Title: Endoscopic ultrasonography findings of pancreatic parenchyma for predicting subtypes of intraductal papillary mucinous neoplasms

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Short title: Prediction of IPMN subtype by EUS

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Abstract

Background and Aims:

The subtypes of intraductal papillary mucinous neoplasms (IPMNs) are closely associated with the clinicopathological behavior and recurrence after surgical resection. However, there are no established non-invasive methods to confirm the subtypes of IPMNs without surgery. The aim of this study is to predict the subtypes of IPMNs using the findings of endoscopic ultrasonography (EUS).

Methods:

Sixty-two consecutive patients with IPMNs who underwent EUS before surgery were retrospectively reviewed. The following EUS findings were analyzed and their relationship with the subtypes was evaluated: diameter of the main pancreatic duct, cyst size, number of cysts, height of mural nodule, early chronic pancreatitis (CP) finding, fatty parenchyma and atrophic parenchyma.

Results:

The subtypes of IPMNs were as follows: gastric (G)-type 38 (61%), intestinal (I) -type 14 (23%) and pancreatobiliary (PB) -type 10 (16%). Fatty parenchyma was significantly associated with G-type ($P < 0.0001$). Early CP findings ≥ 2 and atrophic parenchyma were significantly correlated with I-type ($P < 0.0001$). PB-type was significantly associated with pancreatic parenchyma without early CP findings or fatty degeneration in comparison to the other subtypes ($P < 0.0001$). Using the above characteristic EUS

findings, the sensitivity, specificity, and accuracy were as follows: 63%, 92% and 74%, respectively, in G-type, 57%, 96% and 87% in I-type, and 90%, 94% and 94% in PB-type.

Conclusions:

The evaluation of EUS findings, especially focused on the pancreatic parenchyma, has the potential to predict the subtypes of IPMN.

INTRODUCTION

Intraductal papillary mucinous neoplasm (IPMN) was defined as a grossly visible, intraductal, epithelial neoplasm composed of mucin-producing cells, arising in the main pancreatic duct (MPD) and/or its branches[1,2]. IPMNs correspond to various pathological entities, including adenoma, carcinoma *in situ*, and invasive carcinoma. Thus, the preoperative assessment of their malignancy is critical for determining the indications for surgical resection. The World Health Organization classification of IPMNs published in 2019 has revised the classification, with IPMNs classified into 3 subtypes based on their histomorphology and mucin phenotype, namely the gastric (G), intestinal (I) and pancreatobiliary (PB) types [1].

Recent studies have shown that these histological subtypes are closely associated with malignancy, the prognosis, and the rate of recurrence after surgical resection [3-6]. Thus, preoperatively assessing the subtypes of IPMN may contribute to the better clinical management of patients with IPMNs.

To date, several methods have been used for the prediction of the histological subtypes of IPMNs before surgery [7-11]. Hibi et al. and Hara et al. reported that the diagnostic accuracy of pancreatic juice cytology with mucin staining for the subtypes of IPMN were 79% and 89% respectively [7,8]. The carcinoembryonic antigen (CEA) levels of cyst fluid have also been reported; however, the subtypes with the highest concentration of CEA differed among the studies [10,11]. It was noted that the performance of

endoscopic retrograde cholangiopancreatography (ERCP) and/or endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) to obtain specimens was associated with the risk of adverse events such as pancreatitis. Previous studies reported characteristic images for each subtype of IPMN [1,2,10,12]. According to the reports, G-type IPMN is more commonly associated with branch duct IPMN (BD-IPMN) and multiple cysts. I-type IPMN is significantly associated with main duct IPMN (MD-IPMN) and larger cysts in comparison to other subtypes. PB-type IPMN is significantly associated with the detection of mural nodules. However, the diagnostic yield was not evaluated in these studies.

Recently, endoscopic ultrasonography (EUS) is increasingly utilized in the evaluation of IPMN. EUS provides more detailed information about cystic lesions and pancreatic parenchymal characteristics, such as fibrosis and fatty degeneration in comparison to CT and/or MRI. The evaluation of the detailed findings by EUS has the potential to predict the subtypes of IPMNs. Until now, non-invasive method to confirm the subtypes of IPMNs without surgery has been established. The aims of this study are to identify the characteristic EUS findings of each subtype and to predict the subtypes of IPMN based on the EUS findings.

