RESEARCH ARTICLE

Effectiveness of Focal Pancreatic Parenchymal Atrophy in Diagnosing High-Grade Pancreatic Intraepithelial Neoplasia/Carcinoma in Situ

Authors
Masataka Kikuyama[1], Jun Nakahodo[1], Goro Honda[2], Shinichiro Horiguchi[3], Mizuka Suzuki[4], Kazurou Chiba[1], Hiroki Tabata[1], Yuichiro Ome[2]. Terumi Kamisawa[1]

Affiliations
1. Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
2. Department of Surgery, Tokyo Woman Medical University, Tokyo, Japan
3. Department of Pathology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
4. Department of Radiology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

Corresponding Author:
Masataka Kikuyama,
Department of Gastroenterology, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan
3-18-22, Honkomagome, Bunkyo-ku, Tokyo, 113-8677, Japan
Email: kikuyama110@yahoo.co.jp

Abstract:

To improve the poor prognosis of pancreatic ductal adenocarcinoma (PDAC), the diagnosis of early-stage PDAC is essential. In particular, the diagnosis of high-grade intraepithelial pancreatic neoplasia/carcinoma in situ (HG-PanIN/CIS) is the best option. However, it is almost impossible to directly observe HG-PanIN/CIS. Thus, identifying a secondary imaging finding due to the disorder is important. Focal pancreatic parenchymal atrophy (FPPA) and hypoechoic area have been reported as preferred secondary signs. We studied 50 patients to clarify the effectiveness of FPPA in diagnosing HG-PanIN/CIS. Most patients had the opportunity to undergo further examination due to the presence of a cyst. Among the 50 patients, 23 (46%) had positive results for serial pancreatic-juice aspiration cytologic examination (SPACE), which has high sensitivity and specificity for diagnosing PADC; 20 of the 23 (87.0%) patients underwent surgery to resect the pancreatic part including the FPPA. Distal pancreatectomy and pancreatoduodenectomy were performed in 19 patients and one patient, respectively. In 13 of the 20 (65%) patients, histopathological examination revealed HG-PanIN/CIS in the pancreatic ductal epithelium of the resected specimens. FPPA could indicate HG-PanIN/CIS, but not satisfactorily. One of the factors for the unsatisfactory results might be the difficulty in identifying FPPA in the pancreatic head area. On the other hand, a pancreatic cyst, especially in the area of FPPA, could lead to the diagnosis of HG-PanIN/CIS. The size of the cyst does not affect the diagnosis of HG-PanIN/CIS.

Key words: pancreatic cancer, PDAC, serial pancreatic-juice aspiration cytologic examination, SPACE, hypoechoic area, pancreatic cyst

1. Introduction

The prognosis of pancreatic duct adenocarcinoma (PDAC) is the poorest among all major organ cancers, with a survival rate of 5%. [1] One of the reasons for its poor prognosis is that the commonly used diagnostic methods, such as computed tomography (CT) or magnetic resonance imaging (MRI), cannot adequately diagnose small pancreatic cancer. [2, 3]

Recently, endoscopic ultrasonography (EUS) has been used for diagnosing early stage PDAC, [4-6] as the advanced EUS apparatus can detect small lesions that are undetected by CT or MRI. Thus, EUS has an excellent negative predictive value for PDAC. [4] Although PDAC tumors detected using EUS are small, the tumors are invasive and have the potential to metastasize. In fact, we encountered a case of minimally invasive PDAC with a diameter of 4 mm that metastasized to the lymph nodes around the pancreas.[7]

Cancer limited to the pancreatic duct epithelium as high-grade pancreatic intraepithelial neoplasia (HG-PanIN)/carcinoma in situ (CIS) may be appropriately termed as early pancreatic cancer because it does not metastasize. However, epithelial findings suggestive of cancer have not been thoroughly investigated because direct observation of the epithelium of a normal-sized pancreatic duct through an endoscope is difficult. Thus, it is currently impossible to diagnose HG-PanIN/CIS by direct observation of the pancreatic epithelium.

Although HG-PanIN/CIS cannot be diagnosed by identifying HG-PanIN/CIS itself, identifying secondary signs associated with HG-PanIN/CIS can help in the diagnosis of early stage PDAC. Furthermore, we have devised a new method for pancreatic juice cytology that uses a nasopancreatic duct drainage tube, [8] named pancreatic-juice aspiration cytologic examination (SPACE). [9] This development provides us with high sensitivity and specificity for diagnosing PCAD in patients with suspicion of PDAC. SPACE has allowed HG-PanIN/CIS to become a target for diagnosis and treatment; moreover, new findings related to HG-PanIN/CIS have been explored. The main pancreatic duct (MPD) stricture has been accepted as a secondary sign of PDAC, while recent reports have stated that HG-PanIN/CIS influences the surrounding parenchyma and induces focal atrophy of the parenchyma. [9, 10] Focal atrophy of the pancreatic parenchyma can be identified on CT or MRI, and this finding could provide an opportunity to diagnose HG-PanIN/CIS. We named this change focal pancreatic parenchymal atrophy (FPPA). [11]

