Understanding Pancreatic Cancer: Treatment Approaches

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DukeMedicine

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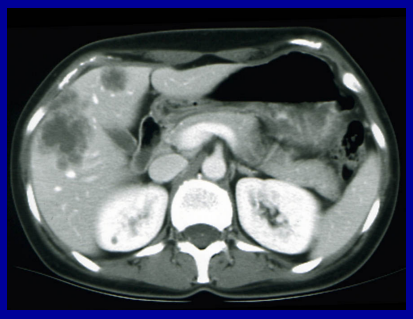
ADVANCE RESEARCH. SUPPORT PATIENTS. CREATE HOPE.

What is "Pancreatic Cancer"?

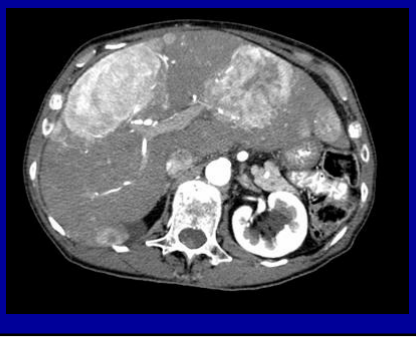
Adenocarcinoma

- 95% of all pancreas tumors
- Faster growth rate
  - Changes in weeks / months
- Hypovascular (fewer blood vessels)



Neuroendocrine

- 4% of all pancreas tumors
- Slower growth rate
  - Changes in months / years
- Hypervascular (more blood vessels)



What is “Pancreatic Cancer”?

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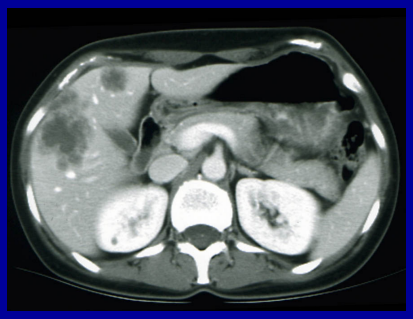


The problem

2012

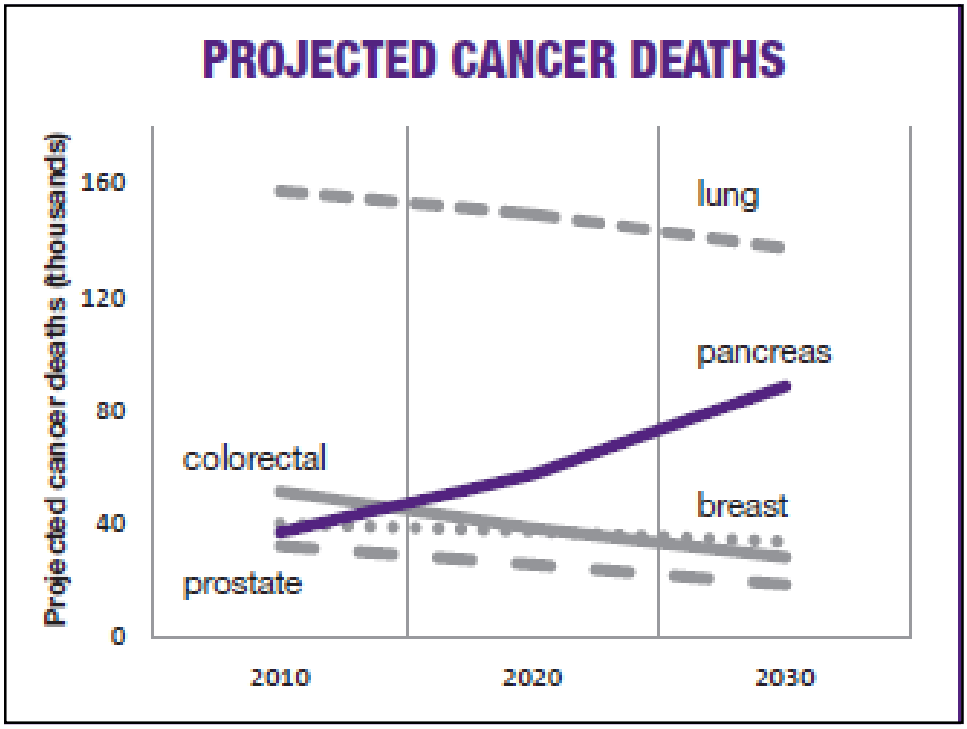
~ 44,000 new cases

~ 37,000 deaths

Siegel et al. CA, 2012

Males			Females		
Prostate	241,740	29%	Breast	226,870	29%
Lung & bronchus	116,470	14%	Lung & bronchus	109,690	14%
Colon & rectum	73,420	9%	Colon & rectum	70,040	9%
Urinary bladder	55,600	7%	Uterine corpus	47,130	6%
Melanoma of the skin	44,250	5%	Thyroid	43,210	5%
Kidney & renal pelvis	40,250	5%	Melanoma of the skin	32,000	4%
Non-Hodgkin lymphoma	38,160	4%	Non-Hodgkin lymphoma	31,970	4%
Oral cavity & pharynx	28,540	3%	Kidney & renal pelvis	24,520	3%
Leukemia	26,830	3%	Ovary	22,280	3%
Pancreas	22,090	3%	Pancreas	21,830	3%
All Sites	**848,170**	**100%**	**All Sites**	**790,740**	**100%**

