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


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

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

5-6% of cases
Size Really Does Matter!

Li D, et al. JAMA, 2009

Size and Survival

Li D, et al. JAMA, 2009
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?

<table>
<thead>
<tr>
<th>NSABP P-1 Study</th>
<th>Placebo</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC Cases</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>PC Deaths</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>


Pancreatic Adenocarcinoma
Is it Chemopreventable?

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

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

Metformin appears to reduce the risk of pancreatic cancer. Insulin and sulfonylureas increased risk of pancreatic cancer!

Li D, et al. JNCI, 1998
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?

<table>
<thead>
<tr>
<th>Time Period</th>
<th>K-RAS Mutation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980’s-1990’s</td>
<td>85-90%</td>
</tr>
<tr>
<td>2000’s-2010’s</td>
<td>70%</td>
</tr>
</tbody>
</table>

- Does the treatment remain the same?
Pancreatic Adenocarcinoma
Is NOT a SINGLE DISEASE!

RESPONSE RATE

SURVIVAL

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

RESPONSE RATE

SURVIVAL

- Smoking Related
- Genetically Driven
- Obesity/DM/Obesity

?IGF inhibitors
?Metformin

Platinum PARP inhibitors

Nothing works

1950-1990
1990-2030
2030-2050

These people can be identified and subjects of focused screening!
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

<table>
<thead>
<tr>
<th>Individuals</th>
<th>Gene</th>
<th>Chrom</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNPCC</td>
<td>hMLH1/HMSH2</td>
<td>2, 3</td>
<td>?</td>
</tr>
</tbody>
</table>

*2 first degree relatives

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

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

#### Identify and screen!!!!

<table>
<thead>
<tr>
<th>Individuals</th>
<th>Gene</th>
<th>Chrom</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAMMM</td>
<td>p16</td>
<td>9p</td>
<td>10</td>
</tr>
<tr>
<td>Peutz-Jeghers</td>
<td>STK11</td>
<td>10p</td>
<td>66</td>
</tr>
<tr>
<td>Fam pancreatitis</td>
<td>PRSS1</td>
<td>7q</td>
<td>25</td>
</tr>
<tr>
<td>Fam Pancreas Ca*</td>
<td>?</td>
<td>?</td>
<td>10</td>
</tr>
</tbody>
</table>

*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

September 13, 2007

February 11, 2010
Pattern of Spread: Lymph Nodes

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

Locally advanced, inoperable tumor, responds to chemotherapy and radiation....
…..but then spreads to peritoneum and causes fluid to build up

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).

Locally advanced pancreatic cancer
Pancreatic Cancer - Stages

Metastatic Pancreatic Cancer

- Resectable Pancreatic Cancer
- Locally Advanced Pancreatic Cancer
- Metastatic Pancreatic Cancer

Tumor

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

Chemoradiation 1st ➔ Recovery ➔ Chemotherapy

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

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

Burris H, et al. JCO 1997
Von Hoff, et al. GI ASCO 2013
Conroy T, et al. NEJM 2011
## Resectable Pancreatic Cancer & Upfront Surgery
### Randomized Trials of Adjuvant Therapy

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

Neoptolemos JP, et al. NEJM 2004
Neoptolemos JP, et al. JAMA 2010

### Metastatic at Restaging
- 17

### RO or R1 Resections
- 870

### Upfront Surgery
- 889

### The Denominator at the Johns Hopkins
1993-2005

Herman J et al. JCO 2008

The Numerator

Adjuvant Therapy 53%
MS = 21.2 M

The Eligible
- 482

The Fit
- 465

T4 or Metastatic
- 19

Did not receive adjuvant rx
- 345

Death
- 43

The Numerator

Adjuvant Therapy 53%
MS = 21.2 M

The Eligible
- 482

The Fit
- 465
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

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

RTOG 9704: Patients with R1 Resections > 35%!!!!
Pancreatic Cancer – The Reality

Even when the tumor appears operable....

Pancreatic Cancer – Resectable Upfront?

Tumor

Tumor
Pancreatic Cancer - Reality
There are tumor cell beyond the visible mass.

