



## Maximizing the endosonography: The role of contrast harmonics, elastography and confocal endomicroscopy

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### Abstract

New technologies in endoscopic ultrasound (EUS) evaluation have been developed because of the need to improve the EUS and EUS-fine needle aspiration (EUS-FNA) diagnostic rate. This paper reviews the principle, indications, main literature results, limitations and future expectations for each of the methods presented. Contrast-enhanced harmonic EUS uses a low mechanical index and highlights slow-flow vascularization. This technique is useful for differentiating solid and cystic pancreatic lesions and assessing biliary neoplasms, submucosal neoplasms and lymph nodes. It is also useful for the discrimination of pancreatic masses based on their qualitative patterns; however, the quantitative assessment needs to be improved. The detection of small solid lesions is better, and the EUS-FNA guidance needs further research. The differentiation of cystic lesions of the pancreas and the identification of the associated malignancy features represent the main indications. Elastography is used to assess tissue hardness based on the measurement of elasticity. Despite its low negative predictive value, elastography might rule out the diagnosis of malignancy for pancreatic masses. Needle confocal laser endomicroscopy offers useful information about cystic lesions of the pancreas and is still under evaluation for use with solid pancreatic lesions of lymph nodes.

**Key words:** Endosonography; Endosonography-fine needle aspiration; Contrast-enhanced; Harmonics; Elastography; Endomicroscopy; Pancreas; Lymph nodes; Cyst

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**Core tip:** Contrast-enhanced harmonic endoscopic ultrasound, elastography and needle confocal laser endomicroscopy represent new, emerging technologies for improving the diagnosis obtained using endoscopic ultrasonography. This paper reviews the principle, indications, main literature results, limitations and future expectations for each of these methods, such as their use in the guidance or orientation of endoscopic ultrasound fine needle aspiration, molecular imaging and neurophysiology assessment in gastroenterology.

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## INTRODUCTION

New technologies in endosonography assessment are under development due to the limitations of standard endoscopic ultrasound-fine needle aspiration (EUS-FNA): the diagnostic accuracy for pancreatic masses is as high as 95% for cytology<sup>[1,2]</sup> and 86% for histology<sup>[3]</sup>, the sensitivity for diagnosing lymph nodes is 90%<sup>[4]</sup>, correct diagnosis is difficult for submucosal neoplasms<sup>[5]</sup>, the differential diagnosis of pancreatic cysts is approximately 20%-30%<sup>[6]</sup>, and the malignancy potential is sometimes challenging<sup>[7]</sup>.

## CONTRAST HARMONICS ENDOSONOGRAPHY

The use of Doppler contrast-enhanced EUS using a high mechanical index has been abandoned due to artifacts such as blooming, motion artifacts, poor spatial resolution, and low sensitivity to slow-flow structures<sup>[8]</sup>.

The principle of contrast-enhanced harmonic imaging is to selectively depict signals from the microbubbles of ultrasound contrast agents, which resonate non-linearly when exposed to ultrasonic beams<sup>[9]</sup>. Background tissue signals are automatically subtracted, and only signals from the contrast agent are enhanced. The mechanical index (MI), which represents the ratio between the peak negative pressure amplitude and the square of the frequency, is related to the oscillation of the microbubbles. For an MI value of lower than 0.1, the bubble oscillation is linear, and no harmonics are produced. For an MI value of higher than 0.6, the microbubbles are destroyed. For this reason, an MI value of 0.14-0.4 is used during contrast-enhanced harmonics EUS (CH-EUS). This method enables the dynamic observation of microvessels with slow flows that are not revealed by

Doppler color, which differentiates perfused and non-perfused tissue; however, image resolution is reduced compared to that in B-mode harmonic images.

## EQUIPMENT AND CONTRAST SUBSTANCE

CH-EUS can be performed using dynamic contrast harmonic imaging (dCHI) implemented on the Hitachi platform and using the extended pure harmonic (ExpH) as technique implemented on Aloka platforms. The principle behind the first method is based on the emission of consecutive waves in phase inversion, followed by non-linear oscillation of the microbubbles<sup>[10]</sup>. The second system produces two transmitted pulses that consecutively reach the microbubble, yielding a phase shift between the two received waves<sup>[10]</sup>. The acoustic power used is low to avoid rapid destruction of the microbubbles (0.2-0.4). A suitable dynamic range that enables good visualization of small differences between vessels and the parenchyma and the focus under the target lesion should be fixed before the contrast injection starts.

Two major contrast substances have been used. Sonovue (Bracco Imaging, Milan, Italy) contains microbubbles of sulfur hexafluoride gas enclosed in a lipid shell. Its injection is followed by an arterial phase (the first 25-30 s after the injection) and a venous phase (30-45 s after the injection). Sonazoid (Daiichi-Sankyo, Tokyo, Japan), which is unavailable in Europe and comprises perfluorobutane in a lipid shell, is uptaken by Kupffer cells, conferring a longer duration than Sonovue.

## INDICATIONS FOR THE USE OF CH-EUS

(1) Assessment of solid and cystic lesions of the pancreas; (2) characterization of submucosal neoplasms; (3) assessment of biliary neoplasms; and (4) assessment of lymph nodes.

## SOLID PANCREATIC MASSES

CH-EUS helps in mass differentiation, the differentiation between vascular (solid) and avascular (liquid/necrotic) components of the lesion, and the depiction of the dimensions and margins of the pancreatic mass, including its relationship with adjacent vessels.

### Mass differentiation

CH-EUS examination has to report three descriptors<sup>[11,12]</sup>, and the resulting pattern differs between lesions, enabling differentiation before the pathology result is available (Tables 1 and 2).

**Qualitative assessment:** Adenocarcinoma. Contrast uptake by small vessels reveals the low vascularity of these lesions. The hypoenhanced aspect has been

**Table 1** Descriptors used in harmonic contrast-enhanced endoscopic ultrasound examination

Descriptors	Enhancement	Pattern of distribution	Wash-out
Corresponding feature	Hyper/iso/hypoenhancement Arteriolar density compared to the adjacent normal parenchyma	Homogenous/inhomogenous Vascularity architecture	Slow/Fast Velocity of the venous blood flow
Phase	Arterial	Arterial	Venous

Arterial phase: 20 s to 30-45 s after injection; Venous phase: Later than 30-45 s after contrast injection.

