Cystic tumours of the pancreas

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Cystic lesions of the pancreas

- Diagnosed more frequently with increasing use of modern imaging techniques (CT, MRI, MRCP, EUS)
- Majority are asymptomatic and diagnosed incidentally (2-45% of patients) during investigation for non-pancreatic indications
  - Girometti R et al. Abdo Imaging 2011; 36: 198-205
  - Canto MI et al. Gastroenterol 2012; 142:798-804
- Pseudocysts most common, but not often resected
- Intraductal papillary mucinous neoplasm (IPMN) is the most commonly resected cystic neoplasm
  - Velentzas et al. Surgery 2012; 152 (3 Suppl 1): 84-12

Classifications of cystic lesions of the pancreas

- Congenital vs. acquired
- True cysts vs. cystic degeneration
- Epithelial vs. non-epithelial
- Neoplastic vs. non-neoplastic
- Benign or premalignant vs. malignant

Secondary cystic change (degeneration)

Epithelial
- Solid-pseudopapillary neoplasm
- Pancreatic endocrine neoplasm
- Pancreatic ductal adenocarcinoma
- Undifferentiated carcinoma with osteoclast-like giant cells
- Acinar cell carcinoma
- Metastases (eg. RCC, ovarian)
- Pancreatoblastoma (Beckwith-Wiedeman syndrome)
Classification of cystic lesions

**Neoplastic epithelial**
- Serous cystic neoplasm
- Mucinous cystic neoplasm
- Intraductal papillary neoplasm
- Solid pseudo-papillary neoplasm
- Pancreatic endocrine neoplasm
  - Acinar cell cystadenoma
- Cystic acinar cell carcinoma
  - Cystic teratoma
- Cystic ductal adenocarcinoma
- Cystic pancreaticoblastoma
  - Cystic metastasis

**Non-neoplastic epithelial**
- Congenital cyst (in malformation syndromes)
- Duplication (enterogenous) cyst
  - Choledochal cyst
- Cystic hamartoma
- Lymphoepithelial cyst
- Mucinous non-neoplastic cyst
  - Retention cyst
- Paraduodenal wall cyst or groove pancreatitis
- Endometrial cyst
  - Epidermoid cyst in intrapancreatic heterotopic spleen

**Neoplastic non-epithelial**
- Lymphangioma
- Haemangioma
- Cystic schwannoma
- Cystic degeneration in PNET
- Cystic degeneration in leiomyosarcoma
- Cystic degeneration in GIST
- Cystic degeneration in malignant PNST
- Cystic degeneration in paraganglioma

**Non-neoplastic non-epithelial**
- Pseudocyst
- Parasitic cyst

Kosmahl et al. Mod Pathol 2005; 18: 1157-64
Pre-operative diagnosis

- Not all cystic lesions require resection (morbidity and mortality risk)
- Imaging: rate of inaccurate pre-operative diagnoses for pancreatic cystic lesions is 22%
- Cytology: false negatives and positives, tiny cysts
  - Dagn Cytopathol 2014 Apr; 42(4): 333-71
- Biochemical analysis cyst fluid (CEA, amylase, Ca19-9)
  - EUS-FNA of IPMN’s not increase risk of peritoneal seeding
- Need for novel diagnostic approaches to better characterize these lesions

Biochemical analysis of cyst fluid

<table>
<thead>
<tr>
<th></th>
<th>CEA</th>
<th>Amylase</th>
<th>CA19-9</th>
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<tbody>
<tr>
<td>Pseudocyst</td>
<td>&lt;5ng/mL</td>
<td>&gt;250U/L</td>
<td>&lt;37U/mL</td>
</tr>
<tr>
<td>Serous cyst</td>
<td>&lt;5ng/mL</td>
<td>&lt;250U/L</td>
<td>&lt;37U/mL</td>
</tr>
<tr>
<td>Mucinous cyst</td>
<td>&gt;800ng/mL</td>
<td>&lt;250U/L</td>
<td>&gt;50000U/mL</td>
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</tbody>
</table>

Activating GNAS mutations

- GNAS mutations identified (cyst fluid & resected specimen) in 66% of IPMN’s (not oncocyctic or IPMN) but not in SCN, MCN or PDAC arising in absence of IPMN
- GNAS mutations identified in 64% IPMNs in duodenal collections of pancreatic juice and before IPMN can be identified on imaging
- GNAS not distinguish LGD from HGD in IPMN
- mAb Das-1 (monoclonal antibody against a colonic epithelial phenotype) for high risk IPMN
- Panels of miRNAs in cyst fluid for HG vs LG IPMN

