Pancreatic cystic lesions: risk stratification and management based on recent guidelines

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ABSTRACT

Pancreatic cystic lesions (PCLs) can present complex diagnostic and management challenges with uncertainty as to the most appropriate investigations, interventions and surveillance. Guidelines have been developed to aid decision making, including the European Study Group, American College of Gastroenterology and International Study Group guidelines. This paper presents issues relating to risk stratification and the appropriate management of patients with PCLs, reviewing these recently published guidelines. While there are similarities across these expert guidelines, there are notable differences in terms of features associated with increased risk of malignant transformation, the most appropriate imaging modality and timing of interval imaging. Where variations exist, this reflects differing interpretations of a limited evidence base, and decision making will likely evolve further as experience with these guidelines develops.

INTRODUCTION

The prevalence of pancreatic cystic lesions (PCL) is increasing, associated with the increasing use of CT and MRI to investigate potential intra-abdominal pathology and possibly related to an ageing population. PCLs may be detected in up to 3% of patients undergoing contrast-enhanced CT and up to 45% of patients undergoing MRI/magnetic resonance cholangiopancreatography.¹ Most are asymptomatic, but if symptoms are present they are generally non-specific. PCLs represent a spectrum of disease from benign to malignant potential, to frankly malignant lesions. They may occur as solitary lesions or in association with disorders such as polycystic kidney disease or von Hippel-Lindau syndrome.

While incidental detection of a likely malignant or premalignant PCL may

be fortuitous, surgical intervention to remove a PCL which is subsequently found to be benign may expose the patient to considerable unnecessary risk. Characterisation and risk stratification of PCLs can be challenging, necessitating multi-modality investigation which may include cross-sectional imaging, endoscopic ultrasound (EUS) and tissue sampling. Recognising these diagnostic and management difficulties, guidelines have recently been developed in an attempt to aid decision making.

The International Consensus Guidelines, published in 2012, were ‘consensus-based’, rather than ‘evidence-based,’ guidelines and were updated in 2017.^{2,3} More recently, both the American College of Gastroenterology (ACG) and the European Study Group (ESG) on Cystic Tumours of the Pancreas have provided evidence-based guidance centred on systematic review of the literature, using criteria for assessment of study quality in addition to expert opinion.^{4,5}

The aim of this review is to highlight the key points from these guidelines, including differences and controversies, to assist in PCL decision making and the development of local protocols.

Classification of PCLs

PCLs can be defined as (1) inflammatory fluid collections; (2) non-neoplastic; or (3) neoplastic (table 1). A history of pancreatitis should always be sought during the initial work-up of a patient with a PCL. Non-neoplastic pancreatic cysts do not require resection unless symptomatic. Of the neoplastic pancreatic cysts, mucinous, intraductal papillary mucinous, solid pseudopapillary and neuroendocrine lesions have malignant potential, and resection should be considered dependent on the risk of malignant transformation balanced

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Table 1 Pancreatic cystic lesions

Inflammatory fluid collection	Non-neoplastic pancreatic cysts	Neoplastic pancreatic cysts
Acute peripancreatic fluid.	Benign epithelial.	Serous.
Pseudocysts.	Retention.	Mucinous.*
Walled-off necrosis.	Mucinous non-neoplastic.	Intraductal papillary mucinous.*
	Lymphoepithelial.	Solid pseudopapillary.*
		Neuroendocrine.*

*Potential for malignancy.

against the risks of intervention or continued surveillance.⁶ Serous cystic tumours are a benign entity and resection is only indicated if symptomatic. **Figure 1** shows example images for serous cystadenoma, intraductal papillary mucinous neoplasm (IPMN) and mucinous cystic neoplasms (MCN).

INVESTIGATIONS

Following identification of a PCL, subsequent investigations should proceed in a stepwise fashion. Inflammatory fluid collections are often clearly defined based on patient history and imaging findings, although an underlying pancreatic lesion should be considered. In terms of true PCLs, CT and MRI have similar reported accuracy for identifying the specific type, 40%–95% and 40%–81%, respectively.⁴ Across the guidelines MRI is recommended as the preferred investigation for PCLs, with MRI best demonstrating communication with ductal system, internal septations or mural nodules without the radiation exposure of CT and interventional risks associated with EUS.^{4,5} Differentiating cyst type is problematic, with MRI and other imaging modalities showing 40%–50% accuracy in determining cyst type and 55%–76% in identifying malignancy.⁵ CT can provide further information when performed in addition to MRI where there is diagnostic uncertainty, to detect features of chronic pancreatitis, to differentiate pseudocysts from true PCLs and where there is suspicion of a malignant PCL or pancreatic cancer, although this is based on low-quality evidence.