Males			Females		
Lung & bronchus	87,750	29%	Lung & bronchus	72,590	26%
Prostate	28,170	9%	Breast	39,510	14%
Colon & rectum	26,470	9%	Colon & rectum	25,220	9%
Pancreas	18,850	6%	Pancreas	18,540	7%
Liver & intrahepatic bile duct	13,980	5%	Ovary	15,500	6%
Leukemia	13,500	4%	Leukemia	10,040	4%
Esophagus	12,040	4%	Non-Hodgkin lymphoma	8,620	3%
Urinary bladder	10,510	3%	Uterine Corpus	8,010	3%
Non-Hodgkin lymphoma	10,320	3%	Liver & intrahepatic bile duct	6,570	2%
Kidney & renal pelvis	8,650	3%	Brain & other nervous system	5,980	2%
All Sites	**301,820**	**100%**	**All Sites**	**275,370**	**100%**


PROJECTED CANCER DEATHS
Projected cancer deaths (thousands)
160
120
80
40
0
2010
2020
2030
lung
pancreas
colorectal
breast
prostate


…but signs of progress!
45000
43000
41000
39000
37000
35000
33000
31000
29000
27000
25000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
New Cases
Deaths
Jemal et al. CA, 2002-2010.

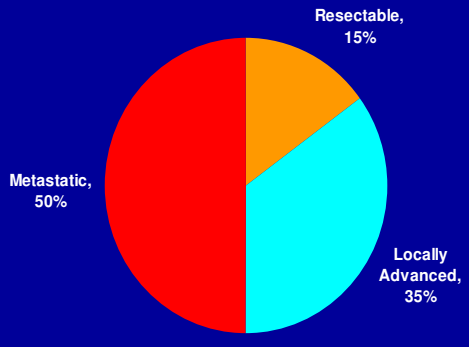
Why is it so deadly?

Early symptoms are non-specific.

- Loss of appetite (anorexia)
- Weight loss
- Blood clots ("Trousseau's sign")
- Diabetes mellitus
- Depression
- Jaundice
- Abdominal pain

Why is it so deadly?

No good screening study → most patients are unresectable at presentation.



CA19-9

- Carbohydrate (sugar) secreted by some cancer cells
- Useful for monitoring response to therapy but…
- 5-15% of population cannot make this marker
- Not sensitive for small tumors
- Also secreted in some benign conditions

Why is it so deadly?

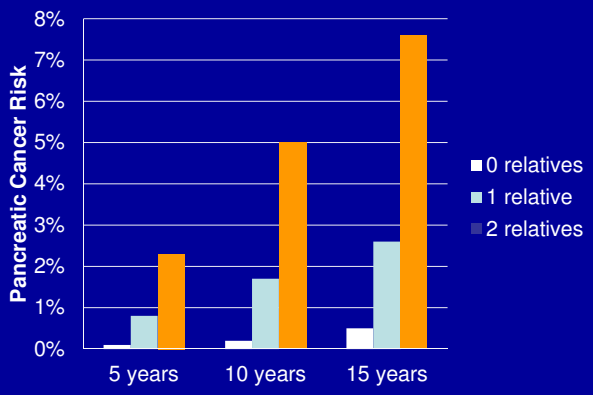
It can affect anyone; no "high risk" population.

- Age (mean=60's, range=30-100+)
- Tobacco abuse (1.3X → 2.5X)
- Chronic pancreatitis (3X)
- Obesity (BMI ≥ 30=1.7X)
- Diabetes (2X → 5X for new-onset)
- Family history (5-10% of patients)

High risk population eligible for screening

- Family history of pancreatic cancer involving:
  - 2 first degree relatives OR
  - 3 relatives (1st, 2nd or 3rd degree)
- Peutz-Jeghers, FAMMM/p16, hereditary pancreatitis
- One 1st or 2nd degree relative with pancreatic cancer and positive for one of the following:
  - BRCA2
  - BRCA1
  - PALB2
  - Lynch syndrome

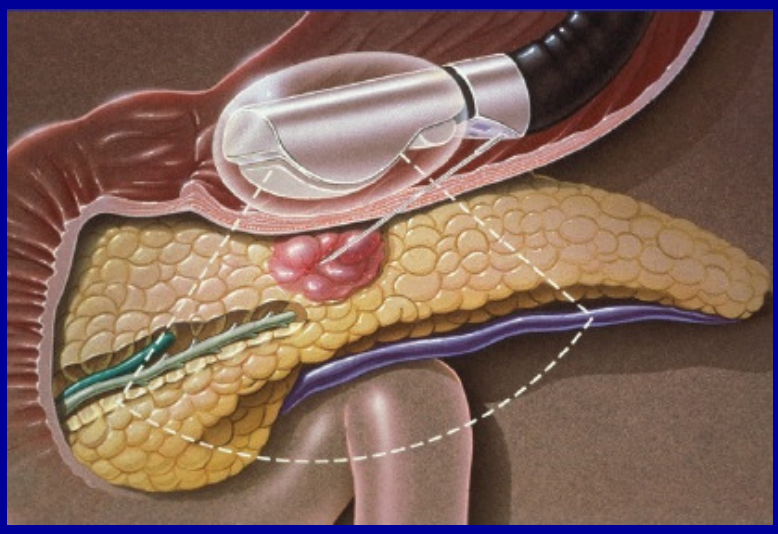
High risk populations



60 year old male with 0 - 2 first degree relatives with onset of pancreatic cancer at 60 years old.