**Table 2** Description of solid and cystic pancreatic lesions during harmonic contrast-enhanced endoscopic ultrasound examination

	Enhancement	Pattern of distribution	Wash-out	
Solid pancreatic lesion	Adenocarcinoma NET Chronic pancreatitis Autoimmune pancreatitis	Hypoenhanced Hyperenhanced > hypoenhanced Isoenhanced/hyperenhanced > hypoenhanced Isoenhanced/hyperenhanced	Homogenous/non-homogenous Homogenous/non-homogenous Homogenous/non-homogenous Homogenous/non-homogenous	Fast Slow > Fast Fast Fast
Cystic pancreatic lesion	SCA MCN Pseudocyst IPMN NET cystic	Hyperenhancement of the vascularized septae, honeycomb aspect highlighted Hyperenhanced thick walls, thick septa and nodules are predictive for malignancy Avascular wall + solid component without any contrast uptake Hyperenhanced septae and vascularized neoplastic nodules Hyperenhanced wall and vascularized nodules	Homogenous Homogenous Fast - Fast Slow	

NET: Neuroendocrine tumor; SCA: Serous cystadenoma; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm.



**Figure 1** Contrast-enhanced harmonics-endoscopic ultrasound of pancreatic adenocarcinoma. Standard endoscopic ultrasound image (left) of a hypoechoic lesion of the pancreatic body. The contrast-enhanced image (right) shows a hypoechoic adenocarcinoma. The dilated pancreatic duct is seen upstream of the lesion.

reported as predictive for malignancy in several series of patients, with sensitivities of 84%-96%, specificities of 64%-94%, and accuracies 82%-92% (Table 3<sup>[12-21]</sup>); further, two studies reported superior results compared to standard EUS<sup>[12,13]</sup>. The pattern of contrast uptake can be inhomogenous when necrosis or intensive fibrosis is present, and fast wash-out is generally seen<sup>[12]</sup>. Some cases (4%-11% of cases) of isoenhanced/hyperenhanced adenocarcinoma aspect have been reported<sup>[14-17]</sup>. However, CH-EUS cannot yet replace EUS-FNA for the differentiation of solid masses<sup>[14,15,17,18]</sup> (Figure 1).

A meta-analysis of the diagnosis of adenocarcinoma published in 2012 proved that hypoenhancement

has a global sensitivity of 94% and a specificity of 89%. However, the main bias of this study was the combination of Doppler and harmonic contrast EUS<sup>[22]</sup>. A second meta-analysis on contrast-enhanced ultrasound included a combination of endoscopic and transabdominal methods, and its results cannot be generalized for CH-EUS<sup>[23]</sup>. In a retrospective study of small pancreatic masses, adenocarcinoma was found in only 40%<sup>[21]</sup> of cases, and CH-EUS might be useful for the identification of such hypoechoic lesions, which can be sent for surgery without EUS-FNA.

Tumor types other than adenocarcinoma, such as neuroendocrine tumors (NET), chronic pancreatitis, autoimmune pancreatitis, serous cystadenoma, and metastasis, are iso/hyperenhanced<sup>[12,14]</sup>, with a sensitivity of 39%-86% and a specificity of 98%<sup>[12,15]</sup>. However, only 69%-100% of NET are hyperenhanced<sup>[12,14,15]</sup>. An inhomogenous pattern in these tumor types corresponding to hemorrhage or necrosis is suggestive of malignancy<sup>[12,24]</sup> and can be seen in 15% of cases<sup>[24]</sup>. Few data are available about the usefulness of CH-EUS compared to standard EUS and were acquired in a very limited number of patients ( $n = 19$ ) (Sn = 78.9%, Sp = 98%), providing a similar value as CT scanning when the small lesions were taken into account<sup>[15]</sup> (Figure 2).

Focal inflammatory mass may have a hypoechoic appearance in standard EUS and may exhibit diffuse iso/hyperenhancement using CH-EUS<sup>[15,16,19]</sup> with homogenous or inhomogenous content and fast wash-out. Sometimes these masses present as hypoechoic lesions (9%-17%) because they exhibit different

**Table 3 Results of contrast-enhanced harmonics-endoscopic ultrasound assessment for solid pancreatic masses in various studies**

Ref.	Type of study	Contrast agent	No. of patients	MI	Hypoenhancement as a sign of adenocarcinoma	EUS diagnostic rate	EUS-FNA diagnostic rate
Napoleon <i>et al</i> <sup>[18]</sup> 2010	Endoscopy	Sonovue	35 PC-18 NET-9 CP-7	0.4	Sn = 89% Sp = 88% PPV = 89% NPV = 88% Acc = 88.5%	-	Sn = 79% Sp = 100% PPV = 100% NPV = 54% Acc = 83%
Fusaroli <i>et al</i> <sup>[12]</sup> 2010	Prospective	Sonovue	90 PC-51, NET-13, CP-13	0.36 radial 0.28 linear	Sn = 96% Sp = 64% Ac = 82%	Sn = 86% Sp = 18% Ac = 57%	-
Ang <i>et al</i> <sup>[19]</sup> 2011		Definity	29 (PC-16, CP-4, Other-9)	0.3	Better detection of vascular invasion and tumor margins	-	-
Matsubara <i>et al</i> <sup>[20]</sup> 2011	Retrospective	Sonazoid	91	0.2	Sn = 87.5% Sp = 77.8%	-	-
Hocke <i>et al</i> <sup>[13]</sup> 2012	Prospective	Sonovue	58	-	Sn = 84% Sp = 76%	Sn = 73% Sp = 61%	-
Kitano <i>et al</i> <sup>[15]</sup> 2012	Prospective	Sonazoid	277 (PC-204, NET-19, CrP-46, Other-8)	0.3	Sn = 95% Sp = 89%	-	Sn = 92% <sup>1</sup> Sp = 100%
Lee <i>et al</i> <sup>[16]</sup> 2013	Prospective	Sonovue	37 (PC-28, NET-5, CP-2)	-	Sn = 93% Sp = 86% PPV = 93% NPV = 75% Acc = 92%	-	-
Gincul <i>et al</i> <sup>[14]</sup> 2014	Prospective	Sonovue	100 (PC-69, NET-10, CP-13, Other-8)	0.4	Sn = 96% Sp = 94% PPV = 94% NPV = 97% Acc = 91%	-	Sn = 95% Sp = 93% PPV = 100% NPV = 100% Acc = 86%
Park <i>et al</i> <sup>[17]</sup> 2014	Retrospective	Sonovue	90	-	Sn = 91.9% Sp = 67.8%	-	Sn = 90% Sp = 100%
Dietrich <i>et al</i> <sup>[21]</sup> 2016	Retrospective	Sonovue	394 PC-146 NET-156	-	Sn = 92%	-	-

<sup>1</sup>91 patients with resected lesions. MI: Mechanical index; PC: Pancreatic cancer; Cp: Chronic pancreatitis; NET: Neuroendocrine tumors; PPV: Positive predictive value; NPV: Negative predictive value; Sn: Sensitivity; Sp: Specificity; EUS-FNA: Endoscopic ultrasound-fine needle aspiration.



