



# Diagnostic Approach to Incidentally Detected Pancreatic Cystic Lesions

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## Abstract

*Purpose of review* The objective of this study is to answer few key questions in order to establish the best possible available diagnostic strategy for incidentally discovered pancreatic cystic lesions (PCLs).

*Recent findings* Advances in EUS-guided sampling techniques, cross-sectional and intracystic confocal imaging, molecular biomarkers analysis, determination of cyst fluid glucose, and artificial intelligence, appear to be associated with an improved diagnostic accuracy in distinguishing mucinous from non-mucinous PCLs.

*Summary* The diagnostic process has the aim of recognizing cysts with malignant potential and identifying those with high-risk stigmata and/or worrisome features. Clinicians should avoid performance of unnecessary tests from one side and misdiagnosis from the other, which can easily result in inadvertent surgery of an otherwise benign lesion or malignant progression of a precancerous cyst. Clinical studies to validate recent reported results utilizing novel diagnostic tests are needed, in order to gradually incorporate and combine them into updated guidelines.

## Introduction

Pancreatic cystic lesions (PCLs) include a broad spectrum of entities, which greatly differ in their malignant potential. Among all incidentally discovered PCLs that can undergo malignant transformation or be malignant at presentation, the most frequently encountered are intraductal papillary mucinous neoplasms (IPMNs), while mucinous cystic neoplasms (MCNs), cystic pseudopapillary neoplasms, and cystic pancreatic neuroendocrine neoplasms are infrequently diagnosed. Conversely, inflammatory pseudocysts and the rarely encountered retention cysts, cystic lymphangiomas, duplication cysts, ciliated foregut cysts, or lymphoepithelial cysts have no malignancy potential. Finally, serous cystic adenomas (SCA) are considered

benign entities, even though rare cases of malignant transformation have been described [1].

Widespread use of imaging modalities, such as abdominal ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI), has led, over the last years, to an exponential increase in the incidental detection of asymptomatic PCLs [2, 3]. Proper diagnostic approach is fundamental to distinguish cysts potentially malignant from non-malignant cysts and to guide subsequent management. In the present review, we will answer few key questions necessary to establish the best possible available diagnostic strategy for incidentally discovered PCLs.

## Epidemiological data

Epidemiological data represent the foundation to formulate key questions on how to approach newly diagnosed PCLs. In a recent meta-analysis, pooled prevalence of incidentally discovered PCLs was 8% (95%CI 4–14%), with considerable heterogeneity among different studies ( $I^2 = 99.5\%$ ) [3]. Real-life distribution of pancreatic cyst cases clearly emerges from a prospective Italian registry, which enrolled 1385 consecutive PCL patients. The vast majority (70.1%) had branch duct IPMN, 6.2% mixed-type IPMN, 4.6% main duct IPMN, 12.7% SCA, 2.8% MCN, 1.5% cystic neuroendocrine neoplasm, 0.7% solid-pseudopapillary cystic neoplasm, 0.3% cystic adenocarcinoma, and 1.2% an undetermined cystic neoplasm [4]. Only a small proportion of these patients (5.7%) underwent surgery after the initial workup, suggesting that more invasive workup should be initially limited to a small proportion of incidentally discovered PCLs, with surveillance playing a major role in the majority of them [4]. Based on the above epidemiological distribution, considering that MCNs are rare and with a characteristic localization and female preponderance, a unilocular or oligocystic lesion should be considered a side-branch IPMN until proven otherwise. Looking at surgical series, however, it appears that the number of patients with totally benign unilocular or oligocystic SCA who erroneously underwent surgery is still significant [5–8]. This phenomenon reflects the difficulty in distinguishing mucinous from non-mucinous cysts. Thus, when facing a newly detected PCL, there are some questions that need to be answered:

1. Are the diagnostic imaging studies performed of enough quality to distinguish mucinous from non-mucinous PCLs, and if not, which and when additional tests should be ordered?

2. In case additional tests fail to distinguish mucinous from non-mucinous PCLs, what else should be done to make this distinction more clear?
3. Are the performed tests of sufficient accuracy to rule out presence of high-risk stigmata and/or worrisome features in large unilocular/oligocystic PCLs, once frank malignancy has been ruled out?

## Are the diagnostic imaging studies performed of enough quality to distinguish mucinous from non-mucinous PCLs, and if not, which and when additional tests should be ordered?

