

# EUS-FNA in cystic pancreatic lesions: Where are we now and where are we headed in the future?

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## ABSTRACT

EUS-FNA is often performed in the evaluation of Cystic Pancreatic Lesions (CPL) for a better preoperative characterization. The objective is to identify premalignant lesions as Mucinous Cystic Neoplasms, and/or a malignant transformation of them (adenocarcinoma). The role of cytological evaluation in this setting is discouraging and intracystic markers analysis, mainly CEA, lacks of a good specificity for the detection of mucinous neoplasms. New devices and approaches have emerged to overcome these problems as the cytology brush (Echobrush), the small mini-biopsy forceps, the cystoscopy and the needle Confocal LASER Endomicroscopy (nCLE), showing in some studies good rates of accuracy for distinguishing among mucinous and non-mucinous neoplasms. However, intracystic molecular marker analysis, by identifying mutations in DNA of particular genes as KRAS,GNAS,VHL, CDKN2A and others constitute the most relevant advancement of last years and will contribute in the next future to a better management of CPL. The role of EUS-FNA according to international guidelines is still controversial. While 2012 Fukuoka guidelines are restrictive in their indications AGA 2015 guidelines support it when high risk features are present, enhancing the role of the cytological evaluation in taking decisions.

**Key words:** Aspiration, biopsy, cystic pancreatic tumors, EUS

## INTRODUCTION

Considering the prevalence of cystic pancreatic lesions (CPLs) in asymptomatic people, these lesions emerge as an important public health problem of developed countries. Due to the widespread use of improved imaging techniques in an aging population more and more incidentally CPL are detected, as is reflected in recent studies, posing a serious problem to the physicians who are attending these patients.<sup>[1]</sup>

CPLs may be classified simply into two main classes such as nonneoplastic and neoplastic cysts [Figure 1]. Neoplastic cysts are more commonly defined as pancreatic cystic neoplasms (PCNs). It is important to distinguish nonneoplastic cysts from neoplastic or nonmucinous from mucinous cysts because the latter are considered being premalignant lesions.<sup>[2]</sup>

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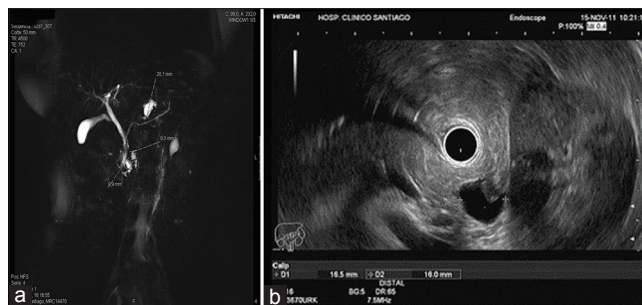
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<p><b>Non-neoplastic cysts</b></p> <ul style="list-style-type: none"> <li>Pseudocyst</li> <li>Simple or congenital cyst</li> <li>Retention cyst</li> <li>Hydatid cyst</li> </ul>
<p><b>Neoplastic cysts (Pancreatic Cystic Neoplasms)</b></p> <p><i>Mucinous cystic lesions</i></p> <ul style="list-style-type: none"> <li>Mucinous cystadenoma/carcinoma</li> <li>Intraductal Papillary Mucinous Neoplasm (IPMN)</li> </ul> <p><i>Non-mucinous cystic neoplastic lesions</i></p> <ul style="list-style-type: none"> <li>Serous cystic neoplasms</li> <li>Cystic endocrine tumor</li> <li>Solid pseudopapillary tumor</li> <li>Acinar cell cystoadenocarcinoma</li> </ul> <p><b>Other neoplastic lesions</b></p> <ul style="list-style-type: none"> <li>Ductal adenocarcinoma with cystic degeneration</li> </ul>

