Pancreatic Cancer Diagnosis & Staging

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Overview

- Epidemiology
- Genetics
- Clinical Presentation
- Diagnosis
- Staging
- Role of surgery, chemotherapy & outcomes
- Multidisciplinary care & high volume centers
Genetics

Hereditary Syndromes

- Familial Pancreatic Cancer (4%-16%)
- Hereditary Pancreatitis (PRSS1 – Trypsinogen 50-fold increased risk of PC)
- Familial Atypical Mole Melanoma (p16/MTS1) 22-fold increased risk
- Peutz-Jeghers Syndrome (STK11 inactivation 4-6% sporadic tumors)
- BRCA-2 (germline & sporadic mutations)
- Hereditary Non-polyposis Colorectal Cancer (HNPPC patients ↑ PC, Microsatellite instability ~ 4% tumors)
**K-ras**

- Ras involved in receptor tyrosine kinase signaling
- Cells with mutant k-ras protein behave as if they were being perpetually stimulated by growth factors
- K-ras mutations noted in >90% PC specimens
- Nonspecific abnormality

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**p53 Tumor Suppressor Gene**

- Upstream controls and downstream actions highly complex
- Cell cycle control arm (p21\(^{WAF1/CIP1}\))
- Apoptotic arm
- Undefined mechanisms
- Mutations in 50-75% of PC specimens

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**DPC4 Tumor Suppressor Gene**

- Initially cloned by mapping a frequent area of homozygous deletions in pancreatic/biliary cancers
- Inactivated in ~ 55% PC
- Germline mutations responsible for 1/3 cases of juvenile polyposis
- Gene codes for Smad-4 protein (mediate signals in TGF-B-pathway)
**p16<sup>INK4a</sup> Tumor Suppressor Gene**

- p16 protein involved in cell-cycle regulation (Rb pathway)
- Inhibits CyclinD/CDK complexes
- Inactivation identified in a wide variety of human tumors and cell lines
- Mechanisms of inactivation
  - Deletion, Mutation, Methylation

**Risk Factors**

- Cigarette Smoking (2-6X increase)
- Occupational Exposure
  - Beta-naphthylamine, benzidine, aluminum
- Diabetes Mellitus (2X increase)
- Chronic Pancreatitis (20X increase)
- Diet
- Weight (BMI)

**Clinical Presentation**

- Pain
- Jaundice
- Incidental
- Weight loss
- New onset diabetes
- Gastric outlet obstruction
- DVT
- Pancreatitis

**Diagnosis**

- Imaging
  - CT
  - MRI
  - Ultrasound
- Endoscopic
  - Endoscopic Ultrasonography (EUS)
- ERCP
- Laboratory Evaluation
  - CA 19-9
Staging

### Practical Staging System

- **Resectable**
  - No vein or artery involvement, no metastases
  - Surgery, adjuvant chemotherapy
- **Borderline Resectable**
  - Vein involvement not precluding reconstruction, limited arterial involvement, no metastases
  - Biopsy, biliary stenting, preoperative chemotherapy +/- RT, surgery w/vein resection

<table>
<thead>
<tr>
<th>Practical Staging System</th>
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</tr>
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<tbody>
<tr>
<td><strong>Locally Advanced</strong></td>
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</tr>
<tr>
<td>(resectable/unresectable)</td>
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</tr>
<tr>
<td>- Arterial involvement (SMA/Celiac), unreconstructable vein, no metastases</td>
<td></td>
</tr>
<tr>
<td>- Biopsy, biliary stenting, chemotherapy +/- RT, surgery with celiac axis resection</td>
<td></td>
</tr>
<tr>
<td><strong>Metastatic</strong></td>
<td><strong>Metastatic</strong></td>
</tr>
<tr>
<td>- Palliative (stenting, surgical bypass, celiac plexus neurolysis, chemotherapy, no radiation)</td>
<td></td>
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</tbody>
</table>

- All patients undergoing pancreatic resections for pancreatic malignancy in N.Y. state from 1984-1991
- 75% of patients underwent resection at minimal-volume (< 10) or low-volume (10-50) centers (98% of the institutions treating PC)
- Two high-volume centers performed >81 each
- Mortality 21.8%, 12.3% and 4.0%
- Surgeons 15.5% (<9) vs. 4.7% (>41)

- National Medicare Claims Data Base and the Nationwide Inpatient Sample
- Examined mortality associated with 6 different types of cardiovascular procedures and 8 types of major cancer resections between 1994 and 1999
- Total number 2.5 million
- Pancreatic Cancer 15.4% (VLV) vs. 3.8% (VHV >16 cases/year)

"In the absence of other information about the quality of surgery at the hospitals near them, Medicare patients undergoing selected cardiovascular or cancer procedures can significantly reduce their risk of operative death by selecting a high-volume hospital."

