

## Contrast Harmonic Echo–Endoscopic Ultrasound Improves Accuracy in Diagnosis of Solid Pancreatic Masses

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**BACKGROUND & AIMS:** Contrast harmonic echo (CHE) has been developed for endoscopic ultrasound (EUS). This new technique detects echo signals from microbubbles in vessels with very slow flow, without artifacts. We assessed whether CHE–EUS increases the accuracy of diagnosis of pancreatic solid lesions. **METHODS:** At a tertiary-care EUS center, we examined 90 patients who were suspected of having pancreatic solid neoplasm. Radial and linear echoendoscopes were used with dedicated software for CHE. SonoVue (Bracco International BV, Amsterdam, The Netherlands) uptake, pattern, and washout were studied; data were compared for pancreatic lesions and adjacent parenchyma. The final diagnosis was obtained based on results of surgical pathology and/or EUS–fine needle aspiration (FNA) analyses. **RESULTS:** The finding of a hypoechoic mass with an inhomogeneous pattern was a sensitive and accurate identifier of patients with adenocarcinoma (96% and 82%, respectively) (49 of 51 patients with primary pancreatic adenocarcinoma had a hypoechoic mass that was inhomogeneous and had fast washout). This finding was more accurate in diagnosis than the finding of a hypoechoic lesion using standard EUS ( $P < .000$ ). Hyperenhancement specifically excluded adenocarcinoma (98%), although sensitivity was low (39%). Of neuroendocrine tumors, 11 of 13 were non-hypo-enhancing (9 hyperenhancing, 2 iso-enhancing). Interestingly, CHE–EUS allowed detection of small lesions in 7 patients who had uncertain standard EUS findings because of biliary stents ( $n = 5$ ) or chronic pancreatitis ( $n = 2$ ). Targeted EUS–FNA was performed on these lesions. **CONCLUSIONS:** **Detection of a hypoechoic and inhomogeneous mass accurately identified patients with pancreatic adenocarcinoma. CHE–EUS increased the detection of malignant lesions in difficult cases (patients with chronic pancreatitis or biliary stents) and helped guide EUS–FNA. A hyperenhancing pattern could be used to rule out adenocarcinoma.**

**Keywords:** Contrast Agents; Image Enhancement; Contrast Harmonic; Echo Features; Pancreatic Lesions.

Intravenous ultrasound contrast agents are made of microbubbles filled with heavy gases that allow a better visualization of the blood supply.<sup>1</sup> Their use has become a standard of practice in transabdominal ultrasound to detect and characterize focal lesions of the liver and the pancreas.<sup>2</sup> Ultrasound contrast agents have been shown to improve the diagnostic accuracy and overcome some technical limitations owing to meteorism and abdominal fat.<sup>3–7</sup>

On the other hand, the use of ultrasound contrast agents in endoscopic ultrasound (EUS) is not widespread yet. The major

limitation is attributable to their use in combination with nondedicated techniques such as color- and power-Doppler<sup>8–15</sup> that are hampered by several artifacts.

A dedicated contrast harmonic echo (CHE) has become available for the enhancement of ultrasound contrast agents in EUS only recently. CHE–EUS is a new technique that is able to detect signals from microbubbles in vessels with very slow flow without the burden of Doppler-related artifacts.

We have used CHE–EUS with SonoVue (sulfur hexafluoride MBs; Bracco International BV, Amsterdam, The Netherlands) for the investigation of patients with pancreatic solid masses since 2007. The aim of our study was to assess whether CHE–EUS increases diagnostic accuracy of pancreatic solid lesions by improving differential diagnosis.

### Materials and Methods

#### Patients

This was a retrospective analysis of prospectively enrolled patients between July 2007 and December 2008.