**Figure 2** Contrast-enhanced harmonics-endoscopic ultrasound of a neuroendocrine pancreatic tumor. Standard endoscopic ultrasound image (left) of a hypoechoic, well-delineated lesion of the head of the pancreas. The contrast image (right) shows a hyperenhanced lesion that is suggestive of a neuroendocrine tumor, as later proved by fine needle aspiration.

degrees of fibrosis<sup>[14,15,25]</sup>. The presence of calcifications is a confounding factor and should be avoided in the region of interest while analyzing contrast uptake. Only one study on solid pancreatic masses compared the low mechanical index of CH-EUS with the high mechanical index of contrast Doppler CEUS, and the second method was found to be superior. The main reason for

this was the lack of contrast enhancement in patients with chronic pancreatitis, which was perhaps related to the machine settings; however, this cannot be assessed because the settings were not fully reported<sup>[25]</sup>. Autoimmune pancreatitis is usually homogeneously isoechoic<sup>[26]</sup> or hyperenhanced<sup>[14]</sup>.

Cancer metastases are hyperenhanced (renal and thyroid carcinomas, lymphoma, and colon cancer)<sup>[14,27,28]</sup> or are hypoechoic (colon cancer, sarcoma, and breast and ovarian cancer)<sup>[27,28]</sup>; melanoma is isoechoic<sup>[27]</sup>.

Interobserver agreement for solid pancreatic mass diagnosis showed modest results for the examinations using Sonovue ( $k = 0.46-0.66$ ) and for the degree of enhancement<sup>[14,29]</sup>. The  $k$  coefficient was 0.94 for Sonazoid, a value that was perhaps related to the signal intensity and its duration. The effect of the endosonographer in CH-EUS was similar for experienced and non-experienced doctors<sup>[14,29]</sup>, except in one study<sup>[30]</sup>.

**Combined use of qualitative CH-EUS with EUS-FNA:** increased the sensitivity of differential diagnosis using Sonazoid from 92% to 100%, and the specificity was maintained at 92%<sup>[15,17]</sup>; these findings were similar to results obtained using Sonovue<sup>[18]</sup>. In

**Table 4** Quantitative assessment studies for differentiating pancreatic masses

Ref.	Type of study	Type of mass	Contrast agent	Type of echoendoscope	MI	Quantitative assessment	Features useful for differentiation	Diagnostic rate
Seicean <i>et al</i> <sup>[31]</sup> , 2010	Prospective	PC-15 CP-12	Sonovue	Radial	0.36	Hue histogram	Uptake index ratio	Sn = 80% Sp = 91% PPV = 92.8% NPV = 78%
Matsubara <i>et al</i> <sup>[20]</sup> , 2011	Retrospective	PC-48 AIP-14 CP-13 NET-16	Sonazoid	Linear	0.20	TIC	Echo intensity reduction rate relative to the peak at 1 min	Sn = 87.5% Sp = 88.9% EUS + TIC Sn = 95.8% Sp = 92.6%
Gheonea <i>et al</i> <sup>[25]</sup> , 2012	Prospective	CP-19 PC-32	Sonovue	Linear	0.20	Postprocessing TIC	Peak intensity intensity TTP AUC	Sn = 93.7% Sp = 89.4%
Imazu <i>et al</i> <sup>[32]</sup> , 2014	Prospective	AIP-8 PC-22	Sonazoid	Radial	0.25-0.3	TIC	Peak intensity Maximum intensity gain	Sn = 100% Sp = 100%
Săftoiu <i>et al</i> <sup>[33]</sup> , 2015	Prospective	PC-112 CP-55	Sonovue	Linear Radial	0.1-0.3	TIC	Peak intensity Wash-in AUC Wash-in rate Wash-in perfusion index	Sn = 87.5% Sp = 92.72%

MI: Mechanical index; PC: Pancreatic cancer; CP: Chronic pancreatitis; NET: Neuroendocrine tumors; AIP: Autoimmune pancreatitis; PPV: Positive predictive value; NPV: Negative predictive value; Sn: Sensitivity; Sp: Specificity.

addition, the hypoenhanced aspect obtained during CH-EUS proved to be useful in false negative cases of adenocarcinoma<sup>[17,18]</sup>.

**Quantitative assessment:** Several attempts were done to quantify the image obtained during contrast injection. The dedicated software installed with the instruments is difficult to use because respiratory movements cannot be corrected by the software, and the time-intensity curve (TIC) has many artifacts.

The first study using quantitative assessment and harmonics was based on a hue histogram analysis, and the uptake ratio index between the mass and the surrounding parenchyma was 0.17, with a sensitivity of 80%<sup>[28]</sup> (Table 4<sup>[20,25,31-33]</sup>). The post-processing analysis of the time-intensity curves using dedicated software showed that the inflammatory mass studied exhibited a dynamic enhancement pattern using CH-EUS that was similar to that obtained for the rest of the parenchyma, while an adenocarcinoma mass presented low contrast enhancement during the early arterial and late venous phases<sup>[25]</sup>. Two other studies showed that peak intensity and the rate of echo intensity decrease relative to the peak obtained at 1 min were useful for differentiating malignant tumors<sup>[13,26]</sup>.

A large multicentric study showed again that peak intensity and features related to the wash-in phase are good parameters for differentiating pancreatic masses, presenting a similar diagnostic rate to that obtained in studies using Sonazoid. However, the time-to-peak value revealed no significance<sup>[33]</sup>. Post-processing analysis of the TIC in a neural network showed even better diagnostic value, but further results are

expected due to the extensive use of this method<sup>[33]</sup>. However, the software available for use with ultrasound machines awaits further refinement.

#### Mass detection

Mass detection is improved only in cases that are poorly seen using standard EUS, such as chronic pancreatitis or biliary stents<sup>[12]</sup>. CH-EUS is superior to CT for the detection of small tumors (Sn = 91.2%, Sp = 94.4%) but not for the detection of all tumors<sup>[15]</sup>.

#### Tumor staging

Tumor staging appears to be better assessed using Sonazoid<sup>[32]</sup>, in particular because the portal vein wall is more clearly seen<sup>[11]</sup>. No superiority in staging was observed when Sonovue was used<sup>[28]</sup>, although vessel invasion and tumor size were more effectively seen in contrast-enhanced images<sup>[28]</sup>.

#### CH-EUS-FNA

The orientation of the EUS-FNA after contrast injection in the hypoenhanced areas was first described by Kitano and then applied in 26% of cases with mixed adenocarcinoma to aid needle placement in the hypoenhanced area<sup>[14]</sup>.