Multiple guidelines have been published on the diagnostic approach to PLCs [9–13], but no one has clearly answered this important issue. The answer to this question starts from asking if subsequent imaging modalities would change the decision-making process. When CT/MRI imaging tests disclose presence of multifocal cystic disease, the pre-test probability for a diagnosis of IPMN is extremely high, and unless a large lesion is present, no further diagnostic workup is necessary. This approach can also be adopted for single lesions < 2 cm, where a more appropriate imaging modality, when needed, can be ordered at the subsequent surveillance visit. Conversely, when a > 2 cm lesion is first detected, alone or in the context of a multifocal disease, differentiation between mucinous and non-mucinous disease becomes mandatory. Indeed, association of unilocular SCA in the context of multifocal side-branch IPMN has been described and has occurred multiple times in our experience [14]. Conversely, diagnosis of a > 2 cm IPMN, especially in young/middle-aged patients, will require a more strict surveillance and an attempt to establish a more precise diagnosis.

New advances in cross-sectional imaging have dramatically improved image quality for pancreas evaluation, a fact responsible for the cyst pandemic we are observing [2]. The most important finding to investigate is the presence of communication of the cyst with the main pancreatic duct (MPD), which when present strongly indicate side-branch IPMN [15•]. Endoscopic retrograde pancreatography (ERP), best test to assess this task, has been abandoned because of the high risk for adverse events (AEs). Among imaging studies, new-generation dedicated pancreatic protocol CT and pancreatic MRI/MRCP have similar accuracy for characterization of PCLs, while MRI/MRCP seems more sensitive than CT for identifying communication between PCLs and the pancreatic ductal system [15•]. Moreover, MRI/MRCP is not associated with radiation exposure and therefore should also be utilized for surveillance purposes, making this test the preferred one to first re-evaluate newly diagnosed PCLs, with the characteristics described above.

## In case additional tests fail to distinguish mucinous from non-mucinous PCLs, what else should be done to make this distinction more clear?

Pancreatic cystic lesions, in which a distinction between a mucinous and non-mucinous nature could not be reached by imaging modalities, are defined as indeterminate cysts. At this stage even though more invasive than cross-sectional imaging studies, endoscopic ultrasound (EUS) examination with different acquisition techniques becomes appropriate.

EUS-guided cyst fluid sampling is regarded as a safe diagnostic procedure with an overall morbidity and associated mortality of 2.66% and 0.19%, respectively [16]. The most accurate cyst fluid biochemical marker in differentiating mucinous from non-mucinous PCLs is the carcinoembryonic antigen (CEA). The proposed cutoff value of 192 ng/mL, however, has sub-optimal sensitivity (52–78%) and specificity (63–91%) for making such a differentiation [10, 17]. Conversely, when very low (<5 ng/mL), CEA has 50% sensitivity and 95% specificity for a pseudocyst or SCA, while very high CEA levels (>800 ng/mL) have 48% sensitivity and 98% specificity for mucinous cysts [18, 19].

Glucose determination in the cystic fluid has recently been added, and low levels ( $\leq 50$  mg/dL) are extremely sensitive (88–94%), specific (92–96%), and accurate (90–95%), in identifying mucinous pancreatic cysts [20–22]. In a systematic review and meta-analysis, including eight studies and 609 lesions, intra-cystic glucose determination showed a significantly higher sensitivity (91% vs. 56%;  $p < 0.001$ ) and diagnostic accuracy (94% vs. 85%;  $p < 0.001$ ) in differentiating mucinous from non-mucinous PCLs, compared to CEA [23]. This value can be easily obtained just after cyst fluid collection using a glucometer and combined with CEA levels might bring a slightly more increased sensitivity in differentiating PCLs [20, 24].

