Pancreatic Cancer: The ABCs of the AJCC and WHO

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Objectives

• Case presentation
• Discuss pancreatic cancer and clinical relevant subtypes
• Review AJCC 8th edition staging of exocrine and endocrine pancreatic neoplasms
• 2017 WHO classification of pancreatic neuroendocrine neoplasms

Case Presentation

• 78-year-old female presenting with a 1 day history of jaundice and cola-colored urine.
• The patient had elevated serum liver transaminases and elevated serum pancreatic enzymes.
• These findings prompted an abdominal computed tomography (CT) scan.
Pancreatic Mass (5.6 cm)
Adenocarcinoma

- **Definition**: invasive gland-forming epithelial neoplasm
- **Clinical presentation**: diagnosis late in the course
- **Pathology**: varies
- **Precursor lesions**: pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasm (MCN)
- **Evolution's role**: in both familial and sporadic
- **Surgery**: only hope for cure (~15% are resectable)
- **Outcome**: universally poor
Pancreatic intraepithelial neoplasia (PanINs):
Most pancreatic cancers evolve through PanINs:

Pancreatic intraepithelial neoplasia (PanINs):
Most pancreatic cancers evolve through PanINs:

- Low-Grade
- Low-Grade
- High-Grade

Haphazard growth

Histologic Grades of Adenocarcinoma
- Well-differentiated
- Moderately-differentiated
- Poorly-differentiated
Variants of Pancreatic Ductal Adenocarcinoma

Adenosquamous Carcinoma

- A malignant epithelial neoplasm of the pancreas with significant components of both glandular and squamous differentiation
- The squamous component should comprise at least 30% of the neoplasm
- Account for 3-4% of the malignancies of the exocrine pancreas
- Partial response to cisplatinum based chemotherapeutic regimens
Colloid Carcinoma

- An infiltrating adenocarcinoma characterized by mucin producing neoplastic epithelial cells suspended ("floating") in large pools of extracellular mucin
- The colloid component should comprise at least 80% of the neoplasm
- 1-3% of the malignancies of the exocrine pancreas
- Grossly soft gelatinous
- Almost always associated with an IPMN
- 5-year survival rates as high as 57%
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Hepatoid Carcinoma

- A malignant epithelial neoplasm in which a significant component shows hepatocellular differentiation
- Only a handful have been reported
- Large polygonal cells with abundant eosinophilic cytoplasm
- The cells form trabecula and may have a sinusoidal vascularity
- Immunolabeling is similar if not the same as hepatocellular neoplasms
Medullary Carcinoma

- A malignant epithelial neoplasm characterized by poor differentiation, pushing borders, a syncytial growth pattern and necrosis
- May have prominent intratumoral lymphocytes
- Many, but not all, carcinomas with medullary histology have microsatellite instability
- Family history of cancer (Lynch syndrome)
- Trend towards longer survival and response to immune checkpoint inhibitors
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Undifferentiated Carcinoma

- A malignant epithelial neoplasm with a significant component showing no glandular structures or other features to indicate a definite direction of differentiation
- Range from pleomorphic epithelioid mononuclear cells containing abundant eosinophilic cytoplasm admixed with bizarre frequently multinucleated tumor giant cells, to relatively monomorphic spindle cells
- Mean survival of 5 months after diagnosis
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Undifferentiated Carcinoma with Osteoclast-like Giant Cells

- Malignant epithelial neoplasm composed of large benign appearing multinucleated giant cells admixed with atypical neoplastic mononuclear cells
- The atypical mononuclear cells variably express markers of epithelial differentiation
- The osteoclast-like giant cells express markers of histiocytic/macrophage differentiation (benign)
- Highly aggressive neoplasms with a mean survival of only 12 months
Macrophage marker (CD68)

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How is Pancreatic Cancer Staged?