The guidance of the needle during the venous phase of contrast EUS was reported in some case reports and in three series<sup>[34]</sup>. The diagnostic value was similar to that of standard EUS-FNA in all three studies<sup>[28,35,36]</sup>. In one randomized control study, the first pass provided better cytology results than standard puncture and limited the number of passes<sup>[35]</sup>. Our results showed that a combination of two passes under contrast



**Figure 3** Contrast-enhanced harmonics-endoscopic ultrasound-fine needle aspiration of solid pancreatic adenocarcinoma. Standard endoscopic ultrasound view of a hypoechoic, inhomogeneous adenocarcinoma of the head of the pancreas, showing anechoic parts suggestive of necrosis. The contrast image (right) highlights these avascular parts of the lesion, and the needle inside is clearly seen as avoiding them.

and two standard passes improved core histology-based diagnosis<sup>[28]</sup> (Figure 3). However, further larger multicenter studies are needed to establish the value of this method, which is safe, rapid, and entails minimal extra costs.

## CYSTIC LESIONS OF THE PANCREAS

In cystic lesions of the pancreas (PCL), the cystic wall, septae and nodules are assessed for vascularization using the contrast-enhancing bubble movement<sup>[37]</sup>, with the goal of obtaining a differential diagnosis of PCL and identifying malignancy risk features (vascularized wall nodules and the intracystic solid component).

### Differential diagnosis

The CH-EUS degree and pattern of enhancement aids in the differentiation of PCL when used as an additional examination (Table 2). The method cannot replace EUS-FNA, except for with typical serous cystadenoma (SCA), because in 86% of cases, the aspect is hyperenhanced, with slow wash-out in 78% of cases<sup>[38]</sup>. Mucinous cystadenoma with neoplastic transformation presents thick septa and hyperenhanced mural nodules but cannot be differentiated from macrocystic SCA using CH-EUS<sup>[38]</sup>. Pancreatic pseudocysts have an avascular wall. However, in a series of 46 pseudocysts, three exhibited some wall vascularity<sup>[37]</sup>. These cysts can have a solid component without any contrast uptake during CH-EUS, thus avoiding EUS-FNA with a potential risk of infection<sup>[38]</sup>. Neuroendocrine tumors (NET) with a cystic aspect, despite the presence of a hyperenhanced rim, should be sampled by EUS-FNA to differentiate them from cystic adenocarcinoma.

The wall nodules of mucinous cystic neoplasms (MCNs) or intraductal papillary mucinous neoplasms (IPMNs) at risk of becoming malignant appear as hyper/isoechoic without a hyperechoic rim or are smooth edged, and the Doppler vascularity is seldom



**Figure 4** Contrast-enhanced harmonics-endoscopic ultrasound in mucinous cystadenomashowing features suggestive of malignancy. Standard endoscopic ultrasound image (left) of a macrocystic lesion of the pancreas with mural nodules and thin septae inside. The contrast image (right) shows vascularized mural nodules and no contrast uptake in some of the septae.

positive (2 of 14 cases were resected)<sup>[39]</sup>. CH-EUS is superior to EUS because it reveals small vessels by intense uptake of the contrast substance and differentiates the vessels from mucus or debris, which are not enhanced. Moreover, the CH-EUS may orientate/guide the EUS-FNA<sup>[38]</sup>.

### Identification of risk features for malignancy

CH-EUS differentiates unenhanced mucus or debris from the malignant nodules of MCNs or IPMNs, which are hyperenhanced, and fast wash-out has been reported in some retrospective studies (Table 5; Figure 4). The CH-EUS detection rate of malignant nodules (84%-98%) was found to be superior to that of standard EUS and CT scan in three studies using Sonazoid<sup>[40-42]</sup>. The quantitative analysis of contrast uptake may add supplementary data for use in nodule assessment<sup>[43]</sup>. Several parameters have been described in a retrospective study using Sonazoid, such as the echo intensity change, echo intensity reduction rate and nodule/pancreatic parenchyma contrast ratio. The nodule size on CH-EUS was found to be predictive of malignancy (4 mm and 8 mm)<sup>[41,42]</sup>; however, another study found that size did not have predictive value<sup>[43]</sup>. Hyperenhancement of the solid component might orientate/guide EUS-FNA and help the operator to avoid puncturing debris, sludge and mucus plugs<sup>[38]</sup> (Figure 5).

**Interobserver agreement:** For cyst assessment was moderate for the uptake ( $k = 0.557$ ), slight for the pattern ( $k = 0.083$ ), and fair for the washout ( $k = 0.350$ )<sup>[29]</sup>. Considering mural nodules, interobserver agreement was excellent using Sonazoid as the contrast agent<sup>[42]</sup>.

**Submucosal neoplasms:** Hyperenhancement of the submucosal neoplasm during contrast injection was considered suggestive of gastrointestinal stromal tumor (GIST) and is useful for differentiation from benign hypoechoic lesions, such as lipoma and

**Table 5** Contrast-enhanced endoscopic ultrasound for use in characterizing mural nodules in cystic pancreatic lesions

Ref.	Type of study	MI	No. of patients	Type of cystic lesions	Contrast substance	Detection of mural nodules accuracy	Diagnosis of malignancy	Cut-off height for malignancy diagnosis(mm)
Yamashita <i>et al</i> <sup>[40]</sup> 2013	Retrospective	0.36	17	IPMN	Sonazoid	EUS-0 CT-71% CH-EUS-94%		
Hocke <i>et al</i> <sup>[37]</sup> 2014	Retrospective	0.02-0.18	125	1 MCN 6 MD-IPMN 16 BD-IPMN 103 others	Sonovue	Not defined	Not defined	-
Harima <i>et al</i> <sup>[41]</sup> 2015	Retrospective	-	50	IPMN BD	Sonazoid	CT-92% EUS-72% CH-EUS-98%		8.8 (AUROC = 0.93)
Kamata <i>et al</i> <sup>[42]</sup> 2016	Retrospective	0.30	70	6 MCN 42 BD-IPMNs 4 SCN 18 other	Sonazoid	EUS-73% CH-EUS-84%	EUS-64 CH-EUS-84	EUS-8 mm (AUROC = 0.84) CH-EUS-4 mm (AUROC = 0.93)
Yamamoto <i>et al</i> <sup>[43]</sup> 2016	Retrospective	0.20	30	6/18/2006 MD/BD/Mixt IPMN	Sonazoid		Echo intensity change-0.8 Echo intensity reduction rate-0.9 Nodule/pancreatic parenchyma contrast ratio-0.89	No effect on malignancy rate

IPMNs: Intraductal papillary mucinous neoplasms; CH-EUS: Contrast-enhanced harmonics-endoscopic ultrasound; MCN: Mucinous cystic neoplasm.



**Figure 5** CH-endoscopic ultrasound-fine needle aspiration of a vascularized mural nodules within mucinous cystadenoma. An endoscopic ultrasound-fine needle aspiration needle during the puncture of one of the mural nodules is better seen on the contrast image (right).



