Incidental Pancreatic Solid Mass

- 7% of pancreatic solid masses are incidental findings (24/321 over 8 years)
- 50% Adenocarcinoma, 50% NET

DDX

- Primary exocrine pancreatic (95%); Ductal Adenocarcinoma (85%), IMPN with invasive cancer, MCN with invasive cancer, SPN, Acinar cell carcinoma, Pancreatoblastoma, Serous cystadenocarcinoma
- NET
- Metastases
- Lymphoma
- SCC
- Benign conditions: AIP, focal CP, accessory spleen, lymph nodes

Benign Lesions

- Pancreatic surgical specimens 2005-11 in Mainz, Germany
- 8.8% (33/373 patients)
- 25 (8.4%) of 298 in the pancreatic head and 8 (10.7%) of 75 in the body-tail resections
- In pancreatic head resections, the most frequent diagnoses were paraduodenal pancreatitis (13/298, 4.4%) and AIP (9/298, 3%)
- Body-tail, the most frequent diagnoses were accessory spleen (3/75, 4%), chronic pancreatitis (3/75, 4%), and AIP (2/75, 2.7%).

Vitali F et al Pancreas. 2014 Nov;43(8):1329-33
Initial Labs and Imaging

- LFTs (especially if jaundiced or mass in HOP)
- Pancreatic enzymes (especially if epigastric pain)

Abdominal contrast-enhanced triple-phase helical CT scan

Pancreas scan in the arterial phase, pancreatic phase and portal phase with a delay of 30 s, 50 s and 70 s respectively, with a slice of 2.5 mm thickness. At last liver scans were performed with a slice of 5mm thickness. Each was completed within one breathhold.

<table>
<thead>
<tr>
<th>CT results</th>
<th>Surgical results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Resectable</td>
</tr>
<tr>
<td>Resectable</td>
<td>40</td>
</tr>
<tr>
<td>Unresectable</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>49</td>
</tr>
</tbody>
</table>

NPN 93%
PPV 90%
E Ergul et al The Internet Journal of Radiology. 2007 Volume 8 Number 1.
Size Matters

• Thin-section triple phase (20, 40, and 70 sec after the start of injection)
• Sensitivity was 100% percent for tumors >2 cm, but only 77 % for tumors ≤2 cm in size


Classic Finding: ill-defined hypo-attenuating mass within the pancreas

• Other findings (important for smaller tumors)
  • PD cutoff
  • dilatation of the PD or CBD
  • parenchymal atrophy
  • contour abnormalities
  • double duct sign
CT Pancreatic Protocol

• Arterial phase of enhancement = first 30 seconds after the start of the contrast injection
  • Excellent opacification of the celiac axis, SMA, and peripancreatic arteries

• Pancreatic phase; after peak enhancement of the aorta in the arterial phase but before peak enhancement of the liver
  • An attenuation difference between tumor and normal pancreas, which increases lesion conspicuity, is best achieved

• The portal venous phase = 60 - 70 seconds after the start of the contrast injection
  • Better enhancement of the SMV, SV and PV
  • Hepatic metastases

Why is it Important?

• Local and regional disease extent
• Determines resectability
• Distant metastatic spread
CT Pancreatic Protocol for Diagnosing Vascular Invasion

• 2004-2008 CT has shown a higher diagnostic accuracy
• Pooled sensitivity 85%
• Pooled specificity 82%
• CT imaging with vascular reconstruction, the pooled sensitivity and specificity were 84% and 85%, higher than the estimates in studies without reconstruction

Zhao WY et al Hepatobiliary Pancreat Dis Int. 2009 Oct;8(5):457-64

MRI/MRCP

• Pancreatic protocol MRI/MRCP is also effective
• May be preferable for cystic neoplasms of the pancreas
• Evaluate biliary anatomy in case of biliary obstruction or concern for choledocholithaisis
• Increased sensitivity and specificity of diffusion-weighted MR imaging (DWI) for the detection of small liver metastases (86.7% and 97.5%) compared with MDCT 53.3% and 77.8%

McIntyre CA, Winter JM Semin Oncol. 2015 Feb;42(1):19-27
Holzapfel K et al Abdom Imaging. 2011 Apr;36(2):179-84
Do You Have To Do An EUS for Staging/Resectability?