Where there are clinical or radiological features of concern, EUS is recommended as an adjunct to cross-sectional imaging. However, if patients are deemed not fit for surgery, then further investigation for incidental cysts would not be appropriate. While EUS is helpful at identifying the different features of PCLs, the guidelines acknowledge that EUS remains imperfect at identifying the exact type of PCL. Contrast-enhanced EUS should be considered to assess mural nodules and can help identify vascularity within the PCL. Hyperenhancement raises suspicion for malignant transformation, and in these cases tissue sampling should be considered. EUS-fine needle aspiration

Figure 1 Pancreatic cystic lesions. (A) EUS image showing serous cystadenoma (microcystic variant); (B) EUS image showing main duct intraductal papillary mucinous cystadenoma; (C) EUS image showing malignant mucinous cystadenoma. EUS, endoscopic ultrasound.

(FNA) increases diagnostic accuracy when considering mucinous versus non-mucinous PCLs, especially when combined with cyst fluid carcinoembryonic antigen (CEA), lipase levels and cytology. Although EUS-FNA is a relatively safe procedure, complications such as pancreatitis and infection can occur, with one study reporting an adverse event rate of 6%.⁷ There is a lack of evidence regarding the utility of brush cytology and forceps biopsy at EUS, but these techniques may find a role as experience with different methods of tissue

Recommendation 1: cross-sectional imaging

MRI is the preferred investigation for pancreatic cystic lesions. CT should be performed in addition to MRI if differentiation of inflammatory cystic lesions from true cystic lesions is required, to detect features of chronic pancreatitis and where malignant lesions are suspected.

sampling develops. Endoscopic retrograde cholangiopancreatography does not have a role in the characterisation of PCLs, although pancreatoscopy may be helpful in differentiating chronic pancreatitis from main duct-IPMN.⁴

While cyst fluid analysis is recommended, interpretation of results may be challenging with limited sensitivity and accuracy. When differentiating mucinous from non-mucinous lesions, cytological analysis of cyst fluid has a sensitivity as low as 40%, with cyst fluid CEA level having a sensitivity between 50% and 80%.⁴ However, specificity is reportedly higher, with 99% specificity for cytological analysis and 60%–90% specificity for a cyst fluid CEA level ≥ 192 ng/mL.⁴ No serum markers are currently available for routine use, although CA 19.9 levels may be elevated in the context of malignant transformation. Mutational analysis of cyst fluid appears promising but remains investigational at present.

Risk of malignancy

IPMN is the most common mucinous lesion occurring, with equal male to female ratio in their 50s–70s, either incidentally, on a background of pancreatitis or related to malignancy. IPMN can be defined as either main duct (MD-IPMN), branch duct (BD-IPMN) or mixed type (MT-IPMN) based on the cyst's communication with the pancreatic ductal system. MD-IPMN and MT-IPMN display similar, relatively high, propensity for malignant transformation (30%–91% of lesions where the main pancreatic duct was ≥ 5 mm).⁴ BD-IPMN has a lower risk of high-grade dysplasia or malignancy (3%–47% at >30 mm maximum cyst diameter), but features predictive of malignancy and high-risk features are the same (table 1).⁴ Risk of malignancy is lower for mucinous cystic neoplasm, although still significant (11%–38%).^{8,9} Mucinous neoplasms are found predominantly in women aged 50–70 years old presenting with abdominal pain, as an incidental finding or in relation to malignancy. Table 2

Recommendation 2: endoscopy

Endoscopic ultrasound (EUS) is recommended where there are radiological features of concern or diagnostic uncertainty. Contrast-enhanced EUS can aid assessment of vascularity of the lesion and guide tissue sampling. Fine needle aspiration improves diagnostic accuracy.