Tumor Cells—Seen and Unseen
## It’s a Systemic Disease!

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

## 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 – Rationale for Preoperative Therapy

- Chemotherapy
- Radiation Field
- Chemotherapy

- Tumor
- Chemotherapy
- Chemotherapy
Pancreatic Cancer – Preoperative Therapy

Living Tumor

Negative Surgical Margin!

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

<table>
<thead>
<tr>
<th>Fri</th>
<th>Mon</th>
<th>Fri</th>
<th>Mon</th>
<th>Fri</th>
<th>Fri</th>
<th>Fri</th>
<th>Fri</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td></td>
<td>G</td>
<td></td>
<td>G</td>
<td></td>
<td>G</td>
<td></td>
</tr>
</tbody>
</table>

1 2 3 4 5 6 7

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 pre-operative therapy (those revealed to be unfit).

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.

<table>
<thead>
<tr>
<th>Protocol Regimen Number</th>
<th>Resection Rate</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA 01-341*</td>
<td>Gem/XRT</td>
<td>86</td>
</tr>
<tr>
<td>MDA 01-341^</td>
<td>Gem/Cis</td>
<td>90</td>
</tr>
</tbody>
</table>

* Evans DB, et al. JCO 2008
^ Varadhachary GR, et al. JCO 2008

The Denominator at M.D. Anderson: 85 patients restaged (1 did not undergo restaging after radiation component)

The Numerator: 86 eligible patients

To OR 74

Metastatic at Exploration 10

The Eligible 64

Completed Therapy

74%

Median Survival

34 M

Poor Surgical Risk

4

Mets on restaging CT

7

Evans DB et al. JCO 2008
Chemoradiation for Locally Advanced Disease

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

<table>
<thead>
<tr>
<th>Arm</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. 6000 Radiation Alone</td>
<td>22.9 weeks</td>
</tr>
<tr>
<td>2. 4000 Radiation + Bolus 5-FU</td>
<td>42.2 weeks</td>
</tr>
<tr>
<td>3. 6000 Radiation + Bolus 5-FU</td>
<td>40.3 weeks</td>
</tr>
</tbody>
</table>

**Traditional Strategy** for Locally advanced pancreatic cancer

Chemoradiation → Recovery → Chemotherapy

Metastatic

2nd Line Rx or Best Supportive Care
# Upfront Chemoradiation for Locally Advanced Disease

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

**MD Anderson¹**
- ChemoRx
- ChemoXRT 12 mo
- 318 Pts

**UCSF²**
- Induction Gem/Cis
- Cape/XRT 17 mo
- 25 Pts
- 28% Progressed
- 10 mo

**GERCOR³**
- Induction ChemoRx
- ChemoXRT 15 mo
- 181 Pts
- 29% Progressed
- Continued Chemo 12 mo

¹Krishnan S et al. *Cancer*, 2007
²Ko A et al. *Int J Rad Oncol Biol Phys*, 2007
³Huguet F et al. *JCO*, 2007
**New Strategy** for Locally advanced pancreatic cancer

1. **Chemotherapy 2-3 months**
2. **CT scan**
3. **- Mets**
4. **Consider ChemoRadiation**

2nd Line Chemotherapy or Best Supportive Care

**Induction Chemotherapy then Chemoradiation for Locally Advanced Disease**

<table>
<thead>
<tr>
<th>Author Year</th>
<th>Number of patients</th>
<th>Induction Chemo</th>
<th>% Progressed</th>
<th>Radio-sensitizer</th>
<th>Median Survival (all components)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007</td>
<td>76</td>
<td>Gem-based</td>
<td>Not stated</td>
<td>5-FU, cape, or Gem</td>
<td>11.9 months</td>
</tr>
<tr>
<td>Ko 2007</td>
<td>25</td>
<td>Gem/Cis</td>
<td>28-32%</td>
<td>Capecitabine</td>
<td>17 months</td>
</tr>
<tr>
<td>Huguet 2007</td>
<td>181</td>
<td>Gem-based x 3 months</td>
<td>29%</td>
<td>Not stated</td>
<td>15 months</td>
</tr>
<tr>
<td>Moureau-Zobotto 2008</td>
<td>59</td>
<td>Gem/Ox X 2 months</td>
<td>11%</td>
<td>5-FU</td>
<td>12.6 months</td>
</tr>
<tr>
<td>Reni 2009</td>
<td>91</td>
<td>PEGF and variants</td>
<td>23%</td>
<td>5-FU, cape, or Gem</td>
<td>16.2 months</td>
</tr>
<tr>
<td>Crane 2011</td>
<td>69</td>
<td>Gem/Ox + Cetuximab x 2 months</td>
<td>2%</td>
<td>Capecitabine + Cetuximab</td>
<td>19 months</td>
</tr>
</tbody>
</table>
Simplified version of LAP07 study