**Figure 1.** Classification of cystic pancreatic lesions

EUS and magnetic resonance imaging with magnetic resonance cholangiopancreatography are considered the most accurate techniques for detecting mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN)<sup>[3]</sup> [Figure 2a and b]. EUS is particularly valuable in assessing diagnostic features and potential predictors of malignancy, including size, shape, number of cysts, septa, nodules, solid masses associated with the cyst, pancreatic duct diameter, communication with pancreatic duct, and lymph nodes. Certain CPL have some characteristic appearance: Serous cystadenoma (SCA) is often depicted as a microcystic and honeycomb pattern although recently some authors have proposed new endosonographic criteria,<sup>[4]</sup> a CPL without septations and solid component in a parenchyma with features of chronic pancreatitis suggests a pseudocyst with high certainty.<sup>[5]</sup> MCN can be usually diagnosed when there is a cyst with septation of variable thickness, a visible wall and a peripheral calcification. Some predictors of malignancy can also be assessed by EUS, as the presence of mural nodules and its differentiation from mucus. Mucin globules are hypoechoic, have smooth edges and hyperechoic rims, and move when patients are repositioned while mural nodule is isoechoic or hyperechoic and has irregular margins.<sup>[6,7]</sup> The use of contrast enhancement is of great value in these circumstances, as the mural nodule must enhance after the administration of the contrast,<sup>[8]</sup> while mucin, as an avascular structure, must not.

However, despite the utility of EUS imaging in diagnostic evaluation and estimating malignant potential



**Figure 2.** (a) Small cystic lesion of 16 mm × 16 mm placed in the tail of the pancreas with a small solid component, concordant with a branch-duct intraductal papillary mucinous neoplasm. (b) Magnetic resonance cholangiopancreatography of a multifocal branch-duct intraductal papillary mucinous neoplasm

of CPL, EUS alone is not adequate for the diagnosis of pancreatic cysts.<sup>[9]</sup> When surgical histology is used as a reference standard, the diagnostic accuracy of EUS imaging ranges from 40% to 96%. A single prospective study demonstrated that the sensitivity (56%) and specificity (45%) of EUS morphology alone for differentiating mucinous cysts from nonmucinous cysts were low, resulting in poor overall accuracy (51%).<sup>[10]</sup> Furthermore, EUS performance is highly operator dependent and the interobserver agreement of morphological features of EUS when evaluating a CPL leaves much to be desired, even when the endoscopist performing the EUS is an expert.<sup>[11]</sup> In this scenario, when EUS-FNA is often performed.

In this review, we will try to explain first which is the starting point of EUS-FNA, how can we optimize its diagnostic yield and finally which place EUS-FNA occupy according to the international consensus guidelines.

## WHEN AND HOW TO PERFORM AN EUS-FNA AND WHAT INFORMATION IS USUALLY OBTAINED?

There is not an specific minimum limit on size for performing an EUS-FNA. As explained below, there are different recommendations according to guidelines about when performing FNA regarding size, but at this point, no solid statement based on a high level of evidence can be established.

EUS-FNA of CPL is a well-established procedure that is commonly performed using different size standard needles. Depending of the size, the location and the presumed difficulty of perforating the lesion is possible to choose among a 19G needle (mainly for

lesions placed in the body or tail of the pancreas) and 19G flexible or 22G for lesions placed in the head or uncinate process. 25G-EUS needles should only be used in those cases with a clear solid component as the viscosity of the fluid when aspirated may preclude to obtain material from the cyst with needles of small calibers (a thicker needle means better aspiration).

One major concern when doing an EUS-FNA in this setting is the development of complications. Infection is the most well documented and that is the reason why is recommended (without any kind of evidence) the administration of antibiotics periprocedure. Bleeding must be also keep in mind and so an EUS-FNA should neither be performed without normal coagulation parameters nor in a patient taken oral anticoagulants or ADP antagonists (clopidogrel, prasugrel, and ticagrelor). Even aspirin intake or nonsteroidal anti-inflammatory drugs in this scenario are considered as a contraindication by some guidelines.<sup>[12]</sup>

By performing an EUS-FNA in a CPL is possible to do a macroscopic subjective evaluation of the fluid aspirated from the cyst. Liquid from MCNs tend to be clear and high viscosity while a thin, muddy-brown fluid is usually obtained from a pseudocyst. Finally, an hematic sample is commonly observed in rich vascularized tumors as SCA. However, only by the macroscopic evaluation of the fluid is not possible obtain in the majority of the cases a final reliable diagnosis. An interesting approach to evaluate the viscosity of the sample is the “string sign.” This is a very simple and cheap test that consists on placing a drop of the fluid aspirated between two fingers and spreading them apart. The test is considered to be positive when the string that is formed has a length of more than one cm or lasts more than 1 s before disruption. This string sign positive have demonstrated to be very specific for the diagnostic of mucinous lesions, but with a poor sensitivity of 58%.<sup>[13]</sup>

