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# Lobularity rather than hyperechoic foci/stranding on endoscopic ultrasonography is associated with more severe histological features in chronic pancreatitis

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KOBE UNIVERSITY

*Original article*

**Lobularity rather than hyperechoic foci/stranding on endoscopic ultrasonography is associated with more severe histological features in chronic pancreatitis**

**Short title:** Endoscopic ultrasonography and Histology

**Disclosure statement**

The authors have no conflicts of interest to declare.


**ABSTRACT**

*Background and Aim*

Endoscopic ultrasonography (EUS) findings of the pancreatic parenchyma, such as hyperechoic foci/stranding and lobularity, may be associated with the severity of chronic pancreatitis (CP). However, the correlation between parenchymal EUS findings and histology remains unclear. We designed a large-scale retrospective study analyzing over 200 surgical specimens to elucidate the association between parenchymal EUS findings and histological features.

*Methods*

Clinical data of 221 patients with pancreatobiliary tumors who underwent preoperative EUS and pancreatic surgery between January 2010 and November 2020 were reviewed to investigate the association between parenchymal EUS findings and histological features at the pancreatic body. None of these patients met the definition of CP.

*Results*

Of the 221 patients, 87 (39.4%), 89 (40.2%), and 45 (20.4%) had normal EUS findings, hyperechoic foci/stranding without lobularity, and hyperechoic foci/stranding with lobularity, respectively. In the

multivariate analyses, parenchymal EUS findings significantly correlated with histological CP findings of fibrosis, inflammation, and atrophy (hyperechoic foci/stranding without lobularity vs hyperechoic foci/stranding with lobularity, odds ratio [95% confidence interval]: 4.1 [2.2-7.9] vs 31.3 [9.3-105.6], $P_{trend} < 0.001$; 3.9 [1.9-8.2] vs 21.8 [8.0-59.4], $P_{trend} < 0.001$; and 4.0 [2.0-7.8] vs. 22.9 [7.0-74.5], $P_{trend} < 0.001$, respectively). Further, a trend toward higher histological grade was observed in the following order: normal findings, hyperechoic foci/stranding without lobularity, and hyperechoic foci/stranding with lobularity.

*Conclusions*

EUS findings of the pancreatic parenchyma may be associated with the histological conditions in CP, such as pancreatic fibrosis, inflammation, and atrophy. Lobularity reflects more severe histological conditions than does hyperechoic foci/stranding.

KEYWORDS: chronic pancreatitis, hyperechoic foci/stranding, lobularity, endoscopic ultrasonography, histology

## INTRODUCTION

Chronic pancreatitis (CP) is a multifactorial, pathogenic, fibroinflammatory syndrome in which repetitive episodes of pancreatic inflammation lead to extensive fibrotic tissue replacement[1,2]. Advanced CP causes severe chronic pain, exocrine and endocrine pancreatic insufficiency, and pancreatic cancer[1,3], leading to a low quality of life (QOL) and poor prognosis. The number of patients with CP has been increasing annually, with estimated prevalences of 45, 163, and 73 per 100,000 in Japan, the United Kingdom, and the United States, respectively[3–5]. CP is usually diagnosed at an irreversible stage with severe pancreatic dysfunction, for which no curative treatment is currently available. Therefore, an early diagnosis is essential to improve the QOL and prognosis in patients with CP.

Owing to technological developments, endoscopic ultrasonography (EUS) now plays a pivotal role in diagnosing CP[6]. In the Rosemont classification[7] and new Japanese diagnostic criteria 2019 (DC2019) of early CP[3], hyperechoic foci, stranding, and lobularity are considered representative pancreatic parenchymal EUS findings in CP. Some previous studies suggested the association between these EUS findings and CP histological features, such as fibrosis, inflammation, and atrophy, in patients with CP[8–13]. However, these studies were limited by their small sample size (at most 100 patients), and the accumulated evidence on parenchymal EUS findings was insufficient. Moreover, these studies suggested that parenchymal EUS findings could help identify the degree of fibrosis in patients with CP but did not clarify whether these findings helped detect early CP in the general population without CP. Parenchymal EUS findings, such as hyperechoic foci, stranding, and lobularity, are sometimes found clinically even in patients who do not meet the definition of CP. A previous study indicated that approximately 17% of patients who underwent EUS for indications unrelated to pancreatobiliary disease had some abnormal parenchymal EUS findings and that these EUS findings were associated with alcohol consumption and smoking, which were risk factors for CP[14]. However,

that study could not evaluate the histology of the pancreas, and whether these parenchymal EUS findings reflect CP histological features in patients without CP remains unclear.

Therefore, we aimed to elucidate the frequency of pancreatic parenchymal EUS findings, such as hyperechoic foci, stranding, and lobularity, in patients without CP as well as the association between these EUS findings and CP histological features by designing a large-scale retrospective study analyzing over 200 surgically resected specimens of several types of pancreatobiliary diseases.

## METHODS

### Patients and data collection

We retrospectively collected the medical data of 221 consecutive patients with pancreatobiliary tumors who underwent preoperative EUS and pancreatic surgery between January 2010 and November 2020 at our hospital. None of these patients met the definition of CP. Pancreatobiliary tumors included intraductal papillary mucinous neoplasms (IPMNs), pancreatic ductal adenocarcinomas (PDACs) in the body or tail of the pancreas, pancreatic neuroendocrine neoplasms (p-NENs), and distal cholangiocarcinomas. We excluded patients whose surgically resected specimens did not include the pancreatic body, because EUS and histological findings were assessed at the pancreatic body as mentioned below, as well as patients with PDACs in the head of the pancreas because the effects of obstructive pancreatitis on pancreatic parenchymal EUS images could not be eliminated at the caudal side of PDACs. We collected clinical information including age, sex, body mass index (BMI), diabetes mellitus (DM), alcohol consumption (<60 g/day or ≥60 g/day regularly), and smoking status (never, former, or current). DM was diagnosed according to the criteria of the Japan Diabetes Society[15]. Never smokers were defined as those who had never smoked a cigarette in their lifetime, former smokers as those who had ceased smoking at least 1 year before the surgery, and current smokers as those who had been smoking at the time of the surgery. The current study was approved by the ethics committee

of our hospital (approval number: B210183) and was registered in the University Hospital Medical Information Network (UMIN) clinical trial registry (UMIN ID: 000045497).

