Pancreatic Conundrums

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Sunnybrook ODETTE CANCER CENTRE
Objectives

- The mysterious **solid incidentaloma**
- The mysterious **cystic "IPM-something"**
- It's **cancer** - now what?
  - evaluating for resectability
  - operative issues
  - where are we at with [neo]adjuvant therapies?

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CHAPTER 1

“Incidental Solid Pancreas Lesions”

The Good
The (could be) Bad
The (clearly) Ugly

Sunnybrook
Odette Cancer Centre
Overview

- Getting the differential right!
- How to talk to your radiologist?
- What to ask from your lab?
- How might your friendly neighbourhood gastroenterologist help?
- Formulating a plan.
## Where do they come from?

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>GU/Renal</td>
<td>16</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>13</td>
</tr>
<tr>
<td>Screening / Surveillance</td>
<td>13</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>6</td>
</tr>
<tr>
<td>Cholangitis/Cholecystitis/Biliary Colic</td>
<td>6</td>
</tr>
<tr>
<td>Trauma / Emergency</td>
<td>5</td>
</tr>
<tr>
<td>Vague Abdominal Symptoms</td>
<td>5</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>4</td>
</tr>
<tr>
<td>Gastroesophageal Reflux</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>3</td>
</tr>
<tr>
<td>Integumentary</td>
<td>3</td>
</tr>
<tr>
<td>All Others</td>
<td>3</td>
</tr>
</tbody>
</table>
Incidental ≠ Asymptomatic

- Truly asymptomatic and truly incidental
- Symptomatic but not related and truly incidental finding
- Symptomatic related and found a pancreatic lesion
Incidental Cystic ≠ Incidental Solid

- Incidental cystic lesions of the pancreas have been well described with size criterion and consensus management strategies (Sendai Conference guidelines)
- SOLID incidental lesions have not had the attention or well described consensus strategies developed
- There is a higher rate of malignancy or at least significant neoplasm in SOLID incidental lesions.
Quick Differential Diagnosis

Solid mass of Pancreas
- Malignant
- Benign

Primary
- Inflammatory
- Structural
- Neoplastic
  - Focal Pancreatitis
  - Focal Fatty Infiltration
  - Other: small, spine, cystic in disguise
  - IPMN
  - Solid Papillary Tumour

Secondary
- Direct Invasion
  - Duodenal CA
  - Ampullary CA
- Distant Mets
  - Renal Cell CA
  - Melanoma

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Quick Malignant Differential Diagnosis

Primary Malignant
- Exocrine
  - Ductal Adenocarcinoma
  - Acinar Cell Carcinoma
- Endocrine
  - Gastrinoma (60-90%)
  - Insulinoma (10-15%)
  - VIPoma (60-80%)
  - Glucagonoma (60-70%)
  - PPoma (60%)
  - Somatostatinoma (90%)

Lymphoma
Classic Rash
Rash Resolution
How to talk to your radiologist

• Give a good history
  • interpretation always in context

• Getting the right test

  • **CT Scan – “Pancreas Protocol”**
    • ALWAYS better than a standard “screening” single phase scan
    • NOT THE SAME as a standard “triphasic” scan either

  • **MRI / MRCP**
    • MRCP portion can help identify relationships to ducts
    • Interpretation aided with contrast
    • Can do correlative US that day if planned

• Full staging investigations
  • Depends on the clinical suspicion for malignancy

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How to talk to your radiologist

- What might they find?
  - 10-15% of the time – really nothing or something other than pancreatic tissue
  - Remainder of the time:
    - Suspect adenocarcinoma
    - Suspect pancreatic neuroendocrine tumour
    - The peripancreatic “haze” factor – itis versus oma
    - “I can’t see a thing” – which is not always the same as really nothing.....
What to ask for from the lab?

- What am I thinking about?
- Inflammatory – any signs of pancreatitis?
- Malignant – Exocrine
- CA19-9
- Malignant – Lymphoma
- LDH, Blood Smears, etc.
- Malignant – Endocrine
- Ok which one?
<table>
<thead>
<tr>
<th>Type</th>
<th>Suggested Labs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrinoma</td>
<td>(fasting) serum gastrin</td>
</tr>
<tr>
<td></td>
<td>Secretin stimulation test (reactive serum gastrin)</td>
</tr>
<tr>
<td>Insulinoma</td>
<td>(fasting) serum insulin</td>
</tr>
<tr>
<td></td>
<td>(fasting) serum pro-insulin</td>
</tr>
<tr>
<td></td>
<td>(fasting) serum C-peptide</td>
</tr>
<tr>
<td>VIPoma</td>
<td>(fasting) vasointestinal polypeptide</td>
</tr>
<tr>
<td></td>
<td>(fasting) PHM (peptide-histidine-methionine)</td>
</tr>
<tr>
<td></td>
<td>WDH - watery diarrhoea/hypokalemia/achlorhydria</td>
</tr>
<tr>
<td>Glucagonoma</td>
<td>(fasting) plasma glucagon</td>
</tr>
<tr>
<td></td>
<td>(fasting) pancreatic polypeptide</td>
</tr>
<tr>
<td></td>
<td>Hypoproteinaemia</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Ppoma</td>
<td>(fasting) plasma glucagon</td>
</tr>
<tr>
<td></td>
<td>(fasting) pancreatic polypeptide</td>
</tr>
<tr>
<td></td>
<td>Hypoproteinaemia</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Somatostatinoma</td>
<td>(fasting) plasma somatostatin</td>
</tr>
</tbody>
</table>
How EUS can help.