Confocal laser endomicroscopy

- Vessels in SCN
- Papillary proliferations in IPMN
  - Kanda YJ et al. Gastrointest Endosc 2011; 74: 1049-58

Sampling of cystic lesions

- Establishing the diagnosis on microscopy can be problematic
- Epithelium of neoplastic cysts can become denuded and, with inadequate sampling, lead to misdiagnosis of pseudocyst
- Epithelial lining partly denuded in 40-72% of cystic neoplasms
- Area of denuded epithelium averaged 40% of the wall (range 5-98%) in the denuded neoplasms
- Always prudent to consider sampling entire cyst wall to identify/exclude lining epithelium

Sampling mucinous neoplasms

- Extensive sampling important to confirm diagnosis, to establish highest grade of dysplasia, and exclude invasive carcinoma
- In large mucinous cystic neoplasms (MCNs), capsule become sclerotic
- Macroscopic papillary areas and solid areas in MCN likely to show HGD or invasive carcinoma and should always be sampled
Sampling mucinous neoplasms

- Solid areas and mucoid areas in wall of IPMN should always be sampled as likely represent invasive carcinoma
- HGD and invasive carcinoma may be focal or multifocal
- In absence of macroscopic invasive carcinoma, embedding entire mucinous neoplasm (MCN or IPMN) should be considered, particularly if microscopy reveals HGD but no invasion


Cyst classification - epithelial lining (non-neoplastic or neoplastic)

- Acinar
- Mucinous
- Pancreatobiliary
- Serous
- Squamous

Acinar cell-lined cystic lesions

- Acinar cell cystadenoma or cystic acinar transformation
- Cystic change/degeneration in acinar cell carcinoma
- Acinar cell cystadenocarcinoma - a rare variant of acinar cell carcinoma with (non-degenerative) cyst formation


'Acinar cell cystadenoma'

- Rare, benign, F:M 7:3, mean age 48yrs, range 9-71yrs
- Head & body, solitary or multifocal
- Mean size 8cm diameter, range 1.5-10cm (but can be microscopic), unilocular or multilocular, contain watery fluid

Kloppel G. Sam Dias Pathol 2000; 17: 7-18
Albom-Cassedo, Ann Diaps Pathol 2002; 8: 113-8
- Polyclonal (not neoplastic)

Bergmann F et al. Oncol Lett 2014; 8: 682-8

'Mucinous epithelium-lined cystic neoplasms'

- Mucinous cystic neoplasm (MCN)
- Intraductal papillary mucinous neoplasm (IPMN)
Mucinous Cystic Neoplasm

- Female: Male 20:1, mean age 45 yrs (range 19-95)
- Solitary, well-demarcated, thick-walled cyst in body/tail
- Uniocular or multiocular (daughter cysts)
- 'Egg-shell' calcification in wall in 20% of cases
- No communication with duct system
- Features suggestive of malignancy include large size, irregular thickening of cyst wall, mural nodules, and/or papillary excrescences
- Sampling

Mucinous Cystic Neoplasm

MCN - Microscopy

- Tall columnar mucin-producing epithelial cells, which resemble gastric-type epithelium, but there may be intestinal differentiation with goblet cells and occasional paneth cells
- Endocrine cells more numerous in higher grade neoplasms
- Ovarian-type stroma (PGR+ on IHC) may have entrapped normal acini, islets and ducts
- Band of collagen between cyst and adjacent pancreas

MCN (WHO 2010)

Premalignant lesions:
- Mucinous Cystic Neoplasm with low-grade dysplasia
- Mucinous Cystic Neoplasm with intermediate-grade dysplasia
- Mucinous Cystic Neoplasm with high-grade dysplasia

Malignant:
- Mucinous Cystic Neoplasm with an associated invasive carcinoma

MCN with an associated invasive carcinoma

- Patients 5-10 yrs older than those with non-invasive MCNs
- Invasive component usually conventional ductal adenocarcinoma
- Variants described include undifferentiated carcinoma, undifferentiated carcinoma with osteoclast-like giant cells, and adenosquamous carcinoma

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Intraductal papillary mucinous neoplasm (IPMN)

- Mean age 65yrs (range 25-94yrs), M:F ratio 1.5:1.0
- Patients with associated invasive carcinoma tend to be 3-5yrs older than those with non-invasive IPMN
- Association with PJS, FAP, Familial Pancreatic Cancer
- Familial form described

