PANCREATIC CANCER: 2013

Robert A. Wolff, M.D.
University of Texas M.D. Anderson Cancer Center

PANCAN
September 24th, 2013

rwolff@mdanderson.org

Objectives

- Pancreatic Cancer 101
  - Highlight that the causes of pancreatic cancer are changing
  - Emphasize this is a preventable disease for many!
  - It's a systemic disease and a local problem
- Summarize current data regarding standard treatments for pancreatic cancer
  - Resectable, locally advanced, and metastatic
- Review emerging strategies for resectable, borderline resectable, locally advanced, and metastatic disease
- Future directions
- Meet a few of my patients along the way

Pancreatic Cancer 101
Introduction

- 43,920 New Cases in 2012 in U.S.
- 2% of All Cancer Cases
- 6% of All Cancer Deaths
- Major Cause of Cancer Death

Siegel R, et al. CA Cancer J Clin, 2012

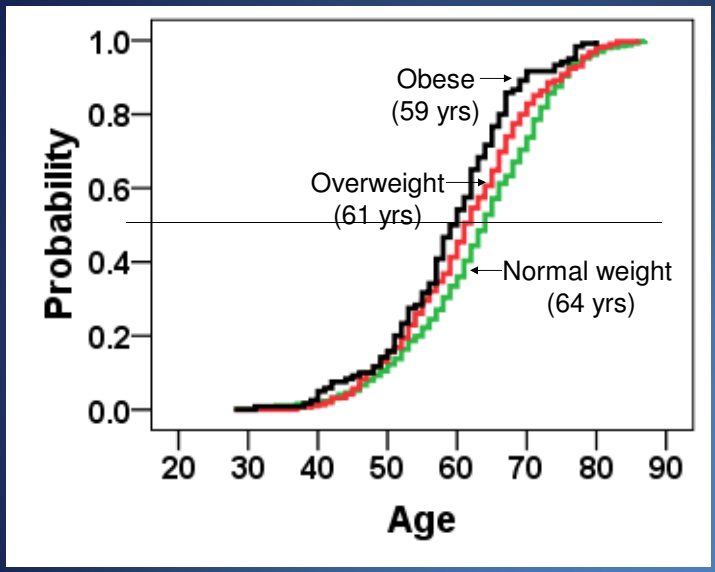
Pancreatic Cancer 101
Risk Factors

- Cigarette Smoking RR = 1.3-5.6
  Approximately 30% of all pancreatic cancer mortality!
  Smokeless tobacco products also implicated
- Body Mass Index RR = 2.0
  - Higher the BMI, younger age of onset!!!!
- Diabetes (> 1 yr before) RR = ~ 2.0
- Metabolic syndrome* RR = 2.0
- Pancreatitis (Tropical, familial, chronic)
- Other factors
  - Known genetic risks
  - Familial Pancreatic Cancer

5-6% of cases

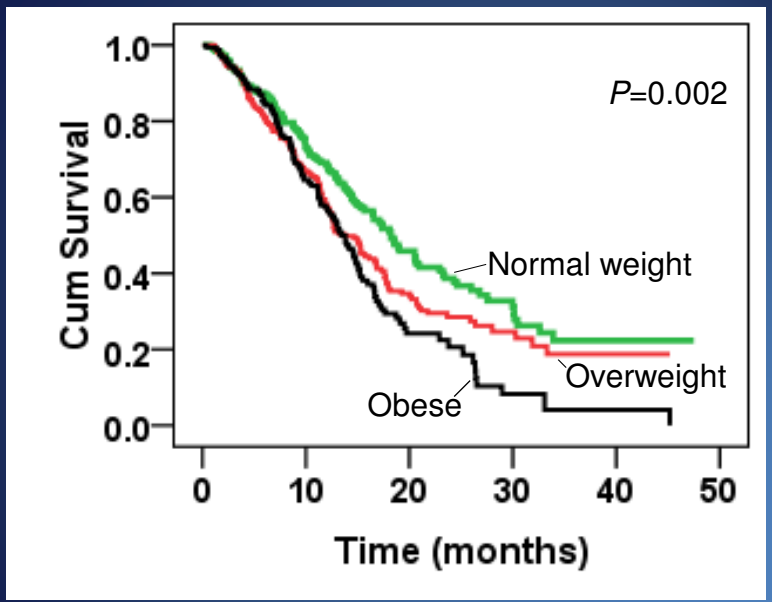
*Metabolic syndrome: HIGH BLOOD PRESSURE, DIABETES, HIGH CHOLESTEROL

Size Really Does Matter!



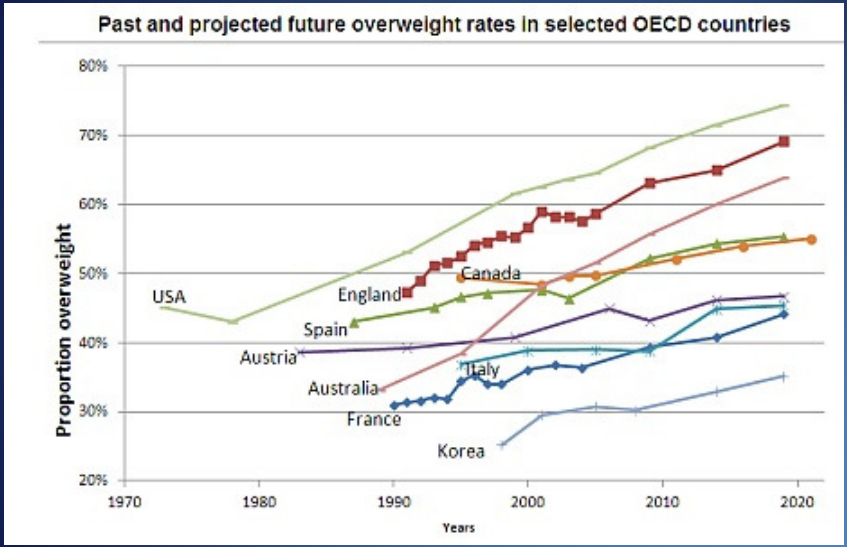
Li D, et al. JAMA, 2009

Size and Survival



Li D, et al. JAMA, 2009

Proportion of Overweight Individuals



Pancreatic Adenocarcinoma
IS PREVENTABLE!!!!

- Stop smoking or never start
- Don't chew or dip
- Keep your weight DOWN!
- WORK to avoid Type II DM

Pancreatic Adenocarcinoma
Is it Chemopreventable?

NSABP P-1 Study	Placebo	Tamoxifen
PC Cases	7	4
PC Deaths	6	2

Fisher B, et al. JNCI, 1998

Pancreatic Adenocarcinoma
Is it Chemopreventable?

Case/Control Studies of Metformin Use and Risk of Pancreatic Cancer

Author/Year	Cases/Controls	Odds Ratio	95% CI
Li 2010	873/863	0.38	0.22-0.69
Bodmer 2012	2,763/16,578	0.87	0.59-1.29
Bodmer (Women)	1487/8922	0.43	0.23-0.80

Metformin appears to reduce the risk of pancreatic cancer
Insulin and sulfonylureas INCREASED RISK of Pancreatic Cancer!

Li D, et al. JNCI, 1998
Bodmer M, et al. Am J Gastroenterol, 2012

Pancreatic Adenocarcinoma

Bystander Chemoprevention?

- Tamoxifen?
- Finasteride?
- Metformin
- Statins?

Large numbers of people take these medications for other reasons, but this may decrease the incidence of pancreatic cancer!

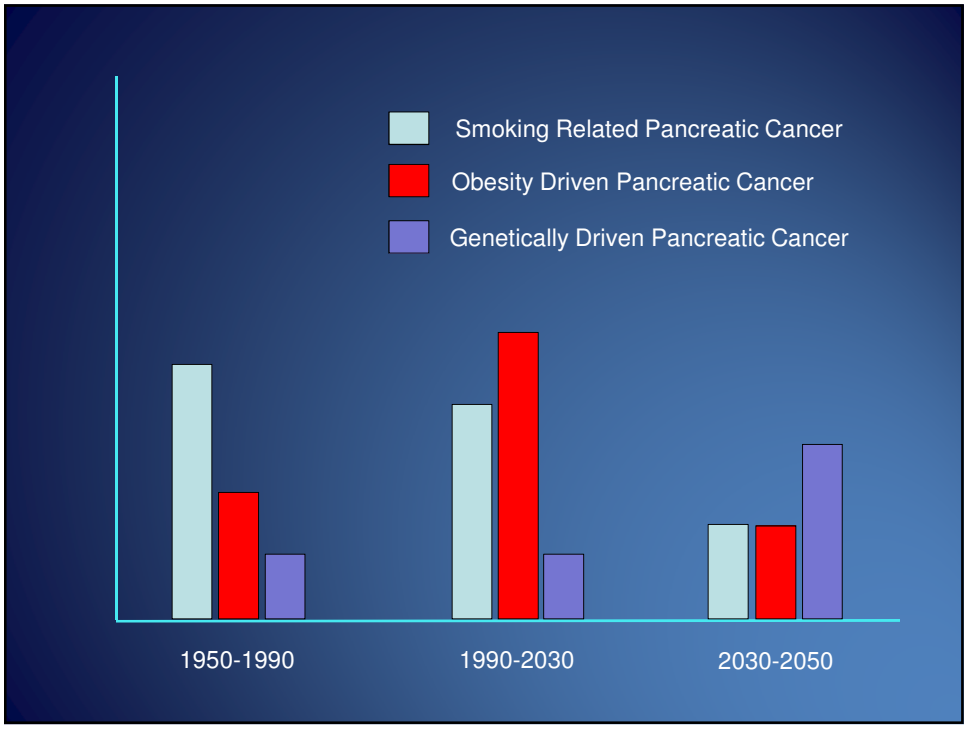
Pancreatic Adenocarcinoma

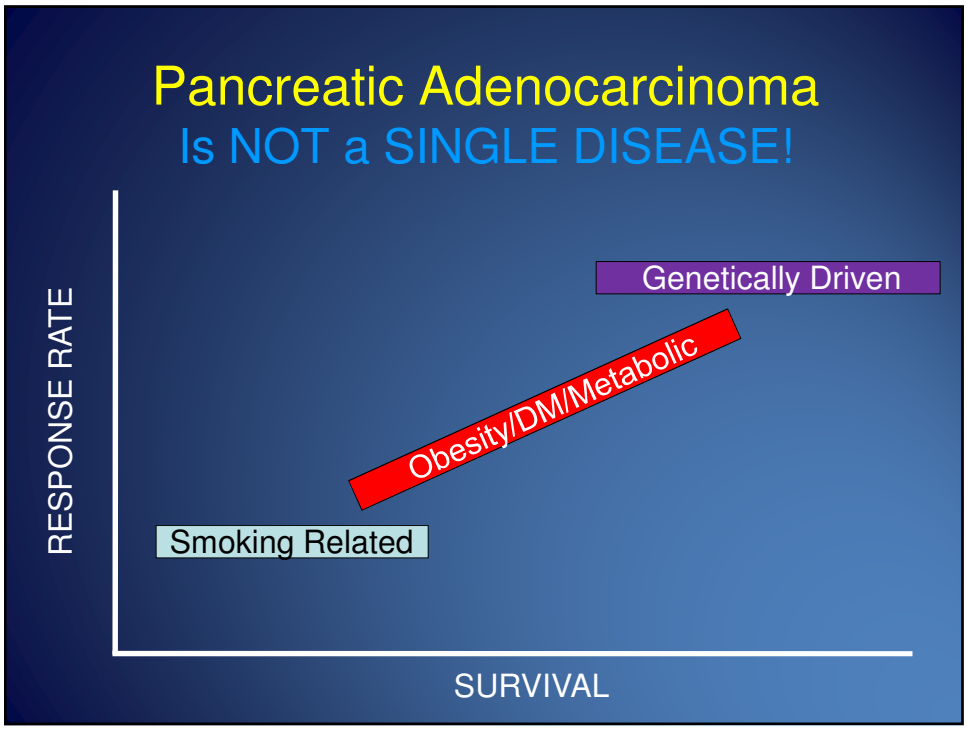
Changing Causes-Changing Biology-Changing Treatment?

