Pancreatic Cystic Neoplasms: Do's and Don'ts

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Diagnosis of Pancreatic Cysts

- Most PC are detected on imaging for non-pancreatic indication
- Prevalence in asymptomatic people: 2.4-13%
  - MRI for non-pancreatic indication in pts >70: 40% have incidental pancreatic cysts!*
- Cysts >2 cm incidence much lower: 0.8%
- Increased recognition likely due to both use of more, & better quality imaging, not increased incidence

* Lee KS Am J Gastro 2010

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Pancreatic Cysts: Why all the Hype?

- Some PCs are precursor of cancer, although vast majority don't progress
- What is the cancer risk?
  - IPMNS: Low risk 7.7% at 10 yrs; High risk 24.6% at 10 yrs*
  - Study of 1404 pts followed over 20 years**:
    - Panc cancer: 3.3% at 5 yr, 6.6% at 10 yr, 15% at 15 yr
    - Even small (<15 mm) cysts had 7-fold increased risk
    - 44% were concomitant PDAC, 56% were IPMN-derived carcinomas

*Choi Clin Gastro Hep 2017 ** Oyama Gastro 2020

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Issues Impacting Pancreatic Cyst Management Decisions

- Frequent detection with low risk of cancer
- High cost of cyst surveillance
- Benefits of surveillance unproven
  - Unclear if cancers are prevented / detected early
- Risks of pancreatic surgery for cysts is high:
  - Mortality 2.1%; Morbidity 30%
- Cysts often found in elderly pts with co-morbidities

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Classification of Pancreatic Cyst Types

- Neoplastic: Most PCs
  - Most are benign but some have malignant potential
- Non-neoplastic: pseudocysts
- Mucinous: Have malignant potential
- Non-Mucinous: Serous cystadenoma most common

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Three Common Types of Pancreatic Cysts

- IPMN (Intra-ductal Papillary Mucinous Neoplasm):
  - Side Branch IPMN is by far the most common incidentally found cyst
  - Main duct: entire duct or segmental; uncommon
  - Mixed: side branch plus main duct; rare
- Serous Cystadenoma
- Pseudocysts

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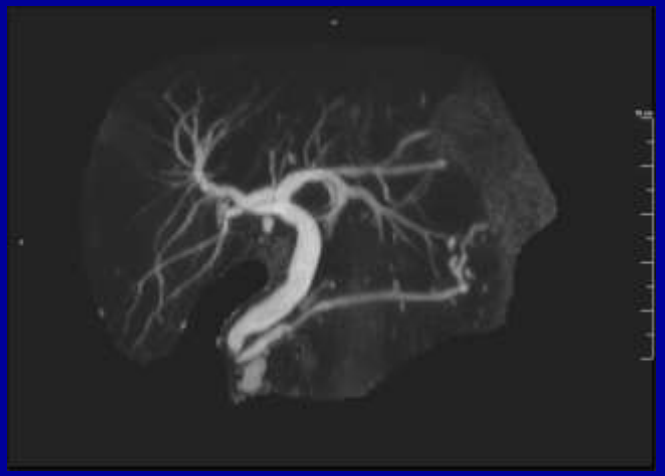
Intraductal Papillary Mucinous Neoplasm (IPMN)

- Equal incidence in men & women
- Often diagnosed in 7th decade
- Asp: high CEA, high lipase
- Side Branch: Communicates with PD, 40% multifocal, multi-focality doesn't increase cancer risk
- Main Duct: much less common than SB, 38-68% cancer risk*, patulous papilla in 50%
- Mixed: same cancer risk as MD



*Stark JAMA 2016

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Serous Cystadenoma

- 75% are women, 6th decade most common
- 0.1% risk of serous cystadenocarcinoma*; Do not require surveillance
- Microcystic / honeycomb; oligocystic less common
- Rarely cause symptoms when very large
- Central scar: <30%; Aspirate: low CEA, low lipase

*Law JK Pancreas 2014

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Pseudocysts

- Non-neoplastic cyst
- Occur in acute or chronic pancreatitis
- Aspirate: brown, high lipase, low CEA
- No surveillance or treatment indicated in asymptomatic pts
- Neoplastic cysts can cause idiopathic pancreatitis in up to 20% of pts >40 yo

Caution: Cyst at initial presentation requires investigation

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Less Common Pancreatic Cysts