**Figure 6** Contrast-enhanced harmonics endoscopic ultrasound of gastric gastrointestinal stromal tumor. Endoscopic ultrasound standard image (right) of a gastric gastrointestinal stromal tumor of the muscularis propria. The contrast image (left) shows hyperenhancement of the lesion.

leiomyoma<sup>[44]</sup>. The consideration of irregular vessels as predictors of GIST malignancy has shown a sensitivity of 100% and a specificity of 63%<sup>[45]</sup>. Interobserver agreement was substantial ( $k = 0.63$ ) for the uptake, slight for the pattern ( $k = 0.18$ ), and fair for the washout ( $k = 0.39$ )<sup>[29]</sup> (Figure 6).

**Biliary tumors:** Biliary polyps have been assessed using CH-EUS. Cholesterol polyps revealed heterogeneous enhancement, and adenoma exhibited homogenous enhancement with a sensitivity and specificity of 75% and 66%, respectively<sup>[46]</sup>. However, the heterogeneous aspect of a cholesterol polyp could be mistaken for adenoma due to the presence of microvessels with hyaline fibrosis<sup>[46]</sup>.

Ampullary carcinoma and biliary tumors are hyper-enhanced with fast wash-out<sup>[19,46]</sup>. The thick wall of the gallbladder makes it difficult to differentiate between malignant tumors and inflammatory modifications using standard EUS; however, CH-EUS improves the accuracy (94% vs 73%)<sup>[47]</sup>. The interobserver accuracy obtained when Sonazoid was used to examine the gallbladder wall was substantial ( $k = 0.77$ )<sup>[47]</sup>.

**Lymph node assessment:** Round shape, sharp edge, and a short axis exceeding 8.3 mm are significantly associated with malignant cytology in LNs<sup>[48]</sup>. A retrospective study of CH-EUS use in LNs showed that 83% of malignant nodes presented a heterogeneous pattern with distorted vessels and



**Figure 7 Elastography of pancreatic neuroendocrine tumor - qualitative assessment.** Endoscopic ultrasound standard image (right) showing a well-delineated hypoechoic lesion of the head of the pancreas. The elastography image (left) exhibits a blue pattern in this neuroendocrine tumor.

that a homogenous enhancement was suggestive of reactive lymph nodes<sup>[43]</sup>. The diagnostic value of CH-EUS for malignancy was characterized by a sensitivity, a specificity and an accuracy of 83%, 91% and 88% respectively<sup>[49]</sup>. Similar results have been reported for the characterization of intra-abdominal lesions of unknown origin<sup>[50]</sup>. The interobserver agreement obtained for LN assessment was excellent ( $k = 0.81$ )<sup>[49]</sup>.

**Limitations:** (1) the duration of contrast enhancement is short, especially for SonoVue; (2) quantitative assessment is difficult due to respiratory movements; and (3) technical standardization is lacking.

**Future perspectives:** The contrast guidance of EUS-FNA could become a routine technique. Because CH-EUS has proven its role to show the change of size and tumor vascularity during chemotherapy for gastric cancers<sup>[51]</sup>, it can be used also assess therapy in other digestive tumors.

### Elastography

**Principle:** This technique assesses the hardness of the tissue by measuring its elasticity, similar to a virtual palpation. The compression of a target tissue by an echo-endoscopic probe produces a displacement of the tissue called "strain", which correlates with the hardness of the structure.

**Technique:** It is essential to establish a large region of interest (ROI) that half comprises the lesion and half comprises the surrounding tissues such that the hardness of the lesion and that of the surrounding tissue can be compared. The probe of the echoendoscope, when upright, creates some pressure, and very small additional movements are important for obtaining the image.

Qualitative assessment is based on superimposing a colored image over the conventional gray-scale EUS image in a region of interest. The strain level of the hard tissue is colored in blue, and the soft tissue is colored

in green. An elastic score has been proposed for the pancreas: homogeneously hard, heterogeneously hard, mixed, heterogeneously soft, and homogeneously soft<sup>[52]</sup>.

Two semiquantitative approaches are included in the software and can be accessed during the EUS procedure. One approach calculates the hue histogram (strain histogram) as the ratio of the strain between two areas that are selected by the investigator, which are situated at the same distance from the transducer to obtain a similar compression by the probe<sup>[13]</sup>. The new generation of EUS elastography enables the operator to calculate the mean strain ratio (SR) within a selected area inside the ROI as the difference in elasticity between the targeted lesion and the surrounding tissue, yielding an objective numeric value. However, it is important to obtain a still image, and for this reason, multiple measurements are performed in each patient<sup>[53]</sup>.

**Indications:** (1) differentiation of the pancreatic masses; (2) differentiation of the lymph nodes; and (3) assessment of fibrosis.

**Differentiation of pancreatic masses:** Normal pancreas tissue appears as soft tissue (green color) in E-EUS. A pancreatic mass, which is usually hypoechoic in standard EUS, appears as homogeneously or inhomogeneously green or blue, depending on tissue hardness<sup>[54-57]</sup>.

Based on this qualitative assessment, the global sensitivity and specificity for pancreatic mass assessment were considered to be 100% and 67%, respectively<sup>[58]</sup>; however, a later multicentric European study found a sensitivity of 93.4% and a specificity of 66%, with a global accuracy of 85.4%<sup>[58]</sup>. Other studies obtained similar sensitivities and lower specificities for discriminating malignant pancreatic masses (Table 6). It was hoped that this examination could discriminate inflammatory changes from tumor involvement of the vessel wall<sup>[59]</sup>, which has not yet been demonstrated (Figure 7).

Using the hue histogram, a value of 175 was found to be suggestive of malignancy<sup>[60,61]</sup>. However, artifacts related to the presence of surrounding structures with excessive or insufficient stiffness<sup>[61]</sup> are very important; therefore, the selection of appropriate regions of interest is of great importance.

Postprocessing analysis of the hue histogram using an artificial neural network enabled an optimal prediction of all types of pancreatic lesions and provided better results than hue histogram analysis<sup>[60,62]</sup>. However, the procedure is complex, and further studies on its practical applicability are warranted.

