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

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Pancreatic ductal carcinomas (DCs) are solid carcinomas with poor prognoses.[1,2] These carcinomas are rarely detected in a stage in which surgical resection is indicated.[3] 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.[4] Reports in recent years have stated that contrast-enhanced harmonic EUS (CEH-EUS) is useful for the diagnosis of pancreatic diseases.[5,6]

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.

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 hypovascular 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

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EUS was performed using an electric radial-type endoscope (GF-UE260-AL5; Olympus, Tokyo, Japan) and an ultrasound system (ProSound SSD α-10; Hitachi Aloka Medical, Tokyo, Japan). To perform the CEH-EUS, we used Sonazoid® (Daichi 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 µL) 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
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.¹⁴⁻¹⁶ 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 perfluorobutane (C₄F₁₀). Sonazoid® has superior in vivo stability and resistance to ultrasound destruction and can stably exert a good contrast effect for a prolonged period.¹⁶ 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.¹⁷⁻¹⁹ Sonazoid® can also be used in patients with renal and hepatic disorders due to its pulmonary clearance.¹⁷ 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.¹²⁻¹³ 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%)
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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         | 0        | 1         |

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

|                  | B-mode EUS | CEH-EUS |
|------------------|------------|---------|
|                  | Sensitivity (%) | Specificity (%) | Accuracy (%) | PPV (%) | NPV (%) |
| Inner echo       | 89.2       | 16.7    | 71.4       | 76.7    | 33.3    |
| Distribution     | 58.5       | 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%).

However, the majority of the previous reports lack detailed descriptions of the time phases in which the blood flows were evaluated with CEH-EUS. Lee et al. divided the time for the evaluation into early (0–30 s) and late (30–120 s) phases. 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%/91.7%, 97.0%/91.7%, and 77.6%/85.7%, respectively.

When a mass diagnosed as DC was hypovascular on CEH-EUS, 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-isovalidular. 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.

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Conflicts of interest
There are no conflicts of interest.

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