• 62 consecutive patients with pancreatic carcinoma judged fit for laparotomy were studied by EUS, CT, MRI, and Angio

• CT had the highest accuracy in assessing extent of primary tumor (73%), locoregional extension (74%), vascular invasion (83%), distant metastases (88%), tumor TNM stage (46%), and tumor resectability (83%)

• EUS had the highest accuracy in assessing tumor size (r = 0.85) and LN involvement (65%)

• In those cases with potentially resectable tumors a sequential approach consisting of helical CT as an initial test and EUS as a confirmatory technique seems to be the most reliable and cost minimization strategy


Does Pre-Op EUS Improve Survival?

• 8616 patients with pancreatic adenocarcinoma aged 65 years and older (SEER-Medicare database between 1994 and 2002)

• 610 (7.1%) patients underwent EUS evaluation

• In the EUS group
  • Median survival was significantly higher in patients with locoregional cancer (10 vs. 6 months)
  • More patients with early-stage disease (69.3% vs 36.2%, P < .001)
  • Curative-intent surgery, chemotherapy, and radiation therapy were also performed more frequently (improved stage-appropriate management)

Ngamruengphong S et al Gastrointest Endosc 2010 Jul;72(1):78-83
CA 19-9

- CA 19-9 level >37 Units/mL sensitivity 77% and specificity 78% for pancreatic cancer
- Other malignant conditions: biliary cancers, HCC, gastric, ovarian, colorectal, lung, breast uterine
- Benign conditions: acute cholangitis, cirrhosis, cholestatic diseases
- **Expert guidelines recommend against the use of CA 19-9 as a screening test for pancreatic cancer**
- Serial monitoring of CA 19-9 levels (Q1-3 months) is useful to follow patients after potentially curative surgery and for those who are receiving chemotherapy for advanced disease

Kim HJ et al Am J Gastroenterol. 1999;94(7):1941

What if Imaging is Negative

- If high index of suspicion → EUS with tissue sampling
- 116 patients suspected of having pancreatic cancer, but with inconclusive findings on CT scan
- EUS with FNA: sensitivity 87% and specificity 98% for diagnosing a pancreatic malignancy
- Independent risk factors associated with EUS detection of pancreatic ductal adenocarcinoma
  - pancreatic ductal dilation on CT scan (OR 4.1)
  - tumor size detected by EUS of ≥1.5 cm (OR 8.5)

Stage Before Biopsy

- If surgically fit patient, and tumor is evident, and clearly resectable can proceed to surgery without tissue diagnosis
- If any doubts about the diagnosis e.g possible CP, or AIP → Biopsy
- Percutaneous FNA biopsy of a pancreatic mass can be performed using either ultrasound or computed tomographic (CT) guidance
- Theoretical concern is that percutaneous FNA biopsy of the pancreas may disseminate tumor cells intra-peritoneally or along the needle path in patients who are believed to be candidates for potentially curative resection

ERCP

- A tissue diagnosis can be obtained via ERCP biopsy and brush cytology
- The sensitivity rate for ERCP-directed brush cytology or biopsy is 30% to 50%, with a combination achieving sensitivity rates of 65% to 70%
- Pancreatosiscopy allows direct visualization of ductal structures and can be helpful in distinguishing pancreatic adenocarcinoma from IPMN and other cystic neoplasms

Hawes RH et al Gastrointest Endosc 2002;56(Suppl 6):S201-5
EUS guided biopsy

- Meta-analysis: 41 studies with 4766 patients
  - Pooled sensitivity 89%
  - Pooled specificity 96%
- Lower in the setting of CP (74% vs. 91% in one report)

Varadarajulu S et al Gastrointest Endosc. 2005;62(5):728

Does EUS-FNA Impair Survival (seeding effect)?

- 2034 patients with locoregional pancreatic cancer (90% adeno) who underwent curative intent surgery from 1998 to 2009 (SEER-Medicare data)
- Pre-op EUS-FNA 498 patients (24%)
- In multivariate analysis
  - EUS-FNA was marginally associated with improved overall survival (HR 0.84, 95% CI 0.72 to 0.99)
  - Did not affect cancer-specific survival (HR 0.87, 95% CI 0.74 to 1.03)

Ngamruengphong S et al Gut.2015 Jul;64(7):1105-10
Accessory Spleen

- DDX mainly NET
- MRI usually shows similar images to the spleen in all sequences
- EUS: Adjacent to the spleen, well demarcated, similar echogenicity to the spleen
- Tc-colloid SPECT/CT will show focal uptake

AIP

Revised HISORt Criteria for AIP

- **(H) Histology** suggestive of AIP
- **(I) Pancreatic imaging** suggestive of AIP
- **(S) Serology** (IgG ≥2 times the upper limit of normal)
- **(O) Other** organ involvement
- **(Rt) Response to steroid treatment** - Resolution/marked improvement of pancreatic and extrapancreatic manifestations


