Introduction

- Pancreatic cystic neoplasms (PCNs) - first described in 1824
- Increasing number of pancreatic cysts detected as an incidental finding on cross-sectional imaging
- The natural history of cysts has only begun to be fully appreciated in the last 20 years
- Despite the risk of malignancy being greater in symptomatic cysts, up to 47% of the incidental cysts can be malignant or premalignant

Epidemiology

- No large data available for exact incidence or prevalence of PCNs
- Prevalence on autopsy in Japan 24.3 
  - Frequency was related to age
  - Lesions evenly distributed among pancreas
- Screening MRI studies in the U.S. has shown a prevalence of 15-20%
Introduction

• Either *Inflammatory* or *Proliferative* in nature

• The majority are slow-growing and asymptomatic

• When symptoms do occur, they are usually secondary to a mass effect and tend to be vague and poorly localized in nature

• No formal classification of pancreatic cysts exists at present and there are other descriptions of them based on the nature of the cyst wall lining

Introduction

Pancreatic cystic tumors fall into one of three major groups;

• **Serous tumors** (including serous cystadenoma and cystadenocarcinoma)

• **Mucinous tumors** (including mucinous cystadenomas, mucinous cystadenocarcinomas, intraductal papillary mucinous neoplasms)

• **Solid pseudopapillary tumors** (SPT)

Classification
Malignant Potential

- Retention cyst — None
- Pseudocyst — None
- Serous cystadenoma — Very Low
- Pseudopapillary neoplasm — Moderate
- Mucinous cystadenoma — High
- IPMN — High

Pathogenesis

- Serous cystadenomas strongly associated with VHL gene up to 77% pancreatic involvement
- Mucinous cystadenomas (MCAs) and IPMNs frequently contain mutation of Kras oncogene and p53 tumor suppressor gene
- The degree of mutation is linearly related to degree of dyplasia in MCAs but not in IPMNs

Pancreatic Pseudocysts
Pancreatic Pseudocysts

- Majority of all cystic lesions within the pancreas >75%
- Collections arising from around the pancreas
- Lack an epithelial lining
- Occur following acute pancreatitis, chronic pancreatitis or secondary to pancreatic trauma
- Normally contain necrotic fat and a mixture of necrotic cells, including neutrophils surrounded by granulation tissue, which eventually matures to form a fibrotic pseudocapsule

Pancreatic Pseudocysts

Present in a variety of different ways ranging from
- Abdominal pain
- Gastric outlet obstruction
- Obstructive jaundice
- Nausea
- Sepsis secondary to infection
- Fistulation into nearby structures like CBD or esophagus (rarely reported)
- Haemorrhage (only 5%) mortality >40% with hemorrhage

The cause of bleeding is due to pressure erosion of nearby blood vessels by the pseudocyst; the commonest arteries affected are the splenic, gastroduodenal and superior pancreaticoduodenal arteries

Pancreatic Pseudocysts

- Usually straightforward diagnosis with a clear history of either acute or chronic pancreatitis, or associated abdominal trauma
- While pseudocysts have no malignant potential, many cystic neoplasms of pancreatic origin may mimic pseudocysts
- Case reports of cystadenomas, papillary cystic tumours and giant cell tumours of the pancreas all misdiagnosed as pseudocysts are described in the literature
- For this reason, proper sampling of pseudocysts is essential and should consist of the cyst wall during open procedures or cyst contents during minimal access drainage procedures
Pancreatic Pseudocysts

- Can often be managed conservatively
- Pseudocysts which have not regressed or have increased in size may require drainage
  - > 5-10 cm in size
  - Persisting for > 6 weeks
  - Symptomatic cysts
- Different methods of drainage:
  - Open/laparoscopic cystogastrostomy or cystojejunostomy
  - Percutaneous aspiration
  - Endoscopic transmural or transpapillary drainage
Pancreatic Pseudocysts

• Open drainage of pancreatic pseudocysts has been increasingly surpassed by laparoscopic and endoscopic techniques

• A recent systematic review of 19 reported cohort series of laparoscopic drainage and 25 cohort series of endoscopic drainage of pseudocysts revealed no significant differences in success rates, complication rates, mortality rates or need for reintervention

Pancreatic Pseudocysts

• Randomized trial comparing endoscopic and surgical cystogastrostomy; Varadarajulu et al.

