Resectable, Borderline, and Locally Advanced Pancreatic Cancer

Surgical Oncologist Perspective

Mike Moser

Disclosure

I do not have a financial interest, arrangement, or affiliation with a commercial organization that may have a direct or indirect interest in the subject matter of my presentation.
The question

- Few actual surgical RCT’s

- The question to be answered in this talk is:
  - Surgery first or something else first?

- AHPBA, ISGPS, ASCO, MDACC, AJCC, European Alliance, etc.

Challenges

- no standard definition of borderline resectable

- high and medium volume centres

- most of the literature focused on cancers in the head of the pancreas
Assessment of resectability

“It’s about the vessels”

- CT scan Abd +/- chest and pelvis.
- MRI used as a problem-solving tool
- EUS
- PET
- laparoscopy

Tumor contact with vessels

<table>
<thead>
<tr>
<th>Contact Type</th>
<th>Degree of Contact</th>
<th>Invasion Chance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abutment</td>
<td>&lt; 180°</td>
<td>40%</td>
</tr>
<tr>
<td>Encasement</td>
<td>&gt; 180°</td>
<td>80%</td>
</tr>
<tr>
<td></td>
<td>&gt; 270°</td>
<td>100%</td>
</tr>
</tbody>
</table>

(40% chance of invasion)  (80% chance of invasion)  (100% chance of invasion)
SMV / PV resection

- Compared 128 pts with vein resection to 449 without vein resection between 1994 and 2005
- Complications were about 40% in each group and mortality was approx. 4% in each group.

SMV / PV resection

- meta-analysis examining 19 studies including 661 patients with venous resection versus 2247 patients without.
- Again, no difference in perioperative morbidity or mortality
- Similar survival at 1, 3, and 5 years (61, 19, 12 for patients with venous resection) versus (62, 27, 17 for those without)
- In centres comfortable with vein resection, vein resection does not increase the morbidity nor mortality, nor decrease overall survival.

Zhou et al, HPB Surg 2012

Arterial resection

- 29 patients with arterial resection (largest series)
- 449 standard pancreatic resection
- higher morbidity (38% vs. 20%) and higher mortality (14% vs 4%)
- Similar median survival (14 vs. 15.8 months)

Bockhorn et al, BJS 2010
Arterial resection: meta-analysis

• 26 studies; all retrospective; small numbers.

Perioperative mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Arterial resection</th>
<th>No arterial resection</th>
<th>Odds Ratio M-H Random 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beeghly (2006)</td>
<td>4</td>
<td>29</td>
<td>0.92 (0.5, 1.6)</td>
</tr>
<tr>
<td>Wang (1998)</td>
<td>3</td>
<td>14</td>
<td>0.65 (0.3, 1.2)</td>
</tr>
<tr>
<td>Koenig (2011)</td>
<td>2</td>
<td>6</td>
<td>3.52 (1.8, 6.8)</td>
</tr>
<tr>
<td>Klennsorkir (1994)</td>
<td>5</td>
<td>16</td>
<td>9.45 (4.2, 21.1)</td>
</tr>
<tr>
<td>Hartman (1997)</td>
<td>0</td>
<td>5</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Ogawa (2007)</td>
<td>5</td>
<td>21</td>
<td>2.45 (1, 6.2)</td>
</tr>
<tr>
<td>Okada (2006)</td>
<td>1</td>
<td>8</td>
<td>1.31 (0.4, 3.9)</td>
</tr>
<tr>
<td>Shiraki (2006)</td>
<td>0</td>
<td>12</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Shintani (2001)</td>
<td>0</td>
<td>5</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Wang (2006)</td>
<td>1</td>
<td>9</td>
<td>3.12 (1.1, 8.3)</td>
</tr>
<tr>
<td>Wu (2013)</td>
<td>0</td>
<td>9</td>
<td>0.69 (0.3, 1.5)</td>
</tr>
</tbody>
</table>

Total (95% CI) 133 1002 1000 1.00 (1.25, 0.45)

Mollberg et al, Ann Surg 2011

No consensus among the consensuses

<table>
<thead>
<tr>
<th>Blood Vessel</th>
<th>AHPBA/Consensus</th>
<th>MD Anderson Cancer Center</th>
<th>National Comprehensive Cancer Network</th>
<th>Alliance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMV/PV</td>
<td>Abutment, encasement of the SMV/PV or short segment encasement of the SMV/PV</td>
<td>Abutment, short segment occlusion, resectible necrosis of the SMV/PV</td>
<td>Distortion or narrowing of the vessel wall, and/or resectible occlusion of the vessel wall</td>
<td>Tumor-vessel interface is 90 degrees of the circumference of the vessel wall, and/or resectible occlusion</td>
</tr>
<tr>
<td>SMA</td>
<td>Abutment</td>
<td>Abutment</td>
<td>Tumor-vessel interface is 180 degrees of the circumference of the vessel wall</td>
<td>Tumor-vessel interface is 180 degrees of the circumference of the vessel wall</td>
</tr>
<tr>
<td>CA</td>
<td>Uninvolved</td>
<td>Abutment</td>
<td>Tumor-vessel interface is 180 degrees of the circumference of the vessel wall, and/or resectible occlusion of the vessel wall</td>
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</tr>
<tr>
<td>HA</td>
<td>Abutment or short segment encasement</td>
<td>Abutment or short segment encasement</td>
<td>Reconstructible short segment interface between tumor and vessel</td>
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</tr>
</tbody>
</table>