NET

- Highly vascular with enhancement in the early arterial phase and washout in the early portal venous phase
68Ga-DOTA-TATE PET/CT

- (Tyr\(^3\))-octreotate, binds to SSR 2 and SSR 5
- Performs better than 111-In-Octreotide scan
- Indications:
  - staging, re-staging after therapy
  - identification of the site of the unknown primary
  - selection of cases eligible for therapy

Buchmann et al, EJNM (2007); 34:1617-26
Sadowski et al, JACS (2015); 221:509-17

DDX of Pancreatic Solid Mass

31 YO PC
NET
AIP

SCC
Renal Met
lymphoma
Approach To Pancreatic Mass

- Triple-phase MDCT
- If poor surgical candidate, unresectable, or borderline resectable → EUS with tissue sampling
- If resectable either
  - Confirm resectability with EUS, sample LNs, exclude other tumors/etiologies if suspicious
  - Surgical resection/staging laparoscopy

Pancreatic Cysts Pathological Classification

- Based on presence or absence of epithelium lining the cyst
- Pseudocyst: lack of an epithelial lining
- All other cysts: epithelial lining
Pancreatic Cysts With Lining

<table>
<thead>
<tr>
<th>Lining</th>
<th>Cyst type(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucinous</td>
<td>MCN, IPMN</td>
</tr>
<tr>
<td>Serous</td>
<td>SCA, VHL</td>
</tr>
<tr>
<td>Squamous</td>
<td>Lymphoepithelial cyst</td>
</tr>
<tr>
<td>Acinar</td>
<td>Acinar cell carcinoma</td>
</tr>
<tr>
<td>Solid tumor degeneration</td>
<td>NET, lymphangioma, sarcoma, SPT, PDAC, Pancreaticoblastoma</td>
</tr>
</tbody>
</table>

Garcia G Pancreatology 2008;8:236-51

Workup of Pancreatic Cysts

- Symptoms/signs
- Imaging
- Endoscopic Ultrasound (EUS) features
- Cyst fluid evaluation
  - CEA
  - Amylase
  - Cytology
  - Pancreatic cyst fluid DNA analysis
  - String sign
- Cystoscopy
- nCLE
Imaging CT and MRI:

• **40-60% accurate** in predicting histology
• 70-90% accurate in differentiating aggressive from non-aggressive lesions
• 1.5-2% of all cancers in the US are related to radiation from CT
• The risk of cancer of a 40-year-old female having a single phase abdominal CT is estimated to be 1:850


How Good Is EUS Alone In Differentiating Mucinous From Non-mucinous Lesions

• 341 patients/12 centers/112 underwent surgical resection
• EUS imaging features alone
  • **51% Accurate**
  • 56% Sensitive
  • 45% Specific

Brugge WR et al Gastroenterology 2004;126:1330-6
How Good Is EUS In Differentiating Benign From Malignant Cysts

- 114 patients with PCL who underwent resection between 1992-2006
- EUS did not seem to improve ability to preoperatively differentiate benign from malignant cysts (P > 0.05)

Morphological Classification

<table>
<thead>
<tr>
<th>Unilocular</th>
<th>Microcystic</th>
<th>Macrocystic</th>
<th>Cyst with solid component</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pseudocyst</td>
<td>SCA</td>
<td>MCN</td>
<td>MCN</td>
</tr>
<tr>
<td>Retention cyst</td>
<td>IPMN</td>
<td>IPMN</td>
<td>IPMN</td>
</tr>
<tr>
<td>IPMN</td>
<td></td>
<td>SCA</td>
<td>SPT</td>
</tr>
<tr>
<td>MCN</td>
<td></td>
<td>Acinar cell</td>
<td>PET</td>
</tr>
<tr>
<td>SCA</td>
<td>cystadenoma</td>
<td>Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lymphangioma</td>
<td>Metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lymphoepithelialu</td>
<td>Acinar cell</td>
<td></td>
</tr>
</tbody>
</table>

Donahue T et al Pancreas. 2010 Nov;39(8):1271-6

Pittman M Cancer Cytopathology. 2010; 118:1-13
Cyst Fluid Analysis

- Cytology
- Biochemical analysis
- Tumor Markers
- DNA analysis

Cytology in Diagnosis of Mucinous PCLs

- Meta-analysis
- 376 patients from 11 distinct studies
- Pooled sensitivity **0.63** (95% CI, 0.56–0.70)
- Pooled specificity **0.88** (95% CI, 0.83–0.93)
- Positive likelihood ratio 4.46 (95% CI, 1.21–16.43)

