World Gastroenterology Organisation Global Guidelines

Pancreatic cystic lesions

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WGO Review Team

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1.1 Key points and main practice statements

- A careful patient history and physical evaluation are necessary.
- At the initial cyst fluid aspiration: carry out carcinoembryonic antigen (CEA), amylase, and cytology testing.
- Cysts should be assessed to determine the risk for malignancy or complications.

  In patients with **symptomatic** cysts, cysts larger than 3 cm, with solid components, or with ductal dilation:

  — Perform endoscopic ultrasonography (EUS) with or without fine-needle aspiration (FNA)* and consider surgical evaluation.

  In patients who have cysts with **low-risk** features:

  — Continue noninvasive surveillance for at least 5 years, on the basis of some of the guidelines, although the longer-term risk for the development of malignancy is not very clear.

  — Consider the patient's age and comorbidities and continue surveillance as appropriate until there is better evidence for definite discontinuation of surveillance and risk stratification.

  — The patient's preferences and understanding of the risk should be taken into consideration.

  In patients who have **indeterminate** cysts:

  — Surveillance with cyst fluid analysis and/or imaging features.
- Molecular testing is not routinely done because of limited data and the expense, but it does hold promise for the future.
- A thorough discussion with the patient regarding the diagnosis, current dilemmas in diagnosis and treatment, and the economic and emotional burden of investigations should be conducted before initiating any surveillance strategy.

* FNA may not be performed if the lesion is in the pancreatic body or tail if there is any concern about malignancy, due to the risk of seeding along the FNA track that may not be addressed by subsequent surgery. In patients who have lesions in the body or tail, the stomach is not removed, whereas in those with lesions in the pancreatic head, the duodenum is removed at surgery.

1.2 WGO cascades for pancreatic cystic lesions

WGO cascades: a hierarchical set of diagnostic, therapeutic, and management options to deal with risk and disease, ranked by the resources available.

WGO guidelines and cascades are intended to highlight appropriate, context-sensitive and resource-sensitive management options for all geographical areas, regardless of whether they are "developing," "semi-developed," or "developed." WGO cascades provide options that are not necessarily defined solely by resource priorities and may, for example, also include cost–benefit factors, patient preferences, and the availability of equipment, skills, and expertise.

Most asymptomatic incidental cysts are diagnosed in resource-enabled countries when imaging is being carried out to evaluate symptoms not necessarily related to pancreatic disease. For the Asian–Pacific region, for instance, two recent papers from Korea and Japan—

both affluent countries—report asymptomatic cyst incidence rates of 2.2% and 3.5% [1,2]. In low-resource countries, most diagnoses are established at surgery or autopsy.

The authors of this guideline have therefore chosen not to use the conventional "cascade" pattern, but rather to make recommendations based on the current evidence. We understand that all the resources are not available everywhere, and an informed decision should be made in discussion with the patient regarding the risk for malignancy, available resources, and cost.

2 Introduction

2.1 Scope and goals

This guideline aims to provide physicians worldwide with a reasonable, up-to-date approach to the management of pancreatic cystic lesions. Since pertinent diagnostic and therapeutic resources are not uniformly available in different areas of the world, these guidelines are meant to be used as appropriate, with local resources and patient preferences being kept in mind.

2.2 Definitions

"Pancreatic cystic lesions" is a conventional term that refers to a well-defined lesion in the pancreas that contains fluid. Most small lesions are detected incidentally when scanning is performed for evaluation of non–pancreas-related indications or symptoms. The etiology of pancreatic cysts is variable; they may be inflammatory or posttraumatic, or may have no known etiology. While most small lesions are benign, some lesions can lead to malignancy and hence a need for further work-up, surveillance, and management decisions. It is therefore necessary to obtain a good patient history and assess the nature of the lesion through appropriate investigations as needed, in order to assess the risk for malignant progression. Since potentially malignant lesions cannot be distinguished reliably from benign lesions on the basis of the clinical and morphological features alone, further evaluation and/or surveillance may be necessary.

Premalignant cystic lesions of the pancreas include mucinous cystic neoplasms and intraductal papillary mucinous neoplasms. As indicated above, some pancreatic cystic lesions may evolve into adenocarcinoma of the pancreas [3].

Since *pancreatic ductal adenocarcinoma* (PDAC) and *pseudopapillary tumors* rarely present as cystic lesions, they are not covered in the present guideline.

Pancreatic pseudocysts, which lack a definite cyst wall, usually occur in patients who have a history of pancreatitis or trauma. Pseudocysts are benign and often resolve spontaneously without any need for intervention, unless they are symptomatic; they are not the subject of the current guideline. However, it is important to ensure that the lesion is in fact a pseudocyst and not a true pancreatic cyst. While the management of benign or obviously malignant lesions is less ambiguous, treatment for indeterminate-risk or intermediate-risk lesions is unclear, and these guidelines will hopefully provide guidance on the appropriate work-up and management.

3 Cystic lesions of the pancreas

Pancreatic cysts are often asymptomatic; they are often benign, but some have malignant potential.

