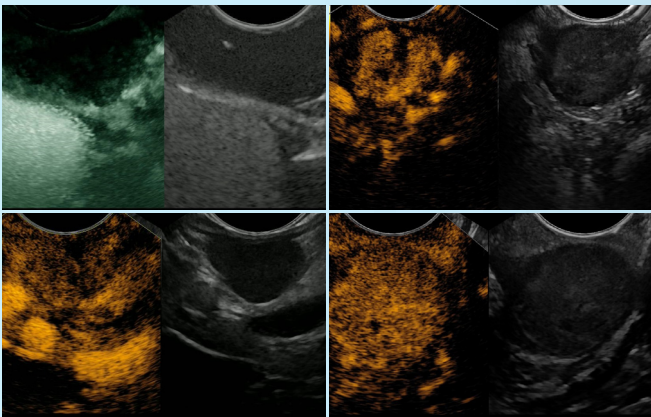


# EUS

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### SPECIAL ISSUE ON CONTRAST-ENHANCED ENDOSCOPIC ULTRASOUND (PART II)

· Guest Editors: Pietro Fusaroli, Adrian Saftoiu

### HIGHLIGHT ARTICLES

- Role of contrast-enhanced endoscopic ultrasound in lymph nodes
- Dynamic contrast-enhanced endoscopic ultrasound: A quantification method
- Role of contrast harmonic-endoscopic ultrasound in pancreatic cystic lesions
- Harmonic contrast-enhanced endoscopic ultrasound fineneedle aspiration: Fact or fiction?

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# Role of contrast harmonic-endoscopic ultrasound in pancreatic cystic lesions

Marta Serrani, Andrea Lisotti, Giancarlo Caletti, Pietro Fusaroli

Department of Medical and Surgical Science, Gastroenterology Unit, Hospital of Imola, University of Bologna, Bologna, Italy

## ABSTRACT

Incidental pancreatic cysts (PCs) are frequently encountered in the general population often in asymptomatic patients who undergo imaging tests to investigate unrelated conditions. The detection of a PC poses a significant clinical dilemma, as the differential diagnosis is quite broad ranging from benign to malignant conditions. Endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) has been reported to be an accurate tool in the differential diagnosis; however, its sensitivity is suboptimal and false negative results do occur. Contrast harmonic EUS (CH-EUS) was demonstrated to be a useful tool to investigate pancreatic solid lesions to differentiate between benign and malignant ones. In the setting of PCs, CH-EUS could help identify areas of malignant growth inside the cystic cavities. Several studies have reported promising results showing malignant areas in PCs as hyperenhanced lesions. Confirmation of malignancy can then be obtained by FNA, which should be precisely targeted according to the findings of the contrast harmonic study.

**Key words:** Contrast agents, contrast harmonic endoscopic ultrasound, endoscopic ultrasound, fine-needle aspiration, pancreatic cysts

## INTRODUCTION

The incidental detection of asymptomatic pancreatic cysts (PCs) in the general population has increased as a consequence of the wide use of computed tomography (CT) and magnetic resonance imaging (MRI), ranging from 0.5% to 45%.<sup>[1-5]</sup>

PCs comprise a large variety of different lesions, some of which are benign, i.e., pseudocysts and dysontogenetic cysts, whereas others are malignant or harbor malignant potential.

The latter cysts, from now on called pancreatic cystic lesions (PCLs), are mainly composed (90%) by intraductal papillary mucinous neoplasms (IPMN), mucinous cystadenoma (MCA), serous cystadenoma (SCA), and pseudopapillary neoplasms.

