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CLINICAL REVIEW

Current indications and yield of endoscopic ultrasound and ancillary techniques in pancreatic cystic neoplasms

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Abstract
An increase in the diagnosis of pancreatic cystic neoplasm has been described lately. Surgical treatment or surveillance is advised depending on the type of lesion diagnosed. The most accurate diagnostic approach is needed to make the best therapeutic decision. Endoscopic ultrasound is a very valuable tool in the evaluation of pancreatic cystic neoplasm. It generates high-quality images and allows the possibility of sampling the cystic fluid for cytology, microbiological and molecular evaluation. Even with this evaluation, the sensitivity of this approach is not always adequate. New technological resources have been developed to try to improve the diagnostic accuracy of pancreatic cystic neoplasms. The two most promising techniques are needle-based confocal laser endomicroscopy and contrast-enhanced harmonic endoscopic ultrasound. Needle-based confocal laser endomicroscopy allows a microscopic evaluation of mucosal glands and vascular pattern, to differentiate mucinous from non-mucinous lesions. Contrast-enhanced harmonic endoscopic ultrasound is used for the vascular evaluation of the microcirculation of the cyst wall and mural nodule, mainly to make the difference between malignant nodules and mucus plugs. A combination of these different diagnostic techniques can improve the diagnostic accuracy of pancreatic cystic neoplasms to offer the adequate therapeutic decision.

Keywords Pancreatic cystic neoplasm · Endoscopic ultrasound · Fine-needle aspiration · Endomicroscopy · Contrast-enhanced harmonic endoscopic ultrasound

Introduction

Pancreatic cystic neoplasms are lesions that lately have been diagnosed more frequently. As a consequence of an increased use of cross-sectional imaging studies [magnetic resonance imaging (MRI) and computed tomography (CT) scan], a greater number of patients with asymptomatic pancreatic cysts are diagnosed. The prevalence of detection of these lesions has been reported in up to 19.6% of cross-sectional abdominal scans [1]. A pancreatic cyst neoplasm can be found in 25% of autopsies, 16% with atypical epithelium and 3% with in situ carcinoma [2]. Studies have shown that once a pancreatic cystic neoplasm has been diagnosed, the risk of malignant transformation is 0.24% per year [3]. Only 1 in every 10,000 cystic lesions diagnosed incidentally are invasive neoplasms [4], but some of these lesions have a higher risk of malignant transformation. Since the life expectancy of pancreatic cancer at 5 years is less than 5%, with the prognosis of cystic carcinomas not much different from pancreatic ductal adenocarcinoma, finding and treating adequately a potential cystic precursor of cancer is currently one of the only available avenues to improve pancreatic cancer outcome [5].

Many different types of pancreatic cystic neoplasms have been described, but five of them are the most frequently found. Intraductal papillary mucinous neoplasm (IPMN) is the most frequent, with serous cystadenomas (SCA), mucinous cystadenomas (MCA), cystic neuroendocrine tumors, and solid pseudopapillary neoplasms following suit. Since the risk of malignant transformation is different in each group, an adequate classification of each lesion is of paramount importance.

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Serous cystadenomas are cuboidal cells pancreatic neoplasms, often composed of multiple microcysts (defined as cysts measuring less than 2 cm), presenting with honeycomb pattern or a "cluster of grapes" [6–8]. A central calcification is pathognomonic, but only found in 20% of the cases. The risk of malignant transformation is estimated at 0.11% [9]. Time span for malignant transformation is difficult to predict, as only 25–30 of serous cystadenocarcinomas have been reported in the literature [10]. Some SCA present as purely macrocystic or exceptionally as pseudosolid lesions, with very densely arrange microcysts [11]. Hereditary predisposition to develop this type of cysts is seen in Von Hippel–Lindau syndrome. Hemangioblastomas, pheochromocytomas, clear cell renal carcinoma, as well as pancreatic, renal and hepatic cysts are features of this syndrome [12]. Between 35 and 70% of patients with this syndrome develop pancreatic SCA [13].