**CEA in Diagnosing Mucinous PCLs**

- > 192 ng/ml 79% accurate (Brugge WR et al Gastro 2004;126:1330-6)
- > 192 ng/mL 82% sensitivity (Sawhney MS et al GIE 2009;69:1106-10)
- > 192 ng/ml 66% sensitivity, 78.6% specificity (Sreenarasimhalah J et al JOP 2009 Mar 9:10(2):163-168)
  - PPV 57%
  - NPV 84.6%
- 148 ng/ml 67% sensitivity and specificity (Khalid A et al GIE 2009;69:1095-102.)
  - 192 ng/mL 64% sensitivity, 83% specificity
- ≥ 200 ng/ml 60% sensitivity, 93% specificity, 72% diagnostic accuracy (Park WG et al Pancreas 2011;40: 42-45)

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**Cyst Amylase**

![Box plot showing cyst amylase levels in different conditions](image.png)

Park WG et al Pancreas 2011;40: 42-45
12 studies with data from 450 patients

- Amylase concentration of <250 U/L were serous or mucinous (not pseudocyst) with a sensitivity of 44% and specificity of 98%
- A CEA level <5 ng/mL suggested a pseudocyst or serous lesion (50% sensitivity and 95% specificity)
- A CEA level >800 ng/mL suggested a mucinous lesion (sensitivity of 48% and specificity of 98%).


Pancreatic Cyst Fluid DNA Analysis

- k-ras mutation non-mucinous 1/25 vs. mucinous 40/88 P< .0001 (.0003) **Sensitivity 45%**, Specificity 96%
- k-ras followed by allelic loss non-mucinous 0/25 vs. mucinous 17/88 P = .017 **Sensitivity 19%**, Specificity 100%
- k-ras mutation premalignant 20/48 vs. malignant 21/40 P=NS
- k-ras followed by allelic loss premalignant 2/48 vs. malignant 15/40 P< .0001 **Sensitivity 37%**, Specificity 96%
- Selection bias?

Khalid A et al GIE 2009;69:1095-102
Criteria For Integrated Molecular Pathology Diagnostic Categories

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Molecular Criteria</th>
<th>Co-existing concerning clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign</td>
<td>DNA lacks molecular criteria</td>
<td>Not considered for this diagnosis</td>
</tr>
<tr>
<td>Statistically Indolent</td>
<td>DNA meets 1 molecular criteria</td>
<td>None</td>
</tr>
<tr>
<td>Statistically higher risk (SHR)</td>
<td>DNA meets 1 molecular criteria</td>
<td>1 or more</td>
</tr>
<tr>
<td>Aggressive</td>
<td>DNA meets at least 2 molecular criteria</td>
<td>Note considered for this diagnosis</td>
</tr>
</tbody>
</table>

Four molecular criteria that have been independently correlated with pancreatic malignancy or HGD are used to make an integrated molecular pathology diagnosis:
- i) a single high-clonality mutation
- ii) elevated level of high-quality DNA
- iii) multiple low-clonality mutations
- iv) a single low-clonality oncogene mutation

Cytologic evidence of HGD.

Benign DNA lacks molecular criteria. Not considered for this diagnosis.

Statistically Indolent DNA meets 1 molecular criteria. None.

Statistically higher risk (SHR) DNA meets 1 molecular criteria. 1 or more.

Aggressive DNA meets at least 2 molecular criteria. Note considered for this diagnosis.


Their Conclusions

- IMP more accurately determined the malignant potential of pancreatic cysts than a Sendai 2012 guideline management criteria model.
- IMP may improve patient management by justifying more relaxed observation in patients meeting Sendai surveillance criteria.
- IMP can more accurately differentiate between the need for surveillance or surgery in patients meeting Sendai surgical criteria.
String Sign

- Positive if ≥1 cm string formed in cyst fluid and lasted for ≥1 second
- 98 histologically proven cases, for diagnosis of mucinous cyst
  - Sensitivity 58%, **Specificity 95%**, PPV 94%, NPP 60%
- String sign results and CEA concentration (≥200 ng/mL) combined → diagnostic accuracy improved from 74% and 83%, respectively, to 89% (P≤0.03)
- The sequential cyst fluid test interpretation model (including cytology, mucin stain, CEA, and string sign) yielded an overall sensitivity for mucinous lesions of 96%, with a specificity of 90%

