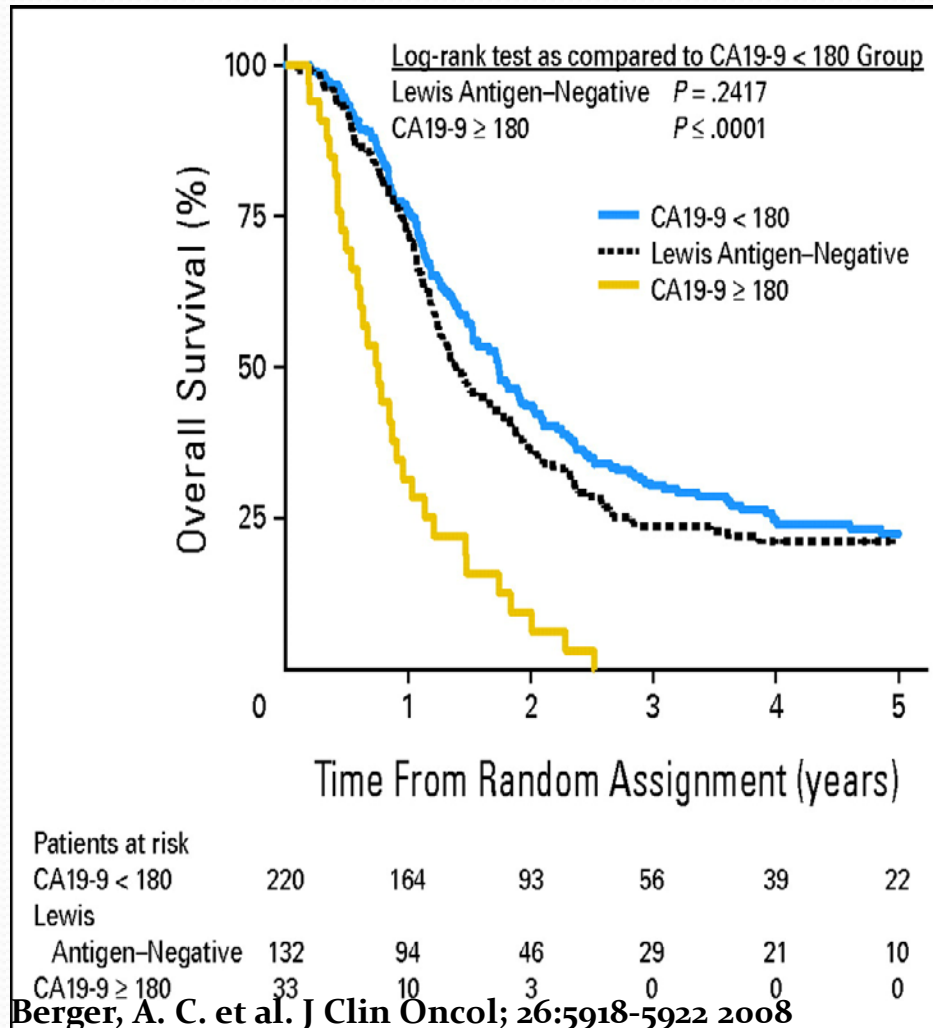
# Then what about screening for Pancreas cancer?

Screening tests or exams are used to look for a disease in people who have no symptoms (and who have not had that disease before).

# Carbohydrate Antigen 19-9

- Protein found on surface of cancer cells
- The degree of elevation post op is predictive of long term survival
- Patients that are Lewis antigen negative do not have elevated CA19-9
- CA19-9 is elevated can be elevated in other cancers (e.g., gastric, bladder, biliary...)
- Elevated levels can also be seen in benign conditions: Biliary obstruction, Cholangitis, IBD, Cirrhosis, Thyroid disease, Pancreatitis...

# Kaplan-Meier survival curve by CA 19-9 level



# US Preventative Task Force Stance on Screening for Pancreas Cancer

- **Summary of Recommendation: *Grade D*** (The USPSTF recommends against the service. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits).

***Rationale:*** The USPSTF found no evidence that screening for pancreatic cancer is effective in reducing mortality. There is a potential for significant harm due to the very low prevalence of pancreatic cancer, limited accuracy of available screening tests, the invasive nature of diagnostic tests, and the poor outcomes of treatment. As a result, the USPSTF concluded that the harms of screening for pancreatic cancer exceed any potential benefits.