• Primary end point → Pseudocyst recurrence after 24 months follow up

• Secondary end points → Treatment success or failure, complications, re-interventions, length of hospital stay, physical and mental health scores, and total costs

Gastroenterology. 2013 Sep;145(3):583-90

Pancreatic Pseudocysts

• None of the patients in the endoscopy group had pseudocyst recurrence during the follow-up period. However, endoscopic treatment was associated with shorter hospital stays, better physical and mental health of patients, and lower cost.

• The total mean cost was lower for patients managed by endoscopy than surgery ($7011 vs $15,052; P = .003).
Pancreatic Pseudocysts

• Practice trends at a large tertiary care center over ten years duration were studied
• There was a significant trend in the management of pancreatic fluid collections (PFCs) with all pseudocysts presently being treated only by endoscopy
• The ability of EUS to access smaller size PFCs and those not causing luminal compression has significantly expanded the role of endoscopy in PFC management

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Mucinous Cystic Neoplasm

- 2-5% of all exocrine neoplasms of pancreas
- Usually found in the body and tail of the pancreas
- Generally solitary lesions
- Size range varies from small to large
- Consisting of several large cysts with thick fibrotic walls
- Almost exclusively in women (mean age 40 yrs)

• The contents of the cyst are usually thick but may be hemorrhagic, watery or necrotic
Mucinous Cystic Neoplasm

- Solid areas may exist within MCNs, which may occasionally harbour high-grade dysplasia or invasive carcinoma
- Resemble MCNs which occur elsewhere such as the retroperitoneum, ovary and liver
- There is a presence of a distinctive stroma, usually referred to as 'ovarian stroma', and has become a prerequisite for a histological diagnosis

Mucinous Cystic Neoplasm

- MCNs typically present with vague abdominal discomfort or pain
- Symptoms such as weight loss and anorexia may be associated with frankly malignant changes
- On cross-sectional imaging seen as single cysts with no communication with the pancreatic duct and multiple large locules
- The outer wall and septae are often of similar thickness
- Peripheral calcification, a thickened wall, the presence of papillary proliferations, vascular involvement and a hypervascular pattern are suggestive of MCN with malignant changes
“Every now and then a disease emerges that manages to transform a medical field. Such is the case of IPMN in pancreatology. Over the last 20 years the diagnosis has permeated the thinking of physicians and researchers involved in pancreatic diseases, and suddenly pancreatic symptoms have a broader differential diagnosis, cysts and dilated pancreatic ducts have different implications, and even pancreatic cancer is being seen through a different prism…”

Castillo & Adsay. Gastroenterology, Sept. 2010
IPMNs

• IPMNs were first described in 1982 by Ohashi et al.
• Account for only 5% of all cystic pancreatic lesions, but they are being reported in increasing numbers.
• IPMNs are considered premalignant or may be frankly malignant.
• Details of their progression to invasive disease are not clear, but estimated to range from 5 to 7 years.
• Histologically, IPMN displays neoplastic mucin producing cells arranged in a papillary pattern.

IPMNs

• Mucin production by the cells leads to intraductal mucin accumulation and subsequent cystic dilation.
• The mucin production may be so great that mucin is seen extruding from the ampulla of Vater, which is a finding pathognomic of IPMN.
• IPMNs normally > 1 cm in size with a range of cell atypia from slight dysplasia to frank carcinoma.
• These cell types may coexist within the same lesion.

IPMNs

• IPMNs commonly occur in males—median age 70 yrs.
• Located mostly in the head of the pancreas.
• Many patients may have been misdiagnosed as having chronic pancreatitis.
• Patients may frequently complain of epigastric pain. Also can have weight loss, fever and jaundice.
• Excess mucin production leads to blockage of the pancreatic duct, which may explain the pain exacerbated by food.
IPMNs

CLASSIFICATION

• **Main Duct IPMN (MD-IPMN)** → PD dilated > 5 mm without other cause for obstruction

• **Branch Duct IPMN (BD-IPMN)** → Pancreatic cyst > 5mm communicating with the main PD

• **Mixed Type IPMN** → Meet criteria for both MD-IPMN & BD-IPMN

IPMNs

- **The intestinal subtype** shows abundant extracellular mucin as it progresses towards invasive malignancy and has a good prognosis following surgical resection.

- **The pancreaticobiliary subtype** evolve into ductal adenocarcinoma and have a poor prognosis.

- **The gastric foveolar subtype** arise in the branch-type IPMNs and rarely progresses towards frank malignancy.

