Pancreatology xxx (xxxx) xxx

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Utility of multiphase contrast enhancement patterns on CEH-EUS for the differential diagnosis of IPMN-derived and conventional pancreatic cancer

Jun Yashika [a], Eizaburo Ohno [a], Takuya Ishikawa [a], Tadashi Iida [a], Hirotaka Suzuki [a], Kota Uetsuki [a], Kenta Yamada [a], Masakatsu Yoshikawa [a], Noriaki Gibo [a], Yoshie Shimoyama [c], Eri Ishikawa [a], Kazuhiro Furukawa [a], Masanao Nakamura [a], Takashi Honda [a], Masatoshi Ishigami [a], Yoshiki Hirooka [d], Hiroki Kawashima [b, *], Mitsuhiro Fujishiro [a]

[a] Department of Gastroenterology and Hepatology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[b] Department of Endoscopy, Nagoya University Hospital, Nagoya, Japan
[c] Department of Pathology, Nagoya University Hospital, Nagoya, Japan
[d] Department of Gastroenterology and Gastroenterological Oncology, Fujita Health University, Fujita Health University of Medicine, Toyoake, Aichi, Japan

ARTICLE INFO

Article history:
Received 26 August 2020
Received in revised form
28 December 2020
Accepted 29 December 2020
Available online xxx

Keywords:
CEH-EUS
IPMN
IPMC
PDAC

ABSTRACT

Background: Intraductal papillary mucinous neoplasm (IPMN) is reported as a high-risk factor for pancreatic cancer (PC) that includes IPMN-derived cancers (IPMC) and the development of invasive pancreatic ductal adenocarcinoma (PDAC) concomitant with IPMN. Since invasive IPMC and PDAC exhibit different oncological behaviors, their differentiation is clinically important. We aimed to investigate the use of contrast-enhanced harmonic endoscopic ultrasound (CEH-EUS) for the differential diagnosis between invasive IPMC and PDAC.

Methods: This study involved 183 consecutive patients with PC (invasive IPMC: 42, PDAC concomitant with IPMN: 9, without IPMN: 132) who underwent CEH-EUS preoperatively. While investigating the patterns, enhanced effects in the solid part of the tumor were compared with those in the surrounding pancreatic parenchyma after administration of Sonazoid® and evaluated as hyperenhanced, iso-enhanced, or hypoenhanced. We retrospectively compared the enhanced pattern of CEH-EUS by using multiphasic analysis and clinicopathological factors between invasive IPMC and PDAC.

Results: In multiphase evaluations at 20, 40 and 60 s in CEH-EUS, 75.2% (106/141) of PDACs were hypoenhanced (−) at ≥2 of the 3 time points, with significant differences from those of invasive IPMC ($P < 0.001$). The solid tumor diameter was significantly larger in PDAC than in invasive IPMC, and the tumor stage and preoperative serum carbohydrate antigen 19-9 level were higher. After propensity score matching of stage and solid tumor diameter, contrast enhancement patterns were significantly more persistent in invasive IPMC than in PDAC ($P = 0.0013$).

Conclusions: Multiphase evaluation using CEH-EUS is a useful method for differentiating between invasive IPMC and PDAC.

Introduction

Intraductal papillary mucinous neoplasm (IPMN) is a pancreatic epithelial tumor characterized by mucus production [1]. IPMN slowly progresses from low-malignancy adenoma to noninvasive carcinoma, microinvasive carcinoma, and invasive carcinoma [2]. In addition, IPMN is a risk factor for pancreatic ductal adenocarcinoma (PDAC), which develops separately from IPMN and is referred to as PDAC concomitant with IPMN [3–5]. The development site of PDAC concomitant with IPMN cannot be predicted, which makes early diagnosis difficult. The biological malignancy of PDAC concomitant with IPMN also differs from that of IPMN-derived carcinoma

* Corresponding author. 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550, Japan.
E-mail address: h-kawa@med.nagoya-u.ac.jp (H. Kawashima).

https://doi.org/10.1016/j.pan.2020.12.022
1424-3903/

Please cite this article as: J. Yashika, E. Ohno, T. Ishikawa *et al.*, Utility of multiphase contrast enhancement patterns on CEH-EUS for the differential diagnosis of IPMN-derived and conventional pancreatic cancer, Pancreatology, https://doi.org/10.1016/j.pan.2020.12.022

(intraductal papillary mucinous carcinoma (IPMC)) [1,6,7], and it is difficult to distinguish whether invasive carcinoma arising from the vicinity of the existing IPMN is invasive IPMC or PDAC concomitant with IPMN. Differentiation between PDAC and invasive IPMC may be based on differences in the genetic profile of cancer cells, in addition to continuity of epithelial atypia in IPMN and the presence or absence of a transition in pathological findings of resected specimens [8].