We studied 27 patients with HG-PanIN/CIS

by histopathological evaluation of their resected specimens. Fifteen (55.6%) patients were reported to have FPPA on preoperative CT or MRI, [11] while the remaining 12 patients (44.4%) had no malignancies and had negative results on SPACE, without any changes in MPD disorders, such as strictures for 6 months or more. FPPA proved to be a significant finding for diagnosing HG-PanIN/CIS. A hypoechoic area [12] was recognized in 74.1% of patients with HG-PanIN/CIS, which was also significant for diagnosing HG-PanIN/CIS. However, other disorders, including MPD stricture or chronic pancreatitis, were not significantly associated with HG-PanIN/CIS.

Herein, we studied the contribution of FPPA to the effective diagnosis and surgical treatment of HG-PanIN/CIS, that is, what rate of patients with FPPA had a positive result of cancer on a preoperative cytologic examination by SPACE and a final diagnosis of HG-PanIN/CIS on a histopathological examination of the resected specimen.

2. Subjects and Methods

2.1. Subjects

For a year (beginning in August 2019), 50 patients with FPPA detected on CT or MRI without any tumor on EUS were enrolled in this study, who underwent SPACE and were suspected to have HG-PanIN/CIS.

2.2. Study design

We retrospectively analyzed the characteristics, including location of FPPA, type of FPPA, positive ratio of adenocarcinoma on SPACE, and positive ratio of HG-PanIN/CIS on resected specimens in manner of an observation study. Moreover, factors between groups with positive SPACE and negative SPACE were compared.

2.3. Definition of FPPA

FPPA was defined as follows: focal and detectable pancreatic parenchymal atrophy on CT od MRI (Figure 1), [9-13] and asymmetric change with respect to the MPD, which did not require a MPD stricture but accompanied a hypoechoic area on endoscopic ultrasonography (Figure 2). [12-14] FPPA was classified into three types: cave-in, slimness, and slit (Figure 3). [11]

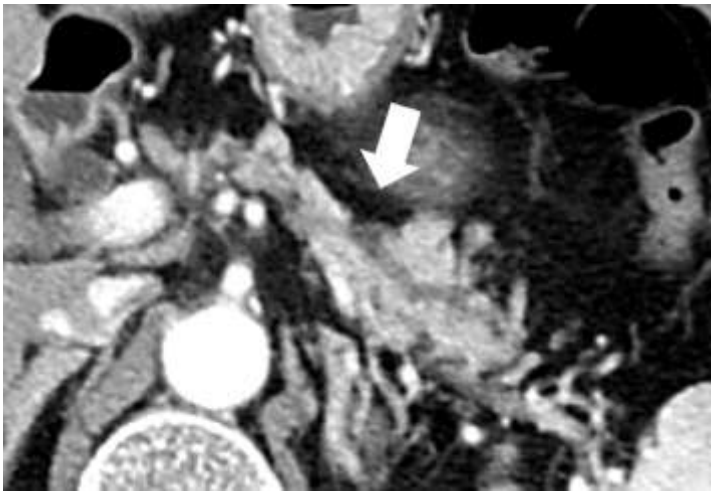

Figure 1. Focal pancreatic parenchymal atrophy, FPPA

Contrast-enhanced computed tomography of the abdomen revealing focal and asymmetric defects of the pancreatic parenchyma (arrow) with respect to the MPD replaced by fat. This type of FPPA is Cave-in.

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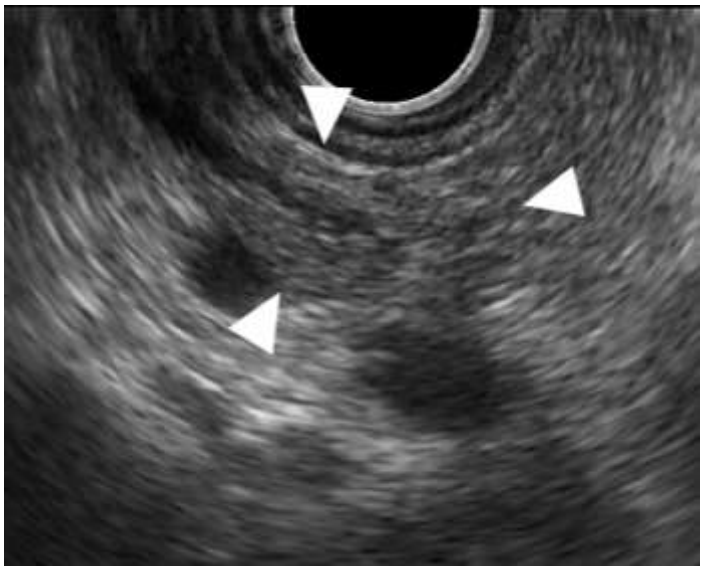

Figure 2. Hypoechoic area

Endoscopic ultrasound showing a blurred hypoechoic area (arrowheads) in the part equivalent to FPPA.

