Pancreatic Cancer Updates in Management

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Division of Surgical Oncology
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2017 Estimated Deaths from Cancer in the United States

<table>
<thead>
<tr>
<th>Estimated Deaths</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>84,590</td>
<td>71,280</td>
</tr>
<tr>
<td>Prostate</td>
<td>26,730</td>
<td>23,110</td>
</tr>
<tr>
<td>Pancreas</td>
<td>22,300</td>
<td>20,790</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>19,610</td>
<td>14,080</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,300</td>
<td>10,920</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,720</td>
<td>10,200</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,240</td>
<td>9,310</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,450</td>
<td>8,690</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,620</td>
<td>7,080</td>
</tr>
<tr>
<td>All Sites</td>
<td>318,420</td>
<td>282,500</td>
</tr>
</tbody>
</table>

2020 Pancreas cancer will be the 2nd leading cause of death in the US
Aims

• Discuss management and surveillance of premalignant lesions of the pancreas
• Work-up of newly diagnosed pancreas cancer
• Define resectable, borderline and locally advanced unresectable pancreas cancer
• Surgical updates and safety
• Outline neoadjuvant treatment options
• Clinical trials

Genetics

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Estimated Cumulative Risk Pancreatic Cancer</th>
<th>Estimated Increased Risk Compared to General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peutz-Jeghers syndrome (STK11)</td>
<td>11-36% by age 65-70 years</td>
<td>132 fold</td>
</tr>
<tr>
<td>Familial pancreatitis (PRSS1, SPINK, CFTR)</td>
<td>45-53% by age 70-75 years</td>
<td>26-87 fold</td>
</tr>
<tr>
<td>Melanoma Pancreatic Cancer Syndrome (CDKN2A)</td>
<td>14-17% by age 70-75 years</td>
<td>20-47 fold</td>
</tr>
<tr>
<td>Lynch Syndrome (MLH1, MSH2, MSH6)</td>
<td>4% by age 70 years</td>
<td>9-11 fold</td>
</tr>
</tbody>
</table>
### Genetics

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Estimated Cumulative Risk Pancreatic Cancer</th>
<th>Estimated Increased Risk Compared to General Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary breast and ovarian syndrome</td>
<td>1.4-1.5% (women), 2.1-4.1% (men) by age 70</td>
<td>2.4-6 fold</td>
</tr>
<tr>
<td>Familial pancreatic cancer</td>
<td>&gt;3 first degree relatives, 7-16% by age 70</td>
<td>&gt;3 first degree relatives - 32 fold</td>
</tr>
<tr>
<td></td>
<td>2 first degree relatives</td>
<td>&gt;2 first degree relatives - 6.4 fold</td>
</tr>
<tr>
<td></td>
<td>3% by age 70</td>
<td>1 first degree relative - 4.6 fold</td>
</tr>
</tbody>
</table>

### Background-Premalignant lesions of pancreas

- Pancreatic cysts are identified in 2.4-19% of patients undergoing CT or MRI
- Most common
  - Intraductal papillary mucinous neoplasm (IPMN)
  - Mucinous cystic neoplasm (MCN)
  - Solid pseudopapillary neoplasm (SPN)
  - Serous cystadenoma (SCA)
  - Pseudocyst

Laffan et al. AJR Am J Roentgenol 2008;191:802-807
Lee et al. Am J Gastroenterol 2010;105:2079-2084
Premalignant lesions of pancreas

Pancreatic Cystic Lesions

Neoplastic

Main Duct IPMN
Mucinous Cystic Neoplasm (MCN)
Solid Pseudopapillary (SPN)

Side Branch IPMN
Serous Cystic Neoplasm (SCN)