- AJCC (7th Edition):
  - T-staging is prognostically significant
  - Problematic areas for pathology include identifying extension beyond the pancreas
  - >70% of resected pancreatic cancers are T3

AJCC 8th Edition Staging

- Size rather than tumor extension
- Primary tumor (pT)
  - pTX  Primary tumor cannot be assessed
  - pT0  No evidence of a primary tumor
  - pTis High-grade dysplasia (carcinoma in situ)
  - pT1  Tumor size ≤ 2 cm
  - pT2  Tumor size > 2 cm and ≤ 4 cm
  - pT3  Tumor size > 4 cm
  - pT4  Tumor involves the celiac axis, superior mesenteric artery and/or common hepatic artery

Tis: High-grade dysplasia (carcinoma in situ)

Adapted from https://www.cancer.gov/types/pancreatic

dT1: Tumor ≤ 2 cm in size

Adapted from https://www.cancer.gov/types/pancreatic
AJCC 8th Edition Staging

- Size rather than tumor extension
- Primary tumor (pT)
  - pT1  Tumor size ≤ 2 cm
  - pT1a Tumor size ≤ 0.5 cm
  - pT1b Tumor size > 0.5 cm and < 1.0 cm
  - pT1c Tumor size 1.0 to 2.0 cm

- pT1a through pT1c is primarily for pancreatic adenocarcinomas arising from IPMNs

pT2: Tumor > 2 cm but < 4 cm in size

Adapted from https://www.cancer.gov/types/pancreatic

pT3: Tumor ≥ 4 cm in size

Adapted from https://www.cancer.gov/types/pancreatic
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Tumor extends beyond the pancreas (doesn’t matter – still based on tumor size)

Tumor extends beyond the pancreas (into the spleen) is staged based on size

pT4: Tumor involves the celiac axis, superior mesenteric artery &/or common hepatic artery

Adapted from https://www.cancer.gov/types/pancreatic
**AJCC 8th Edition Staging**

- Regional lymph nodes (pN)
  - pNX: Unable to assess regional lymph nodes
  - pN0: No regional lymph node involvement
  - pN1: Metastasis in 1 to 3 regional lymph nodes
  - pN2: Metastasis in 4 or more regional lymph nodes

**AJCC 8th Edition Staging**

- Regional lymph nodes (N)
  - Superior to the pancreatic head/uncinate and body/tail
  - Inferior to the pancreatic head/uncinate and body/tail
  - Anterior: pancreaticoduodenal and proximal mesenteric
  - Posterior: pancreaticoduodenal and proximal mesenteric
  - Pancreatic head/uncinate: stomach pylorus (infrapyloric and subpyloric), hepatic artery, common bile duct and celiac
  - Pancreatic body/tail: tail of pancreas, splenic hilum and pancreaticocolic

**N1 and N2: Regional lymph node involvement**

Adapted from https://www.cancer.gov/types/pancreatic
AJCC 8th Edition Staging

- Distant Metastases (pM)
  - pM0 No distant metastasis
  - pM1 Distant metastasis

**Note: M1 disease is typically a contraindication for surgical resection, so frequently a pathologic M0.**

Adapted from https://www.cancer.gov/types/pancreatic

AJCC 8th Edition Staging

- T- and N-staging are prognostically significant

Variants

- Adenosquamous carcinoma
- Colloid carcinoma
- Hepatoid carcinoma
- Medullary carcinoma
- Undifferentiated carcinoma
- Undifferentiated carcinoma with osteoclast-like giant cells

Liver
Kidneys
Bile Duct
Head of the Pancreas
Pancreatic Mass (5.6 cm)

Pancreatic Head Mass: Sarcoma???
No Glandular Differentiation Identified
Spindled Neoplastic Cells

Residual Pancreatic Parenchyma

Neuroendocrine Neoplasms

Incidence per 100,000 (NET/NEC)

Neuroendocrine Neoplasms

- Lung
- Rectum
- Jejunum/Ileum
- Stomach
- Colon
- Duodenum
- Cecum
- Appendix
- Pancreas
- Other
- Lung
- Rectum
- Jejunum/Ileum
- Stomach
- Colon
- Duodenum
- Cecum
- Appendix
- Pancreas
- Other
Differentiation