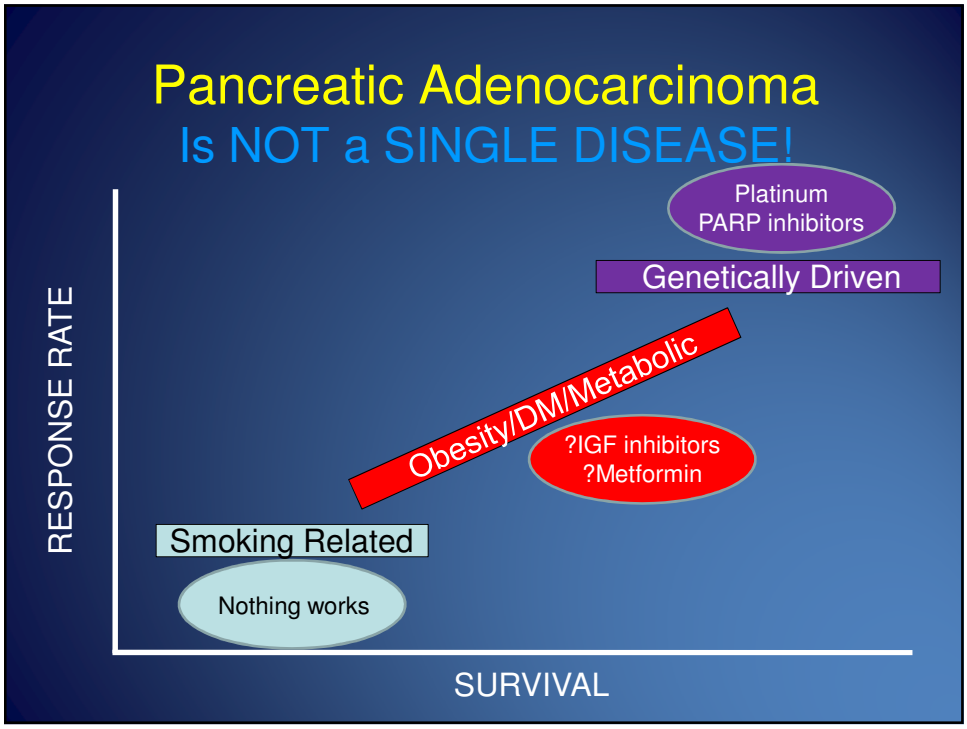
- Smoking is on the decline (yay!)
- Obesity is on the rise!
- Does the cancer remain the same?

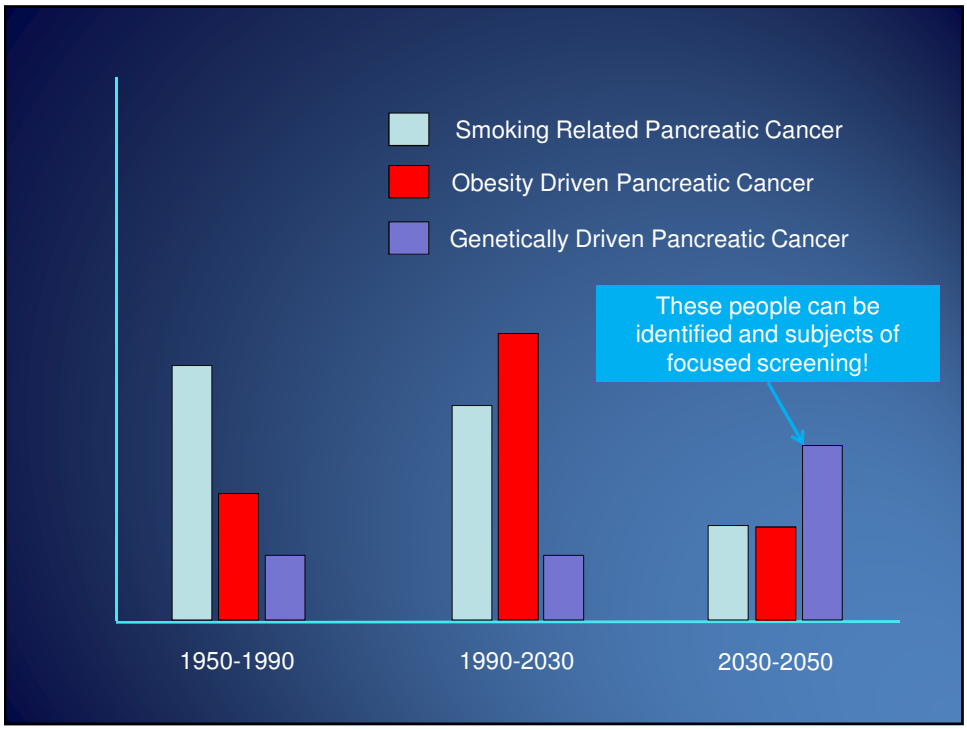
Time Period	K-RAS Mutation Rate
1980's-1990's	85-90%
2000's-2010's	70%

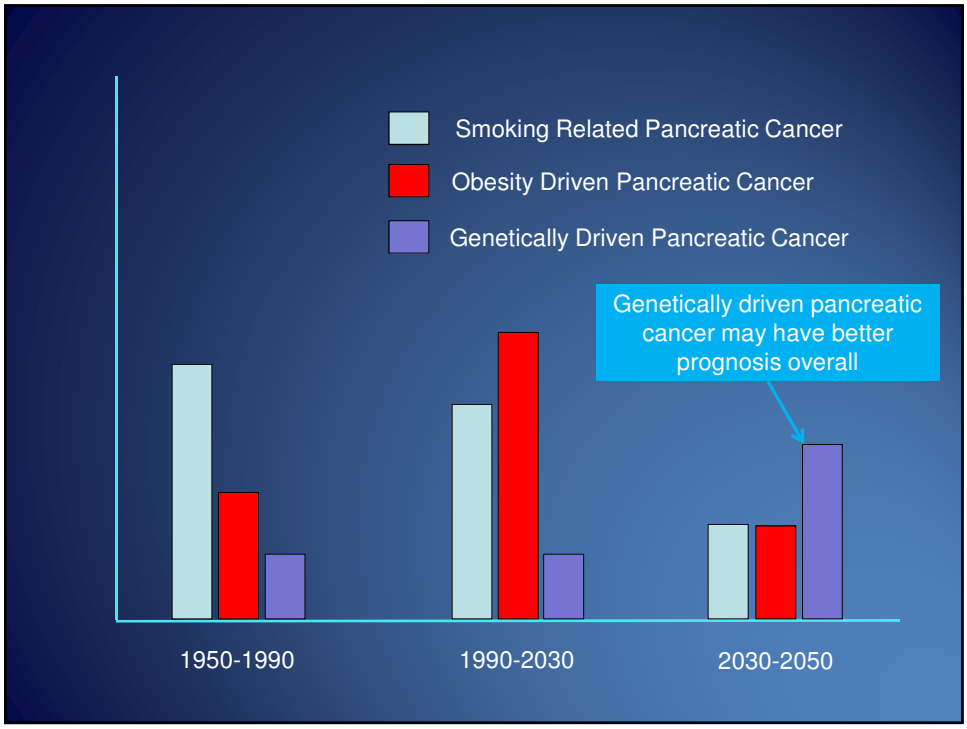
- Does the treatment remain the same?


Smoking Related Pancreatic Cancer
Obesity Driven Pancreatic Cancer
Genetically Driven Pancreatic Cancer
1950-1990
1990-2030
2030-2050


Pancreatic Adenocarcinoma
Is NOT a SINGLE DISEASE!
RESPONSE RATE
Genetically Driven
Obesity/DM/Metabolic
Smoking Related
SURVIVAL


Pancreatic Adenocarcinoma
Is NOT a SINGLE DISEASE!
Platinum
PARP inhibitors
Genetically Driven
Obesity/DM/Metabolic
?IGF inhibitors
?Metformin
Smoking Related
Nothing works
RESPONSE RATE
SURVIVAL


Smoking Related Pancreatic Cancer
Obesity Driven Pancreatic Cancer
Genetically Driven Pancreatic Cancer
These people can be identified and subjects of focused screening!
1950-1990
1990-2030
2030-2050



Genetically Driven Pancreatic Cancer

LC

Breast Cancer Survivor

Known BRCA2 Mutation

Pancreatic Cancer: October, 2003

Preoperative Therapy 11/01/03-1/24/04 with CISPLATIN (BRCA mutations are sensitive to platinum analogs).

Tumor removed 03/15/04

97% of tumor dead at surgery!

Cancer Free 2013!

Pancreatic Cancer

Genetic Factors

Individuals	Gene	Chrom	RR
HNPCC	*hMLH1/HMSH2*	2, 3	?

This list of mutations is certain to expand over time!!!!

***2 first degree relatives**

5-6% of patients have a family history of pancreatic cancer

Pancreatic Cancer

Genetic Factors

Individuals	Gene	Chrom	RR
HNPCC	*hMLH1/HMSH2*	2, 3	?
FAMMM	*p16*	9p	10
Peutz-Jeghers	*STK11*	10p	66
Fam pancreatitis	*PRSS1*	7q	25
Fam Pancreas Ca*	?	?	10

Identify and screen!!!!

***2 first degree relatives**

5-6% of patients have a family history of pancreatic cancer

Pancreatic Adenocarcinoma
Clinical Realities

- Cure is rare and only seen in resected patients
- 100 Patients
  - 15 - 20 resectable tumors
  - 1 in 5 have longterm survival
  - 3 - 4% five year survival
- Tumors are both radio- and chemoresistant
- Survival for most patients is measured in months

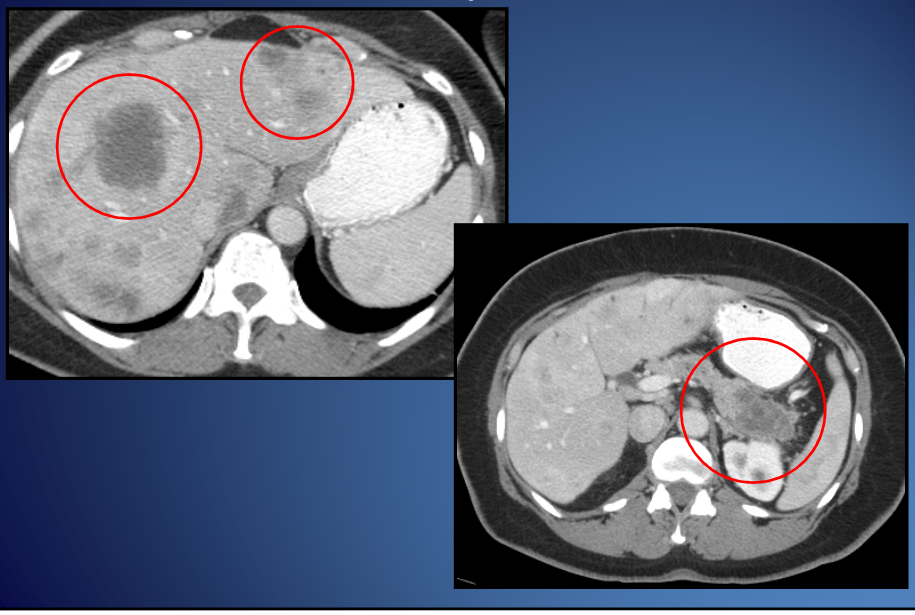
Pancreatic Cancer Biology

- Pancreatic cancer is ALMOST ALWAYS metastatic at diagnosis.
  - Operable cancer: Cancer *appears* confined to the pancreas.
  - But 80% of time, even with surgery the cancer relapses locally or to other organs
  - This can occur within WEEKS of surgery!
- When tumor is locally advanced, virtually certain to have microscopic spread.
- Metastatic disease is by definition, already seen to have spread.

