Surgical Management of Pancreatic (and Distal Biliary) Cancers

Matthew HG Katz, MD
Assistant Professor of Surgical Oncology
The University of Texas
MD Anderson Cancer Center

SUMO Fall Meeting
Society of Utah Medical Oncologists
September 29, 2013
HOUSTON, TX
Visitors welcome!
Texas Medical Center

In 2009:

- 1000 acres
- 49 member institutions
- 13 hospitals
- 140 buildings
- 21,000 physicians, scientists and researchers
- 6 million annual visits
- 160,000 daily visitors
Lecture Outline

• Describe standard of care therapy for anatomically resectable pancreatic cancer

• Good surgery is key

• Strategy for selection and timing of surgery
<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>5-yr OS (%)</th>
<th>Median OS (Mos.)</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable -&gt; OR</td>
<td>2736</td>
<td>24.6</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>Resectable -&gt; No OR</td>
<td>3644</td>
<td>2.9</td>
<td>8.4</td>
<td>2.24 (2.07 – 2.43)</td>
</tr>
<tr>
<td>Stage III or IV</td>
<td>68521</td>
<td>0.8</td>
<td>4.2</td>
<td>4.16 (3.86 – 4.48)</td>
</tr>
</tbody>
</table>

Pancreatic Cancer Survival by Stage/Treatment
National Cancer Database

Billimoria, Ann Surg 2007
CONKO-001

Disease-Free Survival

Log-Rank $P < .001$

Cumulative Percentage

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Gemcitabine</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>179</td>
<td>175</td>
</tr>
<tr>
<td>12</td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td>24</td>
<td>43</td>
<td>24</td>
</tr>
<tr>
<td>36</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>48</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>60</td>
<td>11</td>
<td>6</td>
</tr>
<tr>
<td>72</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>84</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>96</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DFS with surgery alone: DISMAL
DFS with postoperative gemcitabine: BETTER

Oettle, JAMA 2007
**Evidence in support of adjuvant therapy**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>n</th>
<th>Treatment arm</th>
<th>Control arm</th>
<th>Median OS (mos) (treatment v. control)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>GITSG</td>
<td>1985</td>
<td>43</td>
<td>5-FU-based chemoradiation followed by maintenance 5-FU</td>
<td>Observation</td>
<td>21.0 v. 10.9</td>
<td>0.03</td>
</tr>
<tr>
<td>EORTC</td>
<td>1999</td>
<td>114</td>
<td>5-FU-based chemoradiation</td>
<td>Observation</td>
<td>17.1 v. 12.6</td>
<td>NS</td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>2001</td>
<td>541</td>
<td>Chemotherapy</td>
<td>No chemotherapy</td>
<td>19.7 v. 14.0</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemoradiation</td>
<td>No chemoradiation</td>
<td>15.5 v. 16.1</td>
<td>NS</td>
</tr>
<tr>
<td>ESPAC-1</td>
<td>2004</td>
<td>289</td>
<td>Chemotherapy</td>
<td>No chemotherapy</td>
<td>20.1 v. 15.5</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chemoradiation</td>
<td>No chemoradiation</td>
<td>15.9 v. 17.9</td>
<td>0.05</td>
</tr>
<tr>
<td>CONKO</td>
<td>2008</td>
<td>368</td>
<td>Gemcitabine</td>
<td>Observation</td>
<td>22.8 v. 20.2</td>
<td>0.005</td>
</tr>
<tr>
<td>RTOG 97-04</td>
<td>2008</td>
<td>388</td>
<td>Gemcitabine, 5-FU-based chemoradiation, Gemcitabine</td>
<td>5-FU, 5-FU-based chemoradiation, 5-FU</td>
<td>20.5 v. 16.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Systemic gemcitabine +/- CXRT is standard postoperative therapy*
DFS with adjuvant therapy for the “best of the best”
Let’s face it: also pretty dismal.

Median age: 61
Median PS: 80
Postop CA 19-9:< 2.5 ULN
Median time to randomization: 3 weeks

CONKO-001
Oettle, JAMA 2007
Evolution of Metastases

Rhim Cell 2012
Occult Microscopic Disease

Rapid recurrence common following “radical” resection +/- postop therapy due to existing disease that is not dealt with surgically

Van den Broeck, E J Surg Onc 2009
M&M From Distant and Local Recurrence

A: bowel ischemia (local)
B: cholangitis (local)
C: hepatic failure (distant)

20% LR, 20% DR, 60% both

Iacobuzio-Donahue, JCO 2009
Unacceptable Progress

Despite an increase in use of adjuvant therapy and technical improvements, not much has changed...

But some are cured

Median OS 19 mo;
5-yr OS 20%
What must the surgeon do?