EVALUATION: non progressive
EVALUATION: non progressive
Until Progression

Overall survival by Random 2 status

HR = 95% CI = 1.03 - [0.79; 1.34]
logrank p = 0.8295
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

Outcome: 01 chemotherapy vs no chemotherapy

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>log(hazard ratio)</th>
<th>95% CI</th>
<th>Hazard Ratio (random)</th>
<th>Weight %</th>
<th>Hazard Ratio (random)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mallison 1980</td>
<td>-1.2900</td>
<td>(0.2000)</td>
<td>1.47</td>
<td>0.28</td>
<td>(0.15 to 0.92)</td>
<td></td>
</tr>
<tr>
<td>Ferl 1981</td>
<td>0.2200</td>
<td>(0.1700)</td>
<td>1.25</td>
<td>0.15</td>
<td>(0.99 to 1.74)</td>
<td></td>
</tr>
<tr>
<td>Andersen 1983</td>
<td>0.0890</td>
<td>(0.6900)</td>
<td>Not estimable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palmer 1984</td>
<td>-0.4597</td>
<td>(0.2021)</td>
<td>1.61</td>
<td>0.01</td>
<td>(0.75 to 1.06)</td>
<td></td>
</tr>
<tr>
<td>Gillmor 1988</td>
<td>-0.3000</td>
<td>(0.2000)</td>
<td>1.71</td>
<td>0.74</td>
<td>(0.98 to 1.10)</td>
<td></td>
</tr>
<tr>
<td>Huguet 2001</td>
<td>-0.3500</td>
<td>(0.2000)</td>
<td>1.85</td>
<td>0.79</td>
<td>(0.88 to 2.22)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>100.00</td>
<td>0.64</td>
<td>(0.42 to 0.98)</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $I^2 = 22.13, (P = .0059), F = 72.6$
Test for overall effect: $z = 2.07, (P = .04)$

Sultana A, et al. JCO 2007
Gemcitabine: Our “go-to” drug 1996-2010

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

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

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Delivered Therapy</th>
<th>No of Pts</th>
<th>% METS</th>
<th>Response Rate (%)</th>
<th>Overall Survival (Median Days)</th>
<th>1-year survival rate</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Cutsem</td>
<td>2004</td>
<td>Gem + placebo vs Gem + Tipifarnib</td>
<td>347</td>
<td>76</td>
<td>8</td>
<td>182</td>
<td>24%</td>
<td>0.75</td>
</tr>
<tr>
<td>Bramhall</td>
<td>2002</td>
<td>Gem + placebo vs Gem + Marinastat</td>
<td>119</td>
<td>58</td>
<td>11</td>
<td>164</td>
<td>18%</td>
<td>0.95</td>
</tr>
<tr>
<td>Moore</td>
<td>2005</td>
<td>Gem vs Gem + Erlotinib</td>
<td>284</td>
<td>75</td>
<td>8.0</td>
<td>177</td>
<td>17%</td>
<td>0.025</td>
</tr>
<tr>
<td>Kindler</td>
<td>2007</td>
<td>Gem + placebo vs Gem/Bevacizumab</td>
<td>300</td>
<td>85</td>
<td>10</td>
<td>180</td>
<td>20%</td>
<td>0.40</td>
</tr>
<tr>
<td>Philip</td>
<td>2007</td>
<td>Gem vs Gem/Cetuximab</td>
<td>369</td>
<td>79</td>
<td>13</td>
<td>177</td>
<td>NR</td>
<td>0.14</td>
</tr>
<tr>
<td>Van Cutsem</td>
<td>2008</td>
<td>Gem + Erlotinib + P vs Gem + Erlotinib + Bev</td>
<td>301</td>
<td>100</td>
<td>8.6</td>
<td>180</td>
<td>NR</td>
<td>0.21</td>
</tr>
</tbody>
</table>