Table 2 Risk of malignancy in pancreatic cystic lesions

Pancreatic cystic lesion	Risk of malignancy
Intraductal papillary mucinous neoplasm	
Main duct	60% ²
Mixed type	(consider as 'Main Duct')
Branch duct	8% ¹⁷
Mucinous neoplasm	11% ⁹
Solid pseudopapillary	15% ⁴
Cystic neuroendocrine	20% ⁴

Note: These figures are variable between series and based on surgical resection. Therefore, they cannot be used to define risk during assessment prior to surgery.

provides an indication of malignant risk associated with the type of lesion. It is important to note that this reflects pathological assessment of these lesions following resection and so cannot be used to estimate malignant risk prior to surgery.

The ESG, International Consensus Group (ICG) and ACG guidelines have defined features indicating high risk for malignancy and/or high-grade dysplasia for mucinous lesions including IPMN and mucinous cystic neoplasm (table 3). The ESG describes a separate set of 'high risk factors' for both IPMN and mucinous cystic neoplasia, while the ICG and ACG consider both subtypes together as 'mucinous lesions'. While there is general consistency across the guidelines, there are some key differences, such as cut-off values for cyst size, growth rate and associated features. Where there are differences this has resulted from different interpretations of a limited literature base without sufficient evidence to support one approach over another. Across the guidelines the most concerning features include obstructive jaundice occurring secondary to the cyst, presence of a mural nodule or solid component, and main pancreatic duct dilatation. The correct balance of risk will become apparent as experience with these recently published guidelines expands.

There are limited data regarding risk of malignancy in solid pseudopapillary neoplasms (SPN), although two series have reported that approximately 15% of resected SPNs were malignant.^{10,11} Cystic pancreatic neuroendocrine tumours have approximately 20% risk of malignancy, although when ≤ 20 mm they usually are considered low risk.¹²

Management: resection

Indications for resection of PCLs can be categorised as absolute, relative or 'no surgery indicated'. While minimally invasive techniques are increasingly being used for pancreatic resections, risks remain considerable, with approximately 40% of patients undergoing distal pancreatectomy experiencing a degree of leak from the pancreatic stump.¹³ The incidence of new-onset insulin-dependent diabetes mellitus (8%), pancreatic fistula (5%), intra-abdominal abscess (4%) and postoperative bleed (4%) are not insignificant.¹⁴ It is therefore essential

Table 3 High-risk features of mucinous cysts (IPMN and mucinous) according to the guideline**European guidelines⁴**

<i>'Features highly predictive of malignancy'</i>	<i>'Features associated with an increased risk of high-grade dysplasia or cancer'</i>
Jaundice.	Enhancing mural nodule (<5 mm).
Enhancing mural nodule (≥5 mm).	Main pancreatic duct (5–9.9 mm).
Solid component.	Growth rate ≥5 mm/year.
Main pancreatic duct ≥10 mm.	Increased level of serum CA 19-9 (>37 U/mL).
	Cyst diameter ≥40 mm.
	Symptomatic cysts (including NODM, acute pancreatitis due to the cyst).

American College Gastroenterology guidelines⁵*'High risk characteristics'*

Jaundice.
Acute pancreatitis secondary to the cyst.
Elevated CA 19-9 when no benign cause for elevation.
Mural nodule or solid component.
Main pancreatic duct diameter >5 mm.
Change in main duct with upstream atrophy.
Cyst diameter ≥30 mm.
Increase in cyst size ≥3 mm/year.

International Consensus Group guidelines^{2,3}

<i>'High risk stigmata'</i>	<i>'Worrisome features'</i>
Obstructive jaundice.	Enhancing mural nodule (<5 mm).
Enhancing mural nodule (≥5 mm).	Main pancreatic duct (5–9.9 mm).
Main pancreatic duct ≥10 mm.	Growth rate ≥5 mm/2 years.
	Increased serum CA 19-9.
	Cyst diameter ≥30 mm.
	Abrupt change in calibre of pancreatic duct with distal pancreatic atrophy.
	Lymphadenopathy.

IPMN, intraductal papillary mucinous neoplasm; NODM, new-onset diabetes mellitus.

to ensure indications for surgery are appropriate and the risk/benefit ratio is considered.