Contrast-enhanced harmonic endoscopic ultrasonography (CEH-EUS) using a second-generation ultrasound contrast agent can evaluate the hemodynamics in a region of interest continuously in real time [9,10]. Dedicated software enables time-intensity curve (TIC) analysis of time-course changes in the echo intensity continuously and quantitatively. However, TIC analysis requires special analytical tools and a complicated analytical procedure. To solve these problems, we proposed a multiphase evaluation using a simplified CEH-EUS approach and showed its usefulness for the differential diagnosis of pancreatic diseases, including PDAC and tumor-forming pancreatitis [11]. The objective of this study was to evaluate the utility of multiphase contrast enhancement patterns in CEH-EUS and clinicopathological findings for the differential diagnosis of invasive IPMC and PDAC concomitant with IPMN.

Methods

Patients

The subjects were 183 consecutive patients examined by CEH-EUS using Sonazoid® (Daiichi-Sankyo, Tokyo, Japan; GE Healthcare, Milwaukee, WI, USA) between January 2007 and May 2019 and diagnosed by pathological examination of a resected specimen with invasive IPMC, PDAC concomitant with IPMN (hereafter, PDAC with IPMN), or PDAC without IPMN. Data for these subjects were retrospectively reviewed. There were 42 patients with invasive IPMC and 141 with PDAC (PDAC with IPMN: 9, PDAC without IPMN: 132), and all had imaging data from injection of a contrast agent to 1 min later (Fig. 1). There were 116 male patients and 67 female patients, and the median age was 68 years (range: 36–83 years). All were treated surgically and diagnosed pathologically using a surgical specimen. This study was approved by the Institutional Review Board of Nagoya University Hospital and was conducted in accordance with the Declaration of Helsinki (No. 2015-0316-6880).

EUS and CEH-EUS settings

All EUS examinations were performed by endoscopists with experience of more than 5000 cases. After providing written informed consent, the patients received conscious sedation with intravenous diazepam or midazolam under appropriate cardiorespiratory monitoring. To investigate the enhancement pattern of the tumors, CEH-EUS was performed using Sonazoid®. A vial of Sonazoid® (16 μL as perflubutane) was suspended in 2 mL of water for injection, and the suspension was administered by bolus intravenous injection of 0.015 mL/kg. Sonazoid® is composed of perflubutane microbubbles. Endoscopic and ultrasound observations were performed using the following instruments: an EG-3670URK (Pentax Co., Ltd., Tokyo, Japan) and a Hi Vision Ascendus or Hi Vision 900 (Hitachi-Aloka Medical, Ltd, Tokyo, Japan); a GF-UE260-AL5 (Olympus Co., Ltd., Tokyo, Japan) and Prosound α-10 (Hitachi-Aloka Medical); or an EG-580UR/UT and Sonart SU-1 (both Fujifilm Co., Ltd., Tokyo, Japan). In CEH-EUS using EG-3670URK with a Hi Vision Ascendus or Hi Vision 900, the broadband pulse inversion method was used, and the mechanical index was automatically set at 0.16–0.23 to follow the focus point. With GF-UE260-AL5 and Prosound α-10, the extended pure harmonics detection method was used, and the mechanical index was set at 0.25. With EG-580UR/UT and Sonart SU-1, the pulse inversion method was used, and the mechanical index was automatically set at 0.2–0.4. A single focus was set on the distal side of the target lesion.

Multiphase evaluation using CEH-EUS

First, we evaluated the localization of solid tumors for IPMN-related pancreatic cancer cases. The localization of the solid tumors was divided into three groups: within the cyst, beside the cyst