## Gemcitabine/nab-paclitaxel

<table>
<thead>
<tr>
<th>Burris 1996</th>
<th>Number of Patients</th>
<th>Response Rate</th>
<th>Median Survival</th>
<th>1 year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>430</td>
<td>7%</td>
<td>6.7 months</td>
<td>22%</td>
</tr>
<tr>
<td>Gemcitabine nab-paclitaxel</td>
<td>431</td>
<td>23%</td>
<td>8.5 months</td>
<td>35%</td>
</tr>
</tbody>
</table>
FOLFIRINOX

<table>
<thead>
<tr>
<th>Conroy 2011</th>
<th>Number of Patients</th>
<th>Response Rate</th>
<th>Clinical Benefit Response*</th>
<th>Median Survival</th>
<th>1 year survival rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>171</td>
<td>9.4%</td>
<td>x</td>
<td>6.2 months</td>
<td>20.6%</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>171</td>
<td>31.6%</td>
<td>x</td>
<td>11.1 months</td>
<td>48.4%</td>
</tr>
</tbody>
</table>

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

Positive Surgical Margin

Not Good!
R1 Resections Don’t Do Well

<table>
<thead>
<tr>
<th>Institution</th>
<th>Margin Rate (%)</th>
<th>Median Survival R0 (Mo)</th>
<th>Median Survival R1 (Mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo¹</td>
<td>24%</td>
<td>18-19</td>
<td>15</td>
</tr>
<tr>
<td>Hopkins²</td>
<td>42%</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>MGH³</td>
<td>30%</td>
<td>22</td>
<td>15</td>
</tr>
</tbody>
</table>

¹Fatima J et a, Arch Surg, 2010  
²Winter JM et al, J Gastrointest Surg, 2006  
³Konstandinidis et al, GI ASCO 2010

After Preoperative Chemotherapy and ChemoXRT

Viable Tumor  
Non-viable rim  
Negative Surgical Margin!

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?

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resectable Pancreatic Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upfront Surgery + Post Op Therapy</td>
<td>20-21 Months</td>
<td>21-23 months</td>
</tr>
<tr>
<td>Preoperative Therapy + Surgery</td>
<td>18-20 Months</td>
<td>31-34 months</td>
</tr>
<tr>
<td><strong>Locally Advanced Pancreatic Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ChemoRadiation then Chemotherapy</td>
<td>9-10</td>
<td>10-12 months</td>
</tr>
<tr>
<td>Chemotherapy 1st then Chemoradiation</td>
<td>?</td>
<td>12-19 months</td>
</tr>
<tr>
<td><strong>Metastatic Pancreatic Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single Agent Chemotherapy</td>
<td>5-6 months</td>
<td>5-6 months</td>
</tr>
<tr>
<td>Combination Chemotherapy</td>
<td>6-7 months</td>
<td>9-11.1 months</td>
</tr>
</tbody>
</table>
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

“You know, I have a confession to make, Bemla. Win or lose, I love doing this.”
Molecular Therapies + Blunt Trauma

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

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
4. Takahashi Y et al Pancreas, 2005
Pre-Operative Therapy for Resectable Pancreatic Cancer: Chemo “Lite” Works

<table>
<thead>
<tr>
<th>Study</th>
<th>Gemcitabine Dose (mg/m²)</th>
<th>Total Intended Gemcitabine Dose (mg/m²)</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONKO 001</td>
<td>1,000 mg/m² 3 wk on, 1 off X 6 cycles</td>
<td>18,000 mg/m²</td>
<td>23 months</td>
</tr>
<tr>
<td>Gem/XRT</td>
<td>400 mg/m² Weekly X 7</td>
<td>2,800 mg/m²</td>
<td>34 months</td>
</tr>
<tr>
<td>Gem/Cis</td>
<td>750 mg/m² q 2 wks X 4 doses 400 mg/m² X 4</td>
<td>4,600 mg/m²</td>
<td>31 months</td>
</tr>
</tbody>
</table>