**Evaluation of EUS findings of the pancreatic parenchyma**

EUS was performed using echo-endoscopes (GF-UCT240, GF-UCT260, or GF-UE260 [Olympus, Tokyo, Japan]) and endoscopic ultrasound processors (ProSound α10, Aloka Arietta 850 [HITACHI, Tokyo, Japan] or EU-ME2 Premier Plus [Olympus, Tokyo, Japan]).

We measured hyperechoic foci, stranding, and lobularity on pancreatic parenchymal EUS images (Figs. 1a, b, c) and treated hyperechoic foci and stranding in the same category according to DC2019[3]. We evaluated these EUS findings at the pancreatic body because of the difficulty in assessing pancreatic parenchymal EUS images at the pancreatic head (pancreatic parenchyma at the pancreatic head was visualized as a hypoechoic lesion on EUS)[9] and because of the difficulty in eliminating the effects of obstructive pancreatitis on pancreatic parenchymal EUS images at the caudal side of PDACs.

An experienced endosonographer, blinded to the patients' clinical information, retrospectively reviewed the EUS findings, followed by re-review by a second experienced endosonographer blinded to the clinical information. A strong correlation between the first and second endosonographers was observed in the assessment of pancreatic parenchymal EUS findings ($\kappa$=0.74 for hyperechoic foci/stranding, $P$<0.001; $\kappa$=0.66 for lobularity, $P$<0.001). If the first and second endosonographers made different diagnoses, they rechecked the EUS images and reached a diagnosis in consensus.

**Histological evaluation of surgically resected specimens**

A pathologist blinded to all clinical information reviewed the hematoxylin and eosin-stained tissue

sections from all resected specimens of IPMN, PDAC, p-NEN, and distal cholangiocarcinoma, followed by re-review by a second pathologist blinded to the clinical information. Pancreatic parenchymal fibrosis, infiltration of inflammatory cells, and atrophy were evaluated in the pancreatic parenchyma. The severity of parenchymal fibrosis, inflammation, or atrophy was graded as 0 (none), 1 (mild), 2 (moderate), or 3 (severe), as described previously[16,17] (Fig. 2). In all patients, histological evaluation was performed at the resected margin, the pancreatic body, and at 1 to 6 cm from the original tumor nodules to match the EUS evaluation sites. A strong correlation between the first and second pathologists was observed in the assessment of pancreatic parenchymal histology ($\kappa$=0.93 for fibrosis, P<0.001; $\kappa$=0.87 for inflammation, P<0.001; $\kappa$=0.89 for atrophy, P<0.001). If the first and second pathologists made different diagnoses, they rechecked the sections and reached a diagnosis in consensus.

**Statistical analysis**

All statistical analyses were conducted using IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA). A trend toward a higher grade of fibrosis and atrophy was observed in the following order: normal findings, hyperechoic foci/stranding without lobularity, and hyperechoic foci/stranding with lobularity. Thus, our primary hypothesis testing involved the linear trend test in an ordinal logistic regression model to assess the association between EUS findings (normal, hyperechoic foci/stranding, and hyperechoic foci/stranding with lobularity as an ordinal variable) and histological features (absence or presence of pancreatic fibrosis, inflammation, or atrophy as a categorical variable). The binary categorical variable (absence or presence) of pancreatic parenchymal histology (pancreatic fibrosis, inflammation, or atrophy) was used as an outcome variable. The model was adjusted for clinical characteristics, including age, sex, BMI, smoking status, alcohol consumption, DM, and type of underlying tumor necessitating pancreatic surgery. A backward stepwise elimination with a

threshold of $P$=0.05 was used to select covariates in the final models. The Chi-square test (or Fisher's exact test, if appropriate) was used for statistical comparison between categorical data. A *t*-test or one-way analysis of variance was used for statistical comparison between continuous data. In all analyses, $P$-values were two-sided, and statistical significance was set at $P$<0.05.

## RESULTS

### Different characteristics of patients with each pancreatic parenchymal EUS finding

We categorized 221 patients on the basis of the clinical characteristics associated with CP findings on EUS (Table 1). Of the 221 patients, 87 (39.4%) had normal EUS findings, 89 (40.2%) had hyperechoic foci/stranding without lobularity, and 45 (20.4%) had lobularity. All patients with lobularity had hyperechoic foci/stranding. Based on these EUS findings, we classified the 221 patients into three groups: normal, hyperechoic foci/stranding without lobularity, and hyperechoic foci/stranding with lobularity (Fig. 3).

Regarding smoking status, the proportion of current smokers was significantly higher among patients with pancreatic parenchymal EUS findings (i.e., hyperechoic foci/stranding without lobularity and with lobularity) than among those with normal findings ($P$=0.03). This finding was consistent with smoking being related to pancreatic fibrosis[18]. For the underlying tumor necessitating pancreatic surgery, the proportion of PDACs and distal cholangiocarcinomas was also significantly higher in patients with pancreatic parenchymal EUS findings than in those with normal findings ($P$=0.005). Other than the smoking status and underlying tumor necessitating pancreatic surgery, no significant difference was observed in the following clinical characteristics: age, sex, BMI, alcohol consumption, and DM.