Although performed since many years, the role of the cytological evaluation of CPL by EUS-FNA is still controversial. When doing a cytological evaluation of a CPL, is possible to obtain relevant information about the type of lesion being evaluated: inflammatory cells, as histiocytes, macrophages or neutrophils, are commonly seen in the context of a pseudocyst; cuboidal cells which stain for glycogen, are typical of

the SCA, while epithelial mucinous cells or extracellular mucin, are considered diagnostic of a mucinous lesion. Although this approach identifies tumors with close to 100% of specificity, it has a low level of sensitivity, as is reflected in recent metanalysis which establish a rate of 54%<sup>[14]</sup> Other authors reported a diagnostic accuracy of only the 31% for the cytological evaluation in a prospective cohort of 128 CPL.<sup>[15]</sup> The low sensitivity results from factors such as the low yield of lesion cells from the aspirate, insufficient sample volume, and contamination of samples with gastrointestinal wall cells.<sup>[16]</sup>

An important point that must be highlighted about the role of cytology in EUS-FNA of CPL is the fact that the majority of studies report low rates of sensitivity mainly based on just aspirating the fluid of the cyst (of poor cellularity). Other studies have, besides sending the aspirated cyst fluid for cytology, also performed FNA of cyst wall or its solid component (mural nodule or mass lesion), leading to a significant increase in diagnostic yield. Lim *et al.*<sup>[17]</sup> showed that in the absence of solid component, the cytology yield was 28.8% while if the mural nodule was sampled with FNA, the yield was 78%. Similarly, Shirley *et al.*<sup>[18]</sup> showed diagnostic cytology findings in 89.6% of patients with suspicious imaging findings (mural nodules/masses, *etc.*) while no diagnostic cytology finding in any case without such imaging findings (*i.e.*, when only cyst fluid was aspirated for cytology). For all this reasons, at present, the real role of the cytological evaluation by EUS-FNA in CPL remains, at least, controversial, with some guidelines supporting its role<sup>[19]</sup> as others being very strict in their indications.<sup>[20]</sup>

Another possibility available when doing an EUS-FNA is performing an intracystic marker analysis of the fluid aspirated. Excluding the role of the intracystic molecular markers (explained below), this topic is focused on different common markers (used in other typical cancers) that help us to distinguish among different kinds of CPL. Among them, Ca 19.9, Ca 125, CEA, amylase, Ca 72.4, and Ca 15.3 has been used in several trials, but by far the most common evaluated is the CEA. Since many years, the cut-off point of CEA intracystic level commonly considered to differentiate between mucinous lesions from nonmucinous lesions was 192 ng/mL, according to the cooperative study performed by Brugge *et al.*<sup>[10]</sup> However, over the years, this level has been declining, and some recent trials provide new cut-off levels

of 105 ng/mL, 50 ng/mL, and even 7 ng/mL for distinguishing mucinous of nonmucinous lesions.<sup>[21-23]</sup> Therefore, it is possible to conclude that CEA alone is a suboptimal marker for this task.

## HOW CAN WE OPTIMIZE THE ROLE OF EUS-FNA, WHAT IS EXPECTED FOR THE NEAR FUTURE?

Considering the low diagnostic yield of cytologic evaluation and the lack of specificity of intracystic common markers for achieving a final preoperative diagnosis, of at least for doing a differentiation among mucinous or nonmucinous lesions, some devices and technologies have emerged trying to overcome this problems.