- Maximize local disease control
  - Good anatomic staging
  - Good surgery
  - Preoperative chemoradiation

- Offer aggressive surgical procedures at the right time to the right patients
  - Demonstrate early systemic control
  - Optimize patient physiology

*We use a “selectively aggressive” approach*
What can the surgeon do?

• Maximize local disease control
  – Good anatomic staging
  – Good surgery
  – Preoperative chemoradiation

• Offer aggressive surgical procedures at the right time to the right patients
  – Demonstrate early systemic control
  – Optimize patient physiology

We use a “selectively aggressive” approach
Surgical Quality Matters

### Annual Hospital Volume

<table>
<thead>
<tr>
<th>Surgical Cases</th>
<th>Very Low (&lt;1)</th>
<th>Low (1-2)</th>
<th>Medium (3-4)</th>
<th>High (5-13)</th>
<th>Very High (&gt;13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated Patients/yr</td>
<td>518</td>
<td>914</td>
<td>625</td>
<td>718</td>
<td>715</td>
</tr>
<tr>
<td>Operative Mortality (%)</td>
<td>16.3</td>
<td>14.6</td>
<td>11.0</td>
<td>7.2</td>
<td>3.8</td>
</tr>
</tbody>
</table>

- **Operative Mortality Difference**
- **Late Mortality Difference**

$\Delta = 1.9$ years

Finlayson, JACS 2003
### Influence of margin status on survival

<table>
<thead>
<tr>
<th>Series (Year)</th>
<th>N</th>
<th>Margin Status</th>
<th>%</th>
<th>Median OS (Mos.)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johns Hopkins (2006)</td>
<td>1175</td>
<td>R1/R2</td>
<td>42</td>
<td>14</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R0</td>
<td>58</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>University of Leeds -</td>
<td>26</td>
<td>R1</td>
<td>85</td>
<td>11</td>
<td>0.01</td>
</tr>
<tr>
<td>UK (2006)</td>
<td></td>
<td>R0</td>
<td>15</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>ESPAC -1 (2001)</td>
<td>541</td>
<td>R1</td>
<td>19</td>
<td>11</td>
<td>0.006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R0</td>
<td>81</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>University of Naples -</td>
<td>75</td>
<td>R1/R2</td>
<td>20</td>
<td>9</td>
<td>0.001</td>
</tr>
<tr>
<td>Italy (2000)</td>
<td></td>
<td>R0</td>
<td>80</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Rush-Presbyterian-St.</td>
<td>75</td>
<td>R1</td>
<td>29</td>
<td>8</td>
<td>0.01</td>
</tr>
<tr>
<td>MGH (1993)</td>
<td>72</td>
<td>R1/R2</td>
<td>51</td>
<td>12</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R0</td>
<td>49</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

At least *macroscopically complete resection is critical to OS*
Prospective identification of anatomically resectable pancreatic cancer

- Absence of extrapancreatic disease
- Tissue plane between tumor and SMA/CA
- Patent SMV-PV confluence

Criteria yield high rates of microscopically complete (R0) resection
Rectal Cancer: Lessons Learned & Ignored

SMA margin positive 10 – 85% and 80% die with LR

Good staging is not enough!
Proper dissection of SMA (mesopancreas)
R0: CT is Not a Microscope

Occult vascular/neural extension ubiquitous
The SMA margin distance is routinely overestimated by preoperative CT.
SMA margin distance measured histopathologically following pancreaticoduodenectomy

<table>
<thead>
<tr>
<th>SMA Margin Distance</th>
<th>N (n = 194)</th>
<th>Preop CXRT (n = 147)</th>
<th>Initial Surgery (n = 47)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>8</td>
<td>3 (2)</td>
<td>5 (11)</td>
<td></td>
</tr>
<tr>
<td>≤1mm</td>
<td>40</td>
<td>28 (19)</td>
<td>12 (26)</td>
<td>0.01</td>
</tr>
<tr>
<td>&gt;1mm &lt; 1cm</td>
<td>72</td>
<td>53 (36)</td>
<td>19 (40)</td>
<td></td>
</tr>
<tr>
<td>≥1cm</td>
<td>66</td>
<td>57 (39)</td>
<td>9 (19)</td>
<td></td>
</tr>
</tbody>
</table>

* Not recorded in 8 patients

Preop CXRT associated with longer SMA margin distance even though include all patients with borderline resectable disease
Time to Local Recurrence

Preoperative CXRT prolongs time to LR

Greer, JACS 2008
Disease Free Survival

Margin length and preop CXRT prolong DFS

Katz, JOGS 2011
Local Resectability

Technically, a R0 resection can only be predicted from an analysis of the relationship between the treated anastomosis and the surrounding vasculature.
# Surgery First: PDAC with Vascular Involvement