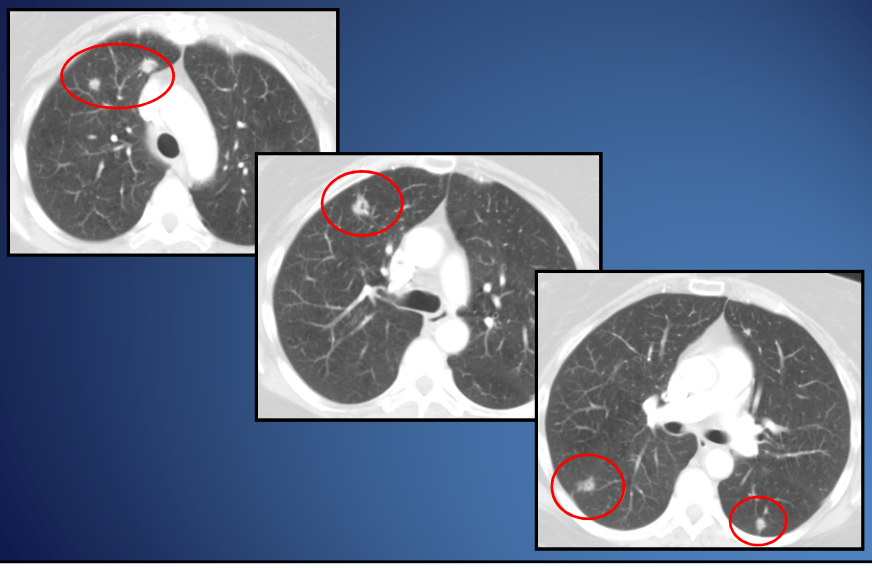
Pattern of Spread

- Liver
- Lung
- Lymph Nodes
- Peritoneum
- Bone and skin

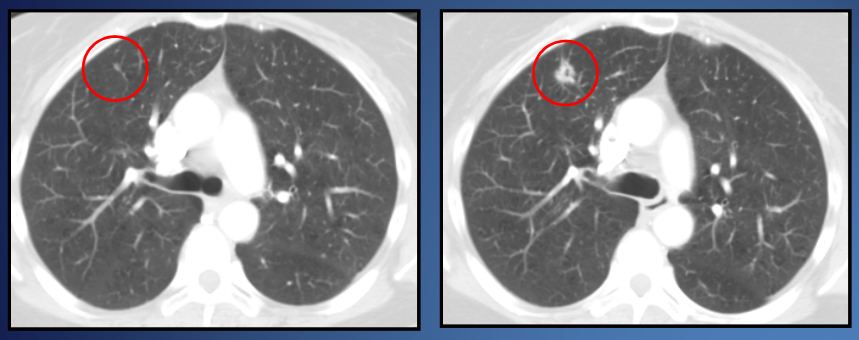
Pattern of Spread: Liver



Pattern of Spread: Lung

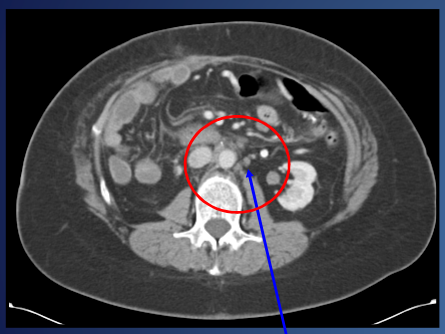


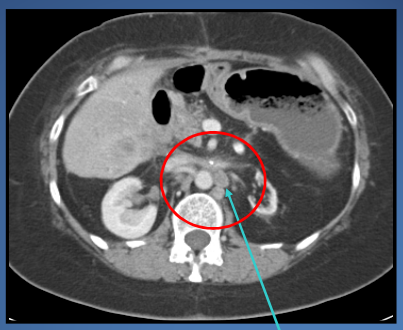
Pattern of Spread: Lung



September 13, 2007 February 11, 2010

Pattern of Spread: Lymph Nodes

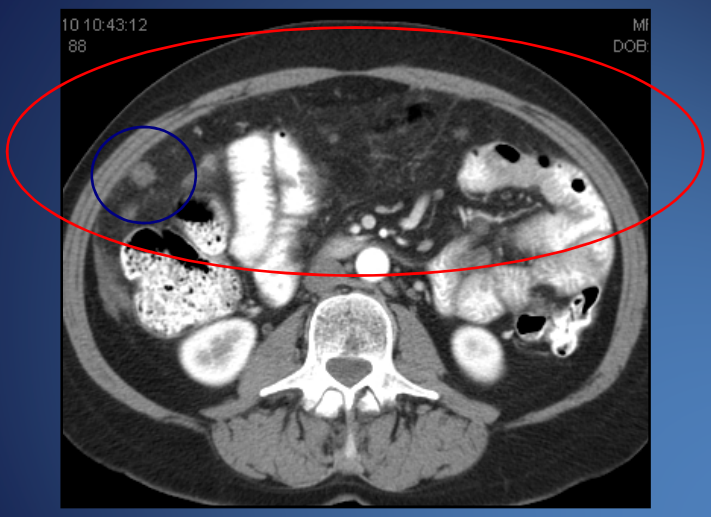




Normal Lymph Node

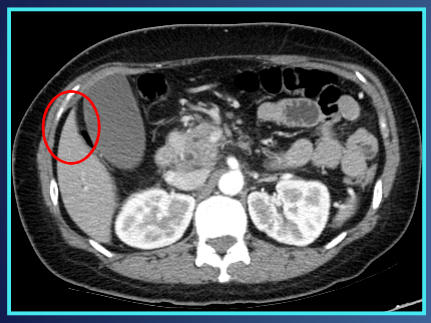
Enlarged cancerous Lymph Node

Pattern of Spread: Peritoneum

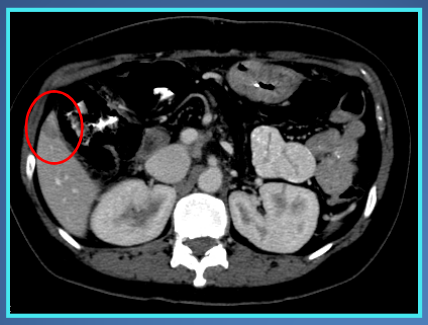


Tumor can relapse within weeks of surgery

Patient with tumor in pancreas, removed 12/01/08. In the liver by 01/22/09!



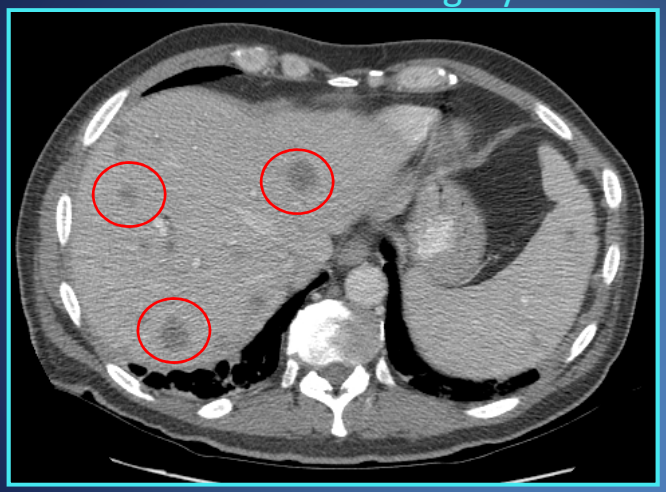
November 25, 2008



January 22, 2009

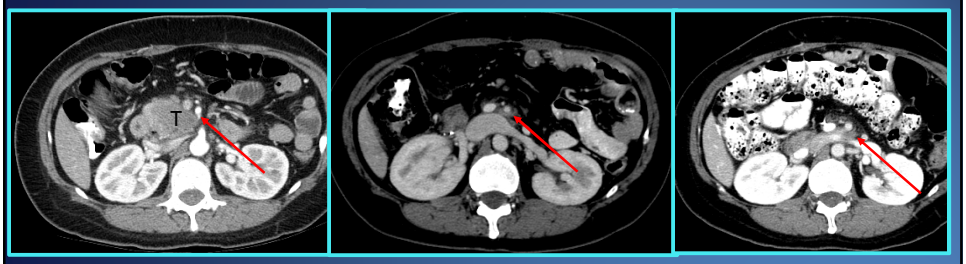
Tumor relapse after surgery

7 weeks after surgery



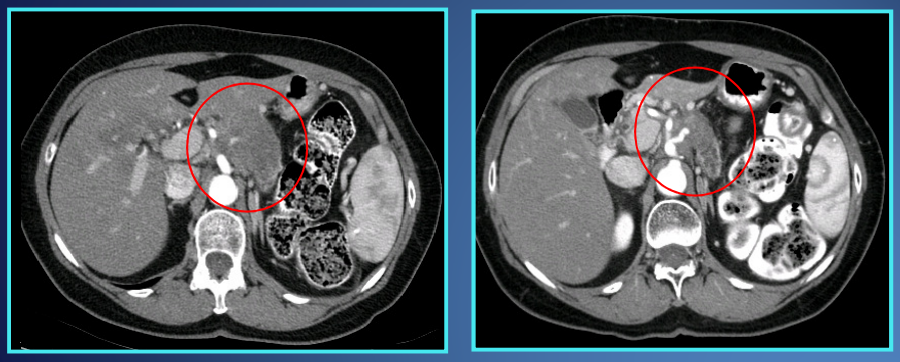
Tumor can also recur locally!

Patient with tumor in pancreas, removed 12/01/08. Clear local recurrence 03/09/10



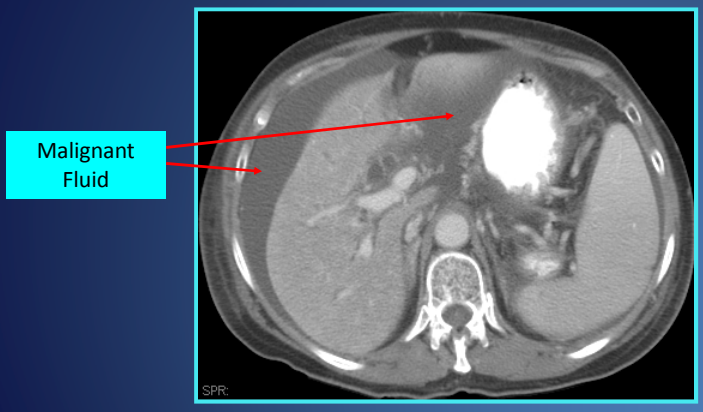
November 25, 2008 January 22, 2009 March 9, 2010

Locally advanced, inoperable tumor, responds to chemotherapy and radiation….



March, 2006 August, 2006

…..but then spreads to peritoneum and causes fluid to build up



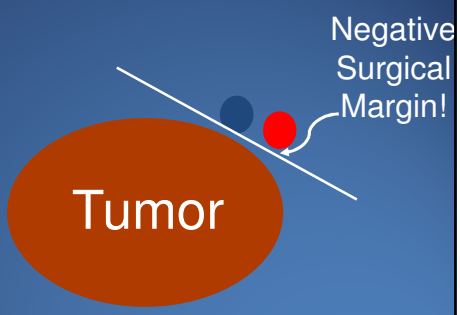
April, 2007

Pancreatic Cancer - Stages

- Resectable pancreatic cancer (operable).
- Borderline resectable (to discuss later)
- Locally advanced pancreatic cancer
- Metastatic pancreatic cancer

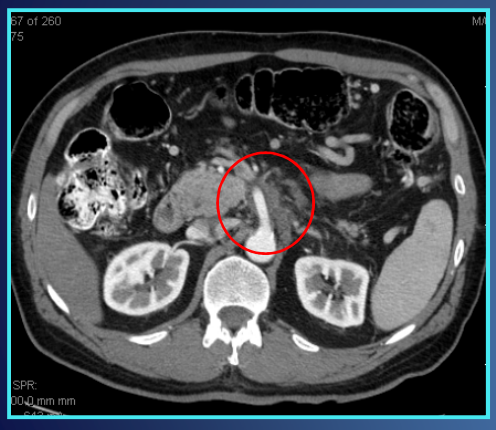
Pancreatic Cancer - Stages

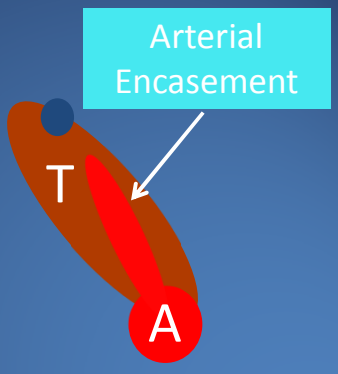
Resectable pancreatic cancer (operable).