**Histological grade of pancreatic fibrosis, inflammation, and atrophy in several types of pancreatobiliary tumors**

To clarify whether the progression of pancreatic fibrosis, inflammation, and atrophy was correlated, we initially performed a correlation analysis of each pathological finding. A positive correlation was observed between the histological features of pancreatic fibrosis, inflammation, and atrophy (fibrosis-inflammation: r=0.581, $P$<0.001; inflammation-atrophy: r=0.641, $P$<0.001; atrophy-fibrosis: r=0.604, $P$<0.001) (Fig. 4a, b, c).

To explore the effect of the underlying tumor on the pancreas, we assessed the histological grades of pancreatic fibrosis, inflammation, and atrophy in each type of pancreatobiliary tumor (Supplemental Table 1). Regarding the histological grade of fibrosis, of the 104 patients with IPMNs, 28 (26.9%) had grade 1 fibrosis, 15 (14.4%) had grade 2 fibrosis, and 8 (7.7%) had grade 3 fibrosis. Of the 47 patients with PDACs, 28 (59.6%) had grade 1 fibrosis, 1 (2.1%) had grade 2 fibrosis, and 1 (2.1%) had grade 3 fibrosis. Of the 36 patients with p-NENs, 14 (38.9%) had grade 1 fibrosis, 3 (8.3%) had grade 2 fibrosis, and 1 (2.8%) had grade 3 fibrosis. Of the 34 patients with distal cholangiocarcinomas, 20 (58.8%) had grade 1 fibrosis, 4 (11.8%) had grade 2 fibrosis, and 0 (0.0%) had grade 3 fibrosis. The percentage of grade 1, 2, or 3 fibrosis was significantly higher in patients with PDACs and distal cholangiocarcinomas than in those with other diseases ($P$=0.003). The histological grades of pancreatic inflammation and atrophy in patients with each type of pancreatobiliary tumor tended to be similar to those of fibrosis, even though no significant differences were observed (inflammation: $P$=0.27; atrophy: $P$=0.06).

**Each pancreatic parenchymal EUS finding and histological grade of pancreatic fibrosis, inflammation, and atrophy**

We next examined the relationship between pancreatic parenchymal EUS findings and histological grade of fibrosis, inflammation, and pancreatic atrophy (Table 2). Regarding the histological grade of fibrosis, of the 87 patients with normal findings, 82 (94.3%) had grade 0 or 1 fibrosis. Of the 89 patients with hyperechoic foci/stranding without lobularity, 86 (96.6%) had grade 0, 1, or 2 fibrosis. Of the 45 patients with hyperechoic foci/stranding with lobularity, 41 (91.1%) had grade 1, 2, or 3 fibrosis. The histological grade of atrophy in each pancreatic parenchymal EUS finding was similar to that of fibrosis. These results suggested a trend toward a higher grade of fibrosis and atrophy in the following order: normal findings, hyperechoic foci/stranding without lobularity, and hyperechoic foci/stranding with lobularity.

Regarding the histological grade of inflammation, of the 87 patients with normal findings, 82 (94.3%) had grade 0 or 1 inflammation. Of the 89 patients with hyperechoic foci/stranding without lobularity, 86 (96.6%) had grade 0, 1, or 2 inflammation, including 53 (59.6%) with grade 0 inflammation. Of the 45 patients with hyperechoic foci/stranding with lobularity, 34 (75.6%) had grade 1, 2, or 3 inflammation. These results suggested a trend toward a higher grade of inflammation in the following order: normal findings, hyperechoic foci/stranding without lobularity, and hyperechoic foci/stranding with lobularity. Moreover, unlike fibrosis and atrophy, hyperechoic foci/stranding without lobularity was observed even in the lower-grade inflammation stages.

**Association between each pancreatic parenchymal EUS finding and histological feature**

The above results suggested that normal findings, hyperechoic foci/stranding without lobularity, and hyperechoic foci/stranding with lobularity may have an ordinal correlation with histological CP findings. Therefore, to clarify whether each pancreatic parenchymal EUS finding reflected the histological features, such as pancreatic fibrosis, inflammation, and atrophy, we performed ordinal logistic regression analysis (Table 3).

Our findings revealed that pancreatic parenchymal EUS findings, namely, hyperechoic foci/stranding without lobularity and with lobularity, were more significantly correlated with histological CP findings of fibrosis than were normal findings (hyperechoic foci/stranding without lobularity: multivariate odds ratio [OR] =4.1, 95% confidence interval [CI] =2.2-7.9; hyperechoic foci/stranding with lobularity: multivariate OR=31.3, 95% CI=9.3-105.6; $P_{trend}$<0.001).

The correlation between pancreatic parenchymal EUS findings and inflammation was similar to that of fibrosis (hyperechoic foci/stranding without lobularity: multivariate OR=3.9, 95% CI=1.9-8.2; hyperechoic foci/stranding with lobularity: multivariate OR=21.8, 95% CI=8.0-59.4; $P_{trend}$<0.001). The correlation between pancreatic parenchymal EUS findings and atrophy was also similar (hyperechoic foci/stranding without lobularity: multivariate OR=4.0, 95% CI=2.0-7.8; hyperechoic foci/stranding with lobularity: multivariate OR=22.9, 95% CI = 7.3-74.5; $P_{trend}$<0.001).

To determine whether hyperechoic foci/stranding without lobularity or with lobularity strongly correlated with histological CP findings, we performed a logistic regression analysis (Supplemental Table 2). This analysis revealed that hyperechoic foci/stranding with lobularity was more strongly correlated with all histological CP findings than was hyperechoic foci/stranding without lobularity (fibrosis: multivariate OR=5.8, 95% CI=1.9-17.5, $P$<0.001; inflammation: multivariate OR=4.6, 95% CI=2.0-10.1, $P$<0.001; atrophy: multivariate OR=4.9, 95% CI=1.8-13.8, $P$<0.001). These data confirmed that hyperechoic foci/stranding with lobularity, hyperechoic foci/stranding without lobularity, and normal findings strongly correlated with histological CP findings in that order.

