Cystic tumours of the pancreas

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Sarajevo, November 2015

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

Lee KS et al. Am J Gastroenterology 2010; 105: 2079-84
Girometti R et al. Abdo Imaging 2011; 36: 196-205
Canto MI et al. Gastroenterol 2012; 142:796-804

- Pseudocysts most common, but not often resected
- Intraductal papillary mucinous neoplasm (IPMN) is the most commonly resected cystic neoplasm

Valsangkar et al. Surgery 2012; 152 (3 Suppl 1): S4-12

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

Ligneau et al. Am J Surg Pathol 2001; 25: 752-60

- Pancreatic ductal adenocarcinoma
- Undifferentiated carcinoma with osteoclast-like giant cells
- Acinar cell carcinoma
- Metastases (eg. RCC, ovarian)
- Pancreatoblastoma (Beckwith-Wiedeman syndrome)

Drut R & Jones MC. Pediatr Pathol 1988; 8: 331-9

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 pancreatoblastoma
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%

  Salvia R et al. Surgery 2012; 152 (3 Suppl 1): S135-42
- Cytology: false negatives and positives, tiny cysts

  Diagn Cytopathol 2014 Apr; 42(4): 333-71
- Biochemical analysis cyst fluid (CEA, amylase, Ca19-9)
- EUS-FNA of IPMNs not increase risk of peritoneal seeding

  Yoon WJ et al. Endoscopy 2014; 46: 382-7
- Need for novel diagnostic approaches to better characterize these lesions

Biochemical analysis of cyst fluid

	CEA	Amylase	CA19-9
Pseudocyst	<5ng/mL	>250U/L	<37U/mL
Serous cyst	<5ng/mL	<250U/L	<37U/mL
Mucinous cyst	>800ng/mL	<250U/L	>50000U/mL

Activating GNAS mutations

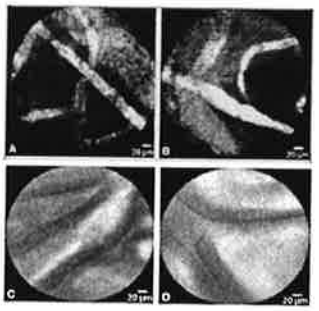
- GNAS mutations identified (cyst fluid & resected specimens) in 66% of IPMNs (not oncocytic or ITPN) but not in SCN, MCN or PDAC arising in absence of IPMN
- GNAS mutations identified in (64%) IPMNs in duodenal collections of pancreatic juice, and before IPMN can be identified on imaging

  Kanda M et al. Gut 2013; 62: 1024-33
- GNAS not distinguish LGD from HGD in IPMN
- mAb Das-1 (monoclonal antibody against a colonic epithelial phenotype) for high risk IPMNs

  Das KK et al. Gut 2014 Oct;63(10):1626-34
- Panels of miRNAs in cyst fluid for HG vs LG IPMN

  Matthaei H et al. Clin Can Res 2012; 18: 4713-24

Confocal laser endomicroscopy



Vessels in SCN

Papillary proliferations in IPMN

Konda VJA et al. Gastrointest Endosc 2011; 74: 1049-60

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

  Warshaw et al. Ann Surg 1990; 212: 432-43
- 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

Del Chiaro et al. Dig Liv Dis 2013; 45: 703-11

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

Cantrell et al. Cancer. 1981; 47: 410-6

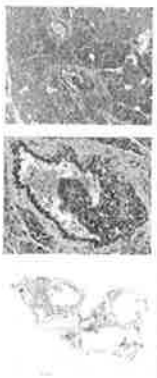
'Acinar cell cystadenoma'

- Rare, benign, F:M 7:3, mean age 48yrs, range 9-71yrs
- Head & body, solitary or multifocal
- Mean size 6cm diameter, range 1.5-10cm (but can be microscopic), unilocular or multilocular, contain watery fluid

Klöppel G. Sem Diagn Pathol 2000; 17: 7-15
Albores-Saavedra. Ann Diagn Pathol 2002; 6: 113-5
Zamboni et al. Am J Surg Pathol 2002; 26: 698-704
Khor et al. Am J Surg Pathol 2012; 36: 1579-91

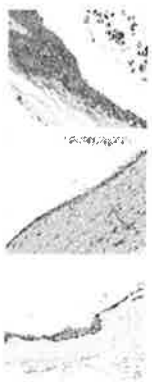
- Polyclonal (not neoplastic)

Singhi AD et al. Am J Surg Pathol 2013; 37: 1329-35
Bergmann F et al. Oncol Lett 2014; 8: 852-8



'Acinar cell cystadenoma'