Pancreatic cystic lesions may be classified as:

- *Benign cysts*—e.g., simple cysts, pseudocysts, and serous cystic neoplasms (SCNs)
- *Cysts with malignant potential*—e.g., pancreatic cystic neoplasms (PCNs) such as mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs)
- *Malignant cysts:* neoplastic cysts such as pancreatic adenocarcinomas with cystic degeneration, and cystic pancreatic neuroendocrine tumors

Pancreatic cystic neoplasms may have a malignant potential; these include MCNs and IPMNs. Alternatively, they may have no malignant potential; these include serous cystic neoplasms (SCNs). Benign cystic lesions may be managed conservatively, while those with a significant malignant potential need surgical intervention [4].

Table 1 Clinical features of cystic lesions of the pancreas

Pancreatic cyst type, clinical features	Usual age at initial presentation	Usual location in pancreas	Malignancy rate*
Mucinous cystic neoplasm	40–60 y	Body and tail	10–17%
— Mucin-producing			
— More frequent in women (> 95% female)			
— No/occasional communication with duct			
— Ovarian-type stroma is diagnostic			
Serous cystadenoma	50–70 y	Anywhere (50% body/tail)	< 1%
— Predominant in women (approx. 75% female)			
— Benign, slow-growing			
— Rarely in communication with duct			
— Microcystic variant may have honeycomb appearance and central scar; macrocystic variant appears similar to mucinous lesions on imaging			
— Multiple in von Hippel–Lindau syndrome			
Solid pseudopapillary neoplasm	20–40 y	Anywhere	8–20%
— Uncommon			
— Predominant in women (> 80%)			
— Most benign behavior			

Pancreatic cyst type, clinical features	Usual age at initial presentation	Usual location in pancreas	Malignancy rate*
— Rarely in communication with duct			
— Morphological features: large, mixed solid and cystic lesion			
Cystic neuroendocrine neoplasm			6–31%
— Most nonfunctional			
— Less likely to metastasize			
— May be associated with multiple endocrine neoplasia type 1 (MEN1)			
— Neuroendocrine tumors (NETs) tend to be larger if cystic and smaller if solid			
Intraductal papillary mucinous neoplasm (IPMN)†	60–70 y	Mainly head	
— Typically presents in communication with duct			
—**Branch-duct type** (BD): dilation of one or multiple branch ducts ≥ 10 mm, communication with main pancreatic duct; main pancreatic duct diameter < 5 mm. Approx. 55% female (if BD is dilated but diameter is < 10 mm, defined as "dilated BD")	12–47%		
— **Main-duct type** (MD): duct dilation diameter > 10 mm highly suggestive and 5–9 mm rarely suggestive of malignancy; patient may present with pancreatitis secondary to mucinous main pancreatic duct obstruction	38–68%		
— **Mixed type**: branch duct with > 5 mm dilated main duct	38–65%		
Other cystic lesions			
Retention cyst — Rarely in communication with duct		Mainly head	0%
Pseudocyst — Frequently in communication with duct	40–60 y	Anywhere (65% body/tail)	0%
— More frequent in men (< 25% female)			

* Defined as carcinoma in situ and invasive disease.

† MD-IPMNs and mixed types are more common in males, particularly in Asia. Up to 40% of BD-IPMNs (the majority of incidentally found pancreatic cysts) are multifocal.

The table is mainly based on data from Western countries, which has an impact on the "global" prevalence data [5–9].

3.1 Classification of pancreatic cystic lesions

Table **2** presents the World Health Organization (WHO) histological classification of pancreatic cysts, which also includes solid pseudopapillary neoplasms.

Origin of lesions—relevant to management of precursor lesions:

- From progression of an intraductal papillary mucinous neoplasm (IPMN)
- From progression of a mucinous cystic neoplasm (MCN)

Table 2 Revised WHO histological classification of pancreatic cystic neoplasms

Class	Group	Subgroups	Type
Serous cystic neoplasm (SCN)	1 Serous cystadenoma	a Serous microcystic adenoma	Benign
		b Serous oligocystic adenoma	
	2 Serous cystadenocarcinoma		Malignant
Mucinous cystic neoplasm (MCN)	1 Mucinous cystadenoma		Benign
	2 Mucinous cystic neoplasm	a Low-grade	Borderline
		b High-grade*	Carcinoma in situ
	3 Mucinous cystadenocarcinoma	a Noninvasive	Malignant
		b Invasive	
Intraductal papillary mucinous neoplasm (IPMN)	1 Intraductal papillary mucinous neoplasm	a Low-grade	Borderline
		b High-grade*	Carcinoma in situ
	2 Intraductal papillary mucinous carcinoma	a Noninvasive	Malignant
		b Invasive	
Solid pseudopapillary neoplasm (?)	1 Solid pseudopapillary neoplasm		Borderline
	2 Solid pseudopapillary carcinoma		Malignant

* A two-tiered classification, low-grade versus high-grade, was recommended to replace the former three-tiered classification for pancreatic intraepithelial neoplasm (PanIN), IPMN, and MCN. The former PanIN-2 and intermediate-grade dysplasia IPMN/MCN categories are now to be categorized as low-grade. The term "high-grade" is to be reserved only for the uppermost end of the spectrum—i.e., the most advanced dysplasia. High-grade dysplasia is sometimes referred to as "carcinoma in situ" [3]. Sources: [3,10–13].