PancPRO (University of Texas)

Endoscopic ultrasound (EUS)



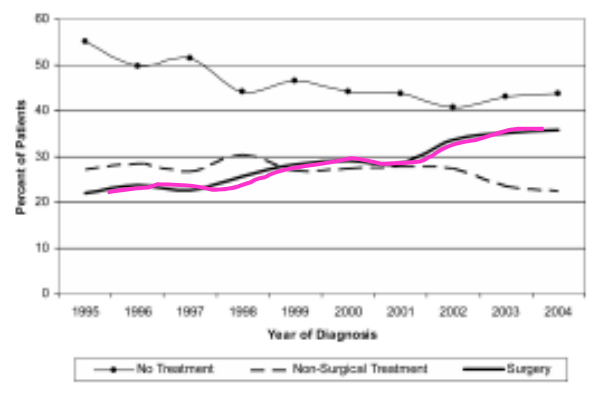
Why is it so deadly?

It is difficult to treat.

- Complicated anatomy ("Don't mess with the pancreas.")
- Unique tumor microenvironment
- PESSIMISM

Failure to operate

Proportion of patients with stage I disease undergoing surgical therapy.



Bilimoria et al., Annals of Surgery, 2007

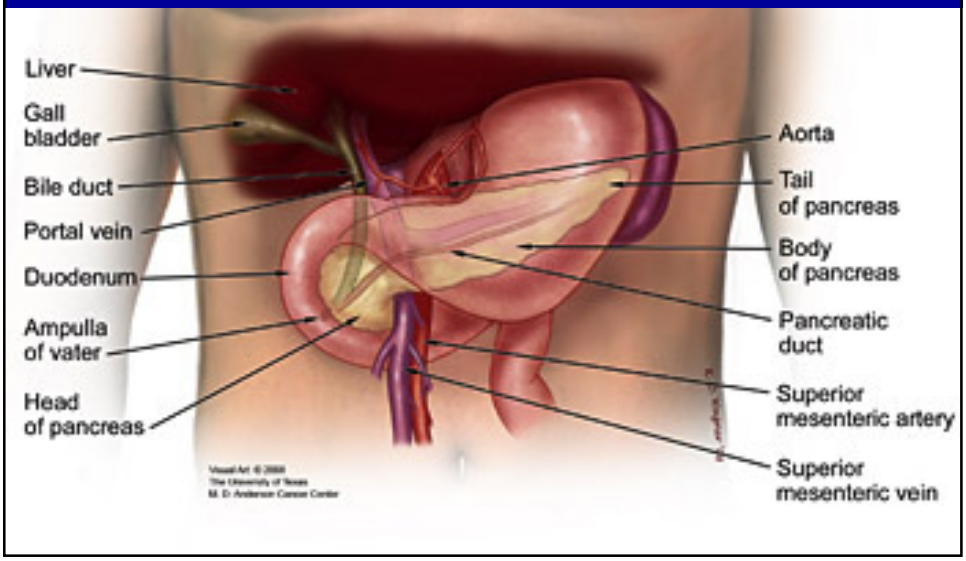
Treatment principles

- Resection is necessary for cure.
- Resection is not usually sufficient for cure.
- Resection is not beneficial unless all disease can be removed.
- Treatment is guided by stage and location.
- Quantity of life is not the only goal.

Staging

AJCC Staging	Practical Categorization
IA: < 2 cm; in pancreas	Resectable Disease
IB: > 2 cm; in pancreas	
IIA: extends out of pancreas	
IIB: involves local nodes	
III: involves large vessels	"Borderline" Resectable Disease
	Locally Advanced Disease
IV: metastatic	Metastatic Disease

Anatomy

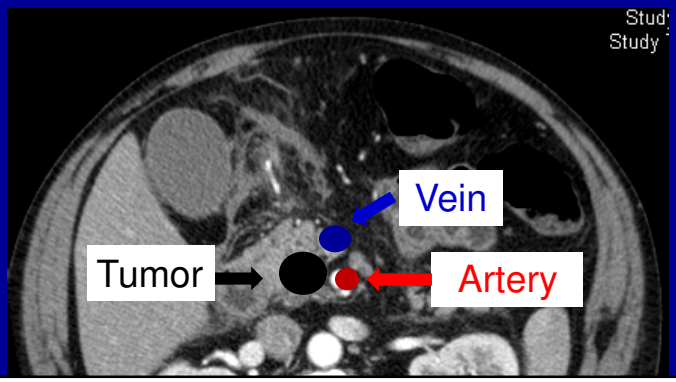


Staging/Resectability

"Resectable" =

no metastatic disease

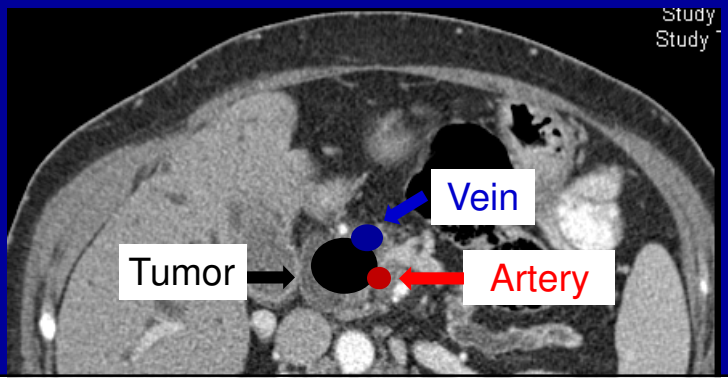
no involvement of adjacent blood vessels