MATERIALS AND METHODS

Patients

The medical records of all patients who underwent EUS to evaluate IPMNs before surgical resection at Okayama University Hospital between October 2003 and February 2020 were retrospectively reviewed.

A total of 153 cases underwent resection of IPMNs during the study period. And the histological subtype was confirmed based on the histopathological examination of surgical specimens in 71 cases. All patients underwent CT and/or MRI before surgery. Six patients with poor EUS studies and three patients with severe MPD obstruction by invasive carcinoma derived from IPMNs in the pancreatic head were also excluded, because obstruction of the pancreatic duct affected the assessment of the parenchyma.

The surgical indications for IPMN were in line with the international consensus guidelines for the management of IPMNs [13,14]. All patients provided their written informed consent for treatment. This study was approved by the institutional review board of our hospital (Approved number: 2006-030).

EUS procedures

EUS examinations were performed by four experienced endoscopists using a radial or a curved linear array scanning scope (UCT240, UE260, UCT260; Olympus, Tokyo, Japan) with an Aloka console

(Prosound SSD-α10, HITACHI Aloka, Tokyo, Japan) or EU-ME1/EU-ME2 (Olympus medical systems, Tokyo, Japan) monitor/processing unit. The head of the pancreas was examined through the duodenum, and the body to tail was examined through the stomach. All EUS images obtained during the procedure were stored on a computer as electronic images. The evaluations of EUS images were conducted using still images. The presence or absence of defined findings in these images was evaluated by three experienced endoscopists (A, B and C) who blinded to clinical information of the patients. When the three endoscopists exhibited different evaluations, the majority decision was recorded and used for the analysis. The interobserver agreement was also evaluated.

The evaluation and definition of EUS images

The following EUS findings of cystic lesions were analyzed: the diameter of the MPD, cyst size, number of cysts, and the height of the mural nodule. The pancreatic parenchyma was evaluated on the head-side from the IPMN and the following EUS findings were analyzed: early chronic pancreatitis (CP) findings, fatty parenchyma, and atrophic parenchyma. A homogeneous and fine-reticular pattern without dilated ducts was regarded as a normal pancreatic parenchyma (Figure 1a) [15]. EUS images of early CP were classified according to the Japanese diagnostic criteria 2019 for early CP based on the Rosemont

classification (Figure 1b-f) [16], and the definition of early CP was judged by more than 2 EUS imaging findings. Based on a previous study, fatty parenchyma was defined as >80% of the parenchyma being more hyperechoic in comparison to the spleen, the main pancreatic duct margins were moderately or severely obscured, and the fine-reticular pattern in the pancreatic parenchyma was moderately or severely blurry (Figure 1g) [17]. We measured the maximum and minimum diameter of the pancreatic body without cystic lesions, and then calculated the average pancreatic body width. Pancreatic atrophy was defined as an average pancreatic body width of <10 mm (Figure 1h) [18, 19].

Histological examination of IPMN

The pathological slides from the surgical specimen were reviewed by two pathologists. The histological subtype, grade of dysplasia, and type of duct involvement by IPMN were evaluated. In patients who underwent the resection of multiple cysts, all specimens were reviewed. The subtype was classified into three distinct types on the basis of the histomorphology and mucin phenotype [1]. When the IPMN exhibited a heterogeneous histological subtype, the predominant subtype or the subtype with the higher degree of epithelial dysplasia was recorded as the subtype and used for the analysis.

The grade of dysplasia was reported based on the highest degree of dysplasia identified and was categorized according to the WHO classification, which included low-grade dysplasia, high-grade dysplasia, and invasive carcinoma derived from the IPMN [1]. The type of duct involvement was determined based on the pathology and the results of imaging examinations, and was classified as follows based on the World Health Organization classification 5th edition, as follows: BD-IPMN, MD-IPMN and mixed duct-type IPMN［1].

Statistical analyses

Categorical variables were reported as percentages and continuous variables were reported as the median and interquartile range (IQR). The sensitivity, specificity, and accuracy of the EUS diagnosis for each subtype were calculated with 95% confidence intervals. Wilcoxon's rank sum test and the Kruskal-Wallis test were used to compare continuous data. Fisher's exact test was used to compare categorical data. Cohen's κ coefficient was calculated to assess the interobserver agreement between each endoscopists. The agreement was regarded as excellent for a κ coefficient of ≥ 0.8, good for <0.8 to ≥ 0.6, moderate for < 0.6 to ≥ 0.4, and poor for < 0.4. The analyses were performed using JMP Pro13 for Mac (JMP 15, SAS Institute Inc., Cary, NC, USA).

