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Review Article

Clinical role of contrast-enhanced harmonic endoscopic ultrasound in differentiating pancreatic solid lesions

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ABSTRACT

Accurate diagnosis of pancreatic solid lesions is often difficult using conventional imaging modalities. With the recent introduction of contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS), it is now possible to evaluate the microvascular environment and dynamic enhancement of a variety of pancreatic lesions. With CEH-EUS, three patterns of pancreatic lesion enhancement compared with the normal pancreatic tissue (fast, simultaneous, or slow), two washout patterns (fast or slow) and two distribution patterns (homogeneous, inhomogeneous) can be described. By evaluating the microvasculature, enhancement speed, and washout pattern, CEH-EUS may help to differentiate pancreatic adenocarcinoma from other masses and differentiate between pancreatic neuroendocrine tumor (pNET) and inflammatory masses. The finding of a hyperenhancing lesion on CEH-EUS, both with homogeneous and inhomogeneous patterns, was a strong predictor of histology different from adenocarcinoma (94% positive predictive value). pNET was the most common hyperenhancing lesions overall. Although CEH-EUS is useful for ruling out pancreatic ductal adenocarcinoma, making the differential diagnosis between pNETs and pseudotumoral pancreatic masses is difficult because both may share an isovascular or hypervascular appearance. Currently the interpretation of CEH-EUS findings is examiner-dependent. In the future, digital image analysis by image-processing techniques should allow more objective interpretation.

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Keywords: Contrast-enhanced endoscopic ultrasound; Mass-forming pancreatitis; Pancreatic ductal adenocarcinoma; Pancreatic neuroendocrine tumor

Introduction

Accurate diagnosis of pancreatic solid lesions is often difficult using conventional imaging modalities. With the recent introduction of contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS), it is now possible to evaluate the microvascular environment and dynamic enhancement of a variety of pancreatic lesions. CEH-EUS enables real-time perfusion imaging absent of Doppler-related artifacts, and visualizes not only pancreatic parenchymal perfusion but also the microvasculature of the pancreas.¹

Up until now, power or color-Doppler mode has been used for dynamic real time imaging of the pancreatic perfusion.^{2–6} However, Doppler related artifacts such as blooming and overpainting, are unavoidable and may hinder differential diagnosis. Another limitation of Doppler mode is that it has limited value in producing parenchymal perfusion images when contrast agents are used. In contrast with CEH-EUS, contrast-enhanced power-Doppler EUS

(CED-EUS) was unable to show parenchymal perfusion images and branching vessels, whereas blooming artifacts of large vessels were observed. These results indicated contrast harmonic technology could improve the accuracy in evaluating tissue vasculature with EUS imaging.

Dietrich et al.⁷ first described CEH-EUS using a preliminary prototype. This technique was subsequently improved and validated by Kitano et al.⁸ The authors reported their experience with dedicated contrast enhancement harmonics and a prototype linear echo-endoscope in various clinical environments such as pancreatobiliary carcinomas. Pancreatic ductal carcinomas are most commonly seen as hypovascular lesions on contrast enhanced computed tomography (CT).^{9–13} Contrast-enhanced ultrasound (CEUS) also demonstrates pancreatic ductal carcinomas as hypovascular lesions but their vascular structures are visualized with more clarity than contrast enhanced CT. CEUS depicts vessels in 36% to 75% of pancreatic ductal carcinomas, whereas, contrast-enhanced CT fails to depict vessels in most pancreatic ductal car-

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cinomas.^{14–21} Because EUS is superior to transabdominal US and CT with respect to spatial resolution, contrast-harmonic technology in the field of EUS should be the most useful tool for depicting small tumors, as well as for differentiating pancreatic solid lesions.

Technique of CEH-EUS

A commercially available radial echo-endoscope (GIF-UE250; Olympus, Tokyo, Japan) is used for the diagnostic imaging. The Aloka α -10 (Aloka, Tokyo, Japan) which incorporates dedicated software for the CEH-EUS is used as the ultrasound processor. The EUS examinations are performed with the patient under conscious sedation and lying on the left lateral decubitus position.

SonoVue[®] (Bracco, Milan, Italy) is used as the contrast agent. CEH-EUS is begun immediately after an intravenous injection of 2.4-mL SonoVue[®]. The second dose of 2.4-mL SonoVue[®] can be administered if the first exam is inconclusive.²² The extended pure harmonic detection mode, which combines receiving frequencies of filtered fundamental and second harmonic components with a transmitting frequency of 3.4 MHz, is used for CEH-EUS.⁸ For an optimal visualization of the microbubbles a mechanical index of 0.36 is required with the radial echo-endoscope.