• Lung (Differentiation):
  • Carcinoid and Atypical carcinoid
  • Neuroendocrine carcinoma
    • Small cell carcinoma
    • Large cell carcinoma

• Gastroenteropancreatic (Differentiation):
  • Well-differentiated neuroendocrine tumor (NET)
  • Poorly-differentiated neuroendocrine carcinoma (NEC)
    • Small cell carcinoma
    • Large cell carcinoma
Carcinoid / Well-Differentiated Neuroendocrine Tumors

Microscopic criteria:
- Various “organoid” histologic patterns: nesting, trabecular, glandular, gyriform, tubuloclinar or pseudorosette arrangements
- Uniform, finely granular, amphophilic-to-eosinophilic cytoplasm
- Coarsely clumped nuclear chromatin (“salt and pepper”)
- Resemblance to islets of Langerhans
Poorly-Differentiated Neuroendocrine Carcinomas

Microscopic subtypes:

**Small cell carcinoma**
- Small cells with scant cytoplasm
- Fine chromatin
- Nuclear molding
- Diffuse growth pattern

**Large cell carcinoma**
- Prominent nesting pattern
- Moderate amphophilic cytoplasm
- Large nuclei with clumped chromatin
- May have prominent nucleoli
Carcinoid / Well-Differentiated Neuroendocrine Tumors

Histologic Grade:
• Lung (< 11 mitoses per hpf):
  ▪ Carcinoid: < 2 mitoses per 10 hpf
  ▪ Atypical carcinoid
    ▪ 2-10 mitoses per 10 hpf
    ▪ Tumor necrosis
• Gastroenteropancreatic (mitoses & Ki-67):
  ▪ Low-grade (G1)
  ▪ Intermediate-grade (G2)
  ▪ High-grade (G3)

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Ki-67 Proliferation Index

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Ki-67 and Mitotic Index

<table>
<thead>
<tr>
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<th>Grade</th>
<th>Ki-67 Index</th>
<th>Mitotic Count</th>
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<tbody>
<tr>
<td>Well-differentiated</td>
<td>Low-grade (G1)</td>
<td>&lt; 3%</td>
<td>&lt; 2 / 10 HPF</td>
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<td>Intermediate-grade (G2)</td>
<td>3 – 20%</td>
<td>2 – 20 / 10 HPF</td>
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<tr>
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<td>High-grade (G3)</td>
<td>&gt; 20%</td>
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Ki-67 and Mitotic Index

* If Ki-67 and mitotic counts are discordant, it is recommended to assign a higher grade

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Calculation of the Ki67 index in pancreatic neuroendocrine tumors: a comparative analysis of four counting methodologies

Michelle O'Reilly, Polina Bogatyi, Nobuyuki Okado, Stephen Suki, Jack Eduerd Sweeney, Neeraj Sharma, Debika Roy, Ryan Carey, Ken-Tek Jung, Tzong-Kye Liou, Olga Robinson, Je Youn Koo, Michael Goldsmith, Grade Akin, and Valbon Adney

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G3: NETs vs. NECs

- WD-NET (low-intermediate grade), n=329
- PD-NEC, n=35
- WD-NET with HG component (mixed grade), n=21

P < 0.001

G3: NETs vs. NECs

Well-differentiated Neuroendocrine Tumors
- Surgical resection with curative is the most effective treatment
- Medical therapy:
  - Somatostatin analogues (imaging)
  - mTOR inhibitors
  - Alkylating agents
  - Peptide receptor radionucleotide therapy

Poorly-differentiated Neuroendocrine Carcinomas
- Platinum-based chemotherapy

Well-differentiated Neuroendocrine Tumor (G3) or Poorly-differentiated Neuroendocrine Carcinoma (G3)
Pancreatic: NETs vs. NECs

Well-differentiated Neuroendocrine Tumor (G3) or Poorly-differentiated Neuroendocrine Carcinoma (G3)