Pancreatic Cancer - Stages

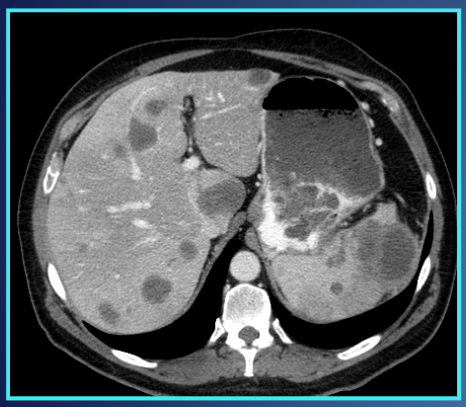
Locally advanced pancreatic cancer

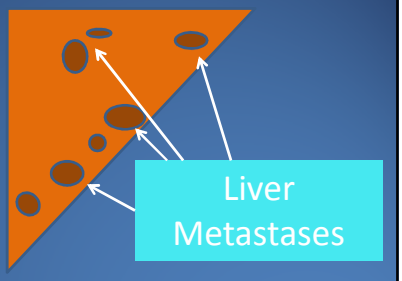




Pancreatic Cancer - Stages

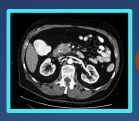
Metastatic Pancreatic Cancer





Pancreatic Cancer – Common Approaches

- Resectable Pancreatic Cancer

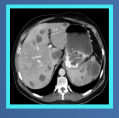


Surgery 1st → Recovery → Post-operative Treatment (Adjuvant Treatment)

- Locally Advanced Pancreatic Cancer

Chemoradiation 1st → Recovery → Chemotherapy

- Metastatic Pancreatic Cancer



Full Dose Chemotherapy #1 → Full Dose Chemotherapy #2

Pancreatic Cancer - Current Knowledge

- Resectable Pancreatic Cancer
  - PancreaticoDuodenectomy (Whipple) leads to 20% Long-term Survival
  - Gemcitabine for 6 months is best level 1 evidence
  - 6 months of 5FU/leucovorin = 6 months of gemcitabine
- Locally Advanced Pancreatic Cancer
  - Chemoradiation then chemotherapy
  - On average patients survive 10-12 months using this approach
- Metastatic Pancreatic Cancer

Drug	Response Rate	Median Survival	1 year survival rate
5-FU	0	4.5 months	2%
Gemcitabine	10%	5.7 months	18%
Gemcitabine/Erlotinib	8%	6.4 months	24%
Gemcitabine+nab-paclitaxel	22%	8.5 months	35%
FOLFIRINOX	32%	11.1 months	48%

Burris H, et al. JCO 1997
Von Hoff, et al. GI ASCO 2013
Moore M, et al. JCO 2007
Conroy T, et al. NEJM 2011

Pancreatic Cancer - Current Knowledge

- Resectable Pancreatic Cancer
  - PancreaticoDuodenectomy leads to 20% Long-term Survival
  - Gemcitabine for 6 months is best level 1 evidence
  - 6 months of 5FU/leucovorin = 6 months of gemcitabine
- Locally Advanced Pancreatic Cancer
  - Chemoradiation then chemotherapy
  - On average patients survive 10-12 months using this approach
- Metastatic Pancreatic Cancer

Drug	Response Rate	Median Survival	1 year survival rate
5-FU	0	4.5 months	2%
Gemcitabine	10%	5.7 months	18%
Gemcitabine/Erlotinib	8%	6.4 months	24%
Gemcitabine+nab-paclitaxel	22%	8.5 months	35%
FOLFIRINOX	32%	11.1 months	48%

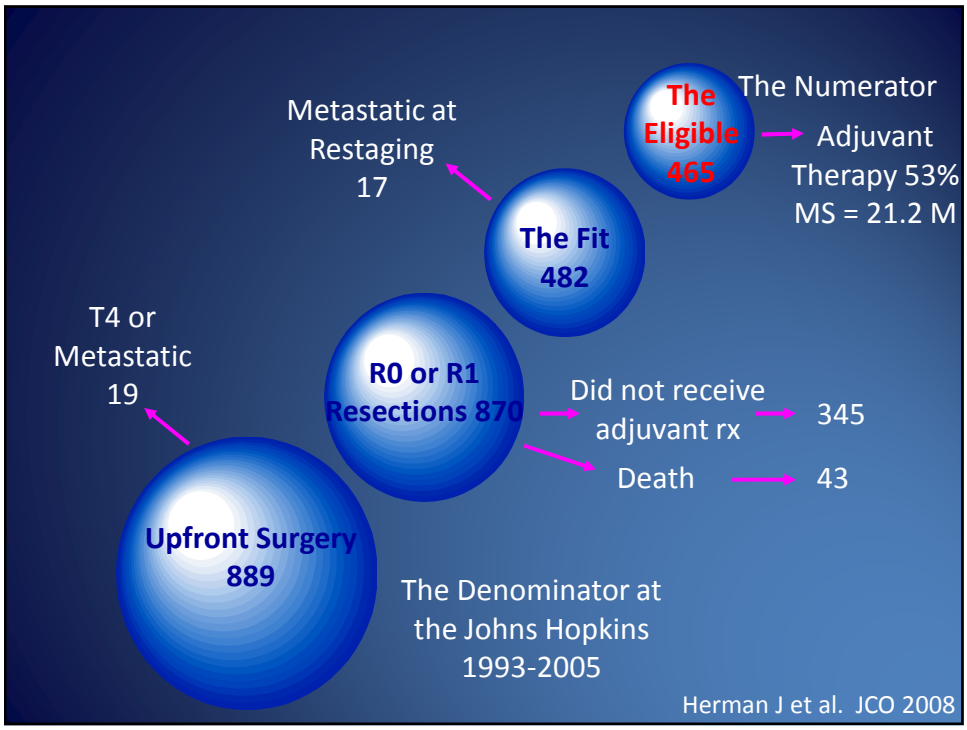
Burris H, et al. JCO 1997
Von Hoff, et al. GI ASCO 2013
Moore M, et al. JCO 2007
Conroy T, et al. NEJM 2011

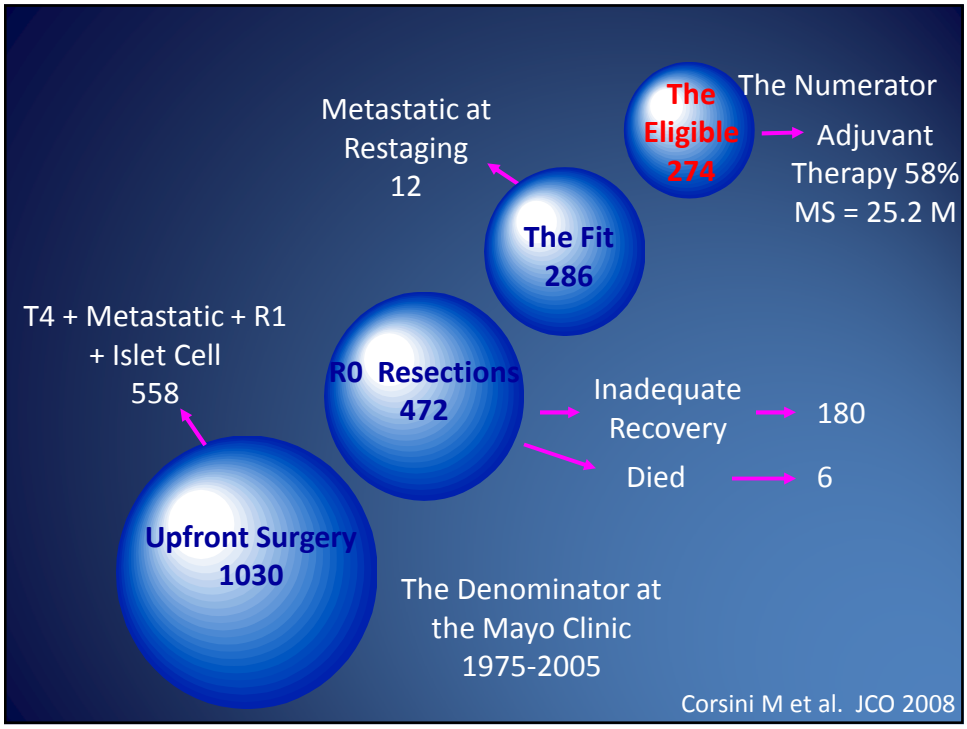
Resectable Pancreatic Cancer & Upfront Surgery Randomized Trials of Adjuvant Therapy

Study (Year)	Number of Patients	R1 Resection (%)	Treatment Assignment Median Survival Months	Treatment Assignment Median Survival Months	p value
GITSG (1985)	49	0	5-FU Chemoradiation 21.0	Observation 10.9	0.035
ESPAC-1 (2004)	289	18	5-FU/Leucovorin Chemotherapy 20.1	No Chemotherapy 15.5	0.009
RTOG 9704 (2006)	380 (Head lesions)	> 35	Gemcitabine + 5-FU/EBRT + Gemcitabine 20.6	5-FU + 5-FU/EBRT + 5-FU 16.9	0.09
CONKO-001 (2007)	388	19	Gemcitabine 22.8	Observation 20.2	0.005
ESPAC-3 (v2) (2010)	1088	18	Gemcitabine 23.6 months	5FU/Leucovorin 23 months	0.39

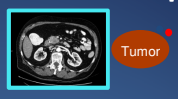
Kalser MH, et al. Arch Surg 1985
Neoptolemos JP, et al. NEJM 2004

Regine W, et al. JAMA 2008
Oettle H, et al. JAMA 2007
Neoptolemos JP, et al. JAMA 2010





Upfront Surgery and Adjuvant Therapy



- Upfront surgery for resectable pancreatic cancer is standard of care
- Adjuvant therapy with gemcitabine for 6 months is standard of care
- This strategy is probably applied to about 60% of patients who go to the OR
- We have made no progress using this strategy over the last 25 years
- Local recurrence is still a problem

Upfront Surgery-Why No Progress?

- It's a locally invasive disease!
- It's a systemic disease!
- Too often, multidisciplinary care begins in the recovery room.
- The very act of doing surgery first may promote tumor progression (inflammatory cytokines, immunosuppression).

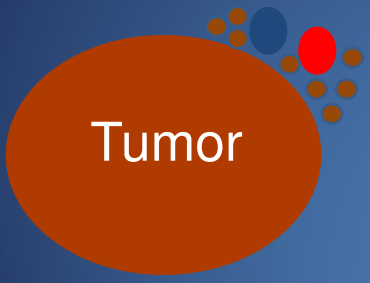
Local Invasion: Margin + Resections are Frequent and have Poor Prognosis

Author - Country	Number of Patients	Margin + Resection Rate	Median Survival	Independent Prognostic Factor
Winter-U.S.	1175	42%	14 m	Yes
Richter-Germany	194	37%	12 m	Yes
Kuhlmann-Netherlands	160	50%	NS	Yes
Takai-Japan	89	47%	8 m	Yes

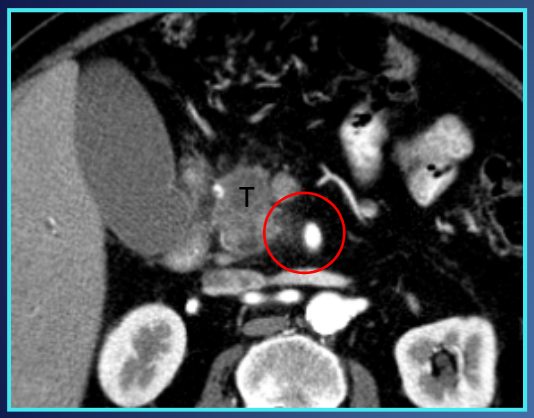
RTOG 9704: Patients with R1 Resections > 35%!!!!

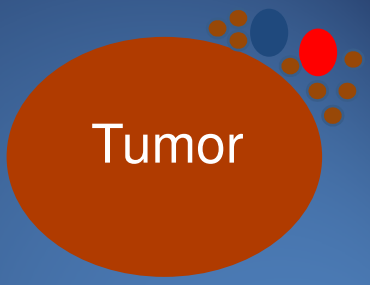
Pancreatic Cancer – The Reality

Even when the tumor appears operable….



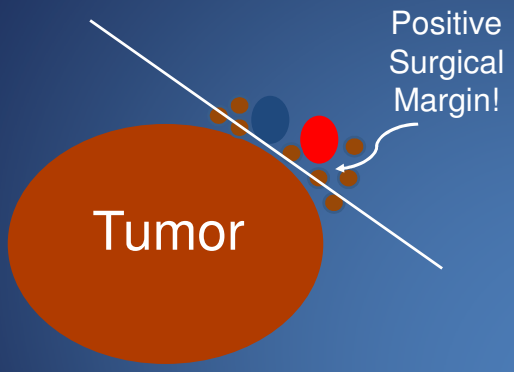
Pancreatic Cancer –Resectable Upfront?