RESULTS

Patient characteristics

The patient's characteristics are shown in Table 1. The median age was 70 years (IQR: 66-74), and 53% of the patients were male. The subtypes of 62 patients with IPMNs were as follows: G-type 61% (38), I-type 23% (14), PB-type 16% (10). Regarding the macroscopic type, MD-IPMNs were observed in the I type more frequently than the other-types. ($P = 0.0006$) The proportions of invasive carcinomas in G-type, I-type and PB-type IPMNs were 13% (5/38), 29% (4/14) and 100% (10/10), respectively ($P < 0.0001$). Invasive carcinoma was found in PB-type IPMNs more than other types.

EUS findings for each subtype

Table 2 shows the associations between the histological subtypes and the EUS findings. The EUS findings of number of cysts ≥ 2 ($P = 0.0014$) and fatty parenchyma ($P < 0.0001$) were significantly associated with G-type. The following EUS findings were significantly correlated with I-type: MPD ≥10 mm ($P = 0.0011$), < 30 mm in size ($P = 0.0017$), hyperechoic foci without shadowing or strands ($P < 0.0001$), early CP findings ≥ 2 ($P < 0.0001$), and atrophic parenchyma ($P < 0.0001$). A pancreatic

parenchyma with none of the early CP findings (P = 0.0005) or no fatty degeneration (P = 0.025) was significantly associated with PB-type (Supplemental table 1).

Prediction for each IPMN subtype according to the EUS findings

Table 3 shows the diagnostic yields of subtypes according to the characteristics of the EUS images with the highest accuracy. The EUS findings of pancreatic parenchyma including fatty degeneration, early CP findings and atrophy were important factors for predicting the subtypes. Using the above characteristic EUS findings, the sensitivity, specificity, and accuracy were 63% (24/38), 92% (22/24) and 74% (46/62), respectively, in G-type, 57% (8/14), 96% (46/48) and 87% (54/62) in I-type, 90% (9/10), 94% (49/52) and 94% (58/62) in PB-type. Interobserver agreement between each endoscopists had a κ coefficient of 0.71−0.80 in fatty parenchyma, 0.68−0.74 in findings of early CP ≥ 2 and atrophy, and 0.65−0.71 in no findings of early CP and fatty parenchyma.

We also evaluated the EUS findings in patients with (n=19) or without (n=43) invasive carcinoma. Fatty parenchyma was significantly related to G-type IPMN with (P = 0.0001) and without (P = 0.0082) invasive carcinoma. Early CP findings ≥ 2 and atrophic parenchyma were correlated with I-type IPMN with (P = 0.0003) and without (P = 0.001) invasive carcinoma.

Typical pathological slides from surgical specimens are shown in Figures 2-4. The pathological findings of each subtype in these slides were generally found to coincide with the EUS findings of each subtype: fatty change in G-type, fibrosis and atrophy in I-type and an almost normal parenchyma in PB-type.

Relationship between EUS findings and patient characteristics

We surveyed the relationship between EUS findings with significant differences and the following factors, which may affect changes in pancreatic parenchyma: age, sex, body mass index, diabetes mellitus, hypertension, hyperlipidemia, tobacco use, ethanol use, medical history of nonalcoholic steatohepatitis, medical history of acute pancreatitis and family history of pancreatic cancer (Supplemental Table 2). Although the EUS finding of pancreatic parenchyma with early CP ≥ 2 and atrophy was associated with a medical history of acute pancreatitis (P=0.012), the other EUS findings were not associated with these factors.

We also evaluated the relevance of the metabolic risk factors affecting fatty degeneration in G-type and non-G-type IPMNs. Consequently, the median body mass index was 20.3 (interquartile range: IQR 18.6-22.0) kg/m^2 in G-type vs. 21.5 (IQR: 19.6-23.8) kg/m^2 in non-G-type (P = 0.19), the rate of

diabetes mellitus was 26% (10/38) in G-type vs. 33% (8/24) in non-G-type (P = 0.55), the rate of hypertension was 34% (13/38) in G-type vs. 46% (11/24) in non-G-type (P = 0.36), and the rate of hyperlipidemia was 18% (7/38) in G-type vs. 25% (6/24) in non-G-type (P = 0.54). None of these factors differed to a statistically significant extent between G-type and non-G-type.

