Population Covered By The Guidance

This pathway provides guidance on the investigation of adult patients with pancreatic cysts incidentally discovered on imaging performed for other reasons and their subsequent investigations.

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Quick User Guide

Move the mouse cursor over the PINK text boxes inside the flow chart to bring up a pop up box with salient points. Clicking on the PINK text box will bring up the full text. The relative radiation level (RRL) of each imaging investigation is displayed in the pop up box.

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Pathway Diagram
### What do I need to know?

1. What is the size of the lesion?
2. Are there any concerning imaging features?
3. What is the patient's age and associated comorbidities? (Is the patient a surgical candidate?)
4. Is there a family history of pancreatic cancer?
5. Is the patient symptomatic?
6. Has an MRI been performed?

### Pancreatic Cyst (Incidental on CT, Ultrasound or MRI)

- **≤1 cm**
  - Decision to follow-up is dependent on patient's age and comorbidities

- **1-3 cm**
  - Concerning imaging features (for malignancy)
    - Size >3 cm
    - Dilated main pancreatic duct
    - Solid component / mural nodules
  - Risk stratification
  - If not performed
    - MRI (or CT if not previously performed or MRI unavailable / contraindicated)
    - ≥2 concerning imaging features
    - No
    - Yes
      - EUS + FNA
      - Any 'red flag' features
        - Suspicious cyst morphology on EUS
        - Cytology suspicious or positive for malignancy
        - CEA >192 ng/mL
      - No
      - Inconclusive
      - Yes
        - Close surveillance every 3-6 months
        - Consider surgery
        - No further surveillance

- **>3 cm**
  - History, physical examination and laboratory tests
  - MRI (or CT if not previously performed or MRI unavailable / contraindicated)
  - ≥2 concerning imaging features
  - No
  - Yes

### Image Gallery

*Images pending consent clarification*

### Teaching Points
Most incidental pancreatic cysts are <10mm in size and are difficult to characterise on imaging.

- Dedicated MDCT or MRI / MRCP is adequate for initial cyst characterisation. MRI is recommended for surveillance for its superior spatial resolution and lack of ionising radiation, especially in younger patients.
- EUS with FNA is complementary to cross-sectional imaging and is recommended for lesions >2cm in diameter where nonsurgical diagnosis of pancreatic cystic-appearing lesions will change patient management.
- Preoperative imaging modalities can demonstrate helpful characteristics but are not sufficient for a specific diagnosis. The risks of surgery must be weighed against the likelihood of malignant potential and management is influenced by factors such as patient age, comorbidities and development of symptoms.
- The level of evidence for non-operative management and appropriate surveillance duration is low.
- Current recommendations are based on consensus guidelines.

Pancreatic Cyst (Incidental on CT, Ultrasound or MRI)

- Incidental pancreatic cysts may be documented on CT, ultrasound or MRI performed for symptoms unrelated to the pancreas.
- Identification of increasing numbers of pancreatic cysts in asymptomatic patients has become a clinical problem. The true prevalence is contentious. The authors of the recent AGA guidelines use 15% in their estimates, but this figure largely results from studies in patients within a hospital setting. It has been suggested that the prevalence is 2.4% increasing to 10.6% in the 8th decade of life. In this study the median cyst size was 8 mm, and only in 20 patients was the cyst >1 cm (0.7% of the cohort).
- The vast majority of these incidentally discovered cysts are small (average size is about 8 mm), and many may be branch duct (BD) intraductal papillary mucinous neoplasms (IPMNs), although firm pathologic proof that this is the case is lacking. As long as BD-IPMNs are limited to the branches of the pancreatic ductal system, the overall risk of these cysts harbouring high-grade dysplasia or invasive cancer is very low.
- The development of sub-centimetre cysts may be part of the aging process.
- Appropriate management of incidental pancreatic cysts is unclear. Surveillance and treatment of these lesions carries potential benefits as well as costs for patients.
  - The baseline probability that any given cyst is malignant is only 0.25%.
  - Similarly the transformation into mucin-producing adenocarcinoma in patients with pancreatic cysts is thought to be a very rare event.
  - A recent publication suggested that most low-risk and indeterminate risk lesions do not increase in size during a minimum follow-up period of 2 years. Another study showed that asymptomatic cysts of <1.5 cm in diameter can safely be followed-up by imaging and are expected to undergo little change during a median follow-up of 5 years.
- There are several published expert consensus guidelines, but all are hindered by the lack of good quality evidence. Very low quality of evidence supporting almost all pancreatic cyst outcomes that would be important to patients. This suggested diagnostic imaging pathway attempts to incorporate components of these existing guidelines.
- The SENDAI guidelines of 2006 addressed branch-duct IPMNs and suggested limiting surgery to patients who had:
  - Symptoms, or
  - A cyst >3 cm, or
  - Presence of nodules, or
  - An associated dilated pancreatic duct.
- The guidelines were highly sensitive in identifying malignant, mucin-producing cysts; it has been
shown that no cases of invasive cancer were missed if the guidelines had been followed in the past, although some cases with high-grade dysplasia would have been missed and not have undergone resection. However, 75% of patients who undergo surgical resection according to SENDAI 2006 guidelines for BD-IPMN do not have invasive cancer or high grade dysplasia. In one study, using these guidelines, pre-operative imaging, using a variety of methods, was able to correctly distinguish mucinous from non-mucinous pancreatic cystic neoplasms in 74% of cases.

