3D MDCT Detection of Extrapancreatic Perineural Spread in Pancreatic Adenocarcinoma: A Radiologic Biomarker?

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No Disclosures

- Neither the author or his immediate family members have a financial relationship with a commercial organization that may have a direct or indirect interest in the content.
Objectives

- Briefly review epidemiology of and current treatment options for pancreatic adenocarcinoma
- Review current staging classification of pancreatic adenocarcinoma
- Illustrate pathways of extrapancreatic perineural spread and discuss its implications in management and impact on surgical staging
- Showcase our current work and where we are headed.
Background

- Fourth leading cause of cancer related deaths in the U.S.
- **Overall 5-year survival rate is < 5%**
- Risk factors:
  - Diabetes
  - Smoking
  - Chronic pancreatitis
  - Occupational chemical exposure
  - Genetic syndromes
59 year old male with jaundice. Patient underwent resection (R0) but expired in 11 months. Perineural invasion was seen on pathologic examination.
Current Treatment - Whipple

- Only *curative* option is pancreaticoduodenectomy
- Median survival 17 months after surgery
- Perioperative mortality of 5% and morbidity of 20-30%
Current Treatment - Whipple

<table>
<thead>
<tr>
<th>Survival (yr)</th>
<th>R0 (%)</th>
<th>R1, R2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>34</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

Current Treatment – Systemic Therapy

- Optimum approach is controversial

- Current practice is to administer post-operative adjuvant therapy

- However, many patients will be ineligible for therapy due to post-operative morbidity

- Neoadjuvant therapy is gaining much attention
Factors Contributing to Poor Survivability

- Lack of tumor marker for early detection
- Systemic therapy not as effective as for other tumors
- Aggressive biological behavior with early dissemination, even with small tumors (<2 cm)
- Perineural invasion highly contributes to subclinical early dissemination

Can we identify a radiologic biomarker that predicts aggressiveness?
# Staging – TNM Classification

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor (T)</strong></td>
<td></td>
</tr>
<tr>
<td>TX</td>
<td>Primary tumor not assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor less than or equal to 2 cm in diameter and <strong>confined to the pancreas</strong></td>
</tr>
<tr>
<td>T2</td>
<td>Tumor greater than 2 cm in diameter and <strong>confined to the pancreas</strong></td>
</tr>
<tr>
<td>T3</td>
<td>Tumor <strong>extends beyond</strong> the pancreas but does not <strong>involve the celiac axis or SMA</strong></td>
</tr>
<tr>
<td>T4</td>
<td>Primary tumor <strong>involves</strong> either the celiac axis or the SMA</td>
</tr>
<tr>
<td><strong>Node (N)</strong></td>
<td></td>
</tr>
<tr>
<td>NX</td>
<td>Regional lymph nodes not assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No involvement of the regional lymph nodes</td>
</tr>
<tr>
<td>N1</td>
<td>Involvement of the regional lymph nodes</td>
</tr>
<tr>
<td><strong>Metastases (M)</strong></td>
<td></td>
</tr>
<tr>
<td>MX</td>
<td>Distant metastases cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

Brennan D et al. Radiographics 2007;27:1653-1666
Staging – T1 & T2

Tamm E P et al. AJR 2003;180:1311-1323
Staging – T3

Tamm E P et al. AJR 2003;180:1311-1323

Coronal 3D VR
Staging – T4

Tamm E P et al. AJR 2003;180:1311-1323
### Staging of Adenocarcinoma according to the TNM System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>TNM Levels</th>
<th>Additional Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Resectable</td>
<td>T1 or T2, N0, M0</td>
<td>No extrapancreatic disease, no encasement of the celiac axis or SMA</td>
</tr>
<tr>
<td>II</td>
<td>Typically</td>
<td>T1 or T2, N1, M0;</td>
<td>Regional lymph nodes may be involved, no encasement of the celiac axis or SMA, possible extrapancreatic involvement</td>
</tr>
<tr>
<td></td>
<td>resectable</td>
<td>T3, N0 or N1, M0</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>Unresectable</td>
<td>T4, N0 or N1, M0</td>
<td>Regional lymph nodes may be involved, encasement of the celiac axis or SMA</td>
</tr>
<tr>
<td>IV</td>
<td>Unresectable</td>
<td>T (any), N (any), M1</td>
<td>Liver, peritoneal, lung metastases</td>
</tr>
</tbody>
</table>

Brennan D et al. Radiographics 2007;27:1653-1666
- Biphasic breath-hold exam:
  - late arterial phase after 35-40 seconds
  - portal venous phase after 60-70 seconds
  - 1.25 mm images

- Post-processing – stay tuned!
Why Do We Scan This Way?