Staging/Resectability

"Borderline resectable" =

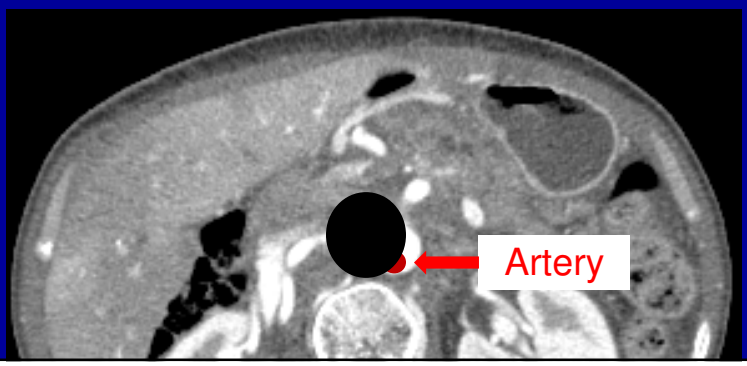
limited vascular involvement that is technically resectable



Staging/Resectability

"Locally advanced" =

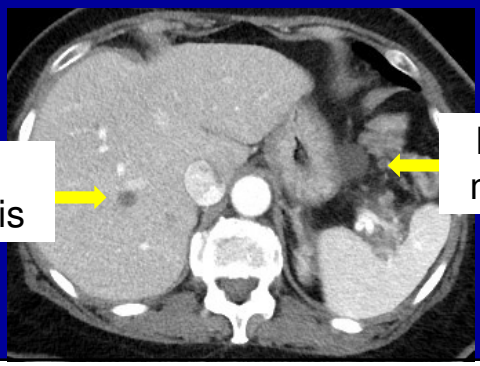
arterial encasement OR non-reconstructable venous occlusion



Staging/Resectability

"Metastatic" =

Disease outside the region of the pancreas (liver, peritoneal surfaces, lung)



Treatment—metastatic disease

- Cytotoxic chemotherapy
  - Not specific for cancer cells but kills all rapidly dividing cells
  - 5-fluorouracil (5-FU) or capecitabine (oral 5-FU)
  - Gemcitabine (Gem)
  - Oxaliplatin
  - Irinotecan
- "Targeted" or "biologic" therapies
  - Epidermal Growth Factor Receptor (EGFR) inhibitors
  - Vascular Endothelial Growth Factor (VEGF) inhibitors
  - Nab-paclitaxel (Abraxane)

Treatment—metastatic disease

Randomized controlled trials (a.k.a. phase III trials) determine which treatments are most effective.

Improvements in Survival and Clinical Benefit With Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial

By Howard A. Burris III, Malcolm J. Moore, John Andersen, Mark R. Green, Mace L. Rothenberg, Manuel R. Modiano, M. Christine Cripps, Russell K. Portenoy, Anna Maria Storniolo, Peter Tarassoff, Robert Nelson, F. Andrew Dorr, C.D. Stephens, and Daniel D. Von Hoff

- Median survival with Gem only 6 weeks longer than 5-FU but…
- Very well tolerated and "clinical benefit response" in >20% of patients.

Burris et al., Journal of Clinical Oncology, 1997.

Treatment—metastatic disease

Targeted/biologic therapies have (until recently) not made a big impact.

Erlotinib Plus Gemcitabine Compared With Gemcitabine Alone in Patients With Advanced Pancreatic Cancer: A Phase III Trial of the National Cancer Institute of Canada Clinical Trials Group

Malcolm J. Moore, David Goldstein, John Hamm, Arie Figer, Joel R. Hecht, Steven Gallinger, Heather J. Au, Pawel Murawa, David Walde, Robert A. Wolff, Daniel Campos, Robert Lim, Keyue Ding, Gary Clark, Theodora Voskoglou-Nomikos, Mieke Ptasynski, and Wendy Parulekar

- EGFR inhibitor erolitinib (Tarceva) + Gem improved survival by 2 weeks vs. Gem alone
- First positive study of Gem + Drug X…

Moore et al., Journal of Clinical Oncology, 2007.

Treatment—metastatic disease

A combination of colon cancer drugs (5-FU + oxaliplatin + irinotecan = FOLFIRINOX) is at least twice as effective as Gem but at a price...

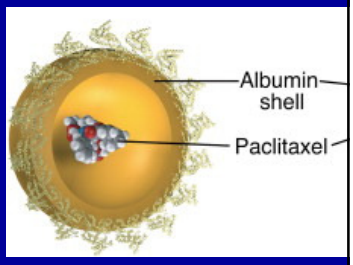
Adverse Event	FOLFIRINOX (N = 171)	Gem (N = 171)	P-value
Neutropenia (low WBC)	46%	21%	< 0.001
Febrile Neutropenia	5%	1%	0.03
Thrombocytopenia (low platelets)	9%	4%	0.04
Fatigue	24%	18%	NS
Vomiting	15%	8%	NS
Diarrhea	13%	2%	< 0.001
Neuropathy	9%	0%	< 0.001

Conroy T et al., New England Journal of Medicine 2011

Treatment—metastatic disease

Although not truly a "targeted" therapy, Abraxane (albumin-bound Paclitaxel, a cytotoxic drug) is attracted to proteins on tumor cells.

- Gem + Abraxane improved survival and response by ~30% over Gem alone.
- Intermediate efficacy and toxicity between Gem and FOLFIRINOX
- Recently FDA-approved for pancreatic cancer!



