The Multidisciplinary Management of Patients With Pancreas Cancer

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Head Gastrointestinal Comprehensive Center
Director of Pancreatic Disease Center

The UC Pancreatic Disease Center
Specialists In Pancreatitis & Pancreatic Cancer Treatment

Faces of Pancreatic Cancer

Champion
Detection
Believe
Hope

Dream
Future
Research
Truths Regarding Pancreatic Cancer

• Eighth most common malignancy
• Fourth leading cause of cancer death among men and women
• Incidence rates and mortality rates are almost identical
• Risk of pancreatic cancer increases after the age of 50
• Surgery Remains only hope for long-term cure
Truth Regarding Pancreas Cancer

- Last year 45,220 patients were diagnosed with pancreas cancer in 2013
  - 38,460 patients died of pancreas cancer
- Despite decades of effort, the 5-year survival rate remains at around 5%
- There are no early detection tests, symptoms or signs
  - Most patients are diagnosed late in their disease state after metastases have formed

Cancer Rates

- Frequency increases with age
  - The mean onset of pancreatic cancer is 65 years
  - 80% of patients are older than 60
  - Patients at younger age usually have an undiagnosed genetic risk factor
- Higher rates in men compared to women
  - Most likely due to differences in smoking
  - As more women are smoking, these differences are disappearing
Cancer Rates

- Racial Differences
  - Rates in African Americans 50% greater than Whites
  - Rates in non-Whites, non-AA are similar to Whites

- Regional
  - Highest: North America, Europe
  - Lowest: Africa, Asia, South America
  - May be related to differences in cigarette smoking

Modifiable Risk Factors

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>RISK ESTIMATE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Cigarette Smoking</td>
<td>OR = 2.20 (1.71-2.83)</td>
</tr>
<tr>
<td>Past Cigarette Smoking</td>
<td></td>
</tr>
<tr>
<td>1-10 years since quitting</td>
<td>OR = 1.64 (1.36-1.97)</td>
</tr>
<tr>
<td>15-20 years since quitting</td>
<td>OR = 1.12 (0.86-1.44)</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td></td>
</tr>
<tr>
<td>&lt;3 years</td>
<td>RR = 7.94 (4.70-12.55)</td>
</tr>
<tr>
<td>&gt;10 years duration</td>
<td>OR = 1.51 (1.16-1.96)</td>
</tr>
<tr>
<td>BMI (≥35 vs 18.9-24.9)</td>
<td>OR = 1.55 (1.16-2.07)</td>
</tr>
<tr>
<td>Heavy Alcohol (≥6 drinks/day)</td>
<td>OR = 1.46 (1.16-1.83)</td>
</tr>
<tr>
<td>Pancreatitis (&gt;2 years)</td>
<td>2.71-fold (1.96-3.74)</td>
</tr>
</tbody>
</table>

Wolfgang CL et al. CA Cancer J Clin, 2013
Inherited Risk Factors

Wolfgang CL et al. CA Cancer J Clin, 2013

- Ductal Adenocarcinoma
- Acinar Cell Carcinoma
- Serous Cystic Neoplasia
- Mucinous Cystic Neoplasia
- IPMN
- Solid-pseudopapillary
- Pancreatic Endocrine Neoplasms.

Malignant Tumors of the Pancreas
Clinical Presentation

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight Loss</td>
<td>90%</td>
</tr>
<tr>
<td>Pain</td>
<td>75%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>75%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>70%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>60%</td>
</tr>
<tr>
<td>Pruritis</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15%</td>
</tr>
</tbody>
</table>

Pre-operative Evaluation

- Performance Status
  - Cardiac
  - Pulmonary
  - Nutrition
- Blood Work
- CT scan
- Endoscopic Ultrasound
- ERCP
- MRI
Resectability Rates Stratified by CT Technique

<table>
<thead>
<tr>
<th>Author</th>
<th>Group</th>
<th>Helical CT</th>
<th>No. Considered Resectable</th>
<th>No. Resected</th>
<th>Resection Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conlon MSKCC ('96)</td>
<td>Some</td>
<td>115</td>
<td>61</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Rumstadt Manheim ('97)</td>
<td>All</td>
<td>194</td>
<td>172</td>
<td>89</td>
<td></td>
</tr>
<tr>
<td>Holzman Duke ('97)</td>
<td>All</td>
<td>23</td>
<td>18</td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Spitz MDACC ('97)</td>
<td>All</td>
<td>118</td>
<td>94</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Fries Bern ('98)</td>
<td>All</td>
<td>159</td>
<td>119</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Reber UCLA ('98)</td>
<td>All</td>
<td>32</td>
<td>24</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Saldinger BI (2000)</td>
<td>All</td>
<td>68</td>
<td>52</td>
<td>76</td>
<td></td>
</tr>
</tbody>
</table>