# Precancerous lesions to be monitored

- Pancreatic Intraepithelial Neoplasia (PanIN): grades 1->3
- Intraductal Papillary Mucinous Neoplasm (IPMN)
- Mucinous Cystic Neoplasm

# Symptoms based on location

	Head of Pancreas cancer (>75%)	Body/Tail of pancreas cancer (<25%)
Weight loss	85-90%	95-100%
Jaundice	80-90%	5-10%
Abdominal pain	70-80%	80-90%
Anorexia	60-70%	30-40%
Nausea	40-50%	40-50%
Acholic stool	60-65%	Low

% of patients with symptoms

# Examination can give clues....

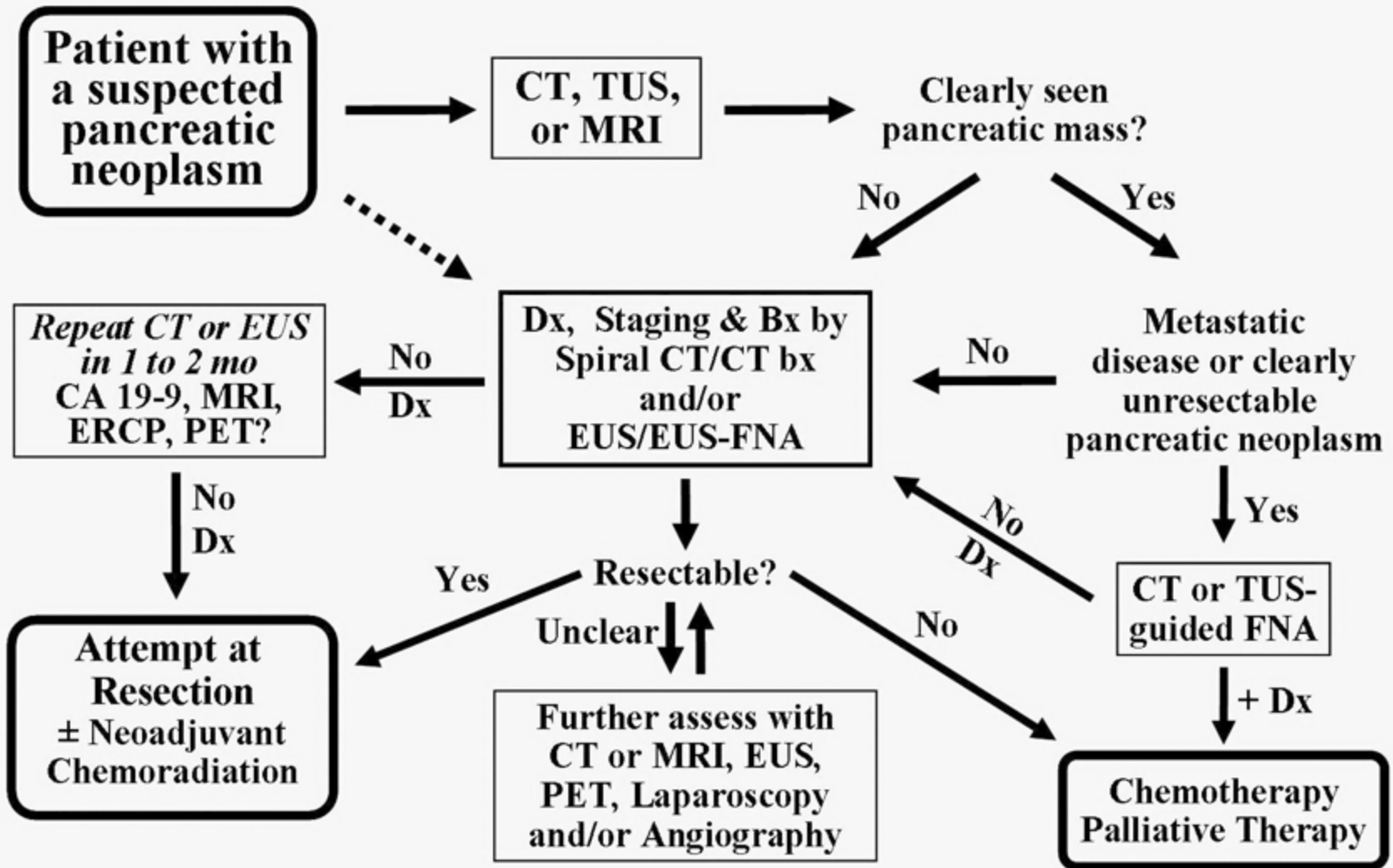
- Normal
- Jaundice
- Cachexia/weight loss
- Abdominal tenderness/mass
- Ascites
- Thrombophlebitis/Thrombosis (? increased Tissue factor)