- Further clarification of lesional characteristics:
  - Vascular / neovascular
  - Density
  - Small lesions (especially insulinoma, or any <2 cm)

- Tissue diagnosis without disruption of an “operative plane”
  - FNA / Tru-cut possible
Distributions in the Pancreas
So now what do we do?

- We're going to see more due to imaging but we must demand that the imaging **tell us more** at the same time!
- Solid lesions in the pancreas are **more likely to be malignant** than cystic lesions
- Must be sharp about **differentiating incidental from asymptomatic**
- If resectable but not resected, must be **followed closely** for interval growth
What typically happens?

- Solid Type of Lesion
  - Non-Operative:
  - Operative:
  - Observed

- Cystic Type of Lesion
  - Non-Operative:
  - Operative:
  - Observed

Siddh et al. 2009
What kind of risks are we talking about?

- Boston series:
  - 110 Asymptomatic pancreatic lesions
  - 24% malignancy rate including *in situ*
  - 17% invasive malignancy rate
  - 94% in solid lesions
  - 47% had lesions harboring potential for malignant degeneration
    - IPMN, MCA, PNET etc.
  - Total: 71% of asymptomatic solid lesions had some malignancy or risk of malignancy
The good, the bad and the ugly?

• The good:
  • Truly asymptomatic
  • Benign structural lesions like fatty replacement

• The (could be) bad:
  • Anyone with possibly related symptoms
  • Non-specific but possibly new solid lesions
  • Stable lesions but have a PNETs appearance

• The (definitely) ugly:
  • Symptomatic PNETs
  • Adenocarcinoma
The good.....

- Unless 110% sure:
- Interval follow-up at 6-12 months with imaging and clinical exam to rule out new or intervening symptomatology
The (could be) bad...

- Multidisciplinary discussion is mandatory
- Utilize all methods of further diagnosis:
  - Laboratory examination / screening
  - EUS
  - Better protociled CT / MRI / MRCP
- Discussion with patient for consideration of surgical excision
  - Depends on location of tumour
  - Depends on patient factors
- If observation chosen, strict and mandatory follow-up
  - 3-6 month maximum repeat imaging and clinical evaluation for at least 1-2 years unless operated on, or before consideration of lengthening follow-up

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The (definitely) ugly

- Immediate detailed staging with imaging and biochemistry
- Rapid decision: operative management
- If not resectable:
  - Definitive diagnosis must be sought – EUS bx, Percutaneous Bx etc.
  - Multidisciplinary management – especially involving medical oncology and radiation oncology – especially if there are symptoms.
Summary

- Careful evaluation with all modalities required:
  - Clinical, Radiological, Endoscopic, Biochemical, Multidisciplinary, Time
- Low threshold overall and over time for surgical intervention
- The initial workup should be the most intensive work-up!

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CHAPTER 2

The mysterious cystic “IPM-Something”
Is it a wolf in sheep's clothing?
Is it a wolf in sheep’s clothing?

Or

Are we killing a fly with a shotgun?
Objectives

- What is “IPMT”?
- The multidisciplinary approach to IPMT
  - The *radiologist* – what you need to tell the team?
  - The *endoscopist* – maneuvers that make a difference
  - The *surgeon* – making intervention decisions
  - The *pathologist* – optimizing the diagnosis
- What follow-up do we recommend?
What is IPMT?
A Background

• An autopsy series of 300 patients showed:
  1. 50% had cystic lesions in the pancreas of which 4% had epithelial atypia
  2. prevalence increased with age

• So…if you buy better imaging devices and you have an aging population…
What is IPMT?
Some history

- Therefore cystic neoplasms were increasing being reported
- 1996: WHO introduced a classification:
  - Took mucin producing cystic neoplasms and classified them as:
    - Intraductal Papillary Mucinous Tumour (IPMT)
    - Mucinous Cystic Tumour (MCT)
  - In 2004, WHO renamed “tumour” as “neoplasms” (ie. IPMN, MCN)
IPMTs