Resectable Pancreatic Cancer

- No radiographic evidence of vascular encasement
  - SMA
  - Celiac
  - Hepatic Artery
  - SMV/ Portal Vein
- Patency of SMV-Portal Vein Confluence
- No Extra-Pancreatic Disease
- Adequate Performance Status
CT Scans: Pancreas Cancer.

EUS: Pancreas Cancer.
Triple Phase Spiral CT Imaging

Localized  Locally Advanced  Unresectable
Resectable  Resectable

Diagram showing different phases of CT imaging:
- Duodenum
- Tumor
- Superior Mesenteric V.
- Superior Mesenteric A.
- Aorta
- Inferior Vena Cava
What’s A Whipple Operation??

Allen O. Whipple, MD

1958-59 Resident Group

11
Step 1: exposure of SMV

Step 2: Kocher maneuver
Step 3: portal dissection

Common Bile Duct

Common Hepatic Artery

Portal Vein

Gastroduodenal Artery

Step 4: gastric transection

Common Bile Duct

Common Hepatic Artery

Gastroduodenal Artery

Superior Mesenteric Artery

Superior Mesenteric Vein
Step 5: mobilization of the duodenum/jejunum

Step 6: division of pancreas and the retroperitoneal dissection
Retroperitoneal Margin

- PV
- SMV
- IVC
- SMA
- Replaced R Hepatic A
Counter-Clockwise Reconstruction

1. End-to-side pancreaticojunostomy (jejunal limb brought retrocolic to left of MCA)
2. End-to-side choledochojunostomy
3. End-to-side gastrojunostomy (antcolic)
4. Gastrostomy tube
   Jejunostomy tube
   Drains

Retroperitoneal Margin

Slide Courtesy Of Doug Evans, MD
SMPV resection with preservation of the splenic vein

SMV reconstruction with IJ vein
Techniques For Venous Reconstruction

2004 SSAT Annual Meeting
Pancreatoduodenectomy With Vascular Resection: Margin Status and Survival Duration

<table>
<thead>
<tr>
<th>Vascular resection</th>
<th>Standard PD</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Ns of patients</td>
<td>110</td>
<td>181</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>69 (63)</td>
<td>106 (97)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (37)</td>
<td>74 (68)</td>
</tr>
<tr>
<td>Median (mean) age (yr)</td>
<td>63.9 (62.1)</td>
<td>63.9 (63.6)</td>
</tr>
<tr>
<td>Range</td>
<td>45-81</td>
<td>30-81</td>
</tr>
<tr>
<td>Reseption PD, n (%)</td>
<td>27 (25)</td>
<td>27 (24)</td>
</tr>
<tr>
<td>Operative blood loss (ml)</td>
<td>1600 (1829)</td>
<td>800 (927)</td>
</tr>
<tr>
<td>Range</td>
<td>250-6000</td>
<td>180-7900</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mean)</td>
<td>1.0 (1.2)</td>
<td>2.8 (2.9)</td>
</tr>
<tr>
<td>Range</td>
<td>1.0-6.0</td>
<td>0.2-6.0</td>
</tr>
<tr>
<td>Positive resection margin (RR), n (%)</td>
<td>29 (25)</td>
<td>31 (27)</td>
</tr>
<tr>
<td>Positive lymph node (NL), n (%)</td>
<td>50 (45)</td>
<td>95 (82)</td>
</tr>
<tr>
<td>Major perioperative complications, n (%)</td>
<td>20 (18)</td>
<td>39 (32)</td>
</tr>
<tr>
<td>Perioperative death</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (mean)</td>
<td>11.5 (11.9)</td>
<td>12.0 (13.3)</td>
</tr>
<tr>
<td>Range</td>
<td>7-108</td>
<td>5-70</td>
</tr>
<tr>
<td>Intensive radiation therapy, n (%)</td>
<td>31 (28)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>Adjuvant therapy (neoadjuvant or postop), n (%)</td>
<td>19 (18)</td>
<td>101 (91)</td>
</tr>
<tr>
<td>Preoperative chemoradiation</td>
<td>82 (73)</td>
<td>107 (78)</td>
</tr>
<tr>
<td>Postoperative chemoradiation</td>
<td>25 (23)</td>
<td>59 (20)</td>
</tr>
</tbody>
</table>

J Gastroint Surg 2004
Venous Resection During Pancreaticoduodenectomy

More Than Right Lateral Wall??
Abutting But Not Involving Artery??