## DISCUSSION

Our study yielded two significant findings. First, a good correlation existed between EUS findings and histological features of the pancreatic parenchyma, such as pancreatic fibrosis, inflammation, and

atrophy. Second, a trend toward a higher grade of histological CP findings was observed in the following order: normal EUS findings, hyperechoic foci/stranding, and lobularity; moreover, lobularity reflected more severe histological conditions than did hyperechoic foci/stranding. A strength of this study is that it evaluated pancreatic parenchymal EUS findings in a large number of patients (>200), making the sample size the largest among similar studies. These EUS findings based on pancreatic parenchymal histology might be valuable markers for promptly diagnosing early CP.

Histological evaluation of the pancreas is challenging in patients without significant pancreatic diseases, such as pancreatic cancer and autoimmune pancreatitis, because these diseases do not usually necessitate pancreatic surgery and biopsy. Only a few previous reports have indicated a correlation between EUS findings and histological features, especially fibrosis, in patients with established CP who underwent surgery or autopsy[8,10–13] and in canine models of CP[19]. In addition, these were all small retrospective studies with ≤100 patients, and none of their evidence was conclusive. Moreover, no studies have focused on the association between pancreatic parenchymal EUS findings and histological features in patients without CP. Our study enabled the comparison between EUS findings and histological features in over 200 patients by obtaining surgical specimens from patients with pancreatobiliary tumors who underwent preoperative EUS and pancreatic surgery. The current study demonstrated a good correlation between pancreatic parenchymal EUS findings and histological features, such as pancreatic fibrosis, inflammation, and atrophy. These results suggest that EUS may be a helpful tool for promptly diagnosing early CP.

Furthermore, our findings indicated that normal EUS findings, hyperechoic foci/stranding, and lobularity had an ordinal correlation with histological CP findings. These results suggested that pancreatic parenchymal EUS findings might change from normal to hyperechoic foci/stranding to lobularity with the progression of CP. To the best of our knowledge, this is the first report to describe that lobularity reflected more severe histological conditions than did hyperechoic foci/stranding.

DC2019 considers lobularity and hyperechoic foci/stranding as imaging findings of early CP[3]. However, our results suggest the urgency to treat these EUS findings of the pancreatic parenchymal separately.

In the current study, we also demonstrated a positive correlation between the histological features of pancreatic fibrosis, inflammation, and atrophy and showed that pancreatic parenchymal EUS findings correlated with all these histological features. These results suggested that pancreatic parenchymal EUS findings might reflect not just a specific histological feature but comprehensive histological CP conditions.

In DC2009, hyperechoic foci, stranding, and lobularity were defined as an independent category[3], which resulted in very low interobserver reliability (IOR) ($\kappa$=0.23 for hyperechoic foci/stranding; $\kappa$=0.44 for stranding; $\kappa$=0.34 for lobularity)[3,20]. Therefore, these findings were unified into two categories, namely, hyperechoic foci/stranding and lobularity, in DC2019 to improve the diagnostic accuracy of EUS findings[3]. This revision resulted in a higher IOR than that obtained when using DC2009[21]. However, no further reports are yet available. Our study confirmed the validity of this criterion by demonstrating a high IOR for EUS findings ($\kappa$=0.74 for hyperechoic foci/stranding; $\kappa$=0.66 for lobularity) and the correlation between EUS findings and histological features. However, the IOR for lobularity is insufficient to make reproducible decisions in the clinical setting. Thus, further improvement of the IOR is a future challenge.

Nevertheless, our study had several limitations. The first and most significant limitation was the patient selection bias. Since we only analyzed patients with pancreatobiliary tumors who underwent surgery, we could not eliminate the effects of tumors on the adjacent pancreatic parenchyma. However, a good correlation was observed between pancreatic parenchymal EUS findings and histological features, regardless of the type of tumor. These results suggest that EUS findings can help predict the histological condition of the pancreas, although their usefulness in examinations for the

general population should be carefully discussed. Second, because this was a retrospective study, we could not obtain all clinical information related to early CP criteria, such as medical history, risk factors, and other biomarkers. Thus, we could not precisely assess how many patients met the early CP criteria in this study and whether pancreatic parenchymal EUS findings led to the diagnosis of early CP. Third, some patients did not have histological CP features in the pancreas despite showing pancreatic parenchymal EUS findings. That would be because it is difficult to match the assessment site of EUS images and histology completely and because these EUS findings were sometimes found in localized, but not the entire, pancreatic parenchyma. These results highlighted the difficulty in diagnosing early CP using EUS findings alone. The evaluation methods of pancreatic parenchymal EUS findings need to be optimized for precisely diagnosing early CP.

In conclusion, pancreatic parenchymal EUS findings are associated with the histological conditions of CP, such as pancreatic fibrosis, inflammation, and atrophy. Moreover, lobularity reflected more severe histological conditions than did hyperechoic foci/stranding.

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**Table 1. Different characteristics of patients with each pancreatic parenchymal EUS finding, such as normal, hyperechoic foci/stranding, and lobularity**