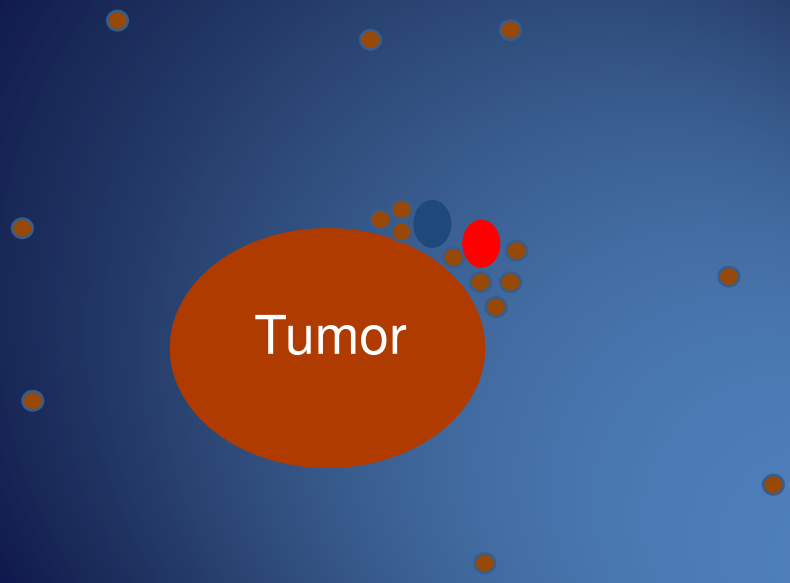


Pancreatic Cancer - Reality

There are tumor cell beyond the visible mass.



Tumor Cells–Seen and Unseen

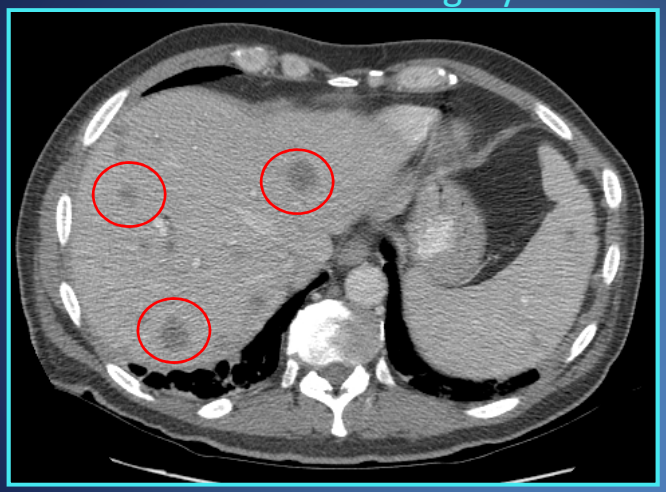


It's a Systemic Disease!

Author Year	Number of Patients	Duration of Pre-Operative Therapy (Weeks)	Elapsed Time to Restaging (Weeks)	Patients with Radiographic Evidence of Metastatic (%)
Evans, 1992	28	5.5	9.5-10.5	5 (18%)
Pisters, 1998	35	2	6-8	5 (14%)
Hoffman, 1998	53	5.5	9.5-11.5	6 (11%)
White, 2001	111	5-5.5	8-9.5	19 (20%)
Pisters, 2002	35	2	6-8	7 (20%)
Totals	**262**			**42 (16%)**

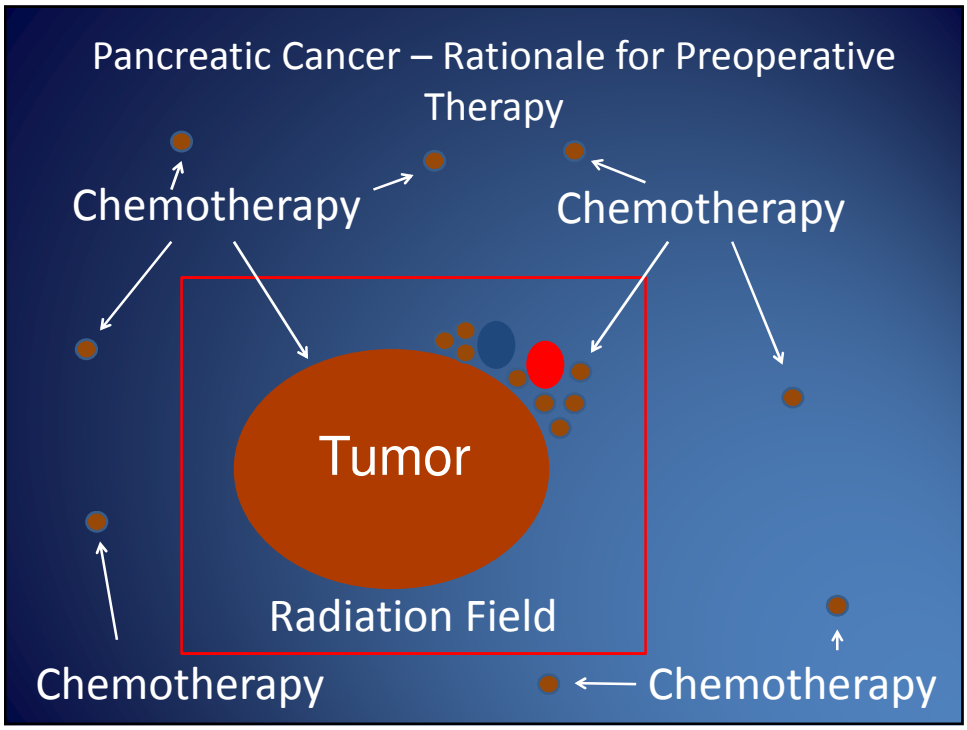
Tumor relapse after surgery

7 weeks after surgery

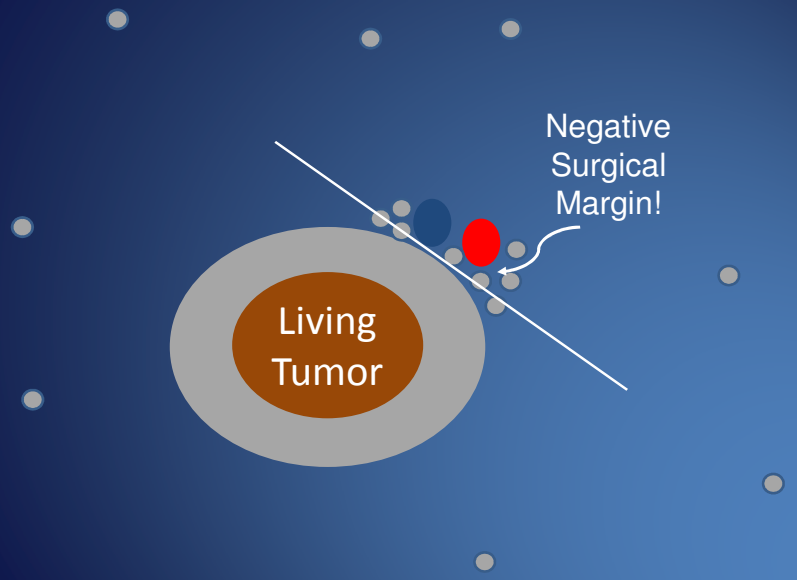


Pre-Operative Therapy

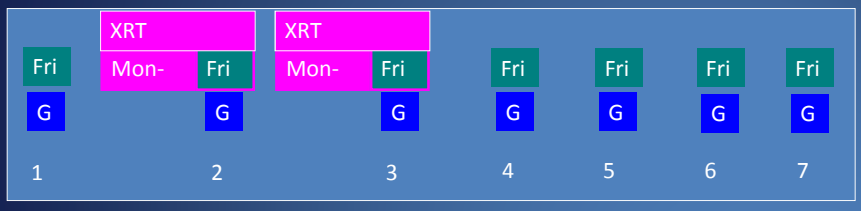
- Provides early treatment of micrometastatic disease.
- Primary tumor is intact and relatively well-perfused.
- Avoids surgery in patients with rapidly progressive dz.
- Observe patient tolerance to preoperative chemoXRT.
- Appears to improve R0 resection rate and decrease local failure.



Pancreatic Cancer – Preoperative Therapy



MDA 98-020: Pre-Operative Gemcitabine-based Chemoradiation for Resectable Pancreatic Cancer



G = gemcitabine @ 400 mg/m2 over 30 min (13 mg/m2/min) weekly x 7

XRT = 300 cGy/fraction x 10 fractions to total dose of 30 Gy

Pre-Operative Therapy Selects Patients Better than Upfront Surgery

- Avoids surgery in patients with rapidly progressive disease (unfavorable tumor biology).
- Avoids surgery in patients unable to tolerate the stress of

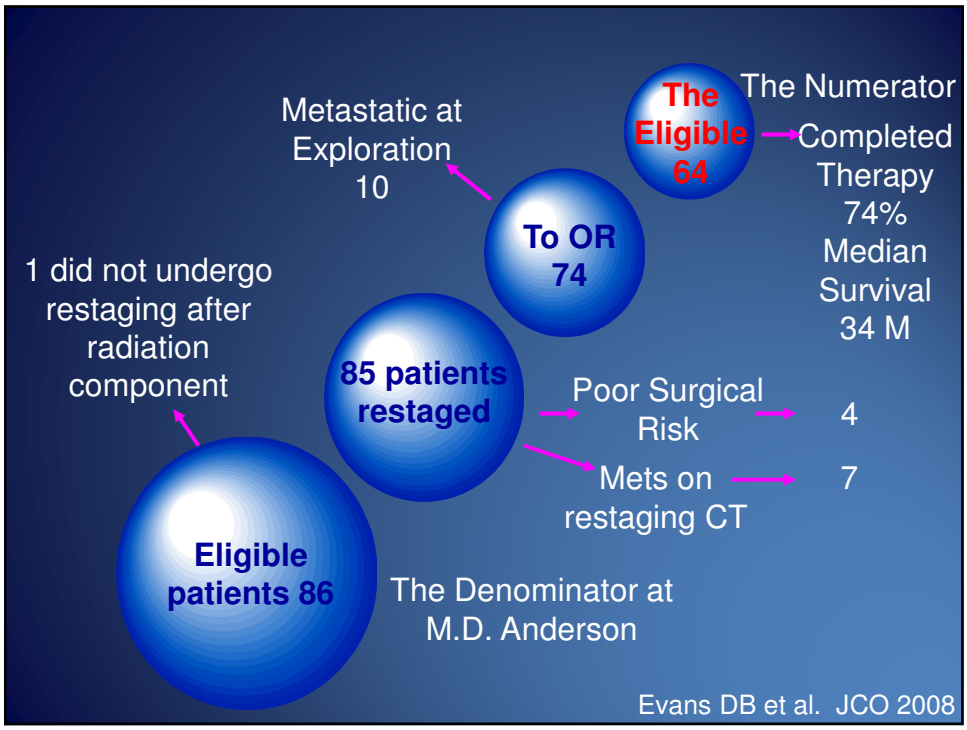
●Surgery was avoided in 25-35% of the patients; their median survival was 7-10 mo.

●Local failure occurred in 10-25% of patients undergoing resection; suggesting radiation may have a role in preoperative setting.

MDA 01-341^	Gem/Cis Gem/XRT	90	66%	31 mo

*Evans DB, et al. JCO 2008

^Varadhachary GR, et al. JCO 2008



Chemoradiation for Locally Advanced Disease

1981 GITSG Trial randomized 194 patients with locally advanced disease to 1 of 3 arms:

	Arm	Median OS
1.	6000 Radiation Alone	22.9 weeks
2.	4000 Radiation + Bolus 5-FU	42.2 weeks
3.	6000 Radiation + Bolus 5-FU	40.3 weeks

Traditional Strategy for Locally advanced pancreatic cancer

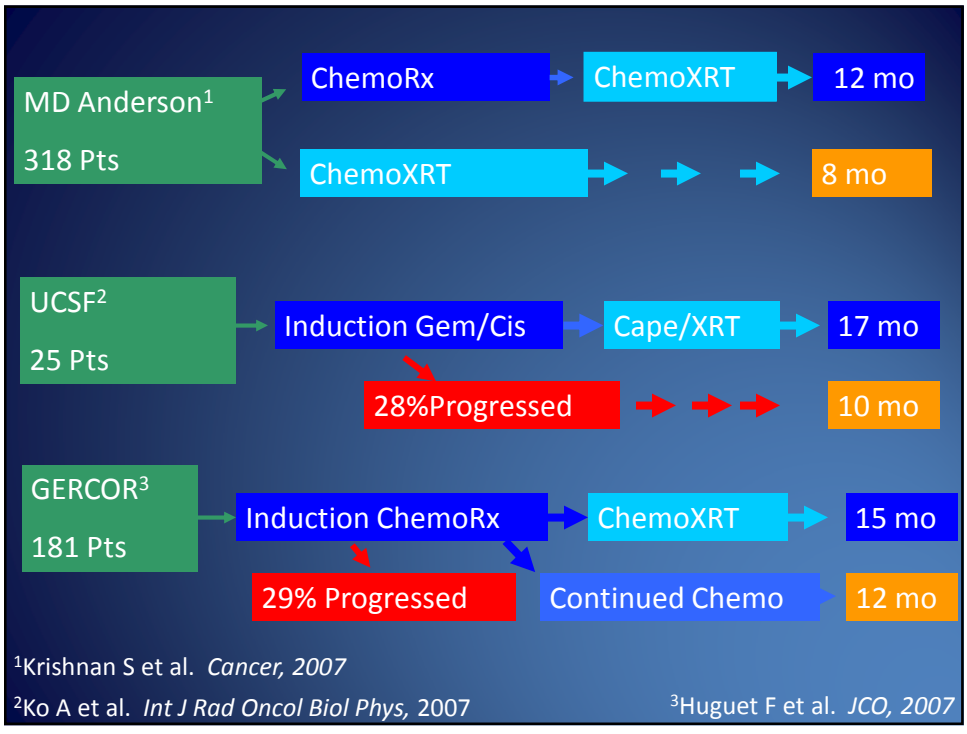
Chemoradiation → Recovery → Chemotherapy