- Rehounse et al. Dig Liver Dis 2012; 44: 443-6
- Classify IPMN: location, epithelium, grade of dysplasia
- Classify IPMN with invasive carcinoma: type of invasive carcinoma

IPMN - location

- Clinically important for assessing cancer risk
- On radiology, vast majority are either branch duct or main duct IPMNs. On histology most are mixed-type

Corren-Galligo et al. Pancreatology 2010; 10: 144-50
Takaka M. Nat Rev Gastroenterol Hepatol 2011; 8: 56-66
- Correlation between radiology and histology is ~70%


IPMN - location

<table>
<thead>
<tr>
<th>Location</th>
<th>Main duct</th>
<th>Branch duct</th>
<th>Mixed</th>
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<tr>
<td>Invasive cancer*</td>
<td>48%</td>
<td>11%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Invasive cancer**</td>
<td>44% (11-81%)</td>
<td>17% (1-37%)</td>
<td>45% (19-68%)</td>
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</table>

*Grips et al. Clin Gastroenterol Hepatol 2010; 8: 213-8

IPMN - epithelial subtype

- Gastric
- Intestinal
- Pancreatobiliary
- Oncocytic

IPMN - immunohistochemistry

<table>
<thead>
<tr>
<th>Type</th>
<th>MUC1</th>
<th>MUC2</th>
<th>CDX2</th>
<th>MUC5AC</th>
<th>MUC6</th>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
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<tr>
<td>Intestinal</td>
<td>-</td>
<td>+</td>
<td>*</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Pancreato-</td>
<td>-</td>
<td>-</td>
<td>*</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>biliary</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>*</td>
<td>-</td>
</tr>
<tr>
<td>Oncocytic</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ITPN</td>
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<td>-</td>
<td>-</td>
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</table>

IPMN – dysplasia (WHO 2010)

- Premalignant lesions:
  - IPMN with low-grade dysplasia
  - IPMN with intermediate-grade dysplasia
  - IPMN with high-grade dysplasia

- Malignant:
  - IPMN with an associated invasive carcinoma
IPMN – invasive cancer phenotypes

<table>
<thead>
<tr>
<th>Tubular</th>
<th>Colloid</th>
<th>Oncocytic</th>
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<tbody>
<tr>
<td>60%</td>
<td>16%</td>
<td>13%</td>
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<tr>
<td>80%</td>
<td>100%</td>
<td>100%</td>
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Intraductal tubulopapillary neoplasm (ITPN)

- Rare ~3% of intraductal neoplasms
- Mean age 56yrs (ie. 10 years younger than typical IPMN)
- Most have HGD and ~40% have associated invasive (duodenal) carcinoma
- Prognosis unclear but 5yr SR is >30%

Yamaguchi et al., Am J Surg Pathol 2009; 33: 1164-72

IPMN - epithelial phenotype and prognosis

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Tubular</th>
<th>Cropped Tubular</th>
<th>Oncocytic</th>
<th>IDC</th>
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<tr>
<td>35-49%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
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<tr>
<td>35-39%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
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<td>7-21%</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
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<tr>
<td>&gt;21%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
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<tr>
<td>Location</td>
<td>Tubular</td>
<td>Cropped Tubular</td>
<td>Oncocytic</td>
<td>IDC</td>
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<tr>
<td>MD-MD</td>
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<td>0%</td>
<td>0%</td>
<td></td>
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<tr>
<td>MD-HD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>HD-HD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
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</table>

IPMN - invasive cancer & prognosis

- Patients with invasive IPMN have significantly better outcome than those with conventional PDAC (median survival 58m vs. 16m, 5yr SR 47% vs. 16%, 10yr SR 34% vs. 4%)

Minis-Konstantinou et al. Gut 2011; 60: 1712-20

- Prognosis for colloid or oncocytic carcinoma arising in IPMN is significantly better than for tubular carcinoma arising in IPMN (5yr SR 61-89% vs. 37-58%)

Minis-Konstantinou et al. Gut 2011; 60: 1712-20

- IPMN with tubular carcinoma has prognosis equivalent to that of conventional PDAC (median 35m vs. 16m, 5yr SR 37% vs. 16%)

Nakada et al. Pancreas 2011; 40: 661-7
Yamaguchi et al., Am J Surg 2011; 202: 866-7
Minis-Konstantinou et al. Gut 2011; 60: 1712-20

- Tubular cancer arising in gastric type IPMN has significantly worse survival than tubular cancer arising in other types of IPMN (median survival 28m vs. 89m)