- Main duct IPMTs
  - associated with a dilated (<1 cm) pancreatic duct
  - Have a relatively higher predilection to malignancy
- Branch Duct IPMTs
  - Often multifocal but smaller
  - Relatively lower predilection to malignancy
- Mixed IPMTs
  - Usually a branch duct IPMT that shows some changes in the main duct as well
  - No established criteria to say "how much duct involvement" makes it a "true main duct IPMT"
Malignant risk in IPMT subtypes

<table>
<thead>
<tr>
<th>Reference (first author)</th>
<th>Year published</th>
<th>Patients</th>
<th>Malignant including CIN, %</th>
<th>Invasive malignancy, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kerbel [16]</td>
<td>1999</td>
<td>13</td>
<td>92</td>
<td>23</td>
</tr>
<tr>
<td>Di [18]</td>
<td>2002</td>
<td>22</td>
<td>83</td>
<td>Not stated</td>
</tr>
<tr>
<td>Matsunuma [19]</td>
<td>2003</td>
<td>27</td>
<td>63</td>
<td>Not stated</td>
</tr>
<tr>
<td>Choi [20]</td>
<td>2003</td>
<td>34</td>
<td>85</td>
<td>Not stated</td>
</tr>
<tr>
<td>Kitagawa [21]</td>
<td>2003</td>
<td>37</td>
<td>65</td>
<td>54</td>
</tr>
<tr>
<td>Sugiyama [22]</td>
<td>2003</td>
<td>30</td>
<td>70</td>
<td>55</td>
</tr>
<tr>
<td>Sato [23]</td>
<td>2004</td>
<td>60</td>
<td>Not stated</td>
<td>45</td>
</tr>
<tr>
<td>Saive [24]</td>
<td>2004</td>
<td>140</td>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td>Mean of all series</td>
<td></td>
<td>70</td>
<td>43</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference (first author)</th>
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<th>Patients</th>
<th>Malignant including CIN, %</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Kerbel [16]</td>
<td>1999</td>
<td>17</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>Tavris [17]</td>
<td>2000</td>
<td>13</td>
<td>15</td>
<td>0</td>
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<tr>
<td>Di [18]</td>
<td>2002</td>
<td>26</td>
<td>46</td>
<td>Not stated</td>
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<td>Matsunuma [19]</td>
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<td>Sugiyama [22]</td>
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<td>32</td>
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<td>9</td>
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<td>Sato [23]</td>
<td>2004</td>
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<td>Not stated</td>
<td>10</td>
</tr>
<tr>
<td>Mean of all series</td>
<td></td>
<td>25</td>
<td>15</td>
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</table>
Natural History of IPMT?

- No reliable data to document natural history
- Limited data from Johns Hopkins and a combined Massachusetts General and University of Verona experience
- Suggested time lag of 5-10 years from non-invasive to invasive lesions
Mucinous Cystic Neoplasms

- True MCNs have **ovarian like stroma** and are thought to originate from **ovarian rests**
- **Solitary** and **do not recur** following resection
- Occurs much more commonly in **females** of child bearing age
Why differentiate MCN vs. IPMT?

- Different biological behaviours
- Different management strategies
- Different prognoses
- Different follow-up care
## MCN versus Branch Duct IPMT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MCN</th>
<th>Branch duct IPMN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% female)</td>
<td>&gt;95%</td>
<td>~30%</td>
</tr>
<tr>
<td>Age (decade)</td>
<td>4th and 5th</td>
<td>6th and 7th</td>
</tr>
<tr>
<td>Location (% body/tail)</td>
<td>95%</td>
<td>~30%</td>
</tr>
<tr>
<td>Common capsule</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Calcification</td>
<td>Rare, curvilinear, in the wall of cyst</td>
<td>No</td>
</tr>
<tr>
<td>Gross appearance</td>
<td>Orange-like</td>
<td>Grape-like</td>
</tr>
<tr>
<td>Internal structure</td>
<td>Cysts in cyst</td>
<td>Cyst by cyst</td>
</tr>
<tr>
<td>Pancreatic duct communication</td>
<td>Infrequent</td>
<td>Yes (though not always demonstrable)</td>
</tr>
<tr>
<td>Main pancreatic duct</td>
<td>Normal or deviated</td>
<td>Normal, or if dilated, suggests combined type</td>
</tr>
</tbody>
</table>
Diagnostic Imaging and IPMT

- Relevant clinical questions are:
  - What is the relationship to the pancreatic duct?
  - Is there duct dilatation or papillary formations?
  - Is it unifocal or multifocal?
  - Is this a MCN or an IPMT
  - Is this a main duct IPMT or branch duct IPMT?
Diagnostic Imaging for IPMT