Von Hoff D et al., New England Journal of Medicine 2013

Treatment—locally advanced tumors

- Chemotherapy
- Radiation therapy
  - Internal radiation (brachytherapy)—rarely used
  - External Beam Radiation Therapy (EBRT)

Treatment—locally advanced tumors

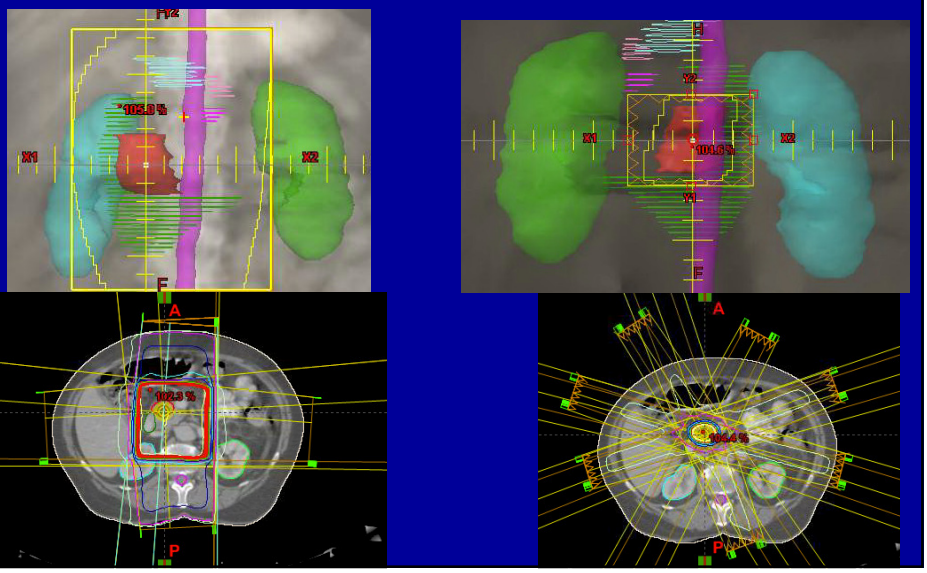
External Beam Radiation Therapy

- Standard RT
- Intensity-Modulated RT (IMRT)

} 5 days/week x 5 weeks

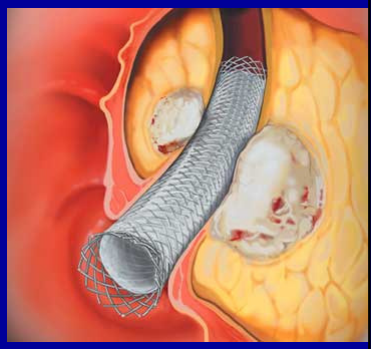
- Stereotactic Body Radiation Therapy (SBRT or Cyberknife™)
  - Precise tumor localization
  - Larger dose/fraction
  - Fewer number of fractions (1-5 treatments)
- RT improves survival and symptoms (but unknown which method is best)

Standard RT vs. SBRT



Treatment—locally advanced tumors

- Cytotoxic chemotherapy
- Radiation therapy
- Endoscopic palliation
  - Bile duct stents for relief of jaundice
  - Duodenal stents for relief of nausea/vomiting due to obstruction
  - Celiac plexus nerve blocks for pain relief



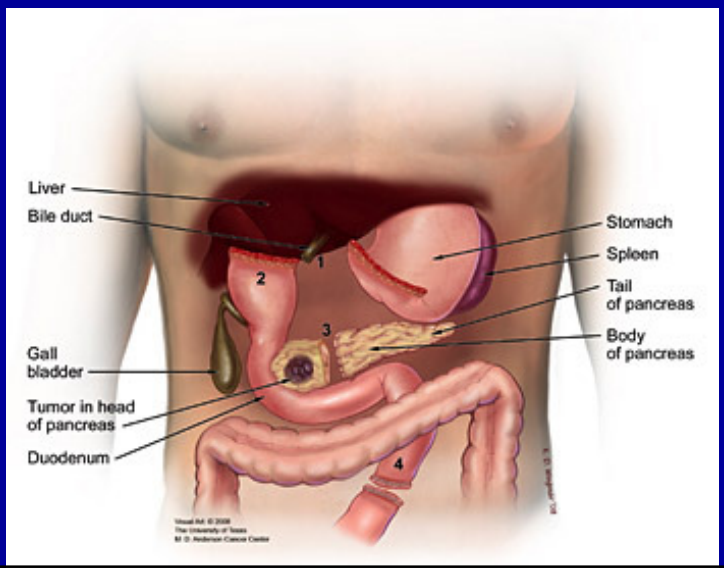
Treatment—locally advanced tumors

- Cytotoxic chemotherapy
- Radiation therapy
- Endoscopic palliation
- Experimental therapies
  - Radiofrequency (thermal) ablation
    - Pancreatitis
    - "Heat-sink" effect from vessels
  - Irreversible (non-thermal) electroporation
    - No "heat-sink" effect
    - Promising phase I/II data

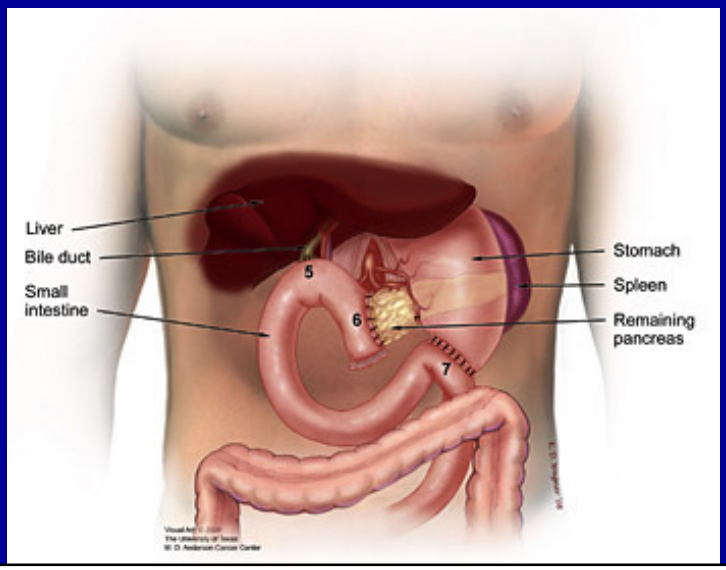
Treatment—resectable tumors

- Resection is necessary but usually not sufficient for cure.
- High rates of recurrence with resection alone
  - Local (the tumor bed)
  - Regional (lymph nodes)
  - Distant (liver, lungs, peritoneum)
- Type of resection depends on location