| | | Normal | Hyperechoic foci/stranding | | *P*-value |
|---|---|---|---|---|---|
| | | | Without lobularity | With lobularity | |
| All patients | 221 | 87 | 89 | 45 | |
| Mean age ± SD (years) | 67.7 ± 11.0 | 66.4 ± 12.0 | 69.2 ± 9.7 | 67.5 ± 11.3 | 0.25 |
| Sex | | | | | 0.32 |
| Male | 127 (57.5%) | 52 (59.8%) | 46 (51.7%) | 29 (64.4%) | |
| Female | 94 (42.5%) | 35 (40.2%) | 43 (48.3%) | 16 (35.6%) | |
| BMI (kg/m$^2$) | | | | | 0.71 |
| ≥25 | 21 (9.5%) | 10 (11.5%) | 7 (7.9%) | 4 (8.9%) | |
| <25 | 200 (90.5%) | 77 (88.5%) | 82 (92.1%) | 41 (91.1%) | |
| Smoking status | | | | | 0.03 |
| Never | 155 (70.1%) | 66 (75.9%) | 59 (66.3%) | 30 (66.7%) | |
| Former | 53 (24.0%) | 21 (24.1%) | 23 (25.8%) | 9 (20.0%) | |
| Current | 13 (5.9%) | 0 (0.0%) | 7 (7.9%) | 6 (13.3%) | |
| Alcohol consumption | | | | | 0.46 |
| ≥60 g/day | 32 (14.5%) | 13 (14.9%) | 15 (16.9%) | 4 (8.9%) | |
| <60 g/day | 189 (85.5%) | 74 (85.1%) | 74 (83.1%) | 41 (91.1%) | |
| DM | | | | | 0.25 |
| Present | 66 (29.9%) | 24 (27.6%) | 24 (27.0%) | 18 (40.0%) | |
| Absent | 155 (70.1%) | 63 (72.4%) | 65 (73.0%) | 27 (60.0%) | |
| Underlying tumor | | | | | 0.005 |
| IPMN | 104 (47.0%) | 53 (60.9%) | 34 (38.2%) | 17 (37.8%) | |
| PDAC | 47 (21.3%) | 13 (14.9%) | 26 (29.2%) | 8 (17.8%) | |
| p-NEN | 36 (16.3%) | 15 (17.3%) | 12 (13.5%) | 9 (20.0%) | |
| Distal cholangiocarcinoma | 34 (15.4%) | 6 (6.9%) | 17 (19.1%) | 11 (24.4%) | |

Percentage (%) indicates the proportion of patients with specific clinical features among those with each pancreatic parenchymal EUS finding.

EUS, endoscopic ultrasonography; SD, standard deviation; BMI, body mass index; DM, diabetes

mellitus; IPMN, intraductal papillary neoplasm; PDAC, pancreatic ductal carcinoma; p-NEN, pancreatic neuroendocrine neoplasm.

**Table 2. Histological grade of pancreatic fibrosis, inflammation, and atrophy classified according to each EUS finding**

| EUS finding | No. of patients | Fibrosis | | | |
|---|---|---|---|---|---|
| | | Histological grade | | | |
| | | 0 | 1 | 2 | 3 |
| Normal | 87 | 62 (71.3%) | 20 (23.0%) | 4 (4.6%) | 1 (1.1%) |
| Hyperechoic foci/stranding Without lobularity | 89 | 32 (36.0%) | 44 (49.3%) | 11 (12.3%) | 3 (3.4%) |
| With lobularity | 45 | 4 (8.9%) | 26 (57.8%) | 8 (17.8%) | 7 (15.5%) |
| **EUS finding** | **No. of patients** | **Inflammation** | | | |
| | | Histological grade | | | |
| | | 0 | 1 | 2 | 3 |
| Normal | 87 | 73 (83.9%) | 9 (10.4%) | 3 (3.4%) | 2 (2.3%) |
| Hyperechoic foci/stranding Without lobularity | 89 | 53 (59.5%) | 29 (32.6%) | 4 (4.5%) | 3 (3.4%) |
| With lobularity | 45 | 11 (24.4%) | 22 (48.9%) | 7 (15.6%) | 5 (11.1%) |
| **EUS finding** | **No. of patients** | **Atrophy** | | | |
| | | Histological grade | | | |
| | | 0 | 1 | 2 | 3 |
| Normal | 87 | 56 (64.4%) | 23 (26.4%) | 6 (6.9%) | 2 (2.3%) |
| Hyperechoic foci/stranding Without lobularity | 89 | 34 (38.2%) | 43 (48.3%) | 10 (11.2%) | 2 (2.2%) |
| With lobularity | 45 | 5 (11.1%) | 19 (42.2%) | 16 (35.6%) | 5 (11.1%) |

Percentage (%) indicates the proportion of patients with each histological grade among those with each pancreatic parenchymal EUS finding.

**Table 3. Ordinal logistic regression analysis of the association between pancreatic parenchymal EUS findings and histological features**

| EUS finding | No. of patients | No. of patients with fibrosis (%) | Fibrosis (outcome variable) | |
|---|---|---|---|---|
| | | | Univariate OR (95% CI) | Multivariate OR# (95% CI) |
| Normal | 87 | 26 (29.9%) | 1 (reference) | 1 (reference) |
| Hyperechoic foci/stranding Without lobularity | 89 | 57 (64.0%) | 4.2 (2.2-7.9) | 4.1 (2.2-7.9) |
| With lobularity | 45 | 41 (91.1%) | 24.0 (7.8-74.0) | 31.3 (9.3-105.6) |
| $P_{trend}$* | | | <0.001 | <0.001 |
| **EUS finding** | **No. of patients** | **No. of patients with inflammation (%)** | **Inflammation (outcome variable)** | |
| | | | Univariate OR (95% CI) | Multivariate OR# (95% CI) |
| Normal | 87 | 14 (16.1%) | 1 (reference) | 1 (reference) |
| Hyperechoic foci/stranding Without lobularity | 89 | 36 (40.4%) | 3.5 (1.7-7.2) | 3.9 (1.9-8.2) |
| With lobularity | 45 | 34 (75.6%) | 16.1 (6.6-39.1) | 21.8 (8.0-59.4) |
| $P_{trend}$* | | | <0.001 | <0.001 |
| **EUS finding** | **No. of patients** | **No. of patients with atrophy (%)** | **Atrophy (outcome variable)** | |
| | | | Univariate OR (95% CI) | Multivariate OR# (95% CI) |
| Normal | 87 | 31 (35.6%) | 1 (reference) | 1 (reference) |
| Hyperechoic foci/stranding Without lobularity | 89 | 55 (61.8%) | 2.9 (1.6-5.4) | 4.0 (2.0-7.8) |
| With lobularity | 45 | 40 (88.9%) | 14.5 (5.2-40.4) | 22.9 (7.0-74.5) |
| $P_{trend}$* | | | <0.001 | <0.001 |

* $P_{trend}$ is calculated via ordinal logistic regression analysis across the ordinal categories (normal, hyperechoic without lobularity, and hyperechoic foci/stranding with lobularity) of pancreatic parenchymal EUS findings.