#### Inclusion Criteria

Inclusion criteria for the study were as follows: echofeatures of an undetermined, predominantly solid pancreatic lesion seen at standard EUS (ie, the solid component was  $\geq 50\%$  of the total volume of the lesion). All the patients had been referred for EUS after detection of the lesions by transabdominal ultrasound and/or computerized tomography and/or magnetic resonance imaging.

#### Exclusion Criteria

Exclusion criteria were a known or suspected unstable coronary disease or patients unwilling to consent.

This study was approved by our local ethics committee.

#### Gold Standard of Diagnosis

The final diagnosis was achieved either by surgical pathology ( $n = 65$ ) or by aspiration cytology/histology with EUS–fine-needle aspiration (FNA) ( $n = 78$ ). Some patients had both techniques performed ( $n = 60$ ). Patients with EUS–FNA–nega-

**Abbreviations used in this paper:** AUC, area under the curve; CHE, contrast harmonic echo; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; NET, neuroendocrine tumors; ROC, receiver operator characteristic.

tive results for malignancy were always followed up with clinical and instrumental examinations to rule out false-negative results (minimum follow-up period, 12 months).

### ***Echoendoscopes and Standard Endoscopic Ultrasound Technique***

We used radial and linear echoendoscopes for this study. Both echoendoscopes were equipped with a pink ultrasound transducer purposely developed for CHE-EUS.

A commercially available radial echoendoscope (GFUE160; Olympus, Tokyo, Japan) was used for the pure diagnostic imaging. A prototype linear echoendoscope (XGF-UCT180; Olympus) was used both for diagnostic imaging and for EUS-FNA. The ultrasound processor was the Aloka Alfa-10 (Aloka, Tokyo, Japan), which incorporates dedicated software for the CHE.

The EUS examinations were performed under conscious sedation using meperidine and midazolam with patients lying on the left lateral decubitus.

All the EUS examinations were performed by experienced endosonographers (G.C. and P.F.). The techniques of EUS examination and of EUS-FNA were described in detail elsewhere.<sup>16</sup>

### ***Technique of Contrast Harmonic Echo-Endoscopic Ultrasound***

Sonovue was used as the contrast agent in all the cases.

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, was used for CHE-EUS.<sup>17</sup>

For an optimal visualization of the microbubbles a mechanical index of 0.36 was required with the radial echoendoscope and of 0.28 with the linear echoendoscope.

The standard dose of Sonovue was 2.5 mL. Notably, no difference in image quality was obtained by using a full vial or a half vial of Sonovue (5 vs 2.5 mL) in our experience before this study (data not shown).

After having performed a complete EUS examination of the pancreas in B-mode, the echoendoscope was placed in front of the pancreatic area of interest and switched to the CHE mode. The intermittent modality of the monitor was activated to keep a reference B-mode imaging beside the CHE image. For each examination, 2.5 mL of Sonovue rapidly was injected intravenously followed by a 5-mL flush of saline. Then, Sonovue uptake and washout were evaluated for at least 150 seconds in each lesion.

The CHE screen is almost black at baseline. A few seconds after infusion the microbubbles of Sonovue are seen as strong white echo-signals depicting large and small vessels. Arterioles and venules, both within the parenchyma and into the tumor, are visualized, too.

Perfusion of the pancreatic lesions was continuous with dynamic observation of the shift from the unenhanced phase to the contrast-enhanced phase. The enhancement pattern of the lesions was compared with that of the adjacent normal parenchyma and was 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 was observed as hyperechogenicity of the aorta and other major perilesional arteries. Approximately 40 seconds after in-

fusion the venous phase began as recognized by the hyperechogenicity of the splenomesenteric-portal vessels.

Similarly to transabdominal ultrasound, the Sonovue uptake was differentiated into 3 patterns (hyperenhancement, iso-enhancement, and hypoenhancement). We also defined 2 distribution patterns (homogeneous, inhomogeneous), and 2 types of washout (slow, fast).

Each examination was recorded on DVD. The videos were reviewed carefully by the endosonographers after each examination and a definition of Sonovue uptake, pattern, and washout was reached by consensus in all cases.