3.2 Pancreatic intraepithelial neoplasm (PanIN)

Many would agree that the main difference between IPMN and PanIN is size: PanIN lesions are microscopic flat or papillary lesions that arise in the small intralobular pancreatic ducts, usually measure less than 5 mm in size, very rarely form cystic structures, and are commonly undetectable on cross-sectional imaging or EUS. Maire et al. [14] tried to correlate the EUS findings with histopathology in a selected population. When the lesion is larger than 10 mm, IPMN is the preferred term, while below 10 mm the term "dilated side branch" is appropriate. Doubts have been expressed regarding the histological characterization of lesions between 0.5

and 1 cm. Molecular, genetic, or epigenetic markers may be helpful for differentiating between PanINs and IPMNs [3,14].

3.3 Differential diagnosis of pancreatic cysts

The following list highlights particularly common potentially confusing appearances that need to be considered in the differential diagnosis:

- Chronic pancreatitis, versus intraductal papillary mucinous neoplasms
- Postpancreatitis pseudocysts, versus serous neoplasms, versus mucinous cystic neoplasms
- Serous cystic neoplasms, versus branch-duct intraductal papillary mucinous neoplasms, versus acinar cell cystadenoma
- Solid variants of serous cystic neoplasm (SCN), versus neuroendocrine tumor, versus solid pseudopapillary tumors
- Cystic forms of any solid tumor
- Rare pancreatic or peripancreatic cystic lesions (e.g., epithelial cysts)

4 Clinical presentation

Most pancreatic cysts are *asymptomatic and are discovered incidentally* on diagnostic imaging that is carried out for an unrelated symptom or reason. In a minority of cases, the initial presentation may be due to a symptomatic cyst manifesting as acute pancreatitis, bleeding, jaundice, or palpable mass. In areas of the world in which advanced diagnostic imaging technology is unavailable or is applied with more restricted criteria, pancreatic cystic lesions may be discovered at a later stage, but this usually implies a larger size or progression to neoplasia.

In patients with a *symptomatic cyst,* pain is the most common manifestation. Pain may alert the physician to a greater likelihood for malignancy, except in postpancreatitis pseudocysts, and the risk of malignancy may be related to the duration of symptoms [15,16]. Other symptoms include jaundice, nausea, and vomiting secondary to compression of the stomach, or gastric outlet obstruction secondary to extrinsic compression of the duodenal lumen.

Patients with MCNs may also present with pain, an abdominal mass, or weight loss that may have been present for years before the diagnosis [17]. However, most MCNs are discovered on cross-sectional imaging in otherwise asymptomatic patients.

Patient interview: history and background

- Reasons for consultation
- Demographic parameters
- Family and personal history, including pancreatic diseases (e.g., pancreatic cancer, pancreatitis, diabetes)
- Alcohol use, smoking, drugs, medication
- Body mass index

Potential clinical presentations related to specific types of cyst: it should be noted that most patients with pancreatic cysts are asymptomatic.

Table 3 Types of cyst and potential clinical presentations

Cyst type	Clinical presentations	
Serous cystic neoplasm (SCN)	Symptoms	— Most patients are generally asymptomatic — Large cysts may be associated with abdominal discomfort
	Signs	Large cysts: palpable mass
	Other features	Large cysts: bile duct obstruction, gastric outlet obstruction
Mucinous cystic neoplasm (MCN)	Symptoms	— Most patients are asymptomatic — Abdominal pain, back pain
	Signs	Palpable mass may be present
	Other features	— Recurrent pancreatitis, gastric outlet obstruction — Jaundice and weight loss are more common with malignant lesions
Intraductal papillary mucinous neoplasm (IPMN)	Symptoms and signs	— Mostly asymptomatic — Some patients have symptoms suggestive of chronic pancreatitis, which result from intermittent obstruction of the pancreatic duct with mucus plugs — Manifestations such as back pain, jaundice, weight loss, anorexia, steatorrhea, and diabetes are harbingers of malignancy
	Other features	Some patients have a long-standing history of recurrent acute pancreatitis
Solid pseudopapillary neoplasm (SPN)	Symptoms	— May present with abdominal pain, nausea, vomiting, and weight loss — Other symptoms include gastric outlet or intestinal obstruction, anemia, jaundice, and pancreatitis
	Signs	Palpable mass (most common presenting feature in children)
Neuroendocrine tumors (NET)		— May rarely manifest as cystic lesions — Most are asymptomatic, but symptoms or signs secondary to production of hormone may be present

5 Assessment of cystic lesions

5.1 Introduction

The increasing numbers of patients all over the world with incidentally discovered cysts require further refinement of the recommendations for which imaging should be carried out [6,8].

The approach to pancreatic cysts continues to be problematic, due to the lack of good natural history data, few published studies with long-term follow-up data, and possible bias, since most of the reports are from centers that specialize in the treatment of pancreaticobiliary disorders.

- In general, patients with smaller lesions (< 2 cm) are less likely to be symptomatic, and the lesion is often discovered incidentally.