- The SENDAI guidelines were revised in 2012. In these guidelines, cyst size was de-emphasised in that the recommendations sought to minimize operations on low-risk larger cysts and decrease the frequency of imaging (to every 2-3 years) for cysts <1 cm in size. The guidelines also recommended endoscopic ultrasonography (EUS) and fine needle aspiration (FNA) for:
  - Cysts <3 cm with ‘worrisome’ features (mural nodules, thickened cyst walls, dilated MPD 5-9 mm, abrupt change in MPD calibre with distal pancreatic atrophy, lymphadenopathy), and
  - Cysts >3 cm, to further risk stratify patients before surgery was considered.
  - For cysts without ‘worrisome’ features, observation with follow-up imaging was recommended. In view of the frequency of pancreatic asymptomatic cysts, SENDAI guidelines could add to the already high cost and imaging risks if they were applied to the entire large population of individuals with asymptomatic pancreatic cyst(s).

- The most recent expert consensus guidelines are from the American Gastroenterological Association Institute. However, despite a very extensive review of the literature, the AGAI pointed out that the quality of supporting evidence is generally poor. Despite 10 recommendations, the majority of these are ‘conditional’ - that is relatively weak recommendations, due to the admitted low quality of the evidence informing them.

- The recommendations have been called into question by a number of expert editorials. The guidelines recommend that most patients should have surveillance less often and there should be a higher threshold than previously to offer surgery. In particular, there should be much less surveillance for cysts that have a very low prevalent and incident cancer risk. For those patients entered into a surveillance programme, to stop imaging at some point is an important and unique feature of the AGA guidelines, although the timing of this is somewhat arbitrary.

- The AGA guidelines emphasise risk stratification, dependent on the presence / number of high risk stigmata, which have been narrowed down to three in number (size >3 cm, dilated pancreatic duct, solid component on MRI), with only those with ?2 stigmata or those in whom management would change by further characterization, proceeding to EUS. However, there is some contention regarding the reliance on MRI without EUS to determine risk and outcome.

- Since the estimated prevalence of cancer at the time of diagnosis of any pancreatic cyst, according to the AGAI authors, is not greater than 1 in 10,000 (contentious, but very low prevalence), an increased odds ratio as indicated by the three criteria (above) still indicates malignancy to be a rare event in an incidental pancreatic cyst.

- Incidence of cancer in BD-IPMNs is low compared to MD-IPMNs.

- The AGA guideline criteria upon which increased risk of malignancy is based are:
  - Size
    - Prevalent risk of malignancy in cysts >3 cm compared with those <3 cm in size is mildly increased (odds ratio [OR], 2.97)
  - Pancreatic duct
    - Dilated main pancreatic duct compared with those with a normal duct is increased modestly (OR, 2.4)
  - Solid component
    - Cysts with a solid component were associated with the highest risk for prevalent malignancy (OR, 7.7). The presence of a solid component in a cyst is highly specific (pooled specificity, 91%; range, 88%-93%). But note that the baseline risk of any cyst being malignant (0.25%) is increased by the presence of the solid nodule alone.
to just under 2% (Note also that the post-operative mortality of pancreatic surgery is also around 2%)

Two or more of these criteria should be present for the patient to undergo further investigation

- A family history of pancreatic cancer in a first or second degree relative changes the pre-test probability of pancreatic cancer, although the cancers don't seem to occur in pre-existing IPMNs. These patients may need to be managed differently 21