PanNETs

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<tr>
<th>Genes</th>
<th>Mutation Frequency</th>
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<tr>
<td>MEN1</td>
<td>44%</td>
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<tr>
<td>DAXX/ATRX</td>
<td>43%</td>
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<tr>
<td>PIK3CA, PTEN, TSC1, &amp; TSC2</td>
<td>15%</td>
</tr>
<tr>
<td>TP53</td>
<td>3%</td>
</tr>
<tr>
<td>RB1</td>
<td>0%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>0%</td>
</tr>
<tr>
<td>KRAF</td>
<td>0%</td>
</tr>
<tr>
<td>TGFBR1, TGFBR2, SMAD4</td>
<td>0%</td>
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PanNECs

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<tr>
<td>RB1</td>
<td>74%</td>
</tr>
<tr>
<td>CDKN2A</td>
<td>32%</td>
</tr>
<tr>
<td>KRAF</td>
<td>29%</td>
</tr>
<tr>
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Pancreatic NET vs. NECs

Pancreatic NET

Pancreatic NEC

ATRX

RB

High-grade Pancreatic Neuroendocrine Neoplasm
(mitotic activity >20 per 10 high-power fields and/or Ki-67 index >10%)

Clinical Presentation and Associated Features
- Incidental or asymptomatic due to neuroendocrine secretion
- Diabetic syndrome
- Neuroendocrine markers (e.g., chromogranin-A, neuron-specific enolase, serotonin, insulin)
- Abdominal pain, jaundice, weight loss, anorexia, and/or diabetes

Pathologic Examination
- A consistent lower grade (PankNET) is present
- Pet scan results provide a lower grade PanNET (a prospective biopsy)
- A consistent conventional carcinoma (e.g., adenocarcinoma)
- Otherwise homogeneous neoplasm that lacks a low-grade component

Ancillary Immunohistochemistry
- Loss of nuclear expression for S100 and calretinin
- Loss of p53 and aberrant cyclin D1 expression (high nuclear or lack of immunoreactivity)

PanNET, WHO Grade 3

PanNEC, WHO Grade 3
How is a Gastroenteropancreatic Neuroendocrine Carcinoma (NEC) Staged?

Primary tumor (pT)
Regional lymph nodes (pN)
Distant metastases (pM)

Staged as other malignancies arising from that site (e.g. pancreatic adenocarcinoma)
How is a Gastroenteropancreatic Neuroendocrine Tumor (NET) Staged?

Primary tumor (pT)
Regional lymph nodes (pN)
Distant metastases (pM)

Different from other malignant neoplasms at the same organ site

How is a Pancreatic NET T-Staged?

Primary tumor (pT)
– pTX Tumor cannot be assessed
– pT1 Tumor limited to the pancreas, < 2 cm
– pT2 Tumor limited to the pancreas, 2 to 4 cm
– pT3 Tumor limited to the pancreas, > 4 cm, or invading the duodenum or common bile duct
– pT4 Tumor invades adjacent organs (stomach, spleen, spleen, adrenal gland) or wall of large vessels (the celiac axis or superior mesenteric artery)

pT1: Tumor limited to the pancreas, < 2 cm

Tumor size 2 cm

Duodenum
Pancreas
Cancer

Adapted from https://www.cancer.gov/types/pancreatic
pT2: Tumor limited to the pancreas, 2 to 4 cm

pT3: Tumor > 4 cm or extending into the duodenum or common bile duct

pT4: Tumor invades adjacent organs (e.g. spleen), celiac axis or SMA
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How is a Pancreatic NET N- and M-Staged?

Regional lymph nodes (pN)
- pNX Unable to assess regional lymph nodes
- pN0 No regional lymph node involvement
- pN1 Regional lymph node involvement

Distant metastases (pM)
- pM1 Distant metastases
- pM1a Metastasis confined to liver
- pM1b Metastasis to at least extrahepatic site (e.g. lung, ovary, bone, etc.)
- pM1c Both hepatic and extrahepatic metastases