### ***Statistical Analysis***

The sensitivity, specificity, positive predictive value, negative predictive value, and accuracy in the characterization of adenocarcinoma were calculated for standard EUS and CHE-EUS, and in the characterization of lesions other than adenocarcinoma for CHE-EUS.

In addition to evaluation of adenocarcinoma, receiver operator characteristic (ROC) analysis was performed for a comparison between standard EUS and CHE-EUS to examine the interaction between sensitivity and specificity, and to quantify test performance using the area under the curve (AUC) and *P* value.<sup>18,19</sup>

Statistical data analysis was performed with the statistical software SPSS 15.0 for Windows (SPSS Inc, Chicago, IL).

## **Results**

In the study period, 114 patients were referred to our gastrointestinal unit for suspected pancreatic solid neoplasms. Among these, 24 patients were excluded because no solid tumors were found at standard EUS (cystic lesions, 17; bile duct stones, 5; inability to image the entire pancreas because of previous gastric surgery, 2).

CHE-EUS was performed on 90 patients who constituted our study group. Their echofeatures at standard EUS were as follows: hypoechoic lesions either with regular or irregular margins (*n* = 76), isoechoic lesions (*n* = 5), hyperechoic lesions (*n* = 1), and ill-defined lesions owing to concomitant chronic pancreatitis and/or biliary stents (*n* = 8). The final diagnosis for

**Table 1.** Population Characteristics

Median age, <i>y</i> (range)	67 (34–86)
Sex	44 M, 46 F
Median size of the lesions, <i>mm</i> (range)	25.0 (9–100)
Location of the lesions	Head, 57; body, 30; tail, 3
Final diagnosis	
Adenocarcinoma	51
NET	13
Focal pancreatitis	13
No pathologic finding	5
Metastasis, renal	2
Metastasis, melanoma	1
Metastasis, sarcoma	1
Abscess	1
Schwannoma	1
Juxta-ampullary carcinoma	1
Intrapancreatic lymph node	1

**Table 2.** Correlation Between Final Diagnosis and Sonovue Pattern

Final diagnosis according to Sonovue pattern					
Hypoenhancing (n = 63)		Hyperenhancing (n = 16)		Isoenhancing (n = 11)	
Adenocarcinoma	49	NET	9	NET	2
Focal pancreatitis	9	Metastasis (renal)	2	No pathologic finding	4
NET	2	Juxta-ampullary carcinoma	1	Focal pancreatitis	4
Intrapancreatic lymph node	1	Metastasis, melanoma	1	Adenocarcinoma	1
Metastasis, sarcoma	1	No pathologic finding	1		
Schwannoma	1	Abscess	1		
		Adenocarcinoma	1		

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

each case according to either surgical pathology or EUS-FNA combined with follow-up evaluation is reported in Table 1.

The classification of final diagnosis according to the Sonovue patterns of uptake, distribution, and washout is shown in Table 2. The analysis of Sonovue patterns in relation to the final diagnosis also is shown in Table 2.

Primary pancreatic adenocarcinoma was the most frequent lesion in our population. Of note, of 51 adenocarcinomas, 49 turned out to be hypoenhancing, inhomogeneous, and with fast washout (Figure 1). Sensitivity, specificity, and overall accuracy were 96%, 64%, and 82%, respectively. In comparison, the finding of a hypoechoic lesion on standard EUS showed lower sensitivity, specificity, and overall accuracy (86%, 18%, and 57%, respectively) (Table 3).

The AUC of the ROC analysis for standard EUS was 0.521 (standard error, 0.062) ( $P = NS$ ), whereas for CHE-EUS the AUC was 0.801 (standard error, 0.051), (extremely significant:  $P < .001$ ) (Supplementary Figure 1). The ROC curve calculated for CHE-EUS showed an AUC greater than standard EUS (difference between areas, 0.280).