After having performed a complete EUS examination of the pancreas in B-mode, the echo-endoscope is placed over the area of interest and switched to the CEH mode. The intermittent modality of the monitor is activated to keep a reference B-mode imaging beside the CEH image.

The examination should continue until 150 seconds after SonoVue[®] bolus injection for complete observation of the arterial and venous phases. Ten to 30 seconds after SonoVue[®] is regarded as the early phase, followed by the late phase (30–150 seconds). A few seconds after infusion the microbubbles of SonoVue[®] can be seen as strong white echo-signals depicting large and small vessels. Arterioles and venules, both within the parenchyma and into the tumor, are visualized, as well.²²

Perfusion of the pancreatic lesions is continuous with dynamic observation of the shift from the unenhanced phase to the contrast-enhanced phase. The enhancement pattern of the lesions is compared with that of the adjacent normal parenchyma and is the result of the internal vascular architecture of the lesion (hypovascular or hypervascular, regular or disrupted vessels). A few seconds after infusion of SonoVue[®] the arterial phase is indicated as a strong hyperechogenicity of the aorta and other major per-

ilesional arteries. Approximately 30 seconds after infusion the venous phase begins as recognized by the hyperechogenicity of the splenomesenteric-portal vessels.²²

Usually three patterns of pancreatic mass enhancement compared to the normal pancreatic tissue (fast, simultaneous, or slow), two types of washout (fast or slow) and two types of distribution (homogeneous or inhomogeneous) are described.²² Each examination should be recorded on digital versatile disc (DVD). The videos are reviewed carefully by the endosonographers after each examination and a definition of SonoVue[®] uptake, pattern, and washout is reached.

Differential Diagnosis of Solid Lesions of the Pancreas

Traditionally, contrast-enhanced imaging, such as dynamic computed contrast-enhanced imaging has been used to assess pancreatic tumor vascularization, and thus help with differential diagnosis of pancreatic solid lesions.^{23–27} CEH-ultrasonography enables visualization of the microcirculation and can display information on very small blood flows. Recently several studies have shown that CEH-ultrasonography is an accurate tool for distinguishing pancreatic tumors by displaying their vascularization patterns.^{16,18,28,29}

One retrospective analysis of prospectively enrolled patients showed that among 51 adenocarcinomas, 49 were hypo-enhancing, inhomogeneous, and with fast washout. Sensitivity, specificity, and overall accuracy were 96%, 64%, and 82%, respectively.²² In comparison, the finding of a hypoechoic lesion on standard EUS showed lower sensitivity, specificity, and overall accuracy (86%, 18%, and 57%, respectively) (Table 1).³⁰ The area under the curve (AUC) was extremely high (AUC, 0.801; $P = 0.001$), reflecting a higher diagnostic accuracy for CEH-EUS compared with standard EUS (AUC, 0.521; $P > 0.05$).²² Moreover, the receiver operator characteristic curves showed a greater AUC for CEH-EUS than for standard EUS, confirming a better performance of CEH-EUS for evaluation of adenocarcinoma.²² However, the specificity of CEH-EUS findings for the prediction of adenocarcinoma was lower than in the study by Dietrich et al.⁷ This may be due to the inclusion of focal pancreatitis in this study. However, the differentiation between adenocarcinoma and focal mass-forming pancreatitis was not possible by the sole means of CEH-EUS in 9 of 13 focal pancreatitis cases.

Another recent retrospectively analysis showed among pancreatic carcinomas, 28 out of 30 lesions (93%) had persistent hy-

Table 1 Diagnostic Performance of EUS-FNA and CEH-EUS in Characterizing Solid Pancreatic Lesions in 35 Patients³⁰

	Diagnostic value				
	Sensitivity	Specificity	PPV	NPV	Accuracy
EUS-FNA					
Solid pancreatic masses overall	79 (62–96)	100 (93–100)	100 (98–100)	54 (23–85)	83 (69–97)
Pancreatic adenocarcinoma	72 (49–96)	100 (97–100)	100 (96–100)	77 (57–97)	86 (73–99)
CEH-EUS					
Hypointense echo signal as a sign of adenocarcinoma	89 (64–98)	88 (62–98)	89 (64–98)	88 (62–98)	88.5 (72–96)
Hyperintense echo signal as a sign of lesions other than adenocarcinoma	88 (62–98)	89 (64–98)	88 (62–98)	89 (64–98)	88.5 (72–96)

Values are presented as % (95% confidence interval).