# Workup of pancreatic mass

- History
- Examination
- Laboratory tests: CBC, Metabolic panel, Tumor markers....? circulating tumor cells
- Imaging studies: CT, US, PET/CT, MRI, ERCP, EUS
- Biopsy

# Workup of pancreatic mass



# Which imaging to choose?

	Sensitivity	Specificity
Ultrasound	50-70%	50-60%
CT with contrast	75-90%	85-90%
CT with pancreatic protocol	Helpful to evaluate resectability	
MRI	85-90%	
PET/CT	75-90%	65-70%
ERCP with brush cytology	35-70%	85-90%
Endoscopic Ultrasound	80-95%	75-95% (for T and N staging)

# Pancreatic cancer stage specific survival

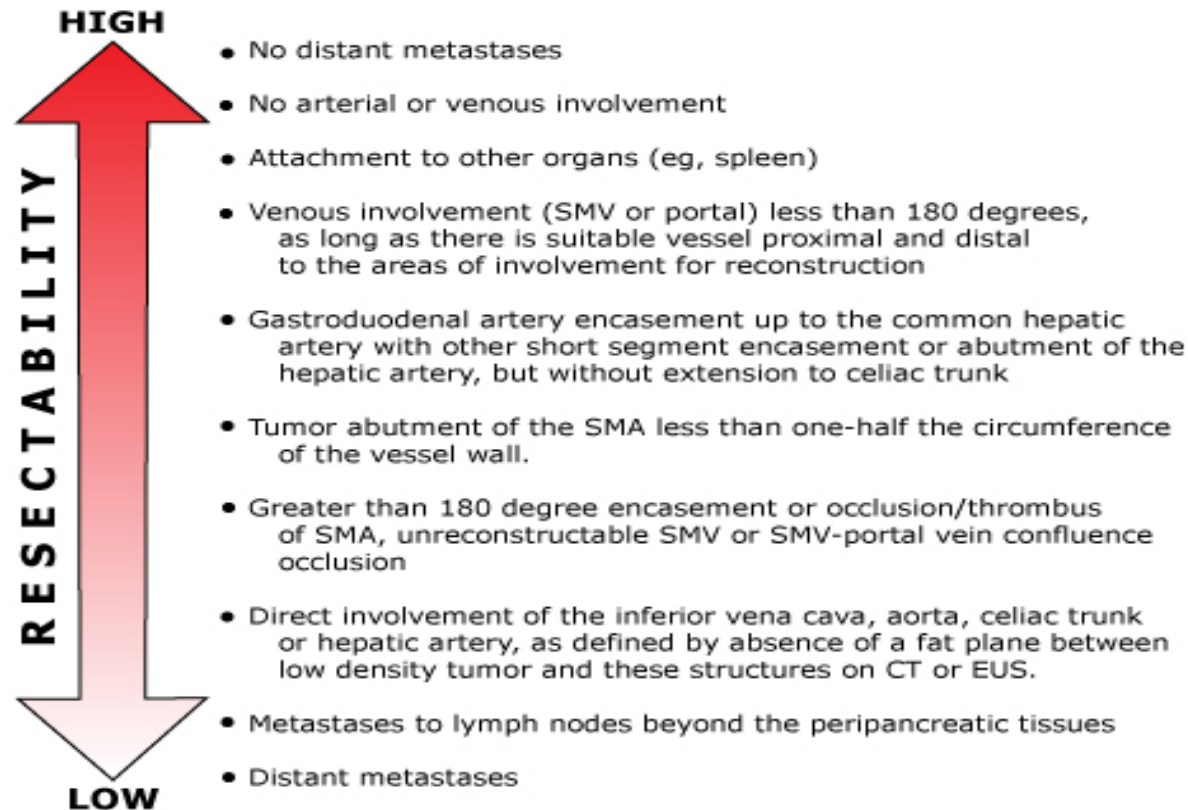
Stage	TNM	Clinical category	% of pts	Treatment strategies	5 yr survival
0	TisNoMo	Localized	5-8%	Surgery	20-25%
IA	T1NoMo	Localized	5%	Surgery	15%
IB	T2NoMo	Localized			12%
IIA	T3NoMo	Locally invasive	15-20%	Surgery+/- chemo	7%
IIB	T1-3, N1	Locally invasive		Surgery + chemo/RT	5%
III	T4, any N	Locally advanced	25-30%	Neo adj chemo/RT or chemo	3%
IV	M1	Metastatic	40-50%	Chemo	<2%