Mucinous cystadenoma is a mucin-producing cystic lesion, composed of a columnar epithelium with an ovarian-like stroma, the reason why it is almost exclusively diagnosed in women in their middle age [14, 15]. They are either multi- or unilocular macrocystic lesions, and exclusively located in the pancreatic body and tail. A mural nodule or a peripheral calcification, are features that can help make the diagnosis. Thin small cystic septation or mural cyst found on EUS, are typical features of mucinous cystadenomas [16]. The risk of malignant transformation is between 0 and 33%, and this risk is higher in tumors larger than 4 cm and with mural nodules [14]. In lesions smaller than 4 cm, invasive carcinoma is found only in 0.03% of the cases [17]. Time span for malignant transformation is difficult to define, since guidelines recommend surgery in all diagnosed mucinous cystadenomas. Interestingly, in a series of 163 resected mucinous cystadenomas, malignant tumors were found to be 5.5 years older than patients with adenomas. Importantly patients with invasive carcinoma were 11 years older than those with non-invasive mucinous cystadenomas [18].

Intraductal papillary mucinous neoplasms (IPMN) are cysts composed of mucin-producing cells, that originate from a pancreatic duct [8, 19, 20]. Three variants are described: main-duct IPMN bears a risk of malignant transformation of 50%, whereas branch-duct IPMN has a lower risk of malignant transformation of less than 17%. They have an estimated risk of malignant transformation of 2–3% per year [21, 22]. The third type, mixed IPMN, involves both main-duct and branch-duct neoplasms, and bears a risk of malignancy similar to main-duct type [20]. Since IPMN is by far the commonest incidental finding and has one of the highest risks of malignancy, it has been the subject to many recent investigations of risk factors, which have been detailed below.

Solid pseudopapillary neoplasm is a low-grade malignant lesion, composed of branching papillary clusters with fibrovascular cores [23]. They are frequently presented as a solid lesion in its early stages of development. It is composed of pseudopapillary structures with necrotic-hemorrhagic content and becomes cystic while increasing in size [24]. It is almost exclusively found in young women in their second and third decade [8].

Pancreatic neuroendocrine tumors (NETs) are mainly solid, but 17% of resected NETs have a cystic component [25]. Most of them are non-functional and discovered either incidentally or during the evaluation of patients with known multiple endocrine neoplasm type 1 (MEN-1) [26]. Radiological appearance is variable. Pancreatic neuroendocrine cysts with septations or solid components have been described in about 30% of the cases [27]. The behavior of these lesions seems to be less aggressive than solid pancreatic neuroendocrine neoplasms [26]. Cystic NETs have a 20% risk of malignancy, with small lesions usually harboring an indolent behavior [28]. Observation instead of surgical resection has been proposed for lesions smaller than 20 mm in diameter [29]. Interestingly, a more aggressive behavior has been described in functional cystic neuroendocrine tumors, probably because of higher incidence of MEN-1, compared with non-functional lesions [30, 31].

The treatment is individualized depending on the type of pancreatic cystic neoplasm that has been diagnosed. An adequate classification of the lesion is crucial, because treatment involves surgery in most cases. Pancreatic surgery is a high-risk procedure. In a meta-analysis of hospitals with a high volume of pancreatic surgery, mortality and morbidity due to surgical resection are 2.1% (1.5–2.7% CI 95%) and 30% (25–35% CI 95%), respectively [3].

Serous cystadenomas should be managed surgically only in symptomatic patients, because of their low risk of malignant transformation. Symptoms are uncommon and can include abdominal pain, jaundice and gastrointestinal obstruction. Symptoms are mostly dependent on size [15]. In one study, 72% of cysts of more than 4 cm, presented symptoms, compared with only 22% of the cases in patients with cysts of less than 4 cm [32]. In the absence of symptoms, no surveillance is recommended for SCA.

Mucinous cystadenomas, main-duct IPMN, solid pseudopapillary neoplasms and cystic pancreatic endocrine neoplasms should all be managed surgically. Because of their higher risk of malignant transformation, a surgical resection is advised once an adequate diagnosis has been done [18, 24]. However, small MCAs of less than 40 mm have recently been found to have a low risk of malignancy and can be submitted to surveillance instead of resection [17, 33].