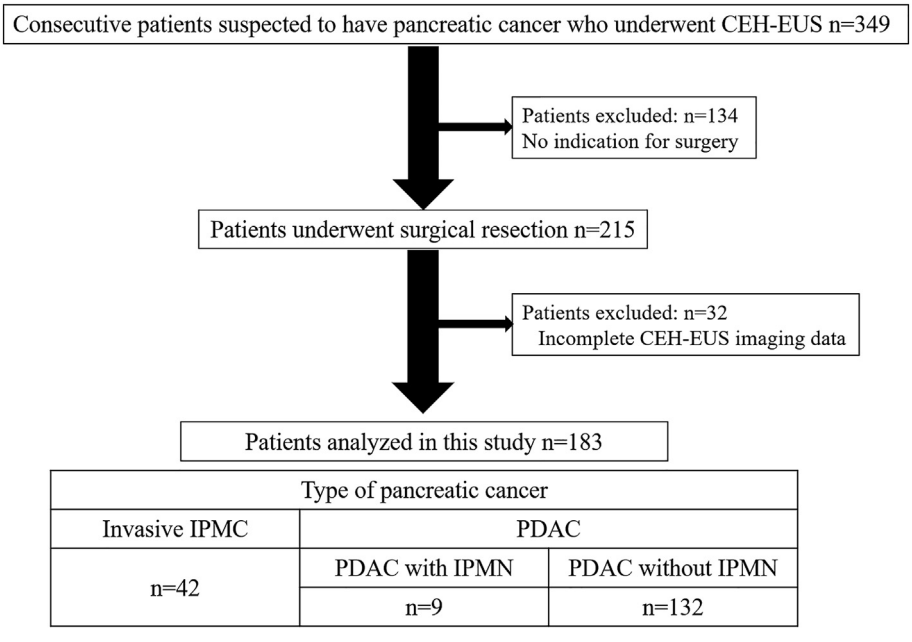

Fig. 1. Flow diagram of the study.
CEH-EUS: contrast-enhanced harmonic endoscopic ultrasonography, IPMC: intraductal papillary mucinous carcinoma, PDAC: pancreatic ductal adenocarcinoma, IPMN: intraductal papillary mucinous neoplasm.

and distant from the cyst. Then, we performed CEH- EUS on the site of the solid tumor. After injection of Sonazoid®, CEH-EUS was continued for 60 s, and the video recorded during this time was stored for subsequent analysis. Images at 20, 40, and 60 s were classified into three contrast enhancement patterns (hyperenhanced (+), isoenhanced (0), and hypoenhanced (−)) by comparing the echogenicity of the lesion with that of the surrounding pancreatic parenchyma (Fig. 2). All data were retrospectively reviewed individually by two endosonographers (JY and EO) who were blinded to US, computed tomography (CT), and magnetic resonance cholangiopancreatography (MRCP) information and the final diagnosis. Multiphase contrast enhancement patterns were classified into 4 patterns as follows: (1) hypoenhanced: (−) at ≥2 of the 3 times (20, 40, and 60 s); (2) isoenhanced: (0) at ≥2 of the 3 times; (3) hyperenhanced: (+) at ≥2 of the 3 times; and (4) others: a different pattern at all 3 times. Agreement in the classification of the CEH-EUS pattern between the two blinded reviewers was evaluated by calculating the κ coefficient. Images for which the classification differed between the reviewers were reevaluated, and an agreement was reached. The patients were divided into three groups (invasive IPMC, PDAC with IPMN, and PDAC without IPMN) based on the histopathological diagnosis after surgery, and the association of the CEH-EUS contrast enhancement pattern with multiphase evaluation was evaluated in each group.

Histopathological investigation

Invasive IPMC was defined as an invasive carcinoma continuous with IPMN with high-grade dysplasia and infiltration of the pancreatic parenchyma by ≥ 5 mm, and IPMN with high-grade dysplasia (carcinoma in situ) only was excluded. PDAC with IPMN was defined as an invasive carcinoma not continuous with IPMN or adjacent to IPMN with low-grade dysplasia without a histological transition. PDAC without IPMN was defined as an invasive carcinoma without pathologically diagnosed IPMN in the resected specimen and cystic lesions in the remnant pancreas suspected to be IPMN based on imaging [12]. Epithelial subtypes of IPMN were classified as gastric, intestinal, pancreatobiliary, and oncocytic types based on cytomorphological features of the papillae and immunohistochemical demonstration of MUC1, MUC2, and MUC5A glycoproteins. IPMN lesions occasionally exhibit multiple epithelial types; in such cases, the most prevalent epithelium associated with the highest degree of dysplasia was captured for analysis. Histological subtypes in the invasive components of invasive IPMC were classified into the colloid, tubular, and oncocytic type. The tumor stage was classified based on the general rules for the study of pancreatic cancer, 7th edition, Japan Pancreatic Society [13].

