Pancreatic Cystic Lesions and Guidelines: A Review

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INTRODUCTION

A pancreatic cystic lesion refers to a round, fluid-filled structure within the pancreas that is seen by imaging. With increased access, use, and advancements in imaging techniques, however, pancreatic cystic lesions are increasingly identified in asymptomatic patients. The prevalence of cystic lesions of the pancreas has been estimated to range from 2.4% to 24% in imaging and autopsy studies.

Broadly, these pancreatic cystic lesions can be classified into neoplastic and non-neoplastic pancreatic cystic lesions. These include inflammatory (pseudocysts), benign (serous), premalignant (mucinous), and malignant (mucinous) lesions.

Two main types of pancreatic cystic lesions are the inflammatory pancreatic pseudocyst and the pancreatic cystic neoplasms. Inflammatory pancreatic pseudocyst is understood to be a collection of pancreatic juice enclosed by a wall of fibrous tissue. Classically, this lesion forms four or more weeks after an episode of acute pancreatitis. Pancreatic pseudocysts can be further subdivided based on their onset into acute and chronic pseudocysts, or based on the presence of complications.

Previously, the commonest encountered pancreatic cystic lesion was the pancreatic pseudocyst. In current practice where there is increasing availability of cross-sectional imaging, pancreatic cystic neoplasms (PCNs) are now the commonest recognised entities. There is great variation in biologic behaviour between the subtypes of PCNs, which one reason that this group of lesions pose a diagnostic challenge. Serous cystic neoplasms (SCNs) and mucinous cystic neoplasms (MCNs) are benign, and pre-malignant or malignant entities respectively, and differentiating between these subtypes affects management and confers a different prognosis of patients. This is particularly important in the context of an asymptomatic patient with an incidental PCN.

Role of imaging:

Imaging plays a large role in the diagnosis and management of pancreatic cystic lesions, and the main modalities are computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS). Pancreatic cystic lesions represent a myriad of pathologies, and can be divided into non-neoplastic and neoplastic types. Non-neoplastic pancreatic cystic lesions consist of pseudocysts, retention cysts, congenital epithelial cysts, lymphoepithelial cysts, endometrial cysts, and enterogenous cysts. Pancreatic cystic neoplasms (PCNs) on the other hand, consist of mucinous cystic neoplasms (MCNs), serous cystic neoplasms (SCNs), intraductal papillary mucinous neoplasms (IPMNs), solid pseudopapillary neoplasms, cystic pancreatic neuroendocrine neoplasms, cystic ductal adenocarcinoma, acinar cell cystadenoma/carcinoma and cystic metastasis. Imaging is utilised to differentiate between these lesions, to show interval stability on follow-up, and can guide biopsy and treatment of these lesions.

CT is the most commonly used imaging modality, and usually is the first modality to detect incidental pancreatic cystic lesions in the asymptomatic patient. CT is relatively easily available, demonstrates calcifications well, and allows the acquisition of thin slices of different enhancement phases in a single breath hold. However, CT may not demonstrate the cystic component of the lesion, for example in microcystic pancreatic cystic neoplasms; and that it does not demonstrate communication with pancreatic duct.

MRI combines parenchymal, ductal and vascular imaging of the pancreas, is able to detect smaller lesions, and shows the relationship of the cyst to the pancreatic duct. However increased cost and imaging time limits its usage, another limitation is that it may not detect smaller central calcifications, unlike CT.

EUS has the highest sensitivity for detecting cysts, is both diagnostic and therapeutic as it can also guide aspiration of pancreatic cysts for fluid analysis. However, this modality is operator dependent, unable to characterise large lesions well, and is an invasive procedure with potential complications.

In view of these strengths and limitations, a combination of these modalities is employed to complement in the management of pancreatic cystic lesions.

Non-neoplastic pancreatic cysts:

Pancreatitis is an inflammatory process of the pancreas with a wide range of manifestations and clinical variation, ranging from local inflammation to systemic manifestations such as organ failure. Inflammatory pancreatic fluid collections are a known complication of pancreatitis, and one of the commonest encountered is the pancreatic pseudocyst, and the frequency has been reported to be as high as 90%.

Pancreatic pseudocysts differ from true cysts as its wall consists of fibrous tissue, rather than an epithelial lining, and are either filled with pancreatic juice or serous fluid, depending on whether the pseudocyst communicates with...
the pancreatic duct. Classically, these patients have typical clinical history and laboratory results expected of pancreatitis.