Reports of cyst fluid molecular analysis to detect different genetic mutations, protein expression, glycoproteomics, and metabolomic profiling have become available. Multiple studies have evaluated genetic molecular markers associated with identification of different PCL types (Table 1) [25–28], which might become a useful tool to reach a more accurate diagnosis. One of these landmark studies has been published in 2015, where 130 PCL patients prospectively enrolled after EUS-FNA underwent surgical resection. Multiple markers for identification of different cyst types were identified. Absence of a KRAS, GNAS, or RNF43 mutation, or absence of aneuploidy in chromosome 5p or 8p, identified SCAs with 100% sensitivity and 91% specificity. Absence of chromosome 3 loss of heterozygosity (LOH), CTNNB1, or GNAS mutations, or aneuploidy in chromosome 1q or 22q, identified MCNs with 100% sensitivity and 75% specificity. Finally, mutation in either GNAS or RNF43, LOH in chromosome 9, or

**Table 1 Cyst fluid molecular biomarkers tested for the proper characterization of pancreatic cystic lesions**

Type of pancreatic cysts	Predictive cyst fluid molecular biomarkers
Intraductal papillary mucinous neoplasm	KRAS/GNAS mutations (Se 94%, Sp 91%, Acc 97%) [29] GNAS mutations (Se 58%, Sp 100%) [25] RNF43 mutations (Se 38%, Sp 99%) [25] TP53 mutations (Se 9%, Sp 99%) [25] SMAD4 mutations (Se 5%, Sp 100%) [25] CDKN2A mutations (Se 3%, Sp 100%) [25]
Mucinous cystic neoplasm	KRAS/GNAS mutations (Se 30%, Sp 100%) [58] RNF43 mutations (Se 8%, Sp 72%) [25]
Serous cystadenoma	VHL mutations (Se 42%, Sp 100%) [25] LOH chromosome 3 (VHL)(Se 64%, Sp 96.9% [25] VEGF-A > 8500 pg/ml (Se 100%, Sp 97%) [62] VEGF-C > 200 pg/ml (Se 100%, Sp 90%) [62] Both VEGF-A and VEGF-C increased (Se 100%, Sp 100%) [62] VEGF-A > 5000 pg/mL and CEA < 10 ng/mL (Se 95.5%, Sp 100%) [63]
Solid pseudopapillary neoplasm	CTNNB1 mutations (Se 100%, Sp 95%) [25] Aneuploidy of chromosomes 11p or 16p (Se 60%) [25] TP53 mutations (Se 10%, Sp 93%) [25]
Pseudocyst	Negative for DNA [64]
Differentiation of mucinous from non-mucinous	KRAS mutations (Se 47%, Sp 98%) [59] KRAS/GNAS mutations (Se 75%, Sp 99%, Acc 97%) [29] LOH (Se 63%, Sp 76%) [59]
Advanced neoplasia in mucinous cysts	Combination of KRAS/GNAS mutations and TP53/PIK3CA/PTEN alterations (Se 89%, Sp 100%) [58]
Differentiation of malignant from benign cysts	KRAS mutations (Se 59%, Sp 78%) [59] LOH (Se 89%, Sp 69%) [59]

aneuploidy in chromosome 1q or 8p was consistent for IPMNs, with 76% sensitivity and 97% specificity [25].

A recent meta-analysis on six studies and 785 lesions suggested that combination of cyst fluid KRAS and GNAS mutations was accurate for the diagnosis of mucinous cystic lesions and IPMNs, better than CEA [29]. The authors estimated that if cyst fluid KRAS/GNAS mutational testing is negative, post-test probability that the patient has an IPMN or a mucinous cystic neoplasm would be approximately 2% and 8%, respectively [29]. Moreover, in a concomitant study on 1290 patients, addition of molecular analysis to the standard workup improved concordance between preoperative and final histopathological PCLs diagnosis in up to 91% of cases [8].

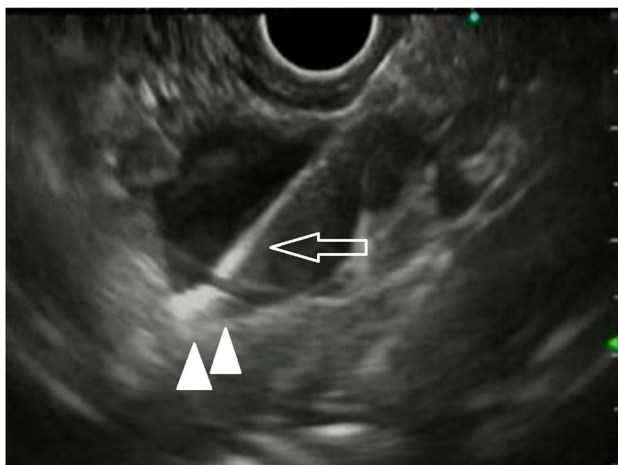
Proteomic profiling on cyst fluid in 91 patients by using mass spectrometry reported significantly differential abundance of 32 peptides and 33 proteins ( $p \leq 0.05$ ) in at least one of the five different cyst type groups, and