Statistical analysis

Categorical parameters were compared among the groups by the χ^2 test and Fisher's exact test. For continuous parameters, items with a normal distribution are shown as the mean ± standard deviation (SD), and others are shown as the median (interquartile range) and compared by the Mann-Whitney *U* test. Multivariate logistic regression analysis was performed using factors that were significant in univariate analysis. Agreement on the CEH-EUS contrast enhancement pattern between the two reviewers was judged to be acceptable at a κ coefficient >0.8. Logistic regression analysis was performed with invasive IPMC and PDAC patients as objective variables and the tumor stage and solid tumor diameter as covariates, and propensity scores were calculated by nearest neighbor matching with a Caliper coefficient of 0.02. Propensity score matching (PSM) based on a propensity score was used to obtain a uniform stage and solid tumor diameter in invasive IPMC and PDAC patients. Statistical analysis was performed using JMP Pro ver. 14 for Windows (SAS Institute Inc., Cary, NC, USA), with $P < 0.05$ regarded as significant.

Results

The clinical characteristics of the 183 patients are shown in (Table 1). All patients underwent surgical resection after CEH-EUS, and the final diagnosis was made based on histopathological findings after surgery. Compared with invasive IPMC patients, PDAC patients were significantly more frequently symptomatic and had a more advanced stage, larger solid tumor diameter, and higher preoperative serum carbohydrate antigen 19-9 (CA19-9) level.

The κ coefficients for interobserver agreement in classification of the CEH-EUS contrast enhancement patterns were 0.954, 0.944, and 0.906 (all P < 0.0001) at 20, 40, and 60 s after Sonazoid® injection, respectively, showing a favorable concordance rate. In multiphase evaluation at 20, 40, and 60 s after intravenous Sonazoid® injection, significantly more PDAC patients were hypoenhanced (−) at ≥2 of the 3 time points than invasive IPMC patients (Fig. 3). Based on these results, we divided the contrast pattern into 2 groups, hypoenhanced and nonhypoenhanced (including hyperenhanced, isoenhanced and others), for subsequent analysis between invasive IPMC and PDAC with or without IPMN. Consequently, the contrast enhancement pattern differed significantly between invasive IPMC and PDAC with IPMN ($P < 0.0001$ at all three time points) (Table 2), but there were no significant differences in the patterns between PDAC with IPMN and PDAC without IPMN ($P = 0.7363/0.0748/0.1602$ at 20/40/60 s) (Table 3). Blood flow was higher in invasive IPMC patients than in PDAC with

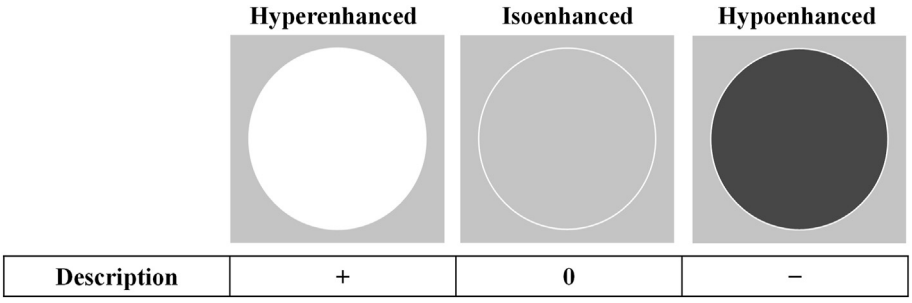

Fig. 2. CEH-EUS protocol.
After intravenous Sonazoid® injection, CEH-EUS was continued for 60 s and recorded as a video. Images at 20, 40, and 60 s after contrast enhancement were classified into 3 contrast enhancement patterns (hyperenhanced (+), isoenhanced (0), and hypoenhanced (−)) and compared with that of the surrounding pancreatic parenchyma.

Table 1
Clinical characteristics of patients with invasive IPMC, PDAC with IPMN and PDAC without IPMN.