Minis-Konstantinou et al. Gut 2011; 60: 1712-20

Serous cystic neoplasms

- Microcystic serous cystadenoma
- Macrocystic serous cystadenoma
- Solid serous adenoma
- von Hippel-Lindau associated
- Mixed serous-neuroendocrine neoplasm
- Serous cystadenocarcinoma

Microcystic serous cystadenoma

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Microcystic serous cystadenoma

- Mean age 60yrs (range 18-91yrs), F>M, body & tail
- Adjacent pancreas is normal
- Irregular extension (‘locally aggressive growth’) into adjacent pancreas, blood vessels, nerves, LNs, duodenum and/or stomach does not warrant a diagnosis of malignancy

Macrocystic serous cystadenoma

- Mean age at presentation 65yrs, M>F, head
- Ill-demarcated, oligocystic
- Smooth inner lining
- No central stellate scar
- Sampling

Solid serous adenoma

- Solid, pale, 2-4cm in size, but may be admixed with typical cystic serous neoplasms
- Lobules of closely packed nests/sheets/acini of clear cuboidal cells
- Differential diagnosis: metastatic renal cell carcinoma

von Hippel-Lindau syndrome

- Serous cystic neoplasms at younger age (mean 42yrs)
- Multiple, macrocystic, involve whole pancreas diffusely or in a patchy fashion
- May develop pancreatic endocrine neoplasms (of clear cell type) and mixed serous-neuroendocrine neoplasm of pancreas (adjacent tumours or admixed)
- Pancreatic cysts may be first presentation of vHL syndrome
- Not all mixed serous-neuroendocrine have a genetic syndrome

Serous cystadenocarcinoma

- Rare case reports
- Synchronous or metachronous distant metastases to liver, peritoneum or lymph nodes
- Morphology of pancreatic primary and metastases similar to that seen in benign serous cystic neoplasms
- Clinical behaviour only way to make diagnosis

'New' serous entity

- 'Microcystic serous cystadenoma with subtotal cystic degeneration'
- Unilocular or multilocular cystic lesion resembling pseudocyst
- Denuded epithelial lining
- Fibrotic wall with associated chronic inflammation, macrophages, cholesterol clefts, haemosiderin, reactive myofibroblasts
- Residual epithelium in the fibrotic wall as solid nests or tiny cysts surrounded by network of capillary-sized vessels

Squamous epithelium-lined cystic neoplasm

Mature cystic teratoma (dermoid cyst)

- Very rare in pancreas
- Monodermal and composed of ectodermal tissue
- Lined by squamous epithelium, but may have intestinal or respiratory epithelium
- Adnexal structures

Solid pseudopapillary neoplasm

- Rare low-grade malignant epithelium neoplasm
- Adolescent girls/young women, mean age 25ys (2-85)
- Males, mean age 35yrs

Solid pseudopapillary neoplasm

- Degenerative changes include haemorrhage, cystic spaces, cholesterol clefts, foreign-body-type giant cells, foamy macrophages, foci of calcification
- Fibrous capsule, but can infiltrate the capsule and adjacent pancreas (of no prognostic significance)

Solid pseudopapillary neoplasm

- Round to oval nucleus with dispersed chromatin
- Nuclei may be indented or have longitudinal grooves
- Eosinophilic globules (now described in 5% of PanNEts)
Solid pseudopapillary neoplasm

- Core panel: vimentin, beta-catenin, progesterone receptor
- Immunopositive for CD10, CD66, cyclin D1, oestrogen receptor beta
- A1AT or A1ACT +ve globules
- May be synaptophysin +ve and AE1/AE3 and CAM5.2 +ve
- Immunonegative for E-cadherin, chromogranin A, trypsin, pancreatic hormones

Solid pseudopapillary neoplasm

- Prognosis is excellent
- Following complete resection 5yr SR 95%
- Incomplete resection leads to risk of recurrence
- Risk factors for recurrence: large tumour size, younger age, tumour rupture, male gender
- Metastases (liver, LNs, peritoneum) occur in 5-15% of patients
- No pathological features that predict prognosis; high-grade transformation may be associated with aggressive behaviour

Conclusions

- Not all cysts need resection
- Need for novel (pre-operative) diagnostic approaches to better characterize these lesions
- Sampling of pancreatic cystic lesions is crucial:

  Establishing the diagnosis
  Identify highest grade of dysplasia (MCN & IPMN)
  Identify invasive carcinoma (MCN & IPMN)

Guidelines