Interestingly, CHE-EUS allowed detection of small hypoenhancing lesions in 7 of 8 patients with uncertain standard EUS findings owing to biliary stents ( $n = 5$ ) or diffuse chronic pancreatitis ( $n = 2$ ) (Figure 1). Targeted EUS-FNA of these hypoenhancing lesions detected malignant cells. The mean size of these lesions was 18.8 mm (range, 15–30 mm).

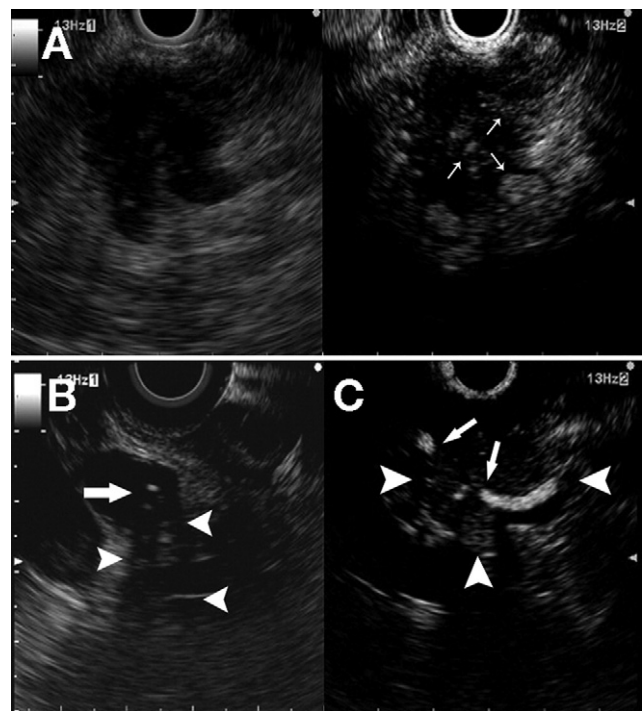
Hyperenhancement was a very specific sign (98%) for exclusion of adenocarcinoma although its sensitivity was low (39%). Moreover, 11 of 13 neuroendocrine tumors (NET) were non-hypoenhancing (9 hyperenhancing, 2 iso-enhancing) (Table 3 and Figure 2).

No complications occurred related to the use of Sonovue.

**Discussion**

Higher sensitivity and specificity have been reported for EUS in the diagnosis of pancreatic malignancies in comparison with transabdominal ultrasound, computed tomography, and magnetic resonance imaging.<sup>20–25</sup>

However, EUS presents some limitations. It is operator-dependent and biliary stents and chronic pancreatitis are well-known confounding factors.<sup>26,27</sup> EUS-FNA often is required for tissue confirmation but it may be hampered by the same factors.<sup>28–31</sup>



**Figure 1.** (A) Left panel: standard EUS shows a hypoechoic mass with irregular margins. Right panel: CHE-EUS shows a hypoenhancing lesion with small and large intratumoral vessels (arrows) with inhomogeneous pattern predicting an adenocarcinoma. (B) Another case in which a biliary stent (arrow) is creating artifacts (arrowheads), hampering the exploration of the pancreatic head. (C) After Sonovue injection a small hypoenhanced area (arrowheads) is detected with disrupted internal vessel (arrows). Targeted EUS-FNA revealed adenocarcinoma.