The Atlanta classification of pancreatitis (revised in 2012) is a functional and morphologic classification that addresses the clinical course and severity of pancreatitis. The goal is to provide a standardised terminology for radiologists, gastroenterologists, surgeons, and pathologists to use when planning treatment and to allow comparison of results among different departments and institutions. The Atlanta classification subdivides inflammatory pancreatic cystic lesions according to the time interval between lesion detection and preceding pancreatitis, the presence of necrosis, and complications related to the inflammatory pancreatic cystic lesion.

Pancreatic pseudocysts are thus divided into acute and chronic pseudocysts according to the time duration from the acute episode of pancreatitis. Another inflammatory pancreatic cystic lesion that is described is walled-off necrosis (WON), which consists of necrotic tissue contained within an enhancing wall of reactive tissue, and has a well-defined inflammatory wall, and usually occurs 2-4 weeks after onset of necrotising pancreatitis. What differentiates WON from a pancreatic pseudocyst is the presence of necrotic tissue within the pancreatic cystic lesion.

Other inflammatory pancreatic/peripancreatic fluid collections described in the classification are the acute peripancreatic fluid collection (APFC) and acute necrotic collection (ANC). These lesions are not encapsulated, unlike pseudocysts, and the clinical significance of these lesions is that long-standing localised APFCs have the potential to eventually become a pancreatic pseudocyst.

The Atlanta classification also places an emphasis on the identification of complications secondary to pancreatic pseudocysts. For example, these complications may be due to mass effect upon the adjacent structures, such as compression of large vessels, gastric or duodenal outlet obstruction, superimposed infection, haemorrhage, or the formation of pancreatico-pleural fistula. The identification of these complications is important, as they are strong indications for intervention in pancreatic pseudocysts, which are normally managed conservatively.

A proportion of inflammatory pancreatic cystic lesions are mistakenly identified as pancreatic cystic neoplasms. This indicates the difficulty in diagnosis by imaging, and identifying features to differentiate between pancreatic pseudocysts and PCNs (in particular unicellular macrocystic PCNs) have been explored, such as the presence of a lobulated contour, the absence of wall enhancement, and location in the pancreatic head, or the identification of internal debris on MRI. However, despite these efforts, pancreatic cystic neoplasms are often misdiagnosed on imaging as pseudocysts, and vice versa. Thus, with no preceding clinical presentation of pancreatitis, every pancreatic cystic lesion should be assumed to be a pancreatic cystic neoplasm, and every effort should be undertaken to exclude neoplasia, such as biopsy of the wall of all ‘pseudocysts’. However the converse is not true, and pancreatic cystic neoplasms may be concomitantly present in patients with pancreatitis, or may cause pancreatitis due to mass effect upon the pancreatic duct.

Pancreatic cystic neoplasms (PCNs): PCNs are less commonly encountered, and represent a diverse group of pathologies, and include: serous cystadenoma, serous cystadenocarcinoma, mucinous cystadenoma, intraductal papillary mucinous adenoma, intraductal papillary mucinous neoplasm, solid pseudopapillary tumours, and cystic degeneration in solid pancreatic tumours. Among all of the PCNs, serous cystic neoplasms, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms are the most prevalent subtypes of PCNs, and account for nearly 90% of all PCNs. The type of epithelium differentiates between these neoplasms; serous epithelium is benign, and mucinous epithelium is premalignant or malignant. These entities are described in more detail below:

Serous cystadenomas (SCNs) These are generally considered to be benign, and thus these are usually managed conservatively. SCN constitute approximately 30% of all cystic pancreatic lesions, and usually occur in females. Classic imaging characteristics are microcystic lesions with honeycombing, and central calcifications can be found in some (20%) patients. Cyst fluid analysis would reveal thin fluid, if sufficient fluid could be aspirated from microcysts. These lesions are considered to be benign, with no malignant potential.

An uncommon presentation of SCN is that of a soft tissue mass in the pancreas, due to the conglomerate of microcysts in the lesion, and solid-appearing SCN is a known mimic of pancreatic adenocarcinoma. Resection is mostly reserved in patients with larger (> 4 cm) lesions that are asymptomatic due to mass effect.

