A Teaching Affiliate of Harvard Medical School

Novel Treatment Approaches in Pancreatic Cancer

Janet E. Murphy, MD MPH

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Objectives

- Provide orientation to pancreas cancer
- Discuss the different stages of the disease
- Review state-of-the-art treatments, focusing on our approach for different stages of the disease
- A few words about immunotherapy
- Provide a personal viewpoint on this disease
- Question period

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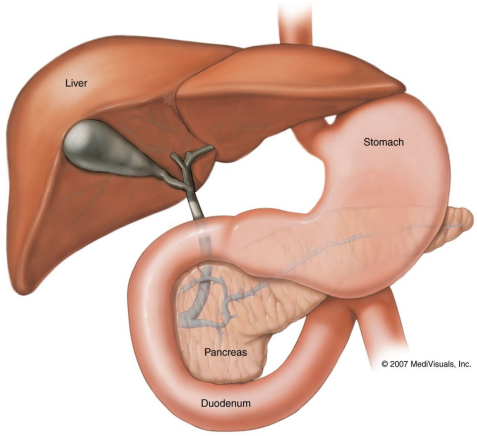
Background

Pancreatic Anatomy



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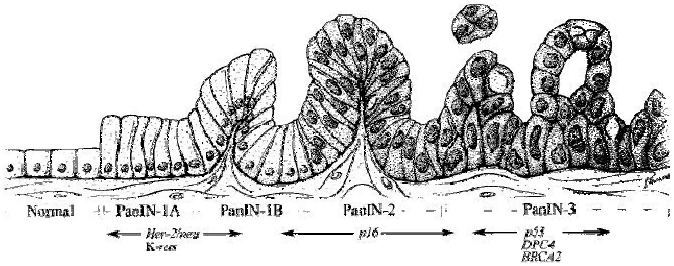
The origins of invasive pancreas cancer



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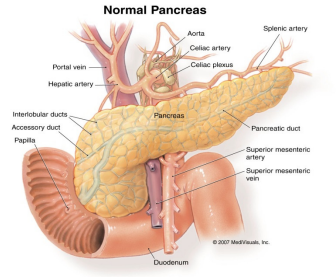
How Medical Oncologists Think About Pancreatic Cancer

Can the cancer be taken out with a surgery?

YES — **NO**

Resectable (20%)	Borderline resectable	Locally Advanced	Metastatic (53%)



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Can the cancer be taken out with a surgery?

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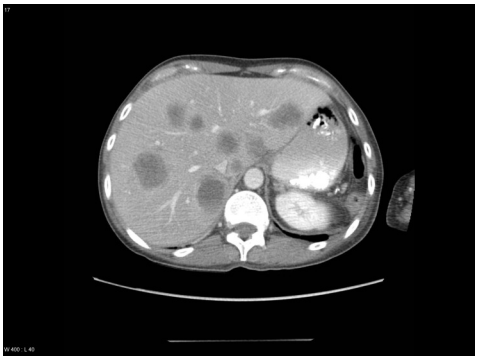

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FOLFIRINOX

PRODIGE4/ACCORD11 study – France

Combination chemotherapy:

5FU + Oxaliplatin + Irinotecan

VS

Gemcitabine

Criteria for enrollment:

- **75 years old or younger**
- **Very fit**

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

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

Conroy *et al* NEJM May 2011

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Gemcitabine-Abraxane

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

Efficacy Variable	nab-Paclitaxel plus Gemcitabine (N=431)	Gemcitabine Alone (N=430)	Hazard Ratio or Response-Rate Ratio (95% CI)*	P Value
Overall survival				
Median overall survival — mo (95% CI)	8.5 (7.9–9.5)	6.7 (6.0–7.2)	0.72 (0.62–0.83)	<0.001
Survival rate — % (95% CI)				
6 mo	67 (62–71)	55 (50–60)		<0.001
12 mo	35 (30–39)	22 (18–27)		<0.001
18 mo	16 (12–20)	9 (6–12)		0.008
24 mo	9 (6–13)	4 (2–7)		0.02
Progression-free survival				
Median progression-free survival — mo (95% CI)	5.5 (4.5–5.9)	3.7 (3.6–4.0)	0.69 (0.58–0.82)	<0.001
Rate of progression-free survival — % (95% CI)				
6 mo	44 (39–50)	25 (20–30)		
12 mo	16 (12–21)	9 (5–14)		
Response				
Rate of objective response				
Independent review				
No. of patients with a response	99	31	3.19 (2.18–4.66)	<0.001
% (95% CI)	23 (19–27)	7 (5–10)		
Investigator review				
No. of patients with a response	126	33	3.81 (2.66–5.46)	<0.001
% (95% CI)	29 (25–34)	8 (5–11)		
Rate of disease control†				
No. of patients	206	141	1.46 (1.23–1.72)	<0.001
% (95% CI)	48 (43–53)	33 (28–37)		
Best response according to independent review — no. (%)				
Complete response	1 (<1)	0		
Partial response	98 (23)	31 (7)		
Stable disease	118 (27)	122 (28)		
Progressive disease	86 (20)	110 (26)		
Could not be evaluated‡	128 (30)	167 (39)		