# Treatment options for pancreatic cancer

- Surgery: Whipple's surgery
  - Monitor for nutritional deficiency post surgery and consider enzyme supplements
- Radiation: Adjuvant or Neoadjuvant
- Chemotherapy
- Combination therapy
- Clinical trials

## Continuum of resectability for pancreatic adenocarcinoma

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SMA: superior mesenteric artery; SMV: superior mesenteric vein; CT: computed tomography; EUS: endoscopic ultrasound.

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Data from:

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology, [www.nccn.org](http://www.nccn.org).

# Metastatic pancreas cancer treatment options

Treatment options (in practice)

- FOLFIRINOX
- Gemcitabine + Nab-Paclitaxel
- Erlotinib
- Capecitabine
- **Clinical Trials**

# Phase III Studies: No Survival Benefit for Gemcitabine Combination vs. Monotherapy

Regimen	Patients, n	Control Arm, Mos	Study Arm, Mos
Gemcitabine vs (gem + cisplatin)	192	6.0	7.6
Gemcitabine vs (gem + oxaliplatin)	313	7.1	9.0
Gemcitabine vs (gem + 5-FU)	322	5.4	6.7
Gemcitabine vs (gem + capecitabine)	533	6.2	7.1
Gemcitabine vs (gem + pemetrexed)	565	6.2	6.3
Gemcitabine vs (gem + irinotecan)	360	6.6	6.3
Gemcitabine vs (gem + exatecan)	349	6.2	6.7

Phase III trials of gemcitabine-based chemotherapy doublets  
(excluding targeted agents)



# Study Schema for Phase III Trial of Gemcitabine vs. FOLFIRINOX

*Stratified by ECOG PS (0 vs 1), center, tumor location (head vs other)*

**Metastatic PDAC**

**Gemcitabine** 1000 mg/m<sup>2</sup>  
weekly x 7 of 8,  
then weekly x 3 of 4  
(n = 171)

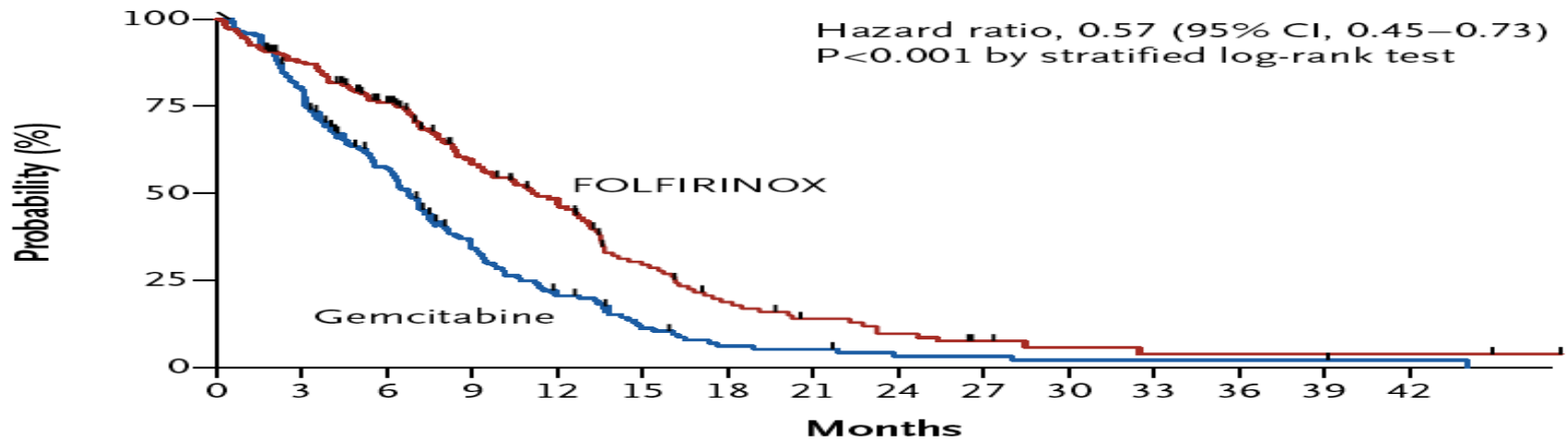
**FOLFIRINOX**  
**Oxaliplatin** 85 mg/m<sup>2</sup>  
**LV** 400 mg/m<sup>2</sup>  
**Irinotecan** 180 mg/m<sup>2</sup>  
**5-FU bolus** 400 mg/m<sup>2</sup>, then  
2400 mg/m<sup>2</sup> infusional over  
46 hrs (n = 171)