19 proteins appeared to be unique to a given cyst type [30]. Nine proteins were found to be differentially expressed in mucinous vs. non-mucinous lesions, and a combination of four of them (AFM, REG1A, LCN2, PIGR) identified mucinous lesions with 81% sensitivity, 90% specificity, and 86% accuracy [31]. Performance of metabolic profiling by untargeted mass spectrometry and quantitative nuclear magnetic resonance in 24 surgically resected specimens reported cyst fluid 5-oxoproline ( $p = 0.01$ ) to differentiate mucinous from non-mucinous PCLs, with 90% accuracy, better than cyst fluid glucose (82% accuracy) [32].

The most recent ACG clinical guideline introduced cyst fluid molecular analysis to be considered in cases of unclear diagnosis to help identify IPMNs and MCNs [9]. However, this was rated as a conditional recommendation, with a very low quality of evidence. We strongly believe that all these tests seem more research tools, with still a limited utility to distinguish unilocular/oligocystic IPMN from SCA or other benign cyst types, a scarce widespread applicability, and costs that remain a major issue to their everyday utilization.

A through-the-needle microforceps biopsy (TTNB) device (Moray™ microforceps, Steris, Mentor, OH, USA), which can be inserted into the cyst through a previously placed 19-gauge needle, has been developed to collect samples from PCLs' wall for histological examination. A meta-analysis on 11 studies and 518 patients reported a 79.6% diagnostic yield and 82.8% diagnostic accuracy [33•], significantly better compared to that of standard cyst fluid analysis. A mean of  $2.47 \pm 0.92$  forceps passes was performed. Interobserver agreement performed among six expert pathologists on the blinded interpretation of TTNB collected biopsy specimens showed a moderate to substantial agreement for the ability to make a specific diagnosis (Gwet's AC1 62%; 95% CI, 57–67%) and substantial agreement (Gwet's AC1, 65%; 95% CI, 59–70%) for differentiating mucinous cysts from all the other diagnoses [34].

One of the main concerns of cyst wall biopsy is the occurrence of adverse events (AEs). In the abovementioned meta-analysis, severe AEs were encountered in 1.1% of cases [33•]. Other non-severe AEs reported in studies were intracystic hemorrhage (26/463 cases, 5.6%) and mild acute pancreatitis (11/463 cases, 2.4%) [35]. In the most recent prospective study, among 101 consecutive PCL patients enrolled in a single academic center, AEs were observed in 10 patients (9.9%) [36•], with acute pancreatitis occurring in nine cases. Four AEs were rated as severe, with one fatal outcome. The procedure changed clinical management in only 11.9% of cases, thus questioning from one side its utility and from the other proper patients' selection. A strategy of perioperative hydration with Ringer's lactate and rectal diclofenac administration was started after the first severe AE, without a statistical reduction in AEs [36•]. The lessons learned from this latter study were that (i) prophylaxis for acute pancreatitis with rectal diclofenac should probably be utilized for EUS-TTNB procedures and (ii) patient selection should be strict and limited to those in whom sampling of cyst walls has a high probability to change their management (Fig. 1).



**Fig. 1** EUS-guided biopsy of the PCL wall using a microforceps (arrowheads) inserted through a regular 19-gauge EUS-FNA needle (arrow)

Virtual histological images of the inner wall of PCLs can be obtained with needle-based confocal laser endomicroscopy (nCLE) (AQ-Flex nCLE miniprobe, Cellvizio, Mauna Kea Technologies, Paris, France). The miniprobe is inserted into the cyst through a standard 19-gauge FNA needle. Its feasibility and safety have been demonstrated by two prospective studies [37, 38•]. In one of this multicenter study including 175 patients with a conclusive diagnosis, the novel developed criteria to distinguish different PCL types showed 95% sensitivity and 100% specificity in differentiating SCAs from mucinous PCLs [37]. Similar nCLE performance has been reported in a study involving 144 patients with suspected PCLs greater than 20 mm, of whom 65 underwent surgical resection [38•]. Sensitivity, specificity, and accuracy were much higher than using combined CEA measurement and cytology determination.

