

# Efficacy of Contrast-enhanced Harmonic Endoscopic Ultrasonography in the Diagnosis of Pancreatic Ductal Carcinoma

Toshiyuki Uekitani, Seiji Kaino, Hirofumi Harima, Shigeyuki Suenaga, Manabu Sen-yo, Isao Sakaida

Department of Gastroenterology and Hepatology, Yamaguchi University Graduate School of Medicine, Japan

**Address for correspondence:**

Dr. Toshiyuki Uekitani,  
Minamikogushi 1-1-1, Ube,  
Yamaguchi 755-8505, Japan.  
E-mail: p003uj@tokuchuhp.jp

## ABSTRACT

**Background/Aims:** Distinguishing pancreatic ductal carcinoma (DC) from other pancreatic masses remains challenging. This study aims at evaluating the efficacy of contrast-enhanced harmonic endoscopic ultrasonography (CEH-EUS) in the diagnosis of DC. **Patients and Methods:** Forty-nine patients with solid pancreatic mass lesions underwent CEH-EUS. EUS (B-mode) was used to evaluate the inner echoes, distributions, and borders of the masses. The vascular patterns of the masses were evaluated with CEH-EUS at 30–50 s (early phase) and 70–90 s (late phase) after the administration of Sonazoid®. **Results:** The final diagnoses included DCs (37), mass-forming pancreatitis (6), endocrine neoplasms (3), a solid pseudopapillary neoplasm (1), a metastatic carcinoma (1), and an acinar cell carcinoma (1). The sensitivity, specificity, and accuracy of the diagnoses of DC in hypoechoic masses using EUS (B-mode) were 89.2%, 16.7%, and 71.4%, respectively. The sensitivity, specificity, and accuracy for the diagnosis of DC in hypovascular masses using CEH-EUS were 73.0%, 91.7%, and 77.6% in the early phase and 83.8%, 91.7%, and 85.7% in the late phase, respectively. **Conclusions:** CEH-EUS for the diagnosis of DC is superior to EUS. CEH-EUS in the late phase was particularly efficacious in the diagnosis of DC.

**Key Words:** Endoscopic ultrasonography, pancreatic cancer, pancreas, sonazoid

Received: 02.09.2015, Accepted: 21.11.2015

**How to cite this article:** Uekitani T, Kaino S, Harima H, Suenaga S, Sen-yo M, Sakaida I. Efficacy of contrast-enhanced harmonic endoscopic ultrasonography in the diagnosis of pancreatic ductal carcinoma. Saudi J Gastroenterol 2016;22:198-202.

Pancreatic ductal carcinomas (DCs) are solid carcinomas with poor prognoses.<sup>[1,2]</sup> These carcinomas are rarely detected in a stage in which surgical resection is indicated.<sup>[3]</sup> Therefore, early detection is important.

Endoscopic ultrasonography (EUS) is an important diagnostic imaging modality in pancreatic disease because it is superior to computed tomography (CT), and magnetic resonance imaging (MRI) in mass detection.<sup>[4-6]</sup> Reports in recent years have stated that contrast-enhanced harmonic EUS (CEH-EUS) is useful for the diagnosis of pancreatic diseases.<sup>[7-15]</sup>

In this study, we used CEH-EUS in patients with pancreatic solid lesions to retrospectively determine the efficacy of this technique for diagnosis of DC.

## PATIENTS AND METHODS

Forty-nine patients with solid pancreatic mass lesions that were histopathologically diagnosed via EUS-guided fine-needle aspiration (EUS-FNA) or surgical resection underwent CEH-EUS at Yamaguchi University Hospital between October 2009 and July 2012. Those not diagnosed with a malignancy by EUS-FNA were followed up using imaging study for at least six months to exclude false-negative diagnoses. This study was approved by the Ethics Committee of Yamaguchi University Hospital.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**For reprints contact:** reprints@medknow.com

Access this article online	
<b>Quick Response Code:</b> 	<b>Website:</b> www.saudijgastro.com
	<b>DOI:</b> 10.4103/1319-3767.182457

EUS was performed using an electric radial-type endoscope (GF-UE260-AL5; Olympus, Tokyo, Japan) and an ultrasound system (ProSound SSD  $\alpha$ -10; Hitachi Aloka Medical, Tokyo, Japan). To perform the CEH-EUS, we used Sonazoid® (Daiichi Sankyo, Tokyo, Japan) as an ultrasound contrast agent.

EUS was performed under midazolam- or propofol-induced sedation with the patient in the left lateral decubitus position. The B-mode was used first to evaluate the inner echo (hypoechoic, isoechoic, or hyperechoic), the distribution (heterogeneous or homogeneous), and the border (regular or irregular) of the mass.

