Pancreatic Cancer Updates in Management

Mary Dillhoff, MD, MS
Associate Professor-Clinical
Department of Surgery
Division of Surgical Oncology
The Ohio State University Wexner Medical Center

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

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>65,380</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>19,819</td>
<td>11,060</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,300</td>
<td>10,800</td>
</tr>
<tr>
<td>Esophageus</td>
<td>12,720</td>
<td>10,200</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>12,243</td>
<td>9,100</td>
</tr>
<tr>
<td>Neuroendocrine tumor</td>
<td>11,450</td>
<td>8,900</td>
</tr>
<tr>
<td>Brain &amp; other nervous system</td>
<td>9,620</td>
<td>7,800</td>
</tr>
<tr>
<td>All Sites</td>
<td>318,429</td>
<td>202,500</td>
</tr>
</tbody>
</table>

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

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

Genetics

Syndrome: Stomach Cancer (CDKN2A)
Estimated Cumulative Risk Pancreatic Cancer: 11-36% by age 65-70 years
Estimated Increased Risk Compared to General Population: 132 fold
# 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 (BRCA1, BRCA2)</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 by age 70</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

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### Premalignant lesions of pancreas

- Pancreatic cystic lesions
  - Neoplastic
    - Main Duct IPMN
    - Mucinous Cystic Neoplasm (MCN)
    - Solid Pseudopapillary Neoplasm (SPN)
  - Non-neoplastic
    - Pseudocyst
    - Retention Cyst
    - Lymphoepithelial cyst
    - Duplication cyst

### Pancreatic Cystic Lesions

- Surveillance or Surgery
- Surgery
<table>
<thead>
<tr>
<th>IPMN</th>
<th>Main duct IPMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Main Duct IPMN</td>
<td>![Image of Main duct IPMN]</td>
</tr>
<tr>
<td>• Branch Duct IPMN</td>
<td>![Image of Branch duct IPMN]</td>
</tr>
<tr>
<td>• Mixed type IPMN</td>
<td>![Image of Mixed type IPMN]</td>
</tr>
</tbody>
</table>

**Branch duct IPMN**

**Mixed type IPMN**

![Image of Branch duct IPMN](image1)

![Image of Mixed type IPMN](image2)
**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

**IPMN**

- Symptoms
  - Most are asymptomatic
  - Vague abdominal pain
  - Nausea/vomiting
  - Pancreatitis
  - Jaundice
  - Weight loss
  - Diabetes
- Most common in males in their 50's

**Diagnosis and Work-up**

- 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

**Treatment Guidelines**

[Image: International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas]
Updated Fukuoka Criteria

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

Consider Surgery

Tanaka et al. Pancreatology 2017

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

EUS

Confirm mural nodule, MD involvement or suspicious or positive cytology

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

Diagnosis of Pancreatic Cystic Neoplasms: A Report of the Cooperative Pancreatic Cyst Study
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

IPMN

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

Basic algorithm for all cancers
Resectable Pancreas Cancer

Borderline Resectable and Locally Advanced Unresectable Pancreas Cancer

Borderline resectable: Abutment SMA
Locally advanced: Encasement SMA

Pancreaticoduodenectomy (Whipple)

Improving surgical outcomes

- 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

Author: Cancer Research UK / Wikimedia Commons
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**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

Birkmeyer et al. N Engl J Med 2003; 349:2117-2127*

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**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

*Allen et al. NEJM 2014*

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**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*

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**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 postoperative pain, quicker recovery

### The role of Neoadjuvant Chemotherapy
Preoperative/Neoadjuvant therapy in pancreatic cancer: Meta-analysis

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimated Median Survival (mo)</th>
<th>Estimated Survival Probability (1-Year)</th>
<th>Estimated Survival Probability (2-Year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resected (Range)</td>
<td>Not Resected (Range)</td>
<td>Resected (Range)</td>
</tr>
<tr>
<td>All patients</td>
<td>11 (6-42)</td>
<td>10 (6-37)</td>
<td>45.0% (30.9-60.2)</td>
</tr>
<tr>
<td>tumor resectable before treatment group 1</td>
<td>11 (6-42)</td>
<td>10 (6-37)</td>
<td>45.0% (30.9-60.2)</td>
</tr>
<tr>
<td>tumor non-resectable before treatment group 2</td>
<td>11 (6-42)</td>
<td>10 (6-37)</td>
<td>45.0% (30.9-60.2)</td>
</tr>
</tbody>
</table>

43 patients
- 18 BRPC
- 25 LAPC
- Modified FOLFIRINOX
- No bolus 5-FU, no LV, decreased irinotecan
- Radiation based on response and intended surgery

Neoadjuvant therapy-The Ohio State Experience

Results

**Results**

- 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

**Neoadjuvant therapy for patients with resectable disease**

**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