# The odds ratio (OR) is adjusted for age, sex, body mass index, smoking status, alcohol consumption, diabetes mellitus, and underlying tumor necessitating pancreatic surgery.
EUS, endoscopic ultrasonography; CI, confidence interval

**Figure Legends**

**Figure 1.** Typical pancreatic parenchymal endoscopic ultrasonography (EUS) findings according to the Rosemont classification: (a) hyperechoic foci, (b) hyperechoic stranding, and (c) lobularity

(a) Hyperechoic foci are echogenic structures ≥ 3 mm in both length and width without shadowing. At least three of these structures are necessary for the feature to be considered present.

(b) Stranding is a hyperechoic line ≥ 3 mm in length seen in at least two different directions in the imaged plane. At least three strands are necessary for the feature to be considered present.

(c) Lobularity is an endosonographically circumscribed structure ≥ 5 mm with rims that are hyperechoic relative of its central echogenicity area. At least three lobules in the pancreatic body or tail are necessary for the feature to be considered present.

**Figure 2.** Grading of pancreatic fibrosis, inflammation, and parenchymal atrophy (all histologic slides are stained using hematoxylin and eosin)

Images a to d represent the grade of pancreatic fibrosis (scale bar, 500 μm). (a) grade 0 (none), (b) grade 1 (mild), (c) grade 2 (moderate), (d) grade 3 (severe). Images e to h represent the grade of inflammation (scale bar, 200 μm). (e) grade 0 (none: no inflammatory cells), (f) grade 1 (mild: inflammatory cells are observed in 1-10% of the pancreatic parenchyma), (g) grade 2 (moderate: inflammatory cells are observed in 11-20% of the pancreatic parenchyma), (h) grade 3 (severe: inflammatory cells are observed in >20% of the pancreatic parenchyma). Images i to l represent the grade of parenchymal atrophy (scale bar, 200 μm). (i) grade 0 (none: 90-100% of the normal pancreatic parenchyma remains), (j) grade 1 (mild: 70-89% of the normal pancreatic parenchyma remains), (k) grade 2 (moderate: 30-69% of the normal pancreatic parenchyma remains), (l) grade 3 (severe: <30% of the normal pancreatic parenchyma remains).

**Figure 3.** Proportion of patients with each pancreatic parenchymal EUS finding, including hyperechoic foci/stranding and lobularity

**Figure 4.** Correlations between the histological features

(a) Correlation between pancreatic fibrosis and inflammation (r = 0.581, $P < 0.001$). (b) Correlation between pancreatic inflammation and atrophy (r = 0.641, $P < 0.001$). (c) Correlation between pancreatic atrophy and fibrosis (r = 0.604, $P < 0.001$).