- MRI / MRCP
  - Best method to outline gross appearance
  - Helpful for demonstrating duct communication
- Criteria for malignancy
  - Main Pancreatic Duct Diameter > 15 mm
  - Branch Duct IPMT
    - Lesion > 3 cm
    - Main Duct > 7 mm
  - Thick enhancing wall
  - Soft tissue nodules
Endoscopic Evaluation of IPMT

- Ductal anatomy – ERCP can be the most definitive test
- Patulous Papilla filled with mucin

- Pancreatostomy
  - “fish egg” appearance
Endoscopic US

- Can give very detailed imaging within cystic neoplasms
- Can perform FNA to allow for cytological and biochemical evaluation
- May assist in deciding on major pancreatic resection versus observation especially where imaging is equivocal
### EUS FNA characteristics of certain pancreatic cystic lesions

<table>
<thead>
<tr>
<th>EUS finding</th>
<th>SCA</th>
<th>MCA</th>
<th>MCAC</th>
<th>IPMN</th>
<th>Pseudocyst</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EUS finding</strong></td>
<td>Multiple small microcysts, dense fibroin septations, honeycomb pattern, Central calcification</td>
<td>Multiple fluid filled cavities, thin septations, Larger than SCA, Peripheral calcification</td>
<td>Dilated pancreatic duct(s), Connection to duct, Multilocular, No septations</td>
<td>Internal echoes representing debris, Unilocular, Pancreatitis paranchymal change</td>
<td></td>
</tr>
<tr>
<td>Amylase</td>
<td>Variable</td>
<td>Variable</td>
<td>Variable</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>CEA</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Variable</td>
<td>Low</td>
</tr>
<tr>
<td>Cytology</td>
<td>No mucus, Glycogen, Flattened Columnar epithelium, Low cellularity</td>
<td>Mucinous Columnar epithelium</td>
<td>Mucinous Columnar epithelium, Atypical nuclei.</td>
<td>Mucinous Columnar epithelium</td>
<td>No mucus, No epithelial lining, Histiocytes</td>
</tr>
</tbody>
</table>

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Creating an algorithm for surgical intervention

Size < 1 cm
MRI / CT in one year

Size < 1 cm
Size 1-2 cm

Size 1-3 cm
EUS / MRCP / ERCP
High risk stigmata?
Mural nodules
Dilated main duct
Positive cytology

No

Yes

MR / CT
1-2 cm - q6-12 months
2-3 cm - q3-6 months

Size > 3 cm?
Symptomatic?
High risk stigmata?

No

Yes
Surgical Issues in IPMT

- Indications for resection
- Main Duct IPMT
- Branch Duct IPMT
- Methods of resection
  - Partial versus Total versus Segmental Pancreatectomy
  - Lymphadenectomy
Main Duct IPMT
Indications for Surgical Resection

- Symptoms
- Pain, jaundice, worsening diabetes
- Criteria for Malignancy
  - > 15mm duct diameter
  - Intraductal papilla or nodules
- Risk of malignancy >60%
- Practical: treat mixed as main duct
Branch Duct IPMT
Indications for surgical resection

- Risks of surgery are more balanced with risk of malignancy since it is lower (estimated < 25%)
- Criteria for higher risk lesions:
  - > 30mm lesion
  - Intraductal papilla or nodules
  - Associated duct dilatation > 7mm
Branch Duct IPMT

- Japanese studies:
  - Branch IPMT <30mm and no mural nodules have no association with invasive cancer and low association with in situ disease

- Controversy:
  - >30mm without symptoms or mural nodules
Method of Pancreatectomy

- Surgery determined by extent of tumour
- If pre-operative investigations suspect malignancy, a standard oncologic resection applies
- Multifocality of IPMT balanced by:
  - Relatively indolent tumour
  - Ability to image in follow-up
  - Limited data showing superiority of total pancreatectomy
Histology Issues

- The dreaded frozen section
- Caveats of FS:
  - Difficulty confirming negative margin
  - Does not account for skip lesions
  - Careful handling required as to not denude the epithelial layer
The positive margin

- Adenoma
- Continued follow-up
- Data indicates minimal risk of progression
- Borderline Atypia
  - Poorly defined category
  - Florid papillary nodules at the margin or presence of high grade dysplasia anywhere in the specimen may be criteria for further resection
- CIS or Invasion
  - Further resection balanced with patient factors
Follow-Up Post Resection

- MCNs are usually cured completely
- No studies to define a guideline
- Prognosis: Invasive Ca identified with IPMT still associated with 60% 5 year OS
- General:
  - 6-12 month follow-up with imaging
  - Continue for 5-10 years
  - No value in doing serum markers