Abstract
With the increasing use of abdominal imaging, cystic lesions of the pancreas are being more frequently detected. These lesions may carry a significant premalignant potential. Current guidelines recommend that mucinous cystic neoplasms, solid pseudopapillary neoplasms, main duct-intraductal papillary mucinous neoplasms and branch duct-intraductal papillary mucinous neoplasms (DB-IPMN) with "high-risk stigmata" for malignancy should be resected while asymptomatic BD-IPMN without mural nodules, no main duct involvement, and a size less than 30 mm can be followed up. Serous cystadenomas carry a very small malignant risk and are usually resected only if they cause symptoms. This review article highlights the common characteristics and recommended management of these cystic lesions of the pancreas.

Keywords
cystic lesions of the pancreas, serous cystadenoma, intraductal papillary mucinous neoplasm, mucinous cystadenoma, solid pseudopapillary neoplasm

Introduction
Cystic lesions of the pancreas (CLP) are relatively common and with the increasing use of high resolution computed tomography (CT) and magnetic resonance imaging (MRI) are being increasingly detected. The prevalence of CLP in autopsy series was as high as 24% and high resolution CT identified these lesions in 2.6% of asymptomatic adults and in 8% of patients older than 80 years.

Pancreatic cystic lesions include serous cystic adenomas (SCA), mucinous cystic neoplasms (MCN), intraductal papillary mucinous tumors (IPMN), solid pseudopapillary tumors (SPN), (which together represent 95% of all CLP) and also less common lesions such as cystic endocrine tumors and lymphangiomas. Distinguishing between these PCLs is extremely important because while some lesions are completely benign, other pancreatic cysts carry a significant premalignant potential and require close follow up or early surgical resection. In this review article, we describe the common characteristics and management of the most common pancreatic cystic lesions.

The prevalence of pancreatic cystic lesions appears to increase with age. In most cases, cystic lesions are detected incidentally by CT or MRI performed for other reasons. MRI/magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) are considered to be complementary diagnostic tools. The added advantage of EUS is that in doubtful cases, cyst fluid analysis may be performed by carrying out a fine needle aspirate of the cyst contents. MRI should always be carried out before EUS as it identifies the number of cystic lesions (which may be multiple in IPMN), the relation of the cysts to the main pancreatic duct, and the size of the lesions. EUS is however superior in evaluating mural nodules (i.e. intracystic nodules arising from the cystic wall lining – these nodules are frequently precursors of malignant transformation and are an indication for surgical resection).

The premalignant risk of CLP varies according to the type of lesion. While main duct-IPMN and MCN carry a significant premalignant risk, SCA are considered to have a very low risk of malignant transformation. A recent study by Rhim et al has shown that patients with CLPs already have pancreatic cancer cells in their circulation before pancreatic tumours actually develop. In this study, circulating pancreas epithelial cells (CECs) in patient blood samples were detected and quantified. The authors identified >3 CECs/ml in 7 of 21 patients (33%) with CLP (predominantly IPMN) and no clinical diagnosis of cancer, in 8 of 11 patients (73%) with pancreatic adenocarcinoma, and in 0 of 19 patients without cysts or cancer (controls). This technique may
in the future be used in risk assessment of CLPs.\textsuperscript{5}

**Intraductal Papillary Mucinous Neoplasms (IPMN)**

IPMN are more commonly found in the head of the pancreas (70\%) with an equal gender distribution. They are commoner in the 6\textsuperscript{th} and 7\textsuperscript{th} decade and can be subclassified into main duct (MD)-IPMN and branch duct (BD)-IPMN based on imaging results and histology. All IPMNs appear to communicate with the main pancreatic duct and may be multifocal. Dilatation of the main pancreatic duct to >5mm on CT or MRI (without other causes of obstruction) suggests the presence of main duct IPMN with a main duct diameter of 5-9mm being considered a “worrisome feature” while a duct of 1cm or more is considered a “high-risk stigmata”. The presence of a mucinous cyst >5mm in diameter communicating with the main duct without causing main duct dilatation is strongly suggestive of branch duct IPMN. Mixed type IPMN have the criteria for both MD-IPMN and BD-IPMN. The difference between the two subtypes can be confirmed using EUS or intraductal ultrasonography. If these techniques are not available, histological analysis of surgically resected specimens can also distinguish between the two.\textsuperscript{6}

MD-IPMN carries a very high risk of malignant transformation (57-92\%)\textsuperscript{7,15} while the risk with BD-IPMN is somewhat lower (6-46\%).\textsuperscript{7,14} MRI has a better sensitivity than CT scan in the detection of CLPs (19.9\% versus 2.6\%)\textsuperscript{2,16} and for this reason is usually preferred in the classification of these lesions. In small cysts (<10mm in diameter), MRI follow up after 2-3 years is recommended. For cysts >10mm in diameter, pancreatic CT or gadolinium-enhanced MRI with MRCP are recommended, though MRI is better in identifying septae, nodules and duct communications.\textsuperscript{17}

The 2012 international consensus guidelines for the management of IPMN \textsuperscript{6} recommend that patients with “high-risk stigmata” on CT or MRI should undergo immediate surgical resection without further testing. These “high-risk stigmata” include obstructive jaundice in a patient with a CLP of the pancreatic head, enhancing solid component in the cyst and a main duct diameter >10mm. “Worrisome features” include cystic lesion >3cms in diameter, thickened enhanced cystic walls, main duct diameter 5-9mm, non-enhanced mural nodules, abrupt change in main pancreatic duct diameter with distal pancreatic atrophy and the presence of lymphadenopathy.\textsuperscript{18-22}

These patients should be further evaluated with EUS, which further risk-stratifies the IPMN. In the presence of a definite mural nodule, if the main duct appears dilated or involved during EUS or if fine needle aspirate cytology from the cystic fluid is suspicious or positive for malignancy, the patient should be referred for surgery. In the absence of these features, follow up will depend on the size of the lesion. For cysts 1-2cms in diameter, yearly CT or MRI for 2 years with lengthening of the imaging interval if the cyst remains unchanged is recommended. For lesions which are 2-3cms in diameter, the guidelines recommend 3-6 monthly EUS with lengthening of the interval, alternating with MRI if there is no change. For cysts larger than 3cms, alternating MRI with EUS every 3-6 months is recommended. In young fit patients with cysts >2cms, surgery may be recommended early to avoid prolonged surveillance.