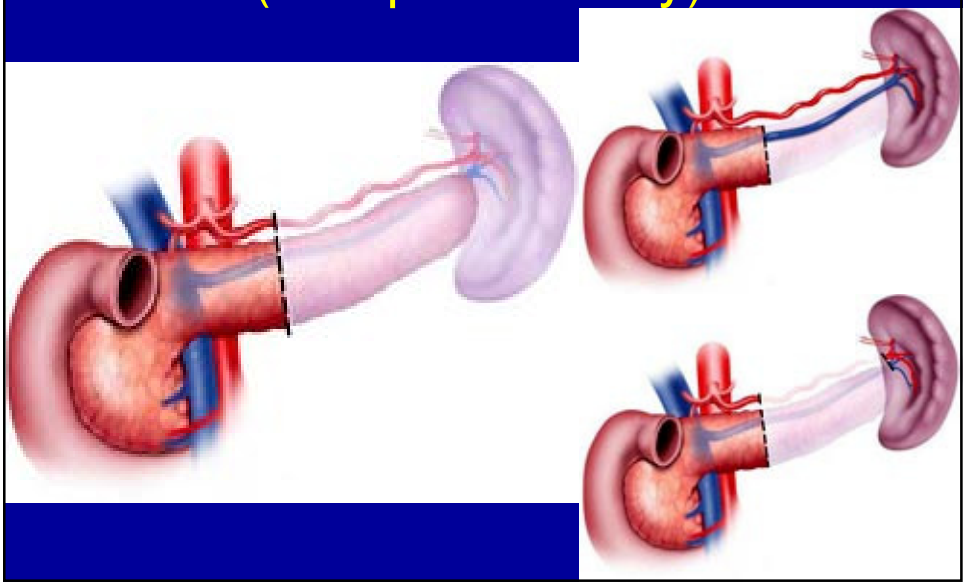
Pancreaticoduodenectomy (a.k.a. Whipple procedure)



Pancreaticoduodenectomy (a.k.a. Whipple procedure)

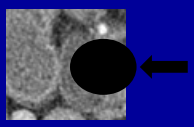


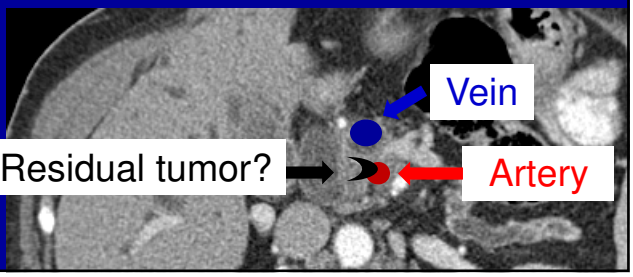
Distal pancreatectomy (+/- splenectomy)



Why can't you just take out the whole pancreas?

The most common site of a "positive margin" and local recurrence is along the blood vessels, not where we divide the pancreas.

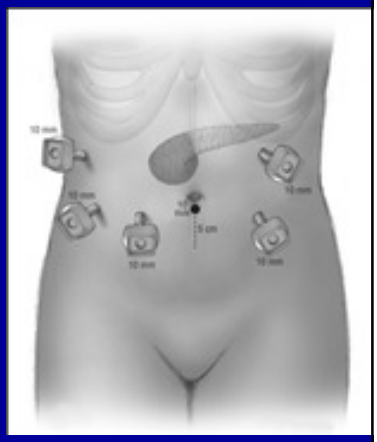




Treatment—resectable tumors

Minimally invasive surgery

- Laparoscopic distal pancreatectomy is common.
- Laparoscopic Whipple is possible but steep learning curve.
- Data suggest shorter hospital stays and comparable lymph node harvest rates.



Kendrick M. Archives of Surgery 2010

Treatment—resectable tumors

"Adjuvant" therapy

- Given after resection to treat presumed microscopic disease
- Nothing to measure
- Arbitrary duration (usually ~4-6 months)
- Role of radiation therapy highly controversial…

Adjuvant Therapy

An alphabet soup of clinical trials

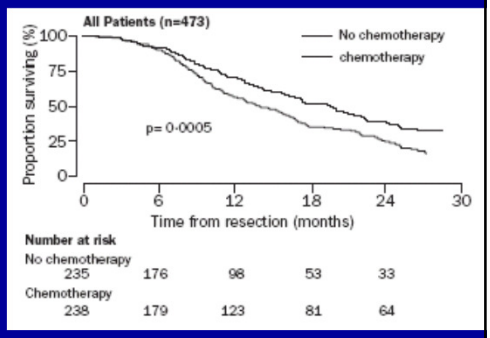
- [1]GITSG 9173: 5-FU + XRT > Observation
- [2]ESPAC-1: 5-FU > no chemo; no XRT > XRT
- [3]CONKO-001: Gem > Observation
- [4]ESPAC-3: Gem = 5-FU
- [5]RTOG 9704: Gem vs 5-FU → XRT → Gem vs 5-FU
  - Gem = 5-FU (except Gem maybe a "winner" in head of pancreas subset)