Factor	Invasive IPMC	PDAC with IPMN	PDAC without IPMN	All PDAC	*P* value
Age (years), mean ± SD	66.0 ± 7.6	71 ± 5.9	66.9 ± 8.6	67.2 ± 8.5	0.2833
Sex, n (%)					
Male	30 (71.4)	5 (55.6)	81 (61.4)	86 (61.0)	0.2178
Female	12 (28.6)	4 (44.4)	51 (38.6)	55 (39.0)	
Symptoms, n (%)					
Present	12 (28.6)	2 (22.2)	65 (49.2)	67 (47.5)	0.0296
Absent	30 (71.4)	7 (77.8)	67 (50.8)	74 (52.5)	
DM, n (%)					
Present	15 (35.7)	2 (22.2)	48 (36.4)	50 (35.5)	0.9760
Absent	27 (64.3)	7 (77.8)	84 (63.6)	91 (64.5)	
CA19-9 (U/mL), median (IQR)	17 (10–45.3)	113 (51.5–984.5)	127.5 (24.3–465)	127 (26.5–470.5)	<0.0001
Tumor size (mm), mean ± SD	13.0 ± 8.4	21.8 ± 4.7	22.7 ± 9.2	22.7 ± 9.0	<0.0001
Tumor stage, n (%)					
I	35 (83.3)	1 (11.1)	6 (4.5)	7 (5.0)	<0.0001
II	6 (14.3)	6 (66.7)	0	6 (4.2)	
III	1 (2.4)	2 (22.2)	52 (39.4)	54 (38.3)	
IV	0	0	74 (56.1)	74 (52.5)	
Follow-up to surgery, n (%)					
Present	8 (19)	2 (22.2)	0	2 (1.4)	<0.0001
Absent	34 (81)	7 (77.8)	132 (100)	139 (98.6)	
IPMN epithelial subtypes, n (%)					
Gastric	17 (40.5)				
Intestinal	17 (40.5)				
Pancreatobiliary	3 (7.1)				
Oncocytic	5 (11.9)				
Histological subtypes of invasive components, n (%)					
Colloid	1 (2.4)				
Tubular	39 (92.8)				
Oncocytic	2 (4.8)				

IPMC: intraductal papillary mucinous carcinoma. PDAC: pancreatic ductal adenocarcinoma. IPMN: intraductal papillary mucinous neoplasm. Symptoms: jaundice and abdominal pain (including pancreatitis). DM: diabetes mellitus. CA19-9: serum level of carbohydrate antigen 19-9. Data for serum CA19-9 levels are shown as the medians (interquartile ranges).
P value for invasive IPMC vs. All PDAC.

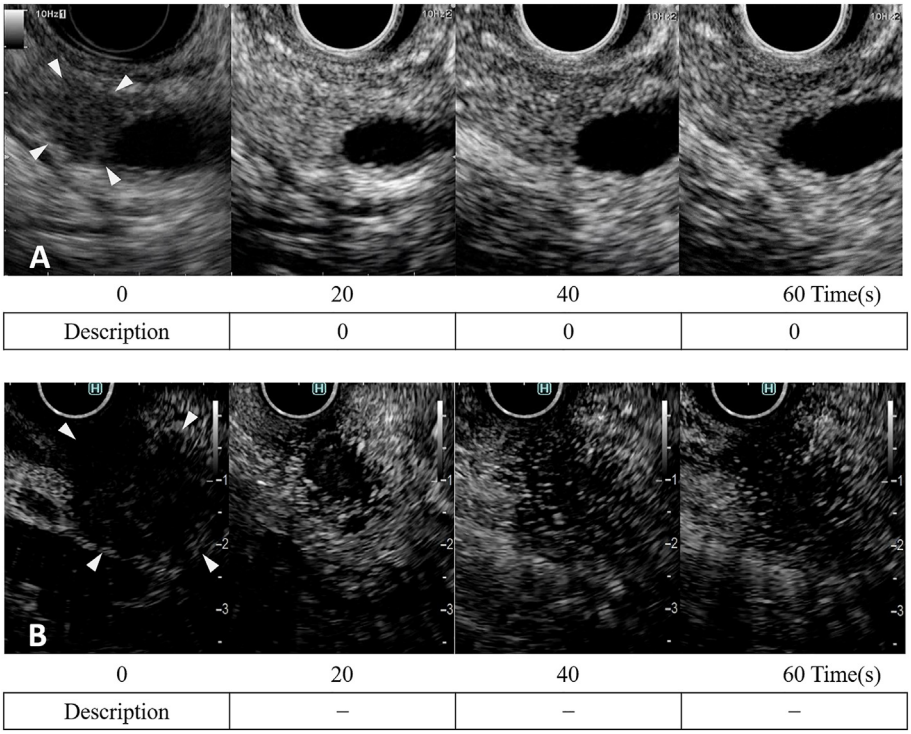

Fig. 3. Typical CEH-EUS images.
The solid part of the tumor showed (A) a 0/0/0 pattern for invasive IPMC and (B) a –/–/- pattern for PDAC without IPMN at 20/40/60 s compared with the pattern of the surrounding pancreatic parenchyma.

Table 2
EUS findings in invasive IPMC, PDAC with IPMN, and PDAC without IPMN patients.