A device through the EUS needle cytology brush, the EchoBrush (ECHO-19-CB; Cook Medical, Bloomington, Ind) has been introduced to the market a few years ago. It allows direct sampling of cystic pancreatic epithelium under EUS guidance [Figure 3]. Previous trials reported increases of diagnostic sensitivity using this brush in the differential diagnosis of CPL.<sup>[24-26]</sup> Some of this studies only reflects the experience of using this technique, others are retrospective and all of them are nonrandomized, hampering a real comparison with conventional EUS-FNA. Even more, this brush can only be introduced inside a 19G-EUS needle, hindering the puncture of lesions placed in the head or uncinate process; in fact, the rigidity of the tip of the brush makes difficult the exit of the needle in certain positions. Our group have demonstrated in a

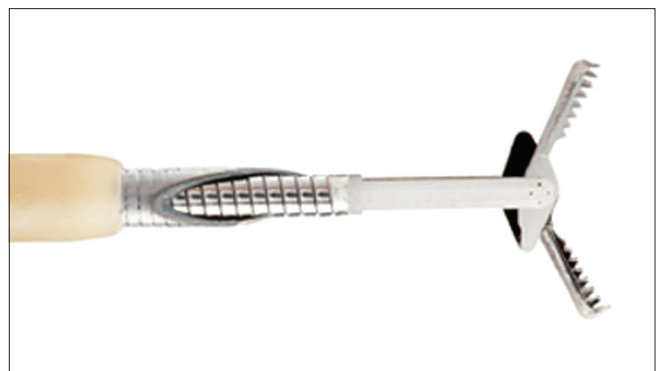


**Figure 3.** Cytologic brush (Echobrush®) used added to EUS-FNA. Look at the hyperechogenic distal tip of the brush targeting the inner wall of the cyst

randomized and multicenter trial that the use of this device did not improve neither the diagnostic adequacy simple nor the diagnostic yield in this setting.<sup>[27]</sup>

Another interesting possibility is the use of a small biopsy forceps inside the 19G working channel of EUS needle for obtaining material for a histological evaluation. This method has been recently evaluated in solid pancreatic lesions with success,<sup>[28]</sup> but the experience in the setting of CPL is scarce and limited to small series and case reports.<sup>[29-31]</sup> A well-designed study with more amount of patients is needed to check the reproducibility, safety, and usefulness of this approach with these new models of mini-biopsy forceps [Figure 4].

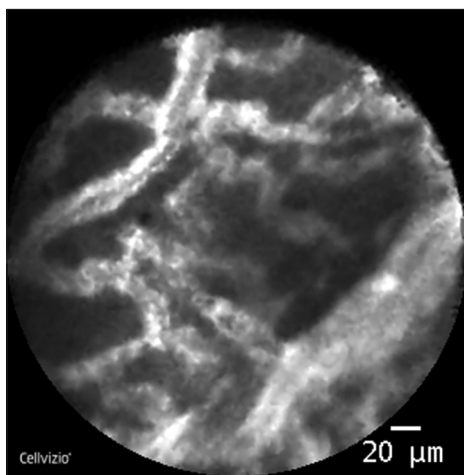
Nevertheless, the most developed new techniques associated with EUS-FNA in CPL in the last years are the cystoscopy and the needle confocal laser endomicroscopy (nCLE). The cystoscopy provides the opportunity of exploring, with a fiberoptic probe introduced through the 19G-EUS needle, the inner part of the cyst, looking for the presence of mucin, commonly seen in mucinous lesions, and also the inner epithelial surface of the cyst trying to identify villous structures that may correspond to a mural nodule, also typical from mucinous neoplasms. The results of the DETECT study,<sup>[32]</sup> which evaluated the role of cystoscopy and nCLE in a cohort of 30 patients (18 of them with proven histological diagnosis) show good rates of sensitivity and negative predictive value for the diagnosis of mucinous lesions, that even reach 88% and 87%, respectively, when combine with nCLE. Introducing a specific probe of Endomicroscopy through a 19G- or 22G-EUS needle (nCLE) enables to perform a microscopic *in vivo* observation of the internal epithelial surface of the cyst. Three main trials have evaluated the role