Mucinous cystadenomas (MCNs) MCNs are considered at the least to be potentially premalignant, and is the most common PCN encountered. MCNs are a heterogeneous group of pathologies, and consist of mucinous cystadenomas, non-invasive, proliferative MCNs and mucinous cystadenocarcinomas. Thus, complete resection of MCN is generally recommended, barring poor surgical candidates. This constitutes approximately 50% of PCN, and occurs almost exclusively in females. Typical imaging characteristics are a unilocular cystic pancreatic lesion, with septations. Thin peripheral eccentric calcifications (approximately 15% of MCNs) and are considered almost pathognomonic of MCNs. These lesions may have a soft tissue component that is highly suspicious for malignancy, and are located mainly in the body/tail of the pancreas.

Intraductal papillary mucinous neoplasms (IPMNs) IPMNs are known to have varying malignant potential, and has not gender predilection. It is a relatively new entity, and is defined as an intraductal mucin-producing neoplasm that involves the main pancreatic duct and/or major side branches and lacks ovarian stroma characteristic of mucinous cystic neoplasms. The typical imaging
Fig. 1: (a, b): Axial and coronal unenhanced CT was performed for this patient with renal impairment and vague symptoms of abdominal discomfort. This reveals a partially rim-calcified complex cystic lesion in the pancreatic body and tail. Abdominal ultrasound (c) performed also demonstrates a complex solid-cystic lesion that corresponds to the above lesion. This patient presented previously with clinical symptoms of pancreatitis, and a review of CECT (d) performed 5 years ago showed that the lesion was unchanged in size and configuration, and subsequent EUS (not included) confirmed that this was a pancreatic pseudocyst. No complications from the pancreatic pseudocyst were detected.

Fig. 1: (a, b): Axial and coronal CECT images of an incidental PCN in a 48 year old female, which reveal a single fine septation (arrow). As the PCN was greater than 3 cm in size, the next step in the management should be to undergo further evaluation either via MRI or EUS, and if the patient is a good surgical candidate she would receive surgical resection. The patient underwent EUS (c, d), which showed internal calcification (arrowhead) and multiple septations. Subsequently, the patient received laparoscopic distal pancreatectomy and splenectomy, and histology of the lesion was a mucinous neoplasm of the pancreas with low-grade dysplasia.
Fig. 3: (a, b): Axial and coronal CECT of the pancreas reveals an incidental 1.2 cm microcystic PCN in the tail, with no pancreatic duct dilatation. As the lesion is between 1 to 2 cm in size, and does have some image characteristics of a serous cystadenoma, interval follow-up with either CT or MRI to show stability. EUS was subsequently performed (c, d, e), which revealed that the lesion has both macrocystic and microcystic components. No mural nodule or pancreatic duct dilatation was detected. Fine needle aspiration was not attempted, as the lesion was closely associated with the splenic vein.

Fig. 4: (a, b, c, d) Axial and coronal CECT of a 75 year old female reveals multiple incidental PCN in the pancreatic head and body, one of which appears to communicate with a side branch of the pancreatic duct (arrow). According to the guidelines discussed, this patient likely has IPMN, and the management options would be either interval follow-up or surgical resection. EUS is also an option, and would confirm the communication with the pancreatic ducts and also detect suspicious features such as mural nodule. Subsequent EUS (e, f) detected a mural nodule (arrow), and fine needle aspiration was then performed, but histology was not conclusive. As the patient was not a good candidate for surgery in view of her age and other co-morbidities, interval follow-up was offered.
characteristics are dilated main pancreatic duct or the side branches, with occasional soft tissue components, and no calcifications. These lesions are subdivided by which part of the pancreatic duct they occur in, and consist of main duct IPMN (MD-IPMN), branch duct IPMN (BD-IPMN), and mixed type IPMN, that has components in the main and branch ducts.

Patients with MD-IPMN or mixed type IPMN have a risk of malignancy, which consists of carcinoma-in-situ and invasive cancer, of approximately 50-60%, and the risk of malignancy increases when the main pancreatic duct is dilated (>1 cm) and when mural nodules (>1 cm) are present. In contrast, patients with branch-duct IPMN have a lower risk of malignancy, and the range is thought to be 6-46%. Therefore, BD-IPMN is usually treated less aggressively than MD-IPMN. Unlike with MCN and SCN, multifocal disease can occur in IPMN. In addition, after resection of either subtype of IPMN, surveillance is necessary as there is a potential risk of recurrence.

