Pancreas adenocarcinoma: Evolving treatment strategies

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SON Fall Update 2016, Oct 22 2016
CONFLICT OF INTEREST DECLARATION

I, Alice Wei declare that in the past 3 years:

I have been a member of an Advisory Board or equivalent with the following companies*: Ethicon, Histosonic, Celgene, Sanofi, Takeda, Bayer

I have been a member of the following speakers’ bureau: None

I have done speaking engagements for the following companies*: Sanofi, Celgene

I have received payment or funding from the following companies* (includes gifts, grants, honoraria, and ‘in kind’ compensation): None

I have done consulting work for the following companies*: Cancer Care Ontario

I have held a patent for a product referred to in the program or that is marketed by a commercial organization: None

I or my family hold individual shares in the following companies*: None

I have participated in a clinical trial for the following companies*: None

MANAGING POTENTIAL BIAS

no commercial uses will be discussed

*pharmaceutical, medical device, or communications companies
Learning Objectives

1. Understand the changing definitions of surgical resectability for pancreas adenocarcinoma

2. Learn about the evolving multi-modality strategies for the treatment of pancreas cancer
1. Survival remains dismal. Survival rates are unchanged over the past few decades
2. Giving chemotherapy +/- radiotherapy before surgery results in better survival than giving it after surgery
3. Borderline resectable tumours are determined by the relationship between the tumour and the vasculature
4. Outcomes following surgery depend on patient comorbidities
### Estimated New Cases of Cancer in 2015

#### Males

<table>
<thead>
<tr>
<th>Site</th>
<th>Percent</th>
<th>New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>23.9%</td>
<td>24,000</td>
</tr>
<tr>
<td>Colorectal</td>
<td>13.9%</td>
<td>13,600</td>
</tr>
<tr>
<td>Lung</td>
<td>13.5%</td>
<td>14,000</td>
</tr>
<tr>
<td>Bladder</td>
<td>6.1%</td>
<td>6,200</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>4.5%</td>
<td>4,500</td>
</tr>
<tr>
<td>Kidney</td>
<td>3.9%</td>
<td>3,900</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3.6%</td>
<td>3,700</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3.5%</td>
<td>3,500</td>
</tr>
<tr>
<td>Oral</td>
<td>2.9%</td>
<td>2,900</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td><strong>2.4%</strong></td>
<td><strong>2,400</strong></td>
</tr>
</tbody>
</table>

#### Females

<table>
<thead>
<tr>
<th>Site</th>
<th>Percent</th>
<th>New Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>25.9%</td>
<td>25,000</td>
</tr>
<tr>
<td>Lung</td>
<td>13.5%</td>
<td>13,000</td>
</tr>
<tr>
<td>Colorectal</td>
<td>11.5%</td>
<td>11,100</td>
</tr>
<tr>
<td>Body of uterus</td>
<td>6.5%</td>
<td>6,300</td>
</tr>
<tr>
<td>Thyroid</td>
<td>5.0%</td>
<td>4,800</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>3.8%</td>
<td>3,700</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3.2%</td>
<td>3,100</td>
</tr>
<tr>
<td>Ovary</td>
<td>2.9%</td>
<td>2,800</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2.8%</td>
<td>2,700</td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td><strong>2.5%</strong></td>
<td><strong>2,400</strong></td>
</tr>
</tbody>
</table>

The pancreas is the 10th most common site of new cancers in Canada (4,800 new cases total).
### Estimated Cancer Deaths in 2015

<table>
<thead>
<tr>
<th>Site</th>
<th>Percent</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>26.60%</td>
<td>10,900</td>
</tr>
<tr>
<td>Colorectal</td>
<td>12.4%</td>
<td>5,100</td>
</tr>
<tr>
<td>Prostate</td>
<td>10.1%</td>
<td>4,100</td>
</tr>
<tr>
<td>Pancreas</td>
<td>5.6%</td>
<td>2,300</td>
</tr>
<tr>
<td>Bladder</td>
<td>4.0%</td>
<td>1,600</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3.9%</td>
<td>1,600</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>3.8%</td>
<td>1,550</td>
</tr>
<tr>
<td>Esophagus</td>
<td>3.5%</td>
<td>1,450</td>
</tr>
<tr>
<td>Stomach</td>
<td>3.2%</td>
<td>1,300</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>3.0%</td>
<td>1,250</td>
</tr>
</tbody>
</table>