- Generally, smaller cystic lesions are less likely to present with concerning radiographic features of malignancy (e.g., solid components or ductal dilation) than larger cysts (> 3 cm).
- The prevalence of pancreatic cysts increases with age, in part due to increased radiographic surveillance generally performed in older patients with more frequent comorbidities (such as a personal history of malignancy). In most cases, cystic lesions are therefore detected incidentally when computed tomography (CT) and magnetic resonance imaging (MRI) are performed for other reasons.
- In 95% of the cases, the spectrum of cystic neoplasia includes intraductal papillary mucinous neoplasia (IPMN), mucinous cystic neoplasia (MCN), serous cystic neoplasia, and solid pseudopapillary neoplasia (SPN).
- The risk of malignancy ranges from 0% to more than 60%. Diagnostic procedures therefore aim to distinguish between neoplastic cystic and nonneoplastic cystic lesions, and also between serous and mucinous lesions, as these have different malignant potentials.
- A precise diagnosis is required so that the surveillance or therapeutic strategy can be adapted accordingly. This can be provided by an analysis of the imaging data in combination with biochemical measurements of cyst fluid and clinical features.
- Pancreatic resection should be avoided in patients in whom there is a low probability of malignancy or transformation toward malignancy [6,18,19].

Evolving technologies, such as molecular analysis (molecular markers, genetic testing) with first-line test results (cytology, imaging, and fluid chemistry), may be more accurate in determining the malignant potential of pancreatic cysts than current diagnostic testing methods [20]. To date, however, not all of the available techniques are routinely included in clinical practice.

5.2 Diagnostic approach options

Patients with pancreatic cystic lesions must be evaluated with sensitivity to:

- Potential risks for the patient if misdiagnosed
- Potential risks for the patient of invasive procedures and surgery
- Cumulative costs incurred
- Unknown impact on quality of life—frequent testing, uncertainty of diagnosis, risk of malignant progression, and financial impact

Conventionally, small lesions (< 2 cm) with uncomplicated features require relatively limited diagnostic evaluation and can be managed with observation and follow-up. At the other end of the spectrum, large lesions with a significant solid component or ductal dilation features may be considered for prompt surgery, in order to avoid circuitous and expensive work-up procedures.

The intermediate group of lesions are those in which a careful, in-depth evaluation may be most appropriate, since surgery carries significant morbidity and mortality risks.

5.2.1 Laboratory studies

There are no specific serological tests available for assessing cystic lesions of the pancreas; serum CA-19-9 may be elevated in malignant cystic lesions, whereas raised amylase and lipase

levels are observed in symptomatic cysts with concomitant pancreatitis. See also Tables **4** and **5**.

5.2.2 Imaging studies

Imaging studies are undertaken to obtain better characterization of cysts. The methods used therefore depend on the initial imaging method that detected the lesion in question.

If resources are constrained, the best choice for assessing pancreatic cysts is CT.

Protocol for CT of the pancreas:

- CT is useful for confirming and characterizing cystic lesions that have initially been identified on ultrasound.
- CT scans should be used judiciously in view of the radiation exposure involved, particularly if multiple/repeat imaging is needed.

Protocol for magnetic resonance cholangiopancreatography (MRCP) :

- MRCP is useful for establishing the relationship between cystic lesions and the biliary and pancreatic ducts.
- MRI has the advantage that it does not involve any radiation exposure, while the pancreatic duct can be visualized better. It is helpful for identifying side-branch IPMNs.
- The disadvantages of MRI are: it is probably more expensive; it is not universally available; and it cannot be carried out in patients who have any metal implants in the body. CT is a reasonable option for surveillance if MRI is not available, expensive, or contraindicated.

Endoscopic ultrasonography (EUS) is highly accurate and:

- Provides the option of fine-needle aspiration (FNA).
- Avoids radiation exposure during surveillance. However, it is an invasive procedure.
- It is useful especially if the cyst morphology changes or the patient develops symptoms, so that a repeat FNA can be performed.

Endoscopic retrograde cholangiopancreatography (ERCP):

- Rarely indicated.
- Tissue sampling has a low diagnostic yield (in contrast to EUS).
- There is no established benefit of pancreatoscopy for IPMNs.

Table 4 Indications for EUS

Test	Clinical utility	Positive result	Sensitivity (%)	Specificity (%)	Likelihood ratio
EUS	Evaluation/FNA	Size/mural nodule	75	83	–
Cyst fluid examination	Serous/mucinous	Mucin	78–97	100	–
CEA cyst fluid	Serous/mucinous	< 5 ng/mL	100	86	–
		> 192 ng/mL	73	84	4.56
Cytology	Malignancy risk	Malignant cells	Poor	96	–
		Atypia	72–83	85–88	4.8–6.92

CEA, carcinoembryonic antigen; EUS, endoscopic ultrasonography; FNA, fine-needle aspiration. Adapted from Stark et al. 2016 [5].

5.2.3 Biopsies—cyst fluid analysis

EUS-guided FNA

Fine-needle aspiration can be carried out with EUS guidance for cytological assessment and cyst fluid drainage, in order to distinguish between serous and mucinous lesions. Where available, EUS-guided FNA is the preferred method, in contrast to percutaneous aspiration with CT guidance or ultrasound guidance.

- The level of carcinoembryonic antigen in the cyst fluid can be examined.
- Cytological identification of lesions with a high risk of malignancy is possible.
- There are at present limited data on the evaluation of molecular markers in cyst fluid.