Branch-duct IPMN management should be individualized. Branch-duct IPMN has an intermediate risk of malignant transformation. Guidelines to follow up these lesions have been developed and reported initially after a consensus meeting in Sendai, Japan, in 2006, and subsequently in the

Fukuoka Guidelines in 2012 [34, 35]. Surgical resection or follow-up approach is decided depending on the presence of worrisome features and/or high-risk stigmata (Table 1). In patients with worrisome features (pancreatic duct dilation between 5 and 9 mm, non-enhanced mural nodule, a cyst larger than 3 cm or an abrupt change in the duct diameter with pancreatic atrophy), an endoscopic ultrasound evaluation followed by surgery or further follow-up depending on findings, is advised. In patients with high-risk stigmata (pancreatic duct dilation of 10 mm or more, enhanced mural nodule, or jaundice), surgical resection is advised.

Since treatment should be individualized depending on the type of cystic lesion that we are evaluating, the most accurate diagnosis should be done with the diagnostic tools that we have available.

Cross-sectional imaging

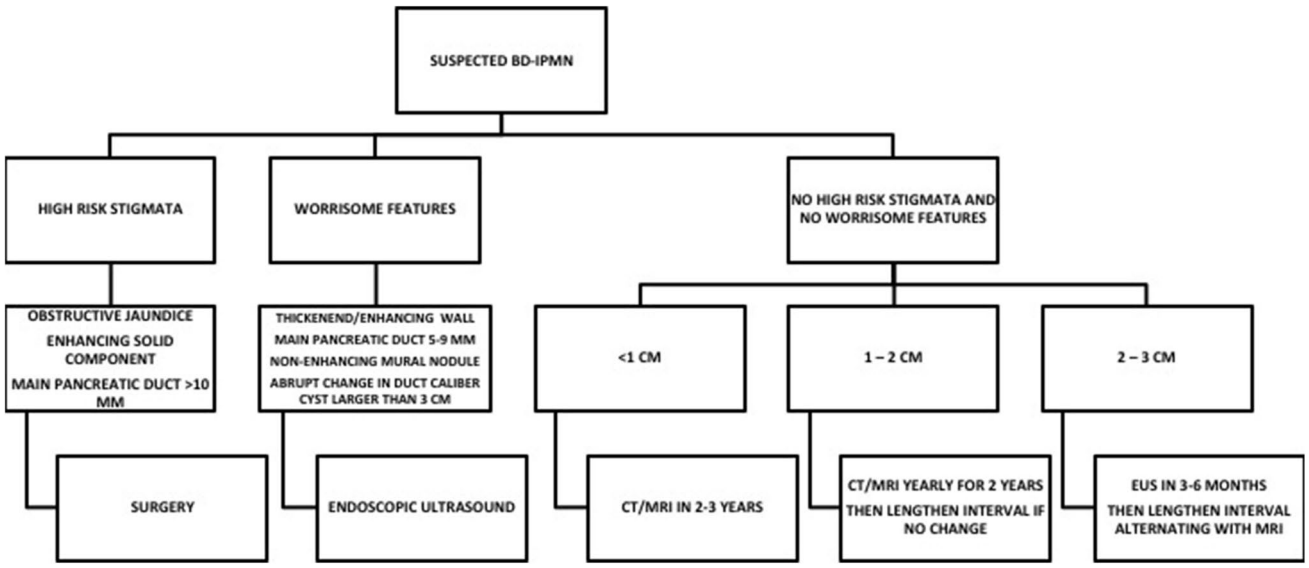
New advances in radiology have improved dramatically the quality of the images obtained for evaluation of the pancreas. Most of the pancreatic cystic neoplasms are diagnosed incidentally during cross-sectional imaging studies. Multidetector computed tomography (MDCT) is probably the most widely used and available imaging study for the evaluation of pancreatic cystic neoplasms. On the other hand, MRI with magnetic resonance cholangiopancreatography has the advantage of a better resolution of the soft tissues, the possibility of evaluating the relation of the cyst with the pancreatic duct and the absence of exposure to radiation [36]. For predicting main pancreatic duct communication, MRI has a sensitivity of 91.4% and specificity of 89.7% [37]. The frequency of detecting pancreatic cysts is higher with MRI than with CT scan (19.9% vs 2.6%) [1, 38]. Studies comparing MDCT vs MRI for an adequate classification of the pancreatic cystic neoplasms have shown no significant difference [39]. They have equivalent accuracy for characterizing benign and malignant pancreatic cystic neoplasms [40]. Another study showed that for predicting malignancy MDCT has a diagnostic accuracy of 61.4%, but this improves to 80.5% when MDCT and MRI are combined [41].