**Multidisciplinary Pancreas Tumor Board**

- Recommended by NCCN guidelines
- Weekly Pancreas Tumor Board instituted in 2011
- All patients with confirmed or suspected pancreatic cancer reviewed
- Consensus recommendation made and documented in electronic chart
- Over 314 discussions (273 patients) have been reviewed since inception
- Change of plan recommended in 42.3%/74.1% implemented
Screening for pancreatic cancer

Biopsy approaches

Pancreatic Cancer Update

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Director, Surgical Oncology Fellowship
Medical Director, GI Cancer Service Line
Division of Surgical Oncology
The Ohio State University Wexner Medical Center
Disclosures

• Financial- None
• Warning: Operative photos will be shown

Pancreatic cancer is ..... 

• Aggressive
  • Early metastases
  • Local invasion
• Silent
  • Vague symptoms (pain, fatigue, cachexia)
• Indiscriminate
  • Equal gender distribution
  • No real risk factors
• Hopeless?
  • Depends upon resectability

Surgery for pancreatic cancer is...

• The only hope for cure
• Complex
• Morbid
• Dependent upon anatomy

Pancreas Vascular Anatomy

Author: Tim Tieu
Pancreaticoduodenectomy (Whipple)

Criteria For Resectability

Resectable
- No evidence of superior mesenteric vein (SMV) or portal vein (PV) occlusion, thrombosis, or tumor thrombus.
- Clear fat planes around the celiac, hepatic, and superior mesenteric artery (SMA).
- Venous involvement of the SMV/PV with tumor involvement which may distal or involve fat latches.
- Enlargement of the SMV/PV but without encasement of the portal vein, or short segment vascular occlusion from other tumors touching or encasing the vessel but without suitable vessel proximal and distal to allow for safe resection and replacement.
- Bland/endothelial artery encasement up to the hepatic artery with short segment vascular occlusion or distal dissection of the hepatic artery without involvement to the celiac axis.
- Tumor involvement of the superior mesenteric artery (SMA) not to extend greater than 180 degrees of the circumference of the vessel wall.
- Greater than 150 degrees involvement of the SMA, celiac axis, or hepatic artery.
- Arterial invasion or encasement.
- Venous thrombosis of the portal vein or SMV extending for several centimeters, making resection impossible.
- No vascular enlargement or hernial nodes beyond the field of inspection.

Resectable Pancreas Cancer

Note: adapted from the consensus statement of the American Hepato-Pancreato-Biliary Association / the Society for Surgery of the Alimentary Tract / the Society of Surgical Oncology / and the Gastrointestinal Symposium Steering Committee. (Cattley, 2009) and the National Comprehensive Cancer Network (NCCN) v.1.2013
Advanced Pancreatic Cancer

Borderline resectable: Short segment SMV occlusion

Locally advanced: SMV occlusion SMA encasement
Table: Estimates of median survival times (mp) in months and survival probabilities.

<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></td>
<td>1 year (range)</td>
<td>2 year (range)</td>
</tr>
<tr>
<td>N agents</td>
<td>13.3 (5.4-26.5)</td>
<td>75% (70-90)</td>
<td>65% (55-75)</td>
</tr>
<tr>
<td>Anti-somatostatin receptor group 1</td>
<td>17.7 (12.7-21.7)</td>
<td>85% (80-90)</td>
<td>75% (70-80)</td>
</tr>
<tr>
<td>Anti-somatostatin receptor group 2</td>
<td>20.5 (16.0-24.0)</td>
<td>90% (85-95)</td>
<td>80% (75-85)</td>
</tr>
</tbody>
</table>

Preoperative/Neoadjuvant therapy in pancreatic cancer: A systematic review and meta-analysis

**Chemotherapy options - 1990**

- **Pancreatic cancer**
  - 5-FU

- **Colorectal cancer**
  - 5-FU

**Chemotherapy options - 2000**

- **Pancreatic cancer**
  - 5-FU

- **Colorectal cancer**
  - 5-FU
  - Gemcitabine
  - Irinotecan (IFL)

**Chemotherapy options - 2010**

- **Pancreatic cancer**
  - 5-FU
  - Gemcitabine

- **Colorectal cancer**
  - 5-FU
  - Irinotecan (FOLFIRI)
  - Oxaliplatin (FOLFOX)
  - Bevacizumab
  - Cextuximab
  - Panitumumab
  - Capecitabine

**Chemotherapy options - 2014**

- **Pancreatic cancer**
  - 5-FU
  - Gemcitabine
  - FOLFIRINOX
  - Nab-paclitaxel

- **Colorectal cancer**
  - 5-FU
  - Irinotecan (FOLFIRI)
  - Oxaliplatin (FOLFOX)
  - Bevacizumab
  - Cextuximab
  - Panitumumab
  - Capecitabine
  - Regorafenib
FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer

FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer


<table>
<thead>
<tr>
<th>Event</th>
<th>FOLFIRINOX (N=293)</th>
<th>Gemcitabine (N=271)</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 (9.2)</td>
<td>31 (11.8)</td>
<td>0.03</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5 (1.7)</td>
<td>16 (5.9)</td>
<td>0.05</td>
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<tr>
<td>Thrombocytopenia</td>
<td>32 (11.0)</td>
<td>36 (13.3)</td>
<td>0.19</td>
</tr>
<tr>
<td>Anemia</td>
<td>15 (5.2)</td>
<td>19 (7.0)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Neurotoxicities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (7.2)</td>
<td>24 (8.9)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20 (6.8)</td>
<td>24 (8.9)</td>
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</tr>
<tr>
<td>Diarrhea</td>
<td>21 (7.2)</td>
<td>26 (9.6)</td>
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<tr>
<td>Headache</td>
<td>17 (5.8)</td>
<td>18 (6.7)</td>
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<tr>
<td>Anorexia</td>
<td>12 (4.1)</td>
<td>15 (5.5)</td>
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<td>Anemia</td>
<td>11 (3.8)</td>
<td>13 (4.8)</td>
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*Events listed are those that occurred in more than 5% of patients in either group. N.S. denotes not significant.


DOI: 10.1056/NEJMoa1304369

Gemcitabine + Nab-paclitaxel vs. Gemcitabine for Metastatic Pancreatic Cancer.


FOLFIRINOX versus Gemcitabine for Metastatic Pancreatic Cancer


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Gemcitabine + Nab-paclitaxel vs. Gemcitabine for Metastatic Pancreatic Cancer.


[Table 5: Common Adverse Events of Cisplatin and Gemcitabine.

<table>
<thead>
<tr>
<th>Event</th>
<th>nab-Paclitaxel</th>
<th>Gemcitabine</th>
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<tbody>
<tr>
<td>Diarrhea</td>
<td>21 (5)</td>
<td>23 (5)</td>
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*All values are not applicable and are not reported.**

Table 6: Common Adverse Events of Cisplatin and Gemcitabine.

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Table 7: Common Adverse Events of Cisplatin and Gemcitabine.

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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
### Neoadjuvant Modified (m) FOLFIRINOX for Locally Advanced Unresectable (LAPC) and Borderline Resectable (BRPC) Adenocarcinoma of the Pancreas

**Characteristic** | **Total** | **LA** (n = 25) | **BR** (n = 18)
--- | --- | --- | ---
Age in years, mean (SD) | 62.4 (9.4) | 62.6 (10.0) | 62.2 (8.7)
Performance Status (ECOG) 0-1 | 43 (100%) | 25 (100%) | 18 (100%)
Female | 23 (53.5%) | 12 (48%) | 11 (61%)
Tumor Location | | | |
   Head | 25 (58%) | 15 (60%) | 8 (44%)
   Body/Tail | 18 (42%) | 10 (40%) | 7 (39%)
Vascular Involvement | | | |
   Arterial | 15 (35%) | 13 (52%) | 2 (11%)
   Venous | 11 (25.5%) | 4 (16%) | 7 (39%)
   Both | 17 (39.5%) | 10 (40%) | 7 (39%)
InFOLFIRINOX cycles, mean (range) | 4.9 (1 – 14) | 5.3 (1 – 14) | 4.4 (1 – 8)

**Chemoradiation** | 23 (54%) | 15 (60%) | 8 (44%)
Median baseline CA19-9 (range) | 335.97 (<15.00–10943.97) | 184.80 (<15.00–1355.05) | 650.88 (<15.00–10943.97)
CA19-9 reduction* | 26/37 (70%) | 13/20 (65%) | 13/17 (76%)
Radiographic response (CR + PR)* | 9/40 (23%) | 2/23 (9%) | 7/17 (41%)
Surgical Exploration | 31 (72%) | 16 (64%) | 15 (83%)
Resected | 22 (51%) | 11 (44%) | 11 (61%)
Vascular Resection | 4/22 (18%) | 3/11 (27%) | 1/11 (9%)
Negative margins | 19/22 (86%) | 10/11 (91%) | 9/11 (82%)

Neoadjuvant Modified (m) FOLFIRINOX for Locally Advanced Unresectable (LAPC) and Borderline Resectable (BRPC) Adenocarcinoma of the Pancreas

<table>
<thead>
<tr>
<th>Group</th>
<th>mPFS in months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resected</td>
<td>18.0 (11.9 – NR**)</td>
</tr>
<tr>
<td>Not Resected</td>
<td>8.0 (4.5 – 10.4)</td>
</tr>
</tbody>
</table>


Postoperative concerns

- Complications
  - Leak
  - Infection
  - Hemorrhage
- Nutrition
  - Delayed gastric emptying
  - Weight loss
- Fatigue
- Cancer