- **Late arterial phase**
  - aka pancreatic parenchymal phase
  - maximum conspicuity of tumors, both hyper- and hypovascular
  - detect vascular invasion

- **Portal venous phase**
  - distant metastases
  - venous invasion
Resectability Checklist – Metastasis

- Easiest to look for when determining surgical candidacy!
- Liver, lung, peritoneal
- Direct invasion into spleen, stomach, or retroperitoneum
# Resectability Checklist – Arteries

<table>
<thead>
<tr>
<th>Vessel</th>
<th>Resectable</th>
<th>Borderline Resectable</th>
<th>Non-resectable</th>
</tr>
</thead>
</table>
| SMA                     | No involvement – clear fat plane or normal pancreatic parenchyma b/ artery and tumor | • Encasement of less than 180°  
  • Tumor forms convex point of contact with vessel                              | • >180° encasement  
  • Occlusion of vessel                                                             |
| Celiac axis or hepatic artery | No involvement                                                            | • Short-segment encasement or abutment of common hepatic artery, usually at the origin of the GDA | • >180° encasement  
  • Vascular reconstruction not possible such as extension to involvement of splenic vein, left gastric artery, or celiac origin |

Brennan D et al. Radiographics 2007;27:1653-1666
Resectability Checklist – Arteries

Curved Planar Reformations
Resectability Checklist – Veins

- Circumferential narrowing or occlusion of SMV or PV

- “Tear-drop” sign – specific for tumor invasion of SMV

- Encasement is a relative contraindication
What About Perineural Invasion (PNI)?

- Currently not taken into account for determination of resectability
What is PNI?

- Abundance of nerve fibers surrounding the pancreas and complex network with 6 extrapancreatic neural plexuses
- Infiltrative *neurotropic growth* along neural fascicles
- Not just *spread* along perineurium, but *invasion* into all 3 layers (epi-, peri-, and endoneurial spaces)
Mechanism of Spread / Invasion

- Direct invasion of nerve

- Spread along perineurium (enters perineurium either by direct invasion or via small perineurial vessels)

- Destroying nerve terminal synapse or invade nerve branching points

- “NEX” – intrapancreatic, extratumoral PNI

Molecular Mechanism

Molecular Mechanism

Extrapancreatic Neural Plexus Anatomy

- Celiac plexus
- Pancreatic head plexuses
- SMA plexus
- Hepatic plexus
- Aortic plexus
- Splenic plexus
Neural Plexus Anatomy – Celiac Plexus

- Largest visceral plexus
- Includes celiac, superior mesenteric, and aorticorenal ganglia
- Sympathetic, parasympathetic, & sensory afferent to upper abdomen viscera
- **Retroperitoneal in location lying the pre-aortic fat just below the celiac origin**
- **Celiac ganglia:**
  - Small, linear structures usually located at T12-L1 level
  - Right between IVC and right diaphragmatic crura
  - Left usually anteromedial to left adrenal gland

Kambadakone A et al. Radiographics 2011;31:1599-1621
In 1950, Yoshioka, et al., determined majority of postganglionic fibers from celiac ganglia join together to enter the medial margin of the uncinate.

They called this large bundle of nerves, "Plexus Pancreaticus Capitalis" or "PPC."

Yoshioka H et al. AMA Archives of Surgery 1958; 76:546-554
Further divide PPC into 2 divisions:

- **PPC I** – fibers run from right celiac ganglion to the medial margin of the head
- **PPC II** – fibers run from SMA to medial margin of uncinate

More on the implications later!
Neural Plexus Anatomy – Pancreatic Head Plexus

- SMA plexus
- Hepatic plexus
- Aortic plexus
- Splenic plexus

What Do We Know About PNI & Pancreatic Adenocarcinoma

- **PNI portends a poor prognosis & lowers survival**
- Significant cause of positive surgical margins
- Increases likelihood of recurrence
- **PNI shown in early stages as well as small (<2 cm) tumors**
- Even short segment of extrapancreatic PNI (2.5 cm) has been shown to reduce survival compared with intrapancreatic PNI
- Seen in 70-100% of pancreatic adenocarcinomas
How Can We Detect PNI?