DISCUSSION

To the best of our knowledge, this is the first report on the prediction of IPMN subtypes using EUS findings, with a particular focus on the pancreatic parenchyma. Each subtype of IPMN has characteristic EUS findings and the diagnostic ability of EUS imaging is relatively high. EUS is a less invasive examination in comparison to ERCP and EUS-FNA for distinguishing the histological subtypes of IPMNs. In this study, we newly reported that each subtype has characteristic EUS findings in the pancreatic parenchyma. We also evaluated the EUS findings in patients with and without invasive carcinoma, considering the changes of the pancreatic parenchyma that occur in association with carcinoma. Consequently, similar results were obtained.

According to a recent report, the stroma around a pancreatic tumor plays an important role in its progression [20,21]. A previous study examined the histological features of the peritumoral stroma in each subtype of IPMN, and demonstrated that subepithelial edema and inflammatory cell infiltration were more commonly observed in G-type IPMN, while atrophy and fibrosis were more commonly observed in I-type IPMN [22]. Our study also showed atrophy and fibrosis of the pancreas parenchyma in I-type IPMN, and these findings may suggest secondary changes due to the elevation of intraductal pressure of the MPD with mucus hypersecretion from the tumor. Although the mechanism of fatty degeneration in

the parenchyma remains to be elucidated, fatty pancreas has been reported to be associated with metabolic risk factors [23-26]. We surveyed the relationship between the EUS findings and the patient characteristics. In addition, none of the metabolic risk factors differed to a statistically significant extent between G-type IPMN and non-G-type IPMN in our study. The results indicated that another mechanism of fatty degeneration may be present in G-type IPMN.

The parenchyma of PB-type IPMN was almost normal in our study. We presume that PB-type IPMN has more aggressive malignant characteristics than the other subtypes; thus, the peritumoral stroma changes have not had fully developed [3,5]. In addition, PB-type IPMN has less mucin in comparison to I-type; thus, atrophic changes and fibrosis in the parenchyma are unlikely to occur [22]. Although these differences of the pancreatic parenchyma make it possible to predict the subtypes of IPMNs, there were some cases in which the diagnosis was inaccurate in the present study. Previous studies reported that approximately 30% of IPMNs had multiple subtypes within one lesion, whereas most studies classified IPMNs into one of the three subtypes [27]. This might influence the difficulty of diagnosing the subtype based on EUS images.

The prognostic value of the histological subtypes has been reported [3-5]. In 2011, Furukawa et al. demonstrated the disease-specific survival was highest in G-type and lowest in PB-type.[3]

Since then, various prognostic results have been reported [4,5,28]. These reports generally showed that PB-type IPMN and G-type IPMN progress to invasive tubular adenocarcinoma, and that a small proportion of G-type IPMNs have a poor prognosis. In this study, most of the patients with G-type IPMN had low-grade dysplasia (71%), while all patients with PB-type IPMN had invasive carcinoma. These results were in agreement with previous reports and indicated that PB-type IPMN is associated with a poor prognosis. In addition, Kwon et al. reported that PB-type and I-type IPMNs—as opposed to G-type—were risk factors for metachronous recurrence of high-risk lesions after partial pancreatectomy for IPMN [6]. In our study, the metachronous recurrence of invasive carcinoma derived from the residual pancreas was observed in one patient with G-type (2.6%), two patients with I-type (14%) and three patients with PB-type (30%). PB-type IPMN was associated with a significantly higher rate of metachronous recurrence in comparison to G-type IPMN ($P = 0.0053$). PB-type IPMN should be carefully evaluated before surgery and close and long-term surveillance of the remnant pancreas should be performed after initial resection. Although the international consensus guidelines defined the management of IPMN, the optimal surgical indication has been investigated [13,14]. In the present study, all patients with PB-type IPMNs had invasive carcinoma; this result indicates that PB-type IPMN can be considered an indication for surgery. Additionally, MPD $\geq$ 5 mm was significantly associated with high-

grade dysplasia or invasive carcinoma in G-type IPMN with fatty parenchyma (60% [9/15] for low or intermediate-grade dysplasia vs. 100% [9/9] for high-grade dysplasia or invasive carcinoma, P = 0.029). IPMN without a dilated MPD can be followed-up in patients with G-type IPMN who show typical EUS findings. Regarding the imaging findings evaluated in this study, no risk factors of high-grade dysplasia or invasive carcinoma were observed in patients with I-type IPMN with findings of early CP and atrophy.