Non-neoplastic

Pseudocyst
Retention Cyst
Lymphoepithelial cyst
Duplication cyst

Surgery
Surveillance or Surgery
IPMN

- Main Duct IPMN
- Branch Duct IPMN
- Mixed type IPMN

Main duct IPMN
Branch duct IPMN

Mixed type IPMN
### IPMN-Incidence of malignancy

<table>
<thead>
<tr>
<th></th>
<th>All (Mean)</th>
<th>Main Duct (Mean)</th>
<th>Branch Duct (Mean)</th>
<th>Mixed Type (Mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant</td>
<td>8.2-66.7%</td>
<td>35.7-100%</td>
<td>6.3-51%</td>
<td>34.6-78.9%</td>
</tr>
<tr>
<td></td>
<td>(40.4)</td>
<td>(62.2)</td>
<td>(24.4)</td>
<td>(57.6)</td>
</tr>
<tr>
<td>Invasive</td>
<td>1.2-49.6%</td>
<td>11.1-80.8%</td>
<td>1.4-30%</td>
<td>19.2-64.9%</td>
</tr>
<tr>
<td></td>
<td>(30.8)</td>
<td>(43.6)</td>
<td>(16.6)</td>
<td>(45.3)</td>
</tr>
</tbody>
</table>

Tanaka et al. Pancreatology 2012

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### IPMN

- **Symptoms**
  - Most are asymptomatic
  - Vague abdominal pain
  - Nausea/vomiting
  - Pancreatitis
  - Jaundice
  - Weight loss
  - Diabetes
  - Most common in males in their 50’s
Referral to pancreatic expert
- History of pancreatitis?
  - YES-Pseudocyst likely
- Symptoms?
- Imaging
  - Detect cystic lesions
  - Determine main vs. branch duct
  - Determine risk of malignancy and ability to resect
- EUS
  - Cyst fluid analysis
  - FNA
  - Presence of mural nodule or other high risk features
**Updated Fukuoka Criteria**

High Risk Stigmata
1. Obstructive jaundice
2. Enhancing nodule
3. MD >1cm

Consider Surgery

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**Fukuoka Criteria 2012**

“Worrisome” features
1. Pancreatitis
2. Cyst >3cm
3. Thickened/enhancing cyst wall
4. MD 5-9mm
5. Non enhancing mural nodule
6. Change in caliber of PD with distal atrophy
7. Elevated Ca 19-9
8. Cyst growth >5mm 2 years

Consider Surgery

Confirm mural nodule, MD involvement or suspicious or positive cytology

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Tanaka et al. Pancreatology 2017
Updated Fukuoka Criteria

How big is it?

- **<1cm**: Imaging 2-3 years
- **1-2cm**: Imaging yearly x 2 years then lengthen
- **2-3cm**: EUS in 3-6 months alternating with MRI. Consider surgery in young patients
- **>3cm**: Close surveillance, MRI and EUS every 3-6 months. Strongly consider surgery

Tanaka et al. Pancreatology 2017

Interpreting Cyst Fluid

Brugge WR et al. Gastroenterology 2004;126:1330-6
Interpreting Cyst Fluid

- CEA
  - Distinguish mucinous from non-mucinous lesions
- >192
  - Sensitivity 73%
  - Specificity 84%


Molecular Analysis of Cyst Fluid

- Interpace Diagnostics
  - Formerly RedPath
- Provide mutational analysis
  - Proprietary test which they do not reveal
  - Mutational Profile
    - LOH markers
    - Oncogenes
    - DNA quantity and quality
    - Clinical information
Fluid Analysis

Pathology: BD-IPMN with high grade dysplasia
Surveillance

- No high quality data to base recommendations
- Great variation in literature
- MCN’s are almost always solitary and require no surveillance imaging

Basic algorithm for all cancers

- NAME IT
- STAGE IT
- TREAT IT
- Presentation: Painless jaundice, weight loss, abdominal pain, diabetes
- Work-up: Cross sectional imaging, labs, EUS/ERCP as necessary
- Preoperative assessment: medical clearance, assess resectability, need for neoadjuvant therapy
- Proceed to OR or chemotherapy
- Patients with distant metastatic disease chemotherapy is the mainstay of treatment
# Defining Resectability