Endoscopic ultrasound

Endoscopic ultrasound (EUS) has been a very important tool in the evaluation of pancreatic cystic neoplasms since the 1980s. Not only the utility of high-quality imaging, but also the possibility of sampling the cystic fluid during fine-needle aspiration (FNA) makes EUS an irreplaceable method to investigate and follow up pancreatic cysts. New ancillary techniques have been developed recently that have improved the diagnostic accuracy of EUS for pancreatic cystic neoplasms. The two most important new advances are the use of needle-based confocal laser endomicroscopy and contrast-enhanced harmonic endoscopic ultrasound (CH-EUS).

The utility of EUS imaging for the evaluation of pancreatic cystic neoplasms has been evaluated. It has very good image resolution because of technical improvement during recent years and due to the contiguity of the stomach and duodenum with the pancreatic parenchyma. It provides important information regarding cyst size, septations, wall thickness, cyst contour, duct communication or dilation, and the presence of nodules. Nevertheless, EUS diagnosis based exclusively on imaging is not highly accurate for the

Table 1 Algorithm for the management of suspected BD-IPMN



classification of pancreatic cystic neoplasms. Diagnostic accuracy between 50% and 75% for EUS imaging without FNA, has been reported [42, 43]. This improves dramatically with cystic fluid analysis, which will be discussed afterwards. The only type of pancreatic cystic lesion which can be characterized adequately with some certainty based exclusively on imaging is pancreatic SCA [43]. It is well-known that the results of EUS are operator dependent. Studies that have evaluated the interobserver agreement of EUS cyst features showed a poor to moderate level of agreement. The results were better for detection of nodules, pancreatic duct communication and suspicion of malignancy [43, 44].

When compared with cross-sectional imaging studies, EUS has a sensitivity of 88%, specificity of 53% and diagnostic accuracy of 70.4% to predict neoplastic cysts. On the other hand, CT scan has a sensitivity of 83%, specificity of 70% and diagnostic accuracy of 61%, but we have seen that the combination of MDCT and MRI may yield slightly better accuracy than EUS imaging alone for neoplastic cyst diagnosis [41]. Kim et al. showed no difference in the characterization of pancreatic cystic lesions and prediction of malignancy when comparing EUS and MRI [45]. Even though there is no difference in diagnostic accuracy, EUS imaging has a better accuracy for the detection of multifocal lesions when compared with CT scan (47% vs 13% $p < 0.0001$) and MRI (58% vs 34% $p < 0.0002$) [46]. Additionally, EUS is better than MDCT and at least equivalent to MRI for the identification of one determining feature of IPMN, the communication between the cyst and the main duct [45].

One of the most important strengths of EUS for the evaluation of pancreatic cystic neoplasms is the ability to differentiate mural nodules from mucin accumulation. Smooth borderline and hyperechoic rim are suggestive of mucin plug (Fig. 1), whereas irregular border without a rim are suggestive of a mural nodule (Fig. 2) [47]. Studies have evaluated the utility of mural nodule detection as a predictor of malignancy [48]. One of them showed an odds ratio of 9.3 in favor of malignancy [49]. The size of the mural nodule can also be measured as a predictor of malignancy. Hinoro et al. analyzed predictors of malignant behavior of branch-duct IPMN. In their multivariate analysis, mural nodule size over 5 mm was an independent factor associated with malignancy [50]. Shimizu et al. in their multivariate analysis of pathological diagnosed IPMN describe that nodules larger than 7 mm had a sensitivity and specificity for malignant diagnosis of 74.3% and 72.7%, respectively [51].