Multiple studies were performed to measure the mean SR and cut-off value for malignancy. No optimal cut-off value has yet been established for use in malignancy diagnosis (Table 6) due to the interobserver variability of the method and the difficulty of

**Table 6** Efficiency of E-endoscopic ultrasound for solid pancreatic mass assessment

Ref.	Type of study	Final diagnosis	No. of patients	E-EUS assessment	Main results
Giovannini <i>et al</i> <sup>[58]</sup> 2006	Prospective Single center	Surgery EUS-FNA	24	Color pattern	Sn = 100% Sp = 67%
Janssen <i>et al</i> <sup>[75]</sup> 2007	Prospective Single center	Surgery EUS-FNA	73	Color pattern	-
Săftoiu <i>et al</i> <sup>[60]</sup> 2008	Prospective Single center	Surgery EUS-FNA	43	Hue histogram cut-off value=175	Sn = 91%, Sp = 87%, PPV = 88%. NPV = 90%, Acc = 89%
Iglesias-Garcia <i>et al</i> <sup>[72]</sup> 2009	Prospective Single center	Surgery EUS-FNA	130	Color pattern	Sn = 100%, Sp = 85%, PPV = 90%, NPV = 100%, Acc = 94%
Giovannini <i>et al</i> <sup>[79]</sup> 2009	Prospective Multicenter	Surgery EUS-FNA	121	Color pattern	Sn = 92% Sp = 80%
Iglesias-Garcia <i>et al</i> <sup>[57]</sup> 2010	Prospective Single center	Surgical FNA	86	SR = 4.62	Sn = 100%, Sp = 92%
Săftoiu <i>et al</i> <sup>[59]</sup> 2011	Prospective Multicenter	Surgery EUS-FNA	258	Hue histogram cut-off value = 175	Sn = 93%, Sp = 66%, PPV = 92%, NPV = 68%, Acc = 85%
Itokawa <i>et al</i> <sup>[73]</sup> 2011	Retrospective	-	109	SR=39.08	-
Hocke <i>et al</i> <sup>[13]</sup> 2012	Prospective Single center	Surgical EUS-FNA	58	Color pattern	Sn = 94.7% Sp = 33.4%
Figueiredo <i>et al</i> <sup>[71]</sup> 2012	Prospective Single center	Surgical EUS-FNA Follow up	47	SR = 8	Sn = 90% Sp = 75%
Dawwas <i>et al</i> <sup>[70]</sup> 2012	Prospective Single center	Surgical EUS-FNA	111	SR = 4.69 (AUC = 0.69) Masks elasticity (AUC= 0.72)	Sn = 100%, Sp = 16.7%, PPV = 86%, NPV = 100%, Acc = 86% Sn = 95%, Sp = 22%, PPV = 86%, NPV = 50%, Acc = 83%
Lee <i>et al</i> <sup>[74]</sup> 2013	Retrospective	-	15	Color pattern SR = 0.02%	-
Havre <i>et al</i> <sup>[54]</sup> 2014	Prospective	Surgery EUS-FNA Follow-up	48	SR = 4.4	Sn = 67%, Sp = 71%
Rustemovic <i>et al</i> <sup>[93]</sup> 2014	Prospective Single center	Surgery EUS-FNA	149	SR = 7.59	Sn = 100% Sp = 45%
Kongkam <i>et al</i> <sup>[69]</sup> 2015	Prospective Single center	Surgery EUS-FNA	38	SR=3.17	Sn = 86%, Sp = 66%
Opačić <i>et al</i> <sup>[94]</sup> 2015	Prospective Single center	Surgery EUS-FNA	105 pancreatic mass 44 controls	Hue histogram	Sn = 98%, Sp = 50%, PPV = 92%, NPV = 100%, Ac = 69%
Mayerle <i>et al</i> <sup>[68]</sup> 2016	Prospective Single center	Surgery EUS-FNA Follow-up	85	SR = 24.82 or 10	Sn = 77%, Sp = 65% Sn = 96%, Sp = 43%

E-EUS: Elastography endosonography; SR: Cut-off value of strain ratio; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; Acc: Accuracy; EUS-FNA: Endoscopic ultrasound-fine needle aspiration.

standardizing the compression.

Two meta-analyses on the differentiation of malignant pancreatic tumors from inflammatory pancreatic masses, each including 13 studies with 1042 and 1044 patients, showed a sensitivity of 95% and a specificity of 67%-69%, with an AUC of 0.86-0.90<sup>[63,64]</sup>. A third meta-analysis included 7 studies and 752 patients, with a global sensitivity of 97%, a specificity of 76% and an AUC of 0.95<sup>[65]</sup>. This meta-analysis serves as a reminder that it is difficult to differentiate adenocarcinoma and neuroendocrine tumor, which are both hard lesions, using elastography<sup>[65]</sup>. A fourth meta-analysis found that the use of a color pattern for elastography EUS interpretation was associated with a sensitivity of 99% and a specificity of 69%-76%<sup>[65-67]</sup>; moreover, using a hue histogram, the sensitivity was 92% and the specificity was lower, 86%<sup>[66]</sup>. Both of the semiquantitative assessments evaluated by other

meta-analyses showed a sensitivity of 96% and a specificity of 76%<sup>[67]</sup>.

A comparison of B mode EUS, EUS-FNA and EUS elastography favored the standard EUS; the accuracies were 87%, 85% and 73%, respectively<sup>[68]</sup>. A combination of EUS-FNA with SR was not superior to EUS-FNA alone in a study involving 28 patients<sup>[69]</sup>. Due to the low negative value of LR (0.09), this method should be indicated to rule out a diagnosis of malignancy and to avoid unnecessary EUS-FNA<sup>[63]</sup>.

**Limitations:** (1) The control of tissue compression (the degree of compression and the angulation) and motion artifacts determined by respiratory and heart movements is difficult<sup>[69-72]</sup>; (2) adjacent structures with very low or very high density should be avoided (the heart, major vessels). The interposition of cysts or dilated ducts should be avoided because these

**Table 7 Efficiency of E-endoscopic ultrasound for LN assessment**

Ref.	Type of study	Final diagnosis	No. of patients	E-EUS assessment	Main results
Giovannini <i>et al</i> <sup>[58]</sup> 2006	Prospective Single center	EUS-FNA	31	Color pattern	Sn = 100% Sp = 50%
Janssen <i>et al</i> <sup>[75]</sup> 2007	Prospective Single center	EUS-FNA	66	Color pattern	Hard - Acc = 81%-86% Soft - Acc = 84%-86%
Săftoiu <i>et al</i> <sup>[95]</sup> 2007	Prospective Single center	Surgery EUS-FNA	78	Hue histogram	Sn = 85% Sp = 91%
Giovannini <i>et al</i> <sup>[79]</sup> 2009	Prospective Multicenter	Surgery EUS-FNA	101	Color pattern	Sn = 91.8% Sp = 82.5%
Larsen <i>et al</i> <sup>[81]</sup> 2012	Prospective Single center	Surgery	56	Color pattern	Sn = 55%-59% Sp = 82%-85%
Paterson <i>et al</i> <sup>[78]</sup> 2012	Prospective Single center	EUS-FNA	53	Strain ratio for malignancy = 7.5	Sn = 83%, Sp = 96%, PPV = 95%, NPV = 86%, Acc = 90%
Knabe <i>et al</i> <sup>[83]</sup> 2013	Prospective	EUS-FNA	40	Color pattern Computed analysis	Sn = 100% Sp = 64% Computed analysis Sn = 88.9% Sp = 86.7%

E-EUS: Elastographic endosonography; SR: Cut-off value of the strain ratio; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value.

may impair the SR<sup>[73,74]</sup>; (3) the size and depth of the region of interest should be similar when SR is calculated<sup>[73]</sup>. This improves with the experience of the endosonographer, and modern equipment automatically selects the best still image that is representative of the mean SR of the lesion; (4) The negative predictive value remains low, at 60%-70%<sup>[69]</sup>; and (5) The procedure is poorly reproducible, and the coefficient of variance is greater than 0.3<sup>[69]</sup>.