Bick BL et al. Endoscopy. 2015 Jul;47(7):626-31
Epithelial Structure

- Finger-like papillary projections - Villous structure
- Dark ring with white core - Villous structure

Superficial Vascular Network

- Vessels with variable width
- Visualization of blood cells
Laith H. Jamil, MD

pCLE in Pancreatic Cysts

• INSPECT Study:
  • The presence of epithelial villous structures based on nCLE was associated with PCN (P= 0.004) Sensitivity 59%, specificity 100%, PPV 100%, and NPV 50%

• Contact study for SCA
  • A superficial vascular network pattern visualized on nCLE was identified as the criterion
  • The accuracy, sensitivity, specificity, PPV, and NPP of this sign for the diagnosis of SCA were 87%, 69%, 100%, 100%, and 82%, respectively

• Detect study
  • Sensitivity of cystoscopy 90% (9/10), nCLE 80% (8/10), and combination 100% (10/10) in 18 high certainty patients

Konda VJ et al Endoscopy. 2013 Dec;45(12):1096-13
Napoleon B et al Endoscopy. 2015 Jan;47(1):26-32
Nakai Y et al Gastrointest Endosc. 2015 May;81(5):1204-14

Indeterminate Pancreatic Cystic Lesions

• 143 patients (median age 63 years; median cyst size 2.8 cm) who underwent EUS, FNA was performed in 128 (90 %)
• Cyst fluid sent for cytology provided adequate cellular material in 44 cases only, accounting for an intention-to-diagnose yield of 31 % (44/143)
• Sufficient fluid for biochemical analysis was obtained in 68 cases (49 %)
• Possible to obtain a classifying cytopathologic diagnosis and a chemical analysis in only a third and a half of cases, respectively

de Jong K et al Endoscopy 2011; 43(7): 585-590
Pancreatic Cyst management

- Serous cyst adenoma: If symptomatic → surgery (some advocate if >4cm)
- Solid Pseudopapillary tumor: Surgery
- NET: Surgery
- MCN: Surgery
- MD-IPMN and Mixed variant IPMN: Surgery
- SB-IPMN: If symptomatic &/or certain features → surgery


Consensus Guidelines

- 14th meeting of the International Association of Pancreatology in Fukuoka, Japan, in 2010
- Levels of evidence for all items addressed: Low
- Thus “consensus”, rather than “evidence-based”, guidelines

Tanaka M et al Pancreatology 12 (2012) 183-197
Symptomatic Cysts

- All symptomatic cysts should be further evaluated or resected for
  - Amelioration of symptoms
  - Higher risk of malignancy

Work up

- Triple phase CT or MRI with MRCP (better) is recommended for cysts \( \geq 1 \) cm, especially in distinguishing BD-IPMN from other cysts
Case

- 67-year-old male with lower AP more recently responding to Bentyl
- CT scan: 1.5 cm Cyst in the uncinate process
- MRI of the abdomen 2 cm mass in the head of the pancreas consistent with small cystic component septations
Path

- EUS-FNA: typical epithelial cells present, consistent with adenocarcinoma
- Whipple: T1

5-Year Survival After Surgery

- IPMNs without invasive cancer: 77%
- IPMN with invasive component: 43%
  - P < 0.0001
- Resected pancreatic ductal adenocarcinoma in the absence of IPMN (averages 15%-25%)
- There appears to be a 5-year lag time from IPMN adenoma (63.2 years) to invasive cancer (68.1 years)
- Long-term surveillance is critical post resection

Cyst work up

Asymptomatic patients, with a solitary cyst that does not communicate with the pancreatic cyst and that have an atypical aspect on EUS

Solitary cyst
- No communication
  - Typical aspect
    - Suspicious cyst SCA
      - Microcystic appearance
        - (EUS-FNA), + Surgery or FU
  - No typical aspect
    - EUS-FNA
      - Positive cytology
        - Low amylase
          - Low CEA
            - Micro/Macrocystic SCA
              - Congenital cyst
      - Negative cytology
        - High amylase
          - High CEA
            - MC, PC, BD IPMN

Multiple cysts
- Communication
  - BD IPMN
  - Polycystic disease

Indeterminate cyst for repeat eval → DNA analysis? nCLE?, cystoscopy?

Observation
- Resection or observation
- Resection

Low amylase
- Low CEA
  - Micro/Macrocystic SCA
  - Congenital cyst

High amylase
- High CEA
  - MC, PC, BD IPMN
Thank You