Cytology, smears

Cyst fluid analysis. When fluid is aspirated, the following tests are recommended in the sequence described, depending on the volume of the aspirate:

- Cytology: glycogen-rich cells (SCNs) or mucin-containing cells (MCNs and IPMNs), but the sensitivity is low.
- Tumor markers: CEA level, an accurate tumor marker for diagnosing a mucinous PCN (the accuracy and cut-off level vary among laboratories).
- Diagnostic molecular markers: *KRAS, GNAS, VHL, CTNNB1.*
- Prognostic molecular markers: *TP53, PIK3CA, PTEN.*
- Mucins: assessment of cyst mucin is complementary to cyst CEA levels and cytology [21,22].
- Viscosity: the "string sign" concept [22,23] is an indirect, inexpensive, but subjective measurement of viscosity, assessed by placing a sample of aspirated fluid between the thumb and index finger and measuring the length of stretch prior to disruption. Leung et al. noted median string signs of 0 mm in benign cysts and 3.5 mm in mucinous cysts, and the risk of a mucinous cyst increased by 116% for every 1 mm increase. Confirmatory research is still required.
- Amylase (or lipase).

Table 5 Cyst fluid analysis

Test	Characteristics	Diagnosis
String sign ≥ 1 cm ≥ 1 s	Specificity 95%, PPV 94%	Mucinous
Cytology	Sensitivity 63%	Mucinous versus malignant
Cyst wall cytology	Increase in diagnostic yield by 29%	Mucinous versus malignant
CEA > 192 ng/mL	Sensitivity 75%, specificity 84%	Mucinous
CEA < 5 ng/mL	Sensitivity 50%, specificity 85%	Serous cystadenoma, pseudocyst, NET
Amylase < 250 U/L	Sensitivity 44%, specificity 98%	Excludes pseudocyst

CEA, carcinoembryonic antigen; NET, neuroendocrine tumor; PPV, positive predictive value.

Based on scattered published studies; numbers are subject to change with future data [24–28].

6 Evaluation, management, follow-up

6.1 Risk factors for malignant progression

Assessing the following risk features is helpful in decision-making between the options of observation versus surgery. Patients with at least two of these risk factors have about a 15% chance of developing pancreatic malignancy:

- Lesion size greater than 3 cm: carries a threefold increase in the malignancy risk.
- Presence of mural nodules: carries an eightfold increase in the malignancy risk.
- Dilation of the main pancreatic duct appears to carry a risk of malignant progression, although the data are supported by retrospective studies [29,30].

Other factors may also be predictive of a higher risk of malignancy [31–38]:

- Family history of pancreatic cancer (increases the risk of IPMN)
- Mutations that predispose to pancreatic cancer (particularly *BRCA2*)
- Abnormal blood levels of CA-19-9
- Unexplained acute pancreatitis, especially in patients aged > 50 y
- Recent-onset diabetes mellitus
- Excess weight
- Low serum levels of pancreatic amylase and lipase
- Coarse calcification

In addition, malignancy may develop in the remnant pancreas after partial pancreatic resection for a prior neoplastic lesion, since premalignant changes may be multifocal. There is a 2.8% risk of invasive cancer elsewhere in the pancreas in patients with IPMN, according to Lafemina et al. [39].

The risks of surgery may be substantial, with a 2% risk of mortality and an up to 40% risk of morbidity, and these should be weighed against the malignancy risks assessed relative to the features listed above. Consideration should always be given to the patient's age and comorbidities, as these are crucial risk modifiers.

Table 6 Differentiation of pancreatic cysts relative to high and low risks for malignant progression [5]

Risk for malignancy: features present	Low risk	High risk
Patient is symptomatic	No	Yes
Main pancreatic duct diameter	< 5 mm	≥ 10 mm; worrisome feature if5–9 mm
Lymphadenopathy	No	Yes
Change in the main pancreatic duct caliber	None	Abrupt
Mural nodule present	No	Yes
Enhancing solid component	No	Yes
Thickened walls	No	Yes
Cyst size	< 3 cm; stronger evidence if < 2 cm	≥ 3 cm

6.1.1 Indications for specialist evaluation

Pancreatic cysts may often be incidentally detected on cross-sectional imaging studies ordered as part of the evaluation of nonspecific abdominal or nongastrointestinal symptoms. At this initial discovery stage, a general practitioner, internist, or surgeon may assume the primary responsibility for evaluating the condition.

Uncomplicated cysts that are small (< 2 cm) and do not have any obvious malignant stigmata may not require specialist referral, since observation at the intervals detailed earlier is appropriate.

Table 7 International Association of Pancreatology (IAP) high-risk stigmata and worrisome features [8,40]. See also Fig. **1** and Table **6**

High-risk stigmata of malignancy
• Obstructive jaundice in a patient with a cystic lesion in the head of the pancreas
• Enhancing mural nodule ≥ 5 mm
• Main pancreatic duct ≥ 10 mm in size
Worrisome clinical features
• Pancreatitis
Worrisome imaging features
• Cyst ≥ 3 cm
• Enhancing mural nodule < 5 mm
• Thickened/enhancing cyst walls
• Main duct size 5–9 mm
• Nonenhancing mural nodule
• Abrupt change in caliber of pancreatic duct with distal pancreatic atrophy
• Lymphadenopathy
• Increased serum level of CA-19-9
• Cyst growth rate ≥ 5 mm / 2 years

6.2 Surveillance

Evaluation, management, and follow-up can be carried out with observation and surveillance if the diagnosis has been reliably established.