In the asymptomatic patient with a PCN, most physicians agree that surgical treatment should be the primary consideration, unless there are contraindications to surgery. Asymptomatic patients with incidental PCN on the other hand, poses both a diagnostic and management challenge, and is a common in current practice owing to increased detection of incidental PCNs. The main difficulty is differentiating between the benign and malignant entities on imaging, as incidental PCNs detected are usually smaller, and the classic imaging features are usually not present for characterisation. The inability to reliably characterise incidental PCN makes it difficult to decide whether the patient should receive curative surgery, or be conservatively managed.

Review of international guidelines:

To address these issues, workgroups have created guidelines to help physicians manage neoplastic pancreatic cystic lesions. Imaging plays a large role in the management of these patients, as it can to characterise lesions, monitor lesion growth over time, identify complications related to the lesions and/or treatment, and finally, imaging can help to guide biopsy and treatment of these lesions. The guidelines formed are based on the strengths and limitations of imaging in the management of pancreatic cystic lesions, the current understanding of the biologic behaviour of pancreatic cystic lesions, and provides a consensus view of the management of the patients with pancreatic cystic lesions.

The target audience of these guidelines is the clinicians and radiologists who encounter incidental PCNs, and the guidelines discussed are the American College of Radiology (ACR) White Paper for management of incidental pancreatic cystic lesions, and the International consensus (Sendai) guidelines 2012 for the management of IPMN and MCN of the pancreas, and the recommendations put forward by the World Journal of Surgery.

American College of Radiology (ACR) White Paper on Managing Incidental Findings on Abdominal CT

The management of the incidental pancreatic cystic lesion in the asymptomatic patient detected on CT, MRI or ultrasound is described in these guidelines. The first step in the management is to stratify the lesions by size.

In incidental pancreatic cystic lesions less than 2 cm in size, interval imaging (preferably with MRI) is recommended. If the lesions are stable in size, these lesions are deemed to be benign and no further follow-up is recommended. Growth of the pancreatic cystic lesion means that the patient should receive further evaluation.

If the incidental pancreatic cystic lesion is 2-3 cm, then imaging characterisation of PCNs is attempted by identifying classic imaging features on CT or MRI. If the lesion can be successfully characterised into SCN, MCN or BD-IPMN, then they are followed up with interval imaging, and that time interval is dependent on their estimated malignant potential.

In the uncharacterised PCN less than 3 cm in size, yearly imaging follow-up is advised. In uncharacterised PCN larger than 3 cm, aspiration of the lesion is advised. In uncharacterised PCN larger than 4 cm should prompt the consideration for surgical resection, as there is increased risk of complications from mass effect of the lesion.

These guidelines do not address patients with symptoms of pancreatitis or pancreatic dysfunction, and it allows for flexibility in the time interval between imaging studies according to factors such as the patient's age and expected life expectancy. In addition, younger patients with incidental PCNs are favoured to undergo surgical resection to alleviate the cost of long-term follow up.

International consensus guideline 2012 for the management of IPMN and MCN of the pancreas

This guideline aims to differentiate between mucinous cystic neoplasms from IPMN, as these entities have fairly similar imaging features, but have significant differences in biologic behaviour that determines management. MCNs are usually solitary, and have a low risk of recurrence following resection. In contrast, IPMNs are usually multiple, have an increased risk of recurrence following resection and thus should be followed-up more regularly after surgery.

Clinical presentation and imaging of these patients are first assessed for high-risk or worrisome features. For example, high-risk findings include obstructive jaundice in the patient with a pancreatic cystic lesion located in the head of the pancreas, the presence of an enhancing solid component, or pancreatic duct dilatation. Examples of worrisome criteria are pancreatitis, size larger or equal to 3 cm, thickened or enhancing cyst walls.

In this group of patients, more aggressive intervention is advised. High-risk patients should be considered for surgical resection. Patients with worrisome features are further evaluated with EUS or cystic fluid analysis, and inconclusive EUS findings warrants close surveillance with MRI and EUS.

In patients with absence of high risk or worrisome features, the pancreatic cystic lesions are managed according to their
size. Lesions less than 1 cm should receive interval imaging in 2-3 years. If the lesion remains stable, then no further follow-up is advised. Lesions that measure 1-2 cm should receive yearly imaging for 2 years, with increasing time intervals between imaging if the lesion remains stable in size. For lesions more than 2 cm, surgery should be considered in good surgical candidates or younger patients with lesions that measure 2-3 cm, and the alternative is close imaging follow-up every 3-6 months.

*World Journal of Surgery*

Patients with an incidental pancreatic cystic lesion should undergo a thorough history, examination and serum amylase, CEA, Ca 19-9 to exclude any related symptoms, evidence of pancreatitis, or metastatic malignancy.