- **The oncocytic subtype** have cells with abundant mitochondria. Despite highly proliferative nature and cellular atypia the rate of invasion is usually limited.
Serous Cystadenoma

- Serous cystadenomas (SCAs) are benign lesions in the pancreas (1-2% of PCNs).
- Characteristic macroscopic appearance of numerous tightly packed small cysts (resembling a sponge) with a stellate scar.
- SCAs are also known as serous microcystic adenomas.
- The lesions are usually <5 cm in diameter with a median size of 25-30 mm.
- The cysts seen in von Hippel-Lindau disease are virtually identical to SCAs except in their distribution, being irregularly scattered around the gland rather than forming a distinct lesion.

Serous Cystadenoma

- SCAs do not produce mucin and the cells have a clear cytoplasm with well-defined borders.
- Histology reveals cuboidal cells which mostly stain positive for glycogen.
- The risk of malignancy in SCAs is very low (case reports).
- Therefore, these lesions should be treated essentially as benign entities.
Serous Cystadenoma

- Most SCAs are asymptomatic and are discovered incidentally
- Large SCAs may cause mechanical symptoms if they compress the bile duct (causing jaundice) or produce a palpable mass
- On ultrasound and CT a well-delineated mass can be seen with multiple small septations and a honeycomb appearance
- In approximately 10–30% of the cases there may be calcification within the septae and a central scar “sun burst appearance”
Solid Pseudopapillary Tumour

- SPT are also known as Hamoudi or Frantz tumours
- SPTs are epithelial neoplasms of low malignant potential. Stain positive for Vimentin and Alpha 1 antitrypsin
- They usually start as solid tumours and undergo massive degeneration giving rise to a cystic appearance on radiological imaging
- The cystic areas consist of blood, necrotic debris and foamy macrophages

Solid Pseudopapillary Tumour

- SPTs are usually large lesions (> 10 cm), well-demarcated and may occur anywhere within the pancreas
- They have malignant potential but no histological features exist which can predict the metastatic potential of these lesions
- Although in one series of resections the presence of vascular invasion and pleomorphic nuclei was associated with subsequent metastases
Solid Pseudopapillary Tumour

- Almost exclusively in young females (mean age 30 years)
- Patients typically present with vague abdominal pain
- Radiologically, SPTs typically have a combination of solid and cystic components, are well marginated and may have central calcification
- The finding of alternate solid and cystic areas is the most characteristic appearance on cross-sectional imaging
Imaging of Cystic Pancreatic Lesions

- CT and MRI are the mainstays in the assessment of pancreatic cystic lesions
- CT is the most accessible investigation and hence the most often employed
- MRI / MRCP can accurately demonstrate cyst communication with the pancreatic duct
- Differentiating cysts with malignant potential from benign cystic lesions by imaging techniques is suboptimal

Imaging of Cystic Pancreatic Lesions

- SCAs – central scar, honeycombed and microcystic appearance
- MCNs – macrocystic, peripheral calcifications
- IPMNs – duct dilations, mural nodules, ductal connections
- Pseudocysts – Acute or chronic pancreatitis changes
EUS

- EUS offers better morphologic analysis of the cysts and a possibility of offering FNA.
- EUS imaging alone is not sufficient to delineate between benign and malignant lesions unless there is evidence of solid mass or invasive tumor.
- As with all dynamic imaging techniques, EUS is highly operator dependent.
- Studies evaluating the accuracy of EUS in distinguishing benign from malignant lesions by EUS imaging alone vary from being as poor as 40 to > 90% accurate.

EUS/FNA

- The greatest utility in the evaluation of pancreatic cystic lesions by EUS may be from data obtained via FNA.
- Cyst fluid can be analyzed through the use of cytology and a variety of tumor markers:
  - Cuboidal cells seen in SCN
  - Epithelial cells with mucin secretion and atypia for MCNs
  - Only inflammatory cells and Amylase in Pseudocysts
  - Mucin and fluid viscosity may also be used.
The major challenge in the evaluation of pancreatic cystic neoplasms (PCNs) is identifying lesions with malignant potential.

Both symptomatic and asymptomatic pancreatic cysts require evaluation, even in patients who have had pancreatitis, since some pancreatic cystic neoplasms can cause pancreatitis, and more than half of cysts in patients with pancreatitis are PCNs.