Serous cystadenomas are uniformly benign. Mucinous lesions, however, are considered premalignant. The risk of malignancy appears to be higher in lesions that are larger than 3 cm at the time of diagnosis, in which surgery is therefore recommended. Smaller lesions may be monitored.

Unfortunately, the ability to reliably differentiate between serous and mucinous lesions preoperatively is limited. Traditional radiologic studies such as CT or ultrasound accurately classify only 10–15% of these lesions in some studies. In addition, the cyst wall is often partly

denuded, so that even intraoperative biopsy is unreliable. Table 7 lists high-risk stigmata and worrisome features.

The size and growth rate of cysts at follow-up examinations can be used as indicators for resection. If there are no worrisome features at MRI/MRCP [41], then MRI should initially be repeated after 1 year and subsequently at 2 years.

- The radiology guidelines advise that surveillance should be suspended after 2 years of stability [42]. The American Gastroenterology Association (AGA) guidelines include a similar recommendation, but after 5 years of stability [43].
- An effective surveillance program has not yet been established for branch-duct IPMNs. The current standard is CT scans alternating with MRCP every 6 months (some have proposed lengthening the screening interval after 2 years of stability).
- The Sendai consensus criteria for prediction of malignancy and the clinical management of branch-duct IPMN were analyzed for accuracy in a recent meta-analysis and showed a pooled sensitivity (from 12 studies) of 56%, with a specificity of 74% [44].
- The Sendai criteria for resection are: clinical symptoms, positive cytology, presence of mural nodules, dilation of the main pancreatic duct (MPD) > 6 mm, and cyst size > 3 cm [45].

Some discrepancies have been noted regarding the way in which surveillance should be managed in patients with premalignant pancreatic cystic lesions. From a systematic review and meta-analysis by Choi et al. [46], it appears that the incidence of progression of low-risk IPMNs (with no main pancreatic duct involvement or mural nodules) to cancer is 1.4% at 3 years, 3.1% at 5 years, and 7.7% at 10 years. The values are higher for IPMNs that have some risk features: 5.7% at 3 years, 9.7% at 5 years, and 24.7% at 10 years. The authors recommend continued long-term surveillance for all types of IPMN [46].

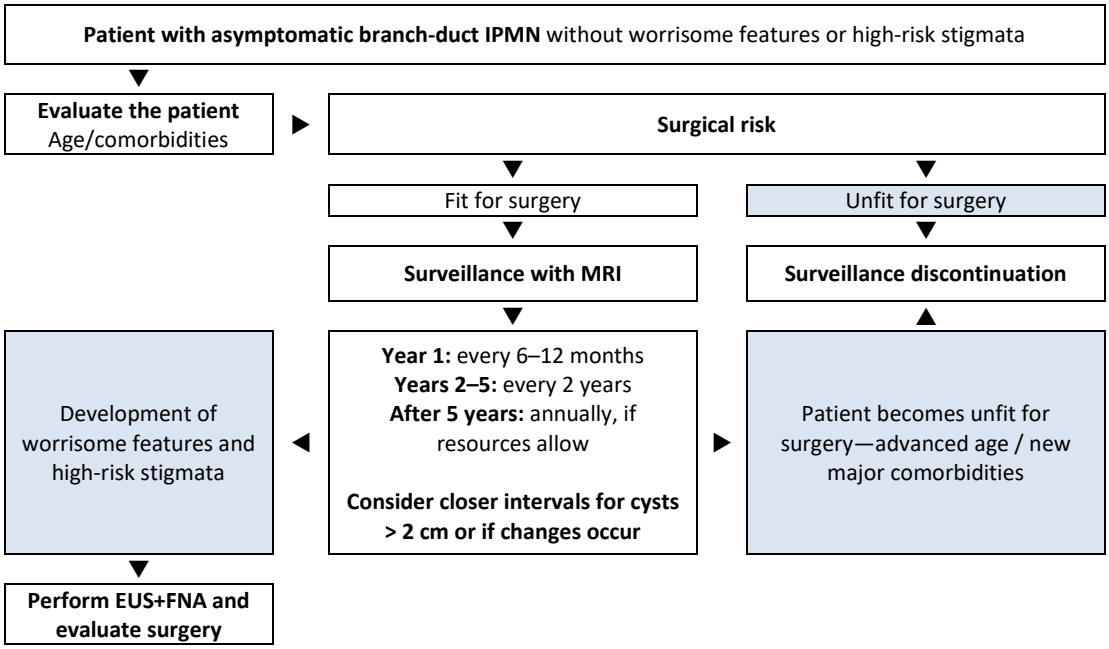

Fig. 1 Surveillance algorithm in asymptomatic branch-duct intraductal papillary mucinous neoplasms (IPMNs) [47].