CT and MRI should be performed to characterise the cyst and determine whether there is communication with the pancreatic duct, the presence or absence of peripheral calcification, or mural nodules/solid component.

Cysts with characteristic features of pseudocyst and SCN can be safely observed unless they develop symptoms or in the case of pseudocysts begin to increase in size. Based on current knowledge, patients (with the appropriate life-expectancy and fitness) who have characteristic features MD-IPMN, mixed-IPMN, or cysts with solid component (or mural nodule), peripheral calcification, or elevated serum tumour markers should be offered surgery.

The remainder of patients with unilocular or macrocysts that are not characteristic of pseudocyst or BD-IPMN, respectively, should undergo EUS with cyst fluid analysis for viscosity and CEA. Patients with no mural nodules or markers of mucinous neoplasms (viscosity \( \leq 1.6 \) and CEA \( \leq 192 \text{ ng/ml} \)) within the cystic fluid can be safely observed. Although some authors have advocated surgery based on size alone, these conclusions often have been reached without the benefit of EUS, cyst fluid analysis, or exclusion of IPMN.

Patients with BD-IPMN and favourable features (size > 3.5 cm, no nodules, Ca 19-9 >25 U/l, and absence of recent onset or worsening diabetes) can be offered observation. The exact modalities, frequency, and length of follow-up currently lack evidence. Increase in cyst size, development of a solid component, mural nodules, or symptoms attributed to the incidental pancreatic cystic lesion are currently an indication for surgery, although in the future better indicators of malignant change are required.

These guidelines generally have the aim of characterising the incidental pancreatic cystic lesion by way of detecting characteristic imaging features. If the lesion can be confidently diagnosed, then treatment will be based on whether the lesion is expected to be benign, in the case of SCN, pre-malignant or malignant. Treatment is then tailored to the expected malignant potential of the incidental pancreatic cystic lesion.

Red flag criteria are present in these guidelines, and this reflects the importance of the non-imaging features of pancreatic cystic lesions such as tumour markers, mass effect of the primary lesion that manifests as obstructive jaundice, and imaging features such as intralobional enhancing soft tissue components.

In the non-characteristic pancreatic cystic lesion, size of the lesion is commonly employed to guide the clinician and radiologist in its management. The rationale behind this is that stable, small lesions are thought to be more likely to be benign, and vice versa. Thus, these guidelines stratify incidental pancreatic cystic lesions into different sizes, which helps to guide the management. For Sendai, the sizes are less than 1 cm, 1-2 cm and larger than 2 cm. In the ACR White Paper for Incidental Findings, the size criteria that prompts the consideration of surgery is more than 4 cm in SCN, and more than 3 cm in all other PCNs. In the recommendations put forward by World Journal of Surgery, size is less of a factor, and surgery is offered based on the expected pathology, such as IMPN, MCN and symptomatic pseudocysts and SCNs.

Continuing in this train of logic, thus the guidelines have different suggestions as to the time interval to follow-up incidental pancreatic cystic lesions, and the interval are an interplay of the costs involved in imaging, strengths and limitations of each modality and the expected aggressiveness of the underlying lesion. Thus, more aggressive lesions are more closely follow-up, and less aggressive and benign lesions are less frequently followed-up, if at all. Only World Journal of Surgery does not include recommendations to the time interval between follow-up imaging of an incidental pancreatic cystic lesion.

The Sendai guidelines differ from the other two as it deals with a more specific diagnostic question, which is the differentiation of BD-IPMN from MCN. Also, it uses size criteria of the lesions in a different context from the other guidelines.

**CONCLUSION**

Pancreatic cystic lesions are commonly encountered, and broadly can be divided into inflammatory and neoplastic lesions. The Atlanta guidelines provide a framework to classify inflammatory pancreatic cystic lesions, and to identify their complications. Incidental PCNs are a diagnostic and management dilemma, and the guidelines reviewed (ACR and Sendai) give both clinicians and radiologists that encounter these patients schema for management and follow-up. Imaging plays a substantial role in these guidelines, and knowledge of the strengths and limitations of each modality, together with knowledge of the biologic behaviour of pancreatic cystic lesions are the foundations of the guidelines described. In the absence of classic imaging Most of these guidelines agree that 3-4 cm is the threshold for aggressive treatment options, such as close imaging follow-up, EUS or surgical resection.
REFERENCES