Recent evidence has shown that PCLs represent roughly half of PCs, the other half being represented by pseudocysts.<sup>[1,6]</sup>

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### Address for correspondence

Prof. Pietro Fusaroli, Department of Medical and Surgical Science, Gastroenterology Unit, Hospital of Imola, University of Bologna, Via Montericco 4, 40026, Imola, Bologna, Italy. E-mail: [pietro.fusaroli@unibo.it](mailto:pietro.fusaroli@unibo.it)

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## PANCREATIC CYSTS DIFFERENTIAL DIAGNOSIS AND RISK STRATIFICATION

It is of paramount importance to obtain an accurate differential diagnosis of PCs to stratify the risks of malignant progression and decide the better clinical pathway for the patients that can comprise surgery or follow-up. Unfortunately, at the present time, the strategy to stratify the risk of malignant progression is poor and up to 75% of patients with PCLs undergo major surgery to remove cysts that demonstrate to have low malignant potential at histological examination of the surgical specimen.<sup>[7]</sup>

Recently, high-quality Italian guidelines focused on PCLs management in asymptomatic patients indicated MRI with magnetic resonance cholangiopancreatography as the first diagnostic step; if this technique turns out to be nondiagnostic or “suspicious” morphological aspects are detected, endoscopic ultrasound (EUS) with or without fine-needle aspiration (EUS-FNA) is suggested.<sup>[8]</sup>

### THE ROLE OF TRADITIONAL B-MODE ENDOSCOPIC ULTRASOUND/ENDOSCOPIC ULTRASOUND-FINE-NEEDLE ASPIRATION

EUS can differentiate among PCLs and point out the so-called worrisome features, which are useful for the diagnosis of malignant or premalignant lesions (carcinoma/high-grade dysplasia) and can help in the definition of a diagnostic and therapeutic pathway.

According to the international guidelines published in 2012, PCLs’ worrisome features are represented by: size >3 cm, thickened enhanced cyst wall, main pancreatic duct (MPD) size of 5–9 mm, and abrupt change in the MPD caliber with distal pancreatic atrophy.<sup>[9]</sup>

Unfortunately, EUS is an operator-dependent technique and the differential diagnosis between PCLs still requires in most cases tissue confirmation with EUS-FNA. However, it should be emphasized that cytopathology analysis of aspirated specimens is diagnostic in no more than half of the cases<sup>[10,11]</sup> and that the detection of markers (e.g., carcinoembryonic antigen) in the cystic fluid can have a contributory role in the diagnostic process although it lacks optimal accuracy.<sup>[12]</sup> New intracystic molecular markers are currently under investigation, but their use is still limited

due to costs and low sensitivity (not adding more than 10%–15% *vs.* cytology) and uneven availability among different laboratories.<sup>[13]</sup>

EUS-FNA is a safe procedure although a recent Italian study reported 6% complication rate in a selected population of patients with PCs.<sup>[14,15]</sup>

### THE ROLE OF ULTRASOUND CONTRAST AGENTS IN PANCREATIC CYSTS

To overcome the limitations of EUS-FNA and improve the characterization of PCs, new techniques were developed.

Concerning PCLs, mural nodules are considered the most important predictive factor of malignancy, particularly in cases showing features of hyperenhancement at CT and/or lesions >7 mm in size.<sup>[9,16-18]</sup>

Unfortunately, CT and MRI are specific in nodules detection but have a low sensitivity.<sup>[19,20]</sup> B-mode EUS is sensitive, but less specific due to the difficulty in distinguishing nodules from mucous clots and debris.<sup>[19]</sup>

Consequently, research is oriented in finding new techniques with high intracystic nodules detection and able to distinguish malignant/premalignant nodules from benign nodules such as mucus clots mimicking solid components or pseudocysts with internal debris.

Recently, contrast harmonic EUS (CH-EUS) has been reported as a useful adjunct in the differential diagnosis of pancreatic solid tumors.<sup>[21-24]</sup> The interest and experience in CH-EUS for the study of PCs are growing due to capability of the technique in visualizing the microvascularization of cystic walls, septae, and most of all, nodules.

The technique for performing CH-EUS has been detailed in other articles of this special issue of *Endoscopic Ultrasound*. CH-EUS, which takes advantage of the intravenous infusion of a contrast medium to visualize the blood flow even in very fine vessels, should be adequate to investigate the small solid components that are sometimes detected inside PCs. In theory, the small neoplastic solid components should exhibit some signs of vascularization [Figure 1] as opposed to debris and mucus that are expected to be completely avascular [Figure 2].