**Males**

- **41,000 Deaths**

<table>
<thead>
<tr>
<th>Site</th>
<th>Percent</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>27.0%</td>
<td>10,000</td>
</tr>
<tr>
<td>Breast</td>
<td>13.6%</td>
<td>5,000</td>
</tr>
<tr>
<td>Colorectal</td>
<td>11.5%</td>
<td>4,200</td>
</tr>
<tr>
<td>Pancreas</td>
<td>6.2%</td>
<td>2,300</td>
</tr>
<tr>
<td>Ovary</td>
<td>4.7%</td>
<td>1,750</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>3.3%</td>
<td>1,200</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3.1%</td>
<td>1,150</td>
</tr>
<tr>
<td>Body of uterus</td>
<td>2.8%</td>
<td>1,050</td>
</tr>
<tr>
<td>Brain/CNS</td>
<td>2.3%</td>
<td>860</td>
</tr>
<tr>
<td>Stomach</td>
<td>2.1%</td>
<td>760</td>
</tr>
</tbody>
</table>

**Females**

- **37,000 Deaths**

Pancreatic cancer incidence ≈ mortality rates

Pancreatic cancer is the 4th leading cause of cancer death among men and women in Canada (4,600 deaths total)
Clinical stage at diagnosis

- Resectable: 50%
- Locally Advanced: 30%
- Metastatic: 20%
# Prognosis and clinical stage

**Observed Survival**

<table>
<thead>
<tr>
<th>Stage</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
<th>5-year</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>40%</td>
<td>30%</td>
<td>20%</td>
<td>10%</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>Stage II</td>
<td>30%</td>
<td>20%</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
<td>20%</td>
</tr>
<tr>
<td>Stage III</td>
<td>20%</td>
<td>10%</td>
<td>5%</td>
<td>2.5%</td>
<td>2.5%</td>
<td>10%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>10%</td>
<td>5%</td>
<td>2.5%</td>
<td>1%</td>
<td>1%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Median survival**

- Stage I: 9.6 months
- Stage II: 8.9 months
- Stage III: 7.7 months
- Stage IV: 2.5 months
- Overall: 4.4 months

Goals of Treatment

- Surgical resection is the only curative treatment for pancreatic cancer
- Primary goals of treatment for locally advanced disease:
  - Conversion therapy
    Neoadjuvant therapy for initially unresectable disease with the goal of conversion to resectable status
  - Improved survival
    - Usually only beneficial to patients with adequate performance status (ECOG performance status 0 or 1, good pain management, patent biliary stent, and adequate nutritional intake)
  - Palliation and improved quality of life
    - Multidisciplinary management of symptoms due to biliary obstruction, gastric outlet obstruction, and cancer-related pain
    - Prevent and lessen/relieve suffering while ensuring optimal quality of life

ECOG, Eastern Cooperative Oncology Group.
How do we get to this?
Role of surgery for pancreatic adenocarcinoma

- best for long term survival
  - median OS 20-27 months\(^1-4\)

- Goals of surgery
  - relief of symptoms
  - obtain R0 resection

- Multi-modality Rx optimal

- MCC discussion required for resectability\(^5\)
  - important for LAPC

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1. Serrano PE, Ann Surg Oncol, April 2015, 22, 1160-7
5. NCCN Pancreatic Cancer Guidelines 2.2015
Adjuvant therapy is important

**Key Points**
- Median OS
  - No adjuvant therapy: 17 (95% CI: 15-22)
  - Adjuvant therapy: 26 (95% CI: 23-31)
  - \( P = 0.02 \)

**Survival Analysis**
- Time from resection, years

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>No Adjuvant Therapy</th>
<th>Adjuvant Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>185</td>
<td>248</td>
</tr>
<tr>
<td>1</td>
<td>127</td>
<td>200</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>130</td>
</tr>
<tr>
<td>3</td>
<td>51</td>
<td>73</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>46</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>36</td>
</tr>
</tbody>
</table>

Serrano PE, Ann Surg Oncol, April 2015, 22, 1160-7
New adjuvant regimens on the horizon?

- 5 FU and gemcitabine\textsuperscript{1,2}
  - OS $\sim$ 20-23 months
  - Gemcitabine $\rightarrow$ ↓ side effects

- ESPAC-4 $\rightarrow$ Gem/capecitabine vs. Gem\textsuperscript{3}
  - 730 pts analyzed
  - OS GEM/CAP = 28.0 months (95% CI: 23.5 – 31.5) vs GEM = 25.5 months (22.7 – 27.9)

- Trial results pending
  - Folfirinox vs. Gem(PA.6)
  - Gem/Abraxane vs. Gem
  - accrual complete
Pancreatectomy has evolved