The observation of different points according to each subtype are also important before surgery. Patients with G-type IPMNs with small cystic lesions were reported to show a tendency to have pancreatic cancers concomitant with IPMNs [29,30]. Thus, the observation of the surrounding pancreatic parenchyma is important, especially in cases of G-type IPMN. In addition, a recent molecular analysis demonstrated the possibility of monoclonal skip implantation in MD-IPMN; thus, clinicians and surgeons should be aware of potential synchronous or metachronous lesions [31]. Careful observation of the MPD is important when we perform EUS screening for MD-IPMN, especially in cases of I-type IPMN.

The present study was associated with some limitations. This study was retrospectively conducted at a single center with a relatively small sample size. The only lesions that could be included in this study were those that had been surgically resected, which resulted in an inevitable selection bias. In cases with severe MPD obstruction in the pancreatic head, it was difficult to evaluate the pancreatic

parenchyma. The defined EUS findings were evaluated by still images, and not videoclips. In addition, we did not use cross-sectional examinations (e.g., CT or MRI) to evaluate the pancreatic parenchyma. Thus, the measured width of the pancreatic parenchyma may differ slightly between CT or MRI and EUS images. Finally, only evaluated the predominant subtypes of IPMN. It is possible that the cases without concordance of the EUS findings and the types of IPMN had multiple subtypes. Thus, we should evaluate the volume or proportion of the predominant subtype and the presence of non-predominant components in a further study.

In conclusion, the evaluation of EUS findings, focusing on the pancreatic parenchyma, has the potential to predict the subtypes of IPMN. Assessing the subtypes of IPMN may contribute to the better clinical management of patients with IPMNs.

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FIGURE LEGENDS

Figure 1. The evaluated EUS findings of pancreatic parenchyma

(a) A homogeneous and fine-reticular pattern is visible in the parenchyma without dilated ducts (circle).

(b) Hyperechoic foci without shadowing.

Echogenic structures of ≥ 3 mm in both length and width with no shadowing (arrowhead). At least 3 of these structures are needed for the feature to be considered abnormal.

(c) Strands.

Hyperechoic lines of ≥ 3 mm in length are seen in at least 2 different directions with respect to the imaged plane (arrowhead). At least 3 strands are considered necessary for this to be considered indicative of early chronic pancreatitis.

(d) Lobularity.

The pancreatic parenchyma is lobulated by well-circumscribed structures of ≥ 5 mm in size, with rims that are hyperechoic relative to the echogenicity of its central areas (circle). The continuity of the lobules does not matter.

(e) Hyperechoic main pancreatic duct margin.

A hyperechoic main pancreatic duct margin is defined by a relatively hyperechoic duct wall in greater than 50% of the entire MPD (circle).

(f) Dilated side branches.

Dilated side branches are defined by the presence of 3 or more tubular anechoic structures, each measuring > 1 mm in width and communicating with the main pancreatic duct (arrowhead).

(g) Fatty pancreatic parenchyma. The pancreatic parenchyma is hyperechoic, and the main pancreatic duct margin is obscured (circle).

(h) Atrophic pancreatic parenchyma. The width of the pancreatic body is less than 10 mm (circle).

Figure 2. Pathological findings in gastric-type IPMN.

The resected specimen showed a dilated pancreatic duct filled with papillary protrusions composed of atypical mucinous cells (a, H&E staining: ×100). MUC1 staining (b, ×100), MUC2 (c, ×100) and CDX2 (d, ×100) staining are negative, and MUC5AC (e, ×100) and MUC6 (f, ×100) staining are diffusely positive in the main lesion. Conspicuous fatty degeneration (asterisk) is confirmed around the IPMN (arrows) (g, H&E staining, ×4).

Figure 3. Pathological findings in intestinal-type IPMN.