"MPACT" study - International

- 10% of patients were older than 75
- 7-8% of patients were less "fit"

VonHoff *et al* NEJM Oct 2013

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"FOLFIRINOX-Plus" Studies in Metastatic Disease

- FOLFIRINOX-LDE 225 (inhibits the "smoothened" pathway, crucial for cancer stem cell maintenance, tissue repair, and proliferation)
- FOLFIRINOX-IPI-926 (inhibits the hedgehog pathway, which interacts with the smoothened pathway)
- FOLFIRINOX-PEGPh20 (hyaluronidase, which breaks down the thick rind around pancreas cancers to enhance drug delivery)
- FOLFIRINOX followed by Immunotherapy

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"Gem-abraxane-plus" studies in metastatic disease

- M402 and ODSH (heparin like molecules with anti-cancer properties)
- PEGPh20 (hyaluronidase)
- Vanictumab and OMP-54F28 (antibodies against Wnt pathway, which allows cancer cell proliferation)
- OMP-59R5 (antibody against Notch3 pathway, which allows cancer cell proliferation and blood vessel formation)
- Dovitinib (small molecule that binds FGFR3, which allows cancer cell proliferation and blood vessel formation)

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“Gem-abraxane-plus” studies in metastatic disease

- Bevacizumab (Avastin – antibody which prevents blood vessel formation)
- PLX7486 (binds several tyrosine kinases which promote cell survival and proliferation)
- IDO inhibitor (blocks the IDO pathway, which supresses the body’s immune system and is overactive in cancer)
- TH-302 (potent chemotherapy that is only activated in low-oxygen conditions like tumors with poor blood supply)

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“Gem-abraxane-plus” studies in metastatic disease

- LCL-161 (small molecule that inhibits anti-cell death proteins in cells to increase sensitivity to cell death with chemotherapy)
- Erlotinib (small molecule that binds to the epidermal growth factor receptor on cell surfaces)
- OGX-427 (inhibits production of Hsp27, a heat-shock protein which prevents cell death)
- Additional chemotherapies – capecitabine, cisplatin

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An important benefit to our new choices

- Lesson from colon cancer: incremental addition of multiple lines of therapy extended average survival from six months to greater than two years
- In pancreas cancer, *choice* of options can also lead to *SEQUENCING* of options.
- Common path in fit patients with metastatic disease:
    1) FOLFIRINOX
    2) Gem-Abraxane
    3) Clinical trial

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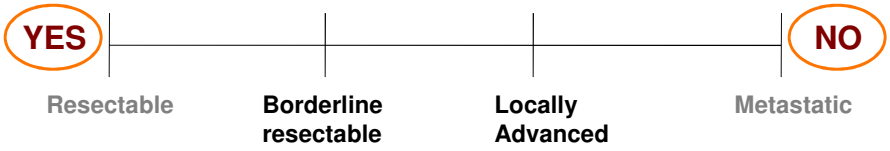
Can the cancer be taken out with a surgery?



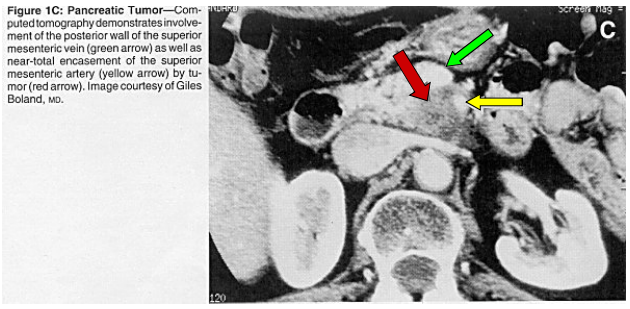


Figure 1C: Pancreatic Tumor—Computed tomography demonstrates involvement of the posterior wall of the superior mesenteric vein (green arrow) as well as near-total encasement of the superior mesenteric artery (yellow arrow) by tumor (red arrow). Image courtesy of Giles Boland, MD.

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Can we convert these cancers to resectable?

- Mainstay of treatment: chemotherapy – to prevent spread and sterilize "micrometastatic" disease.
- The holy grail of locally advanced disease – to get patients to an operation – the only curative treatment.
- Historical rates of conversion very low – less than 10% with gemcitabine chemotherapy.
- HOWEVER, FOLFIRINOX and Gem-Abraxane demonstrate significant ***response rates*** – far higher than gemcitabine alone.