<table>
<thead>
<tr>
<th></th>
<th>R (n = 137)</th>
<th>PV (n = 91)</th>
<th>CHA (n = 21)</th>
<th>SMA (n = 30)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>65%</td>
<td>80%</td>
<td>86%</td>
<td>93%</td>
<td>0.001</td>
</tr>
<tr>
<td>R0</td>
<td>77%</td>
<td>70%</td>
<td>48%</td>
<td>37%</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

R, MST 24.4  
PV, MST 14.9  
CHA, MST 14.3  
SMA, MST 12.8  
UR, MST 8.1

*Yamada, Pancreas 2013*
Surgery First: PDAC with Vascular Involvement

<table>
<thead>
<tr>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
<th>Type D</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Type A" /></td>
<td><img src="image2" alt="Type B" /></td>
<td><img src="image3" alt="Type C" /></td>
<td><img src="image4" alt="Type D" /></td>
</tr>
</tbody>
</table>

![Overall survival graph with legend](image5)

Nakao, Ann Surg 2012
## Local Disease Staging

<table>
<thead>
<tr>
<th></th>
<th>Potentially Resectable</th>
<th>Borderline Resectable*</th>
<th>Locally Advanced</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SMV-PV</strong></td>
<td>T-V-I &lt; 180°</td>
<td>T-V-I ≥ 180° and / or reconstructable occlusion</td>
<td>Unreconstructable Occlusion</td>
</tr>
<tr>
<td><strong>SMA</strong></td>
<td>No T-V-I</td>
<td>T-V-I &lt; 180°</td>
<td>T-V-I ≥ 180°</td>
</tr>
<tr>
<td><strong>CHA</strong></td>
<td>No T-V-I</td>
<td>Reconstructable short-segment T-V-I of any degree</td>
<td>Unreconstructable</td>
</tr>
<tr>
<td><strong>Celiac Trunk</strong></td>
<td>No T-V-I</td>
<td>T-V-I &lt; 180°</td>
<td>T-V-I ≥ 180</td>
</tr>
</tbody>
</table>

*, Intergroup Definition; T-V-I: tumor-vessel interface
Borderline Resectable PDAC Consensus Treatment Algorithm

- Treatment phase
- Break ~ 6 wks

- Staging CT
- Classification as Borderline
- Restaging
- Dropout

- CTX
- CXRT
- Restaging
- OR
- Dropout

Katz, JACS 2008
Callery, Ann Surg Onc 2009
Borderline Resectable PDAC

Low chance of R0 resection based on anatomic relationship of primary tumor with mesenteric vasculature, but technically removable
Change in stage of 122 patients restaged following neoadjuvant therapy

<table>
<thead>
<tr>
<th>Stage Change</th>
<th>Example</th>
<th>N (%)</th>
<th>Resected n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change</td>
<td><img src="image" alt="No change example" /></td>
<td>98 (80)</td>
<td>82 (84)</td>
</tr>
<tr>
<td>Downstaged</td>
<td><img src="image" alt="Downstaged example" /></td>
<td>1 (1)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Upstaged (Local)</td>
<td><img src="image" alt="Upstaged example" /></td>
<td>2 (2)</td>
<td>2 (100)</td>
</tr>
</tbody>
</table>

21 (17%) upstaged due to metastases, 0 resected

Katz, Cancer 2012
## Clinicopathologic Profile of 85 (66%) Resected Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD Anderson Borderline Resectable</td>
<td>46 (54)</td>
</tr>
<tr>
<td>Pancreaticoduodenectomy</td>
<td>76 (90)</td>
</tr>
<tr>
<td>Vascular Resection*</td>
<td>51 (60)</td>
</tr>
<tr>
<td>R0</td>
<td>81 (95)</td>
</tr>
<tr>
<td>N0</td>
<td>41 (48)</td>
</tr>
<tr>
<td>Treatment Effect III/IV</td>
<td>14 (17)</td>
</tr>
<tr>
<td>SMA Margin Distance &gt; 1mm</td>
<td>52 (74)</td>
</tr>
</tbody>
</table>

* 86% venous, 2% hepatic arterial, 12% both
We Operate on Patients Not CT Scans

50% of patients are “borderline”

- A (anatomy): Anatomically borderline resectable tumor
- B (biology): Indeterminant extrapancreatic metastasis
- C (condition): Marginal performance status

Katz, JACS 2008
What must the surgeon do?