Interobserver variability is good in the case of experienced EUS elastography operators ( $k = 0.8$ ) and is fair in the case of unexperienced EUS elastography operators ( $k = 0.24$ )<sup>[73]</sup>. Intraobserver variability was also good ( $k = 0.86-0.94$ )<sup>[59]</sup>.

#### **Differentiation between benign and malignant lymph nodes:**

The main problem in assessing lymph nodes is to determine when to apply EUS-FNA. Using EUS elastography, benign LNs appear homogenous and are colored green, whereas malignant LNs are colored blue<sup>[75]</sup>. The same color differentiation also proved efficient while applying elastography to endobronchial ultrasound<sup>[76]</sup>. Parts of LNs that appear blue can be targeted by the needle to prove the presence of micrometastasis.

The cut-off SR value for differentiating between malignant and benign LNs in 55 patients was considered to be 3.81<sup>[77]</sup>; a value of 7.5 was found in another group of 53 LNs<sup>[78]</sup>. Interobserver agreement was good to excellent, with a K value for ES of 0.58-0.84 and a value of 0.35 for the ES scoring system<sup>[79-81]</sup> (Table 7).

A meta-analysis, including seven studies and 368 patients, revealed a sensitivity of 88% and a specificity of 85% using elastography EUS for differentiating between malignant and benign LNs<sup>[82]</sup>.

Results concerning the superiority of elastography EUS over EUS are conflicting. The color pattern<sup>[79,83]</sup> and strain ratio were found to be of superior value to conventional EUS criteria<sup>[78]</sup>. However, these results were not sustained in another study that included a surgical pathology comparison<sup>[77]</sup>.

**Assessment of pancreatic fibrosis:** The usefulness of elastography for assessing pancreatic fibrosis distal to a tumor and to differentiate chronic pancreatitis from healthy pancreas was previously proven<sup>[84,85]</sup>. Using a radial scope, an SR cut-off value of 2.25 yielded a diagnosis accuracy of 91% for chronic pancreatitis<sup>[1]</sup> and increased the EUS evaluation yield in 18% of cases. Autoimmune pancreatitis exhibits a blue pattern involving both mass-forming autoimmune pancreatitis and surrounding tissue<sup>[86]</sup>.

A direct relationship was found between the SR and the probability of pancreatic exocrine insufficiency, as measured using the <sup>13</sup>C-MTG breath test, and a probability of 87% was found in patients with an SR of higher than 4.5<sup>[87]</sup>. The results were similar for patients with calcifying and non-calcifying chronic pancreatitis<sup>[87]</sup>. No elastographic studies have compared this finding using radial and linear echoendoscopes.

**Other indications:** Few cases of gastric submucosal tumors have been assessed using elastography<sup>[53,88]</sup>. A GIST may have a non-homogenous blue-green structure, and a typical lipoma is mostly soft, green and homogenous; however, differentiation between benign and malignant lesions using elastography EUS remains difficult.

Sessile rectal adenoma and adenocarcinoma were better differentiated using elastography compared to

**Table 8 Needle confocal laser endosonography features of different cystic lesions of the pancreas**

Type of lesion	nCLE features	Diagnostic rate, references
SCA	A vascular network of the cystic wall	Sn = 69%, Sp = 100%, PPV = 100%, NPV = 82% <sup>[100]</sup>
MCN	A gray band delineated by a thin dark line	Sn = 80%, Sp = 100% <sup>[103]</sup>
IPMN	Papillary projections: characterized by the alternation of vascular cores (white) and epithelial borders	Sn = 67%, Sp = 96% <sup>[100]</sup> Sn = 59%, Sp = 100% <sup>[102]</sup> Sn = 80%, Sp = 92% <sup>[100]</sup>
Pseudocyst	Inflammatory cells bright, gray and black particles	Sn = 43%, Sp = 100%, Acc = 87% <sup>[100]</sup>
Cystic NET	Dark irregular clusters of compact cells + gray tissue of fibrovascular stroma	Sn = 67%, Sp = 96%, Acc = 90% <sup>[100]</sup>

nCLE: Needle confocal laser endosonography; SCA: Serous cystadenoma; MCN: Mucinous cystic neoplasm; IPMN: Intraductal papillary mucinous neoplasm; NET: Neuroendocrine tumor; Sn: Sensitivity; Sp: Specificity; PPV: Positive predictive value; NPV: Negative predictive value; Acc: Accuracy.

standard rectal endosonography, with an SR cut-off mean of 1.25, resulting in a sensitivity of 96% and a specificity of 86%; these results are superior to the use of EUS alone<sup>[89,90]</sup>. This could be important for the local resection of rectal tumors, but multiple studies confirming this indication are needed.

The discrimination between T2 and T3 tumors based on identifying “softer” inflammatory tissue and “harder” tumor tissue has not yet been published.

Elastography was not found to be more useful compared to rectal EUS in patients with fecal incontinence, previously irradiated or not<sup>[91]</sup>, where the sphincter appears as an interrupted inhomogenous thickened layer<sup>[53]</sup>, or for the discrimination of Crohn strictures from adenocarcinoma.

Sclerosing primary cholangitis might have a hard or mixed type common bile duct wall compared to controls; this might be related to an extension of the fibrotic change of the wall<sup>[92]</sup>.

**Future:** Site selection for EUS-FNA<sup>[59,65,93-95]</sup>.

### Needle-based confocal endomicroscopy

**Principle:** Standard confocal laser endomicroscopy (CLE) allows the real-time visualization of cellular and subcellular structures with up to 1000 times magnification and a penetration of 100  $\mu$ m below the mucosal surface<sup>[96]</sup>. The studied tissue is illuminated with a low-power laser, and the fluorescence of light reflected from the tissue is subsequently detected through a pinhole<sup>[96]</sup>. The returned light is reflected by the same lens and reaches the detector of the confocal system. The illumination and detection systems are “confocal”, meaning that they are aligned in the same focal plane<sup>[96]</sup>. A contrast agent is administered intravenously (fluorescein) or topically (acriflavine and cresyl violet) to emphasize the cellular, subcellular and vasculature elements.