The indications for EUS evaluation should be based on guidelines. Two different groups have established the utility of EUS in the work-up of pancreatic cystic neoplasms. The Fukuoka Guidelines were developed in 2012 to establish the management of IPMN and mucinous cystic neoplasms of the pancreas. This group recommends EUS evaluation in all patients with IPMN cyst with "worrisome features",

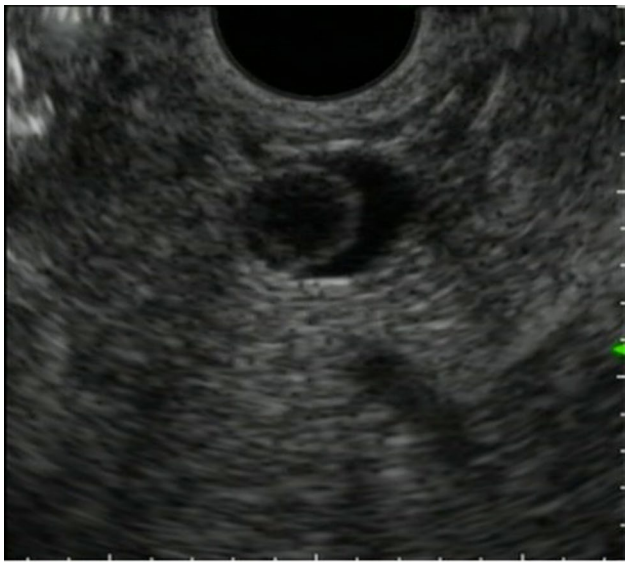


Fig. 1 Pancreatic cyst with nodule. Smooth borderline with hyperechoic rim is suggestive of a mucin plug

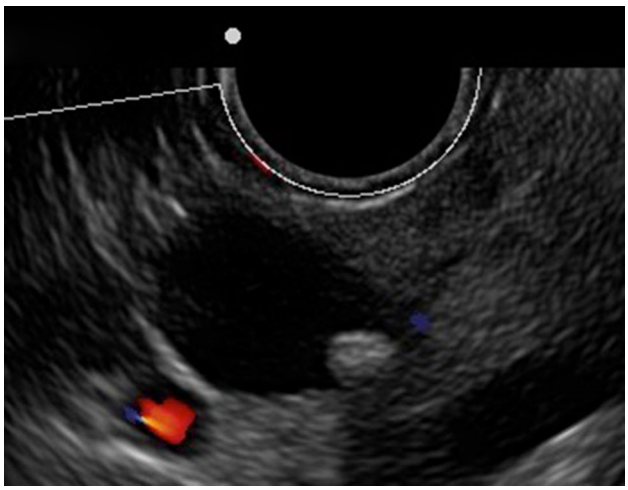


Fig. 2 Pancreatic cyst with nodule. Irregular border without a rim is suggestive of a mural nodule

meaning a cyst larger than 3 cm, thickened enhanced cyst walls, main pancreatic duct size of 5–9 mm, non-enhanced mural nodules, abrupt change in the main pancreatic duct caliber with distal pancreatic atrophy and the presence of lymphadenopathies. In patients with a cyst between 2 and 3 cm in size, surveillance is recommended every 3–6 months with MRI alternating with EUS [35].

The American Gastroenterological Association published their own guidelines in 2015. The objectives of these guidelines were different, as they were developed for the diagnosis and management of asymptomatic pancreatic cysts, regardless of the type of cyst under evaluation. They define

high-risk features as size larger than 3 cm, a dilated main pancreatic duct or the presence of an associated solid component. They recommend that all patients with cysts with at least two high-risk features should be examined with EUS-FNA [4]. This recommendation was based on studies that showed that a cyst larger than 3 cm increased the risk of malignancy approximately 3 times and the presence of solid component increased the risk of malignancy 8 times [3]. As well, they established this recommendation as a conditional recommendation with very low-quality evidence [4].

When surveillance is decided, complete evaluation of the pancreatic parenchyma should be done during follow-up evaluations. Studies have shown a risk of developing cancer as high as 20% during follow-up [52, 53]. Synchronous occurrence of IPMN and ductal carcinoma has been reported. Studies have shown a risk of pancreatic cancer development between 2 and 8% separate from the index cystic lesion during surveillance [54, 55]. Even after resection, periodic evaluation is advised since new cystic lesions can develop in 20% of the cases and cancer in 2% of this group of patients [56].