**Table 3.** Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, and Accuracy of Standard EUS and CHE-EUS

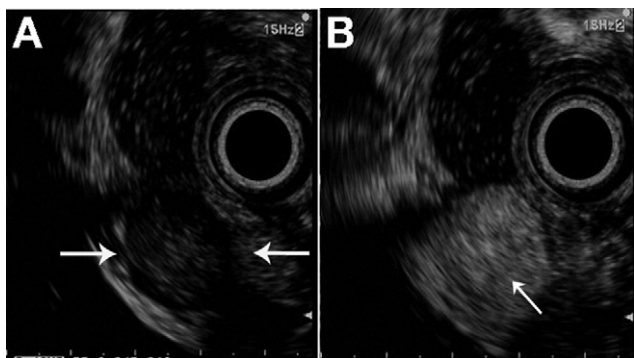
	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Accuracy
Hypoechoic lesion on standard EUS as a predictor of adenocarcinoma	86% (73%–94%)	18% (8%–34%)	58% (47%–69%)	59% (24%–76%)	57% (50%–64%)
Hypoechoic lesion on CHE-EUS as a predictor of adenocarcinoma	96% (85%–99%)	64% (47%–78%)	78% (65%–87%)	93% (74%–99%)	82% (74%–85%)
Hyperenhancing lesion on CHE-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 CHE-EUS as a predictor of NET	69% (46%–86%)	90% (87%–94%)	56% (33%–76%)	95% (87%–98%)	88% (81%–93%)

NOTE. Data in parentheses are 95% confidence intervals.

We have shown that CHE-EUS may overcome some of these 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 hypoechoic lesion clearly was seen only by CHE-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 CHE-EUS was fundamental for targeting EUS-FNA. In this respect, CHE-EUS provided an increase in diagnostic yield of pancreatic adenocarcinoma of almost 8%.

Until now, contrast-enhanced EUS has been performed with power- or color-Doppler. Dietrich et al<sup>8</sup> used contrast-enhanced color-Doppler EUS to investigate patients with an undetermined pancreatic tumor. Ductal adenocarcinoma of the pancreas showed a hypovascularity in 57 of 62 cases whereas all other pancreatic lesions showed isovascularity or hypervascularity (20 neuroendocrine tumors, 10 serous microcystic adenomas, and 1 teratoma). In their experience, hypovascularity as a sign of malignancy in contrast-enhanced EUS obtained 92% sensitivity and 100% specificity.

We used Sonovue in combination with the dedicated CHE-EUS technique. Unlike contrast-enhanced color- and power-Doppler EUS that are limited by movement artifacts (known as ballooning and overpainting), CHE-EUS allowed a clear depiction of small intrapancreatic and intratumoral vessels.



**Figure 2.** (A) Before injection of the contrast a hypoechoic lesion is visible in the pancreatic head (arrows). (B) In the arterial phase, approximately 23 seconds after Sonovue injection, the lesion becomes markedly hyperenhanced with a homogeneous pattern predicting a neuroendocrine tumor (arrow).

The first description of CHE-EUS with a preliminary prototype was given by Dietrich et al.<sup>32</sup> The technique subsequently was improved and validated by a Japanese study<sup>17</sup> reporting the experience with a dedicated CHE and a prototype linear echoscope in mixed clinical conditions such as pancreatobiliary carcinomas, gastrointestinal stromal tumors, and lymph node metastases. In this feasibility study it was shown that a mechanical index of 0.4 allowed a successful visualization of parenchymal perfusion and microvasculature in the pancreas. On the other hand, contrast-enhanced power-Doppler EUS did not depict the parenchymal perfusion images and branching vessels, whereas blooming artifacts of large vessels were observed.

Our finding of a hypoechoic mass with an inhomogeneous pattern was very sensitive and accurate for the prediction of adenocarcinoma (96% and 82%, respectively). The AUC was extremely significant (AUC, 0.801;  $P < .001$ ), reflecting a higher diagnostic accuracy for CHE-EUS compared with standard EUS (AUC, 0.521;  $P = NS$ ).

Besides, the ROC curves showed a greater AUC for CHE-EUS than for standard EUS, confirming a better performance of CHE-EUS for evaluation of adenocarcinoma.