FDR Gemcitabine @ 600 mg/m²
Liver Met 04/01/08  Liver Met 02/05/09

FDR Gemcitabine @ 450 mg/m²

Gemcitabine at 350 mg/m² are systemically relevant

Peritoneal Implant  Complete Response
### GTX Dosing

<table>
<thead>
<tr>
<th></th>
<th>Fine</th>
<th>MDACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>750 mg/m² D4 and D11</td>
<td>350 mg/m² D4 and 11</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>30 mg/m² D4 and D11</td>
<td>35 mg/m² D4 and D11</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>750 mg/m² BID x 14 days</td>
<td>500 mg/m² BID x 14 days</td>
</tr>
</tbody>
</table>


### FOLFIRINOX

<table>
<thead>
<tr>
<th></th>
<th>Conroy</th>
<th>MDACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU/Leucovorin Bolus</td>
<td>400 mg/m²</td>
<td>0 mg/m²</td>
</tr>
<tr>
<td>5-FU Infusion</td>
<td>2400 mg/m²</td>
<td>2000 mg/m²</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>85 mg/m²</td>
<td>75 mg/m²</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>180 mg/m²</td>
<td>150 mg/m²</td>
</tr>
</tbody>
</table>

Conroy T et al. NEJM 2011
Pancreatic Cancer – Newer Approaches

- **Resectable Pancreatic Cancer**
  - Pre-op Rx → Recovery → Repeat Scans → Surgery
  - Cancer Spread: No Surgery

- **Borderline Resectable Pancreatic Cancer**
  - Pre-op Rx → Recovery → Repeat Scans → Tumor Shrinkage or other Evidence of Response
  - No Cancer Spread → Surgery

- **Locally Advanced Pancreatic Cancer**
  - Chemotherapy 1st → 2-3 months → Repeat Scans → 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

Pancreatic Cancer

Pre-Rx Biopsy

Treatment A  Treatment B  Treatment C

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

EGF-R, HER2, IGF-1, FGF-R
RAS-GDP
RAS-GTP
Raf-1
MEK
ERK
MEKK-1
AKT/PI3-K
IKKa + b
IKBa
NFκB/IκB
Metastases
Anti-apoptotic signals
Growth-promoting genes

October, 2011

Anti-apoptotic signals
Chemo/XRT resistance
Over-expression
Mutation
Activation

January, 2012

mTOR
p53
NFκB/1κB

RTK
EGF-R, HER2, IGF-1, FGF-R
SHC/GRB-2
GEF
RAS
RAS-GDP
RAS-GTP
Raf-1
MEK
mTOR
p53
NFκB/1κB
COX-2
Tumor and its Microenvironment

- Adenocarcinoma
- Desmoplasia

**RTK**
- EGF-R
- HER2
- IGF-1
- FGF-R

**SHC/GRB-2**

**GEF**
- RAS-GDP

**RAS-GTP**
- Raf-1
- MEK
- ERK

**MEKK-1**

**AKT/PI3-K**

**IKKa + b**
- IKBa

**NF-kB**

**SpaRC**

**METASTASES**

**CHEMO/XRT RESISTANCE**

**ANTI-APOPTOTIC SIGNALS**

**GROWTH-PROMOTING GENES**

**SPARC**

**COX-2**

**SMOOTH MUSCLE CELLS**

**ENDOTHELION**
- VEG-F
- RAS-GDP
- RAS-GTP
- SHC/GRB-2
- GEF

**EXTRACELLULAR MATRIX**
- Matrix metalloproteinases

**IMMUNE CELLS & STROMAL CELLS**

Molecular Agents to alter the stroma or microenvironment

- Hedgehog inhibitors
- FGF inhibitors
- Immunotherapy!
  - CD40 agonists 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!