Borderline Resectable

Pancreatic cancers which can be technically resected, but which can be expected to have a higher than average incidence of positive margins (and therefore less favorable prognosis) in the absence of pre-operative therapy.

NCCN, 2006
Natural History of Pancreas Cancer

Resectable  Borderline Resectable  Locally Advanced

How Do We Define?

Borderline Resectable Pancreatic Cancer: Need for Standardization and Methods for Optimal Clinical Trial Design

Matthew H. G. Katz, MD, Robert Marsh, MD, Joseph M. Herman, MD, Qian Shi, PhD, Eric Collison, MD, Alan P. Venook, MD, Hedy L. Kindler, MD, Steven R. Alberts, MD, Philip Philip, MD, Andrew M. Lowy, MD, Peter W. T. Pisters, MD, Mitchell C. Posner, MD, Jordan D. Berlin, MD, and Syed A. Ahmad, MD

<table>
<thead>
<tr>
<th>SMV-PV</th>
<th>AHPBA/SSAT/SSO</th>
<th>MD Anderson</th>
<th>NCCN 2013***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abutment, encasement, or occlusion</td>
<td>Occlusion</td>
<td>Abutment with impairment or narrowing</td>
<td></td>
</tr>
<tr>
<td>SMA</td>
<td>Abutment</td>
<td>Abutment</td>
<td></td>
</tr>
<tr>
<td>CHA</td>
<td>Abutment or short-segment encasement</td>
<td>Abutment or short-segment encasement</td>
<td></td>
</tr>
<tr>
<td>Celiac trunk</td>
<td>No abutment or encasement</td>
<td>Abutment</td>
<td></td>
</tr>
</tbody>
</table>

Intergroup trial

Interface between tumor and vessel measuring 180° or greater of the circumference of the vessel wall, and/or reconstrucatable occlusion
Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall
Reconstructable, short-segment interface between tumor and vessel of any degree
Interface between tumor and vessel measuring less than 180° of the circumference of the vessel wall

Ann Surg Oncol, 2013
Portal Vein/Superior Mesenteric Vein

- Tumor abuts SMV without distortion (arrow)
- MD Anderson, NCCN, & Intergroup trial – resectable
- AHPBA/SSAT/S SO – borderline resectable

Portal Vein/Superior Mesenteric Vein

- Tumor encases & narrows SMV (arrow)
- MD Anderson - resectable
- AHPBA/SSAT/S SO, NCCN, & Intergroup trial – borderline resectable
Hepatic Artery

- Short segment encasement of replaced right hepatic artery (arrow)
- Considered borderline resectable by all definitions

University Of Cincinnati Algorithm For Borderline Resectable Pancreas Cancer

Staging and Diagnosis → Chemotherapy → Staging → Chemoradiation → Staging

→ No Local or Systemic Progression → Surgery

We Do Not Base This On RECIST Criteria
## Patterns of Failure After Pancreaticoduodenectomy

<table>
<thead>
<tr>
<th>Study</th>
<th>Chemoradiation</th>
<th>Local Incidence (%)</th>
<th>Incidence of Metastases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Peritoneal</td>
</tr>
<tr>
<td>Tepper et al.</td>
<td>No</td>
<td>50%</td>
<td>-</td>
</tr>
<tr>
<td>GITSG</td>
<td>No</td>
<td>33%</td>
<td>-</td>
</tr>
<tr>
<td>Whittington et al.</td>
<td>No</td>
<td>85%</td>
<td>23%</td>
</tr>
<tr>
<td>Ozaki et al.</td>
<td>No</td>
<td>86%</td>
<td>36%</td>
</tr>
<tr>
<td>GITSG</td>
<td>Yes</td>
<td>51%</td>
<td>-</td>
</tr>
<tr>
<td>Foo et al.</td>
<td>Yes</td>
<td>7%</td>
<td>43%</td>
</tr>
<tr>
<td>Staley et al.</td>
<td>Yes</td>
<td>11%</td>
<td>11%</td>
</tr>
<tr>
<td>Pisters et al.</td>
<td>Yes</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