**Figure 4.** Mini biopsy forceps used inside the EUS-needle working channel (US endoscopy®)

of nCLE in the diagnosis of CPL. The DETECT, above mentioned, and the INSPECT,<sup>[33]</sup> focused mainly in detecting mucinous neoplasms and the French CONTACT<sup>[34]</sup> study. The majority of the papers about nCLE highlight the good specificity of some “endomicroscopic features” (as the observation of papillary projections or a dark ring) for identifying IPMNs while demonstrating a poor sensitivity. In the study of Napoleon *et al.* (CONTACT),<sup>[34]</sup> the sequences of nCLE enables the identification of a particular pattern for the SCA. The pattern was present independently of the morphological presentation of the SCA (*i.e.*, uni- or multilocular) and was described as a densely woven network of tortuous blood vessels with intense and dynamic circulation of blood cells visualized. This characteristic vascular organizational structure of SCA was consensually identified as the superficial vascular network [Figure 5]. Compared with the final diagnosis, the overall accuracy, sensitivity, specificity, PPV, and NPV of the superficial vascular network criterion for the SCA were 87%, 69%, 100%, 100%, and 82%, respectively. Nevertheless, it is important to mention that nCLE is an expensive and time-consuming technique which requires high degree of experience, so its usage, currently, is still limited to select tertiary referral centers.

But what undoubtedly means a complete breakthrough in the diagnosis and characterization of the different CPL is the intracystic molecular marker analysis. This means identifying concrete DNA mutations, in particular genes associated with an specific type of lesion. K-RAS and GNAS genes are the most



**Figure 5.** Needle confocal LASER endomicroscopy of a cystic pancreatic lesion: Serous cystadenoma (courtesy of Dr. Dabizzi (Pancreato-Biliary Endoscopy and Endosonography Division, San Raffaele Scientific Institute IRCCS, Vita Salute San Raffaele University, Milan, Italy)

evaluated but others as VHL, TP53, SMAD4, and CDKN2A have also been studied. Springer *et al.*<sup>[35]</sup> evaluated retrospectively 130 patients with resected PCNs. The molecular marker panel correctly identified 67 of the 74 patients who did not require surgery and could, therefore, reduce the number of unnecessary operations by 91%. In the same way, Al-Haddad *et al.*,<sup>[36]</sup> used the combination of clinical features of EUS with CEA level and cytological evaluation with molecular marker analysis of KRAS and GNAS in an integrated molecular pathology (IMP) analysis. In a retrospective cohort of 492 patients, the IMP analysis was compared to Fukuoka 2012 guidelines<sup>[20]</sup> for the detection of pre/malignant lesions. IMP more accurately determined the malignant potential of pancreatic cysts than Fukuoka 2012 guideline management criteria model. This results are also supported by recent trial<sup>[37]</sup> in which a novel algorithmic pathway using molecular testing of pancreatic cyst fluid detected advanced neoplasia better than AGA guidelines<sup>[19]</sup> criteria. As conclusion, the ability of EUS-FNA to provide samples for doing a molecular marker analysis makes it a very useful tool for identifying preoperatively those CPL with a malignant potential that would benefit for surgical resection. The main drawback of this approach is that this technology is expensive and not widely available to all centers, but in the opinion of the author, molecular marker analysis will become soon as first-line diagnostic test for the characterization of CPL.

## WHICH IS THE ROLE OF EUS-FNA ACCORDING TO THE GUIDELINES?

To help physicians to take decisions when they are facing with a CPL, many guidelines have been developed in last years. However, the specific role of EUS-FNA is sometimes unclear, with some guidelines being critical with it while others supporting and enhancing its use.

The international guidelines for the management of IPMNs and mucinous cystadenoma,<sup>[20]</sup> that are the result of a consensus conference that took place in the city of Fukuoka in 2012, established very strict criteria for the use of EUS-FNA. In fact, they consider the fluid analysis as “still investigational” and that must be performed in centers with expertise in EUS-FNA and cytological interpretation. Fukuoka guidelines consider two scenarios in which EUS-FNA may be useful: (1) Small branch-duct IPMN without worrisome features and (2) for the distinction of a small oligocystic

SCA from a small branch duct IPMN; sometimes this differentiation is challenging and may require EUS-FNA with CEA determination. It is important to highlight that Japanese investigators do not recommend cystic fluid analysis routinely and believe that a cyst of any size with “worrisome features” should not be aspirated, because it may cause leakage of the fluid content, possibly leading to peritoneal dissemination.<sup>[38]</sup> However, the results of the PIPE study,<sup>[39]</sup> in which 175 resected IPMNs with a preoperative EUS-FNA were analyzed and compared with 68 patients with no preoperative tissue sampling, demonstrated that there are no difference of peritoneal seeding by preoperative sampling or not a CPL.