[1]Kalser et al. Arch Surg 1985; [2]Neoptolemos JP et al. NEJM 2004; [3]Oettle H et al. JAMA 2007; 4Neoptolemos JP et al. JAMA 2009;; [5]Regine WF et al. JAMA 2008

Adjuvant Therapy

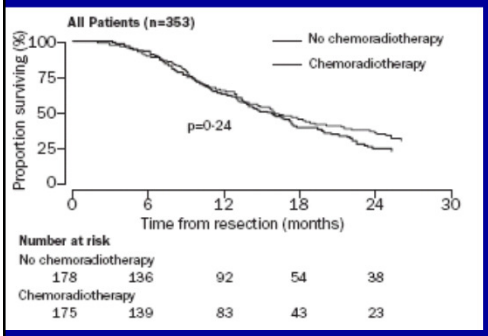
ESPAC-1

- Did NOT compare chemotherapy directly to chemoradiation
- Really 2 studies in one (chemo vs. no chemo and XRT vs. no XRT)
- Positive study for chemotherapy alone



Adjuvant Therapy

ESPAC-1



- Slightly (but not statistically significant) worse survival with chemoradiation
- Heavily criticized study: no radiation quality control, lots of off-protocol treatment

Conclusions: Adjuvant Therapy

- Gem = 5-FU
- Gem vs Gem + 5-FU being studied in ESPAC-4
- Radiation no longer used as adjuvant therapy in Europe
- Role of radiation will hopefully be answered in US with current RTOG-0848 trial

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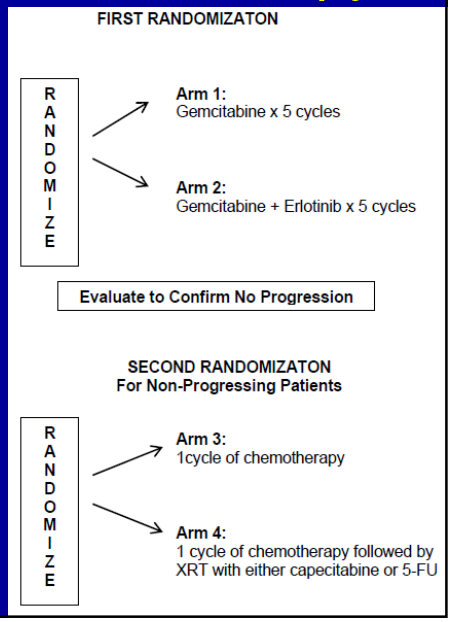


Traditional approach to resectable tumors = "surgery first"

- High incidence of positive lymph nodes and/or positive margins
- Outcomes with positive lymph nodes and/or positive margins are worse.
- Adjuvant therapy (chemotherapy +/- radiation) appears to improve survival…
- But ¼ to ½ of patients who undergo resection do not receive intended postoperative therapy.

Theoretical benefits of "neoadjuvant" (preoperative) therapy

- Delivery of therapy while blood supply to tumor is intact
- Assurance that all patients who undergo resection receive multimodality therapy
- Potential to improve resectability (greater likelihood of achieving negative margins)
- Opportunity for patients with aggressive tumor biology to manifest themselves and avoid a non-beneficial operation

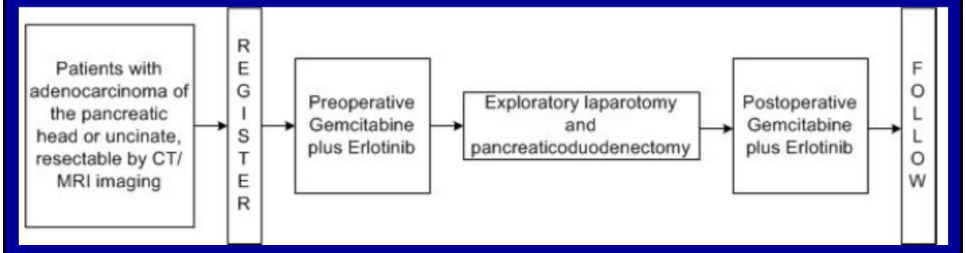
Recent studies of neoadjuvant therapy for resectable pancreatic cancer

Author	N	Regimen	# of patients resected (%)	Median survival (months)
Talamonti 2006	20	XRT+Gem	17 (85%)	26
Varadhachary 2008	90	Gem+Cis → XRT+Gem	52 (58%)	31
Evans 2008	86	XRT+Gem	64 (74%)	34
Takai 2008	32	XRT+5-FU+Cis	24 (75%)	20
Clavien 2008	28	Gem+Cis	24 (86%)	26
Papalezova (Duke) 2012	144	XRT+5-FU	76 (53%)	27

Conclusions: Neodjuvant Therapy

- Neoadjuvant therapy helps to select patients who are most likely to benefit from resection but is controversial for resectable tumors.
- Role of radiation in neoadjuvant therapy is being questioned (just like adjuvant setting).
- An ideal platform to study novel therapies
- Randomized controlled trials are the only way to definitively compare neoadjuvant approaches to each other and to “surgery first”.

First national cooperative group trial of neoadjuvant therapy for resectable pancreatic cancer (ACOSOG Z5041)



Treatment—borderline resectable tumors

- Neoadjuvant therapy is NOT controversial.
- 30-40% of patients are able to undergo successful resection after neoadjuvant therapy.
- Vascular resection is often required to achieve negative margins.