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Superior Response Rates of both FOLFIRINOX and Gem-Abraxane

Table 2. Objectiv

Variable
Response — no.
Complete res
Partial respor
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Progressive d
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95% CI
Rate of disease c
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95% CI
Response duratic
Median
95% CI

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MGH Experience So Far – FOLFIRINOX in LAPC

- 22 patients with LAPC
- 12/22 patients were taken to the operating room for exploration (most with radiation after chemo).
- 5/12 patients underwent R0 resections
- 7/12 patients had surgically unresectable disease, and six of these patients had intraoperative radiation therapy (IORT) administered
- Of the six undergoing IORT, only one patient has experienced progressive disease
- R0 resection rate of 23% (5 of 22 patients) may reflect a new era of converting locally advanced pancreatic cancer into resectable pancreatic cancer with the use of FOLFIRINOX.

Table 3. Objective response rate

Response level	No. of patients (*n* = 22)	Point estimate (%)	95% confidence interval
Complete response	0	0.0	NA
Partial response	6	27.3	(10.7–50.2)
Stable disease	16	72.7	(49.8–89.3)
Progressive disease	0	0.0	NA

Abbreviation: NA, not available.

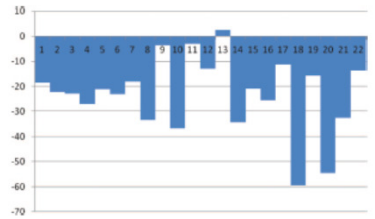

Figure 2. Waterfall plot of maximum percent change from baseline scans during FOLFIRINOX treatment.

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Is there a role for radiation therapy in LAPC?

- Controversial!
- LAP-07 study – ASCO 2013
- Patients randomized to 4 months of gemcitabine vs gemcitabine/erlotinib
- Patients who did not have progression were further randomized to radiation therapy
- No difference in progression-free and overall survival
- What about quality of life? Pain reduction? Time off therapy?

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Strategic additions to chemotherapy in LAPC

Goal: enhance chemotherapy delivery

- FOLFIRINOX Losartan (anti-hypertension drug which has the potential to decrease collagen production around the tumor)
- FOLFIRINOX-PEGPh20 (hyaluronidase)

Goal: Decrease inflammation and enhance immune response

- FOLFIRINOX-PF-04136309 (inhibits inflammation response, proliferation, metastasis)
- FOLFIRINOX or Gem/Abraxane + Algenpantucel-L (vaccine which enhances body's immunity against cancer)

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Summary: What can we hope for in patients with unresectable disease?

- In a small but growing subset, we can convert to "resectable"
- Experimental therapies hope to enhance these odds
- Role of radiation is controversial but, to my view, beneficial
- Potential for durable responses even if surgery is not on the table
- Ultimately, considered by most to be on the spectrum of metastatic disease

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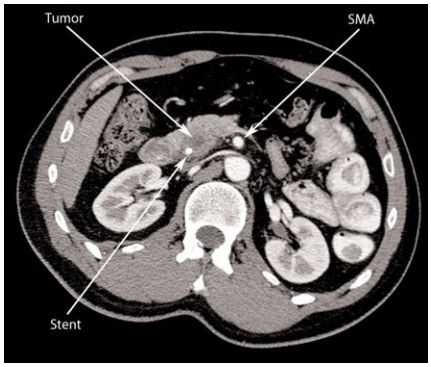
Can the cancer be taken out with a surgery?

Resectable | Borderline resectable | Locally Advanced | Metastatic



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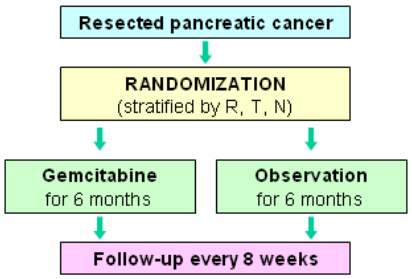
Approaches to the upfront resectable patient

Current standard: Surgery followed by gemcitabine chemotherapy



Gemcitabine after surgery improves:

- **Disease-free survival**
- **Overall survival**

CONKO-001 Study

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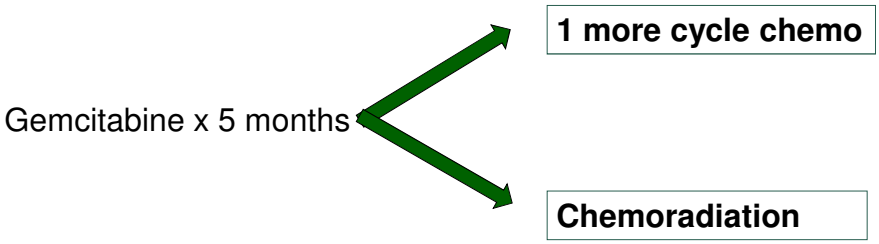
Does radiation enhance the chance of cure?