- Patient selection is better
  - staging is more sensitive
  - CT/ EUS/ MRI

- Pancreatectomy is safer
- Volume-outcome relationship\(^1-4\)
  - \(\uparrow\) volumes =
    - \(\downarrow\) peri-operative mortality
    - \(\downarrow\) cancer related mortality

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1. Finlay C, CPAC 2015
Technical advances allow bigger resections

- Vascular resections
  - PV resection routine
  - arterial resections
    - increasing experience
- Minimally invasive surgery
  - staging laparoscopy
  - laparoscopic/robotic pancreatectomies
- More complex resections
  - obtain negative margin
- Better perioperative care

![Image: SMV and SMA resection with SFV graft]
Key principles of resectability

- Localized disease
  - no evidence of metastatic disease

- Resectable with R0 intent
  - recognition of need for vascular resection/reconstruction
  - judicious use of arterial resection in selected populations may have a role

- Adequate performance status
Important Surgical Outcomes

- **Negative margins**
  - rates of positive margins
  - < 1mm or tumour at margin?
  - difficulty in assessing margins
  - most margins are R1\(^1,2\)
  - 5 mm margin optimal

- **Adequate lymph nodes retrieval**
  - ≥ 12 lymph nodes\(^3\)
  - LN Ratio < 0.2 better if N1\(^4\)

- **Complications**
  - anastomotic leaks
  - delayed gastric emptying
  - bleeding
  - endocrine/exocrine insufficiency

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### Complications after pancreaticoduodenectomy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 635</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Overall complications</td>
<td>323</td>
<td>51</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>14</td>
<td>2.2</td>
</tr>
<tr>
<td>Intra-abdominal bleed</td>
<td>32</td>
<td>5</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>Wound infection</td>
<td>76</td>
<td>12</td>
</tr>
<tr>
<td>Major complications</td>
<td>132</td>
<td>21</td>
</tr>
<tr>
<td>Delayed gastric emptying</td>
<td>72</td>
<td>11</td>
</tr>
<tr>
<td>Pancreatic leak</td>
<td>73</td>
<td>12</td>
</tr>
<tr>
<td>Grade A</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Grade B*</td>
<td>45</td>
<td>7</td>
</tr>
<tr>
<td>Grade C</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Intra-abdominal abscess</td>
<td>133</td>
<td>21</td>
</tr>
<tr>
<td>Clavien Grade IIIa</td>
<td>104</td>
<td>16</td>
</tr>
<tr>
<td>Clavien Grade IIIb</td>
<td>34</td>
<td>5</td>
</tr>
<tr>
<td>Perioperative mortality</td>
<td>9</td>
<td>1.4</td>
</tr>
</tbody>
</table>

1. UHN/ MSH data 2000-2010, manuscript in progress
Assessing resectability

- dedicated pancreatic imaging
  - CT preferred $\rightarrow$ MRI for problem solving
  - What is the relationship to vessels?
  - Are metastases present?
- Tissue diagnosis
  - mandatory for neoadjuvant therapy
  - use EUS unless never-resectable
- Laparoscopy/ PET
  - limited role
Clinical spectrum of resectability

Resectable

Borderline Resectable

Unresectable

R0 likely

R1 likely
Surgery possible but results suboptimal
Resectable pancreatic cancer

- No metastases
- Venous involvement absent or minimal (<180° no deformity)
- Normal arterial tissue planes
- Rx:
  - Upfront resection standard
  - Neoadjuvant therapy only
    - High risk patients
    - Clinical trial

2. NCCN guidelines version 2.2012, assessed March 18 13
Borderline resectable disease

- Technically resectable but high risk for margin-positive resection
- Subset of locally advanced disease
- Various classification systems
  - NCCN Guidelines
  - MD Anderson Cancer Center
- Neoadjuvant treatment common