Revised from the article of Napoleon et al (*Endoscopy*. 2010;42:564–70)³⁰ with permission.

EUS-FNA, endoscopic ultrasound fine-needle aspiration; CEH-EUS, contrast-enhanced harmonic endoscopic ultrasound; PPV, positive predictive value; NPV, negative predictive value.

povascular signals in the early and late phase, which indicates a sensitivity and diagnostic accuracy of 93% and 92%, respectively for the diagnosis of pancreatic cancer (Fig. 1).³¹ Hyperenhancement specifically excluded adenocarcinoma (98%), although sensitivity was low (39%).³¹

Another pilot study reported comparison of CEH-EUS findings with the final diagnosis showed that 16 out of 18 lesions with hypo-intense echo signals were adenocarcinomas, whereas 15 out of 17 lesions with isointense or hyperintense signals were lesions other than adenocarcinoma.³⁰

The results of these studies^{22,30,31} demonstrates that a hypo-enhancing mass with an inhomogeneous pattern is sensitive and accurate for the prediction of adenocarcinoma.

The Differential Diagnosis between Mass-Forming Pancreatitis and Pancreatic Adenocarcinoma

Despite the advances in imaging technology, the differential diagnosis between chronic pancreatitis-related inflammatory masses and pancreatic cancer is challenging. One of the indications for pancreatic CEUS is the depiction of the dimensions, border, and vascularity of the lesion, including its relationship with adjacent vessels, which helps to characterize a pancreatic mass as an adenocarcinoma or endocrine tumor.^{32,33} In a recent study, a qualitative visual hypoenhanced pattern after contrast medium injection was not able to differentiate between a benign mass of chronic pancreatitis and adenocarcinoma.³⁴ In contrast, another study on 38 patients reported a hypo-enhanced appearance to be the only variable predictive of malignancy in focal pancreatic solid lesions.³⁵ The hypo-enhanced inhomogeneous pattern was seen more frequently in patients with chronic pancreatitis (6/12), but was also seen in patients with adenocarcinoma (4/15). These findings were confirmed in other reports.³⁰ According to the 2008 CEUS guidelines,^{32,33} most ductal adenocarcinomas are typically hypoenhanced compared to the adjacent pancreatic tissue and most focal pancreatitis have a similar enhancement feature to the normal pancreatic parenchyma. This report has demonstrated that this visual qualitative appreciation is not orientative for discrimination with chronic pancreatitis nodules. The explanation of the hypo-enhanced pattern with chronic pancreatitis could be found in a previous study which demonstrated that the typical

enhancement pattern in CEUS depends on the extent of fibrosis, the proportion of opened vessels, the diameter and the density.²¹ The severe form of chronic pancreatitis represents a long inflammatory process, which may be related to less intense intralesional enhancement,³⁶ and decreasing vascularization resulting from fibrosis is related to hypoenhanced pattern.

The Differentiation of pNET from Pancreatic Ductal Adenocarcinoma and Mass-Forming Pancreatitis

The occurrence of a hyperenhancing lesion on CEH-EUS, both with homogeneous and inhomogeneous patterns, strongly predicted a histology different than adenocarcinoma (94% positive predictive value), that is, pNET and metastases from renal cancer and from melanoma. Overall, pNET was the most common hyper-enhancing lesions.²² Hyper-enhancement was a very specific sign (98%) for exclusion of adenocarcinoma although its sensitivity was low (39%) (Table 2).²² Moreover, 11 of 13 NETs were nonhypo-enhancing (9 hyperenhancing, 2 isoenhancing) (Table 3).²²

Lee et al.³¹ reported that typical enhancement patterns were seen as follows; most ductal adenocarcinoma showed a hypovascular and inhomogeneous appearance, most pNETs showed a hypervascular and homogeneous appearance and most inflammatory masses showed an isovascular or hypervascular and homogeneous appearance. The enhancement level in early phase was maintained to late phase in most patients with three diseases category. Ninety-four percent of pancreatic carcinoma (28/30) showed a persistent hypovascularity, 75% of pNETs (3/4) showed a persistent hypervascularity (Fig. 2) and 67% of inflammatory masses (2/3) showed a persistent isovascularity.³¹ These results demonstrated that the change of enhancement level as well as the enhancement level in the early phase may be important for the differential diagnosis. Further investigations should evaluate whether not only enhanced echo intensity but also the architecture of the fine vessel network might be helpful in distinguishing pNETs from pancreatitis-associated masses.³⁰