Initially, no CH-EUS dedicated platforms were available; therefore, the first experiences were based on the study of the contrast medium distribution with color Doppler or power Doppler. The latter technique is named contrast-enhanced-EUS (CE-EUS).

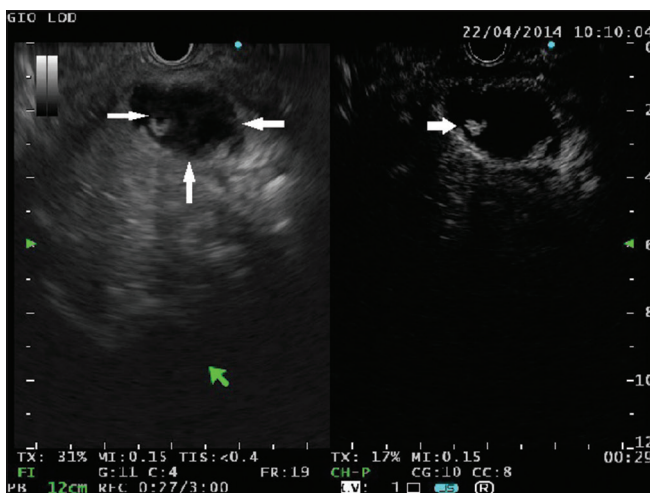
In 2008, Dietrich *et al.* showed that CE-EUS (using Levovist, a first generation ultrasound contrast agent) was useful in differentiating small solid pancreatic tumors that resulted hypovascular in comparison with the surrounding pancreatic parenchyma. The study included for the related risk of detection of ductal adenocarcinoma, also 10 (<40 mm) SCAs that resulted in all hyperenhanced. They collected data also about other PCs, reporting that hyperenhanced mural nodules were identified in 6/6 IPMNs and in 79% (15/19) MCAs. They also reported that only 8/90 pseudocysts presented contrast enhancing vessels. According to the authors, CE-EUS was not useful in differentiating between benign and malignant PCLs.<sup>[25]</sup>

In 2009, Ohno *et al.* used CE-EUS to identify malignant predictors in IPMN. The study was conducted on 87 patients affected by IPMN with mural nodules. The authors classified mural nodules into four types according to the morphology and studied the vascular characteristics of mural nodules with color Doppler after the injection of Levovist. CE-EUS results were compared to CT scan. The study showed that hyperenhanced nodules were significantly correlated

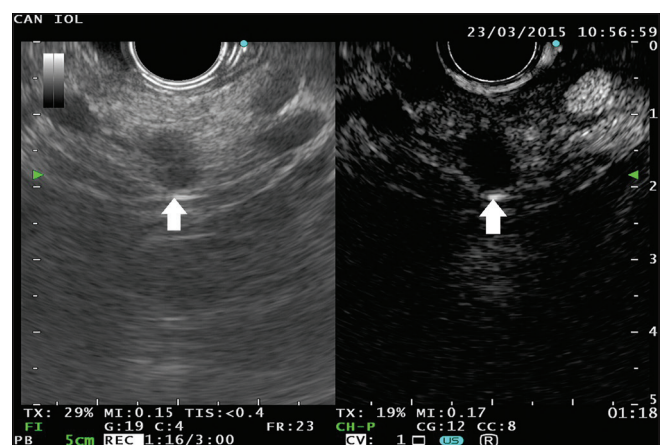
to malignancy and that CE-EUS detected more and smaller mural nodules than CT.<sup>[26]</sup>

In 2013, Yamashita *et al.* used CH-EUS (with Sonazoid) to investigate 17 patients with IPMN with mural nodules. CH-EUS allowed detecting the microvasculature within nodules in 13 patients (76%) unlike CT scan, which showed vascularized mural nodules only in seven patients (41%). Interestingly, in that study, 75% of mural nodules identified by CH-EUS turned out to be intraductal papillary mucinous carcinoma at histopathology.<sup>[21]</sup> One case of a cystic septum that was erroneously interpreted as a hyperenhanced solid component accounted for a false-positive result of CH-EUS.