Figure 1

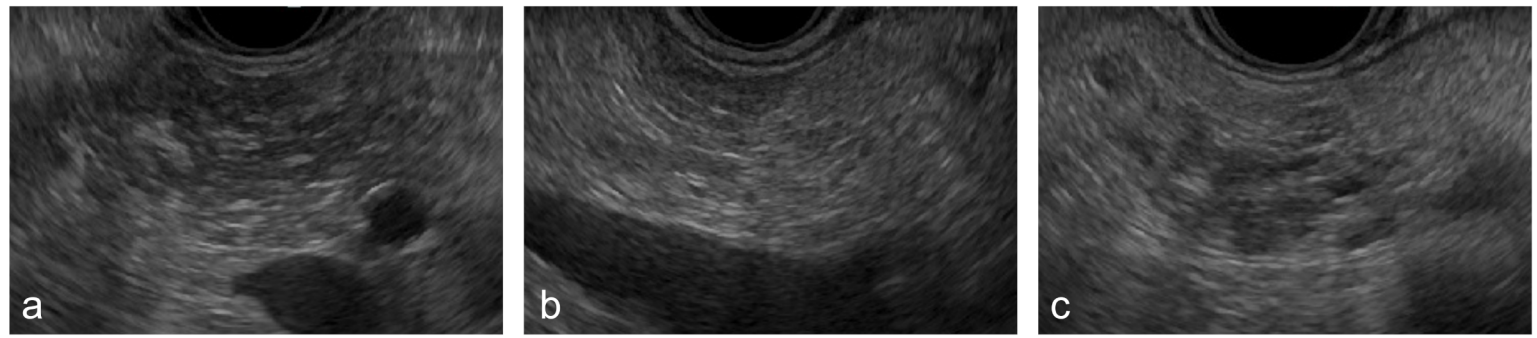


Figure 2

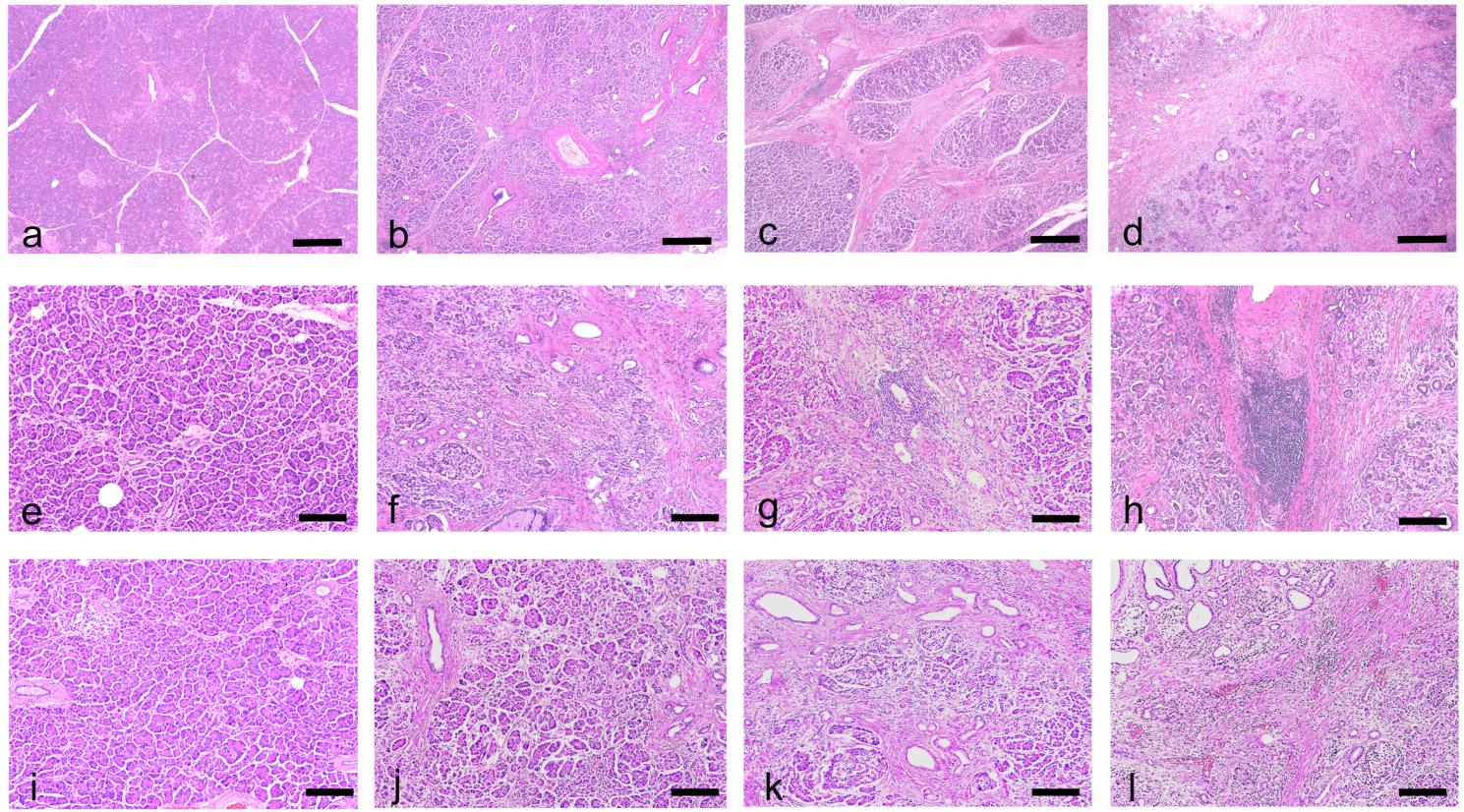


Figure 3

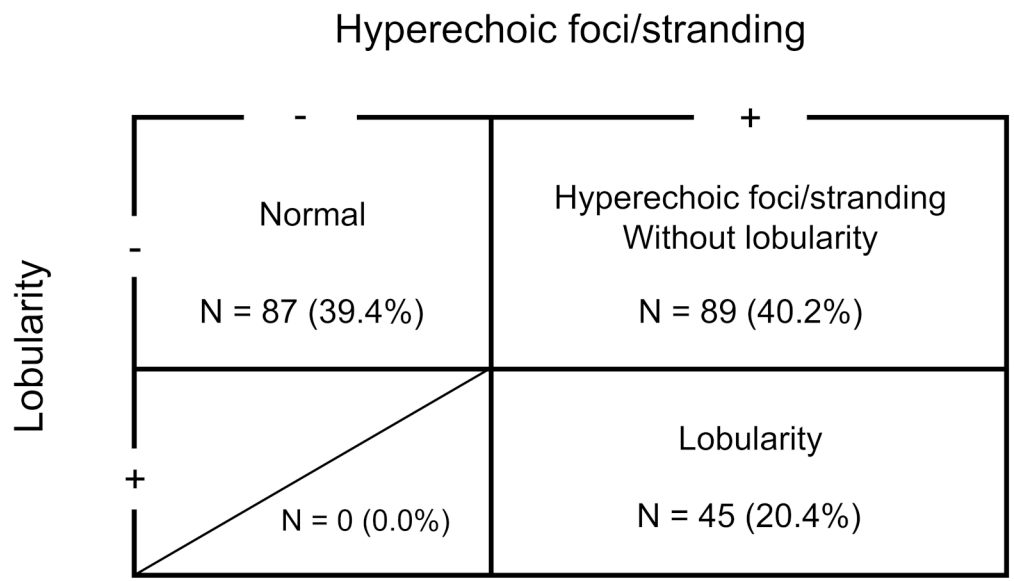
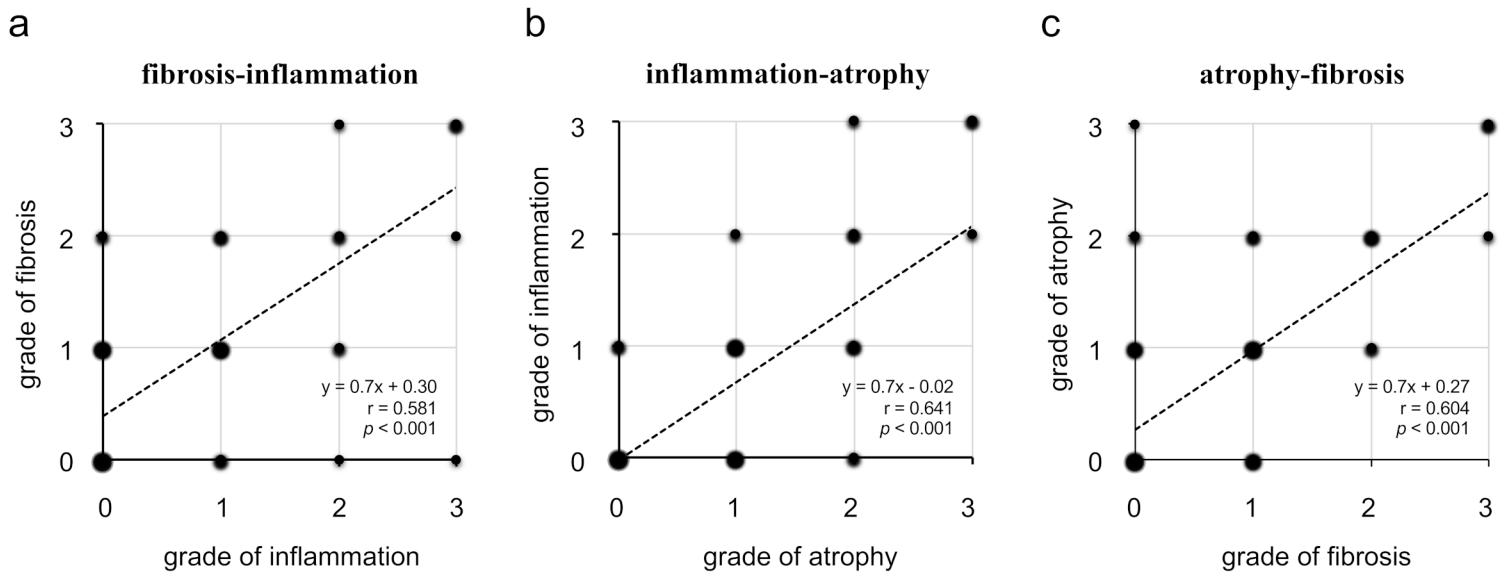
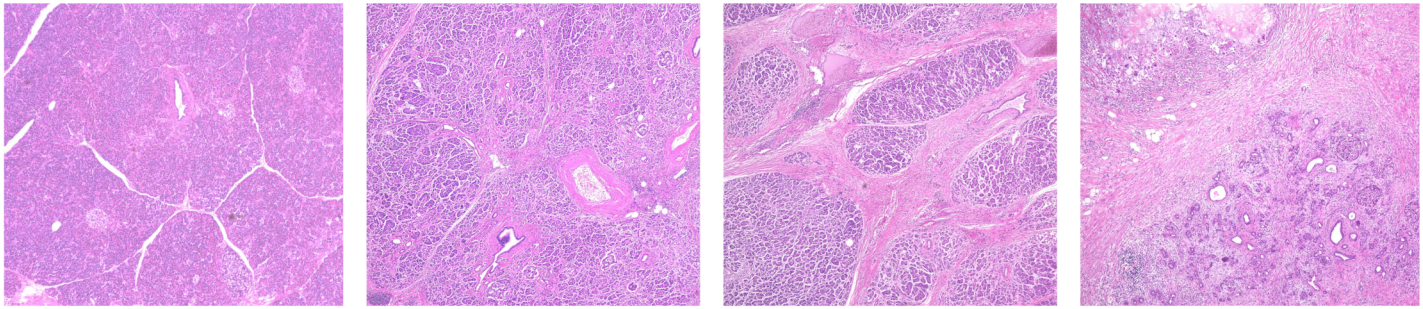

Hyperechoic foci/stranding
-
+
Lobularity
-
+
Normal
N = 87 (39.4%)
Hyperechoic foci/stranding
Without lobularity
N = 89 (40.2%)
N = 0 (0.0%)
Lobularity
N = 45 (20.4%)

Figure 4


a
fibrosis-inflammation