The mode was then changed to extended pure harmonic detection, and the transmission frequency, mechanical index, and focal point were set to 4.7 MHz, 0.35, and the lowest point of the lesion, respectively. Sonazoid® (16  $\mu$ L) was suspended in 2 mL of water, and 0.5 mL of this suspension was intravenously injected followed by a 10-mL saline flush. For 120 s after the initiation of the Sonazoid® administration, the mass and surrounding pancreatic tissue was imaged, and their hemodynamics were observed. Over these 120 s, a video of the sonogram was recorded, and the video was checked after the examination. Based on comparisons of the blood flow between the interior of the mass and the surrounding pancreatic tissue, the contrast pattern of the mass was classified as hypovascular, isovascular, or hypervascular [Figures 1–3]. The evaluations were performed at 30–50 s (early phase) and 70–90 s (late phase) after the initiation of the Sonazoid® administration.

## RESULTS

The mean age and male-to-female ratio of the 49 subjects were 66.5 years (37–83 years) and 23:26, respectively. The mean mass diameter was 31.1 mm (15–68 mm). The positions of the mass were in the head, body, and tail of the pancreas in 23, 21, and five patients, respectively. The final diagnoses included 37 cases of

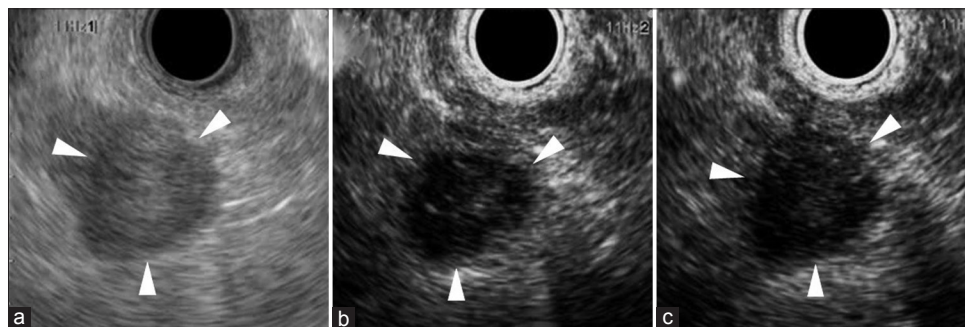
DC, six cases of mass-forming pancreatitis (MFP), three cases of endocrine neoplasms (EN), one case of a solid pseudopapillary neoplasm (SPN), one case of a metastatic carcinoma (MC), and one case of an acinar cell carcinoma (ACC) [Table 1].

The echo findings for each mass by EUS (B-mode) are shown in Table 2. Thirty-three of the 37 DCs (89.2%) were hypoechoic on EUS (inner echo). The other four DCs (10.8%) were isoechoic on EUS (inner echo). Ten of the 12 masses that were not DCs (83.3%) were hypoechoic on EUS (inner echo). Two of the 12 masses that were not DCs were isoechoic on EUS (inner echo).

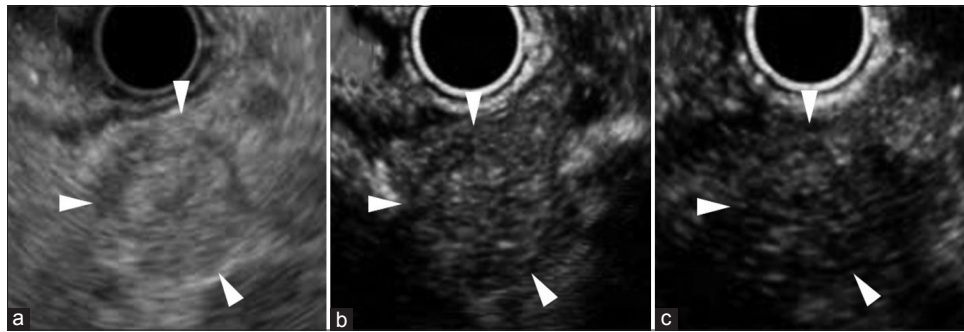
The contrast patterns of each of the masses according to CEH-EUS are shown in Table 2. Twenty-seven of the 37 DCs (73.0%) were classified as hypovascular in the early phase, and four DCs were classified as isovascular in the early phase and changed to hypovascular in the late phase; thus, 31 of the 37 DCs (83.8%) were classified as hypovascular in the late phase. Regarding the cases of MFP, five of the six (83.3%) were classified as isovascular in the early phase. The other MFP case was classified as hypervascular in the early phase and changed to isovascular in the late phase; thus, all six cases of MFP were classified as isovascular in the late phase.