6.3 Intraductal papillary mucinous neoplasm (IPMN)

Indications for surgery [5,48]:

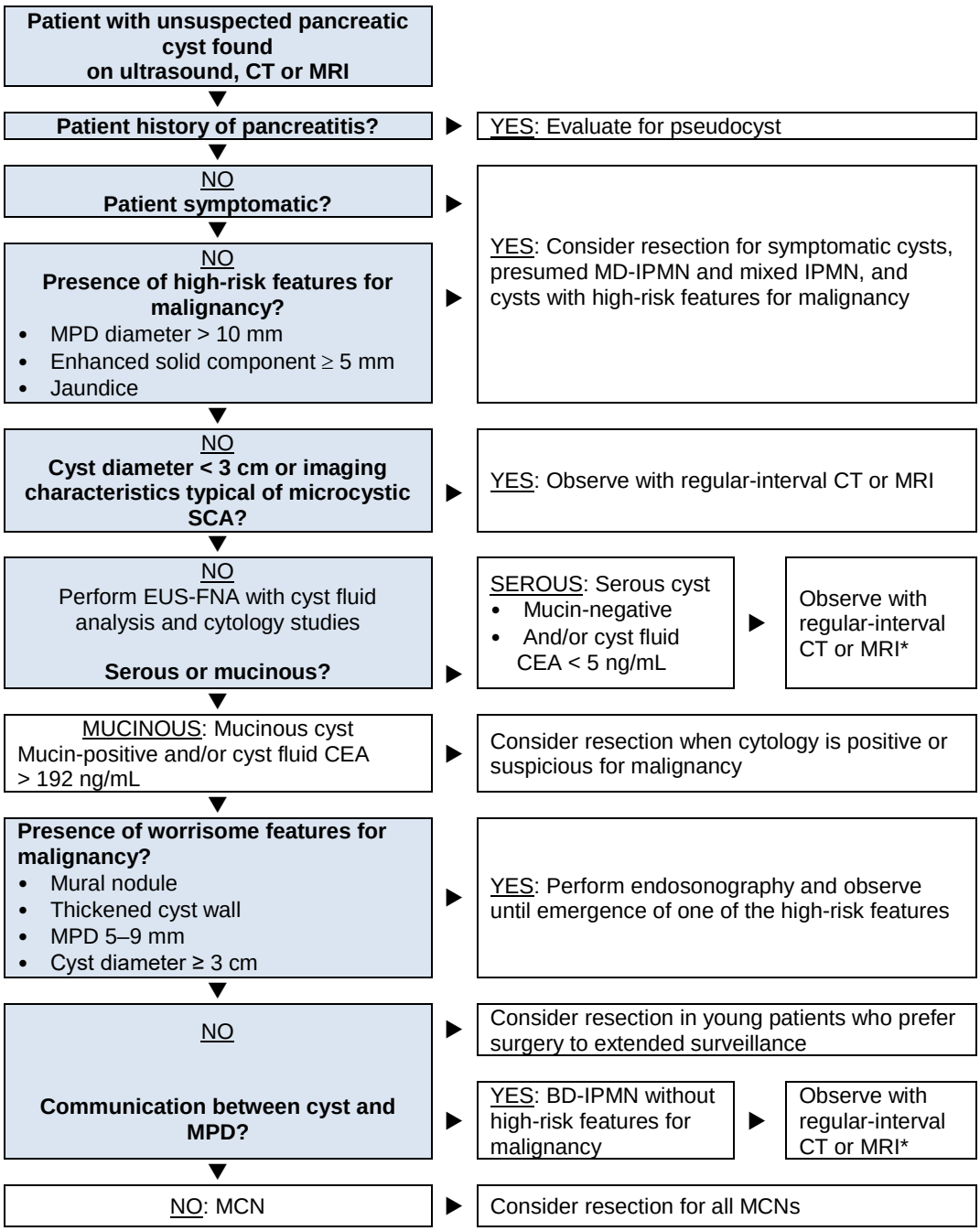

Fig. **2** Proposed strategy for the evaluation and management of a pancreatic cyst [5].
* MRI is recommended (when feasible) to reduce the risks of radiation exposure.
BD-IPMN, branch-duct intraductal papillary mucinous neoplasm; CEA, carcinoembryonic antigen; CT, computed tomography; EUS-FNA, endoscopic ultrasound–guided fine-needle aspiration; IPMN, intraductal papillary mucinous neoplasm; MCN, mucinous cystic neoplasm; MD-IPMN, main-duct intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; MRI, magnetic resonance imaging; SCA, serous cystadenoma.