Magnetic Resonance Imaging / Magnetic Resonance Cholangio-Pancreatography (MRI / MRCP)

- Dedicated MRI with MRCP has been recommended as the imaging procedure of choice to characterise a pancreatic cyst and for surveillance scanning, due to lack of ionising radiation, excellent interobserver agreement and superior contrast resolution to facilitate recognition of concerning cyst morphology and ductal communication 12,22,23,24
- Highly sensitive in determining morphological features such as septa (93.3-94.4%), mural nodules (58.3-87.5%), main pancreatic duct dilatation (85.7-92.9%) and superior to MDCT for smaller cysts. 24,25,26 By detecting debris within the cyst, MRI is useful in differentiating pseudocysts from neoplastic cysts 27
- Superior ability to detect duct communication (93.1% accuracy, 91.4-100% sensitivity and 89.7% specificity) aids in distinguishing BD-IPMNs from mucinous cystic neoplasms (MCNs). The latter have higher malignant potential 22,24,28
- Highly accurate in preoperative characterisation of IPMNs: reportedly 93.2-99.5% accurate, 96.8% sensitive and 90.8% specific for differentiating IPMN from other cystic lesions 28
- MRCP is superior to ERCP in depicting cystic dilated ductal branches 29
- Dependant debris seen on MRI is uncommon but highly specific (95%) for pancreatic pseudocysts, differentiating them from pancreatic cystic neoplasms 27
- Reported 88% accuracy, 91% sensitivity and 78% specificity in differentiating mucinous from non-mucinous cysts. Combination of MRI and EUS improves sensitivity to 100% 30
- Ability to determine malignant from benign cystic lesions varies (accuracy 73.2-91%, sensitivity 50-94.3% and specificity 58.3-88.9%) and is lower in prospective studies limited by small sample size, but is improved by combination with EUS 24,30,31,32
- A recent study 22 showed MRI and EUS to be equivalent in predicting malignancy (approximately 75% accuracy) and suggested that EUS be reserved for those patients likely to require FNA
- A study from Korea describes a scoring system based on EUS features that led to high specificity but only moderate sensitivity in predicting malignancy in BD-IPMNs 33
- MRI (or CT) may be sufficient for diagnosis when pathognomonic features of certain cyst types are present (for example those of a serous cystadenoma) 34,35
- Diffusion Weighted MRI (DWI)
  - May help in distinguishing neoplastic cysts from simple cysts and pseudocysts, 36 but results in distinguishing mucinous from non-mucinous cysts have been disappointing 37,38
- Limitations
  - Like all preoperative diagnostic techniques, MRI performs poorly in the specific diagnosis of lesions compared to resection histopathology (55.6-76.2%) 31,32
  - One study has shown only fair inter-observer agreement among radiologists in classifying pancreatic cysts by MRI 39
Computed Tomography (CT)

- Multi-phase contrast CT scanning with dedicated pancreatic protocol is a widely accepted method for appropriately evaluating pancreatic lesions. CT can reveal the size, location, calcifications, internal septations, internal solid components, resectability of cyst and in relation to major abdominal arteries and veins.
- Sensitive for determining morphological features such as septa (93.6%), mural nodules (71.4%) and main pancreatic duct communication (86.4%). While MRI / MRCP is more sensitive, in most cases MDCT can provide sufficient detail for decision making (40) 82-85% accurate in determining mucinous from non-mucinous cystic lesions (40) reduced in lesions <3 cm.
- Ability to determine malignant from benign cystic lesions varies between studies (63.9-82% accuracy, 57.7-69.2% sensitivity, 63.9-83.3% specificity) (28, 31) but is not significantly different to MRI.
- Reported 85-86% accuracy in differentiating aggressive (moderate grade dysplasia, high grade dysplasia and invasive lesions) from non-aggressive cystic lesions.
- Limitations
  - Exposure to ionising radiation
  - Inferior to MRI/MRCP in evaluation of smaller cysts and classification of IPMN, in detecting ductal communication, small branch duct cysts and estimating main duct involvement.
  - Insufficient accuracy in the specific diagnosis of lesions compared to post-operative histopathology, despite improvements (to 61.9-76.2%) in recent years.