**Table 1: Patient and pancreatic solid lesion characteristics**

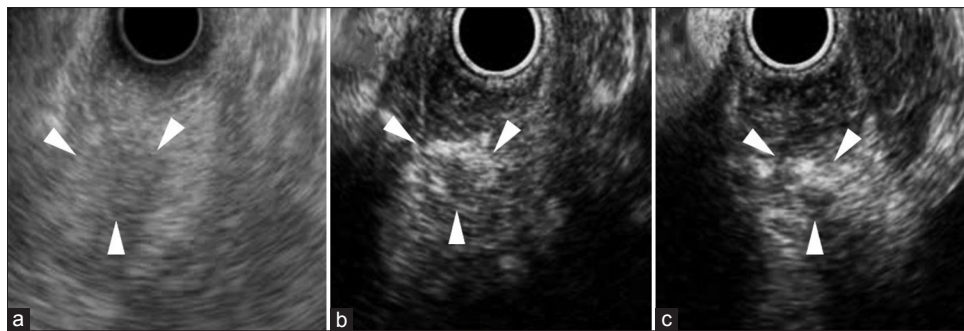
Patient characteristics	n=49
Age	66.5 (37–83)
Gender (male/female)	23/26
Maximum tumor diameter (mm)	31.1 (15–68)
Location of mass (head/body/tail)	23/21/5
Pathological diagnosis	N, total (n, surgically resected)
Ductal carcinoma	37 (14)
Mass-forming pancreatitis	6 (2)
Endocrine neoplasm	3 (3)
Solid pseudopapillary neoplasm	1 (1)
Metastatic carcinoma	1 (1)
Acinar cell carcinoma	1 (1)



**Figure 1:** A case of DC. (a) B-mode image. The inner echo, the distribution, and the border were classified as hypoechoic, heterogeneous, and regular, respectively (b) Early-phase CEH-EUS image. (c) Late-phase CEH-EUS image. The mass was hypovascular in both



**Figure 2:** A case of mass-forming pancreatitis. (a) B-mode image. The inner echo, the distribution, and the border were classified as hypoechoic, heterogeneous, and regular, respectively (b) Early-phase CEH-EUS image (c) Late-phase CEH-EUS image. The mass was isovascular in both



**Figure 3:** A case of metastatic carcinoma. (a) B-mode image. The inner echo, the distribution, and the border were classified as hypoechoic, heterogeneous, and regular, respectively (b) Early-phase CEH-EUS image (c) Late-phase CEH-EUS image. The mass was isovascular in both

The accuracy of the diagnosis of the masses as DCs by EUS (B-mode) when the masses were hypoechoic in terms of the inner echo was 71.4%. The accuracies for the masses diagnosed as DCs by CEH-EUS when the masses were hypovascular were 77.6% in the early phase and 85.7% in the late phase [Table 3].

No adverse procedure-related events were observed among the patients who underwent CEH-EUS.

## DISCUSSION

The diagnostic imaging methods applied to the pancreas include extrasomatic ultrasonography, CT, MRI, and EUS. Although abdominal ultrasonography is easy to perform, some sites are difficult to observe due to overlying intestinal tract or lung tissue. CT provides a high resolution imaging modality but is associated with radiation exposure. MRI involves no radiation exposure but has a lower resolution. EUS is invasive due to the insertion of an endoscope. However, EUS reportedly allows for the observation of the entire pancreas because the observation is performed through the digestive tract, has higher spatial and temporal resolutions, and is superior for the depiction of pancreatic masses compared with abdominal ultrasonography, CT, and MRI.<sup>[4-6]</sup> In the

present study, EUS allowed us to identify the pancreatic masses in all of the patients.

Sonazoid® is a second-generation ultrasound contrast agent that was released for use in 2007 in Japan and consists of phospholipid-encapsulated microbubbles of perflubutane (C<sub>4</sub>F<sub>10</sub>). Sonazoid® has superior *in vivo* stability and resistance to ultrasound destruction and can stably exert a good contrast effect for a prolonged period.<sup>[16]</sup> With Sonazoid®, CEH-EUS is useful for the evaluation of pancreatic disease because it permits the observation of the hemodynamics of masses in real time. This ability makes the qualitative diagnosis of a mass possible, in addition to the confirmation of its presence.<sup>[7-15]</sup> Sonazoid® can also be used in patients with renal and hepatic disorders due to its pulmonary clearance.<sup>[17]</sup> Using this agent, we were able to safely perform CEH-EUS without any adverse procedure-related events.