In clinical practice, two CLE systems are used: an endoscope-integrated CLE and a probe-based CLE (p-CLE), the latter being the widest system used for the assessment of colonic polyps, neoplastic lesions in inflammatory bowel diseases or Barrett’s esophagus<sup>[97-100]</sup>.

Needle-CLE (nCLE) represents an improved version

of CLE and is performed during EUS; the organs within or adjacent to the GI tract are assessed using a miniprobe, which is passed through an endoscopic needle. nCLE allows *in vivo*, real-time histological diagnosis, thus enhancing EUS performance, mainly in the setting of pancreatic and lymph node lesions<sup>[101]</sup>. Inconclusive diagnostic procedures can be decreased using this technique, termed “optical needle biopsy”<sup>[93]</sup>.

**Technique:** The system comprises an AQ-Flex 19 miniprobe, which is inserted through a 19-gauge EUS needle while a fluorescence contrast agent (acriflavine, fluorescein) provides tissue architecture imaging, similar to standard histological examination (depth 40-70 mm, field of view 325 microns, lateral resolution 3.5 mm).

**Indications:** (1) cystic lesions of the pancreas larger than 1 cm; and (2) solid pancreatic masses and lymph node nCLE remain under evaluation.

**Pancreatic cystic lesions:** The management of cystic lesions is currently suboptimal mainly due to a lack of accuracy in discriminating among different types of pancreatic cystic lesions.

The nCLE patterns for pancreatic cystic lesions were recently published<sup>[96,102,103]</sup> and provide a global accuracy for diagnosis ranging from 46% to 90%<sup>[102-106]</sup>, and studies have underlined the importance of nCLE acting as an optical needle biopsy<sup>[93]</sup> (Table 8). Serous cystadenomas presents a superficial vascular network, which can stop their follow-up<sup>[103]</sup> or avoid an unnecessary resection (reported as 60% in a multicentric study of 2622 patients<sup>[105]</sup>). Benign IPMNs appear as finger-like papillary projections with an epithelial border and a vascular core, while malignant IPMNs appear as dark clumps with fluorescent substance leakage due to tumor neo-vascularization<sup>[103]</sup>.

The multicentric INSPECT study<sup>[106]</sup> showed that the accuracy of differentiating between different types of PCL using nCLE was 41.9%, which is greater than that obtained using a carcinoembryonic antigen (CEA) level > 192 ng/mL (28.6%) or cytology results (29.6%). Epithelial villous structures were found to be predictive of PCL with a specificity of 100%, but the sensitivity

and negative predictive value were only 59% and 50%, respectively<sup>[106]</sup>.

In the DETECT trial<sup>[107]</sup>, nCLE was combined with cystoscopy using a SpyGlass fiberoptic probe in 18 patients with a high probability of having PCNs. Cystoscopy and nCLE were reported to have sensitivities of 90% and 80%, respectively; the combination of the two methods reached a sensitivity of 100% for the clinical diagnosis of mucinous cysts. In addition, both cystoscopy and nCLE exhibited higher sensitivity and accuracy than CEA levels (33% and 61%, respectively) in the entire study population<sup>[107,108]</sup>.

**Limitations:** Inter-observer agreement is considered as globally low<sup>[104]</sup> and fair for MCN, moderate for IPMN, and very good for PC and SCA<sup>[102]</sup>; The operator learning curve of the technique influences the results obtained<sup>[103]</sup>; Sampling error is limited by the location and size of the cyst, the angulation of the needle, and the use of a transgastric or transduodenal approach; Incomplete evaluation - needle entry site, a solid mass inside the cyst; Better in combination with cystoscopy for cyst evaluation<sup>[107]</sup>; Complications of nCLE are seen in up to 3.29%-9% of cases such as pancreatitis or bleeding<sup>[102,106,107]</sup>.

**Solid pancreatic lesions:** Few data are available for nCLE assessment in pancreatic solid lesions, and difficulties have been encountered, especially when using the transduodenal approach.

Normal pancreas has been described as having "an appearance of coffee beans corresponding to acinus"<sup>[108]</sup>. Adenocarcinoma has an aspect of dark cell aggregates and irregular vessels with the leakage of fluorescein<sup>[108]</sup>. Chronic pancreatitis presents as residual regular glandular pancreatic structures<sup>[108]</sup> and white fibrous bands<sup>[109,110]</sup>. Neuroendocrine tumors appear as black cell aggregates surrounded by vessels and fibrotic areas<sup>[108]</sup>.

The sensitivity, specificity and accuracy of this technique were 77%, 100% and 85%, respectively, supporting the use of nCLE instead of repeating EUS-FNA after a previous inconclusive biopsy<sup>[108]</sup>.

Another study used nCLE as optical guidance for EUS-FNA and found an accuracy rate of 90.9% with good inter-observer agreement ( $k = 0.82$ )<sup>[109]</sup>.

**Lymph nodes:** On nCLE, benign lymph nodes have a reticular background with lymphocytes<sup>[111]</sup>. Clusters of dark pleomorphic tumor cells are consistent with carcinoma features, while enlarged follicles are less convincing for malignancy<sup>[112]</sup>. Additionally, significant leakage of fluorescent dye due to tumor angiogenesis is suggestive of malignant nodes<sup>[111]</sup>.

**Future:** Molecular imaging of the pancreas might be feasible using nCLE: pancreatic histology assessment

after the use of a fluorescence-labeled anti-EGF-R antibody<sup>[113]</sup> has been reported. One study recently used nCLE for the visualization of the Meissner and Auerbach plexus after the submucosal injection of NeuroTrace<sup>[114]</sup>, a new step in the assessment of functional and motility disorders of the gastrointestinal tract.

*In vitro* imaging of pancreatic carcinogenesis using nCLE combined with molecular markers, such as cathepsin E<sup>[96]</sup>, has also been reported, with important future clinical implications for the monitoring of pancreatic ductal carcinoma.

Despite its high accuracy and the existence of several clinical applications, nCLE is still used only in research trials, probably due to a lack of standardization, availability and reimbursement in some countries, a lengthy physician learning curve and the broad range of histologic diagnoses. A recent study showed the benefit of using nCLE in cases of "diagnostic doubts", impacting diagnosis and management in 40% of cases and the performance of target biopsies in 100% of cases<sup>[115]</sup>.

## CONCLUSION

The new derivative modalities described above represent a step forward in maximizing the results of endoscopic ultrasonography procedures. The complementary role of these techniques is becoming clearer, and elastography and harmonic contrast-enhanced EUS are suitable for routine use in the future. However, none of these techniques is yet able to replace EUS-FNA.

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