Metastatic

2nd Line Rx or Best Supportive Care

Upfront Chemoradiation for Locally Advanced Disease

PI/Group Year	Number of Patients	ChemoXRT 1st* Regimen	Median Survival (Months)
*Moertel/GITSG 1981	65	5FU/XRT	9.8
*Wolff/MDACC 2001 (P1)	18	Gem/XRT	6.0
*Blackstock/CALGB 2003 (P2)	43	Gem/XRT	8.2
*Loerher/ECOG 2008 (P3)	40	Gem/XRT	11.0
Crane/MDACC 2009 (P2)	82	Cape/Bev/XRT	11.9



[1]Krishnan S et al. *Cancer, 2007*

[2]Ko A et al. *Int J Rad Oncol Biol Phys,* 2007

[3]Huguet F et al. *JCO, 2007*

New Strategy for Locally advanced pancreatic cancer

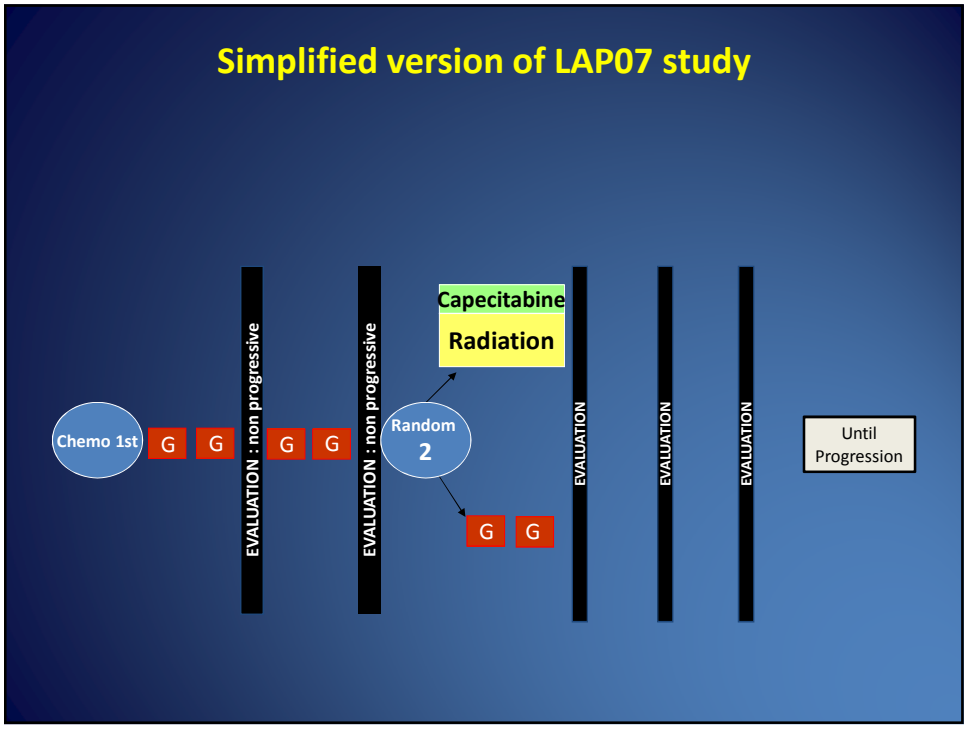
Chemotherapy 2-3 months → CT scan → - Mets → Consider ChemoRadiation

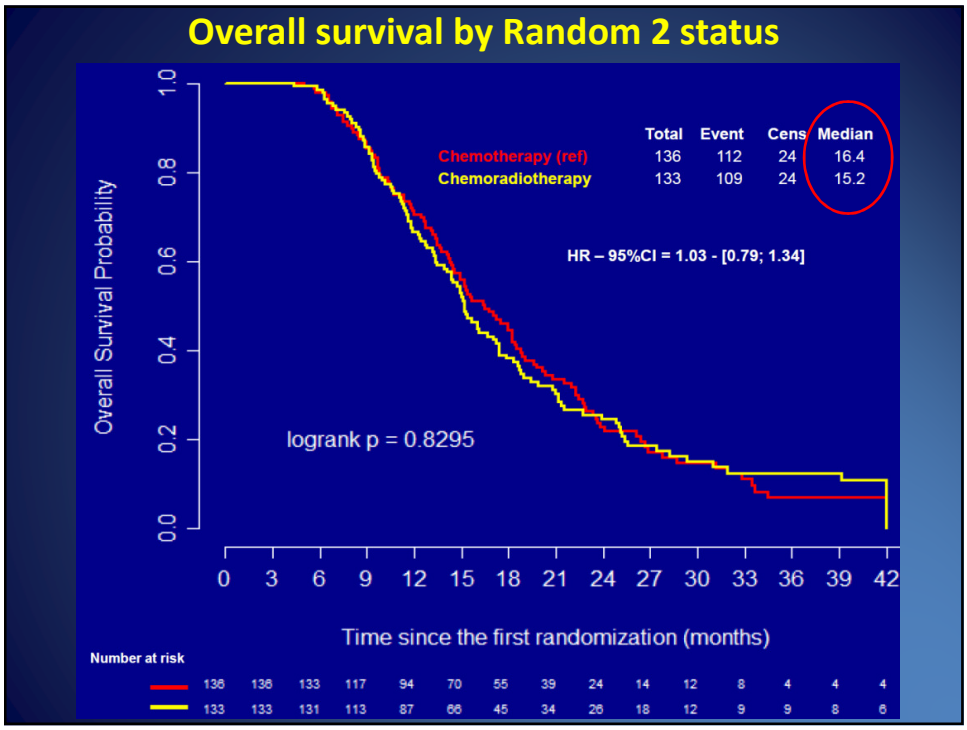
CT scan → Metastatic

2nd Line Chemotherapy or Best Supportive Care

Induction Chemotherapy then Chemoradiation for Locally Advanced Disease

Author Year	Number of patients	Induction Chemo	% Progressed	Radio-sensitizer	Median Survival (all components)
Krishnan 2007	76	Gem-based	Not stated	5-FU, cape, or Gem	11.9 months
Ko 2007	25	Gem/Cis	28-32%	Capecitabine	17 months
Huguet 2007	181	Gem-based x 3 months	29%	Not stated	15 months
Moureau-Zobotto 2008	59	Gem/Ox X 2 months	11%	5-FU	12.6 months
Reni 2009	91	PEFG and variants	23%	5-FU, cape, or Gem	16.2 months
Crane 2011	69	Gem/Ox + Cetuximab x 2 months	2%	Capecitabine + Cetuximab	19 months


Simplified version of LAP07 study
Chemo 1st
G
G
EVALUATION : non progressive
G
G
EVALUATION : non progressive
Random
2
Capecitabine
Radiation
G
G
EVALUATION
EVALUATION
EVALUATION
Until
Progression

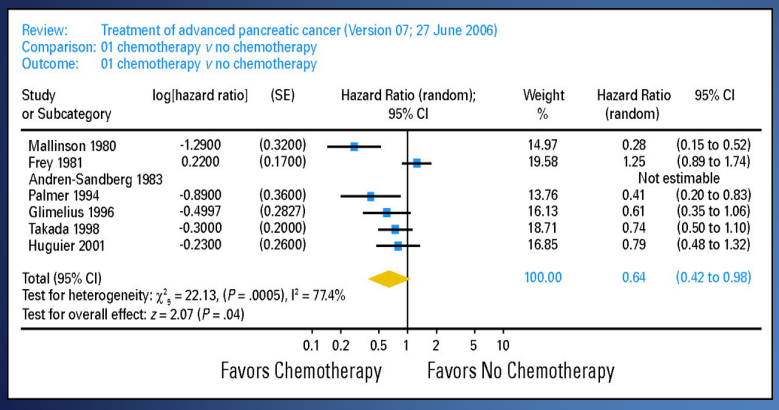

Overall survival by Random 2 status
Overall Survival Probability
0.0
0.2
0.4
0.6
0.8
1.0
Total
Event
Cens
Median
Chemotherapy (ref)
136
112
24
16.4
Chemoradiotherapy
133
109
24
15.2
HR – 95%CI = 1.03 - [0.79; 1.34]
logrank p = 0.8295
0
3
6
9
12
15
18
21
24
27
30
33
36
39
42
Time since the first randomization (months)
Number at risk
136 136 133 117 94 70 55 39 24 14 12 8 4 4 4
133 133 131 113 87 66 45 34 26 18 12 9 9 8 6

Treatment for Locally Advanced Disease

- Most experts agree that patients should start treatment with chemotherapy first.
- If after 2-4 months of chemotherapy there is no sign of spread, it is reasonable to switch to chemoradiation (no consensus on that)
- Chemoradiation should NOT be the first treatment for most patients.

Chemotherapy for Advanced Pancreatic Cancer

Chemotherapy is better than Best Supportive Care



Sultana A, et al. JCO 2007

Gemcitabine: Our "go-to" drug 1996-2010

Burris 1996	Number of Patients	Response Rate	Clinical Benefit Response*	Median Survival	1 year survival rate
5-FU	63	0	4.8%	4.5 months	2%
Gemcitabine	63	10%	23.8%	5.7 months	18%

Cytotoxic Gemcitabine Doublets

Author Year	Number of Patients	% Patients with Metastatic Disease	Gemcitabine Median Survival	Gemcitabine Doublet Median Survival	P value
Berlin 2002	322	90	Gem 5.4 months	Gem + 5FU 6.7 months	0.09
Heinemann 2006	195	58%	Gem 5.4 months	Gem + Cisplatin 7.0 months	0.43
Louvet 2005	313	70%	Gem 7.0 months	Gem + Oxaliplatin 9.0 months	0.13
Poplin 2009	555	88%	Gem 4.9 months	Gem + Oxaliplatin 5.9 months	0.16
Cunningham 2009	533	71%	Gem 6.2 months	Gem + Capecitabine 7.1 months	0.08
Colucci 2010	400	84%	Gem 8.3 months	Gem + Cisplatin 7.2 months	0.38

Berlin J et al. JCO 2002
Heinemann V et al. JCO 2006
Louvet C et al. JCO 2005

Poplin E et al. JCO 2009
Cunningham D et al. JCO 2009
Colucci G et al. JCO 2010

Molecular Therapies

Author Year	Delivered Therapy	No of Pts	% METS	Response Rate (%)	Overall Survival (Median Days)	1-year survival rate	P-Value
Van Cutsem 2004	Gem + placebo vs Gem + Tipifarnib	347 314	76	8 6	182 193	24% 27%	0.75
Bramhall 2002	Gem + placebo vs Gem + Marimastat	119 120	58	11 11	164 165.5	18% 17%	0.95
Moore 2005	Gem vs Gem + Erlotinib	284 285	75	8.0 8.6	177 191	17% 24%	0.025
Kindler 2007	Gem + placebo vs Gem/Bevacizumab	300 302	85	10 11	180 171	20% 18%	0.40
Philip 2007	Gem vs Gem/Cetuximab	369 366	79	13 12	177 192	NR	0.14
Van Cutsem 2008	Gem + Erlotinib + P vs Gem + Erlotinib + Bev	301 306	100	8.6 13.5	180 213	NR	0.21

Gemcitabine/nab-paclitaxel

Burris 1996	Number of Patients	Response Rate	Median Survival	1 year survival rate
Gemcitabine	430	7%	6.7 months	22%
Gemcitabine nab-paclitaxel	431	23%	8.5 months	35%

FOLFIRINOX

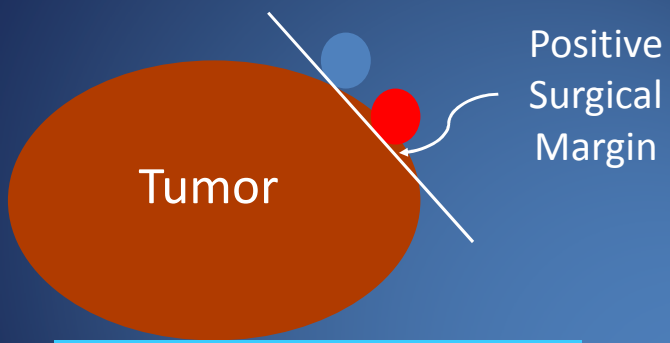
Conroy 2011	Number of Patients	Response Rate	Clinical Benefit Response*	Median Survival	1 year survival rate
Gemcitabine	171	9.4%	x	6.2 months	20.6%
FOLFIRINOX	171	31.6%	x	11.1 months	48.4%

Summary: Chemotherapy for Stage IV Disease

- Chemotherapy prolongs survival compared to best supportive care.
- Gemcitabine is probably slightly better than bolus 5-FU.
- Gemcitabine cytotoxic doublets are not much better than gemcitabine alone.
- FOLFIRINOX better than gemcitabine
- Gemcitabine + nab-paclitaxel (Abraxane) better than gemcitabine
- Molecular therapy has added little benefit thus far.