Napoleon *et al.* reported the usefulness of the application CEH-EUS for pancreatic solid masses.<sup>[12]</sup> They compared the blood flow between the masses and surrounding pancreatic tissues and classified the contrast patterns of the masses as hypovascular, isovascular, or hypervascular when the blood flow was less than, equal to, or greater than that of the surrounding tissue, respectively. According to Fusaroli *et al.*, the ability to diagnose DC (sensitivity: 96%; accuracy: 82%)

**Table 2: B-mode EUS and CEH-EUS findings according to final diagnosis**

Findings	DC (n=37)	MFP (n=6)	EN (n=3)	SPN (n=1)	MC (n=1)	ACC (n=1)
B-mode EUS findings						
Inner echo						
Hypoechoic	33	5	2	1	1	1
Isoechoic	4	1	1	0	0	0
Hyperechoic	0	0	0	0	0	0
Distribution						
Heterogeneous	22	4	2	1	1	0
Homogeneous	15	2	1	0	0	1
Border						
Irregular	15	1	1	0	0	0
Regular	22	5	2	1	1	1
CEH-EUS findings						
Early phase						
Hypovascular	27	0	0	1	0	0
Isovascular	10	5	3	0	0	1
Hypervascular	0	1	0	0	1	0
Late phase						
Hypovascular	31	0	0	1	0	0
Isovascular	6	6	3	0	0	1
Hypervascular	0	0	0	0	1	0

EUS: Endoscopic ultrasonography, CEH-EUS: Contrast-enhanced harmonic-EUS, DC: Ductal carcinoma; MFP: Mass-forming pancreatitis, EN: Endocrine neoplasm, SPN: Solid pseudopapillary neoplasm, MC: Metastatic carcinoma, ACC: Acinar cell carcinoma

**Table 3: The sensitivity, specificity, accuracy, PPV, and NPV of B-mode EUS and CEH-EUS in diagnosing ductal carcinoma**

	Sensitivity (%)	Specificity (%)	Accuracy (%)	PPV (%)	NPV (%)
B-mode EUS					
Inner echo	89.2	16.7	71.4	76.7	33.3
Distribution	59.5	33.3	53.1	73.3	21.1
Border	40.5	83.3	51.0	88.2	31.3
CEH-EUS					
Early phase	73.0	91.7	77.6	96.4	52.4
Late phase	83.8	91.7	85.7	96.9	64.7

EUS: Endoscopic ultrasonography, CEH-EUS: Contrast-enhanced harmonic-EUS, PPV: Positive predictive value, NPV: Negative predictive value

when the mass is hypovascular on CEH-EUS is superior to that when the mass is hypoechoic on EUS (ie, in B-mode, sensitivity: 86%; accuracy: 57%).<sup>[11]</sup>

However, the majority of the previous reports lack detailed descriptions of the time phases in which the blood flows were evaluated with CEH-EUS.<sup>[7-15]</sup> Lee *et al.* divided the time for the evaluation into early (0–30 s) and late (30–120 s) phases.<sup>[9]</sup> However, there have been no reports regarding which time phase is useful for the diagnosis. Therefore, we evaluated the contrast patterns of the masses by defining

30–50 and 70–90 s after the administration of the contrast agent as the early and late phases, respectively. When a mass diagnosed as DC was hypovascular on CEH-EUS, the sensitivity, specificity, and accuracy of the diagnosis (early phase/late phase) were 73.0%/83.8%, 91.7%/91.7%, and 77.6%/85.7%, respectively.

When a mass diagnosed as DC was hypoechoic on EUS (B-mode; inner echo), the sensitivity, specificity, and accuracy of the diagnosis were 89.2%, 16.7%, and 71.4%, respectively, which revealed low specificity. A comparison of EUS (B-mode) and CEH-EUS revealed that the late phase of CEH-EUS was the best for diagnosing DC because it had the highest accuracy.

There were five mass lesions with contrast patterns that differed between the early and late phases, but all of the other masses exhibited the same contrast patterns in both phases. Of these five lesions with different contrast patterns, four were DCs that were isovascular-hypovascular, and the other was an MFP that was hypervascular-isovascular. Hocke *et al.* reported that pancreatic DCs have abundant arterial and poor venous signals compared with chronic pancreatitis.<sup>[15]</sup> This pathological characteristic was probably a factor in the change from isovascular in the early phase to hypovascular in the late phase.

Our study revealed that separate evaluations of the contrast patterns with CEH-EUS in the early and late phases are useful. The evaluations in the late phase were particularly useful for the diagnosis of DC.