<table>
<thead>
<tr>
<th>Resectability Status</th>
<th>Arterial</th>
<th>Venous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable</td>
<td>No arterial contact (celiac, SMA, CHA)</td>
<td>&lt;180 degrees without vein contour irregularity</td>
</tr>
<tr>
<td>Borderline</td>
<td>Tumor contact with CHA, &lt;180 degrees SMA</td>
<td>&gt;180 degrees SMV/PV, reconstruction possible, contact with IVC</td>
</tr>
<tr>
<td>Locally Advanced-Unresectable</td>
<td>Tumor &gt;180 degrees SMA, celiac, first jejunal SMA branch</td>
<td>Unreconstructible SMV/PV,</td>
</tr>
</tbody>
</table>

- **Surgery**
- **Surgery Not yet**
  - Borderline or locally advanced disease
- **No Surgery**
  - Metastatic disease
Resectable Pancreas Cancer

Borderline Resectable and Locally Advanced Unresectable Pancreas Cancer

Borderline resectable: Abutment SMA
Locally advanced: Encasement SMA
Pancreaticoduodenectomy (Whipple)

- Perioperative mortality 2%
- Complication rates remain high 40-50%
- Average length of stay 8 days
- Pancreatic fistula 20%
- Diabetes 20%
- Adoption of minimally invasive and robotic surgery may further reduce length of stay
### Surgeon volume and outcomes

**Quantity matters!**

- High volume improves perioperative and long-term outcomes
- Included 14 different procedure types
- Pancreas surgery
- HV >5 vs. LV <5
- In hospital mortality 2.4 vs. 6.4%
- 51% reduction in hospital mortality


### Pasireotide for postoperative pancreatic fistulas

- **Pasireotide**
  - Somatostatin analogue with longer half life than octreotide and broader binding profile to octreotide receptors
  - Decreases pancreatic exocrine secretions
- Single center randomized trial
  - 152 subcutaneous pasireotide
    - 14 doses, first dose pre-surgery
  - 148 patients placebo
- Results
  - Pancreatic fistula 9% vs. 21% p = 0.006
  - Consistent for both whipple and distal pancreatectomy

_Pasireotide for postoperative pancreatic fistulas_

_Afford et al. NEJM 2014_
### Whipple with or without drains

- Multicenter randomized controlled trial
  - 68 drains
  - 69 no-drain
- Increase in complications in no-drain group
  - 52% vs. 68% p = 0.047
  - Higher average complication severity
  - Higher gastroparesis, intra-abdominal fluid collection, intra-abdominal abscess (10% vs. 25%), severe diarrhea, need for postoperative percutaneous drain, prolonged length of stay
- Data safety monitoring board stopped the study early because of an increase in mortality from 3% to 12% in patients undergoing whipple without drain

*Van Buren et. al Ann Surg 2014*

### Distal pancreatectomy with and without drains

- Multicenter randomized controlled trial
  - Closed suction drain vs. no drain distal pancreatectomy
  - Baylor
  - Ohio State
  - Indiana University
- No difference in complications or fistula rate

*VanBuren Ann Surg 2017*
## Robotic Whipple

- Surgeon sits in room controlling robotic arms to perform surgery through small incisions
- Decrease length of stay, less post operative pain, quicker recovery

### Open Whipple vs Robotic Whipple

<table>
<thead>
<tr>
<th>Open Whipple</th>
<th>Robotic Whipple</th>
</tr>
</thead>
<tbody>
<tr>
<td>![Open Whipple Image]</td>
<td>![Robotic Whipple Image]</td>
</tr>
</tbody>
</table>
The role of Neoadjuvant Chemotherapy
Preoperative/Neoadjuvant therapy in pancreatic cancer: Meta-analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimated Median Survival (n, yr)</th>
<th>Estimated Survival Probability (Resected)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resected (Range)</td>
<td>Not Resected (Range)</td>
</tr>
<tr>
<td>All patients</td>
<td>22.4 (9-62)</td>
<td>9.5 (6-21)</td>
</tr>
<tr>
<td>Tumor resectable before treatment (group 1)</td>
<td>23.0 (12-54)</td>
<td>8.1 (6-14)</td>
</tr>
<tr>
<td>Tumor non-resectable before treatment (group 2)</td>
<td>20.5 (9-62)</td>
<td>10.2 (6-21)</td>
</tr>
</tbody>
</table>

n, number of assessable studies for each group. doi:10.1371/journal.pmed.1000267.t006