# FOLFIRINOX vs. Gemcitabine: Efficacy Results

Outcome	FOLFIRINOX (n = 171)	Gemcitabine (n = 171)
ORR, %	31.6	9.4
Median PFS, mos	6.4	3.3
Median survival,* mos	11.1	6.8
1-yr survival, %	48.4	20.6

\*HR: 0.57;  $P < .001$

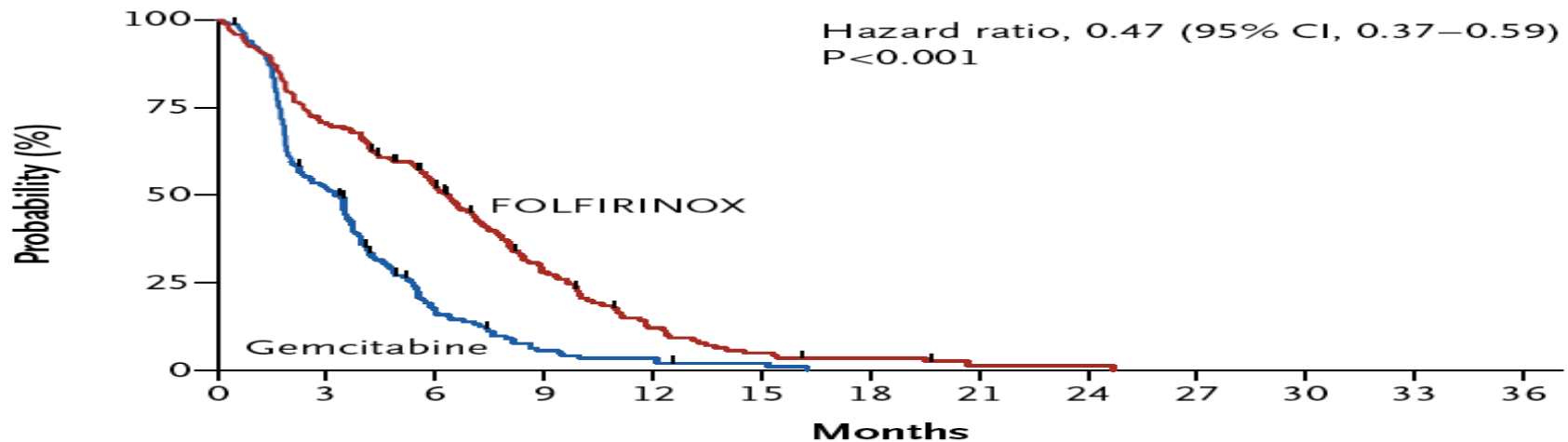
### A Overall Survival



#### No. at Risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2	2

### B Progression-free Survival



#### No. at Risk

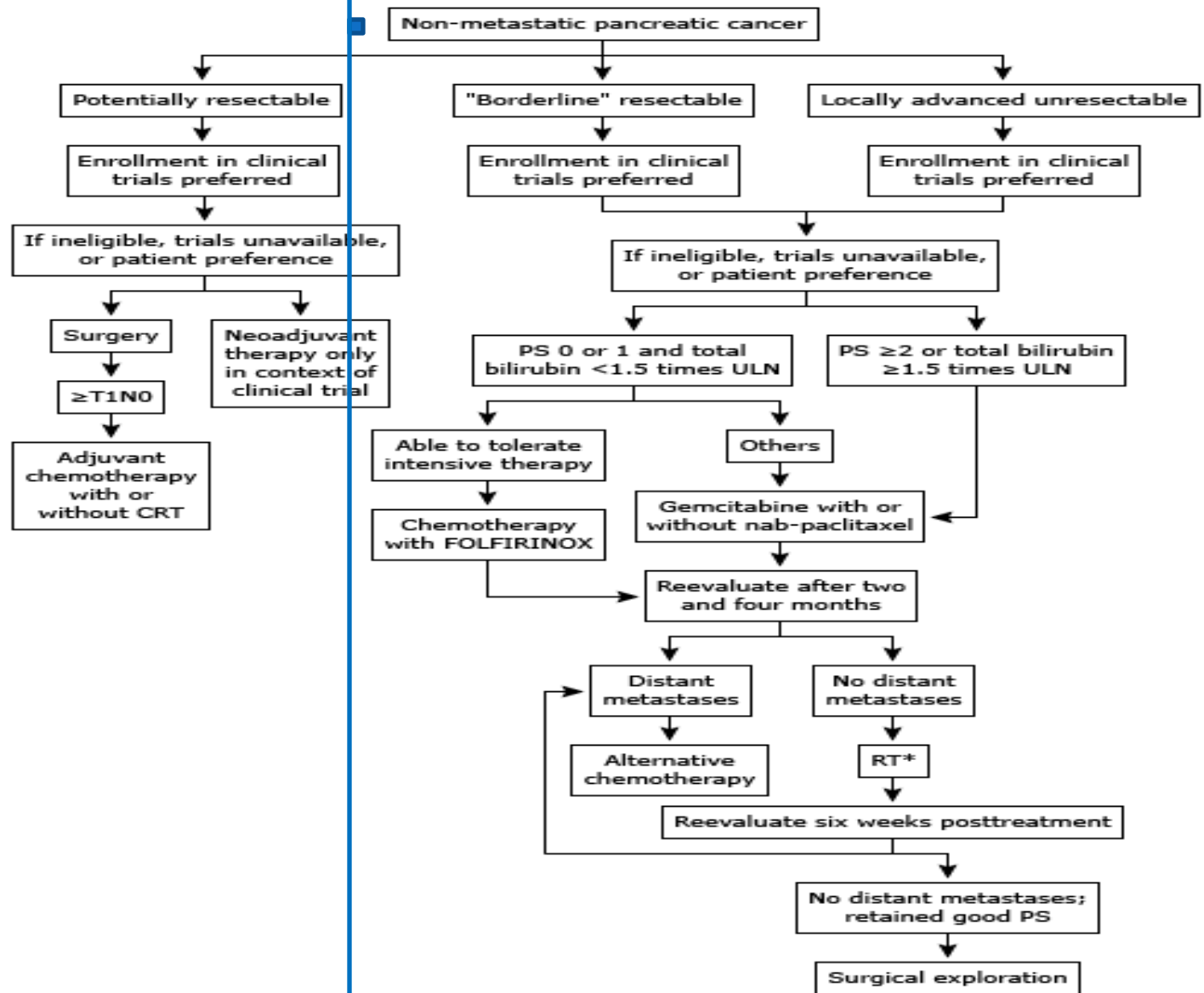
Gemcitabine	171	88	26	8	5	2	0	0	0	0	0	0	0	0
FOLFIRINOX	171	121	85	42	17	7	4	1	1	0	0	0	0	0

**Table 3. Most Common Grade 3 or 4 Adverse Events Occurring in More Than 5% of Patients in the Safety Population.\***

Event	FOLFIRINOX (N=171)	Gemcitabine (N=171)	P Value
	<i>no. of patients/total no. (%)</i>		
Hematologic			
Neutropenia	75/164 (45.7)	35/167 (21.0)	<0.001
Febrile neutropenia	9/166 (5.4)	2/169 (1.2)	0.03
Thrombocytopenia	15/165 (9.1)	6/168 (3.6)	0.04
Anemia	13/166 (7.8)	10/168 (6.0)	NS
Nonhematologic			
Fatigue	39/165 (23.6)	30/169 (17.8)	NS
Vomiting	24/166 (14.5)	14/169 (8.3)	NS
Diarrhea	21/165 (12.7)	3/169 (1.8)	<0.001
Sensory neuropathy	15/166 (9.0)	0/169	<0.001
Elevated level of alanine aminotransferase	12/165 (7.3)	35/168 (20.8)	<0.001
Thromboembolism	11/166 (6.6)	7/169 (4.1)	NS

\* Events listed are those that occurred in more than 5% of patients in either group. NS denotes not significant.