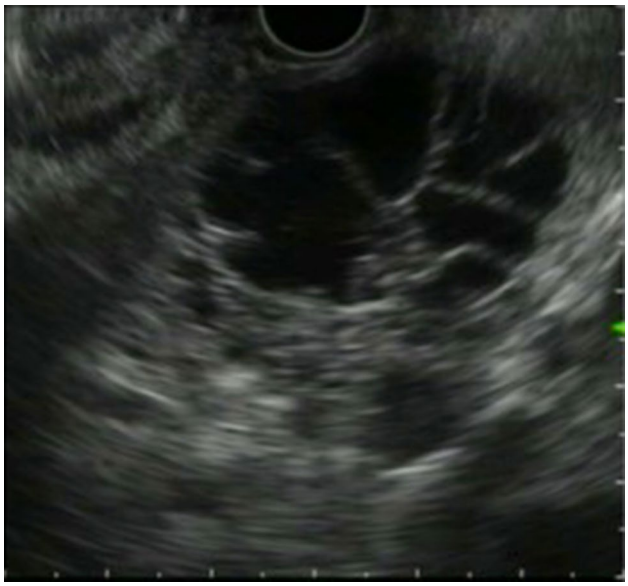


Fig. 3 Pancreatic cystic neoplasm. Endosonographic evaluation of morphological features

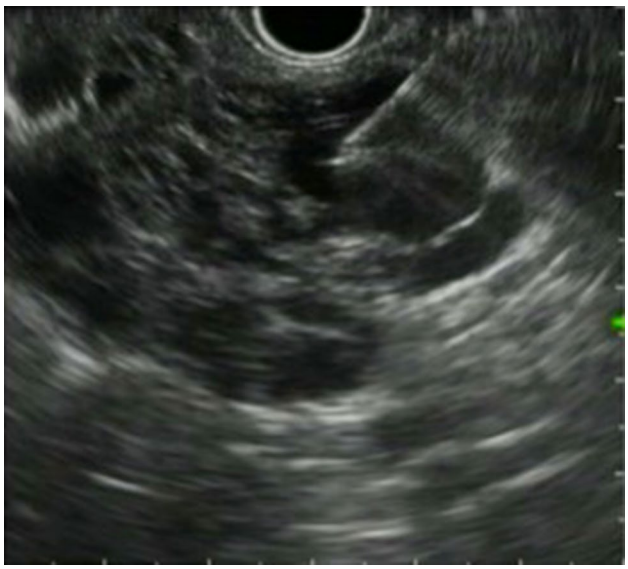


Fig. 4 Endoscopic ultrasound fine-needle aspiration with cystic fluid analysis

Cyst fluid analysis

One of the most valuable features of EUS is the possibility of obtaining fluid for microbiological, cytological and DNA evaluation. FNA is a low-risk procedure, with complications of pancreatitis, bleeding and infection ranging from 0 to 2.5% of the cases [57]. Most adverse events are reported to be mild to moderate in severity [58]. Prophylactic antibiotics are recommended before FNA of a cystic lesion, in contrast to solid pancreatic lesions [59].

Many different types of needles have been developed to sample either fluid or solid components of a cystic lesion. Size ranges from 19 to 25 gauges. When deciding upon which needle to choose, it is important to take account of the location of the cyst, due to the known limitation to access the uncinate process, as well as the potential viscosity of the fluid.

FNA may improve the diagnostic accuracy when compared with imaging techniques (Fig. 3). In a study of patients who underwent surgical resection, EUS with cyst fluid analysis improved the diagnostic accuracy in 36% when compared with CT scan diagnosis and in 54% when compared with MRI diagnosis (Fig. 4) [60].

A number of biomarkers have been studied for the evaluation of pancreatic cystic neoplasms. Carcinoembryonic antigen (CEA) is the most widely used marker to differentiate mucinous from non-mucinous cystic lesions. It is important to point out that high levels of CEA (i.e.,> 200 ng/ml) are predictive of mucinous lesions, but not of malignancy [11].

The threshold for non-mucinous cystic lesions is less than 5 ng/ml and for mucinous cystic lesions is more than 192 ng/ml. Values between 5 and 192 ng/ml are classified as indeterminate. A meta-analysis showed that CEA has a high specificity of 88%, but a low sensitivity of 63% for the diagnosis of mucinous lesions [61].