Abbreviations: AHPBA, American Hepato-Pancreato-Biliary Association; CA, celiac artery; HA, hepatic artery; PV, portal vein; SMA, superior mesenteric artery; SMV, superior mesenteric vein.
NCCN Guidelines 2016

Resectability Status

<table>
<thead>
<tr>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>No arterial tumor contact (pelvic axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).</td>
</tr>
<tr>
<td>Resectable</td>
<td>No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or 15° contact without vein contour irregularity.</td>
</tr>
<tr>
<td>Resectable*</td>
<td>Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.</td>
</tr>
<tr>
<td>Resectable*</td>
<td>Solid tumor contact with the SMA or 15°.</td>
</tr>
<tr>
<td>Resectable*</td>
<td>Presence of variant arterial anatomy (i.e., accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origins of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning.</td>
</tr>
<tr>
<td>Resectable*</td>
<td>Solid tumor contact with the CA of 15°.</td>
</tr>
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<td>Resectable*</td>
<td>Solid tumor contact with the CA of 15° without involvement of the aorta and with intact and uninvolved gastroduodenal artery (some members prefer this criteria to be in the unresectable category).</td>
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<tr>
<td>Unresectable*</td>
<td>Distant metastasis (including non-regional lymph node metastasis) should exclude process.</td>
</tr>
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<td>Unresectable*</td>
<td>Unresectable SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus).</td>
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<td>Contact with mesenteric draining jejunal branch into SMV.</td>
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Resectable

- CHA, CA, SMA: no tumor contact
- SMV = PV: no tumor contact (or abutment of SMV/PV, but without vein contour irregularity)
- 85-90% will indeed be resectable
Locally advanced pancreatic cancer (LAPC)

- SMA encasement
- CA encasement
- First jejunal SMA branch involvement
- SMV/PV Unreconstructible due to tumor involvement or occlusion
- SMV contact with the proximal draining jejunal branch into SMV

Credit: Dr. Michael Choti, UT Southwestern
Treatment of 200 Locally Advanced (Stage III) Pancreatic Adenocarcinoma Patients With Irreversible Electroporation

Safety and Efficacy

Robert C. G. Martin, II, MD, PhD, FACS; David Koo, MD, FACS; Sriharan Chathibanda, MD, FACS; Mary Sellers, MD, MPH, FACS; Eric Koe, MD; Charles Scoggins, MD, MBA, FACS; Kelly M. McMasters, MD, PhD, FACS, and Kevin Whitlow, MD, FACS

• Annals of Surgery September 2015

• Median survival 24.9 months
• Most recurrences were distant
• Zero cases of pancreatitis!

Safe around vessels, ducts, and nerves

• Cell death from punching holes in cells,

• But, since there is no heat
  • there is no effect on the non-cellular parts
  • (collagen scaffolding in vessels, ducts, nerves)
70 microsecond pulses of 3000 V via 19G electrode
90 pulses per pair of electrodes
No heat

Borderline Resectable Pancreatic Cancer (BRPC)

Somewhere in between resectable and locally advanced.
“Imaging features that would make a R0 resection much less likely”
### NCCN Guidelines 2016

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| Borderline Resectable | Pancreatic head 
unresectable process:  
- Solid tumor contact with the SMV at 135°  
- Presence of variant arterial anatomy (e.g., accessory right hepatic artery; replaced right hepatic artery; replaced CA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be specified if present as it may affect surgical planning.  
Pancreatic body:  
- Solid tumor contact with the CA at ≥150°  
- Solid tumor contact with the CA of ≥150° without involvement of the aorta and with intact and unobstructed gastroduodenal artery (some members prefer this criteria to be in the unresectable category). | Solid tumor contact with the CA at ≥150°  
- Solid tumor contact with the CA at ≥135° with or without involvement of the aorta and with intact and unobstructed gastroduodenal artery (some members prefer this criteria to be in the unresectable category). |
| Unresectable         | Distal metastases (including non-regional lymph node metastasis)  
Head/neck/upper torso:  
- Solid tumor contact with the SMA at ≥180°  
- Solid tumor contact with the CA at ≥150°  
- Solid tumor contact with the first jejunal SMA branch  
Body and tail:  
- Solid tumor contact with the SMA at ≥150°  
- Solid tumor contact with the CA at ≥150°  
- Solid tumor contact with the CA at ≥135° with or without involvement of the aorta and with intact and unobstructed gastroduodenal artery (some members prefer this criteria to be in the unresectable category). | Unresectable process:  
- Unresectable SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)  
- Contact with most proximal draining jejunal branch into SMV  
Body and tail:  
- Unresectable SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) |