Endoscopic Retrograde Cholangio-Pancreatography (ERCP)

- ERCP provides direct inspection of the duodenal papilla, internal ductal architecture, pancreatography and pancreatoscopy.
- Advantages
  - In IPMNs, ERCP can demonstrate duct communication and a highly specific but insensitive finding of mucin extruding from the opening of a pancreatic duct which may indicate malignancy, but is comparable to MRCP which is less invasive and can simultaneously deliver more information.
- Limitations
  - Invasive. EUS+FNA is considered safer and more accurate and is the preferred method for cyst fluid analysis in patients without biliary obstruction.

Endoscopic Ultrasound (EUS) + Fine Needle Aspiration (FNA)

EUS

- A multicentre trial found EUS morphology features to be only 51% accurate in distinguishing mucinous from non-mucinous cystic lesions.
- A recent study showed MRI and EUS to be equivalent in predicting malignancy (approximately 75% accuracy) and suggested that EUS be reserved for those patients likely to require FNA. EUS was reasonably sensitive in determining morphological features such as septa (77.8%), mural nodules (58.3%), main pancreatic duct dilatation (85.7%) and duct communication (88.9%), and
not significantly different than MRI in a study limited by small sample size 22
- A study from Korea describes a scoring system based on EUS features that led to high specificity but only moderate sensitivity in predicting malignancy in BD-IPMNs 33

**EUS + FNA**

- While some groups have reported good performance, 22 generally EUS morphology alone is considered inadequate for cyst characterisation. 43 The addition of FNA significantly improves diagnostic accuracy. 30,43 Sensitivity is improved by combination with MRI 30
- Endoscopic ultrasound with fine needle aspiration (EUS + FNA) is increasingly being used to characterise cystic tumours in patients in whom resection is contemplated. Detailed EUS imaging that are identified on other imaging modalities, along with biochemical and molecular cyst fluid analysis, improve the differentiation of pancreatic cysts and helps predict their malignant potential 44
- Parameters that are examined from cyst fluid aspiration include
  - Cytology
    - Cells are often sparse in pancreatic cysts. EUS-FNA has high specificity but only low-moderate sensitivity for distinguishing mucinous and non-mucinous cysts 45,46
    - Cytology of cyst fluid is therefore of limited use, but aspiration cytology of the cyst wall appears to increase the yield significantly 47
    - 67% negative and 92% of non-diagnostic specimens may be associated with malignant or premalignant pathology at surgical pathology. 48 EUS-FNA has low sensitivity for detecting malignancy 30
  - Mucin content
  - Amylase concentration
    - A level <250 units/litre excludes pseudocyst with 98% specificity. 49 Amylase may be slightly raised in BD-IPMNs due to communication with the main pancreatic duct
  - Carcino-embryonic antigen (CEA) levels
    - CEA >192 ng/ml is 79% accurate in diagnosing a mucinous lesion. 43 although there is debate concerning the optimal threshold level to adopt. 49 A CEA level <50 ng/ml is 95% specific for a serous cystadenoma or pseudocyst. 49 CEA levels are not predictive of malignancy 50
  - DNA mutations and microRNA assessment of cyst fluid have considerable promise in diagnosis 51
- A positive EUS+FNA result is highly predictive for a mucinous cyst, reporting a high specificity (93% and 88% for cytology and CEA >192ng/mL respectively) but moderate sensitivity (54% and 63% respectively) and high positive likelihood ratio (5.44 and 4.37) 46, echoing previous studies 30,43,44,45
- The decision to proceed with non-operative management should not be made based on a negative or non-diagnostic FNA alone, as 67% negative and 92% of non-diagnostic specimens may be associated with malignant or premalignant pathology at surgical pathology 48
- Advantages
  - Allows aspiration of cystic lesion for fluid analysis, which has the potential for development of more sensitive biomarkers
- Limitations
  - Invasive. Complications (2.2%) include pancreatitis (2-3%), abdominal pain, retroperitoneal bleed, infection and bradycardia 41,52
  - One group has reported a potential for seeding of malignant cells 53
  - Observer dependent with poor to moderate interobserver agreement 54,55
Requires minimum 1mL of liquid to perform cyst fluid analysis, not feasible in lesions <1cm in size
- Lacks ability to identify malignant spread compared to cross-sectional imaging techniques

Risk Stratification and Recommendations

The revised SENDAI guidelines

- The revised guidelines de-emphasised cyst size, in that the recommendations sought to minimize operations on low-risk larger cysts and decrease the frequency of imaging (to every 2-3 years) for cysts

Information for Consumers

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