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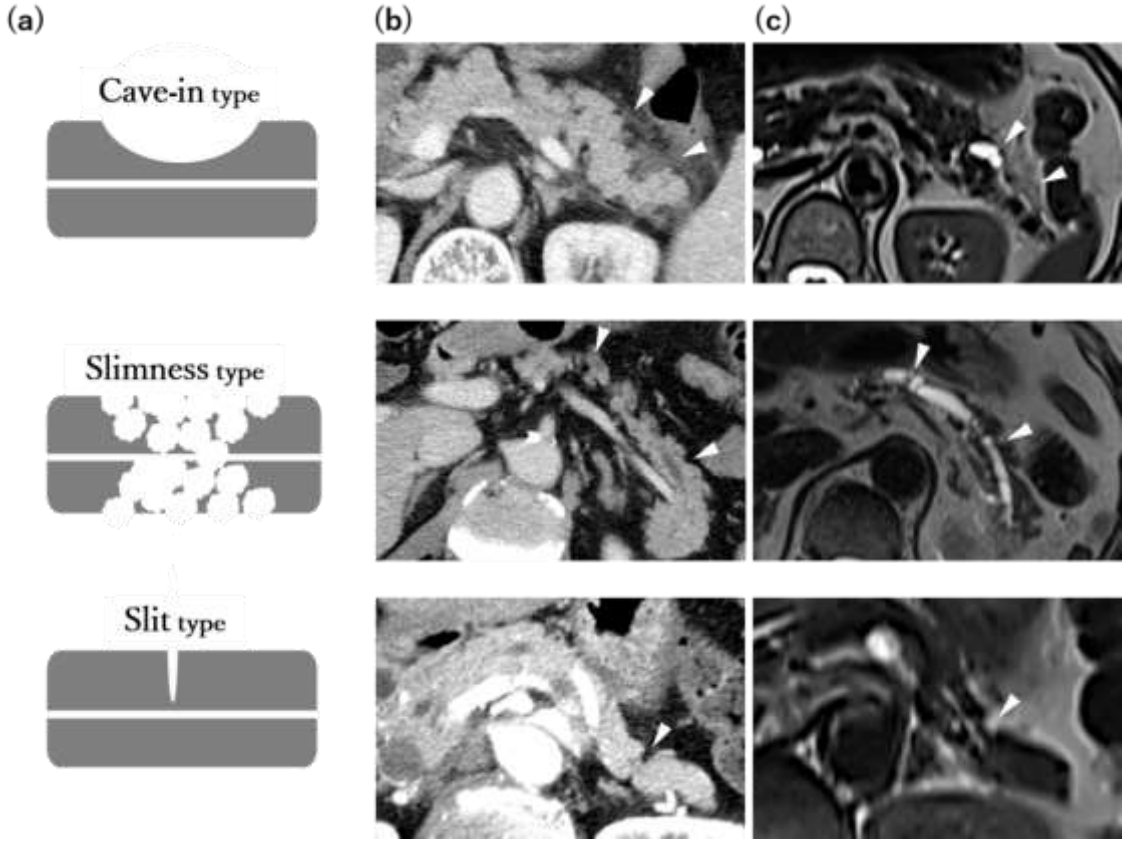

Figure 3. Focal pancreatic parenchymal atrophy (FPPA) images

(a) A Scheme showing three types of FPPA: Cave-in, Slimness, and Slit

(b) Each type of FPPA on contrast-enhanced CT (portal phase) (arrowheads)

(c) An MRI T2-weighted image (arrowheads)

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2.4. Histopathological findings of FPPA

On histopathological examination, FPPA was detected as focal atrophy of the pancreatic parenchyma with clear margins replaced by fat and fibrosis (Figure 4). [5-7] This change existed beside or around HG-PanIN/CIS, which was located not only in the MPD, but also in the branch. [7]