EUS findings	Invasive IPMC	PDAC with IPMN	PDAC without IPMN	All PDAC	*P* value
Location, n (%)					
Head	28 (66.7)	3 (33.3)	86 (65.1)	89 (63.1)	
Body	10 (23.8)	4 (44.5)	26 (19.7)	30 (21.3)	
Tail	4 (9.5)	2 (22.2)	20 (15.2)	22 (15.6)	0.6064
IPMN type, n (%)					
Mixed	18 (43.0)	2 (22.2)		2 (22.2)	
Main duct	12 (28.5)	0		0	
Branch duct	12 (28.5)	7 (77.8)		7 (77.8)	0.0166
Multiplicity of cyst, n (%)					
Present	9 (21.4)	5 (55.6)	3 (2.3)	8 (5.7)	
Absent	33 (78.6)	4 (44.4)	129 (97.7)	133 (94.3)	<0.0001
Retention cyst, n (%)					
Present	0	3 (33.3)	18 (13.6)	21 (14.9)	
Absent	42 (100)	6 (66.7)	114 (86.4)	120 (85.1)	0.0058
Presence of cystic lesion, n (%)					
Cyst Absent	0	0	104(78.8)	104(73.8)	
Cyst Present	42	9	28 (21.2)	37 (26.2)	
Location of solid components, n (%)					
Within the cyst	41 (97.6)	0	0	0	
Beside the cyst	1 (3.4)	3 (33.3)	16 (12.1)	19 (13.5)	
Distant from the cyst	0	6 (66.7)	12 (9.1)	18 (12.8)	<0.0001
CEH-EUS patterns (Multiphase), n (%)					
Hypoenhanced	2 (4.8)	9 (100)	97 (73.5)	106 (75.2)	
Isoenhanced	40 (95.2)	0	34 (25.8)	34 (24.1)	
Hyperenhanced	0	0	0	0	
Others	0	0	1 (0.7)	1 (0.7)	<0.0001

IPMC: intraductal papillary mucinous carcinoma. PDAC: pancreatic ductal adenocarcinoma. IPMN: intraductal papillary mucinous neoplasm. CEH-EUS: contrast-enhanced harmonic endoscopic ultrasound. *P* value for invasive IPMC vs. All PDAC.

Table 3
Hypoenhanced: nonhypoenhanced ratios in contrast enhancement patterns in invasive IPMC, PDAC with IPMN, and PDAC without IPMN patients.

Time point	Invasive IPMC A	PDAC with IPMN B	PDAC without IPMN C	*P* value A vs B	*P* value A vs C	*P* value B vs C
Multiphase	2 : 40	9 : 0	97 : 35	<0.0001	<0.0001	0.0748
Single phase						
20 s	2 : 40	8 : 1	103 : 29	<0.0001	<0.0001	0.7363
40 s	2 : 40	9 : 0	97 : 35	<0.0001	<0.0001	0.0748
60 s	3 : 39	9 : 0	108 : 24	<0.0001	<0.0001	0.1602

IPMC: intraductal papillary mucinous carcinoma. PDAC: pancreatic ductal adenocarcinoma. IPMN: intraductal papillary mucinous neoplasm. Multiphase: hypoenhanced (−) at ≥2 of the 3 time points was defined as hypoenhanced, and other patterns were defined as nonhypoenhanced.

IPMN and PDAC without IPMN patients, and the contrast effect was more persistent. A comparison of the enhanced pattern of CEH-EUS showed no significant difference according to the histological subtypes of invasive components of invasive IPMC.

In the multivariate analysis, the tumor stage, contrast enhancement pattern, solid tumor diameter and preoperative serum CA19-9 level were significant independent factors that differentiated PDAC from invasive IPMC. Patients with PDAC had a higher stage, higher rate of hypoenhanced pattern, larger tumor size, and higher preoperative serum CA19-9 levels than those with invasive IPMC (Table 4).

Propensity scores were calculated for stage and solid tumor diameter to balance these variables between invasive IPMC and PDAC patients. This resulted in the extraction of 13 patients from each group. These patients were included in univariate analysis, which showed significantly higher rates of a nonhypoenhanced pattern at all times ($P = 0.0013$) and of patterns with a persistent contrast effect ($P = 0.0039/0.0013/<0.0001$ at 20/40/60 s) in invasive IPMC patients than in PDAC patients (Table 5). The contrast enhancement pattern at 60 s is the most useful for differentiation. Multiphase evaluation is also useful for differentiation. Thus, diagnosis based on the contrast enhancement patterns in CEH-EUS was a significant factor for differentiating between the two tumors in univariate analyses after PSM.