The resected specimen showed a dilated pancreatic duct filled with villous protrusions composed of atypical mucinous cells (a, H&E staining: ×100). MUC1 staining (b, ×100) and MUC6 staining (f, ×100) are negative, and MUC2 staining (c, ×100), CDX-2 staining (d, ×100) and MAC5AC staining (e, ×100) are diffusely positive in the main lesion. Fibrosis (asterisk) and mucus retention (arrow heads) are observed around an IPMN (arrows) (g, H&E staining, ×4).

Figure 4. Pathological findings in pancreatobiliary-type IPMN.

The resected specimen showed a dilated pancreatic duct filled with arborescent protrusions composed of atypical cells (a, H&E staining: ×100). MUC1 staining (b, ×100) and MUC5AC staining (d, ×100) are partially positive in the main lesion. And MUC2 staining (c, ×100) is negative. (e) Fibrosis and fatty degeneration are not conspicuous, and acinar tissue (asterisk) remains around the IPMN (arrows) (H&E staining, ×4).

Table 1. Patient characteristics

Parameter	Histological subtypes with MUC staining			Total (n = 62)	p value
	Gastric (n = 38)	Intestinal (n = 14)	Pancreatobiliary (n = 10)		
Age, median (IQR), years	70 (65-75)	69 (58-73)	71 (70-78)	70 (66-74)	0.31
Sex, male, n (%)	21 (55)	8 (57)	4 (40)	33 (53)	0.65
Location of main lesion, n (%)					0.81
Head	24 (63)	8 (57)	7 (70)	39 (63)	
Body or tail	14 (37)	6 (43)	3 (30)	23 (37)	
Macroscopic type, n (%)					0.0009
BD-IPMN	16 (42)	1 (7)	6 (60)	23 (37)	
MD-IPMN	1 (3)	6 (43)	2 (20)	9 (15)	
Mixed duct-type IPMN	21 (55)	7 (50)	2 (20)	30 (48)	
Histological classification, n (%)					< 0.0001
LGD	27 (71)	5 (36)	0 (0)	32 (52)	
HGD	6 (16)	5 (36)	0 (0)	11 (18)	
IC	5 (13)	4 (29)	10 (100)	19 (31)	

IQR, interquartile range

MUC, mucin

BD-IPMN, branch duct intraductal papillary mucinous neoplasm

MD-IPMN, main duct intraductal papillary mucinous neoplasm

Mixed duct-type IPMN, mixed duct type intraductal papillary mucinous neoplasm

LGD, low grade dysplasia

HGD, high-grade dysplasia

IC, invasive carcinoma derived from IPMN

Table 2. Endoscopic ultrasonography findings of cystic lesion and pancreatic parenchyma according to the histological subtypes

	Histological subtype			p value
	Gastric (n = 38)	Intestinal (n = 14)	Pancreatobiliary (n = 10)	
Diameter of MPD				
Median (IQR), mm	6 (4-9)	10 (8-13)	5 (4-6)	0.0024
≥10 mm, n (%)	7 (18)	8 (57)	0 (0)	0.0023
Cystic size				
Median (IQR), mm	30 (22-41)	16 (0-26)	25 (11-42)	0.0034
≥ 30 mm, n (%)	20 (53)	1 (7)	4 (40)	0.012
Number of cysts				
Median (IQR), n	2 (1-3)	1 (0-2)	1 (1-3)	0.0001
≥ 2, n (%)	20 (53)	0 (0)	3 (30)	0.002
Features of MN				
Case with MN, n (%)	30 (79)	11 (79)	9 (90)	0.72
Height of MN in cases with MN				
Median (IQR), mm	6 (2-14)	6 (3-7)	11 (3-16)	0.41
≥ 5 mm, n (%)	23 (61)	8 (57)	9 (90)	0.18
The finding of early chronic pancreatitis, n (%)				
Hyperechoic foci without shadowing or Strands	13 (34)	13 (93)	1 (10)	<0.0001

Lobularity	1 (3)	2 (14)	0 (0)	0.16
Hyperechoic MPD margin	11 (29)	7 (50)	1 (10)	0.1
Dilated side branches	6 (16)	5 (36)	0 (0)	0.069
The finding of early chronic pancreatitis ≥ 2	7 (18)	12 (86)	1 (10)	<0.0001
Fatty parenchyma, n (%)	24 (63)	1 (7)	1 (10)	0.0001
Atrophy, n (%)	4 (11)	10 (71)	2 (20)	<0.0001