However, the specificity of this CHE-EUS finding for the prediction of adenocarcinoma was lower than in the study by Dietrich et al.<sup>8</sup> We believe that this difference was owing to the inclusion of focal pancreatitis in our study. We think that the real clinical conditions are better represented this way rather than restricting the analysis only to neoplastic lesions. However, the differentiation between adenocarcinoma and focal mass-forming pancreatitis was not possible by the sole means of CHE-EUS in 9 of 13 focal pancreatitis cases. Recently accomplished improvements of the settings of the CHE in the ultrasound processor are currently under evaluation for differential diagnosis in this respect.

The finding of a hyperenhancing lesion on CHE-EUS, both with homogeneous and inhomogeneous patterns, was a strong predictor of histology different than adenocarcinoma (94% positive predictive value), that is, NET and metastases (from renal cancer and from melanoma). NET were the most common hyperenhancing lesions overall. Based on these findings, we believe that a hyperenhancing lesion in a patient with clinical suspicion of NET mandates surgical resection without the need of EUS-FNA. Metastases from renal cancer showed the same behavior of NET (hyperenhanced, homogeneous pattern, slow washout). In these cases a good knowledge of the patient's

medical history was fundamental to make a distinction between the 2 entities.

CHE-EUS was also helpful in ruling out neoplastic lesions in patients whose final outcome was the absence of pathologic findings. Of 5 cases presenting with mild focal echostructural changes of uncertain interpretation on standard EUS, 4 were iso-enhancing on CHE-EUS (ie, 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.

As far as costs are concerned, we believe that CHE-EUS did not weigh significantly on the whole expenses of the procedure (the cost of half a Sonovue vial is about 10% of the cost of a EUS-FNA needle in our country). Our proposal of a clinical algorithm incorporating CHE-EUS is shown in [Supplementary Figure 2](#).

Lastly, it deserves mentioning another technique of image enhancement. EUS-elastography is used to differentiate potentially neoplastic tissue from inflammation. It is based on the measurement of tissue stiffness performed with the ultrasound processor: this parameter appears to correlate with the malignant potential of the lesions. EUS-elastography is a software-based analysis and no contrast injection is needed.<sup>33</sup> No systematic comparison between CHE-EUS and EUS-elastography has been published. A preliminary experience on 21 patients presented at Digestive Diseases Week reported that CHE-EUS was superior to EUS-elastography for the differentiation between benign and malignant pancreatic lesions.<sup>34</sup> However, larger studies are warranted on this issue.

In summary, CHE-EUS was shown to be feasible and safe for the study of solid lesions of the pancreas. It was able to depict the small vessels by Sonovue enhancement without the common artifacts encountered with contrast-enhanced color- and power-Doppler EUS. The finding of a hypo-enhanced lesion with inhomogeneous uptake was a sensitive and accurate predictor of pancreatic adenocarcinoma. Moreover, CHE-EUS allowed overcoming artifacts induced by biliary stents and chronic pancreatitis and performance of targeted EUS-FNA, to improve the diagnosis of pancreatic adenocarcinoma. On the other hand, the finding of a hyper-enhanced lesion was highly predictive of a lesion different from adenocarcinoma.

## Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at [www.cghjournal.org](http://www.cghjournal.org), and at doi:10.1016/j.cgh.2010.04.012.

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**Reprint requests**

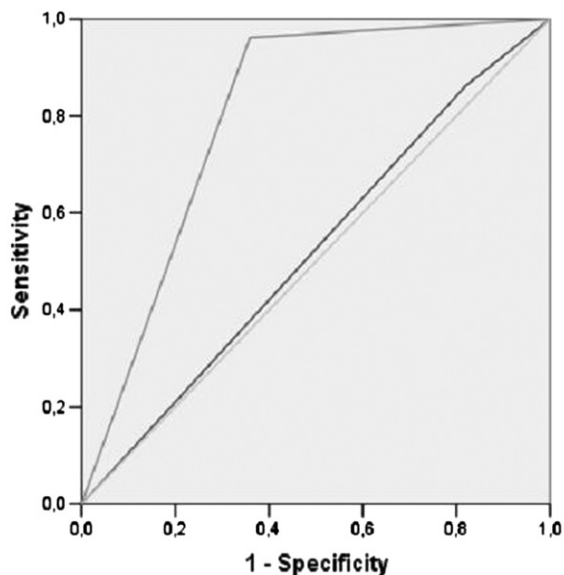
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**Acknowledgments**

The authors thank the Olympus Company for loaning our center the dedicated linear echoendoscope and for providing the Sonovie vials used in this study.