Cystic fluid cytology is highly specific but has a very low sensitivity. The lack of the necessary cellularity for cytologic diagnosis, is the cause for its inadequate sensitivity. In the

same meta-analysis that evaluated CEA diagnostic value, the specificity for cytology was 93%, but once again a low sensitivity was found (54%) [61]. If mucin is detected, this finding predicts the presence of a mucinous cystic lesion. But, mucin is only found in 30% of mucinous lesions and mucin dosage is difficult to standardize and is poorly reproducible. Glucose measurement in cystic fluid has recently been proven as a valuable marker to differentiate between mucinous and non-mucinous lesions. Glucose levels are significantly increased in serous cystadenomas [62]. On the other hand, glucose level below 50 mg/dl has a sensitivity of 95% and a specificity of 57% for the diagnosis of mucinous lesions [63].

In recent years, molecular markers have been evaluated for the diagnosis of malignant cysts. Such tools have been commercially available since 2008. A multicenter study found that *k-ras* mutations, followed by loss of heterozygosity (LOH) have 96% specificity for malignancy detection, but only 19% sensitivity [64]. *GNAS* can also be studied in cyst fluid and is an early predictor of IPMN progression [65]. Vascular endothelial growth factor (VEGF) has also been described as an accurate molecular marker for the diagnosis of pancreatic serous cystadenoma. VEGF-A is overexpressed in SCA. Sensitivity and specificity of 100% and 97%, respectively, have been described [66, 67].

However, there is no difference when comparing molecular markers with CEA level evaluation in terms of prediction of malignancy. The most important utility of DNA evaluation is when cytology is non-diagnostic, CEA level is indeterminate or only a small amount of fluid can be obtained during FNA [68].

Needle-based confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is a laser-assisted microscopic imaging system. It provides real time histopathology images of the tissue under evaluation. For an adequate evaluation of the tissue structure, fluorescein stain is needed. It allows a microscopic evaluation of mucosal glands and the vascular patterns. A needle-based miniprobe was developed for endoscopic ultrasound use. This is a 0.85 mm probe that can pass through a 19-G FNA needle, for real time histopathology evaluation of pancreatic cystic neoplasms epithelium [69]. This technique was initially evaluated on a porcine model for the evaluation of intra-abdominal organs in 2010 [70]. The first experience in humans was reported in 2011 by Konda et al., evaluating the feasibility of needle-based CLE (nCLE) during EUS-FNA of pancreatic lesions [71].

Three clinical trials have evaluated this new technology. The INSPECT, DETECT and CONTACT studies have provided important information about the utility of nCLE for pancreatic cystic neoplasms' evaluation.

The INSPECT study evaluated pancreatic cystic neoplasms, regardless of the type of cyst. As with other diagnostic techniques, nCLE had a high specificity (100%), but a low sensitivity (59%) for mucinous cystic neoplasms (MCA or IPMN), determined by the presence of epithelial villous structures. The most important conclusion was that the presence of a villous or finger like structure was suggestive of IPMN [72].

The DETECT study found a high specificity (100%) and a better sensitivity (80%) for the diagnosis of mucinous lesions. In this study, the combination of a direct endoscopic visualization of the inner cyst wall using the Spyglass™ fiber optic system, improved the sensitivity to 100% in a small number of patients with indeterminate cysts. The quality of the images was considered good in 90% of the cysts [73].

The CONTACT study evaluated the diagnostic yield of nCLE for serous cystadenomas. A "superficial vascular network" has been defined as the typical feature for serous cystadenomas, with a sensitivity of 69%, a specificity of 100%, and a diagnostic accuracy of 87% [74].

It is important to point out that this new technique is not free of complications, with acute pancreatitis being the most frequently reported, in 3–6.6% of the cases. The duration of the procedure and intracystic movement of the probe have been proposed as possible causes of this increased risk, compared with standard FNA [75]. The technical feasibility of this procedure could be limited in patients with a cyst in the uncinated process, due to the known limitation of introducing a 19-G needle into the pancreas through the second part of the duodenum [76].