Discussion

In our study, we found that the contrast enhancement patterns differ between the invasive components of invasive IPMC and the invasive components of PDAC, as well as that the multiphase evaluation method is a simple method to assess contrast enhancement patterns. We believe that these results demonstrate the clinical usefulness of CEH-EUS, which may be difficult to differentiate as a cytological and histological diagnosis by EUS-FNA.

IPMN is a high risk for PDAC and for the progression to malignancy as invasive IPMC [4,14]. In a multicenter prospective observational study performed by Ohno et al. [15], the standardized malignant transformation rate of all pancreatic cystic lesions was 10.0 (95% CI 3.5–16.5) and that of branch-type IPMN was 16.6 (95% CI 5.1–28.1). Thus, pancreatic cystic disease (especially branch-type IPMN) is a risk factor for PC, and continued surveillance is necessary because PDAC may also develop in the extracystic region.

IPMN-derived tubular adenocarcinoma has several similarities with conventional PDAC, including high rates of tumor invasion, local recurrence and lymph node metastasis, and poor prognosis [16–19]. In contrast, the prognosis of IPMN-derived mucinous carcinoma is favorable compared with that of IPMN-derived tubular adenocarcinoma due to low rates of lymph node metastasis, poorly differentiated carcinoma, and vascular invasion

Table 4
Multivariate analysis of clinicopathological findings and CEH-EUS findings in invasive IPMC and PDAC patients.

Factor	Invasive IPMC	PDAC	OR	95% CI	*P* value
Symptoms, n (%)					
Present	12 (28.6)	67 (47.5)	1.55	0.11–22.27	0.7446
Absent	30 (71.4)	74 (52.5)			
CA19-9 (U/mL), n (%)					
<68 U/mL	36 (85.7)	54 (38.3)	0.04	0.002–0.63	0.0046
≧68 U/mL	6 (14.3)	87 (61.7)			
Tumor size (mm), n (%)					
<13 mm	28 (66.7)	14 (9.9)	1.37		0.0001
≧13 mm	14 (33.3)	127 (90.1)			
Tumor stage, n (%)					
I-III	42 (100)	67 (47.5)	1.25		0.0001
IV	0	74 (52.5)			
Follow-up to surgery, n (%)					
Present	8 (19)	2 (1.4)	3.55	0.11–110.54	0.4579
Absent	34 (81)	139 (98.6)			
Multiplicity of cyst, n (%)					
Present	9 (21.4)	8 (5.7)	2.23	0.21–24.17	0.5021
Absent	33 (78.6)	133 (94.3)			
Presence of cystic lesion, n (%)					
Cyst Absent	0	104(73.7)	8.18		<0.0001
Cyst Present	42	37 (26.3)			
CEH-EUS patterns (Multiphase), n (%)					
Hypoenhanced	2 (4.8)	106 (75.2)	148.15	4.01–5472.32	<0.0001
Nonhypoenhanced)	40 (95.2)	35 (24.8)			

OR: odds ratio. CI: confidence interval. Symptoms: jaundice and abdominal pain (including pancreatitis). CA19-9: serum level of carbohydrate antigen 19-9. Multiphase: hypoenhanced (−) at ≥2 of the 3 time points was defined as hypoenhanced, and other patterns were defined as nonhypoenhanced.

Table 5
Univariate analysis after PSM (invasive IPMC: 13 patients, PDAC: 13 patients).

Factor		Invasive IPMC	PDAC	OR (95% CI)	*P* value
Age (years), mean ± SD		67.2 ± 9.1	68.3 ± 7.8	0.59 (0.03–11.21)	0.8370
Sex, n (%)				0.71 (0.13–3.62)	0.6802
Male		8 (61.5)	9 (69.2)		
Female		5 (38.5)	4 (30.8)		
Symptoms, n (%)				0.68 (0.11–3.89)	0.6584
Present		3 (23.1)	4 (30.8)		
Absent		10 (76.9)	9 (69.2)		
CA19-9 (U/mL), median (IQR)		13 (6.5–65.5)	28 (13–154)	0.48 (0.08–2.57)	0.1660
Tumor size (mm), mean ± SD		17.1 ± 8.4	17.0 ± 7.3	1.06 (0.05–22.14)	0.9385
Tumor stage, n (%)					1
I		7 (53.8)	7 (53.8)		
II		5 (38.5)	5 (38.5)		
III		1 (7.7)	1 (7.7)		
IV		0	0		
Location, n (%)					0.3247
Head		9 (69.2)	7 (53.8)		
Body		3 (23.1)	6 (46.2)		
Tail		1 (7.7)	0		
CEH-EUS pattern	Multiphase	1: 12	9: 4	27 (3.54–587.1)	0.0013
Hypoenhanced: Nonhypoenhanced	Single phase				
	20 s	1: 12	8: 5	19.2 (2.58–408.79)	0.0039
	40 s	1: 12	9: 4	27 (3.54–587.1)	0.0013
	60 s	1:12	11:2	66 (7.46–1656.22)	<0.0001