Asymptomatic cysts < 1 cm → follow up imaging (2-3 years) >1 year

All cysts greater than 1 cm should be further evaluated by MRI / MRCP v/s dedicated CT scan and look for “worrisome features” v/s “high-risk stigmata”
MANAGEMENT

• **Worrisome features** → Cysts > 3cm, main PD between 5-9 mm, non-enhanced mural nodules, abrupt change in main PD caliber and distal pancreatic atrophy and lymphadenopathy

• **High-risk stigmata** → Obstructive jaundice in patient with cystic lesion in the pancreatic head, enhanced solid component, main PD > 10 mm

MANAGEMENT

• Cyst > 3 cm with worrisome features → EUS

• Cyst < 3 cm with worrisome features → EUS

• Cysts >3cm without worrisome features→EUS

• Cyst < 3 cm without worrisome features → Surveillance Imaging
**Cyst fluid analysis**

- CEA → Mucinous v/s non-mucinous cysts
- Cut off → 192 ng/ml; sensitivity 73 % & a specificity 83%
- Molecular analysis of cyst fluid is still evolving (K-ras, GNAS)
- k-ras mutation in cyst fluid → sensitivity of 45% & a specificity 96% for MCN (k-ras2 on chromosome 12)
- Somatic mutations in GNAS (R201C or R201H) appear to be highly specific for IPMN (identified in 41 to 66 percent of cases) but are not associated with dysplasia grade or carcinoma

**Cytology**

- Limited usually due to scant cellularity
- Cytology with atypical cells has high PPV (>80%)
- Specificity ~100 % in case of malignancy
- May permit diagnosis if either glycogen-rich cells (serous cystadenoma) or mucin-containing cells (MCNs and IPMNs) are present, but the sensitivity is low

**In a prospective study of 341 patients undergoing EUS-FNA of pancreatic cysts, 112 had their cysts surgically resected**

- When the cytology results were compared with the histologic findings, the sensitivity of cytology for detecting mucinous lesions (MCNs and IPMNs) was 35 percent, and the specificity was 83 percent
**MANAGEMENT**

**INDICATION FOR SURGERY**

**IPMN**

- Mean frequency of malignancy in MD-IPMN $\rightarrow 61.6\%$
- Mean frequency of invasive cancer $\rightarrow 43.1\%$
- 5 year survival rate $\rightarrow 31-54\%$
- So surgery is strongly recommended in surgically fit patients
- The aim of resection is to achieve complete removal with negative margins
MANAGEMENT

• Mean frequency of malignancy in BD-IPMN → 25.5%
• Mean frequency for invasive cancer → 17.7%
• Mostly in elderly patients
• Annual malignancy rate 2-3%
• So conservative management with f/u in patients with no high risk features for malignancy
• Recommend surgery in patients with high risk features and also in those with rapidly growing cyst size and / or high grade atypia
• Younger patients (<65) can be considered for surgery due to increased cumulative risk

MANAGEMENT

MCN
• Prevalence of invasive cancer (<15%)
• Majority in younger patients
• Majority of MCN are in body and tail region
• MCNs have a significant malignant potential → 11-38%
• The prognosis is excellent if the MCN is removed prior to invasion
• So resection is recommended for MCNs in patients with acceptable surgical risk
• Surveillance following surgery is not necessary since these lesions do not appear to recur

MANAGEMENT

SCN
• Management is determined by the presence of symptoms
• Asymptomatic lesions can be observed, as malignant transformation into serous cystadenocarcinoma is exceedingly rare, with only a few case reports in existence
• Resection is indicated for symptomatic SCAs, or if the diagnosis is in doubt.
MANAGEMENT

Solid Pseudopapillary Neoplasms
- The malignant potential has not been well studied ~ 9%
- Over 80% of the SPTs are cured by resection and recurrences are often managed by further resection
- Malignant solid pseudopapillary neoplasms (SPNs) can be cured when completely excised

MANAGEMENT

- Experimental methods — Endoscopic cyst ablation methods
- Ethanol (at various concentrations) +/- Paclitaxel
- Complete resolution reported up to 62%
- Complications → pancreatitis, splenic vein obliteration etc

Management of the Indeterminate Cystic Lesion
- In a significant number of patients the investigative modalities will be unable to differentiate premalignant and malignant cysts from benign ones
- In addition, if these cysts are asymptomatic, their management becomes problematic
- Observation of such cysts would seem to be appropriate unless they increase in size or begin to cause symptoms
Management of the Indeterminate Cystic Lesion