In 2014, Hocke *et al.* performed CH-EUS with Sonovue in 125 patients with undetermined PCs. They evaluated the contrast medium behavior in cystic walls, septae, and nodules. Concerning walls enhancement, the study showed that CH-EUS could identify benign lesions as pseudocysts and dysontogenetic cysts because cystic walls show no vascularization. On the other hand, CH-EUS could not differentiate between serous and mucinous PCLs because the enhancement of walls and septae was similar between the two entities. The authors maintain that EUS-FNA is still required for the differential diagnosis of PCLs and that the usefulness of CH-EUS consist in targeting FNA on those lesions, assumed to be cystic pancreatic tumors, with visible walls, septae, or nodules vascularization.<sup>[27]</sup>



**Figure 1.** A cystic lesion is seen in the pancreatic head containing solid components with mixed echogenicity (left panel, thin arrows). At contrast harmonic-endoscopic ultrasound, a small area of hyperenhancement is clearly visible (right panel, arrow). This finding is highly suggestive of malignancy



**Figure 2.** A small cyst is detected in the pancreatic body. At B-mode endoscopic ultrasound, the lesion appears full of echogenic material (left panel, arrow). At contrast harmonic-endoscopic ultrasound, the cyst is clearly unenhanced thus ruling out malignancy (right panel, arrow)

As a demonstration of the increasing interest on CH-EUS, three different articles have already been published in the current year [Table 1].

Fusaroli *et al.* evaluated the role of CH-EUS in the differential diagnosis of PCs and in the detection of malignancy. The evaluation of 76 patients showed that CH-EUS could distinguish between pseudocysts and other cysts but cannot differentiate between serous and mucinous PCLs because the wall and septae enhancement is not different between these lesions. On the other hand, EUS is a very useful tool in visualizing nodules inside cysts and the nodule enhancement after injection of Sonovue can identify malignant nodules that are clearly hyperenhancing [Figure 3]. In conclusion, CH-EUS can be used as a tool in targeting FNA and avoiding puncture of mucus plugs or debris.<sup>[28]</sup>

Kamata *et al.* showed that standard B-mode EUS had high sensitivity but low specificity (40%) in the study of mural nodules. The addition of CH-EUS increases the specificity up to 75%, whereas maintaining high sensitivity (95%). The Authors have also assessed that the presence of an enhancing nodule  $\geq 4$  mm represented the optimal threshold to discriminate between benign and malignant PCLs.<sup>[29]</sup>

Yamamoto *et al.* evaluated by a time-intensity curve analysis, the diagnostic accuracy of CH-EUS (with Sonazoid) in differentiating the grade of dysplasia inside nodules (low-grade *vs.* high-grade dysplasia/carcinoma). In thirty patients, they observed that among the other parameters taken into account, nodule *versus* pancreatic parenchyma contrast ratio was the most accurate parameter to quantify the blood flow in intracystic nodules. They also correlated the blood flow with contrast enhancement and demonstrated, through histopathology, a correlation between nodule vascularity and dysplasia.<sup>[30]</sup>