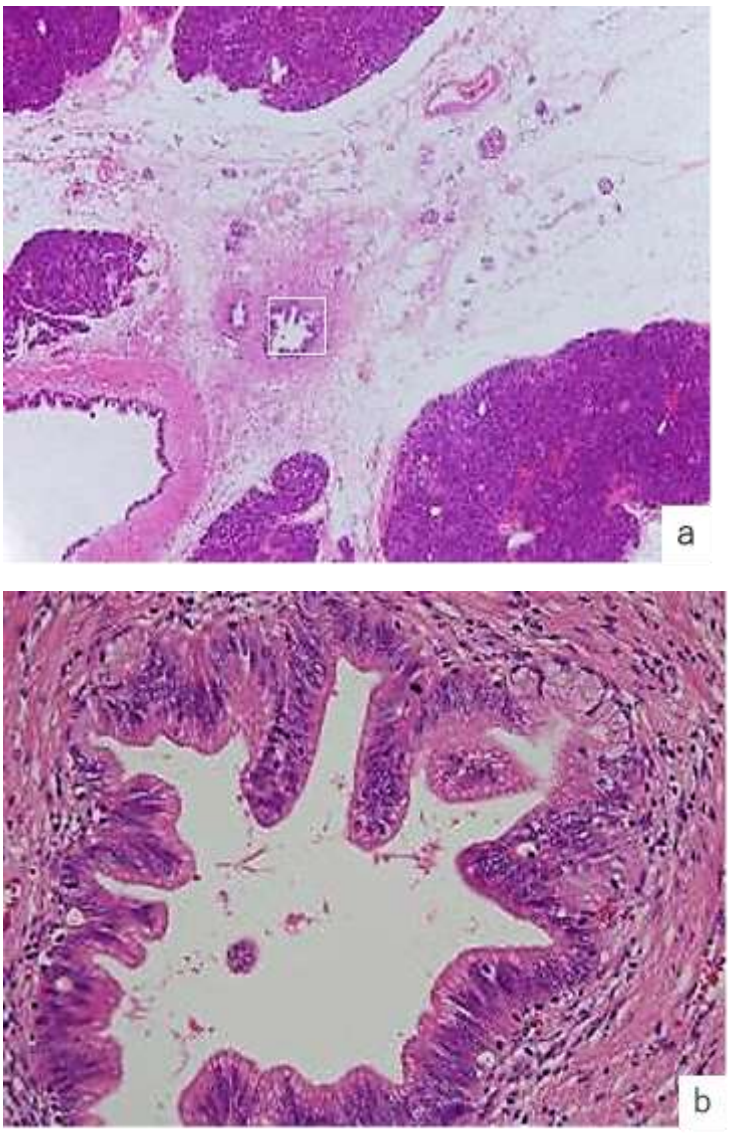

Figure 4. Histopathological findings of focal pancreatic parenchymal atrophy (FPPA).

a. The macroscopic view showing a mildly dilated main pancreatic duct and branch duct (square). The pancreatic parenchyma surrounding these ducts atrophies with fat replacement. The remaining pancreatic parenchyma is normal. The border between the atrophied area and the remaining pancreatic parenchyma is clear.

b. Microscopic view showing dysplastic changes in the epithelium of the branch duct (a. square) with low papillary growth and loss of polarity of the irregularly enlarged nucleus with eosinophilic cytosol, diagnosed as high-grade pancreatic intraepithelial neoplasia/carcinoma in situ.

2.5. SPACE

For SPACE, a 5Fr-pigtail nasopancreatic tube (Olympus, Tokyo, Japan) was placed via the duodenal papilla as upstream to the MPD as possible on day 1 of hospitalization. Before placing the tube, the tip with a pigtail shape was manually straightened. On days 2 and 3 of hospitalization, 10 mL of pancreatic juice obtained through the tube was submitted for cytological analysis 3 times a day, with the patients starting their meals on days 2 of hospitalization. On day 3 of hospitalization, the tube was removed after the last submission of pancreatic juice. In total, pancreatic juice cytology was performed 6 times through the course of each patient's hospitalization. The result was positive if cytology indicated adenocarcinoma or suspected adenocarcinoma.

2.6. Complications of SPACE

Complications related to tube placement and continuation of pancreatic juice drainage, such as post-ERCP pancreatitis, pneumonia, and renal dysfunction, were studied.

2.7. Surgical treatment

In patients with positive results on SPACE, pancreatectomy completely including the part of FPPA was performed by pancreatoduodenectomy or distal pancreatectomy. If a cyst that existed apart from FPPA was not included in the planned portion of resection, was smaller than 30 mm, and did not have a nodule, the part of the cyst was left in the remaining pancreas.

2.8. Statistical analysis

The chi-square or Fisher's exact tests were used to compare clinical features between the positive and negative SPACE groups, and the Mann-Whitney U test was used to assess differences in age and tumor marker levels. Statistical significance was set at $p < 0.05$. Analyses were performed using JMP® statistical software (version 13.2.1; SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patients' characteristics

The patients with FPPA included 28 men and 22 women. The median age of the patients was 72 years (range, 48–84 years). None of the patients had symptoms suggestive of pancreatic disease, including abdominal pain, back pain, and weight loss. Further examination of the pancreas was performed in the following conditions: presence of a pancreatic cyst [41 patients (82 %)], MPD dilation [5 patients (10 %)], pancreatic tumor suspected [2 patients (4%)], MPD stricture [1 patient (2%)], and high carcinoembryonic antigen (CEA) level [1 patient (2%)]. Four patients (8%) had a familial history of PDAC in the first degree. Average levels of CEA and carbohydrate antigen were 2.70 (0.7–13.1) ng/ml and 20.2 (3.1–83.2) U/ml, respectively.