- SFOV (12cm) 3D VR images are key!!
- Allows visualization of small peripancreatic vessels needed to detect PNI
MDCT Appearance of PNI

- PNI follows predictable course along neurovascular bundles
- Must have high-res 3D VR images
- **Confluent soft tissue attenuation, similar to that of primary tumor, extending along known pathways but different from lymphatic invasion**
- Advanced cases may prove difficult to distinguish PNI and lymphatic invasion

Extrapancreatic Perineural Spread

- 4 pathways have been described that predictably follow neurovascular bundles
4 Pathways of Extrapancreatic PNI

- **PPC I**
  - right celiac ganglion → upper medial margin of head/uncinate via posterior to PV

- **PPC II**
  - SMA → uncinate via PIPDA → mesenteric ganglion

- **Anterior Pathway**
  - Anteriorly along GDA → CHA plexus

- **Root of Mesentery Invasion (RMI)**
  - SMA → uncinate via PIPDA → caudally to infiltrate RoM

Deshmukh S D et al. AJR 2010;194:668-674
Plexus Pancreaticus Capitalis I

- Path: posterior to PV to celiac ganglion

- *Characteristic perineural spread for adenocarcinomas of the pancreatic head*
Plexus Pancreaticus Capitalis I

- Path posterior to PV to celiac ganglion

- Characteristic perineural spread for adenocarcinomas of the pancreatic head
PPC I: Case 1

Celiac Ganglia Invasion

Axial 3D VR

Coronal 3D VR
PPC I: Case 2

Coronal 3D VR

Coronal 3D VR
Uncinate to mesenteric ganglion via posterior inferior pancreaticoduodenal artery (PIPDA)

Most often invaded by pancreatic adenocarcinoma of uncinate, reported to be involved in 75-90% of cases
Uncinate to mesenteric ganglion via posterior inferior pancreaticoduodenal artery (\textit{PIPDA})

Most often invaded by pancreatic adenocarcinoma of uncinate, reported to be involved in 75-90\% of cases
Pancreatic Arterial Arcade

Open arrow: Anterior arcade
Solid arrow: Posterior arcade
Green: PIPDA

Axial 3D VR

Coronal 3D VR
PIPDA – Normal Appearance

Coronal 3D VR

Axial 3D VR
PIPDA Origin – Typical Appearance

Axial 3D VR

Coronal 3D VR
PIPDA Origin – Typical Appearance
Variations in PIPDA
Variations in IPDA Origin – Common PDJ Trunk

Axial 3D VR

Coronal 3D VR
Variations in IPDA Origin – Replaced Right Hepatic Artery

Axial 3D VR

Coronal 3D VR
Our study

- IRB approved
- Retrospective analysis of 183 patients who underwent MDCT for pancreatic mass
- All patients were imaged using our pancreas protocol
## Results

<table>
<thead>
<tr>
<th>Anatomy</th>
<th>No. of Patients (n = 183)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPDA origin off of SMA</td>
<td>94 (51%)</td>
</tr>
<tr>
<td>Common IPDA and first jejunal branch trunk</td>
<td>61 (33%)</td>
</tr>
<tr>
<td>Indeterminate anatomy</td>
<td>28 (15%)</td>
</tr>
<tr>
<td>Normal branching of IPDA into PIPDA and AIPDA</td>
<td>155</td>
</tr>
</tbody>
</table>
PPC II: Case 1

Axial 3D VR

Coronal 3D VR
PPC II: Case 2

Axial 3D VR

Coronal 3D VR
Anterior Pathway

- Anterior path along GDA and common hepatic artery to right celiac ganglion

- *Characteristic for adenocarcinomas within the dorsal pancreatic head*
Anterior Pathway: Case 1

Axial 3D VR

Coronal 3D VR
Anterior Pathway: Case 2
Root of Mesentery Invasion

- Relatively new pathway

- Similar to PPCII, in that PIPDA involved, but once reach SMA, *extension is caudally to infiltrate the root of mesentery rather than cranially towards mesenteric ganglion*
RMI: Case 1

Coronal 3D VR

Coronal 3D VR

Stanford Radiology
RMI: Case 2

Coronal 3D VR  Coronal 3D VR
Perineural invasion is one mechanism of pancreatic adenocarcinoma local spread (along with direct invasion and lymphatic invasion).

PNI is known to be associated with poor prognosis/survival and recurrence.

Abundance of nerve fibers around pancreas and complex molecular signaling facilitates early PNI.

SFOV 3D VR MDCT is key to visualize small peripancreatic vessels, and thus, PNI.
Future Areas of Study

- Define imaging biomarkers to predict poor outcomes
- Determine overall accuracy of 3D VR MDCT in detecting perineural invasion compared to conventional CT
- Correlate outcomes with radiologic detection of perineural invasion
- Modify image-based surgical resectability classification to establish PNI as a criteria

All Work In Progress – To Be Continued!!
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