The guidelines vary regarding indications for surgery, ranging from offering specific advice to recommending the patient is referred to the pancreatic multidisciplinary team. For IPMN, the ESG regards one or more of the 'Features highly predictive of malignancy' as an absolute indication for surgery, with relative indications defined as 'Features associated with an increased risk of high-grade dysplasia or cancer' (table 3). The ESG guidelines go on to suggest that patients who have one or more relative indications for surgery and no significant comorbidity should undergo resection, patients with one 'relative indication' plus one 'significant-comorbidity' should undergo intensive surveillance, while those with 'significant comorbidity' and two or more relative indications should undergo surgery. The implementation of this approach would

be problematic given 'significant comorbidity' is not defined and there is insufficient evidence to suitably risk-stratify patients prior to surgery. The ACG does not provide guidance on whether a specific lesion should be resected or not, rather they recommend referral to a pancreatic multidisciplinary team (MDT) for further discussion if there are 'high risk characteristics' present (table 3). The ICG recommends proceeding straight to surgery if clinically appropriate in the presence of 'high risk stigmata' for mucinous cystic lesions and proceeding to EUS in the presence of 'worrisome features' (table 3). If at EUS there is a definite mural nodule, main duct features suspicious for involvement or suspicious/malignant cytology, then surgery is recommended, otherwise the patient should undergo interval imaging (see next section).

With regard to mucinous cystic neoplasms, the ESG recommends that cysts which are symptomatic, ≥40 mm, have mural nodules or show high growth rate should be resected. The ACG does not provide specific guidance regarding surgery, while the ICG recommends that all fit patients undergo resection of MCNs. The ICG acknowledges that although MCNs less than 4 cm are low risk, these lesions generally occur in the distal pancreas, so are amenable to resection which avoids surveillance.

The guidelines agree that all SPNs should be resected. The ESG recommends that pancreatic neuroendocrine tumours >20 mm and those that are ≤20 mm but are symptomatic or show signs of malignant behaviour should be resected, the ACG does not comment on surgery for neuroendocrine tumours, and the ICG does not comment on neuroendocrine PCLs.

The surgical approach to IPMN and mucinous cystic neoplasm should be an oncological resection with standard lymphadenectomy. For MD-IPMN and MT-IPMN with main duct dilatation running the length of the pancreas, intraoperative frozen section of the resection margin is recommended. For the majority of BD-IPMN, an oncological resection with standard lymphadenectomy is recommended. There may be a role for parenchymal sparing pancreatotomy (resection of the lesion and minimal pancreatic tissue) for lesions with very low probability of malignancy, but the morbidity is similar to standard resections and benefits are yet to be demonstrated. Given the rarity of SPN, guidance for appropriate interventions is limited, although even in cases of locally advanced disease, metastatic or recurrent SPN an aggressive surgical approach can be considered. For pancreatic neuroendocrine tumours, surgery should

Recommendation 3: surgical resection

Surgical approach should be tailored to the presence of high-risk features for malignancy or high-grade dysplasia. An oncological resection with standard lymphadenectomy is preferred.

Table 4 Follow-up for undefined cystic lesions of the pancreas according to guideline**Undefined cystic lesions of the pancreas****European Study Group, 2018⁴**

<15 mm	Reimage at 1 year (MRI, CT or EUS); if stable for 3 years reimage 2-yearly.
≥15 mm	Reimage 6 monthly for 1 year then annually.

American College of Gastroenterology, 2018*5

<1 cm	MRI in 2 years ×4 years, then consider lengthening interval.
1–2 cm	MRI in 1 year ×3 years, then if stable lengthen interval.
2–3 cm	If IPMN or MCN MRI in 2–12 months, then if stable lengthen interval. If serous cystadenoma, then no further evaluation if asymptomatic.
>3 cm	EUS±FNA; if no high-risk characteristics, then MRI in 6 months, then if stable MRI alternating with EUS for 4 years.

International Consensus Group, 2012 (updated 2017)†2 3

<1 cm	CT/MRI in 6 months, then every 2 years if no change.
1–2 cm	CT/MRI 6 monthly for 1 year, yearly for 2 years, then lengthen up to 2 years if no change.
2–3 cm	EUS in 3–6 months; then every year alternating EUS and MRI. Consider surgery if young/fit with need for prolonged surveillance.
>3 cm	Alternating MRI/EUS every 3–6 months. Strongly consider surgery in young fit patients.

*For cysts with no high-risk features.

†Undefined cysts and branch duct IPMN (no high risk or worrisome features).

EUS, endoscopic ultrasound; FNA, fine needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasms.