Although CEH-EUS helps to rule out pancreatic adenocarcinoma, differentiation between pNETs and pseudotumoral pancreatic masses is difficult because both may appear as isovascular or hypervascular lesions.³⁷ Recently, one study reported that contrast enhancement and washout speed differed between car-

Fig. 1. Pancreatic adenocarcinoma. (A) The tumor shows a hypointense echo signal with fine branches in the early phase. (B) Persistent hypointensity is noted in the late phase.

cinoma, pNET, and inflammatory masses. The authors showed that the enhancement speed compared to normal pancreatic tissue was slower for most carcinomas (26/30, 87%), simultaneous for inflammatory masses (2/3, 67%), and faster for pNETs (100%). Fast washout was observed in 28 of 30 carcinomas (93%) and all three inflammatory masses, whereas slow washout was observed in three of four pNETs.³¹ In accordance with this, Fusaroli et al²² reported that fast washout was observed in the majority of pancreatic carcinoma and inflammatory mass and that slow washout indicative of pNET. Therefore, among the isovascular/hypervascular masses that were difficult to diagnose differentially, fast enhancement and slow washout suggested pNET, and simultaneous

enhancement and fast washout indicated an inflammatory mass more likely.

Other Exocrine Tumors

The typical imaging pattern of exocrine tumors other than pancreatic adenocarcinoma, which comprise approximately 10% of all exocrine tumors, has not been well described. Lee et al³¹ reported that one acinar cell carcinoma and two intraductal papillary mucinous neoplasms (IPMNs) with invasive adenocarcinoma also had hypovascularity, slow enhancement and fast washout. Two other studies with a total of four patients reported that acinar

Table 2 Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of Standard EUS and CEH-EUS²²

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Hypoechoic lesion on standard EUS as a predictor of adenocarcinoma	86 (73–94)	18 (8–34)	58 (47–69)	59 (24–76)	57 (50–64)
Hypoenhancing lesion on CEH-EUS as a predictor of adenocarcinoma	96 (85–99)	64 (47–78)	78 (65–87)	93 (74–99)	82 (74–85)
Hyperenhancing lesion on CEH-EUS as an exclusion sign of adenocarcinoma	39 (30–41)	98 (92–100)	94 (74–99)	68 (63–69)	72 (65–74)
Hyperenhancing lesion on CEH-EUS as a predictor of NET	69 (46–86)	90 (87–94)	56 (33–76)	95 (87–98)	88 (81–93)

Values are presented as % (95% confidence interval).
Revised from the article of Fusaroli et al (*Clin Gastroenterol Hepatol.* 2010;8:629–34)²² with permission.
EUS, endoscopic ultrasound; CEH-EUS, contrast-enhanced harmonic EUS; NET, neuroendocrine tumor.

Table 3 Correlation between Final Diagnosis and Sonovue Pattern²²

Sonovue pattern according to final diagnosis					
Adenocarcinoma (n = 51)		NET (n = 13)		Focal pancreatitis (n = 13)	
Hypoenhancing	49	Hypoenhancing	2	Hypoenhancing	9
Hyperenhancing	1	Hyperenhancing	9	Hyperenhancing	0
Isoenhancing	1	Isoenhancing	2	Isoenhancing	4
Homogeneous	1	Homogeneous	9	Homogeneous	4
Inhomogeneous	50	Inhomogeneous	4	Inhomogeneous	9
Fast	50	Fast	4	Fast	10
Slow	1	Slow	9	Slow	3

Revised from the article of Fusaroli et al (*Clin Gastroenterol Hepatol.* 2010;8:629–34)²² with permission.

Fig. 2. Pancreatic neuroendocrine tumor. (A) The tumor shows a diffuse hyperintensity persisted in the early phase. (B) Hyperintensity is persistent in the late phase.