A recent consensus statement established that EUS-guided nCLE improves evaluation of PCLs and has a positive impact on patient management [39]. This technology, however, requires a specific structured training for a competent application and additional aspects, such as procedural costs and assessment of criteria for malignancy need to be defined (Fig. 2).



## Are the performed tests of sufficient accuracy to rule out presence of high-risk stigmata and/or worrisome features in large-sized unilocular/oligocystic PCLs?

Enhancing mural nodules and thickened walls/septa are the findings that need to be searched for when assessing the presence of high-risk stigmata and/or worrisome features in unilocular/oligocystic PCLs [40, 41], once frank malignancy has been ruled out by cross-sectional imaging. In a systematic review including 70 studies and 2297 resected IPMNs, the presence of mural nodules had a positive predictive value for malignancy of 62.2%, revealing a considerable effect of their size on predicting both invasive carcinoma and high-grade dysplasia [42]. The 8 mm cutoff was the most accurate, with a sensitivity of 100% and a specificity of 86% [42]. Performance of high-resolution CT and MRI in recognition of mural nodules and distinguishing between benign and malignant unilocular/oligocystic PCLs seems comparable, as recently reported in a meta-analysis [43], even though other data suggested MRI to be superior than CT [44].

When doubts about the presence of mural nodules and worrisome features on cross-sectional imaging remain, contrast-enhanced EUS (CE-EUS) should be performed because of its ability to distinguish hyperenhancing solid components within PCLs, from non-enhancing mucus plugs [45, 46]. Indeed, in a prospective study on 90 PCL patients, CE-EUS was more valuable for precise identification of mural nodules compared to CT ( $p=0.018$ ) and MRI ( $p=0.033$ ) [47]. Similar results have been found for detection of septal thickness [48]. Pooled sensitivity, specificity, and diagnostic accuracy of CE-EUS for identification of high-grade dysplasia were found to be 88.2%, 79.1%, and 89.6%, in a systematic review including ten studies and 532 patients [49•] (Fig. 3).

Once mural nodules are identified, EUS-FNA seems as a logical next step in order to better classify high-risk cysts. Lim et al. considered mural nodules like a neoplastic lesion and showed a 78% diagnostic yield for EUS-guided fine-needle aspiration (FNA), when more than one needle pass (vs. 44% with one pass,  $p=0.016$ ) was performed [50]. These results were confirmed in another study where cytology was diagnostic in 89.6% of patients with worrisome features, while no diagnostic benefit over radiologic findings alone was found if no such imaging findings were present [51].

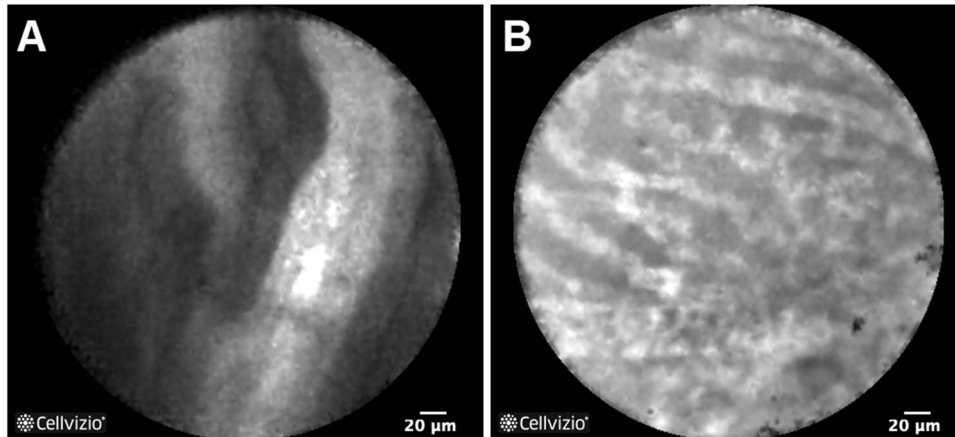
There is, however, no consensus between different guidelines on the use of EUS-FNA in the diagnosis of high-risk PCLs. Two American guidelines (AGA and ASGE) [12, 52] recommend EUS-FNA and use it to direct patients after a high-risk cytology result to surgery, while apparently low-risk lesions can be followed up with no recommendation to perform EUS-FNA. On the other hand, the Japanese guideline does not recommend routinely cyst sampling and address cysts of any size with worrisome features directly to surgery [11]. In comparison with the former, the revised Fukuoka guideline leads to a greater number of benign resections, but fewer missed advanced lesions [53–55]. Perhaps the best approach is the one proposed by the European