### Rationale for Combined Modality Therapy

#### Median Survival - Surgery vs Surgery + CR

<table>
<thead>
<tr>
<th>Institution/Group</th>
<th>First Author (Yr)</th>
<th>No. Resected</th>
<th>Postoperative Treatment</th>
<th>Median Survival (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>GITSG ('87)</td>
<td>22</td>
<td>---</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21</td>
<td>5-FU + 40 Gy</td>
<td>20*</td>
</tr>
<tr>
<td>Hopkins</td>
<td>Yeo ('97)</td>
<td>53</td>
<td>---</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120</td>
<td>5-FU + &gt; 45 Gy</td>
<td>20*</td>
</tr>
<tr>
<td>Wisconsin</td>
<td>Demeure ('98)</td>
<td>15</td>
<td>---</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14</td>
<td>5-FU + &gt; 50.4 Gy</td>
<td>25*</td>
</tr>
<tr>
<td>MSKCC</td>
<td>Conlon ('96)</td>
<td>118</td>
<td>---</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Davis ('96)†</td>
<td>34</td>
<td>5-FU + 50.4 Gy</td>
<td>16</td>
</tr>
</tbody>
</table>

† T3, 85%; N1, 79%; positive margins, 50%

*P < 0.05
**ESPAC-1**

283 Patients with histologically proven adenocarcinoma of the pancreas who had undergone potentially curative resection

- 69 Assigned to observation
- 70 Assigned to chemotherapy
- 75 Assigned to chemoradiotherapy
- 79 Assigned to chemoradiotherapy and chemotherapy

**Treatment comparison**

- No chemotherapy vs. chemotherapy (140 vs. 140)
- No chemotherapy vs. chemotherapy and chemotherapy (140 vs. 140)

**Kaplan-Meier Estimates of Survival**

<table>
<thead>
<tr>
<th>Months</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>75</td>
</tr>
<tr>
<td>24</td>
<td>50</td>
</tr>
<tr>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>48</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
</tr>
</tbody>
</table>

**No. of Risk**

- No chemotherapy 144
- Chemotherapy 140

**No. of Risk**

- No chemotherapy 142
- Chemotherapy 140

Neoptolemos, N Engl J Med 2004
CONKO-001 (German Trial)

Resected Pancreas Cancer Stratified by R, T, N

Gemcitabine for 6 months

Observation

N=368 pts.

Neuhaus et al., ASCO 2005

Disease-Free and Overall Survival (Intent-to-Treat Analysis)

Survival
- Short follow-up
- Relapse in control treated with chemotherapy

### Have We Made Progress?

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Treatment assignment</th>
<th>Median survival (months)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG (1985)</td>
<td>Chemoradiation vs. Observation</td>
<td>21.0 vs. 10.9</td>
<td>.035</td>
</tr>
<tr>
<td>ESPAC-I (2004)</td>
<td>Chemotherapy vs. No chemotherapy</td>
<td>20 vs. 15.5</td>
<td>.009</td>
</tr>
<tr>
<td></td>
<td>Chemoradiation vs. No chemoradiation</td>
<td>15.9 vs. 17.9</td>
<td>.05</td>
</tr>
<tr>
<td>EORTC (2007)</td>
<td>Chemoradiation vs. Observation</td>
<td>15.6 vs. 12.0</td>
<td>.165</td>
</tr>
<tr>
<td>CONKO (2007)</td>
<td>Gemcitabine vs. Observation</td>
<td>22.1 vs. 20.1</td>
<td>.06</td>
</tr>
<tr>
<td>RTOG (2008)</td>
<td>Gemcitabine with 5-FU/EBRT vs. 5-FU</td>
<td>20.5 vs. 16.9</td>
<td>.05</td>
</tr>
<tr>
<td></td>
<td>with 5-FU/EBRT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Time to Understand Biology
**Origin of Pancreatic Ductal Adenocarcinoma**

- To determine the origin of PDA, pancreatic cell populations were labeled and traced after induction of oncogenic of KRAS mutations.
- Evaluated SOX9 expression as a marker for PDA initiation.
- Ductal and centroacinar cells are surprisingly resistant to oncogenic transformation.
- Acinar cells readily form PDA precursors with ductal features.