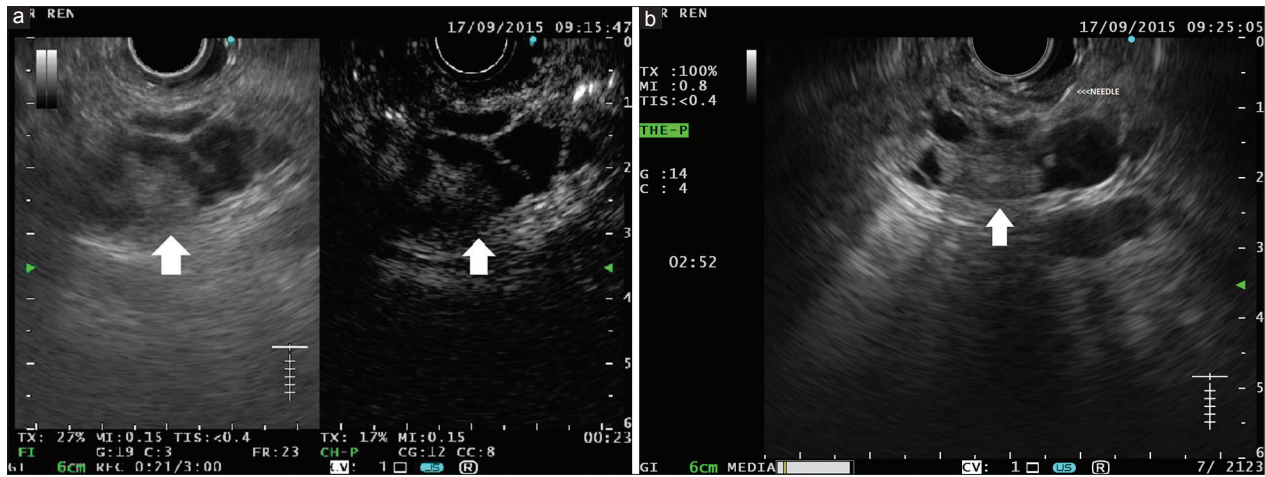
## CONCLUSION

The differential diagnosis of PCs is quite broad encompassing benign, borderline, and malignant entities. Current imaging methods, including EUS and EUS-FNA, show suboptimal accuracy in differentiating PCLs and detecting malignancy. CH-EUS shows no significant differences between the enhancing patterns of cystic walls and septae of mucinous and nonmucinous PCLs. However, CH-EUS appears to be a sensitive and specific adjunct in the differential diagnosis of intracystic solid components to detect malignancy.

**Table 1. Literature pertaining the role of CH-EUS in pancreatic cysts**

Reference	Study design, PCs type population	n	CH-EUS (wall/septae)		Nodules at CH-EUS n	CH-EUS (nodules)		
			Hyper-enhanced	Hypo-enhanced		Hyper-enhanced	Hypo-enhanced	
Kamata <i>et al.</i> Endoscopy 2016	Prospective 70 patients	MCN	6	NA	NA	39	1	0
		IPMN	42				37	0
		SCA	4				0	0
		Nonneoplastic	18				1	0
Yamamoto <i>et al.</i> Endoscopy 2016	Retrospective 30 patients*	IPMN	30	NA	NA	30	30 (14 LGD/16 HGD-cancer)	0
Fusaroli <i>et al.</i> Pancreas 2016	Retrospective 76 patients	MCN	4	24	3	0	0	0
		IPMN	23			10	2	8 (mucus clots)
		SCA	36	31	5	0	0	0
		Cystic NET	3	3	0	2	2	0
		Nonneoplastic	10	1	9	8	0	8
Hocke <i>et al.</i> Endoscopic Ultrasound 2014	Retrospective 125 patients	MCN	1	1	0	NA	NA	NA
		IPMN	22	22	22			
		SCA	26	26	0			
		Cystic NET	4	4	4			
		Nonneoplastic	69	4	65			
		CPC	3	3	0			
Yamashita <i>et al.</i> J Ultrasound Med. 2013	Prospective 45 patients	IPMN	17	NA	NA	17	13 (12 nodules/1 septum#)	4 (mucus clots)
<b>Total</b>	<b>318</b>		<b>318</b>			<b>106</b>	<b>86</b>	<b>20</b>

\*Quantitative CH-EUS, #False positive result. PCs: Pancreatic cyst, CH-EUS: Contrast enhanced endoscopic ultrasound, MCN: Mucinous cystic neoplasm, IPMN: Intraductal papillary mucinous neoplasm, SCA: Serous cystic adenoma, NET: Neuroendocrine tumor, CPC: Cystic pancreatic carcinoma, HGD: High grade dysplasia, LGD: Low grade dysplasia, NA: Not available



**Figure 3.** (a) A complex multiloculated cystic lesion is visible in the pancreatic head, containing a hypoechoic solid component (left panel, arrow). At contrast harmonic-endoscopic ultrasound, the solid component appears hyperenhanced (right panel, arrow), as well as septae and cystic wall. (b) As the contrast harmonic-endoscopic ultrasound finding is highly suggestive of malignancy, selective endoscopic ultrasound-fine-needle aspiration is performed

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### Conflicts of interest

There are no conflicts of interest.

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