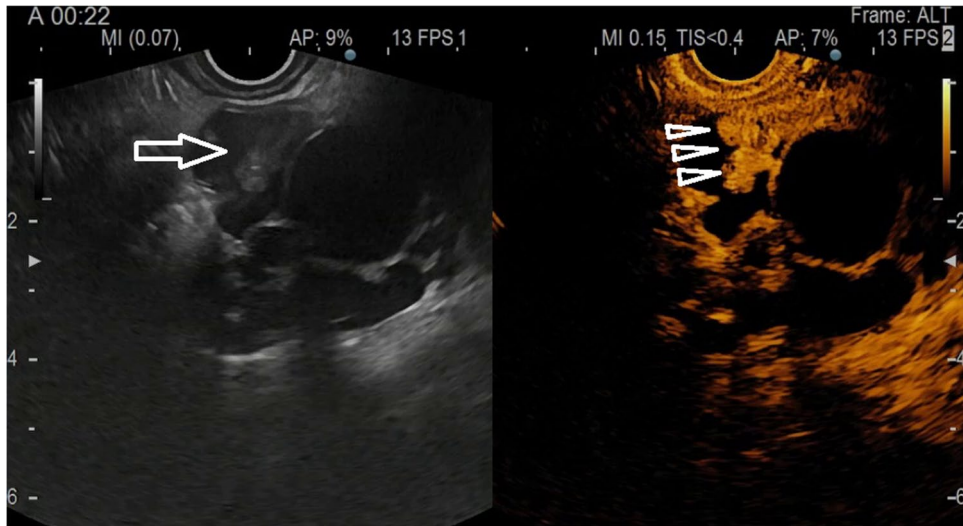
evidence-based guidelines on PCLs, where EUS-FNA was recommended to be carried out after CE-EUS only when the results were expected to change clinical management [10]. In fact, an important drawback of EUS-FNA to take into consideration is the theoretical risk for seeding of malignant cells [56], even though a study showed no difference of peritoneal seeding between 175 resected IPMNs with a preoperative EUS-FNA compared with 68 patients with no preoperative tissue sampling [57]. In our practice, we usually send patients with high-risk stigmata or worrisome features directly to surgery, reserving EUS-guided fine-needle biopsy (FNB) to those with high surgical risk in whom experimental treatments, such as EUS-guided radiofrequency ablation, are offered.

Regarding cyst fluid molecular tests, studies published before 2018 have suggested that detection of certain gene mutations or loss of heterozygosity could be able to differentiate benign from malignant cysts, with high sensitivity and specificity for the presence of high-grade dysplasia or invasive adenocarcinoma [25, 58, 59] (see Table 1). Similar results have been reported for untargeted mass spectrometry and quantitative nuclear magnetic resonance [60].