Table 1. Patients' characteristics (n=50)

Gender	Male/Female	28/22
Age	Average, year old	70.8 (48-84)
Symptom	Abdominal pain	none
	Back pain	none
	Body weight loss	none
Chance for further examination		N (%)
	Pancreatic cyst	41 (82)
	MPD dilation	5 (10)
	Pancreatic tumor suspected	2 (4)
	MPD stricture	1 (2)
	High CEA level	1 (2)
Familial history for PDAC		4 (8)
CEA level	Average, ng/ml	2.70 (0.7-13.1)
CA19-9 level	Average, U/ml	20.2 (3.1-83.2)

MPD, main pancreatic duct; CEA, carcinoembryonic antigen; PDAC, pancreatic ductal adenocarcinoma; CA19-9, carbohydrate antigen

3.2. FPPA and pancreatic cyst

FPPA was localized as follows: head [in 1 patient (2%)], head to body [in 5 patients (10%)]; body [in 14 patients (28%)], body to tail [in 10 patients (20%)], and tail [in 20 patients (40%)] (Table 2). The types of FPPA were Cave-in, Slimness, and Slit in 16 (32%), 28 (56%), and 6 (12%) patients, respectively (Table 3). Many patients had pancreatic cysts. In 16 patients with Cave-in-type FPPA, 14 (14/16=87.5%) had a cyst (Table 4); among these patients, 11 (11/14=78.6%) had a cyst in the area of FPPA (Figure 5). In total, 24 of 29 (24/29=82.8%) patients with Slimness-type FPPA had pancreatic cysts, while 20 (20/24=83.3%) patients had a cyst in the area of FPPA (Figure 5). Thirty-eight of 45 (38/45=84.4%) patients with Cave-in or Slimness-type FPPA had a pancreatic cyst, and 31 of the 38 (31/38=81.6%) patients had a cyst in the area of FPPA (Figure 5). Among the five patients with Slit-type, four (4/5=80%) had a cyst, which was located adjacent to the FPPA (Figure 5).

