Understanding Pancreatic Cancer: Treatment Approaches

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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”? 

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

The problem

2012

~ 44,000 new cases

~ 37,000 deaths

Siegel et al. CA, 2012
...but signs of progress!

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 (1\textsuperscript{st}, 2\textsuperscript{nd} or 3\textsuperscript{rd} degree)
- Peutz-Jeghers, FAMMM/p16, hereditary pancreatitis
- One 1\textsuperscript{st} or 2\textsuperscript{nd} 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.

Billimoria 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

- IA: < 2 cm; in pancreas
- IB: > 2 cm; in pancreas
- IIA: extends out of pancreas
- IIB: involves local nodes
- III: involves large vessels
- IV: metastatic

Practical Categorization

- Resectable Disease
  - “Borderline” Resectable Disease
  - Locally Advanced Disease
  - 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)

Liver metastasis
Peritoneal metastasis

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 I. Rothenberg, Manuel R. Modiano, M. Christina Cripps, Russell K. Portenoy, Anna Maria Stovall, Peter Tomita, 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.


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


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

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...

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>FOLFIRINOX (N = 171)</th>
<th>Gem (N = 171)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia (low WBC)</td>
<td>46%</td>
<td>21%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>5%</td>
<td>1%</td>
<td>0.03</td>
</tr>
<tr>
<td>Thrombocytopenia (low platelets)</td>
<td>9%</td>
<td>4%</td>
<td>0.04</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24%</td>
<td>18%</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15%</td>
<td>8%</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>2%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9%</td>
<td>0%</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

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!

Treatment—locally advanced tumors

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

External Beam Radiation Therapy

- Standard RT
- Intensity-Modulated RT (IMRT)
- 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
    - Pancreatitits
    - “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
Pancreatectoduodenectomy (a.k.a. Whipple procedure)

Pancreatectoduodenectomy (a.k.a. Whipple procedure)
Distal pancreatectomy (+/- splenectomy)

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

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.
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.

“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)


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
Conclusions: Adjuvant Therapy

- Gem = 5-FU
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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

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

<table>
<thead>
<tr>
<th># cases/year</th>
<th>mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>16%</td>
</tr>
<tr>
<td>1-2</td>
<td>14%</td>
</tr>
<tr>
<td>3-5</td>
<td>11%</td>
</tr>
<tr>
<td>&gt;16</td>
<td>4%</td>
</tr>
</tbody>
</table>

Where do we need to make progress?

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

[Bar chart showing National Cancer Institute (NCI) Annual Funding Top Five Causes of Cancer Death 2003-2012]
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.
PESSIMISM
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.