MPD, main pancreatic duct

IQR, interquartile range

MN, mural nodule

Table 3. Diagnostic yield of endoscopic ultrasonography findings in the diagnosis of the histological subtypes of IPMN

Subject for comparison	Characteristic findings	Sensitivity (95%CI) No. of patients	Specificity (95%CI) No. of patients	PPV (95%CI) No. of patients	NPV (95%CI) No. of patients	Accuracy (95%CI) No. of patients	κ value (Endoscopist)
G vs. non-G	Fatty parenchyma	63% (54-67) 24/38	92% (78-98) 22/24	92% (80-98) 24/26	61% (52-65) 22/36	74% (64-79) 46/62	0.80 (A-B) 0.73 (B-C) 0.71 (C-A)
I vs. non-I	Findings of early CP ≥ 2 and atrophy	57% (38-67) 8/14	96% (90-99) 46/48	80% (53-94) 8/10	88% (83-91) 46/52	87% (79-92) 54/62	0.68 (A-B) 0.74 (B-C) 0.69 (C-A)
PB vs. non-PB	None of early CP findings and no fatty parenchyma	90% (66-98) 9/10	94% (90-96) 49/52	75% (55-82) 9/12	98% (93-100) 49/50	94% (86-96) 58/62	0.67 (A-B) 0.65 (B-A) 0.71 (C-A)

G, gastric

I, intestinal

PB, pancreatobiliary

CI, confidence interval

NPV, negative predictive value

PPV, positive predictive value

CP, chronic pancreatitis

A, endoscopist A

B, endoscopist B

C, endoscopist C

Supplemental Table 1. Diagnostic yield of various endoscopic ultrasonography findings in the diagnosis of the histological subtypes of IPMN

Subject for comparison	Characteristic findings	P value	Sensitivity (95%CI)	Specificity (95%CI)	PPV (95%CI)	NPV (95%CI)	Accuracy (95%CI)
G vs. non-G	Number of cysts ≥ 2	0.0014	53% (44-58)	88% (73-95)	87% (72-95)	54% (45-59)	66% (55-72)
	Fatty parenchyma	<0.0001	63% (54-67)	92% (78-98)	92% (80-98)	61% (52-65)	74% (64-79)
	Number of cysts ≥ 2 and fatty parenchyma	0.0013	34% (27-34)	100% (89-100)	100% (80-100)	49% (44-49)	60% (51-60)
I vs. non-I	MPD diameter ≥10 mm	0.0011	57% (36-75)	85% (79-91)	53% (34-70)	87% (81-93)	79% (70-87)
	Cystic size < 30 mm	0.0017	86% (63-96)	50% (44-53)	33% (25-37)	92% (80-98)	58% (48-63)
	Early CP findings ≥ 2	<0.0001	86% (64-96)	83% (77-86)	60% (45-67)	95% (88-99)	83% (74-88)
	Atrophy	<0.0001	71% (50-86)	88% (81-92)	63% (44-76)	91% (85-96)	83% (74-91)
	MPD diameter ≥10 mm and cystic size < 30 mm	0.002	43% (24-58)	92% (86-96)	60% (34-81)	85% (80-89)	81% (72-88)
	MPD diameter ≥10 mm and early CP findings ≥ 2	<0.0001	43% (26-49)	98% (93-100)	86% (52-97)	86% (82-88)	86% (78-88)
	MPD diameter ≥10 mm and atrophy	0.0002	36% (20-42)	98% (93-100)	83% (46-97)	84% (80-85)	83% (77-87)
	Cystic size < 30 mm and early CP findings ≥ 2	<0.0001	71% (51-86)	90% (83-94)	67% (47-80)	92% (85-96)	86% (76-92)
	Cystic size < 30 mm and atrophy	<0.0001	64% (44-79)	92% (86-96)	69% (47-85)	90% (84-94)	86% (76-92)
	Early CP findings ≥ 2 and atrophy	<0.0001	57% (38-67)	96% (90-99)	80% (53-94)	88% (83-91)	87% (79-92)
	MPD diameter ≥10 mm, cystic size < 30 mm and early CP findings ≥ 2	0.0001	29% (15-29)	100% (96-100)	100% (54-100)	83% (80-83)	84% (78-84)
	MPD diameter ≥10 mm, cystic size < 30 mm and atrophy	0.0001	29% (15-29)	100% (96-100)	100% (54-100)	83% (80-83)	84% (78-84)