## CONCLUSIONS

CEH-EUS with Sonazoid® was found to be a safe procedure for diagnosing pancreatic masses. CEH-EUS was able to evaluate the hemodynamics of pancreatic masses in real time. Especially, CEH-EUS was useful for distinguishing pancreatic DC from other pancreatic masses in the late phase.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

## REFERENCES

- Nieto J, Grossbard ML, Kozuch P. Metastatic pancreatic cancer 2008: Is the glass less empty? *Oncologist* 2008;13:562-76.
- Badger SA, Brant JL, Jones C, McClements J, Loughrey MB, Taylor MA, *et al.* The role of surgery for pancreatic cancer: A 12-year review of patient outcome. *Ulster Med J* 2010;79:70-5.

3. Xu Q, Zhang TP, Zhao YP. Advances in early diagnosis and therapy of pancreatic cancer. *Hepatobiliary Pancreat Dis Int* 2011;10:128-35.
4. Yasuda K, Mukai H, Fujimoto S, Nakajima M, Kawai K. The diagnosis of pancreatic cancer by endoscopic ultrasonography. *Gastrointest Endosc* 1988;34:1-8.
5. Müller MF, Meyenberger C, Bertschinger P, Schaer R, Marincek B. Pancreatic tumors: Evaluation with endoscopic US, CT, and MR imaging. *Radiology* 1994;190:745-51.
6. Legmann P, Vignaux O, Dousset B, Baraza AJ, Palazzo L, Dumontier I, *et al.* Pancreatic tumors: Comparison of dual-phase helical CT and endoscopic sonography. *AJR Am J Roentgenol* 1998;170:1315-22.
7. Sakamoto H, Kitano M, Suetomi Y, Maekawa K, Takeyama Y, Kudo M. Utility of contrast-enhanced endoscopic ultrasonography for diagnosis of small pancreatic carcinomas. *Ultrasound Med Biol* 2008;34:525-32.
8. Kitano M, Sakamoto H, Matsui U, Ito Y, Maekawa K, von Schrenck T, *et al.* A novel perfusion imaging technique of the pancreas: Contrast-enhanced harmonic EUS (with video). *Gastrointest Endosc* 2008;67:141-50.
9. Lee TY, Cheon YK, Shim CS. Clinical role of contrast-enhanced harmonic endoscopic ultrasound in differentiating solid lesions of the pancreas: A single-center experience in Korea. *Gut Liver* 2013;7:599-604.
10. Kitano M, Kudo M, Yamao K, Takagi T, Sakamoto H, Komaki T, *et al.* Characterization of small solid tumors in the pancreas: The value of contrast-enhanced harmonic endoscopic ultrasonography. *Am J Gastroenterol* 2012;107:303-10.
11. Fusaroli P, Spada A, Mancino MG, Caletti G. Contrast harmonic echo-endoscopic ultrasound improves accuracy in diagnosis of solid pancreatic masses. *Clin Gastroenterol Hepatol* 2010;8:629-34.
12. Napoleon B, Alvarez-Sanchez MV, Gincoul R, Pujol B, Lefort C, Lepilliez V, *et al.* Contrast-enhanced harmonic endoscopic ultrasound in solid lesions of the pancreas: Results of a pilot study. *Endoscopy* 2010;42:564-70.
13. Park JS, Kim HK, Bang BW, Kim SG, Jeong S, Lee DH. Effectiveness of contrast-enhanced harmonic endoscopic ultrasound for the evaluation of solid pancreatic masses. *World J Gastroenterol* 2014;20:518-24.
14. Kwek BE, Ang TL, Seo DW, Imazu H. Contrast-enhanced harmonic endoscopic ultrasonography of solid pancreatic lesions. *Endosc Ultrasound* 2013;2:142-7.
15. Hocke M, Schulze E, Gottschalk P, Topalidis T, Dietrich CF. Contrast-enhanced endoscopic ultrasound in discrimination between focal pancreatitis and pancreatic cancer. *World J Gastroenterol* 2006;12:246-50.
16. Schutt EG, Klein DH, Mattrey RM, Riess JG. Injectable microbubbles as contrast agents for diagnostic ultrasound imaging: The key role of perfluorochemicals. *Angew Chem Int Ed Engl* 2003;42:3218-35.
17. Toft KG, Hustvedt SO, Hals PA, Oulie I, Uran S, Landmark K, *et al.* Disposition of perfluorobutane in rats after intravenous injection of Sonazoid. *Ultrasound Med Biol* 2006;32:107-14.