IPMC: intraductal papillary mucinous carcinoma. PDAC: pancreatic ductal adenocarcinoma. OR: odds ratio. CI: confidence interval. Symptoms: jaundice and abdominal pain (including pancreatitis). CA19-9: serum level of carbohydrate antigen 19-9. Data for serum CA19-9 levels are shown as the medians (interquartile ranges). Multiphase: hypoenhanced (−) at ≥2 of the 3 time points was defined as hypoenhanced, and other patterns were defined as nonhypoenhanced.

[1,6,7,17,20–22]. Adsay et al. [6] obtained 5-year survival rates of 40–60% in patients with resected IPMN-derived mucinous carcinoma but only 10–15% for resected tubular adenocarcinoma.

Poultsides et al. [23] found that the outcome of invasive IPMC was significantly better than that of PDAC (median survival, 43 vs. 19 months; 5-year survival 42% vs. 19%, P < 0.001). Therefore, there are differences in prognosis between invasive IPMC and PDAC, and differentiation between these diseases is important [1,6,7]. However, clinical differentiation between invasive IPMC and PDAC with IPMN in invasive carcinoma arising from the vicinity of IPMN is difficult in some cases. For this differentiation, a method based on differences in the genetic profile of cancer cells has been reported, in addition to an evaluation based on the continuity of epithelial atypia of IPMN and the presence or absence of a transition in pathological findings of resected specimens [8,24].

The resolution of EUS is higher than those of other modalities, and EUS is used for close evaluation of the pancreas. Diagnostic imaging techniques, such as harmonic imaging and Doppler mode, can be used with EUS, and the hemodynamics in a region of interest can be evaluated continuously in real time using CEH-EUS. We have shown the utility of CEH-EUS for the differential diagnosis of solid pancreatic tumors [3,9,10,25–28], and Yamamoto et al. reported

that TIC analysis based on CEH-EUS is useful for the diagnosis of IPMN malignancy [29]. However, TIC analysis requires specific software and setting parameters for analysis using prepared curves, and interpretation can be complicated. The utility of multiphase evaluation using CEH-EUS was investigated in this study. This evaluation is subjective, but the interobserver agreement was high. Although our method cannot be quantified, unlike TIC analysis, it is capable of evaluating changes in the contrast enhancement pattern dynamically and simply, and its clinical versatility is high. Differences in the contrast enhancement pattern obtained in this study may be due to differences in tissue type, the degree of fibrosis, and the abundance of blood vessels. Further investigation is needed to clarify these points in the future.

There are several limitations of this study. First, this study had a single-center, retrospective design and included a small number of PDAC patients with IPMN. A prospective study with more patients may be necessary; however, the contrast enhancement pattern was similar between the PDAC with IPMN and PDAC without IPMN groups, which suggests that the data were sufficient for differential diagnosis of invasive IPMC. Second, we did not perform genetic mutation analysis to differentiate between invasive IPMC and PDAC with IPMN in this study. Finally, in the actual clinical setting, pancreatitis associated with IPMN may be visualized as a hypoechoic region, so it may be difficult to distinguish it from IPMN-derived invasive cancer lesions by EUS imaging. We will also consider this point in future prospective studies.

In conclusion, a hypoenhanced pattern was more common in PDAC compared with invasive IPMC, which manifested as an isoenhanced pattern. Multiphase evaluation using CEH-EUS is a useful method for differentiating between invasive IPMC and PDAC. The multiphase evaluation method of CEH-EUS can be used to evaluate changes in contrast enhancement patterns simply and dynamically and has clinical versatility.

IPMC: intraductal papillary mucinous carcinoma. PDAC: pancreatic ductal adenocarcinoma. OR: odds ratio. CI: confidence interval. Symptoms: jaundice and abdominal pain (including pancreatitis). CA19-9: serum level of carbohydrate antigen 19-9. Data for serum CA19-9 levels are shown as the medians (interquartile ranges). Multiphase: hypoenhanced (−) at ≥2 of the 3 time points was defined as hypoenhanced, and other patterns were defined as nonhypoenhanced.

Acknowledgments

The authors declare that they have no competing interests. No funding was received for the study.

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