Emerging Entity: Borderline Resectable Pancreatic Cancer

Borderline Resectable Pancreatic Cancer



Not Good!

R1 Resections Don't Do Well

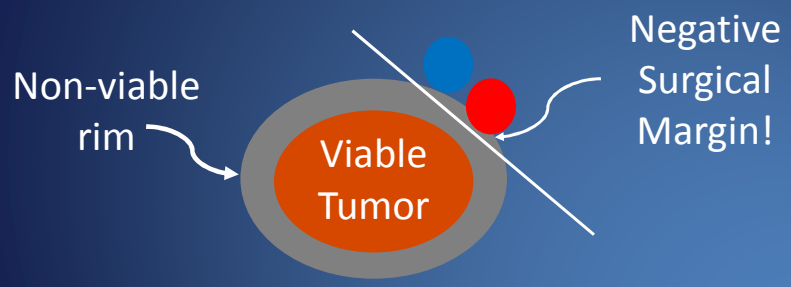
Institution	Margin+ Rate (%)	Median Survival R0 (Mo)	Median Survival R1(Mo)
Mayo[1]	24%	18-19	15
Hopkins[2]	42%	20	14
MGH[3]	30%	22	15

[1]Fatima J et a, Arch Surg, 2010

[2]Winter JM et al, J Gastrointest Surg, 2006

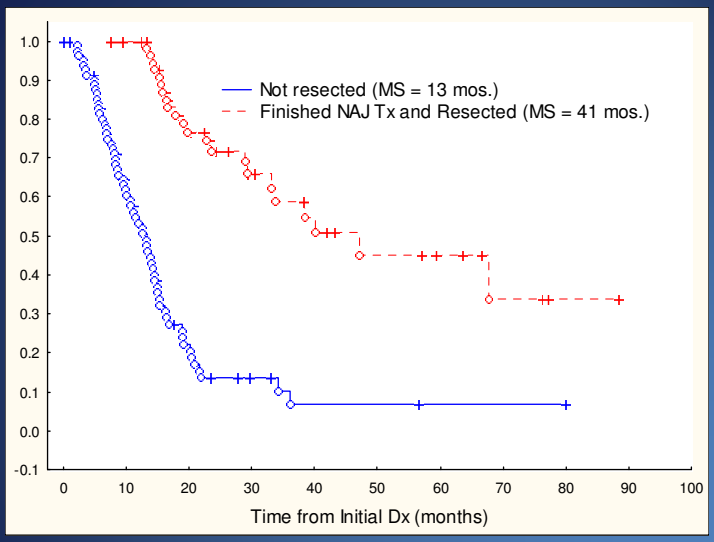
[3]Konstandinidis et al, GI ASCO 2010

After Preoperative Chemotherapy and ChemoXRT



Yipee!!!

Borderline Resectable Pancreatic Cancer
MDACC Results for All Patients



Survival of all borderline patients (156), resected (40%) v. not resected (60%)

Courtesy M. Katz

Borderline Resectable Pancreatic Cancer

JC

Borderline Resectable Pancreatic Cancer: 10/11/2000

Treated with gemcitabine + radiation.

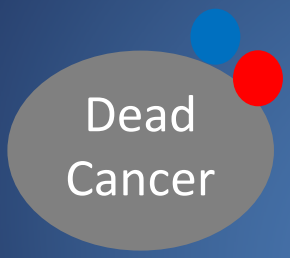
Suffered a heart attack during treatment.

Cancer Free Today.

Never HAD surgery!

Pictured at his 50th High School Reunion-2007

Chemo-Radiation can (on rare occasion) completely kills these cancers!



Are We Making Progress?

Strategy	Median Survival 1980's-1990's	Median Survival 2000's-2010's
Resectable Pancreatic Cancer		
Upfront Surgery + Post Op Therapy	20-21 Months	21-23 months
Preoperative Therapy + Surgery	18-20 Months	**31-34 months**
Locally Advanced Pancreatic Cancer		
ChemoRadiation then Chemotherapy	9-10	10-12 months
Chemotherapy 1st then Chemoradiation	?	**12-19 months**
Metastatic Pancreatic Cancer		
Single Agent Chemotherapy	5-6 months	5-6 months
Combination Chemotherapy	6-7 months	**9-11.1 months**

Future Directions

- Dosing cytotoxic drugs!
- Personalizing therapy
  - Biopsies of tumor
  - Blood samples: Circulating tumor cells and circulating DNA
  - Functional Imaging (PET Scans)
- Modulating the STROMAL COMPONENT, not the tumor cells!!!!

Dosing Chemotherapy

Molecular Therapies + Blunt Trauma

Author Year	Blunt Trauma	Molecular Agent
Van Cutsem 2004	Gemcitabine 1000 mg/m2 over 30 minutes	RAS Inhibitor
Bramhall 2002	Gemcitabine 1000 mg/m2 over 30 minutes	Metalloproteinase Inhibitor
Moore 2005	Gemcitabine 1000 mg/m2 over 30 minutes	EGFR Inhibitor
Kindler 2007	Gemcitabine 1000 mg/m2 over 30 minutes	VEGF Inhibitor
Philip 2007	Gemcitabine 1000 mg/m2 over 30 minutes	EGFR Inhibitor
Van Cutsem 2008	Gemcitabine 1000 mg/m2 over 30 minutes	EGFR and VEGF Inhibition

Lower Doses of Gemcitabine

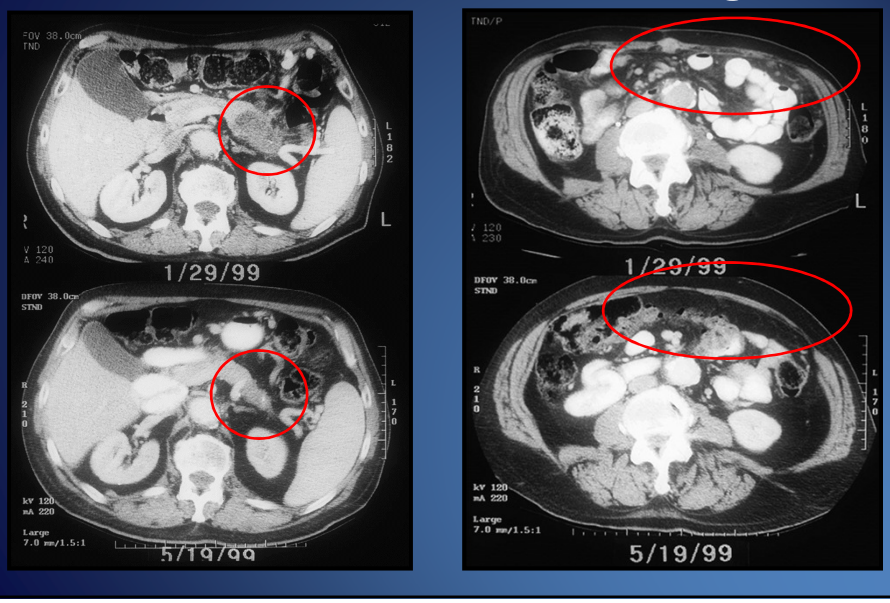
- Gemcitabine is a minimally effective when dosed at 1000 mg/m^2 over 30 minutes.
- In phase I, gemcitabine active at 180-525 mg/m^2 over 30 minutes given weekly. No increase in intracellular levels of gem-triphosphate were observed using higher doses.[1]
- 2 randomized trials demonstrate fixed dose rate gemcitabine at or near MTD is better, but more toxic than standard dose gemcitabine.[2,3]
- Individualized ***maximal repeatable*** doses of gem range of from 300-700 mg/m^2 weekly, closer to FDR gem.[4]

1. Abbruzzese JL et al JCO, 1991
2. Tempero JCO, 2003
3. Poplin E, et al ASCO, 2006
4. Takahashi Y et al Pancreas, 2005

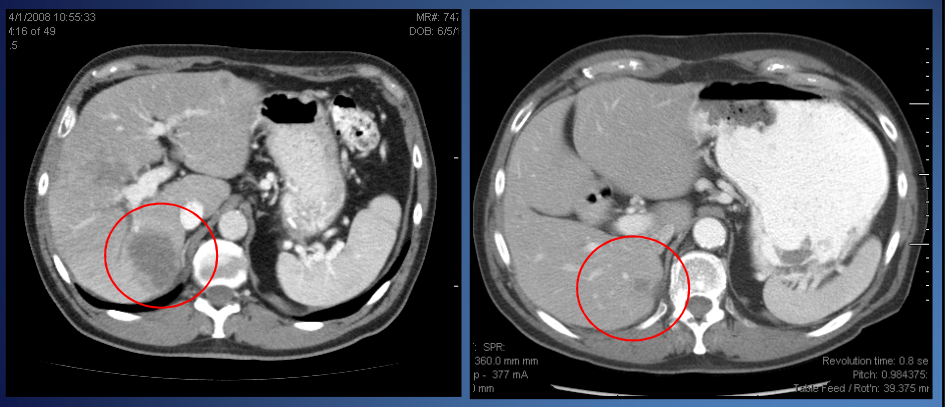
Pre-Operative Therapy for Resectable Pancreatic Cancer: Chemo "Lite" Works

Study	Gemcitabine Dose (mg/m^2)	Total Intended Gemcitabine Dose (mg/m^2)	Median Survival
CONKO 001	1,000 mg/m^2 3 wk on,1 off X 6 cycles	18,000 mg/m^2	23 months
Gem/XRT	400 mg/m^2 Weekly X 7	2,800 mg/m^2	34 months
Gem/Cis Gem/XRT →	750 mg/m^2 q 2 wks X 4 doses 400 mg/m2 X 4	4,600 mg/m^2	31 months

FDR Gemcitabine @ 600 mg/m^2



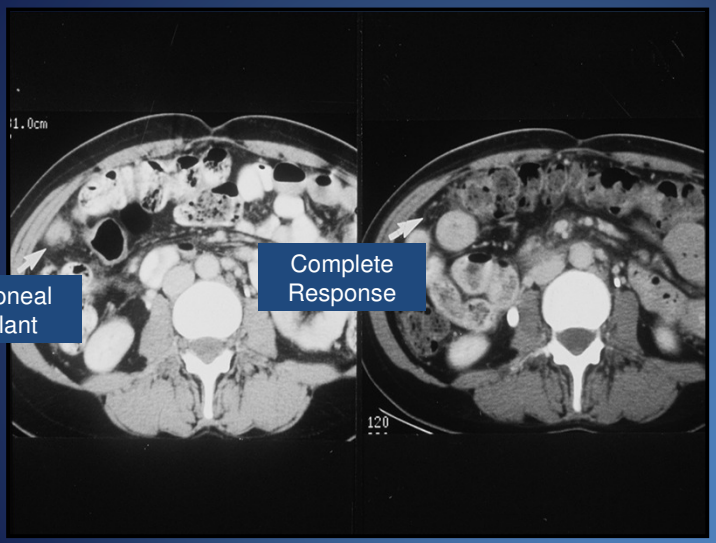
FDR Gemcitabine @ 450 mg/m^2



Liver Met 04/01/08

Liver Met 02/05/09

Gemcitabine at 350 mg/m^2 are systemically relevant



GTX Dosing

	Fine	MDACC
Gemcitabine	750 mg/m^2 D 4 and D11	350 mg/m^2 D4 and 11
Docetaxel	30 mg/m^2 D4 and D11	35 mg/m^2 D4 and D11
Capecitabine	750 mg/m^2 BID x 14 days	500 mg/m^2 BID x 14 days