Neoadjuvant therapy- The Ohio State Experience

- Borderline resectable (BRPC) and locally advanced unresectable (LAPC)
- 43 patients
  - 18 BRPC
  - 25 LAPC
- Modified FOLFIRINOX
  - No bolus 5-FU, no LV, decreased irinotecan
- Radiation based on response and intended surgery

Results

Summary of patient characteristics and responses to therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n = 49)</th>
<th>LA (n = 20)</th>
<th>BR (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62.4 ± 9.6</td>
<td>62.6 ± 10.8</td>
<td>62.1 ± 9.7</td>
</tr>
<tr>
<td>Performance status (ECOG)</td>
<td>53 (108)</td>
<td>15 (100)</td>
<td>18 (100)</td>
</tr>
<tr>
<td>Male</td>
<td>25 (51.0)</td>
<td>12 (60)</td>
<td>13 (68.4)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>25 (51.0)</td>
<td>5 (25)</td>
<td>16 (84.2)</td>
</tr>
<tr>
<td>Body tail</td>
<td>18 (36.7)</td>
<td>16 (80)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Vascular involvement</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial</td>
<td>37 (75.5)</td>
<td>15 (75)</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>Veins</td>
<td>10 (20.5)</td>
<td>2 (10)</td>
<td>9 (47.4)</td>
</tr>
<tr>
<td>Both</td>
<td>17 (34.7)</td>
<td>10 (50)</td>
<td>7 (36.8)</td>
</tr>
<tr>
<td>Mean mifluridine cycle count</td>
<td>4.9 (3-14)</td>
<td>5.3 (4-14)</td>
<td>4.4 (3-4)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>25 (51.0)</td>
<td>15 (75)</td>
<td>8 (42.1)</td>
</tr>
<tr>
<td>Median baseline CA19-9 (muU/mL)</td>
<td>135 (57-1184)</td>
<td>184 (80-1135)</td>
<td>100 (50-136-1645)</td>
</tr>
<tr>
<td>CA19-9 reduction (%)</td>
<td>26.97 (7.46)</td>
<td>20 (66.7)</td>
<td>16 (84.2)</td>
</tr>
</tbody>
</table>

Refractory response: 100 (1-100)

Surgical resection: 52 (106)

Resection: 22 (45)

Overall survival: 102 (2-187)

Negative margins: 54 (109)

No resection: 66 (128)

Log-rank p-value < 0.001

Weeks post treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>mPFS in months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resected</td>
<td>16.0 (11.9 – NR**)</td>
</tr>
<tr>
<td>Not Resected</td>
<td>8.0 (4.5 – 10.4)</td>
</tr>
</tbody>
</table>

Results


Neoadjuvant therapy for patients with resectable disease

- Common in some major cancer centers
- NCCN guidelines now acceptable to offer neoadjuvant therapy
- NEOPAC Trial
  - Accruing in Europe
  - Resectable pancreas cancer
  - Randomized to Surgery vs. preoperative gemcitabine and oxaliplatin followed by surgery
  - All patients adjuvant gemcitabine

ESPAC-4

- Multi-center randomized controlled trial
- 732 patients gemcitabine alone vs. gemcitabine and Capecitabine
- Median OS 28 months vs. 25.5 months (HR 0.82)
- 29% 5 year survival vs. 16%
- No increased toxicity compared with gemcitabine alone
- 60% R1 resection
Making the unresectable, resectable

- Locally advanced and borderline resectable
  - Considered as “potentially” or “never” resectable
- mFOLFIRINOX x 2 months then reassess
-Gemcitabine + radiation (36Gy or 50Gy) if stable or progressive disease
- Surgery after maximum response with planned vascular resection
Conclusions

- Premalignant lesions are common and diagnosis and management best by multidisciplinary teams
- Modest improvement in pancreatic cancer survival with newer chemotherapy options
- Surgery for pancreatic cancer is safe
  - Hospital volume and surgeon volume are important for outcomes
- Management by multidisciplinary teams and enrollment in clinical trials is most important for improving outcomes in the future