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### “Simplified borderline criteria”

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Pancreatic body:  
- Solid tumor contact with the CA at ≥150°  
- Solid tumor contact with the CA of ≥150° without involvement of the aorta and with intact and unobstructed gastroduodenal artery (some members prefer this criteria to be in the unresectable category). | Solid tumor contact with the SMV or PV or ≥135° with or without involvement of the CA in contact or with intact and unobstructed gastroduodenal artery (some members prefer this criteria to be in the unresectable category). |
| Unresectable         | Distal metastases (including non-regional lymph node metastasis)  
Head/neck/upper torso:  
- Solid tumor contact with the SMA at ≥180°  
- Solid tumor contact with the CA at ≥150°  
- Solid tumor contact with the first jejunal SMA branch  
Body and tail:  
- Solid tumor contact with the SMA at ≥150°  
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- Solid tumor contact with the CA at ≥135° with or without involvement of the aorta and with intact and unobstructed gastroduodenal artery (some members prefer this criteria to be in the unresectable category). | Unresectable process:  
- Unresectable SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus)  
- Contact with most proximal draining jejunal branch into SMV  
Body and tail:  
- Unresectable SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus) |
In HPB Rounds

• 56F with painless jaundice, 35 lb weight loss, severe back pain.
• CT shows 2 cm mass in head of the pancreas, no vascular contact, no liver masses, no obvious nodes, no GOO.
• ERCP stent, then CA 19.9 done = 692 U/mL.

Calling a tumor “borderline” on imaging tells us nothing about what we should do with it!

• Anatomy
• Disseminated Disease? (laparoscopy? PET scan)
  • bulky tumor
  • bulky nodes
  • symptomatic patient – esp back pain
  • weight loss > 10%
  • high Ca 19.9 > 400 U/mL.
  • suspicious liver lesion (but not confirmed met)
• Medical: performance status, comorbidities
• Future: genotypes
Back to the question:
Which patients should be offered surgery first?

Resectable

- CHA, CA, SMA: no tumor contact
- SMV / PV: no tumor contact
  - (or abutment of SMV / PV but without vein contour irregularity)*
- ~90% will indeed be resectable
Which patients should be offered surgery first?

- No metastases
- Anatomy: no tumor contact with SMA, HA, CA, SMV, PV
  - (SMV/PV involvement that is amenable to safe and clear resection and reconstruction)
- No hints of disseminated disease: Ca 19.9 > 400 U/mL, tumor > 5 cm, bulky lymph nodes, symptomatic patient, weight loss > 10%, suspicious liver lesion (but not confirmed met)
- Medical: Performance status 0 or 1 with minimal or no comorbidities

Which patients should NOT be offered surgery first?

- Anatomy: Locally advanced (encasement)
- Anatomy: ‘Borderline’- with artery (?) or vein (?) abutment that a program might not be accustomed to doing(?). All borderline?
- Possibility of disseminated disease: One or more of the following: Ca 19.9 > 400 U/mL, tumor > 5 cm, bulky lymph nodes, symptomatic patient, weight loss > 10%, suspicious liver lesion (but not confirmed met).
- Performance status or comorbidity profile not currently appropriate
Questions?

Questions for discussion

• Suspicion of resectable vein involvement: resect first or neoadjuvant first?
• Should all ‘borderline’ tumors go to neoadjuvant first? Venous invasion? Arterial invasion?
• How far do we go in establishing that there is no distant disease in ‘borderline’ and LAPC? laparoscopy? PET scan?
• Upcoming results of studies of neoadjuvant chemoRT in those lesions that appear to be resectable at presentation.
• Is there any role for genotypes currently?
Response of BRPC to Neoadjuvant Rx is not reflected by radiographic indicators.

- 129 patients with Borderline or LAPC with two definitions
- All received Chemo (Gem) +/- Radiation and reimaged (only 12% had a partial response)
- 98 had no disease progression and taken to OR
- 85 underwent resection of which 81 (95%) had an R0 resection

Neoadjuvant Rx in the radiologically resectable patient

- No evidence yet to support an advantage of neoadjuvant in the patient considered to be resectable.
Resectable: surgery or neoadjuvant first?

IN THEORY, Neoadjuvant Chemo ± Radiation

- Possibly sterilize the periphery of the primary tumor to increase the chances of an R0 resection.
- Radiation reduces the pancreatic leak rate
- "Test of time"
- Treatment of micrometastatic disease at distant sites.
Neoadjuvant Rx for “Borderline” MDACC study

- MDACC 1999-2007

160 patients, 3 types of borderline
  - A: Anatomic
  - B: Concern over possible extrapancreatic disease
  - C: Marginal performance status

Neoadjuvant Rx for “Borderline”

- All received neoadjuvant Rx

- 66 / 160 had resection and 94% had R0 resection

- Median survival among those who had resection was 40 months
Neoadjuvant for “Borderline”

- 2 other studies
- different definitions of borderline
- different agents
- no comparison group
- retrospective

... still no good evidence to support neoadjuvant for “borderline”