- Reports from conservatively managed cysts suggest that up to one fifth increase in size over a 16-month observation period

- Increased age and cyst size are associated with a higher probability of cysts enlargement

- The exact size varies between studies from 2cm – 3cm as a cut-off value for potential for malignant transformation and causing symptoms

Management of the Indeterminate Cystic Lesion

- Up to 50% of the incidental cysts turn out to be malignant or premalignant and this malignant potential is greater in older patients (60% are malignant in patients > 70 years of age)

- Hence, even in older patients incidental cysts merit regular follow-up and cannot be dismissed, provided that these patients are fit enough for surgical resection

Management of the Indeterminate Cystic Lesion

- In the largest series of cystic lesions of the pancreas so far (539 patients), the risk of malignancy in cysts < 3 cm, without a solid component, was found to be 3%

- A median post-operative mortality across all studies - 2.9%

- Therefore it seems appropriate to follow with cross-sectional imaging and FNA (if needed), asymptomatic cysts <3 cm in diameter since the risk of malignancy is equivalent to the mortality risk of pancreatic resection
CONCLUSIONS

- PCN are increasingly recognized lesions
- The risk of malignancy or malignant potential is significantly high to warrant evaluation
- EUS with FNA and cyst fluid analysis provide valuable information about the cystic lesions
- Close follow up of the PCNs should be advocated
- Surgical excision is the mainstay of management in symptomatic or malignant / pre-malignant cystic lesions

References

THANK YOU!
**IPMNs**

- Excision of lesions before the neoplasm becomes invasive guarantees an excellent outcome

- 5-year survival following resection of IPMNs with no invasive cancer is > 70% - 90% in most series and > 40% even when invasion is present

- Features predicting reduced survival when invasive cancer was present included lymph node metastases, vascular invasion and positive resection margins

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**IPMNs**

- 20-30% of the IPMNs are multifocal and 5-10% may involve the whole gland

- For this reason, up to 15% of the patients undergoing resection may require a total pancreatectomy and follow-up is important for the remaining ones, since recurrence has been reported even in the presence of negative resection margins, which may represent inadequate sampling of multifocal disease

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Other Pancreatic Cystic Lesions

Acinar Cell Carcinoma
- Acinar cell carcinoma consist of neoplastic cells which form acini
- These spaces are true cysts rather than a degenerative phenomenon. The cysts often contain granules rich in pancreatic enzymes
- Better prognosis than ductal adenocarcinoma but is still an aggressive disease with liver metastases developing early on in its presentation

Cystic Ductal Adenocarcinoma
- Approximately 1% of the cases of ductal adenocarcinoma of the pancreas undergo cystic degeneration
- Cystic degeneration of solid malignancies often presents with a solid component within the cystic compartment and often with disseminated disease elsewhere

Cystic Endocrine Pancreatic Cancers
- Endocrine tumours of the pancreas usually do not develop cystic areas secondary to pancreatic necrosis presumably because of their better blood supply
- Cyst formation is usually unilocular but may occasionally be microcystic in nature
- Histology confirms monomorphic endocrine tumor cells which stain positive for chromogranin and synaptophysin
**Other Pancreatic Cystic Lesions**

**Lymphangioma**
- Lymphangiomas present as pancreatic and peripancreatic cystic masses
- Histologically, the lesions are lined by **endothelial cells**
- Immunohistochemical labeling for epithelial markers (cytokeratins) is consistently negative
- The stroma may contain smooth muscle cells, aggregates of mature lymphocytes, and foamy histiocytes

**Other Pancreatic Cystic Lesions**
- Patients with polycystic kidney disease, both adult and infantile types, and with medullary cystic kidneys may have cystic lesions in the pancreas
- Cystic fibrosis may lead to the cystic dilatation of the pancreatic ducts, generally not clinically detectable, by causing intraluminal impaction

**CONGENITAL CYSTS**

**Duplication (Enterogenous) Cysts**
- Very rarely, congenital cysts of foregut derivation may also occur adjacent to the pancreas
- They may cause pancreatitis and often present in childhood
- Most are found in the head of the pancreas and some communicate with the pancreatic ducts
- They are lined by a variety of epithelia including squamous, gastric, small intestinal, respiratory (bronchogenic), or simple ciliated epithelium
- The wall of the cyst contains bundles of smooth muscles