When to perform an EUS-FNA is something that is much more clear according to the American Gastroenterological Association (AGA) Guidelines.<sup>[19]</sup> These guidelines only consider when evaluating a CPL 3 high-risk features: dilation of main pancreatic duct (MPD), size more than 3 cm, and the presence of a solid component associated with the cyst. When 2 out of these 3 features are present is when an EUS-FNA must be performed. If as a result of the cytologic evaluation of the cyst fluid, a “concerning cytology” (suspicious or positive for malignancy) is found, we must send the patient to surgery. AGA guidelines have been widely criticized in many aspects and one of them is the enhanced role they give to cytological evaluation, taking into account the low diagnostic performance it has in this scenario.

Finally, in 2016, the American Society of Gastrointestinal Endoscopy (ASGE) published a specific document about the role of endoscopy in cystic pancreatic neoplasms.<sup>[40]</sup> The main recommendations about when to puncture a cyst is summarized in: (1) EUS-FNA is recommended in cystic lesions >3 cm or in the presence of mural nodules, MPD dilation or associated mass (moderate level of evidence); (2) EUS-FNA is optional in asymptomatic patients with cysts <3 cm and without mural nodule/associated mass nor MPD dilation (low level of evidence); (3) it is recommended an initial evaluation of intracystic fluid with CEA, amylase, and cytology (moderate level of evidence); and (4) it may be considered a molecular marker analysis when initial evaluation with CEA and cytology is not conclusive (low level of evidence).

According to the abovementioned guidelines, important conceptual differences can be detected:

Fukuoka guidelines<sup>[20]</sup> aim to directly subject the high-risk lesions to surgery (to avoid neoplastic dissemination while performing EUS-FNA, although the results of the PIPE study<sup>[39]</sup> does not support this idea) and to perform EUS-FNA in apparently low-risk lesions (to confirm they are really benign and hence can be followed-up). On the other hand, American guidelines (both AGA and ASGE),<sup>[19,40]</sup> recommend EUS-FNA in apparently high-risk lesions, so that if they have high-risk cytology, they can be subjected to surgery, while apparently low-risk lesions can just be followed up (without performing EUS-FNA). Which of these two approaches about the use of EUS-FNA is better is something that must be demonstrated in well-designed validation studies in the future.

Considering the opinions of the different guidelines on when to perform an EUS-FNA, making a decision on this topic may be difficult in clinical practice. It is author’s opinion that perhaps no cystic lesion below 2 cm deserve an EUS-FNA, unless it has a clear solid component inside it or a surgical procedure is considered. We do also believe that a CPL >2 cm or with high-risk features may be taken into account for the EUS-FNA even when surgical resection seems to be clear. When evaluating the correlation among the presumptive preoperative diagnosis with the histology of the surgical specimens is possible to detect a not insignificant rate of misdiagnosis.<sup>[41-43]</sup> It should be underscored that, even following the guidelines, we are sending to surgery some patients that did not really need it leading to an important morbidity and clinical consequences because of the pancreatic surgery.<sup>[44]</sup>

Finally, it is important to point out, that the clinical conditions of the patient should seriously be considered (age and comorbidities), individualizing case by case when making concrete decisions. This point is not only exclusive of the EUS-FNA but also when referring a patient to surgery or establish a particular surveillance, taking into account that many patients will die of other concomitant pathologies and not by their cystic tumor.<sup>[45]</sup>

## CONCLUSIONS

Despite the wide use of EUS-FNA in CPL over the years, at present, its role remains controversial. Cytological evaluation and intracystic marker analysis (CEA) have been criticized and supported

to the same extent in the literature. New devices as cystoscopy and mainly nCLE seem promising, specifically for some kinds of CPL as SCA. Intracystic molecular marker analysis, by detecting concrete gene mutations, will probably allow, in the near future, not only just the identification of the CPL being faced but also its risk of developing malignancy, becoming a crucial tool to take decisions with our patients.

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### Conflicts of interest

There are no conflicts of interest.

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