- Controversial! No definitive study to prove it does.
- RTOG 0848 Study underway



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Improving on this standard

- Giving stronger “adjuvant” chemotherapy
- Giving “neoadjuvant” chemotherapy
- Adding experimental drugs
- Any of the above, with radiation

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Giving stronger “adjuvant” chemotherapy

- ESPAC-4 trial in Europe: adjuvant gemcitabine vs gemcitabine + capecitabine
- Multiple US studies of adjuvant gemcitabine vs gem-abraxane
- Adjuvant FOLFIRINOX
- Adjuvant FOLFOX-Avastin
- Adjuvant Gemcitabine + pancreas cancer vaccine (GVAX)

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Giving “neoadjuvant” chemotherapy

- Neoadjuvant Gem-Abraxane → Surgery
- Neoadjuvant FOLFIRINOX → Surgery
- Neoadjuvant Gem-Abraxane → Radiation → Surgery
- Neoadjuvant FOLFIRINOX→ Radiation → Surgery

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Adding experimental drugs

- Neoadjuvant Gem-Abraxane-LDE225 (Smoothened pathway inhibitor)
- Neoadjuvant Gem-Abraxane-Hydroxychloroquine (anti-malaria drug with anti-cancer properties)
- Neoadjuvant Hydroxychloroquine + Proton beam radiation (Mass General)

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Immunotherapy

- Pancreas cancer evades the immune system.
- Cells secrete chemicals that actively steer immune cells away from the tumor
- This provides a strong rationale for the development of immune therapy in this disease.

1) Vaccines

2) “Checkpoint inhibitors”

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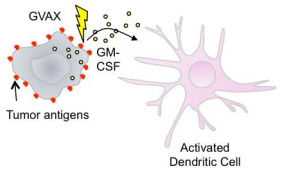
Immune therapy - Vaccines

- How do vaccines work?
- GVAX (previously mentioned in "adjuvant" trial setting)



- Improving on GVAX – how do we rev up the immune system even more?
- Randomized Phase II study at Johns Hopkins
- Patients randomized to GVAX alone versus combination with Listeria vaccine, CRS-207. The two vaccine combination *doubled* the survival time of a small group of patients with advanced pancreatic cancer.
- first positive study that suggests immune therapy has a potential ROLE in pancreas cancer!

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GVAX + CRS 207

3-arm randomized ECLIPSE trial:

- GVAX + CRS 207
- GVAX alone
- Chemotherapy alone

- Target population: previously treated pancreas cancer patients.

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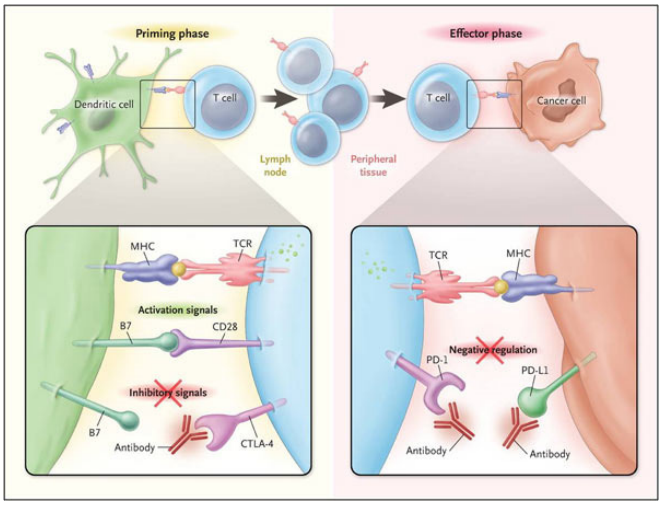
Immune therapy – Checkpoint inhibitors



- **Anti-CTLA4**
- **Anti-PD1**
- **Anti-PDL1**

Tested as single agents and in combination in pancreas cancer in ongoing trials

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Dana-Farber Harvard Cancer Center Clinical Trials

YES — **NO**

Resectable	Borderline resectable	Locally Advanced	Metastatic
Neoadjuvant HCQ with protons Adjuvant gem-abraxane Adjuvant gem-GVAX	Neoadjuvant FOLFIRINOX with Proton beam radiation	Neoadjuvant FOLFIRINOX with Losartan and Proton Beam Radiation	FOLFIRINOX-LDE 225 Gem-abraxane-LDE 225 Gem-abraxane-M402 Gem-abraxane-TH302 Gem-abraxane-PEGPh20

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