# NCCN (2016) Criteria for resectability

<table>
<thead>
<tr>
<th>Resectability Status</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>- No arterial tumor contact (celiac axis [CA], superior mesenteric artery [SMA], or common hepatic artery [CHA]).</td>
<td>- No tumor contact with the superior mesenteric vein (SMV) or portal vein (PV) or ( \leq 180^\circ ) contact without vein contour irregularity.</td>
</tr>
</tbody>
</table>
| Borderline Resectable | - **Pancreatic head/uncinate process:**
  - Solid tumor contact with CHA without extension to celiac axis or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.
  - Solid tumor contact with the SMA of \( \leq 180^\circ \)
  - Presence of variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present as it may affect surgical planning.
  - **Pancreatic body/tail:**
    - Solid tumor contact with the CA of \( \leq 180^\circ \)
    - Solid tumor contact with the CA of \( > 180^\circ \) without involvement of the aorta and with intact and uninvolved gastroduodenal artery [some members prefer this criteria to be in the unresectable category].
| - **Head/uncinate process:**
  - Solid tumor contact with SMA \( > 180^\circ \)
  - Solid tumor contact with the CA \( > 180^\circ \)
  - Solid tumor contact with the first jejunal SMA branch.
  - **Body and tail**
    - Solid tumor contact of \( > 180^\circ \) with the SMA or CA
    - Solid tumor contact with the CA and aortic involvement. |
| Unresectable         | - Distant metastasis (including non-regional lymph node metastasis)
  - **Head/uncinate process:**
    - Unreconstructible 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**
    - Unreconstructible SMV/PV due to tumor involvement or occlusion (can be due to tumor or bland thrombus). |

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1. NCCN, guidelines version 2-2016, assessed Sept 5 2016

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[Logo: UHN Princess Margaret Cancer Centre]
Arterial involvement

- Solid contact with CHA that is reconstructable
- Solid contact with SMA
- Solid contact with celiac axis ≤ 180 (or ≥ 180 when aorta/GDA clear)
Venous involvement

- Solid tumour contact $\geq 180 \text{ or } < 180$ with deformity or thrombus, that is suitable for reconstruction
MD Anderson Classification

- **Type A:** vascular involvement
- **Type B:** potential metastases
- **Type C:** poor performance status

---

Table 1. Clinical and Demographic Characteristics of 160 Patients with Borderline Resectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients</th>
<th>Borderline resectable type</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients, n</td>
<td>160</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td>63 (65)</td>
<td>60 (61)</td>
</tr>
<tr>
<td>Median (mean)</td>
<td></td>
<td>36.90</td>
<td>37.81</td>
</tr>
<tr>
<td>Range</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td>84 (52)</td>
<td>37 (44)</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>47 (56)</td>
<td>18 (41)</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Tumor location in pancreas, n (%)</td>
<td></td>
<td>142 (89)</td>
<td>73 (87)</td>
</tr>
<tr>
<td>Head/uncinate</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Body/tail</td>
<td></td>
<td>18 (11)</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Preference laparotomy, n (%)</td>
<td></td>
<td>38 (24)</td>
<td>16 (19)</td>
</tr>
<tr>
<td>Bypass</td>
<td></td>
<td>31 (19)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>External-beam radiation</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Pretreatment CA19-9, U/mL</td>
<td></td>
<td>7 (4)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Pretreatment</td>
<td></td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>


---

Table 3. Rates of Resection, Pathologic Response, and Survival for 160 Patients with Borderline Resectable Pancreatic Cancer

<table>
<thead>
<tr>
<th>MD Anderson borderline type</th>
<th>Total</th>
<th>Resected</th>
<th>Treatment effect Iib, III, or IV*</th>
<th>Median survival, mo</th>
<th>Patients who did not undergo resection</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>84</td>
<td>52</td>
<td>32 (38)</td>
<td>19 (59)</td>
<td>40</td>
<td>0.001</td>
</tr>
<tr>
<td>B</td>
<td>44</td>
<td>28</td>
<td>22 (50)</td>
<td>13 (59)</td>
<td>29</td>
<td>0.001</td>
</tr>
<tr>
<td>C</td>
<td>32</td>
<td>20</td>
<td>12 (38)</td>
<td>5 (42)</td>
<td>39</td>
<td>0.0009</td>
</tr>
<tr>
<td>Total</td>
<td>160</td>
<td>66</td>
<td>41 (37)</td>
<td>37 (56)</td>
<td>40</td>
<td>0.001</td>
</tr>
</tbody>
</table>

1. Percent of patients with that type of disease who underwent resection treatment effect not reported in 3 of 66 patients who underwent pancreatectomy.
2. p Value for comparison of median survival times of resected and nonresected patients.

---

Conversion therapy → downstaging?

- shrink locally advanced to potentially resectable?
- previous era
  - very little downstaging
  - very little pathologic response
- new regimens
  - Folfirinox
  - Gemcitabine-abraxane
- Radiologic response ≠ tumour response

1 Bloomston M, Ann Surg Oncol, 2015
Case 1

pT3N1 (8/20), extensive residual tumour

6 cycles Gem-Abraxane
Conclusions

- Resectability depends on
  - anatomic features of tumor
  - cancer biology
  - patient physiology
- Borderline resectable/Locally advanced cancers
  - resectability is surgeon dependent
  - multimodality approach
  - vascular reconstruction often required