7 Appendix

7.1 Abbreviations

Table 8 Abbreviations used in this WGO guideline

AGA	American Gastroenterological Association
BD	branch duct
BD-IPMN	branch-duct intraductal papillary mucinous neoplasm
CA-19-9	cancer antigen 19-9
CEA	carcinoembryonic antigen
CT	computed tomography
ERCP	endoscopic retrograde cholangiopancreatography
EUS	endoscopic ultrasonography
FNA	fine-needle aspiration
IAP	International Association of Pancreatology
IPMN	intraductal papillary mucinous neoplasm
MCN	mucinous cystic neoplasm
MD	main duct
MD-IPMN	main-duct intraductal papillary mucinous neoplasm
MEN1	multiple endocrine neoplasia, type 1
MPD	main pancreatic duct
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
NET	neuroendocrine tumor
PanIN	pancreatic intraepithelial neoplasia
PCN	pancreatic cystic neoplasms
PDAC	pancreatic ductal adenocarcinoma
PPV	positive predictive value
SCA	serous cystadenoma
SCN	serous cystic neoplasm
SPN	solid pseudopapillary neoplasm
WGO	World Gastroenterology Organisation
WHO	World Health Organization

7.2 Authors' conflicts of interest reports

First name	Country	Conflicts of interest
Juan Malagelada (Chair)	Spain	None to report
Nalini Guda (Co-chair)	USA	Boston Scientific Corporation

First name	Country	Conflicts of interest
Khean-Lee Goh	Malaysia	None to report
Thilo Hackert	Germany	None to report
Peter Layer	Germany	None to report
Xavier Molero	Spain	None to report
Stephen Pandol	USA	None to report
Masao Tanaka	Japan	None to report
Muhammed Umar	Pakistan	None to report
Anton LeMair	Netherlands	Acting as guideline development consultant for WGO

7.3 Published guidelines

7.3.1 International guidelines

- 2018 Gut. **European evidence-based guidelines on pancreatic cystic neoplasms** [29]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5890653/
- 2018 Am J Gastroenterol. **ACG clinical guideline: diagnosis and management of pancreatic cysts** [49].
- 2017 J Am Coll Radiol. **Management of incidental pancreatic cysts: a white paper of the ACR Incidental Findings Committee** [50]. Available from: https://www.jacr.org/article/S1546-1440(17)30318-6/fulltext
- 2017 Pancreatology. **Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas** [40].
- 2015 Gastroenterology. **AGA guidelines for the management of pancreatic cysts** [43].
- 2015 World J Gastroenterol. **International guidelines for the management of pancreatic intraductal papillary mucinous neoplasms** [51]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4566378/
- 2015 Ann Transl Med [Internet]. **International consensus on the management of intraductal papillary mucinous neoplasm of the pancreas** [45]. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4671873/
- 2013 Dig Liver Dis. **European experts consensus statement on cystic tumours of the pancreas** [52].
- 2012 Pancreatology. **International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas** [8].
- 2006 Pancreatology. **International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas** [53].

7.3.2 Regional and other guidelines

- 2015 J Hepatobiliary Pancreat Sci. **Revised Japanese guidelines for the management of acute pancreatitis 2015: revised concepts and updated points** [54].
- 2015 Gastroenterology. **American Gastroenterological Association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts** [55].
- 2015 Gastroenterology. **AGA Institute guideline on the diagnosis and management of asymptomatic neoplastic pancreatic cysts** [41].
- 2015 Gastroenterology. **AGA guidelines for the management of pancreatic cysts** [43].
- 2015 Ann Oncol. **Cancer of the pancreas: ESMO clinical practice guidelines for diagnosis, treatment and follow-up** [56].
- 2015 Am J Gastroenterol. **ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes** [57].
- 2014 Saudi Med J. **Saudi Oncology Society clinical management guideline series. Pancreatic cancer** [58].
- 2014 RöFo. **S3 guideline for chronic pancreatitis—diagnosis, classification and therapy for the radiologist** [59].
- 2014 Pancreas. **American Pancreatic Association practice guidelines in chronic pancreatitis: evidence-based report on diagnostic guidelines** [60].
- 2014 Jpn J Clin Oncol. **EBM-based clinical guidelines for pancreatic cancer** (2013) **issued by the Japan Pancreas Society: a synopsis** [61].
- 2014 Dig Liver Dis. **Italian consensus guidelines for the diagnostic work-up and follow-up of cystic pancreatic neoplasms** [62].
- 2014 Diagn Cytopathol. **Utilization of ancillary studies in the cytologic diagnosis of biliary and pancreatic lesions: the Papanicolaou Society of Cytopathology guidelines for pancreatobiliary cytology** [63].
- 2014 Diagn Cytopathol. **Postbrushing and fine-needle aspiration biopsy follow-up and treatment options for patients with pancreatobiliary lesions: the Papanicolaou Society of Cytopathology guidelines** [64].
- 2014 Diagn Cytopathol. **Standardized terminology and nomenclature for pancreatobiliary cytology: the Papanicolaou Society of Cytopathology guidelines** [65].
- 2014 Cancer Cytopathol. **Guidelines for pancreaticobiliary cytology from the Papanicolaou Society of Cytopathology: a review** [66].
- 2013 Am J Gastroenterol. **American College of Gastroenterology guideline: management of acute pancreatitis** [67].
- 2012 J Natl Compr Canc Netw. **Pancreatic adenocarcinoma, version 2.2012: featured updates to the NCCN Guidelines** [68].
- 2012 Ann Oncol. **Pancreatic adenocarcinoma: ESMO-ESDO clinical practice guidelines for diagnosis, treatment and follow-up** [69].

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- 2005 Ann Surg Oncol. **Treatment guidelines for branch duct type intraductal papillary mucinous neoplasms of the pancreas: when can we operate or observe?** [71].
- 2004 Gastrointest Endosc. **ASGE guideline: The role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas** [72].
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