- Mucinous cystic neoplasm (MCNs):
  - Almost all women, 5th-7th decade
  - Usually in body or tail; Ovarian stroma on path
  - Mucin producing but no communication to PD
  - Asp: High CEA, variable lipase
  - Risk of cancer lower than previously thought:
    - 10% cancer or HGD in 90 resected MCNs*
    - No HGD or cancer in 344 MCNs < 3 cm with no solid component**

* Park Pancreatology 2014 **Goh World J Surg 2006

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Less Common Pancreatic Cysts

- **Solid-pseudopapillary neoplasm:**
  - **10:1 women : men**
  - **Occur in any part of the pancreas**
  - **3rd decade although wide age range**
  - **Small ones more solid w/o cystic degeneration**
  - **Requires surgical removal**
  - **Aggressive histologic tumor behavior in 10%**
  - **5-year disease free survival 98%***

*Law Pancreas 2014

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Less Common Pancreatic Cysts

- Cystic neuroendocrine tumor:
  - Usually non-functioning, may have MEN 1
  - Equal incidence in men and women
  - 5^{th}-6^{th} decade
  - Asp: low CEA, lipase,
  - EUS FNA often needed for diagnosis: + cytology
- Other rare pancreatic cysts: simple cysts, lymphoepithelial cysts, cystic degeneration of pancreatic cancer, hydatid cysts

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How Do We Determine Cyst Type?

- MRCP: best choice, non-invasive, no radiation, better for PD connection (vs. CT)
  - CT or EUS (w/o FNA) excellent alternatives
  - Indeterminate cyst may benefit from 2nd modality
- Accuracy of all 3 modalities similar: MRI, CT, EUS w/o FNA
  - Accuracy for cyst type: 40-50%
  - Accuracy for determining benign vs. malignant: 55-76%
- When to add FNA or biopsy to assess cyst type:
  - When results may alter management

Diagnostic Accuracy of MRCP, CT & EUS is Relatively Low

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When to add Cyst Fluid Analysis to Assess Cyst Type?

- When results may alter management
  - Would not perform in small cysts (< 1.5 cm) w/o worrisome characteristics
  - May help differentiate SB IPMN from oligocystic serous cystadenoma
  - May help determine need for surgery in large cysts
- FNA complications: 3% (2% pancreatitis)

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Cyst Fluid Analysis: How good is it for determining cyst type?

- CEA: helps differentiate mucinous cysts (IPMNs & MCNs) from other types; not useful for cancer risk
  - CEA>192: 63% sensitive, 93% specific
- Lipase or amylase: High in Pseudocysts & IPMN
  - <250 excludes pseudocyst with 98% accuracy
- KRAS & GNAS: better than CEA for mucinous cyst but costly; also does not determine cancer risk
- Meta-analysis of low Glucose*: More accurate than CEA (94% vs. 85%), combo of CEA & glucose not better
- Cytology: only 34% have adequate cellularity

*McCarty GIE 2021

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Other Cyst Sampling Techniques

- Meta-analysis of micro biopsy forceps thru 19 G needle vs. FNA: *
  - Improved sample adequacy: OR 4.83, accuracy OR 3.44(75-83%) at the cost of more complications (6%)
- Confocal microscopy: harder for GIs to learn; better than CEA / cytology in diagnosing mucinous cysts with 3.5% pancreatitis rate**
- Many new markers under study: NGS, MDMs

*Facciorusso GIE 2020 ** Krishna Clin Gastro Hep 2020

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Cyst Ablation

- Cyst ablation: ethanol, paclitaxel, ethanol plus paclitaxel, RFA, cryotherapy all have been used
  - Cyst resolution low: 33-79%
  - Decreased size common
  - Adverse events: 12%
  - Unclear if ablation therapy decreases cancer risk
- Not ready for prime time

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Who Should Enter Cyst Surveillance Program?

- Surgically fit pts w presumed IPMNs or MCNs
- Asymptomatic pseudocysts and serous cystadenomas need not be followed
- MRCP: preferred modality of surveillance
- EUS: pts who cannot / choose not to have MRIs
  - More accurate in differentiating solid vs. mucin
  - Harmonic-enhancement adds accuracy for mural nodules