- Lined by one or more layers of bland acinar cells
- Acinar cells have eosinophilic granules in apical cytoplasm and basophilic staining at base of cell
- May be apical snouting of cytoplasm
- Basal, uniform nuclei, small nucleolus
- Epithelial heterogeneity – cuboidal ductal epithelium, bland mucinous epithelium
- Zymogen granules – PAS/DPAS
- IHC – trypsin, chymotrypsin



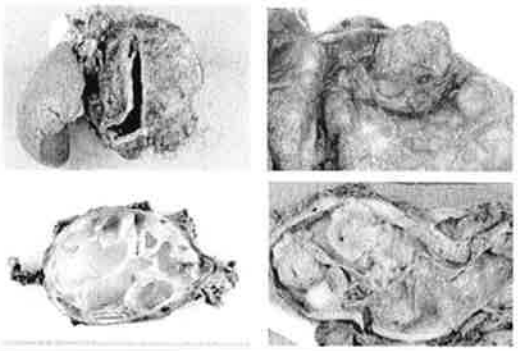
Mucinous epithelium-lined cystic neoplasms

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

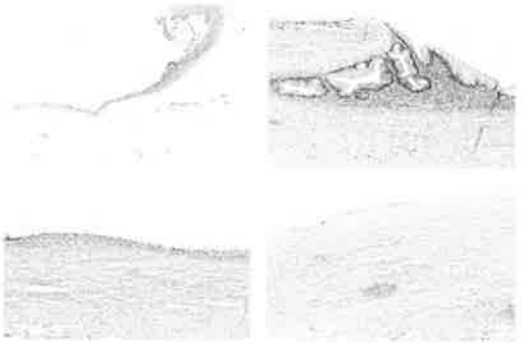
Mucinous cystic neoplasm

- Female:Male 20:1, mean age 45yrs (range 19-95)
- Solitary, well-demarcated, thick-walled cyst in body/tail
- Unilocular or multilocular (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



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

Sano M et al. Gastroenterol 2014; 146: 257-67

- Band of collagen between cyst and adjacent pancreas

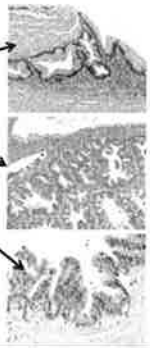
MCN (WHO 2010)

<u>Premalignant lesions:</u>

- Mucinous cystic neoplasm with low-grade dysplasia
- Mucinous cystic neoplasm with intermediate-grade dysplasia
- Mucinous cystic neoplasm with high-grade dysplasia

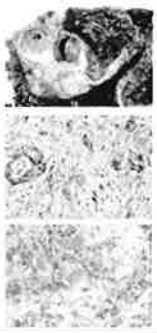
<u>Malignant:</u>

- Mucinous cystic neoplasm with an associated invasive carcinoma



MCN with an associated invasive carcinoma

- Patients 5-10yrs 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



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

Rebours et al. Dig Liver Dis 2012; 44: 442-6

- 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

Correa-Gallego et al. Pancreatology 2010; 10: 144-50
Tanaka M. Nat Rev Gastroenterol Hepatol 2011; 8: 56-60

- Correlation between radiology and histology is ~70%

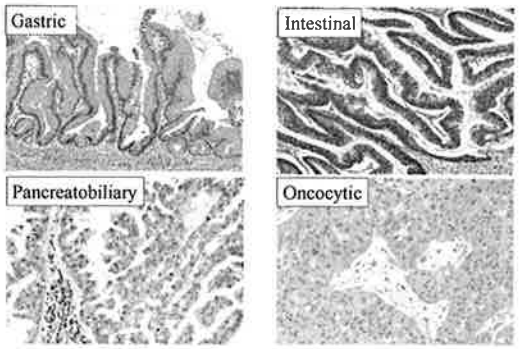
Waters et al. J Gastrointest Surg 2008; 12: 101-9

IPMN - location

	Main duct	Branch duct	Mixed
Invasive cancer*	48%	11%	42%
Invasive cancer**	44% (11-81%)	17% (1-37%)	45% (19-68%)

*Crippa et al. Clin Gastroenterol Hepatol 2010; 8: 213-9
**Tanaka et al. Pancreatology 2012; 12: 183-97

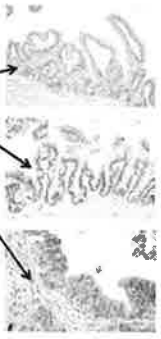
IPMN - epithelial subtype



IPMN - immunohistochemistry

	MUC1	MUC2 (goblets)	CDX2	MUC5AC	MUC6
Gastric	-	-	-	+	+
Intestinal	-	+	+	+	-
Panc-biliary	+	-	-	+	+
Oncocytic	+	-	-	+	+
ITPN	+	-	-	-	+