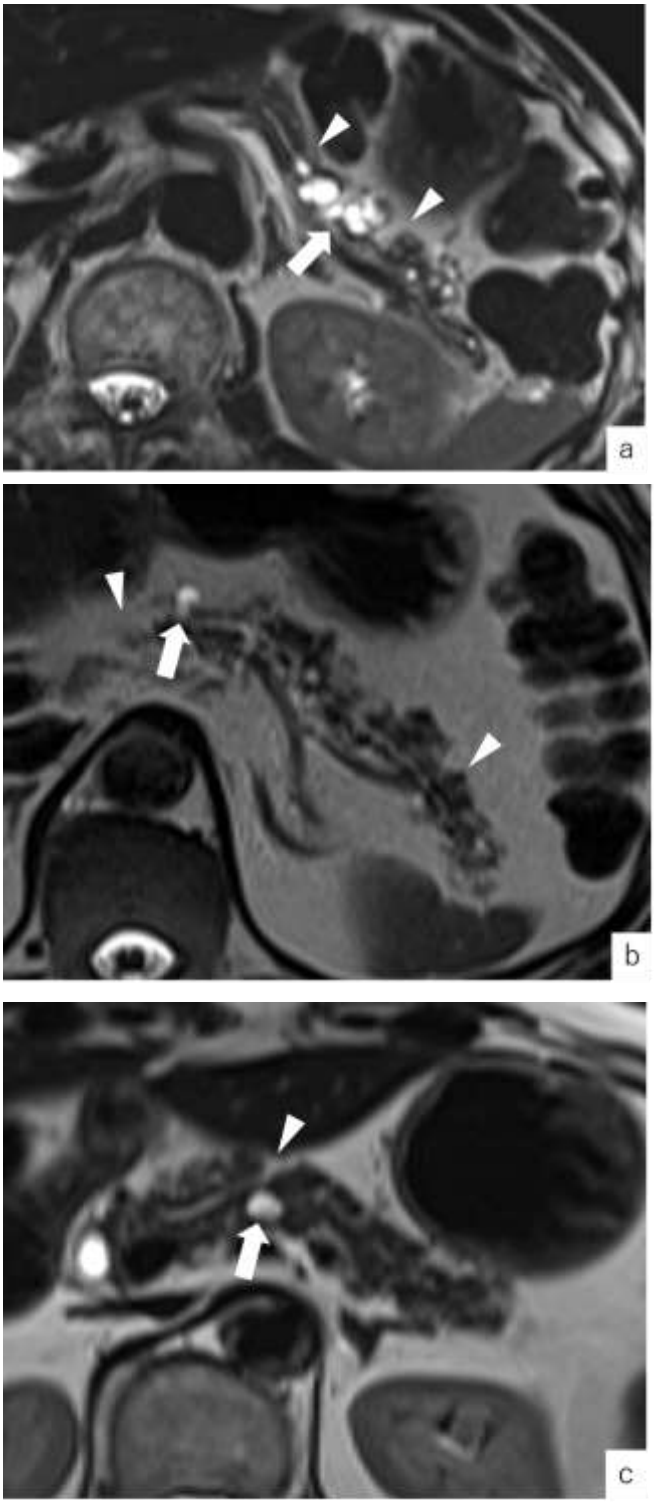

Figure 5. Focal pancreatic parenchymal atrophy (FPPA) and cysts.

a. Multilocular cysts (arrow) in Cave-in type FPPA (between arrowheads).
b. Unilocular cyst (arrow) in Slimness-type FPPA (between arrowheads).
c. Unilocular cyst (arrow) adjacent to Slit-type FPPA (arrowhead).

Table 2. Location of focal pancreatic parenchymal atrophy (n=50)

Location	Head	Head to Body	Body	Body to tail	Tail
	1(2%)	5(10%)	14(28%)	10(20%)	20(40%)

Table 3. Type of focal pancreatic parenchymal atrophy (n=50)

Type	Cave-in	Slimness	Slit
	16(32%)	28(53%)	6(12%)

Table 4. Relationship between the type of focal pancreatic parenchymal atrophy (FPPA) and the location of a pancreatic cyst (n=50)

Type of FPPA	Total	Having a cyst	Cyst in the FPPA
Cave-in	16	14 (14/16=87.5%)	11 (11/14=78.6%)
Slimness	29	24 (24/29=82.8%)	20 (20/24=83.3%)
			Cyst adjacent to the FPPA
Slit	5	4 (4/5=80%)	4 (4/4=100%)

3.3. SPACE result and surgical treatment

Among 50 patients, 23 (23/50=46%) showed positive results on SPACE. Three of the 23 patients with positive results did not undergo pancreatectomy because two refused surgery and one had abnormal blood flow around the pancreatic head, which obstructed pancreatectomy. Finally, 20 (20/50=40%, 20/23=87.0%) patients underwent surgery; 19 (19/20=95%) underwent distal pancreatectomy and one (1/20=5%) underwent pancreatoduodenectomy.

3.4. Histopathological findings of resected specimens and pancreatic cysts

On histopathological examination of the 20 resected specimens, 13 (13/50=26%; 13/20=65%) patients had HG-PanIN/CIS. Of these 13 patients, 10 had tumors measuring 5 mm (10/13=76.9%) and three had tumors measuring 10 mm (3/13=23.1%). These tumors were localized in the area of low-grade (LG)-PanIN. Five of the 13 (5/13=38.5%) patients had positive surgical margins in the resected specimens due to LG-PanIN. Among 13 patients with positive surgical results for HG-PanIN/CIS, 12 (12/13=92.3%) had cysts. All cysts in the area of FPPA were revealed to be dilated branch ducts covered by LG-PanIN. The median size of the cyst was 10 mm (range, 5–40 mm). Five of the 12 (5/12=41.7%) patients had a single cyst in the FPPA area. The other seven (7/12=58.3%) patients had multiple cysts, and at least one of the cysts

was localized in the FPPA area. In all patients with a cyst except for one, a filling defect in the MPD suggesting mucin was not detected. The patient who had a filling defect in the MPD had a large cyst with a size of 20 mm without a nodule in the pancreatic head and two small cysts measuring 6 mm in the area of the FPPA in the body. In the MPD near the large cyst, a filling defect suggesting mucin was detected; the cyst was considered to be an intraductal mucinous neoplasm (IPMN) without a finding of malignancy. The patient underwent distal pancreatectomy. In the remaining seven (7/20=35%) patients without a final diagnosis of HG-PanIN/CIS on resected specimens, the histopathological diagnosis was LG-PanIN in four (4/20=20%) and IPMN in three (3/20=15%). Six of the seven (85.7%) patients had cysts with a median size of 10 (5–27) mm. In three of the four (3/4=75%) patients diagnosed with LG-PanIN, one (33.3%) had double cysts in the area of FPPA, while two (66.7%) had a single cyst outside of the FPPA area. A filling defect suggesting mucin was not observed in any of the patients. Two of the three (66.7%) patients diagnosed with IPMN had double cysts, and the remaining one (33.3%) patient had a single cyst. At least one of the double cysts and a single cyst were located in the area of FPPA. A filling defect suggestive of mucin was recognized in each MPD.