Treatment—borderline resectable tumors

Should we resect veins?

- Vein involvement used to be considered a contraindication to resection…
- Not anymore!
  - Acceptable complication rates
  - Survival comparable to tumors of similar size without venous involvement

Treatment—borderline resectable tumors

Should we resect arteries?

Still probably not...

- Arterial invasion is associated with positive lymph nodes and poor prognosis
- Resection of superior mesenteric artery causes severe diarrhea due to disruption of nerves that run parallel
- Resection of hepatic arteries in very select circumstances

Where have we made progress?

- Greater use of multimodality therapy
- More accurate staging
- Safer surgery

Where have we made progress?

Safer surgery

- Advances in perioperative care, anesthesia
- Better instruments?
- Minimally invasive approaches?
- Better surgeons?

Centralization of surgery

Association between hospital volume and outcomes

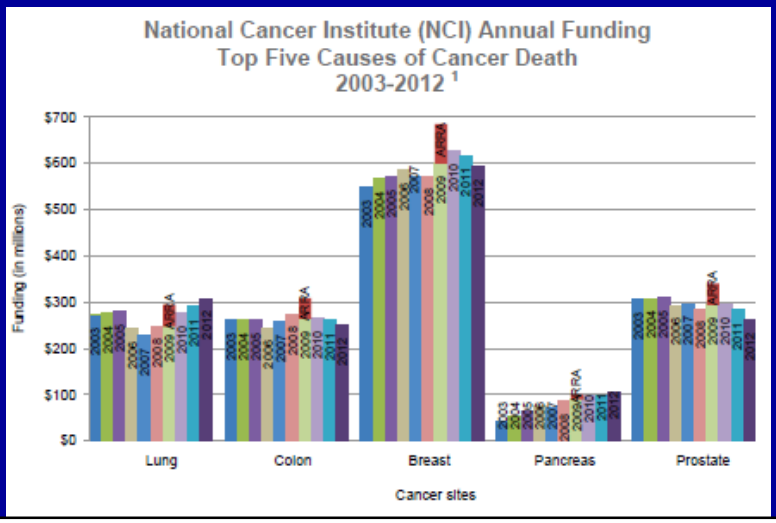
# cases/year	mortality
<1	16%
1-2	14%
3-5	11%
>16	4%

Birkmeyer et al. New England Journal of Medicine 2002

Where do we need to make progress?

- Non-invasive screening test
- More effective drugs
- More research funding for pancreatic cancer!

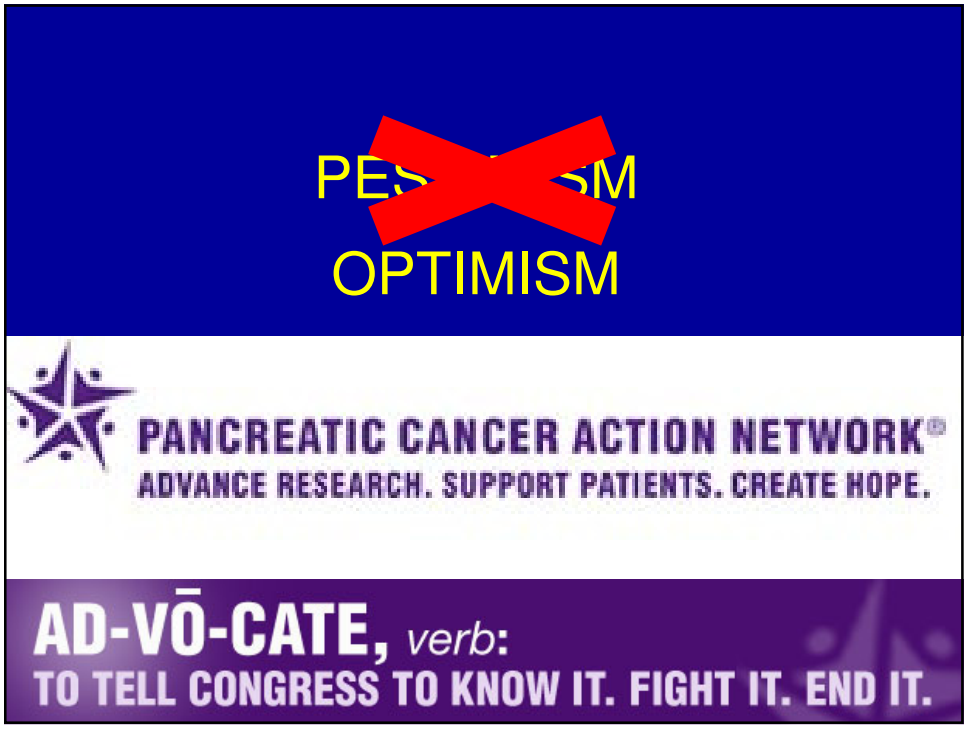
Where do we need to make progress?



Famous victims have increased visibility.

Summary

- Pancreatic cancer requires a multimodality approach…
- But which modalities—and in what order?
- Clinical trial participation should be encouraged.
- Pancreatic cancer research has led to (and will continue to lead to) promising new treatment approaches.


OPTIMISM
PANCREATIC CANCER ACTION NETWORK®
ADVANCE RESEARCH. SUPPORT PATIENTS. CREATE HOPE.
AD-VŌ-CATE, verb:
TO TELL CONGRESS TO KNOW IT. FIGHT IT. END IT.