Table 5 Follow-up for intraductal papillary mucinous neoplasia according to guideline**Intraductal papillary mucinous neoplasm****European Study Group, 2018⁴**

No indication for surgery.	Clinical evaluation, CA 19-9 and EUS every 6 months for 1 year, then yearly.
Resected + invasive malignancy.	As per resected PDAC.
Resected + HGD or MD-IPMN.	6-monthly imaging for 2 years, then yearly surveillance.
Resected + LGD.	Follow-up as per non-resected IPMN.

American College of Gastroenterology, 20185

No indication for surgery.	Imaging according to 'Cyst with no high-risk characteristics'.
Resected with invasive cancer.	As per resected PDAC.
Resected with HGD.	MRI or EUS on a 6 monthly basis.
Resected with low-grade or intermediate-grade dysplasia + IPMN in remnant.	Based on size of the largest cyst.
Resected with low-grade or intermediate-grade dysplasia, no IPMN in remnant.	MRI every 24 months.

International Consensus Group, 2012 (updated 2017)2 3

No indication for surgery.	Clinical evaluation, serum CA 19-9 and EUS every 6 months for 1 year, and then yearly.
Resected + invasive cancer.	Follow local approach to pancreatic cancer.
Resected + HGD at surgical margin, non-intestinal subtype, family history of PDAC.	6 monthly cross-sectional imaging.
Resected with LGD.	6–12 monthly cross-sectional imaging.

EUS, endoscopic ultrasound; HGD, high-grade dysplasia; IPMN, intraductal papillary mucinous neoplasm; LGD, low-grade dysplasia; MD-IPMN, main duct IPMN; PDAC, pancreatic ductal adenocarcinoma.

proceed according to tumour localisation (pancreatoduodenectomy, distal pancreatectomy or enucleation).

Management: surveillance and follow-up

While there is general consistency between guidelines regarding the highest risk PCL features, there is variation in the approach to small undefined PCLs (table 4), which constitute the majority of cases. The ESG considers EUS, CT or MRI as appropriate investigations, the ACG favours MRI, while the ICG considers MRI or CT appropriate for smaller cysts, with EUS in addition for larger lesions. Evidence to support one strategy over another is lacking, and therefore follow-up strategies may be designed according to local resources. By way of consolidation, MRI would seem most appropriate as the surveillance imaging of choice given the radiation exposure associated with CT and interventional risks of EUS. If the initial investigation was CT, then small cysts do not necessarily require repeat imaging in the form of MRI or EUS at the initial stage. If patients cannot tolerate MRI, then CT or EUS may also be acceptable forms of surveillance.

For patients who have undergone resection of IPMN, the length of follow-up should be tailored to the individual concerned and includes perceived cancer risk, comorbidity and patient preference. All guidelines recommend following local PDAC (pancreatic ductal adenocarcinoma) protocols where invasive cancer is found and 6-monthly follow-up imaging initially where high-grade dysplasia is evident in the resected specimen (table 5). It is important to note that patients who develop pancreatic cystic neoplasia have a tendency to develop further lesions which can recur over 10 years following resection of the first lesion.¹⁵ Indeed in a series of 130 patients, 62% had developed another IPMN by 10 years (4% at 1 year, 25% at 5 years).¹⁶ For this reason all guidelines recommend that follow-up should be

Recommendation 4: surveillance

All guidelines advocate surveillance imaging for undefined pancreatic cystic lesions regardless of size. Following resection of IPMN surveillance should continue while the patient remains a surgical candidate. Surveillance is not required following resection of mucinous cystic neoplasm. Appropriate imaging modality varies according to guideline; however, MRI represents a good balance between risk and benefit of the investigation. Surveillance may not be appropriate in frail or elderly patients or those with significant comorbidities.

continued as long as the patient is considered a surgical candidate.

There is good evidence that resected mucinous cystic neoplasia in the absence of invasive malignancy do not recur, and the guidelines agree that postoperative surveillance is not required for these patients.²⁻⁵

SUMMARY

PCLs present a range of complex diagnostic and management dilemmas. Expert working groups have aided decision making through the development of guidelines addressing the key issues. While there is some consistency as to the features associated with high risk of cancer or high-grade dysplasia, the limited evidence base has resulted in variation in recommendations regarding indications for surgery or surveillance and the modalities and frequency of surveillance. Ultimately, the various guidelines are iterative and will hopefully converge with more experience and review of large patient series.

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