Kopp JL et al., Cancer Cell 2012

**How long does it take for metastases to form?**

- Sequenced genomes of seven pancreatic cancer metastases.
- Evaluated clonal relationship among primary and metastatic lesions.
- Clonal populations that give rise to metastases are found within primary.
- Clones are genetically evolved from original parental clone.
- Analysis of the timing of genetic evolution determined that it takes 5-10 years for metastases to form.

Genetic Alterations

- Cancer is fundamentally caused by inherited (germline) and acquired (somatic) mutations in cancer causing genes
- The exomes of PDA have been completely sequenced
- This revealed that 4 genes are altered in >50% of cancers

Wolfgang CL et al. CA Cancer J Clin, 2013

<table>
<thead>
<tr>
<th>Invasive ductal adenocarcinoma</th>
<th>KRAS</th>
<th>95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16CDKN2A</td>
<td>95%</td>
<td></td>
</tr>
<tr>
<td>TP53</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>SMAD4</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>MLL3, TGFBR2, ESR2, and ATM</td>
<td>&lt;5%</td>
<td></td>
</tr>
</tbody>
</table>

KRAS mutations occur early, and KRAS mutations may be a target for early detection.

SMAD4 loss is associated with poor prognosis and widespread disease.

Some of these, such as ATM, may be targetable therapeutically.

Cancer Progression: KRAS

- KRAS is an oncogene on chromosome 12
- Activated by point mutation in 95% of invasive PDA
- Protein coded for by KRAS is a small GTPase that signals via MAPK pathway
- Occur early and target codons 12, 13, and 61
EGFR signal transduction in tumor cells

Gene transcription
Cell cycle progression

proliferation/maturation
chemotherapy/radiotherapy resistance
survival/anti-apoptosis
metastasis
angiogenesis

Importance of KRAS

KRAS will not promote cancer growth without acquisition of additional mutations in tumor suppressor genes: p16, p53

Magliano MP et al., Gastro, 2013
KRAS Promotes Tumor Growth In Microenvironment

KRAS mediates interactions between tumor cells by secreting molecules in paracrine manner to stimulate fibroblasts and immune cells which then promote tumor growth.

Magliano MP et al., Gastro, 2013

KRAS Summary

- Oncogenic Addiction- KRAS not only initiates disease but is required for tumor maintenance
- In mice, inactivation of KRAS leads to tumor regression
- In human, KRAS has remained an undruggable target
- Constitutively active
  - Can increase activity with external stimuli
  - Oncogenic KRAS inhibitors are in the pipeline
  - Strategy thus far has focused on upstream and down-stream inhibition of KRAS
    - MAPK (PD325901)- Negative
    - RAF inhibitors- Negative
    - MEK (GDC0941)- Negative
    - AKT (AZD6244)- Negative
- Minimal effects with EGFR inhibition
Erlotinib Plus Gemcitabine v. Gemcitabine: Phase III NCI of Canada

- 569 patients randomized
- Erlotinib is HER1/EGFR tyrosine kinase inhibitor
- Clinically insignificant benefit


Phase III Study Comparing Gemcitabine v. Gemcitabine plus Cetuximab (S0205)

Any Progress??

Two Positive Clinical Trials?

Gem versus FOLFIRINOX

Gem versus Gem/ Abraxane
Future

- Understanding redundancy of pathways
- Direct KRAS targeting
- Targeting stroma
- Targeting other genetic abnormalities
- Targeting multiple pathways- i.e. ERK/ AKT
- Combining biologic and cytotoxic chemotherapy
- Target Stem Cells???

Role of Pancreas Stem Cells?

- Inactivation of KRAS tumors regress
- Minor population of tumor infiltrating cells survive
- These cells have stem cell property
- These cells repopulate when KRAS re-expressed
- Resistant to KRAS, AKT, MEK, PI3K inhibition
- c-myc inhibited- tumor regression
- Population of surviving cells express stem cell markers
- NEED TO TARGET BOTH TUMOR CELLS AND STEM CELLS

Lin W. et al, Cancer Res 2013