grade of fibrosis
grade of inflammation
y = 0.7x + 0.30
r = 0.581
p < 0.001
b
inflammation-atrophy
grade of inflammation
grade of atrophy
y = 0.7x - 0.02
r = 0.641
p < 0.001
c
atrophy-fibrosis
grade of atrophy
grade of fibrosis
y = 0.7x + 0.27
r = 0.604
p < 0.001

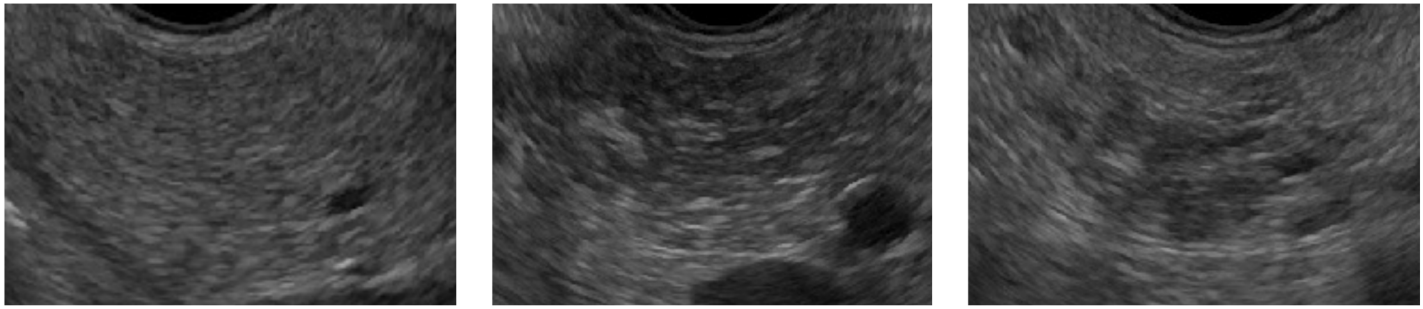
# Progression of CP histology



Normal

Hyperechoic foci
Stranding

Lobularity



## EUS findings of the pancreatic parenchyma