# Treatment algorithm for non-metastatic exocrine pancreatic cancer



CRT: chemoradiotherapy; PS: performance status; RT: radiation therapy; ULN: upper limit of normal

# Phase III Postop Adjuvant Therapy Trials: What Progress Has Been Made?

RTOG

Patient Factor	GITSG	EORTC	ESPAC-1*	CONKO-001	RTOG	
					Chemoradiation + Fluorouracil	Chemoradiation + Gemcitabine
Patients, n/N (%)						
▪ Microscopically positive margins	0	20/104 (19) <sup>†</sup>	19/147 (28)	34/179 (19)	75/230 (33)	77/221 (35)
▪ T <sub>3</sub> of T <sub>4</sub> disease	NA	0	NA	154/179 (86)	162/230 (70)	178/221 (81)
▪ Lymph node-positive disease	6/20 (30)	23/49 (47)	73/147 (50)	127/179 (71)	148/230 (65)	151/221 (68)
Local recurrence rate, % (n/N)	47 (7/15)	51 (34/67) <sup>†</sup>	63 (99/158) <sup>‡</sup>	37 (NA)	28 (49/173)	23 (35/155)
Median survival, mos	21.0	17.1	20.1	22.1	16.9	20.6
3-year survival, %	24	30	30	34	22	31
5-year survival, %	19	20	21	22.5	NA	NA

\*Chemotherapy only group.

<sup>†</sup>Includes patients with periampullary cancers.

<sup>‡</sup>Among all patients.

# Pancreatic cancer stage specific survival

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# Pancreatic cancer trials at Piper Cancer Center, Scottsdale

Protocol #	Sponsor	Title
ADU-CL-04	Aduro	Efficacy of Combination Listeria/GVAX Immunotherapy in the Pancreatic Cancer Setting (ECLIPSE)
GS-US-370-1369	Gilead	A Phase 1b Study Evaluating Mometotinib Combined with Capecitabine and Oxaliplatin in Subjects with Relapsed/Refractory Metastatic Pancreatic Ductal Adenocarcinoma
MINNELIDE 001	Minneamrita	Study of Minnelide™ in Patients With Advanced GI Tumors
NA 00090282	SU2C	An Exploratory Study of Metformin With or Without Rapamycin as Maintenance Therapy after Induction Chemotherapy in Subjects with Metastatic Pancreatic Adenocarcinoma
PCRT 12-001	Seena	Nab-Paclitaxel+Cisplatin+Gemcitabine in Patients With Previously Untreated Metastatic Pancreatic Ductal Adenocarcinoma (PDA)
PLX119-01	Plexxikon	Phase 1 Study of PLX7486 as Single Agent and With Gemcitabine Plus Nab-Paclitaxel in Patients With Advanced Solid Tumors
SM04755-ONC-01	Samumed	A Phase 1, Open-Label, Dose-Escalation, Dose-Finding Study Evaluating the Safety and Pharmacokinetics of SM04755 in Subjects with Advanced Colorectal, Gastric, Hepatic, or Pancreatic Cancer
SU2C-005	SU2C-005	A Phase I/II/Pharmacodynamic Study of Hydroxychloroquine in Combination With Gemcitabine/Abraxane to Inhibit Autophagy in Pancreatic Cancer
SU2C-007	SU2C 007	A Pharmacodynamic study of the Nab-Paclitaxel/Gemcitabine combo given weekly 3x as induction therapy followed by maintenance every 2 weeks in patients with metastatic pancreatic cancer



# Take home points

- Stage for stage, pancreatic cancer is associated with the lowest survival rates of any major cancer type
- The vast majority of patients are inoperable at the time of diagnosis
- Pancreatic cancer is inherently resistant to most currently available therapies
- Many patients suffer from rapidly declining performance scores and inanition
- Compared with other cancer types, research funding for pancreatic cancer is disproportionately low given its mortality rate (fourth for cancer-related deaths in the US population)