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

	Gastric	Intestinal	Pancreatobiliary	Oncocytic
Tubular cancer	66%	16%	13%	5%
Colloid cancer	-	100%	-	-
Oncocytic cancer	-	-	-	100%

Mino-Kenudson et al. Gut 2011; 60: 1712-20

Intraductal tubulopapillary neoplasm (ITPN)

- Rare ~3% of intraductal neoplasms
- Mean age 55yrs (ie. 10 years younger than typical IPMN)
- Most have HGD and ~40% have associated invasive (ductal) carcinoma
- Prognosis unclear but 5yr SR is >30%

Albores-Saavedra et al. Am J Surg Pathol 2004; 28: 233-8
Yamaguchi et al . Am J Surg Pathol 2009; 33 : 1164-72

IPMN - epithelial phenotype and prognosis

	Gastric	Intestinal	Pancreatobiliary	Oncocytic	ITPN
Frequency	38-49%	36-39%	7-21%	1-8%	~3%
Location	BD>MD	MD>BD	MD~BD	MD~BD	?
Dysplasia	LGD/IGD	IGD/HGD	HGD	HGD	HGD
Invasive cancer	Tubular	Colloid >> tubular	Tubular	Oncocytic> tubular	Tubular
Present with invasion	15%	40-50%	60-75%	25%	40%
Prognosis 5yr SR 10yr SR	 98% 94%	 94% 69%	 50% ?	 84% 73%	 >30% ?

Furukawa et al. Gut 2011; 60: 509-16
Kim et al. Tumour Biol 2011; 32: 535-42
Takasu et al. Pancreas 2010; 39: 604-10
Adsay et al. Am J Surg Pathol 1998;20:980-4
Yamaguchi et al . Am J Surg Pathol 2009;33:1164-72
Furukawa et al. Pancreas 2009 ; 38: 998A

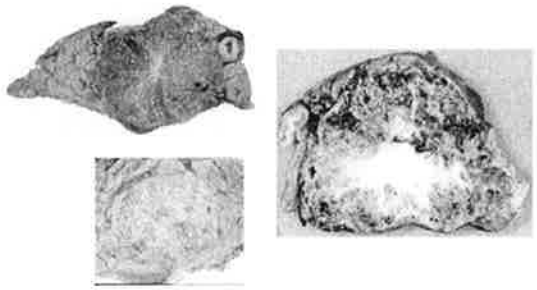
IPMN - invasive cancer & prognosis

- Patients with invasive IPMN have significantly better outcome than those with conventional PDAC (median survival 58m vs. 18m, 5yr SR 47% vs. 16%, 10yr SR 34% vs. 4%)
  Mino-Kenudson 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. 37-55%)
- IPMN with tubular carcinoma has prognosis equivalent to that of conventional PDAC (median 35m vs. 18m, 5yr SR 37% vs. 16%)
  Takasu et al. Pancreas 2010; 39: 604-10
  Nakata et al. Pancreas 2011; 40: 581-7
  Yopp et al. Ann Surg 2011; 253: 968-7
  Mino-Kenudson 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)
  Mino-Kenudson et al. Gut 2011; 60: 1712-20

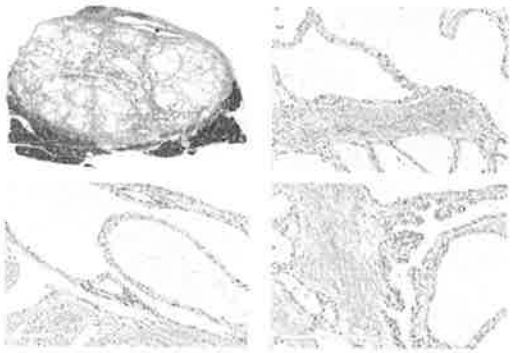
Serous cystic neoplasms

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

Microcystic serous cystadenoma



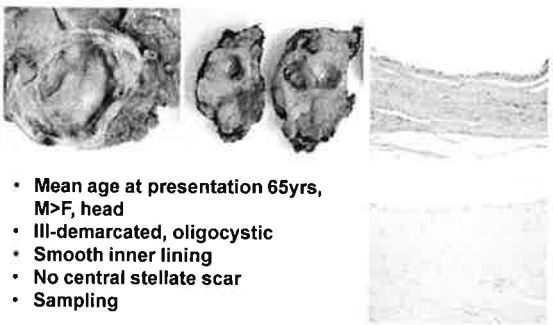
Microcystic serous cystadenoma



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

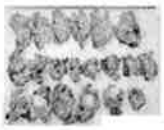
Solid serous adenoma

- Solid, pale, 2-4cm in size, but may be admixed with typical cystic serous neoplasm
- Lobules of closely packed nests/sheets/acini of clear cuboidal cells