Fig. 3. Pancreatic acinar cell carcinoma. (A) The tumor shows a hypointense echo signal with heterogeneous enhancement in the early phase. (B) Persistent hypointensity and heterogeneous enhancement is noted in the late phase.

cell carcinoma showed moderate, heterogeneous enhancement due to its moderate vascularization or slight hypervascularization.^{14,38} In one study,³¹ one patient with acinar cell carcinoma showed heterogeneous, hypo-enhancing pattern (Fig. 3). Since Lee et al³¹ included only one acinar cell carcinoma, it is difficult to say why it showed a hypo-enhancement pattern, in contrast to previous reports. Regarding invasive IPMN, the cyst walls showed hypo-enhancement and the mural nodules revealed branch-shaped enhancement patterns in previous studies.^{39,40} Kurihara et al⁴⁰ reported that the branch-shaped pattern lesion in IPMN was associated with carcinoma. Similarly, in one invasive IPMN case with a mural nodule, Lee et al³¹ showed branch-shaped enhancement in the mural nodule and hypo-enhancement of the cyst wall.

The Advantage and Limitation of CEH-EUS

The advantage of CEH-EUS compared with standard EUS or EUS fine-needle aspiration (EUS-FNA) are as follows. A CEH-EUS may overcome limitations and improve the diagnostic accuracy. Interestingly, in 7 patients whose pancreas was visualized inadequately owing to biliary stents or diffuse chronic pancreatitis, a small hypo-enhancing lesion was clearly seen only by CEH-EUS, allowing targeting of EUS-FNA. The final diagnosis was adenocarcinoma in all these patients. After a careful review of these videos, it was the common opinion of the investigators that these lesions were visualized inadequately with standard EUS and that CEH-EUS was fundamental for targeting EUS-FNA. In this respect, CEH-EUS provided an increase in diagnostic yield of pancreatic adenocarcinoma of almost 8%.²² CEH-EUS was also helpful in ruling out neoplastic lesions in patients without pathologic results. Of 5 cases presenting with mild focal echostructural changes of uncertain interpretation on standard EUS, 4 were iso-enhancing on CEH-EUS (i.e., the uncertain areas showed an identical uptake of SonoVue[®] compared with the normal surrounding parenchyma). The absence of disease was confirmed by negative EUS-FNA and follow-up evaluation.²² On the other hand, the finding of a hyper-enhanced lesion was highly predictive of a lesion different from adenocarcinoma.²²

The limitation of CEH-EUS is that making the differential diagnosis between NET and pseudotumoral pancreatic mass is

difficult because both diseases can have an iso-vascular or hyper-vascular appearance.³⁷ Nevertheless, there is an inverse relation between the echo intensity and the length of the inflammatory process, most likely related to an increase of the fibrosis. Therefore, the sonographic features of pancreatic cancer and chronic pancreatitis can be very similar and may even coexist within the same patient.⁴¹

Future Technique

Currently the interpretation of CEH-EUS findings is examiner-dependent. In the future, digital image analysis by image-processing techniques should allow more objective interpretation.⁴²

Dynamic CEUS (DCE-US) and other novel imaging methods that aim at functional imaging with the potential to provide objective and quantitative information regarding microvasculature have recently been introduced.^{43–48} Quantification was performed using the most recent quantification software (VueBox[®]; Bracco Suisse SA, Geneva, Switzerland). This current software enables the standardization of the quantification process. After uploading the clip-sequences, a calibration of the software (based on ultrasound system, probe, presets, gain used) and motion compensation are required to achieve sufficient reproducibility independent of the used ultrasound equipment. By using quantification techniques in CEUS, an evaluation of the wash-in and wash-out phases at certain points of time and the description of peak enhancement are possible. The examination of tumors in real-time with continuous recording and high temporal resolution is not possible with other noninvasive imaging techniques.

Limitations of DCE-US might be a low quality in necrotic and poorly vascularized lesions with difficulties in the differentiation of malignancy from inflammation (e.g., in pancreatic lesions). Of course this is a common problem in medical imaging and even in the processing of pathologic specimens. VueBox[®] will hopefully help future studies to validate one or the other method, depending on the indications.

Conclusion

Through the evaluation of tumor microvascularization (early

and late phase), enhancement speed, and washout pattern, CEH-EUS may help differentiate adenocarcinoma from other masses and distinguish between pNET and inflammatory masses. Still, larger prospective studies are needed to clarify the clinical role of CEH-EUS in the evaluation of pancreatic solid masses and to characterize the architectural patterns of microcirculation in pancreatic solid lesions. VueBox[®] is now available as a reliable solution to improve the reproducibility of results across centers with different systems due to valid and robust quantification of local contrast agent concentration.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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