3.5. Cytological diagnosis and pancreatic cyst in patients without positive results on SPACE

Among 27 (27/50=54%) patients without positive results on SPACE, 26 (26/27=96.3%) had a cytological diagnosis of “indeterminate” and one (1/27=3.7%) had “negative.” In 23 of the 27 (23/27=85.1%) patients, the identification of a cyst provided an opportunity for further examination of the pancreas. The median diameter of the cyst in these patients was 9 (5-21) mm, and a cyst was localized in the area of Cave-in or Slimness-type FPPA in 17 (17/23=73.9%) patients and adjacent to Slit-type FPPA in one patient (1/23=4.3%).

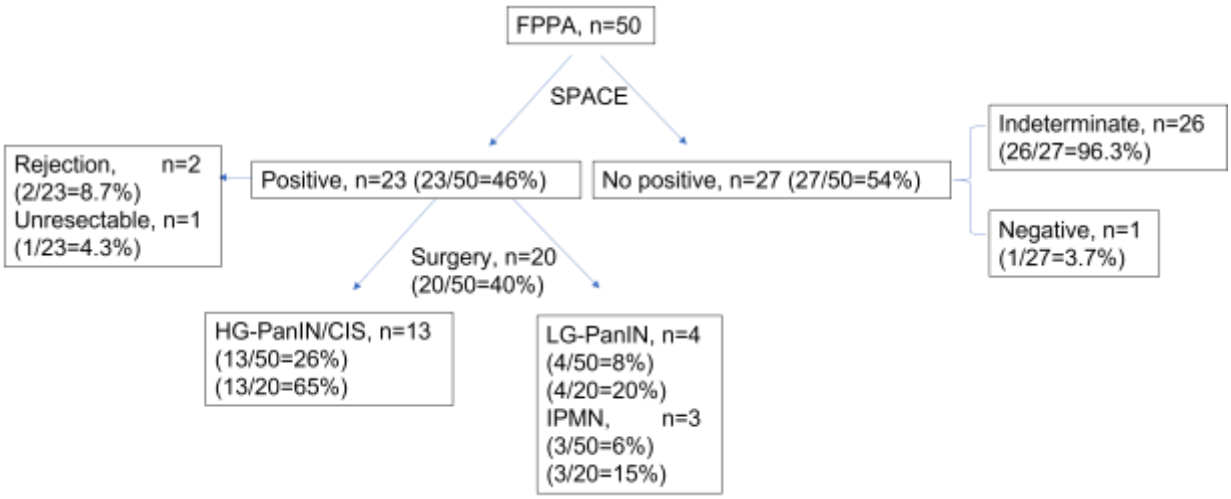

Figure 6. Flow chart of patients with focal pancreatic parenchymal atrophy (FPPA)

Fifty patients with adenocarcinoma or suspected adenocarcinoma on serial pancreatic-juice aspiration cytologic examination were enrolled. Among them, 20 patients (20/50=40%) underwent surgery and 13 patients (13/50=26%, 13/20=65%) had high-grade pancreatic intraepithelial neoplasia/carcinoma in situ on resected specimens.

FPPA; focal pancreatic parenchymal atrophy, SPACE; serial pancreatic juice aspiration pancreatic-juice cytology, HG-PanIN/CIS, high-grade pancreatic intraepithelial neoplasia/carcinoma in situ; LG-PanIN, low-grade pancreatic intraepithelial neoplasia; IPMN, intraductal mucinous neoplasm

3.6. Comparing patients with positive and negative SPACE results

Comparing patients with positive and negative SPACE results, the sex ratio did not significantly differ (p=0.945); the average age of patients was higher in the positive SPACE group than in the negative SPACE group, however, the difference was not significant (72.0 vs. 69.8%; p=0.391); CEA and CA19-9 levels did not significantly differ between the two groups (2.41 vs. 2.95; p=0.682, 21.2 vs. 18.6; p= 0.533) (Table 5).

Table 5. Comparing patients with a positive and a negative SPACE result (n=50)

SPACE	Positive	Negative	
Gender, Male/Female	13/10	15/12	p=0.954
Age, year-old	72.0	69.8	p=0.391
CEA, ng/ml	2.41	2.95	p=0.682
CA19-9, U/ml	21.2	18.6	p=0.533

SPACE, serial pancreatic-juice aspiration cytologic examination; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen

3.7. Complication of SPACE

Regarding complications of SPACE, 23 (23/50=46%) patients had hyperamylasenemia on blood examination without abdominal symptoms the morning after ERCP, while five (5/50=10%) suffered from mild acute pancreatitis. In one (1/50=2%) 66-year old female patient, a volume of about 1 L per day of pancreatic juice was drained, wherein renal dysfunction occurred (Crt=3.63 mg/dl) on day 3 of SPACE. Oliguria was detected, and hemodialysis was required, but it was only performed once for relief of the disorder.