**Figure 1:**

*a). Endoscopic ultrasound view of a 22 mm branch duct IPMN in the head of the pancreas with no mural nodules and a small (<1cm), insignificant peripancreatic lymph node (arrow).*

*b). EUS-guided fine needle aspiration (FNA) of cystic fluid for biochemical and cytological analysis; arrow shows needle passing through pancreatic parenchyma into the IPMN.*
The main advantage of EUS over other imaging modalities lies in its ability to detect mural nodules and invasion, and is most effective in delineating the malignant characteristics of these lesions. In addition, it allows the acquisition of cystic fluid for cytological assessment and biochemical analysis of carcinoembryonic antigen (CEA) and amylase levels. Elevated CEA (>192 ng/mL) is 80% accurate for the detection of mucinous cysts, though it provides no clue to the risk of malignancy. Cyst amylase levels are not uniformly elevated in IPMNs. Molecular analysis of cyst fluid for KRAS (Kirsten Rat Sarcoma) mutations is still mainly an investigational tool; however, KRAS mutations in cyst fluid are more in keeping with a mucinous rather than a malignant cyst. In a study analysing sensitivity and specificity of KRAS mutation in identifying mucinous differentiation, KRAS had a specificity of 100% and sensitivity of 54% for mucinous differentiation. When stratified according to cyst type, KRAS had a sensitivity of 67% for IPMNs and 15% for MCNs.

Serous Cystadenomas (SCA)

SCA represent 10-45% of all PCL and are much commoner in women (70%). They are more common in the body or tail of the pancreas (>80%) and they do not communicate with the pancreatic duct. They may be either polycystic (microcystic), or oligocystic (macrocytic). Typically they present as single lesions with central calcification (in 20%) and high vascularity at EUS. If the diagnosis is still not clear, EUS-FNA may be used for biochemical assessment. SCA typically have low levels of both CEA (<5 ng/mL) and amylase and carry a very small risk of malignant transformation (3%).

Serous microcystic adenomas are glycogen-rich cystadenomas surrounded by fibrous capsules which separate them from normal tissue. CT or MRCP can frequently distinguish SCA from BD-IPMN because of their polycystic or honeycomb pattern. In their interior they form a honeycomb appearance with numerous small, closely packed cysts arranged around a central stellate, calcified scar. Serous macrocystic adenomas are much less common and consist of fewer, larger cysts, typically >1cm in diameter. They are more common in the pancreatic head and in view of their size may present with obstructive jaundice. Serous macrocystic adenomas may be associated with von Hippel Lindau disease. In view of their small risk of malignant transformation, small (<4cms) asymptomatic SCA should undergo periodic follow up while larger, symptomatic cysts should be resected.

Mucinous Cystic Neoplasm (MCN)

MCN include mucinous cystadenomas and mucinous cystadenocarcinomas and account for 10% of PCLs. They are much commoner in women (>95%) and are more prevalent in the 4th and 5th decades. MCN are usually found as a single lesion in the body or tail of the pancreas and they do not usually communicate with the main pancreatic duct. At EUS-FNA, MCN amylase levels may be increased and CEA level is almost always increased. All young and fit patients with MCN should undergo surgical resection because of the elevated risk of malignant transformation and the need for prolonged surveillance. In a large series, up to 10% of MCN had invasive cancer at the time of resection. MCNs <4cms in diameter have 15% risk of malignant transformation and such lesions may be followed up conservatively in elderly or frail patients.

Solid Pseudopapillary Neoplasm (SPN)

SPN represent 10% of all PCLs, and are predominantly found in young women. They may occur anywhere in the pancreas and may occasionally be very large. At EUS, these lesions may appear solid or mixed solid and cystic, with or without septations. SPN frequently undergo central haemorrhagic cystic degeneration with a pseudocapsule which may calcify.

They have an indolent course but if left untreated, they may invade into adjacent organs and major vessels. These tumors are usually very slow growing and carry an excellent prognosis once resected.
Synchronous or metachronous malignant disease in extrapancreatic organs

Synchronous or metachronous malignancy in extrapancreatic organs occurs in 20-30% of patients with IPMN. Extrapancreatic malignancies appear to occur in different organs depending on the incidence of cancer in the general populations in different geographical regions. While there are no current recommendations to screen extrapancreatic organs in patients with IPMN, a reasonable practice would be to carry out serum prostate specific antigen (PSA) assessment, mammography and colonoscopy in patients with these PCLs.

Conclusion

With the widespread use of abdominal imaging, PCLs are increasingly being recognised. In view of the premalignant potential associated with some of these lesions, they need to be accurately classified and followed-up or resected accordingly. MCN, SPN, MD-IPMN and BD-IPMN with "high-risk stigmata" for malignancy should be resected while asymptomatic BD-IPMN without mural nodules, no main duct IPMN and BD followed lesions, they need to be accurately classified and premalignant potential associated with some of these PCLs are increasingly being recognised. In mammography and colonoscopy in patients with these prostate specific antigen (PSA) assessment, a reasonable practice would be to carry out serum regions.

In the general populations in different geographical regions.

Extrapancreatic organs