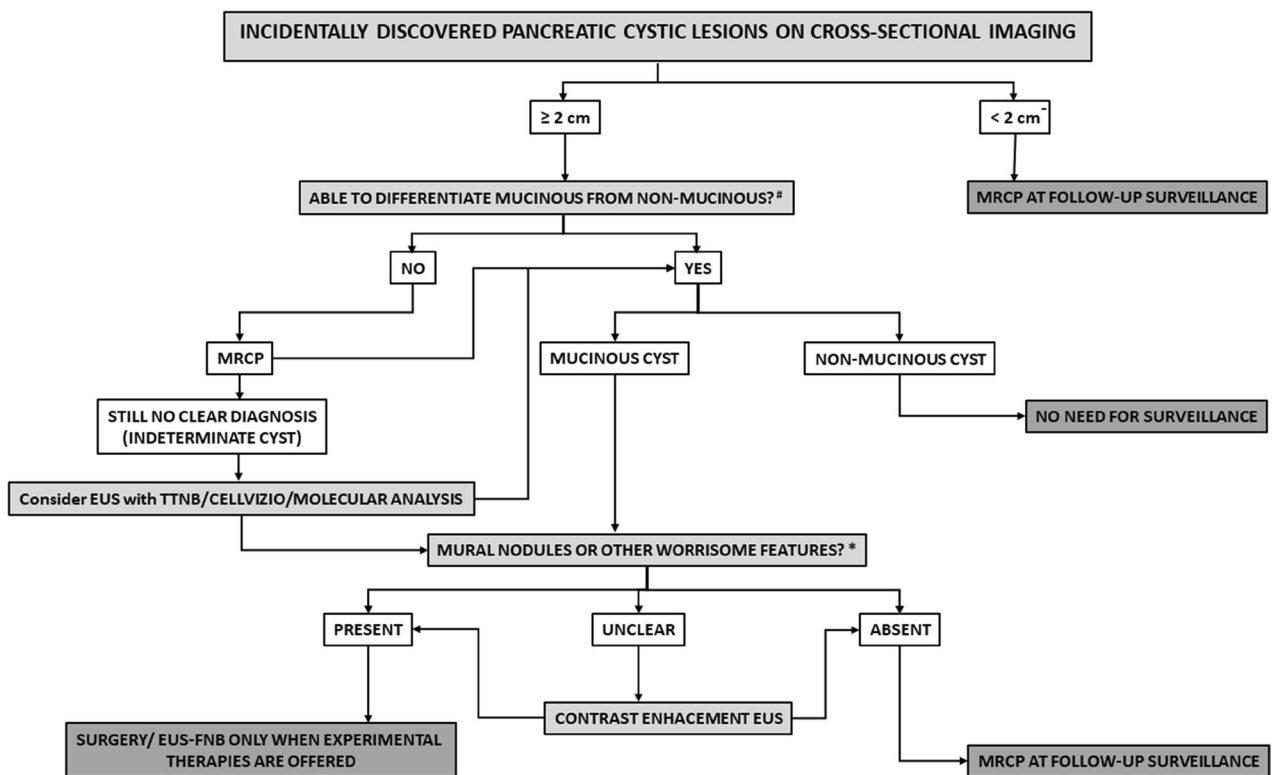
Given the presumed need for multimodal testing, with multiple variables to be computed, artificial intelligence (AI) is expected to play a major role in the proper differentiation of PCLs, as proven by a proof-of-concept study, where AI using deep learning and based on a number of cyst variables predicted cyst malignancy with a sensitivity, specificity, and accuracy of 95.7%, 91.9%, and 92.9%, respectively, much better than any other test [61].



**Fig. 2** Confocal endomicroscopy images from PCLs; **A** branch-duct IPMN (papillae with epithelial border in gray with black fine line in the periphery and white center corresponding to the vascular core filled with fluorescein); **B** serous cystadenoma (tortuous and interconnected vessels with fluorescein appearing white and red cells inside appearing as black points) (courtesy of Bertrand Napoleon MD)



**Fig. 3** Mural nodule continuing as a thick septum in a pancreatic branch-duct IPMN (left panel, arrow) appearing enhanced on CE-EUS examination (right panel, arrowheads)



**Fig. 4** Proposed algorithm for the diagnostic workup of incidentally discovered PCLs; #Mucinous cysts comprise IPMNs and MCNs; \*worrisome features, enhancing mural cyst nodule<5 mm; thickened or enhancing cyst walls or septa; MRCP, magnetic resonance cholangio-pancreatography; EUS, endoscopic ultrasound; TTNB, through-the-needle biopsy; FNB, fine-needle biopsy

## Conclusions

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Increased incidental detection of PCLs, with a potential for harboring or developing malignancy, imposes an accurate baseline diagnostic evaluation strategy to stratify PCL patients into a management decision algorithm (Fig. 4). This process should avoid performance of unnecessary tests from one side and misdiagnosis from the other side, which can easily result in malignant progression of a precancerous cyst or inadvertent surgery of an otherwise benign lesion.

Recent advances in EUS-guided sampling techniques, cross-sectional and intracystic confocal imaging, molecular biomarkers analysis, determination of cyst fluid glucose, and artificial intelligence, appear to be associated with an improved diagnostic accuracy for these lesions. However, better clinical studies to validate these initial results are needed, in order to gradually incorporate these novel tests and combine available tests into future guidelines.

## Declarations

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### Ethics Approval

The paper is in compliance with current ethical standards.

### Conflict of Interest

Dr. Larghi reports personal fees from Boston Scientific and Pentax Medical, grant support from Medtronic, and lecture fees from Taewoong, all outside of the submitted work. Dr. Rimbaş and Dr. Rizzatti have no conflict of interest to declare.

### Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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