• Maximize local disease control
  – Good anatomic staging
  – Good surgery
  – Preoperative chemoradiation

• Offer aggressive surgical procedures at the right time to the right patients
  – Demonstrate early systemic control
  – Optimize patient physiology

*We use a “selectively aggressive” approach*
Resectable Tumor, Borderline Patient

- Indeterminate lung nodules
- CA 19-9: 3000
- LN’s on EUS
- 85 years old
- CHF
- Needs CABG
- PS ECOG 2-

*Preoperative therapy offers a means to determine role for surgery*
ALL PATIENTS PRESENTING WITH DIAGNOSIS OF PANCREATIC ADENOCARCINOMA

RADIOGRAPHIC IMAGING, LABORATORY TESTING, HISTORY AND PE

C:
CONDITIONAL STAGING

PERFORMANCE STATUS FIT FOR SURGERY

NO

Borderline - C
Resectable - C

Unresectable - C

Definitive Non-Surgical Therapy
Prehab, Optimization, Chemo/XRT
Go to Biological Staging B:
Re-Stage ABC

? Y

Borderline - C
Resectable - C

Unresectable - B

Definitive Non-Surgical Therapy
Chemo/XRT
Go to CA19-9
Re-Stage ABC

? NO

Borderline - C
Resectable - B

Unresectable - B

Go to Anatomic Staging A:
Re-Stage ABC

HIGH

LOW

A:
ANATOMIC STAGING

ANATOMIC RESECTABILITY

NO

Borderline - A
Resectable - A

Unresectable - A

Definitive Non-Surgical Therapy
Chemo/XRT
Surgery First Or Neoadjuvant
Re-Stage ABC

? Y

Borderline - A
Resectable - B

Unresectable - B

Go to Anatomic Staging A:
Re-Stage ABC

DISTANT METS

CA19-9 LEVEL

B:
BIOLOGICAL STAGING

NO

Borderline - A
Resectable - B

Unresectable - B

Go to Chemo/XRT T
Re-Stage ABC

? NO

Borderline - B
Resectable - B

Unresectable - A

Go to Definitive Non-Surgical Therapy
Re-Stage ABC

HIGH

LOW
Treatment Program

<table>
<thead>
<tr>
<th>Treatment phase</th>
<th>Break ~ 6 wks</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTX</td>
<td>CXRT</td>
</tr>
</tbody>
</table>

Restaging

Clinical Assessment

Staging CT

- Assessment of “tumor biology”
- Assessment of patient physiologic state
- Local control concerns
- Likelihood of surgery
- Psychosocial concerns and logistics
- Modulate agents based upon PS, etc.
Case A

- A 71 year old woman presented with jaundice and 20 lb weight loss. No pain.
- PMH unremarkable, PS 80
- CA 19-9 431 U/ml, TB 0.5
Case A

• Gem-cis x 4 cycles

• ChemoXRT: 50g with capecitabine

• No change in imaging, but CA 19-9 down to 16 U/ml
Venous/Hepatic Arterial Resection

Vein, artery, splenorenal shunt – selectively aggressive
Case A

• No major complications

• PDAC, 10 – 50% viable, 0/19 LN

• All margins negative, SMA length 3mm
Case B

- 65 yo woman brought in to clinic on stretcher (!?!?)
- New dx PDAC with painless jaundice
- Lethargic, anorexic, PS 50
- Prealbumin 15, CA 19-9 63, TB 13.9
- Admitted for decompression -> syncope
Case B

- EBRT 30g with capecitabine
- Cardiac/medical evaluations, nutrition, physical conditioning
- PS still low so gemcitabine x 3 months
- PS recovered to 70-80
Case B

- Scan unchanged, ca19-9 12 U/ml
- R0 PD with V1a
- Pathology: 1.5cm PDAC, 50% viable, 0/23LN, T1N0 R0, SMA length 10mm
Case C

• 71 yo woman with new PDAC with painless jaundice

• EUS showed mass, FNA regional lymph node positive for cancer

• Ca19-9 864 U/ml, TB 0.5 following stent
Case C
Case C

- Gem-Cis x 3 months
- EBRT 50.4g with capecitabine
- CT unchanged, CA 19-9 177 U/ml
- R0 PD with segmental vein
- 4cm, 80% viable, 3/30 LN, SMA length 5mm
Borderline Resectable Anatomy

Median OS 33 v 12 months, p < 0.001
Borderline Resectable B and C

Survival (Months)

Proportion Surviving

- Resection/BR-B: death/n = 14/19
- Resection/BR-C: death/n = 9/14
- Resection/CR: death/n = 65/103
- No resection/BR-B: death/n = 22/22
- No resection/BR-C: death/n = 24/24
- No resection/CR: death/n = 35/35

$p=0.215$
$p=0.442$
$p<0.001$
Unanswered Questions

• What treatment modalities should be used and when?
• How can treatment sequencing best be individualized?
• What are optimal cytotoxics and radiosensitizers?
• How long is “long enough” (and “too long”)?
• How can response to preoperative therapy be measured?
• When is postoperative therapy also indicated?
Summary

• Surgeon plays a critical role

• Good technical operation is key

• Individualized preoperative strategies can optimize timing and selection for surgery

• Future research is needed!
Thank you

Matthew Katz
mhgkatz@mdanderson.org