Contrast-enhanced harmonic endoscopic ultrasound

Contrast-enhanced harmonic EUS (CH-EUS) is an ultrasonographic technique that uses a microbubble-based contrast agent (Sonovue™ or Sonazoid™) to visualize vascularization and perfusion patterns in the liver, pancreatic parenchyma or lymph nodes [77]. This device has been available for EUS for the last 10 years [78]. Harmonic components of the signals from injected microbubbles, improve the evaluation of the microcirculation, without the Doppler-related artifacts [79]. It can also be used for the evaluation of pancreatic cystic neoplasm allowing a vascular evaluation of cyst walls or more importantly mural nodules. The most important issue when evaluating a mural nodule is to distinguish the difference between mucus clots, necrotic tissue and real neoplastic mural nodules.

A recent study comparing contrast-enhanced harmonic EUS with fundamental B-mode EUS (FB-EUS), found that CH-EUS was more accurate than FB-EUS for detecting true mural nodules (84% vs 64%, $p = 0.0001$). The sensitivity in this study was 97% vs. 97% and specificity was 75% vs. 40%, respectively [80]. A mural nodule of more than 4 mm of height on CH-EUS was a sign of malignancy (0dds ratio 15.17), compared with 8 mm in nodules evaluated with FB-EUS (Odds ratio 56.0) [80].

Malignant nodules from pancreatic cystic neoplasms present an isovascular enhancement pattern of the solid component. This advanced technology could prevent the need for FNA in case of mucus plugs and indicate direct FNA of potential neoplastic areas [81]. On the other hand, this last study showed no difference between SCA and MCN when the cystic lesions were evaluated with CH-EUS.

Three features are analyzed during the CH-EUS evaluation. First, the degree of enhancement (hypo-, iso- or hyperechoic). Second, the pattern of distribution (homogeneous or inhomogeneous). Third, the washout velocity (fast or slow). Cystic NETs solid component has a hyperenhanced homogeneous pattern with a slow washout. Non-invasive pancreatic cancer arising from IPMN is seen as an isoenhanced lesion with a homogeneous pattern and a fast washout, but invasive IPMN-derived cancer can have a hypoenhanced and heterogenous pattern [82].

On the other hand, benign lesions as pseudocyst are anechoic structures with hyperenhancement of the wall [83].

It is usually difficult to distinguish high- and low-grade dysplasia by the pattern of enhancement. Only one study has tried to answer this question. Yamamoto et al. analyzed the time intensity curve in resected IPMNs who underwent CH-EUS. The echo intensity change, echo intensity reduction rate of the mural nodule and the nodule/pancreatic parenchyma contrast ratio were significantly higher in high-grade dysplasia. Of all these parameters, the nodule/parenchyma contrast ratio was the most accurate (93% accuracy) [84].

Blood flow supply to intracystic protrusions during contrast-enhanced EUS has been classified into four different groups: type I: low papillary nodule, type II: polypoid nodule, type III: papillary nodule, and type IV invasive nodule. In a study by Ohno et al., multivariant logistic regression analysis showed that nodules classified as types III/IV in patients with IPMN were significant for malignancy, with an odds ratio of 10.8 (CI 95% 1.37–14.7) [85].

Conclusions

Pancreatic cystic neoplasms are diagnosed frequently and often incidentally. Management depends on the risk of malignant transformation of a given cystic lesion, which is different in each type. The most accurate diagnosis is needed to avoid an unnecessary pancreatic surgery due to the high morbidity involved in this procedure. EUS is a very valuable tool in the evaluation of these pancreatic lesions. Since image is usually not enough to make an adequate diagnosis, FNA has been used to increase the diagnostic accuracy. In some cases, even with CEA levels and DNA evaluation, an accurate diagnosis cannot be done. To try to improve these flaws, new techniques have been developed to improve the diagnostic performance of EUS. nCLE and CH-EUS appear as promising tools for the evaluation of pancreatic cystic neoplasms. More studies evaluating the combination of these techniques are probably needed to improve the diagnostic sensitivity when evaluating pancreatic cystic neoplasms.

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Compliance with ethical standards

Conflict of interest Federico Salom and Frédéric Prat declare that they have no conflict of interest.

Human/animal rights All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent The study did not involve human subjects so no informed consent was obtained.

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