Perez-Ordonez et al. Am J Surg Pathol 1996; 20:1401-5

- 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

Blandamura et al. J Clin Pathol 2007; 60: 278-82

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'

Panarelli et al. Am J Surg Pathol 2012; 36: 726-31

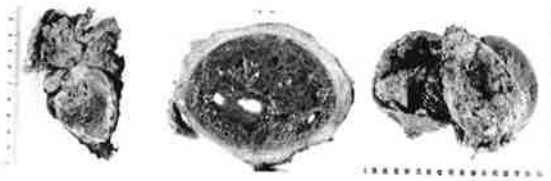
- Unilocular or multilocular cystic lesion resembling pseudocyst
- Denuded epithelial lining
- Fibrotic wall with associated chronic inflammation, macrophages, cholesterol clefts, haemosiderin, reactive myofibroblasts
- Residual epithelium in the fibrotic wall as solid nests or tiny cysts surrounded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

Squamous epithelium-lined cystic neoplasm

Mature cystic teratoma (dermoid cyst)

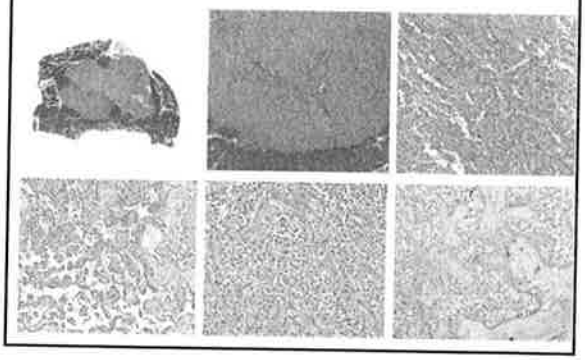
- Very rare in pancreas
- Monodermal and composed of ectodermal tissue
- Lined by squamous epithelium, but may have intestinal or respiratory epithelium
- Adnexal structures

Solid pseudopapillary neoplasm



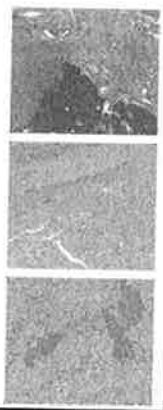
- Rare low-grade malignant epithelium neoplasm
- Adolescent girls/young women, mean age 25ys (2-85)
- Males, mean age 35yrs

Solid pseudopapillary neoplasm



Solid pseudopapillary neoplasm

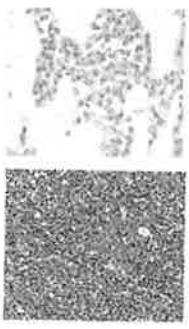
- Degenerative changes include haemorrhage, cystic spaces, cholesterol clefts, foreign-body-type giant cells, foamy macrophages, foci of calcification
- Fibrous capsule, but can infiltrate the capsule and adjacent pancreas (of no prognostic significance)



Solid pseudopapillary neoplasm

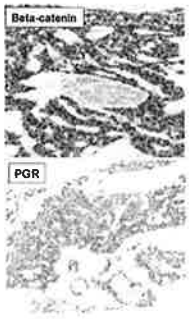
- Round to oval nucleus with dispersed chromatin
- Nuclei may be indented or have longitudinal grooves
- Eosinophilic globules (now described in 5% of PanNETs)

Merlden et al. Am J Surg Pathol 2011; 35: 981-8



Solid pseudopapillary neoplasm

- Core panel: vimentin, beta-catenin, progesterone receptor
- Immunopositive for CD10, CD56, 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

- International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas.Tanaka M et al. Pancreatology 2012; 12: 183-97
- European experts consensus statement on cystic tumours of the pancreas. Del Chiaro M et al. Dig Dis Liv 2013; 45: 703-11
- Papanicolaou Society of Cytopathology guidelines for pancreatobiliary cytology. Diagn Cytopathol 2014 Apr; 42(4): 333-71 & Pitman MB, Layfield LJ. Cancer Cytopathol 2014 Jun; 122(6): 399-411
- Pathologic evaluation and reporting of intraductal papillary mucinous neoplasms of the pancreas and other tumoral intraepithelial neoplasms of pancreatobiliary tract. Adsay V et al. Ann Surg 2015: March 13 [Epub ahead of print]