	MPD diameter ≥10 mm, early CP findings ≥ 2 and atrophy	0.0095	21% (9-27)	98% (94-100)	75% (31-95)	81% (78-82)	80% (75-83)
	Cystic size < 30 mm, early CP findings ≥ 2 and atrophy	<0.0001	50% (32-56)	98% (93-100)	88% (57-98)	87% (83-89)	87% (79-90)
	MPD diameter ≥10 mm, Cystic size < 30 mm, early CP findings ≥ 2 and atrophy	0.0078	14% (5-14)	100% (97-100)	100% (35-100)	80% (78-80)	81% (77-81)
PB vs. non-PB	None of early CP findings	0.0005	90% (63-98)	69% (64-71)	36% (25-39)	97% (90-100)	73% (64-75)
	No fatty parenchyma	0.025	90% (62-98)	48% (43-50)	25% (17-27)	96% (86-99)	55% (46-58)
	None of early CP findings and no fatty parenchyma	<0.0001	90% (66-98)	94% (90-96)	75% (55-82)	98% (93-100)	94% (86-96)

IPMN, intraductal papillary mucinous neoplasm

G, gastric

I, intestinal

PB, pancreatobiliary

CI, confidence interval

NPV, negative predictive value

PPV, positive predictive value

MPD, main pancreatic duct

CP, chronic pancreatitis

Supplemental Table 2. Relationship between EUS findings and patient characteristics

Parameter	EUS finding								
	Fatty parenchyma			Findings of early CP ≥ 2 and atrophy			None of early CP findings and no fatty parenchyma		
	presence (n = 26)	absence (n = 36)	p value	presence (n = 10)	absence (n = 52)	p value	presence (n = 12)	absence (n = 50)	p value
Age, median (IQR), years	70 (65-75)	71 (66-74)	0.95	71 (65-73)	70 (65-75)	0.98	73 (70-77)	69 (64-74)	0.13
Sex, male, n (%)	14 (54)	19 (53)	0.93	3 (30)	26 (50)	0.25	4 (33)	29 (58)	0.12
BMI, median (IQR), kg/m^2	20 (19-23)	21 (19-24)	0.66	20 (20-24)	21 (19-23)	0.76	21 (20-24)	20 (19-23)	0.51
Diabetes mellitus*, n (%)	5 (19)	13 (36)	0.15	5 (50)	13 (25)	0.11	4 (33)	14 (28)	0.71
Hypertension**, n (%)	8 (31)	14 (39)	0.51	5 (50)	17 (33)	0.29	7 (58)	15 (30)	0.07
Hyperlipidemia***, n (%)	6 (23)	7 (19)	0.73	4 (40)	9 (17)	0.11	3 (25)	10 (20)	0.7
Tobacco use, median (IQR), PY	2 (0-42)	0 (0-37)	0.62	1 (0-41)	0 (0-36)	0.94	0 (0-24)	2 (0-39)	0.2
Ethanol use, median (IQR), g/day	5 (0-20)	10 (0-20)	1	0 (0-23)	10 (0-20)	0.31	5 (0-18)	10 (0-20)	0.55
Medical history of NASH, n (%)	0 (0)	0 (0)	-	0 (0)	0 (0)	-	0 (0)	0 (0)	-
Medical history of acute pancreatitis, n (%)	0 (0)	4 (11)	0.08	3 (30)	1 (2)	0.01	0 (0)	4 (8)	0.31
Family history of pancreatic cancer, n (%)	1 (4)	3 (8)	0.48	0 (0)	4 (8)	0.36	1 (8)	3 (6)	0.77

EUS, endoscopic ultrasonography

CP, chronic pancreatitis

IQR, interquartile range

BMI, body mass index

PY, packs/day × no. of years

NASH, nonalcoholic steatohepatitis

* Defined as hemoglobin A1c [NGSP] ≥ 6.5.

** Defined as systolic blood pressure ≥ 140

mmHg or diastolic blood pressure ≥ 90

mmHg

*** Defined as triglycerides ≥ 150 mg/dl, low

density lipoprotein ≥ 140 mg/dl or high

density lipoprotein < 40 mg/dl