Fine R et al. Cancer Chemother Pharmacol 2008

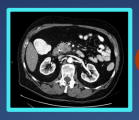
FOLFIRINOX

	Conroy	MDACC
5FU/Leucovorin Bolus 5-FU Infusion	400 mg/m^2 2400 mg/m^2	0 mg/m^2 2000 mg/m^2
Oxaliplatin	85 mg/m^2	75 mg/m^2
Irinotecan	180 mg/m^2	150 mg/m^2

Conroy T et al. NEJM 2011

Pancreatic Cancer – Newer Approaches

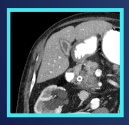
- Resectable Pancreatic Cancer



Pre-op Rx → Recovery → Repeat Scans → Cancer Spread: No Surgery / Surgery

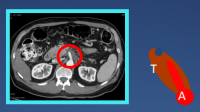
- Borderline Resectable Pancreatic Cancer

Pre-op Rx → Recovery → Repeat Scans → Cancer Spread: No Surgery / Tumor Shrinkage or other Evidence of Response, No Cancer Spread, Surgery



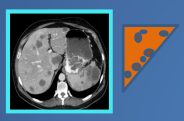
Pancreatic Cancer – Newer Approaches

Locally Advanced Pancreatic Cancer



Chemotherapy 1st → (2-3 months) → Repeat Scans → Cancer Spread: No Radiation / Chemoradiation or continue chemotherapy

- Metastatic Pancreatic Cancer



Chemotherapy Lite #1 → Chemotherapy Lite #2

My Inspiring Patients

Susan S:

Borderline Resectable Pancreatic Cancer: May, 2002

Treated with chemotherapy, then radiation with molecular agent

Surgical Removal, April, 2003

Relapsed Disease, May, 2006

Relapsed Disease, July, 2009

Eventually died January, 2011

2 Grandchildren born in the meantime!

Attitude!

Gayle M:

Pancreatic Cancer: 04/17/06

Metastatic Cancer: 05/31/06

Died: 10/20/07

Survived: 18 months.

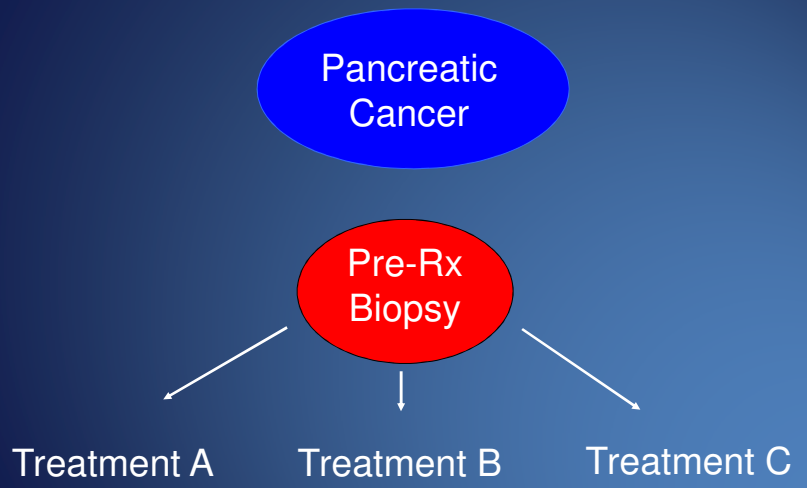
Enrolled in 2 clinical trials.

Tried for a 3rd.

Hospitalized just once.

Able to laugh every visit.

Future Directions
Personalized Cancer Therapies

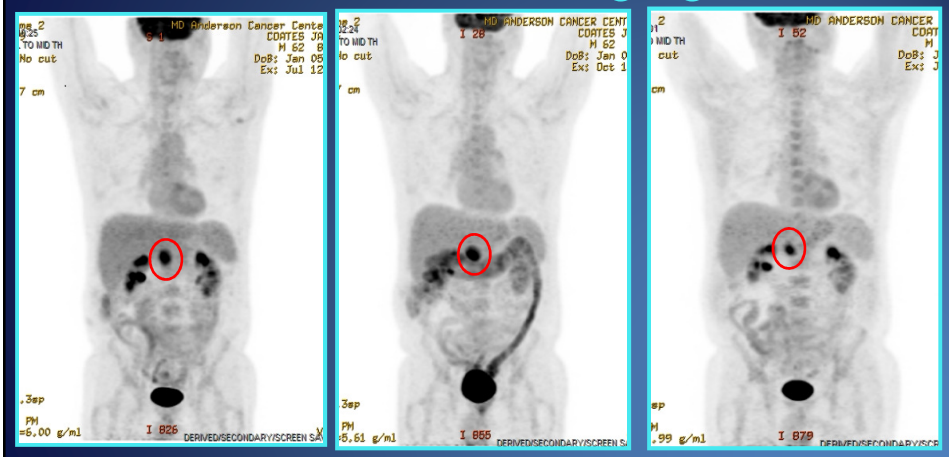


Future Directions
Personalizing Therapy
Blood Tests NOT Biopsies!

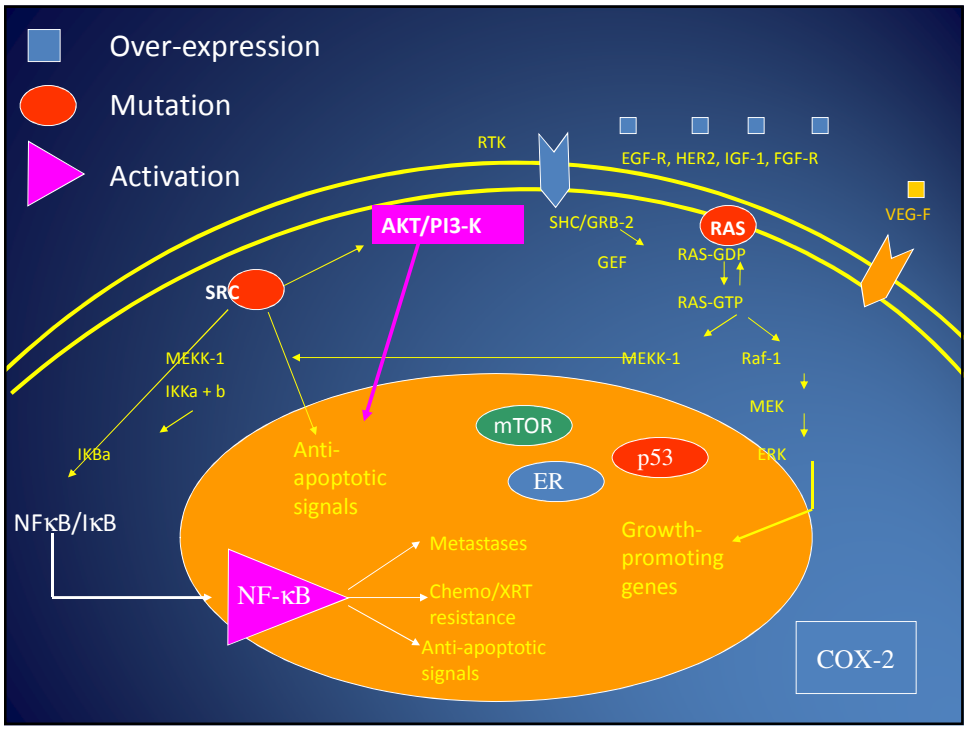
- Capture, quantitate, and profile circulating tumor cells from blood.
- Capture, quantitate, and profile cell-free DNA from blood.

Iacobuzio-Donahue C et al. JCO 2009

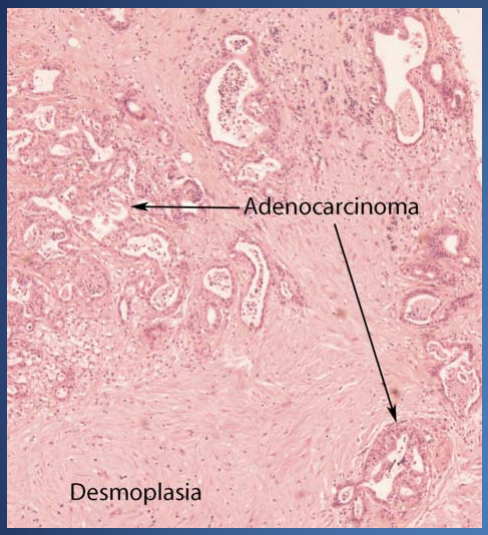
Future Directions
Functional Imaging

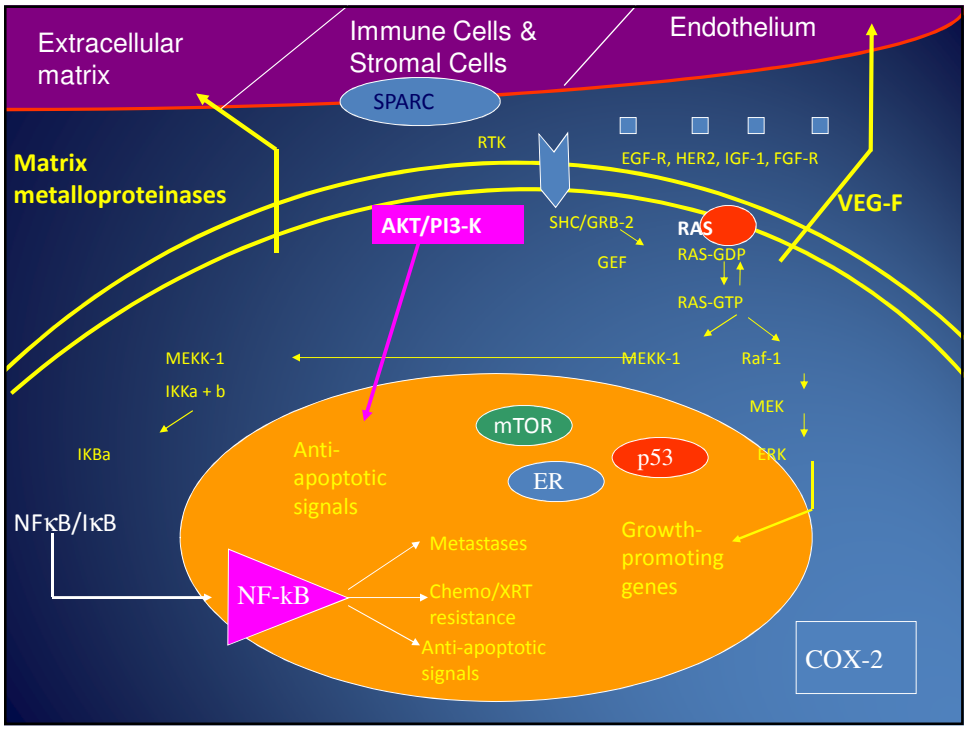


July, 2011 October, 2011 January, 2012



Tumor and its Microenvironment





Molecular Agents to alter the stroma or microenvironment

- Hedgehog inhibitors
- FGF inhibitors
- Immunotherapy!
  - CD40 angonists deplete tumor stroma in PC

Summary-1

- Pancreatic cancer is preventable and possibly chemopreventable.
- Pancreatic cancer is CHANGING!
  - Smoking declining
  - Obesity/Type II/Metabolic Syndrome on the rise (for now)
- We have made virtually no progress with a surgery first anything else second approach to patients with resectable disease.
- Preoperative therapy helps identify bad tumor biology, bad protoplasm, and when used with radiation may help improve margin negative resections.

Summary-2

- Locally advanced pancreatic cancer is an important stage of disease for further investigation of induction cytotoxic chemotherapy followed by chemoradiation for those patients who prove to have more favorable biology.
- Metastatic disease remains a challenge and thus far, molecular therapies have had no impact.
- Combination chemotherapy regimens do improve survival but when given at standard doses, must be limited to patients with good performance status.
- Lower doses of cytotoxic therapy are active and may preserve QOL particularly for less fit patients.

Summary-3

- Future treatments will be based on personalized medicine
  - Based on biopsy and profiling the tumors
  - Isolating circulating tumor cells or circulating DNA
  - Functional imaging with novel radiolabelled probes may help avoid biopsies or tumor cell profiling altogether
- More Focus on the tumor microenvironment
  - Modulating molecular drugs
  - Immunologic therapies

What Can I do?

1. Do NOT panic! Don't let a surgeon or oncologist tell you to BEGIN treatment right away.
2. Consider an opinion at a major medical center.
3. Stay active!
4. Have a positive attitude.
5. Be a realistic optimist!
6. Eat SMART!