4. Discussion

Our study suggests that FPPA could be a sign of HG-PanIN/CIS, although the positive result of 65% for HG-PanIN/CIS on histopathological examination of the resected specimen was not satisfactory. In general, PDAC occurs most frequently in the pancreatic head [1] compared to the other parts, although we found contradictory results. Furthermore, only one patient with HG-PanIN/CIS in the pancreatic head was included in our study. This may have influenced the relatively low positive ratio of the final diagnosis of HG-PanIN/CIS in our study.

One of the factors related to the relatively low positive ratio may be the difficulty in identifying FPPA in the pancreatic head; thus, we might have missed the preoperative diagnosis. This difficulty is associated with the anatomical features of the pancreas. Moreover, the pancreatic body and tail are thin, and even if parenchymal atrophy is mild, changes can be easily observed. The pancreatic head has a large volume; only sharply defined and large deformation of the pancreatic parenchyma can be detected on CT or MRI. Furthermore, there is a possibility that the present classification of FPPA cannot be applied to the features of FPPA in the pancreatic head. More information about FPPA and HG-PanIN/CIS is required to evaluate FPPA in the pancreatic head in more detail. This

would allow us to suspect HG-PanIN/CIS in the pancreatic head, consequently allowing surgical treatment of HG-PanIN/CIS in the pancreatic head. This would lead to a higher positive ratio of the final diagnosis of HG-PanIN/CIS in patients with positive SPACE results and better prognosis of PDAC than the current ratio and prognosis. The use of thin-slice CT or MRI may be one way to resolve this problem.

To elucidate the mechanisms underlying FPPA, there are some parameters. A possible mechanism is that intraepithelial lesions induce focal pancreatitis due to obstruction of the pancreatic juice flow, leading to pancreatic parenchyma atrophy, or to epithelial cell mutation that could influence the basement membrane to induce apoptosis of the nearby acinar cells, which is assumed in the mammary gland model. [15] However, we should remember that more than half of the patients with FPPA did not have a positive SPACE result. Moreover, in patients with negative results for HG-PanIN/CIS in the resected specimens, LG-PanIN or IPMN was detected in the area of FPPA. Furthermore, some neoplastic intraepithelial changes, including LG-PanIN and IPMN, could also induce FPPA. Some of these changes in the epithelium without the diagnosis of malignancy may have biological characteristics similar to that of HG-PanIN/CIS. A definitive diagnosis of carcinoma or differentiation of HG from LG-PanIN could be difficult histopathologically. Genetic analysis may aid in their diagnoses, but a study described that *p53* is rare and that *SMAD4* mutations are not detected in HG-PanIN/CIS without PDAC (isolated HG-PanIN/CIS). Moreover, *KRAS* mutations are common in both HG and LG-PanIN and do not help in differentiating them. [16] Genetic analysis using *p53* or *SMAD4* does not contribute to the diagnosis of HG-PanIN/CIS. Hence, currently, the diagnosis of HG-PanIN/CIS without PDAC (isolated HG-PanIN/CIS) relies on histopathology.

Many patients enrolled in this study had the opportunity to have their pancreas further examined because they had pancreatic cysts; some patients had a single cyst, while others had multiple cysts. In patients with a final diagnosis of HG-PanIN/CIS, the cyst was small, with a median diameter of 10 mm, located in the area of FPPA, and consisted of a dilated branch duct covered by LG-PanIN. In general, pancreatic cysts are frequently diagnosed as IPMNs. According to the International Guideline of IPMN, [17] an IPMN size >30 mm suggests malignancy; surgery is the recommended form of treatment. If a pancreatic cyst is identified, the size is generally a matter of concern with suspicion of IPMN. However, our study indicates that a cyst could be a dilated branch duct related to intraepithelial lesions, PanIN, but not IPMN. Furthermore,

if it is surrounded by FPPA, HG-PanIN/CIS should be considered. Neoplastic changes in the epithelium alone could dilate the branch duct by obstructing pancreatic juice flow or by a mechanism still unknown.

The average age of patients with a positive SPACE result was higher than that of those with a negative SPACE result, although the difference was not significant. Oncogenesis of the pancreatic duct epithelial cells depends on the time course, which is initiated by *KRAS* mutations, with the accumulation of gene mutations leading to carcinogenesis. [18] It takes about 11 years from initiation until the formation of invasive PDAC. [19] Our results indicate that maturation from LG to HG-PanIN takes more than several years, and the pancreatic ductal epithelium in patients with "indeterminate" results of SPACE could lead to cancer in several years.

5. Conclusions

FPPA could indicate HG-PanIN/CIS, especially in the pancreatic body and tail, but not satisfactorily. One of the factors for the unsatisfactory results might be the difficulty in identifying FPPA in the pancreatic head area. A pancreatic cyst, especially FPPA, could lead to the diagnosis of HG-PanIN/CIS. The size of the cyst does not affect the diagnosis of PDAC, such as HG-PanIN/CIS.

6. Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

7. Acknowledgement

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