**Conflicts of interest**

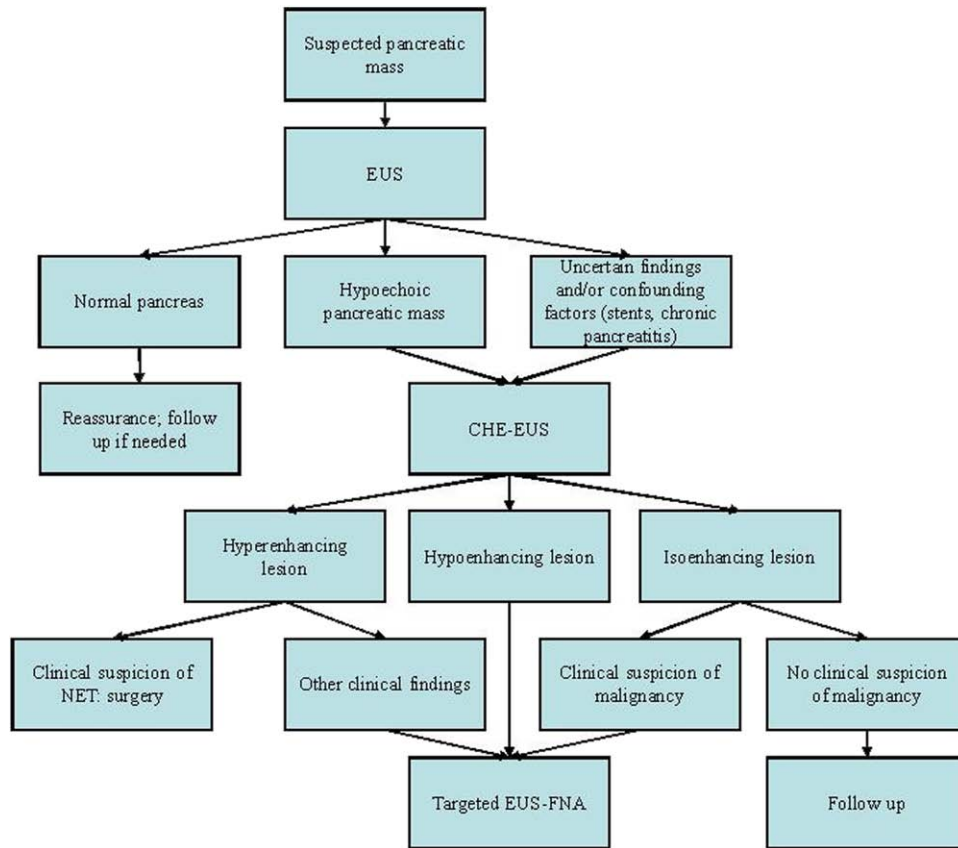
The authors disclose no conflicts.



	<i>AUC</i>	<i>SE</i>	<i>95% CI</i>	<i>Difference between areas</i>	<i>P value</i>
Standard EUS	0,521	0,062	0,400-0,642	0,280	0,732
CHE-EUS	0,801	0,051	0,700-0,901		0,000

AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristic; SE, standard error (95%).

**Supplementary Figure 1.** ROC analysis comparing standard EUS (dark grey line) and CHE-EUS (light grey line). The diagonal line indicates an AUC of 0.500.



**Supplementary Figure 2.** A clinical algorithm incorporating the use of CHE-EUS.