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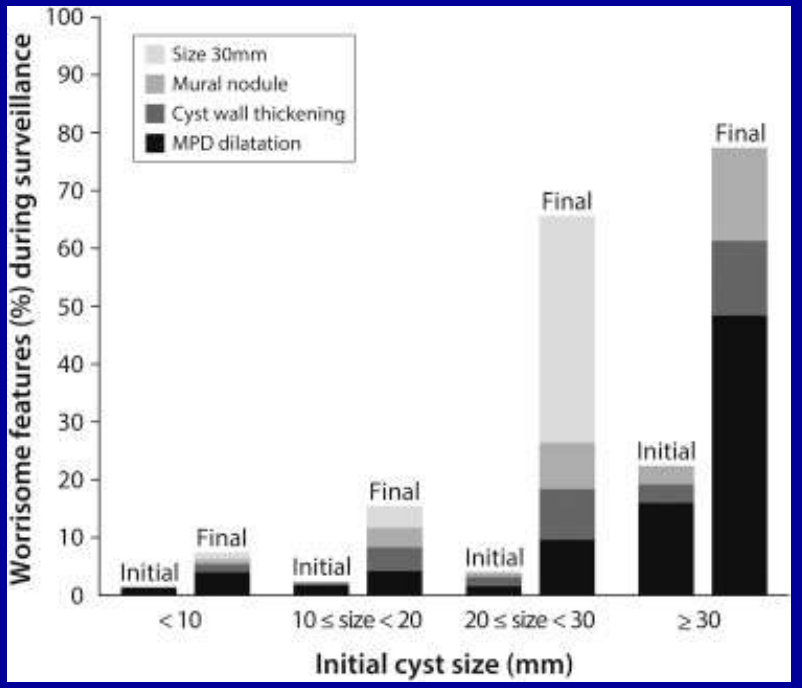
Cyst Surveillance Recommendations

- Surveillance intervals: Primarily based on size:
  - >3 cm: 4-47% have HGD or cancer in 5 surgical series; Some cysts < 3 cm have cancer
  - Initial cyst size correlates with development of worrisome features*
- <1 cm: MRI q 2 yrs
- 1-2 cm: MRI q 1 yr
- 2-3 cm: MRI or EUS q 6-12 mos

*Han Y Gastro 2018



When to Get Worried?

- Consider shorter interval imaging or FNA:
  - New onset / worsening DM
  - Increase cyst size >3 mm/yr (EU: >5 mm/yr)*
- Refer to multi-disc clinic and/or perform FNA:
  - Cyst causing jaundice or acute pancreatitis
  - Elevated serum CA 19-9
  - Mural nodule or solid component
  - MPD>5mm, focal dilation of MPD, or change in PD caliber with upstream atrophy
  - Cyst size ≥ 3 cm (EU guideline: ≥4 cm**)

*Kolb Clin Gastro hep 2018 ** Euro study group Gut 2018

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When to Stop Surveillance for Mucinous Pancreatic Cysts?

- Risk of malignant transformation does not decrease with time; no justification for stopping after 5 yrs
- Stop if patient not a surgical candidate due to age, their wishes, or co-morbidities
- Charlson Comorbidity Index helpful in shared surveillance decisions*
- Recommend stopping between age 76-85

*Chhoda Clin Gastro Hep 2021

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When to Refer to a Multi-Disciplinary Pancreatic Center?

- Any cyst with high-risk features
- Patients should understand the risks of surgery vs. surveillance
- Continued surveillance was recommended in 30% of referred pts in one series*
- Mortality rate at low-volume surgical centers is 3X that of high-volume centers

*Lennon Ann Surg Oncol 2014

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Which Pancreatic Cysts Require Surgery?

- Main duct IPMN or Mixed IPMN
- SB IPMN & MCNs with high-risk features in good surgical candidates
- Solid pseudopapillary neoplasm
- Cystic NETs > 2cm
- Serous cystadenomas causing symptoms due to compression of adjacent organs

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What Follow-up is Required after Surgery?

- Any cyst with cancer should be followed per cancer guidelines
- All IPMNs require post-op surveillance
  - Remnant pancreas is at risk for more IPMNs and other pancreatic cancers
- MCNs w/o cancer do not require f/u
- Solid-pseudopapillary neoplasms: annual imaging for at least 5 yrs.

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Conclusions

- Majority of incidental pancreatic cysts are side branch IPMN
- IPMNs and MCNs have potential for malignancy and require surveillance
- MRCP for cyst diagnosis and surveillance
- May require EUS FNA for unclear diagnosis or worrisome characteristics

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Conclusions

- Pancreatic cysts are very common
- Pancreatic surgery has significant morbidity and some mortality
- Benefit of surveillance not yet proven
- Patients not fit for surgery should not have further evaluation

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